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ALAN R. KATRITZKY, FRS
Kenan Professor of Chemistry
Department of Chemistry
University of Florida
Gainesville, Florida

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CONTRIBUTORS

Numbers in parentheses indicate the pages on which the author's contribution begins.

Tatiana N. Borisova (81)
Organic Chemistry Department, Russian Peoples Friendship University, 6, Miklukho-Maklaya Street, Moscow 117198, Russia

Navneet Kaur (123)
Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

L.S. Konstantinova (175)
N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Larisa N. Kulikova (81)
Organic Chemistry Department, Russian Peoples Friendship University, 6, Miklukho-Maklaya Street, Moscow 117198, Russia

Subodh Kumar (123)
Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

O.A. Rakitin (175)
N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Harjit Singh (123)
Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

D.O. Tymoshenko (1)
Department of Medicinal Chemistry, AMRI, 26 Corporate Circle, Albany, NY 12203, USA

Alexey V. Varlamov (81)
Organic Chemistry Department, Russian Peoples Friendship University, 6, Miklukho-Maklaya Street, Moscow 117198, Russia

Leonid G. Voskressensky (81)
Organic Chemistry Department, Russian Peoples Friendship University, 6, Miklukho-Maklaya Street, Moscow 117198, Russia

PREFACE

Benzoheteropines with fused pyrrole, furan, and thiophene rings, of great interest because of their biological activity, are surveyed by Dr. D.O. Tymoshenko of the Albany Molecular Research Institute, New York. These compound classes were considered in both the first and second editions of *Comprehensive Heterocyclic Chemistry* as part of a host of related multi-atom heterocyclic systems. Other specialized reviews have appeared. However, the present survey is the first comprehensive treatment.

The synthesis of hetero annulated azocines is treated by L.G. Voskressensky, L.N Kulikova, T.N. Borisova, A.V. Varlamov (all of Russian Peoples Friendship University, Moscow). While azocino-[4,3-*b*]indoles have been studied because many alkaloids contain this ring system; the present survey covers all six isomeric azocinoindoles.

S. Kumar, N. Kaur, and H. Singh (Guru Nanak Dev University, Amritsar, India) have followed up their review entitled *Syntheses, Structures and Interactions of Heterocalixarenes* in Volume 89 of *Advances in Heterocyclic Chemistry* with a new consideration of metallacalixarenes and their organo-inorganic hybrid molecular architectures.

The final chapter in this volume covers the use of sulfur monochloride in the synthesis of heterocyclic compounds and is by O.A. Rakitin and L.S. Konstantinova (Zelinsky Institute, Moscow, Russia). It includes a survey of the extensive work carried out by these authors and other friends and associates of the late Charles Rees on heterocycles containing heterocycles with up to five sulfur atoms and often many nitrogen atoms. In addition, the chapter also shows how sulfur monochloride may be used advantageously in the synthesis of other sulfur heterocycles.

Alan R. Katritzky
Gainesville, Florida

CHAPTER 1

Benzoheteropines with Fused Pyrrole, Furan and Thiophene Rings

D.O. Tymoshenko

Contents

Department of Medicinal Chemistry, AMRI, 26 Corporate Circle, Albany, NY 12203, USA

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1. INTRODUCTION

1.1 Scope of the review

Heteropines received much attention, primarily because of continuous interest in the psychopharmacological activity of their bicyclic and tricyclic derivatives. Tricyclic heteropine ring systems have been reviewed in the first (1984CHEC-I(7)593) and second (1996CHEC-II(9)1) editions of *Comprehensive Heterocyclic Chemistry*, where they were treated with other azepine, thiepine, oxepine and related multiheteroatom systems. Synthesis, structures, reactivity and applications of tricyclic heteropines have been a part of the general indole (2001MI361) and seven-membered rings (1994PHC301, 1995PHC294, 1996PHC298, 1997PHC318, 1998PHC320, 1999PHC319, 2000PHC339, 2001PHC340, 2003PHC385, 2004PHC431, 2005PHC389) discussions. The specialized review (1993H601) surveyed the synthesis of 1,5-benzodiazepines with three-, four- and five-membered rings fused to different positions of the 1,5-benzodiazepine skeleton. Synthesis of DNA-interactive pyrrole[2,l-*c*][1,4]benzodiazepines (1994CR433) and medicinal chemistry aspects of the novel thieno benzodiazepine antipsychotic *Olanzapine* (1997MI1743) have been reviewed.

Current work is focused on the benzoheteropines with the fused pyrrole (or indole), thiophene or furan rings, i.e., *ortho*-fused 6 + 7 + 5 ring systems with carbons only on the six-membered ring, one heteroatom on the five-membered ring and one or more heteroatoms on the seven-membered ring. The variety of heteroatoms is limited to nitrogen, oxygen and sulfur. Several examples of the related cyclic systems with the other heteroatom distribution or *peri*-fusion are briefly summarized in Section 4.3. The current first specialized review covers synthetic, reactivity and structural aspects reported from the late 1989 until 2007.

1.2 Structural types and nomenclature

The main surveyed structural types are depicted in Figure 1. They are based on the parent carbocyclic benzoazulene core (Q = A = carbon) which produces a

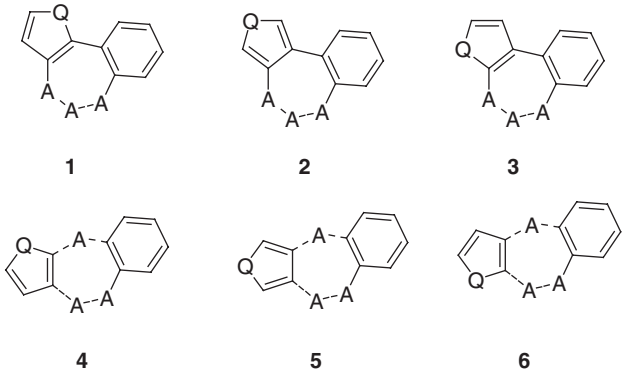


Figure 1 Main structural types.

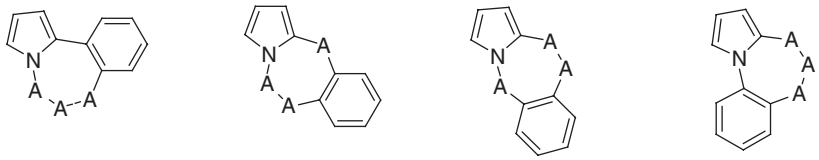


Figure 2 Benzopyrrolo[1,2-*a*]azepine types.

total of three benzo[*e*]azulenes **1**–**3** and three benzo[*f*]azulenes **4**–**6**. The tricyclic ring systems discussed in this review can be generated by defining of the query atoms A (A = C, N, O or S) and Q (Q = N, O or S) of the parent ring.

The special case of the fusion of a five-membered ring to the benzoheteropine ring occurs when the pyrrole or indole N1 and C2 atoms serve as fusion sites (Figure 2). The resultant benzopyrrolo[1,2-*a*]azepines differ by the position of the fused benzo ring and are listed in the order of benzo[*c*]pyrrolo[1,2-*a*]- (**7**), benzo[*d*]pyrrolo[1,2-*a*]- (**8**), benzo[*e*]pyrrolo[1,2-*a*]- (**9**) and benzo[*f*]pyrrolo[1,2-*a*]- (**10**) azepines, respectively.

The nomenclature and numbering used above are recommended by IUPAC (1998PAC143), and they can be further applied to the other cyclic systems with one or more heteroatoms on the heteropine ring using the order of preference rules. Thus, fusion of pyrrole (54), furan (71) or thiophene (78) with azepine (43), oxepine (67) or thiepine (78) results in chemical names in which the parent heterocycle has the lowest preference number and is cited last in the name (preference numbers from Appendix II (1998PAC143) are in brackets). Explanation of the fusion descriptors can be found in the IUPAC recommendations (1998PAC143) and were exemplified in CHEC-I (1984CHEC-1(1)7).

Particular types of seven-membered rings and their fused derivatives are reviewed in the order of nitrogen-, oxygen- and sulfur-containing heteropines, following the same heteroatom order for the five-membered fused rings. Thus, synthesis of benzazepines is discussed in Section 2.1 in the order of fused pyrrole, furan and thiophene derivatives. Discussion of pyrrole, furan and thiophene fused to oxepine and thiepine rings is organized in a similar manner in Sections 2.2 and 2.3, respectively. Section 3 describes the diheteropine systems in the order of benzodiazepines, benzoxazepines and benzothiazepines, followed by benzodioxepines, benzoxathiepines and benzodithiepines. Section 4 deals with the systems with more than two heteroatoms on the heteropine ring and miscellaneous related ring systems.

2. BENZOHETEROPINE RINGS WITH ONE HETEROATOM

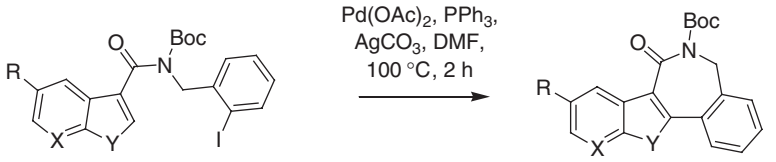
2.1 Benzazepines

2.1.1 Benzazepines with fused pyrrole ring

Two major types of transformations are usually used for the synthesis of benzazepines with the fused pyrrole and indole rings. Construction of the

benzazepine ring by formation of C–C or C–N bonds is most common for the preparation of pyrrole fused systems, while a Fischer synthesis is widely used for the attachment of an indole ring to a preformed benzazepinone. Several other methods, usually involving annulation of a pyrrole ring onto a pre-formed benzazepine, have been developed. Syntheses of benzopyrrolo[1,2]azepines, in which pyrrole or indole N1 and C2 atoms serve as fusion sites, are considered separately in Section 2.1.1.5.

2.1.1.1 Construction of the azepine ring by C–C bond formation. The Heck-type cyclization of amides **11**, easily available by amide bond coupling (EDCI, DMAP) between the corresponding indolo- and pyrrolo-[2,3-*b*]pyridine-carboxylic acids and 2-iodobenzylamine, is effective in the presence of $Pd(OAc)_2/PPh_3$ catalyst and silver carbonate base and leads to excellent yields of the corresponding azepinones **12** (Equation (1) (2005TL8177)).

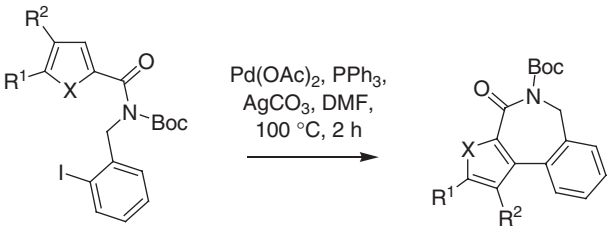


(1)

11 **12**

#	R	X	Y	Yield of **12**, %
11a, 12a	H	CH	N-SO_2Ph	92
11b, 12b	OMe	CH	N-SO_2Ph	96
11c, 12c	H	N	N-SO_2Ph	86
11d, 12d	H	CH	S	100

Suitable amide derivatives of pyrrole- and indole-2-caroxylic acids **13** result in good yields of 5,6-dihydrobenzo[*c*]pyrrolo[3,2-*e*]azepin-4(3*H*)-one **14a** and its indole analog **14c** (Equation (2) (2005TL8177)).

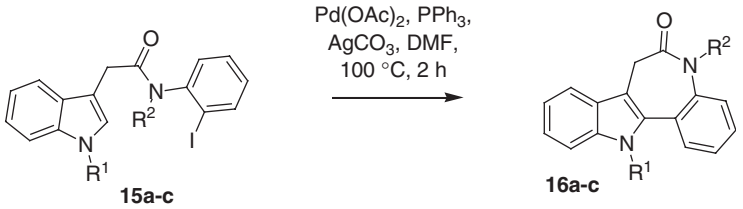


(2)

13a-d **14a-d**

#	R^1, R^2	X	Yield of **14**, %
13a, 14a	$R^1 = R^2 = H$	N-EOM	70
13b, 14b	-CH=CH-CH=CH-	N-Boc	0
13c, 14c	-CH=CH-CH=CH-	N-EOM	96
13d, 14d	-CH=CH-CH=CH-	S	82

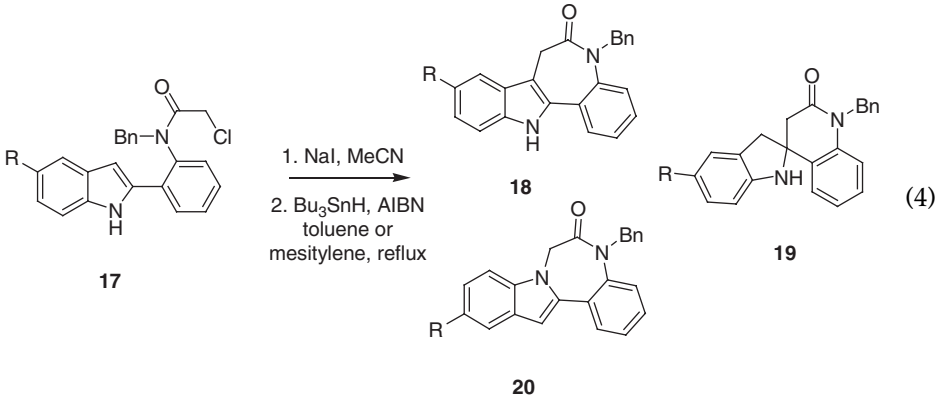
Similarly, 2-iodoanilides of indolyl acetic acid **15** lead to the corresponding 7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-ones **16** (Equation (3) (2005TL8177)). Contrary to *N*-phenylsulfonyl derivatives **11a**,**b** and EOM protected species **13a**,**c**, Boc-derivatives **14b** and **15a** do not tolerate these reaction conditions, and their fast decomposition has been observed.



(3)

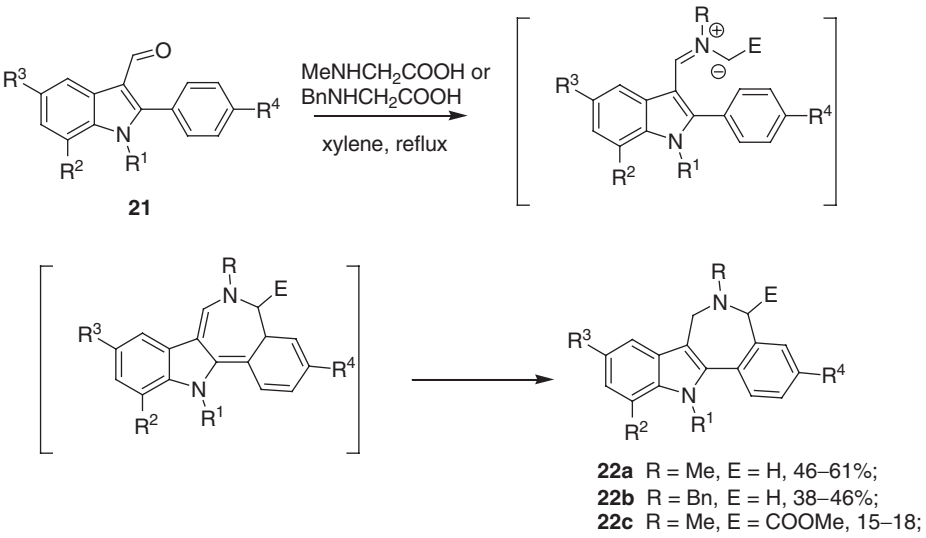
#	R^1	R^2	Yield of **16**, %
15a, 16a	Me	Boc	0
15b, 16b	Me	Me	89
15c, 16c	EOM	EOM	92

Conversion of 2-chloroacetamides **17** into iodoacetamides by iodide exchange followed by reaction with Bu_3SnH in the presence of AIBN affords 7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-ones **18** as products of free radical cyclization (Equation (4) (2005T5489)). Low (8–25%) yields of azepinones **18** are observed in toluene medium, and they are usually accompanied with the product of spiro cyclization **19** and isomeric compound **20**. Yields of the paullone **18** can be increased to 25–52% at higher temperatures (boiling mesitylene).

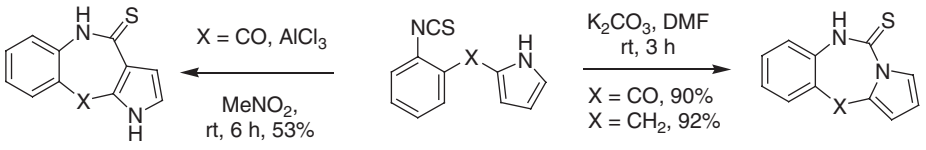


(4)

A new route to the benz[5,6]azepino[4,3-*b*]indole ring has been developed from easily available 3-formyl indole derivatives **21** (Scheme 1 (2005TL377)). Intermediate azomethine ylides are generated from aldehydes in refluxing xylene using decarboxylative condensation with sarcosine or *N*-benzyl glycine. Further 1,7-electrocyclization followed by 1,5-hydrogen shift leads to products **22a**–**b** in good yields. In the case of methyl sarcosinate (R = Me, E = COOMe)



Scheme 1



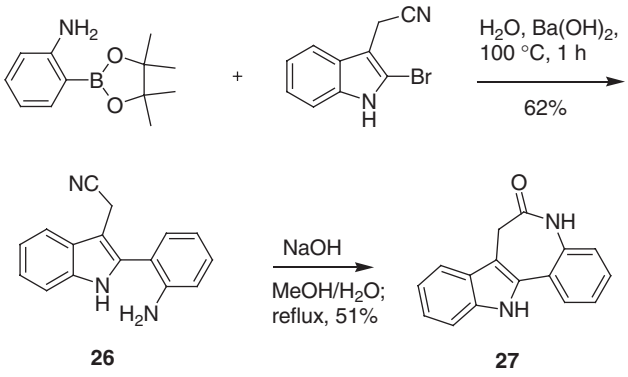
Scheme 2

decarboxylation does not occur and the corresponding ester derivatives **22c** (E = COOMe) were isolated in 15–18% yields.

Isothiocyanate **23** (X = CO), when treated with $AlCl_3$ in nitromethane undergoes ring closure by an intramolecular electrophilic substitution between C3 of the pyrrole ring and the isothiocyanate group to afford pyrrolo[3,2-*c*][1]benzazepine-10(1*H*)-one-4(5*H*)-thione **24** (Scheme 2 (2005BMCL3220, 1998MI197)).

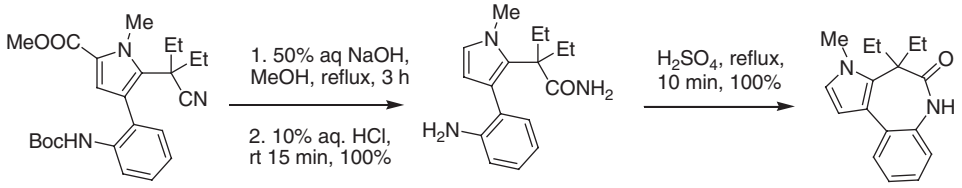
2.1.1.2 Construction of the azepine ring by C–N bond formation. Indole **26**, readily available by the palladium-catalyzed, two-step, one-pot borylation/Suzuki coupling reaction, undergoes cyclization under basic conditions to yield paullone **27** (Scheme 3 (2002JOC1199)).

Basic hydrolysis of **28** followed by treatment with hydrochloric acid gives the primary amide **29**. Further lactamization can be achieved after controlled heating in concentrated sulfuric acid to produce norsecorhazinilam analog **30** (Scheme 4 (2000TL5853)).



26 **27**

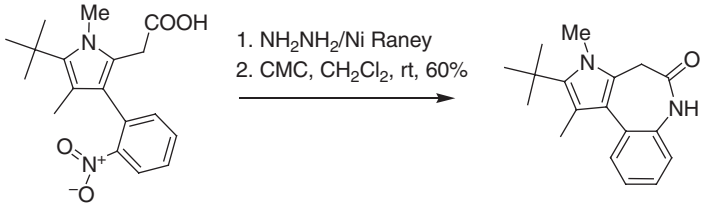
Scheme 3



28 **29** **30**

Scheme 4

Reduction of nitro compound **31** with hydrazine hydrate/Raney nickel affords an amine, which produces pyrrolo-benzazepine **32** under intramolecular amide bond coupling (Equation (5) (1996BCF251).

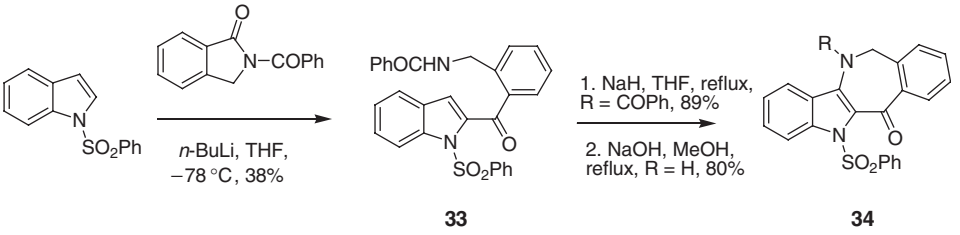


(5)

31 **32**

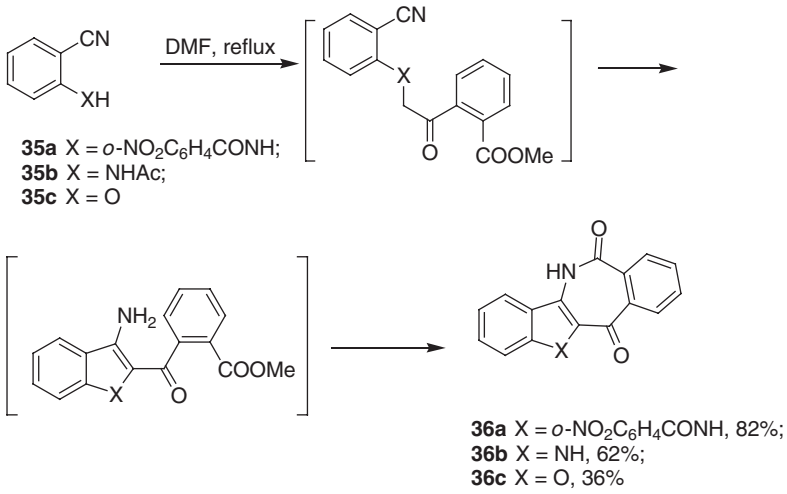
Reaction of *N*-benzoyl isoindolin-1-one with 2-lithio-1-phenylsulfonylindole takes place at both lactam and acyclic carbonyl groups generating a separatable 4:3 mixture of ketone **33** with 2-benzoyl-1-phenylsulfonylindole. When the reaction is allowed to proceed for longer than *ca*. 15 min, cyclized product **34** is formed as the result of an intramolecular nucleophilic substitution. Compound **34** can be obtained from the isolated ketone **33** in good yield on exposure to NaH in refluxing THF (Scheme 5 (1996TL4283)).

2-Aminobenzonitrile **35a** produces the corresponding indolo benzazepine **36a** when reacted with *o*-carboxymethyl bromoacetophenone in refluxing DMF



33 **34**

Scheme 5



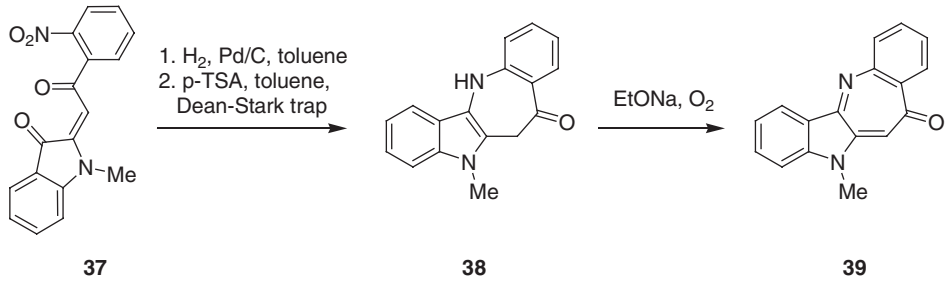
Scheme 6

(Scheme 6 (1991JHC379)). Interestingly, *N*-acetyl derivative **35b** affords *N*-unsubstituted compound **36b** in 62% yield.

Hydrogenation of unsaturated nitro compound **37** (10% Pd/C, toluene) gives a saturated amino intermediate that can be treated with PTSA under Dean–Stark conditions to give the target keto isomer of cryptoheptine **38** in a 44% two-step yield (Scheme 7 (2000JNP643)).

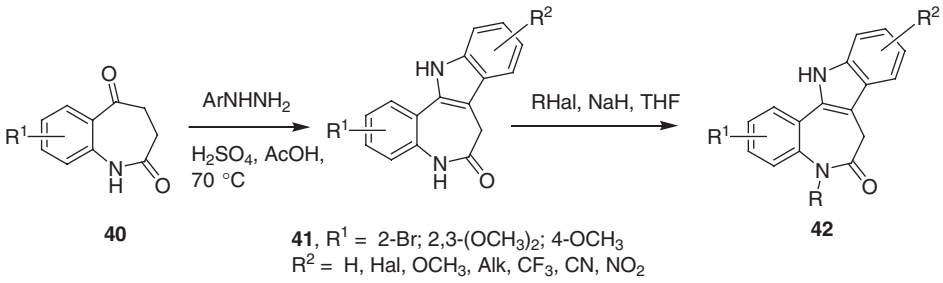
1-Phenylsulfonyl-2-[2′-acetamido-5′-methylbenzoyl]-indole when reacted with chloromethyl methyl ether in acetic acid at room temperature affords 2,5-dimethyl-7-phenylsulfonyl-5,6-dihydroindolo[2,3-*c*]benzazepin-12-one (2005AX(E)o2410).

2.1.1.3 Construction of the indole ring via *Fischer synthesis.* Starting from a variety of 3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-diones **40** and arylhydrazines Fischer syntheses of indolo benzazepinones **41** have been reported (Scheme 8 (1999JMC2909)). Usually, the reaction comprises a two-step one-pot procedure with the formation of intermediate arylhydrazones in warm acetic acid followed



37 38 39

Scheme 7



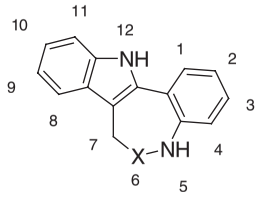
40 42 45 43 44

Scheme 8

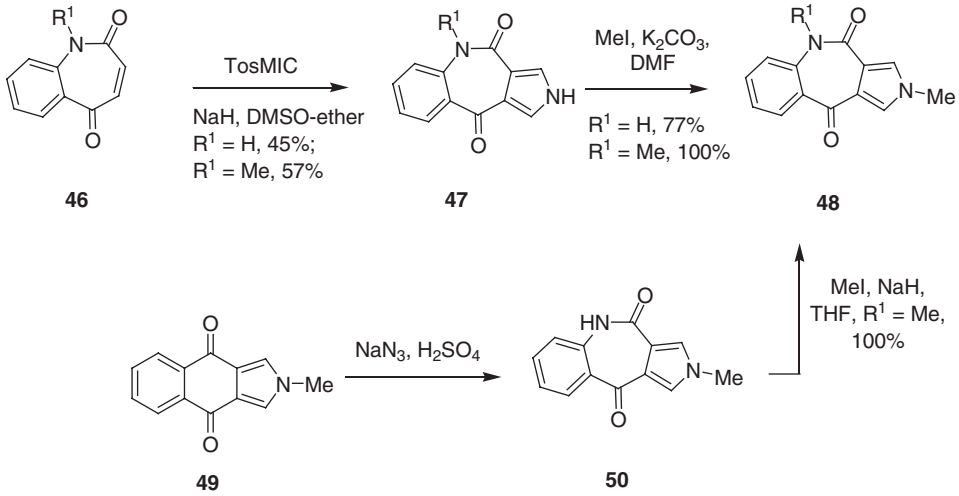
by indole ring formation on treatment with sulfuric acid. Other examples of such transformations, including reaction conditions and yields are listed in Table 1. The protic acid procedure affords products in 33–74% yields, while successful attempts using Lewis acid catalyzed (1993JMC2908, 1992AG(E)1060) or thermal (2005MI541) conditions also has been reported. The Fisher synthesis tolerates diverse substitution including vinyl and allyl (2005EJM655), phthalimide protected amino (2005MI541), nitrile and ester (2005MI541), methoxy (2002AP311), thiomethyl and sulfonamide (2004AP486) derivatives.

2.1.1.4 Miscellaneous reactions. Pyrrolo-benzazepinedione **50** has been synthesized by a Schmidt type rearrangement and ring enlargement of diketone **49**

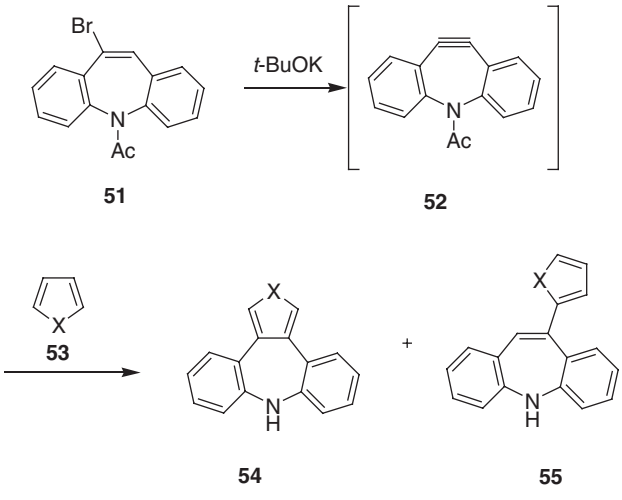
Table 1 Synthesis of indolobenzoheteropines



Substitution on the ring			Conditions	Yield (%)	References
Benzo	Indole	X			
H	H	C=O	H_2SO_4, AcOH, 70 °C, 1 h	70	1992AP297
2-Br	H	C=O	H_2SO_4, AcOH, 70 °C, 1 h	63	1992AP297
H	9-Br	C=O	H_2SO_4, AcOH, 70 °C, 1 h	58	1992AP297
H	11-Cl	C=O	H_2SO_4, AcOH, 70 °C, 1 h	62	1992AP297
H	9-Cl	C=O	H_2SO_4, AcOH, 70 °C, 1 h	83	1992AP297
H	H	C=O	$ZnCl_2$	7.5	1993JMC2908
H	H	C=O	$ZnCl_2$, 170 °C, 5 min	85	1992AG(E)1060
3-Cl	9-OMe	CH_2	HCl, EtOH, reflux, 18 h	53	1994CPB1084
3-Cl	9-OMe, 10-CH_2NR_2	CH_2	HCl, EtOH, reflux, 18 h	49	1994EJM107
2-vinyl	9-Br	C=O	H_2SO_4, AcOH, 70 °C, 2 h	52	2005EJM655
2-allyl	9-Br	C=O	H_2SO_4, AcOH, 70 °C, 2 h	62	2005EJM655
2-*o*-$C_6H_4(CO)_2N$-$(CH_2)_4$	9-NO_2	C=O	Ph_2O, reflux, 2 h	55	2005MI541
2-*o*-$C_6H_4(CO)_2N$-CH_2CH=CH	9-NO_2	C=O	Ph_2O, reflux, 2 h	70	2005MI541
CH_2CH_2CN	9-NO_2	C=O	Ph_2O, reflux, 2 h	72	2005MI541
CH_2CH_2COOMe	9-NO_2	C=O	Ph_2O, reflux, 2 h	56	2005MI541
2-OMe	9-SO_2NH_2	C=O	H_2SO_4, AcOH, 70 °C, 1 h	58	2004AP486
2-OMe	9-SMe	C=O	H_2SO_4, AcOH, 70 °C, 1 h	82	2004AP486
2-I	9-CF_3	C=O	H_2SO_4, AcOH, 70 °C, 1 h	50	2000BMCL567



Scheme 9

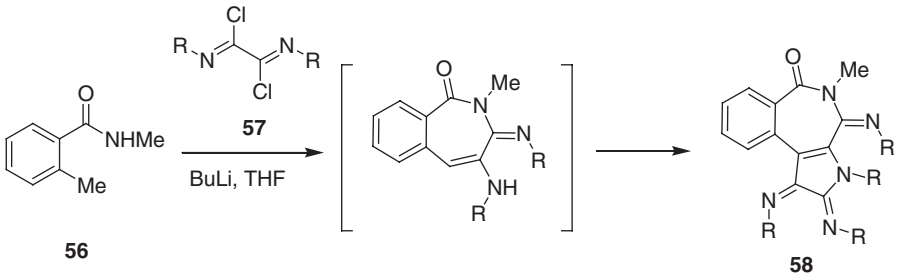


Scheme 10

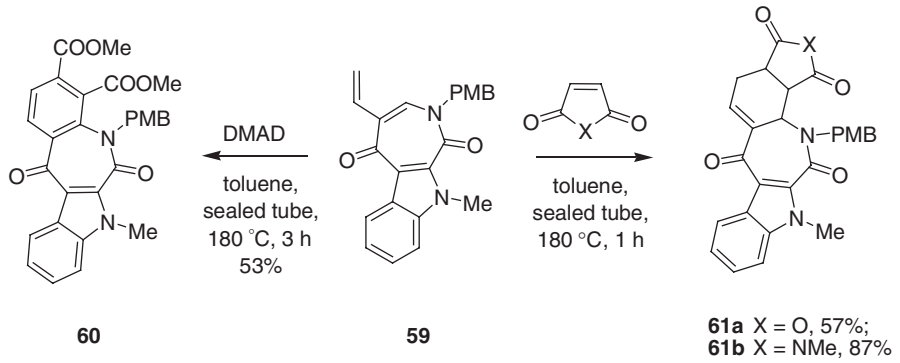
(Scheme 9 (1996SC1839)). Alternatively, this cyclic system has been synthesized by TosMIC addition to 1*H*-1-benzazepine-2,5-dione **46**.

Reaction of *N*-acetyl-10-bromodibenzazepine **51** with potassium *tert*-butoxide yields the reactive intermediate **52** that reacts with *N*-methyl pyrrole **53** (X = NMe) used as a solvent to produce a mixture of Diels–Alder/retro Diels–Alder adduct **54** with the Michael by-product **55** (X = NMe, Scheme 10 (1994JHC293)).

The condensation of dichloride **57** with the dianion of *N*-methyl *ortho*-tolylamide **56** affords pyrrolo[2,3-*d*]-[2]benzazepin-6(1*H*)-one **58** (R = *p*-tolyl). The product **58** contains four rather than just two imino groups. This can be explained



Scheme 11



Scheme 12

by condensation of the enamine function of the initial 1:1 product with a second molecule of the bis(imidoyl) chloride **57** (Scheme 11 (2001EJO1503, 1998SL399)).

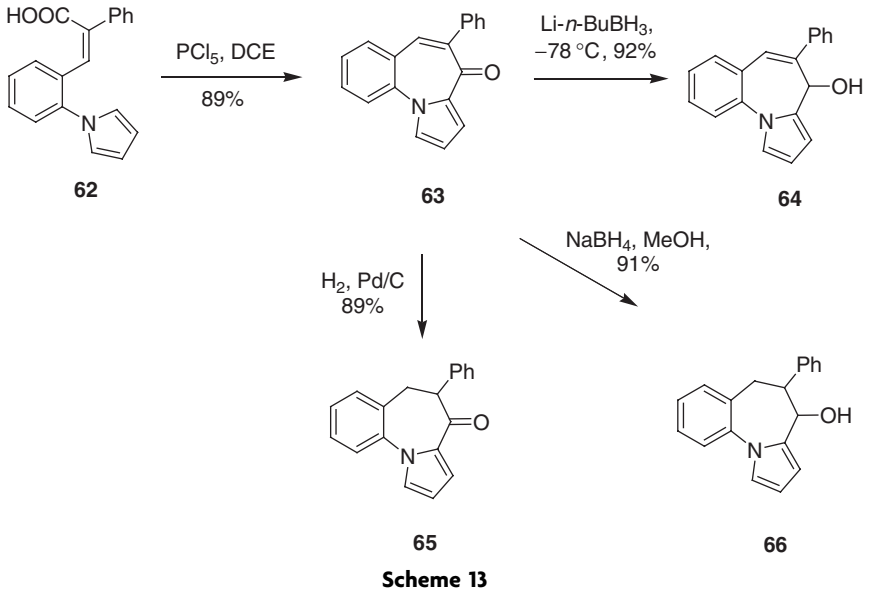
The unusual annulation of a substituted phenyl ring through [4 + 2] cycloaddition of vinyl compound **59** with dimethyl acetylenedicarboxylate (DMAD) as dienophile affords indolo benzazepine **60** in 53% yield, while a similar reaction with *N*-methyl-maleimide or maleic anhydride yields tetracyclic **61a**,**b** in 53–87% yield (Scheme 12 (2003T6659)).

Intramolecular oxidative palladium couplings of alkenylamino indoles allow the preparation of azepinoindole derivatives in high yields (2005MI707).

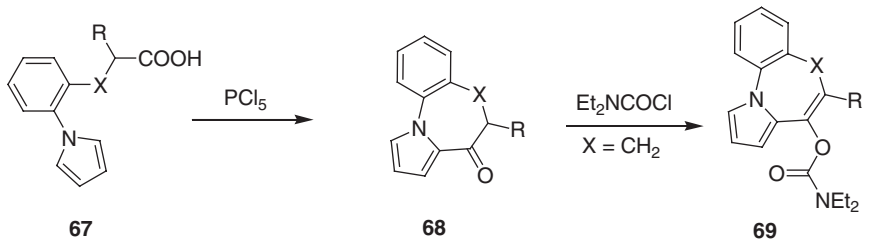
2.1.1.5 Benzopyrrolo[1,2]azepines. Syntheses of benzopyrrolo[1,2]azepines in which pyrrole or indole N1 and C2 atoms serve as fusion sites usually involve preforming the *N*-substituted pyrrole derivatives followed by intramolecular cyclization.

Few examples of the intramolecular electrophilic substitution on a $C2_{pyrrole}$ site have been reported for benzo[*f*]pyrrolo[1,2-a]azepinones. Thus, treatment of acid **62** with phosphorous pentachloride results in Friedel–Crafts product **63** (Scheme 13 (2000T9351)).

Similarly, benzo[*f*]pyrrolo[1,2-a]azepinone **68** (R = Ph; X = CH_2) can be obtained from the corresponding acid **67** *via* intramolecular Friedel–Crafts acylation (Scheme 14 (2002JMC4276)).

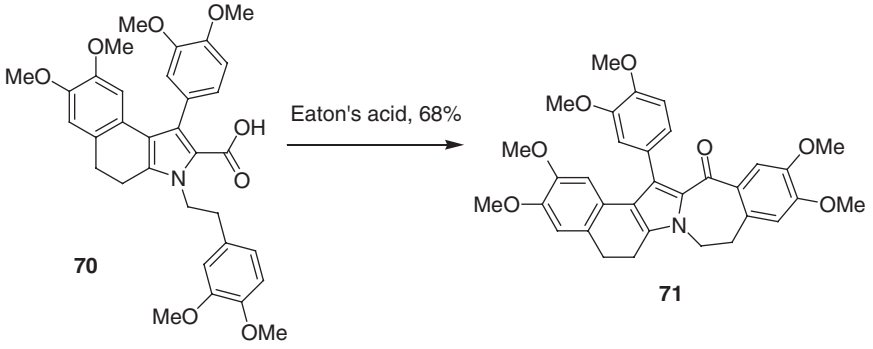


Scheme 13



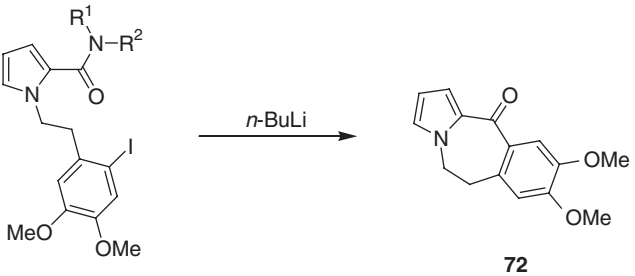
Scheme 14

Intramolecular electrophilic reactions of substituted pyrrole-2-carboxylic acids or their amides lead to benzo[*d*]pyrrolo[1,2-a]azepinones. Acid **70** in this fashion undergoes Friedel–Crafts cyclization to furnish fused azepine **71** in good yield (Equation (6) (2000JOC2479)).



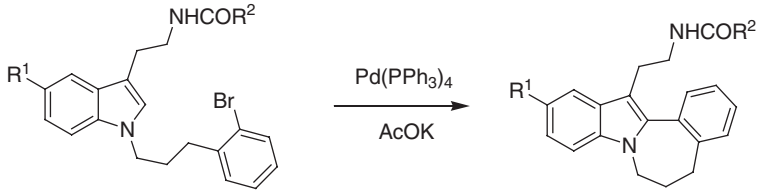
(6)

Likewise, aryllithiums generated by lithium–iodine exchange undergo intramolecular cyclization to give pyrrolo-azepine **72**. The best results were obtained when Weinreb ($R^1 = Me$, $R^2 = OMe$) or morpholine amides were used as internal electrophiles, resulting in 66 and 70% yields, respectively (Equation (7) (2005T3311)).

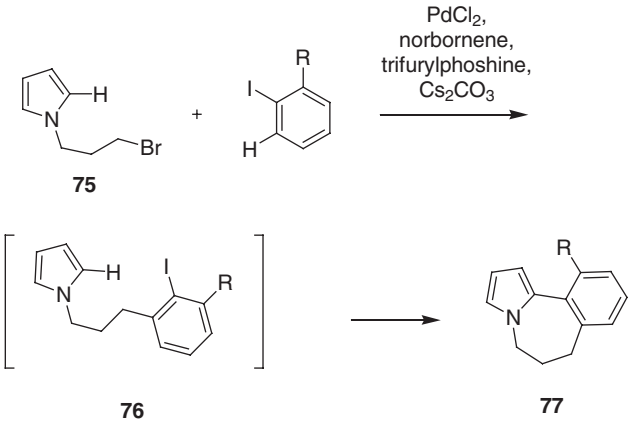


72 (7)

Several azepine ring constructions have been reported using palladium catalyzed C–C bond formation. Palladium catalyzed cyclizations of substituted tryptamine derivatives **73** lead to benzo[*d*]pyrrolo[1,2-*a*]azepinones **74** (Equation (8) (2000JMC1050)).



73 **74** (8)

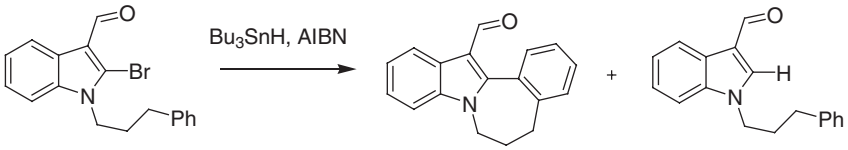


75 **76** **77**

Scheme 15

A variety of substituted seven-membered annulated pyrroles can be synthesized in a one-step process in good yields from readily accessible *N*-bromoalkyl pyrroles **75** and aryl iodides. The synthesis is based on a palladium-catalyzed/norbornene-mediated sequential coupling reaction involving an aromatic sp^2 C–H functionalization as the key step. The proposed mechanism suggests that *ortho*-alkylation with the formation of intermediate **76** most likely precedes aryl–heteroaryl coupling (Scheme 15 (2006OL2043)).

Reaction of the radical derived from substituted 2-bromo indole **78** leads in moderate (37%) yield to benzo[*d*]pyrrolo[1,2-*a*]azepinone **79** along with 32% of the reduction product **80**. The process occurs *via* radical addition to the benzene ring followed by rearomatization (Equation (9) (2000TL4209)).



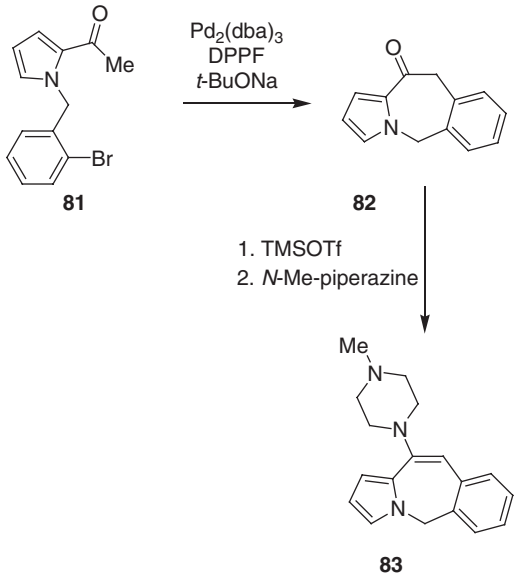
(9)

78 **79** **80**

A similar synthetic transformation has been reported for a variety of substituted indole annulated rings (2005JA13148, 2006OL3601).

Synthesis of benzo[*e*]pyrrolo[1,2-*a*]azepinone **82** was accomplished by palladium catalyzed ring closure of ketone **81** (Scheme 16 (2005JMC1705)).

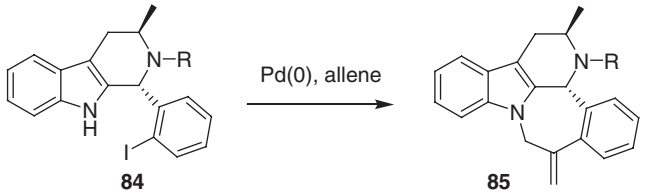
Palladium catalyzed reaction of iodo **84** with allene is an example of a 5 + 2 ring formation and gives access to the fused benzo[*d*]pyrrolo[1,2-*a*]azepinone



81 **82** **83**

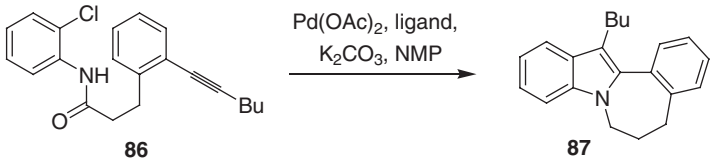
Scheme 16

derivatives **85** in 48–73% yield (Equation (10) (2000T6585)).



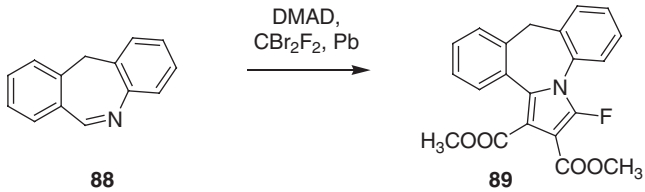
84 **85** (10)

A one-step method has been developed for elaboration of fused indole **87** *via* a palladium-catalyzed intramolecular indolization of 2-chloroaniline **86** bearing tethered acetylene (Equation (11) (2006OL3573)).



86 **87** (11)

1,3-Dipolar cycloaddition is another route to benzopyrrolo[1,2-a]azepines by pyrrole ring formation. The azomethine ylide derived from imine **88** and difluorocarbene adds to DMAD to produce dimethyl 3-fluoro-9*H*-dibenzo[*c,f*]-pyrrolo[1,2-*a*]azepine-1,2-dicarboxylate **89** in 20% yield (Equation (12) (2000JCS(P1)231)).



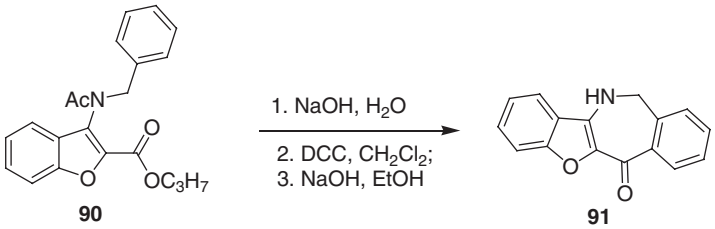
88 **89** (12)

2.1.2 Benzazepines with fused furan ring

An example of the direct annulation of the furan ring onto the benzazepine core has been reported by Cann and co-workers (1990JHC1839). Reaction of *N*-acetyl-10-bromodibenzazepine **51** with potassium *tert*-butoxide yields the reactive intermediate **52**. It further reacts as a dienophile with furan **53** (X = O) to produce 8*H*-furo[3,4-*d*]dibenz[*b,f*]azepine **54** as a sole product (X = O, Scheme 10, Section 2.1.1.4).

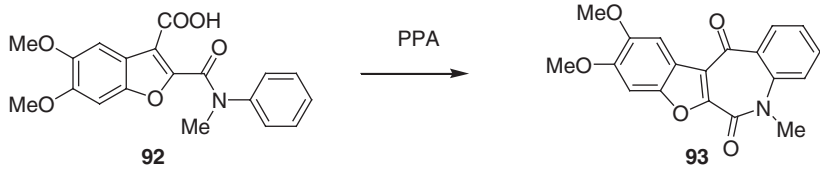
Intramolecular C–C bond formation in the furan precursor is the main synthetic method for furobenzazepines. 2-Hydroxybenzonitrile **35c** produces the corresponding benzofuran benzazepine dione **36c** when reacted with *o*-carboxymethyl bromoacetophenone in refluxing DMF (Scheme 6, Section 2.1.1.2 (1991JHC379)). Alternatively, benzofurobenzazepinone **91** can be synthesized starting from benzofuran amino ester **90** by intramolecular acylation

(Equation (13) (1991JHC379)).



90 91 (13)

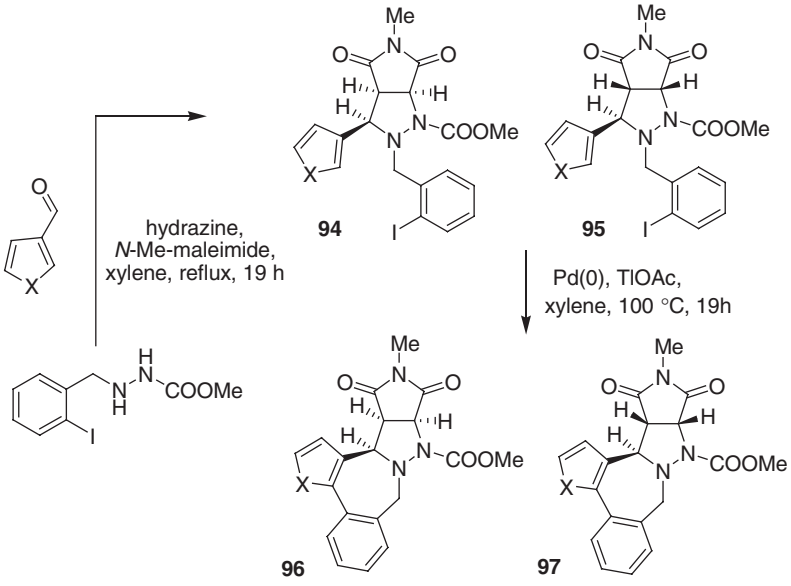
Benzofuro-[2,3-*c*]-[1]-benzazepin-6,12-dione **93** has been reported as a product of cyclization of acid **92** (Equation (14), 2002MI353).



92 93 (14)

In situ generation of azomethine imines from furan-3-carbaldehyde and *N,N′*-disubstituted hydrazines followed by cycloaddition to *N*-methylmaleimide results in a 2.8:1 mixture of pyrazolidines **94** and **95** (X = O) separatable by chromatography. Further Pd(0) catalyzed cyclization involving the aldehyde and hydrazine moieties leads to the formation of benzoxepines **96** and **97** (X = O) in good yield (Scheme 17 (2003T4451)).

The cascade ketene imine [2 + 2] cycloaddition and palladium catalyzed cyclization is a convenient route to furoazepine **98** (X = O) with the fused *β*-lactam

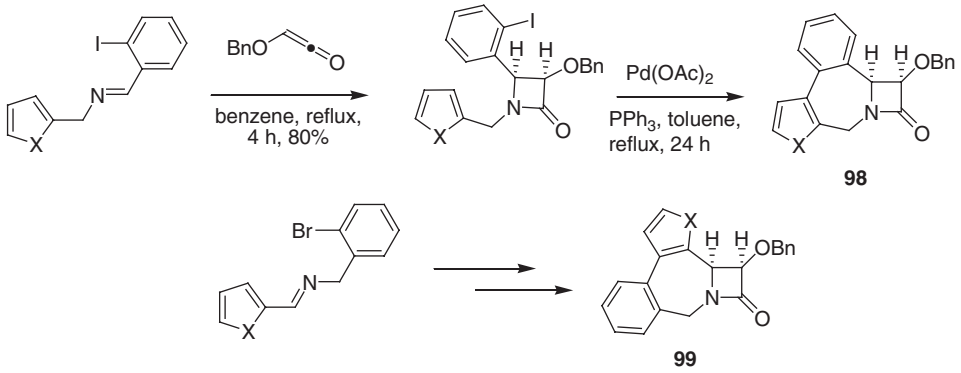


Scheme 17

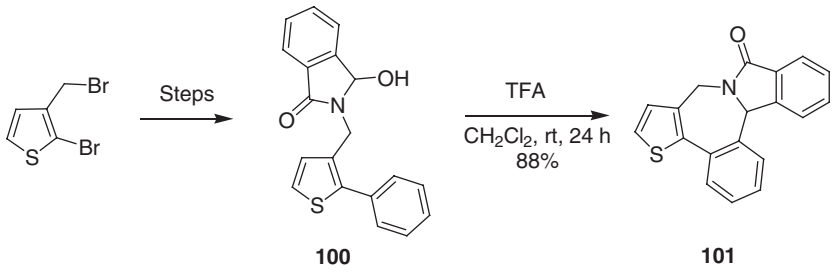
moiety obtained in 52% yield (Scheme 18 (1995TL9053)). Introduction of the furan moiety into aldehyde counterpart gives corresponding **99** (X = O) in 60% yield.

2.1.3 Benzazepines with fused thiophene ring

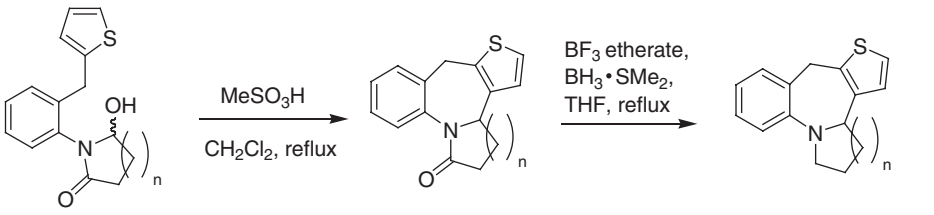
2.1.3.1 Construction of the azepine ring by C–C bond formation. Thieno[2]benzazepine with the annulated isoindole ring **101** is the product of acid-catalyzed cyclization of hydroxylactam **100** obtained in 88% yield (Scheme 19 (1997JHC1495, 1997TL1041)). Similar fused derivatives were synthesized starting from succinimide and tetramethyl succinimide, to give thieno benzazepines in 80 and 85% yields, correspondingly.



Scheme 18



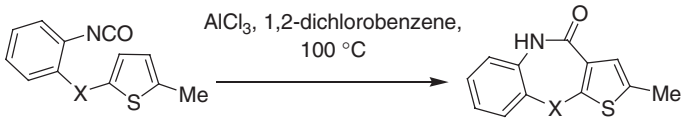
Scheme 19



Scheme 20

Tetracyclic benzo[*f*]-4-oxopyrrolo[1,2-*a*]thieno[3,2-*c*]azepine **103a**, as well as its piperidone homolog **103b**, can be prepared through intramolecular *N*-acyliminium ion cyclization of hydroxylactams **102** (Scheme 20 (2001H1519)).

The synthesis of thieno[3,2-*c*]benzazepine derivative **106b** has been reported by Friedel–Crafts intramolecular cyclization of isocyanates **105** (Equation (15) (2002S355)). Noteworthy, lactam **106b** is formed in 51% yield, while dione **106a** can not be obtained due to the electron-withdrawing effect of the carbonyl group.



105

106a X = CO, 0%;
106b X = CH_2, 51%

(15)

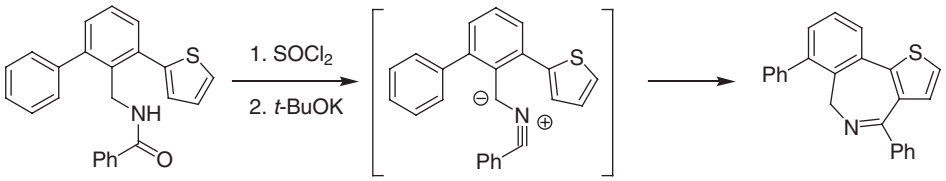
The cyclization of diene conjugated nitrile ylides in which the conjugated system consists of a benzene ring and a five-membered heterocyclic ring provides an effective route to unsaturated heterocycle-fused benzazepines. Thus, nitrile ylide **107** undergoes smooth cyclization onto the substituent at the 6 position without considerable competition from cyclization onto the unsubstituted phenyl group at the 2 position, providing thieno benzazepine **108** in 98% yield (Scheme 21 (1991CC658, 1995JCS(P1)2565)).

Several other examples of a thieno benzazepine synthesized from substituted thieno aryls through nitrile ylides have been reported (1994JCS(P1)1193).

Similar to furo derivatives, cascade ketene imine [2 + 2] cycloaddition and palladium catalyzed cyclization gives thieno benzazepines **98** and **99** (X = S) with the fused *β*-lactam moiety in 65 and 66% yields, correspondingly (Scheme 18, Section 2.1.2 (1995TL9053)).

The Heck-type cyclization in the presence of $Pd(OAc)_2/PPh_3$ catalyst and silver carbonate base leads to good to excellent yields of the corresponding thieno benzoazepinones **12d** and **14d** (see Equations (1) and (2), Section 2.1.1.1 (2005TL8177)).

Similar to the furobenzazepine derivatives (Scheme 17, Section 2.1.2), thieno benzazepines **96** and **97** (X = S) were synthesized in good yields by a multistep procedure involving *in situ* generation of azomethine imines from thiene-3-carbaldehyde and *N*,*N*′-disubstituted hydrazines followed by cycloaddition to

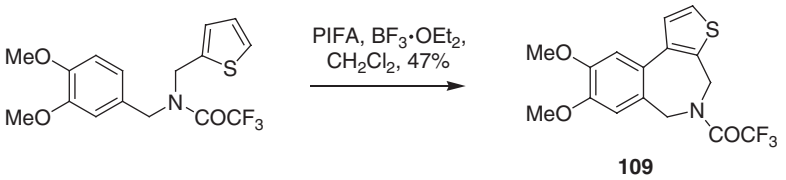


107 **108**

Scheme 21

N-methylmaleimide and Pd(0) catalyzed cyclization of the intermediate pyrazolidines (2003T4451).

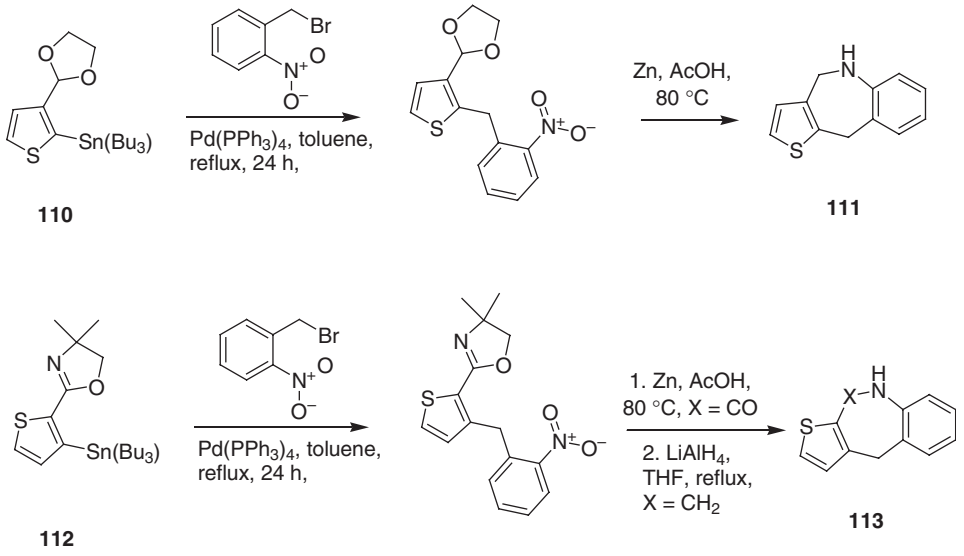
Thieno benzazepine **109** was synthesized in moderate yield by oxidative biaryl-coupling using the hypervalent iodine reagent phenyliodine(III)bis (trifluoroacetate) (PIFA) and $BF_3 \cdot OEt_2$ as the activating agent in methylene chloride (Equation (16) (2002T8581)).



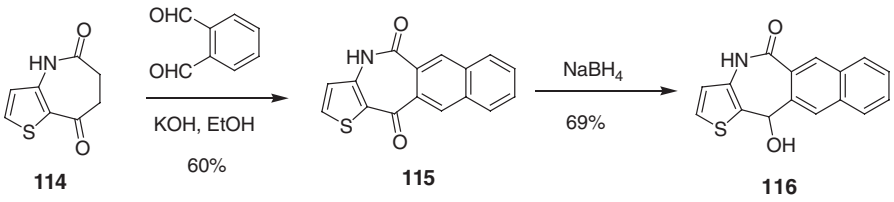
109 (16)

2.1.3.2 Construction of the azepine ring by C–N bond formation. Aranapakam et al. synthesized 5,10-dihydro-4*H*-benzo[*b*]thieno[2,3-*e*]azepine **111** and 4*H*-benzo[*b*]thieno[3,2-*e*]azepin-10(9*H*)-one **113** (X = CO) starting from the corresponding tributylstannyl derivatives **110** and **112**, which react with 2-nitrobenzyl bromide and $[(Ph)_3P]_4Pd$. Sequential deprotection and reductive cyclization were carried out in one step with zinc and aqueous acetic acid (Scheme 22 (1999BMCL1733)).

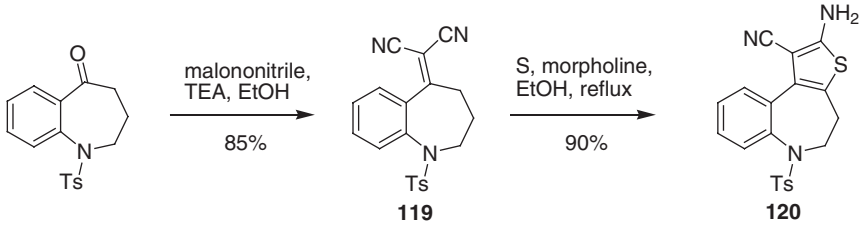
The synthesis of thieno[3,2-*c*]benzazepine-1,6-dione by treatment of 3-methylamino-3-methylthio-1-phenylthioxopropene with 2-hydroxy-1,4-benzoquinone, which serves as enolizable cyclic ketone, has been reported (2000JOC3690).



Scheme 22



Scheme 23



Scheme 24

2.1.3.3 Miscellaneous reactions. Double aldol condensation of phthalic dialdehyde with thieno azepinedione **114** results in a 60% yield of naphtho derivative **115** (Scheme 23 (1999PHA645)).

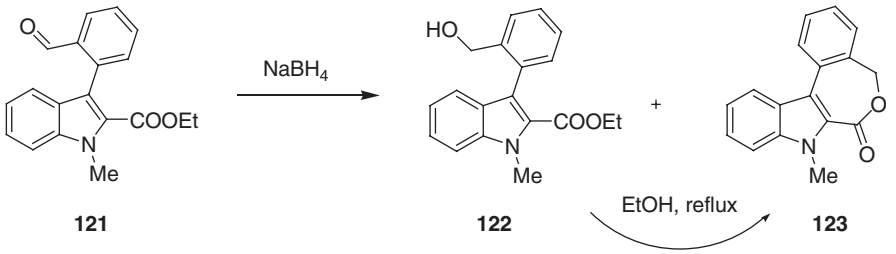
Fusion of a functionalized thiophene ring to a benzazepine can be achieved by a two-step procedure through the dinitrile intermediate **119** (Scheme 24 (2005IJC(B)1257)).

2.2 Benzoxepines

2.2.1 Benzoxepines with fused pyrrole ring

Lactonization of the suitable hydroxy acids or their derivatives is the most common synthetic method for benzoxepinenones with fused pyrrole rings. Therefore, reduction of the formyl group in the ester aldehyde **121** with sodium borohydride gives a mixture of alcohol **122** (80% yield) and lactone **123** (19%). Further heating of the open-chain product **122** in refluxing ethanol affords cyclic lactone **123** quantitatively (Scheme 25 (1998T11079)).

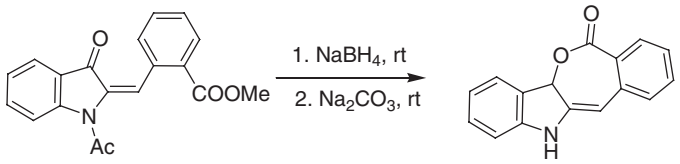
Cyclic lactone **125** has been observed as the only minor product of reduction of ketone **124** under thermal conditions. Stepwise reaction under mild conditions



121 **122** **123**

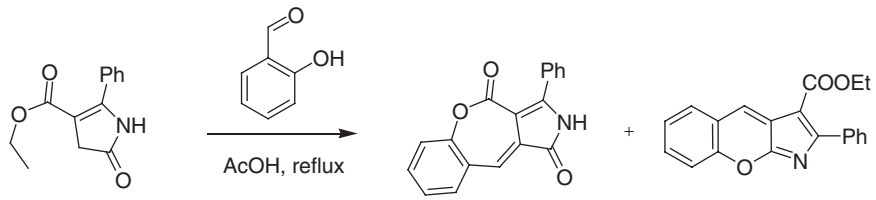
Scheme 25

produces oxepinone **125** in 88% yield (Equation (17) (1993H1287)).



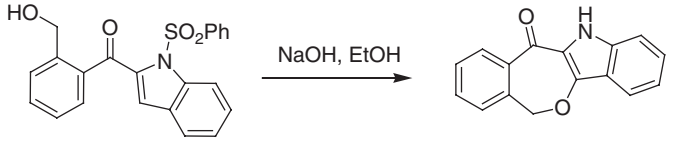
124 **125** (17)

Pyrrolidinone **126** and salicylic aldehyde in acetic acid under microwave irradiation gives in dioxopyrrolo[3,4-*c*]benzoxepine **127** as a mixture with phenyl chromeno[2,3-*b*]pyrrole **128** (8 and 13% yields, correspondingly, Equation (18) (2006T6018)).

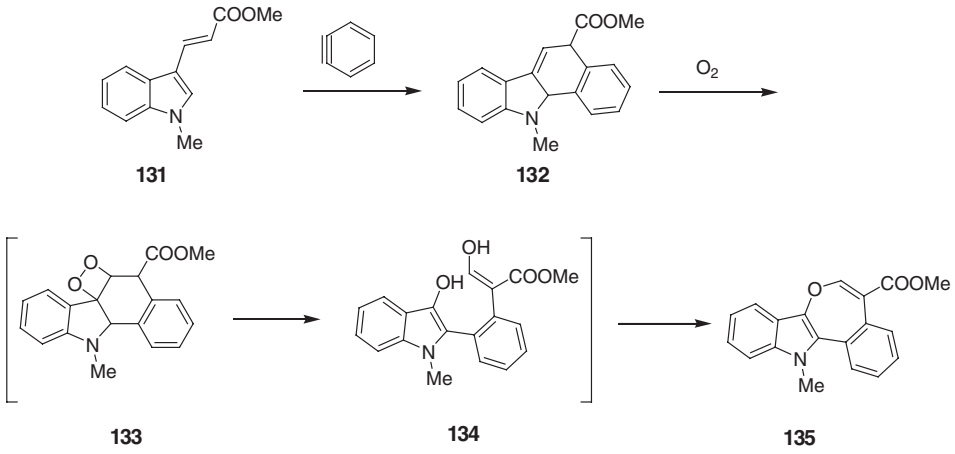


126 **127** **128** (18)

An alternative method for benzoxepine ring assembly uses the formation of cyclic ethers. Thus, benzoxepino[4,3-*b*]indole **130** can be synthesized by the treatment of the keto-alcohol **129** with hot alcoholic base to produce the product in 90% yield as a result of intramolecular nucleophilic substitution (Equation (19) (1993AX(C)2126)).



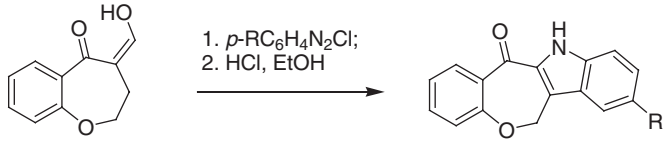
129 **130** (19)



Scheme 26

Diels–Alder reaction of 3-vinylindole **131** with aryne in the presence of air gives, besides primary Diels–Alder product **132**, the methyl 12-methyl-12*H*-[3]-benzoxepino[1,2-*b*]indole-5-carboxylate **135**. This can be explained by the formation of 1,2-dioxetane **133**, its cyclo reversion and final intramolecular cyclization of dienol **134** or its tautomers (Scheme 26 (1996JCS(P1)1767)).

The synthesis of cyclic ethers **137** was achieved by a Fischer indole synthesis starting from cyclic keto arylhydrazones generated *in situ* from 4-(hydroxymethylene)-3,4-dihydrobenzo[*b*]oxepin-5(2H)-one **136** and the corresponding diazonium salt (Equation (20), 1993JHC1481).

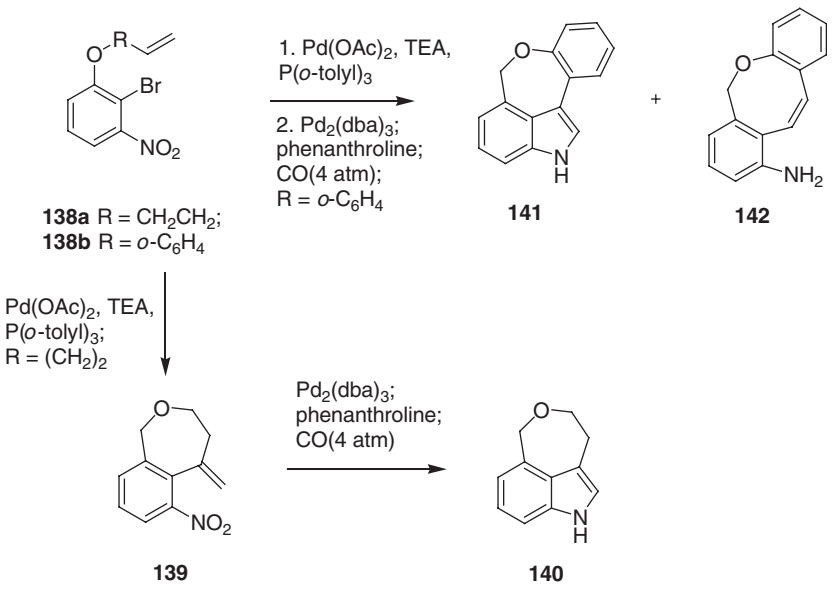


(20)

136 **137**

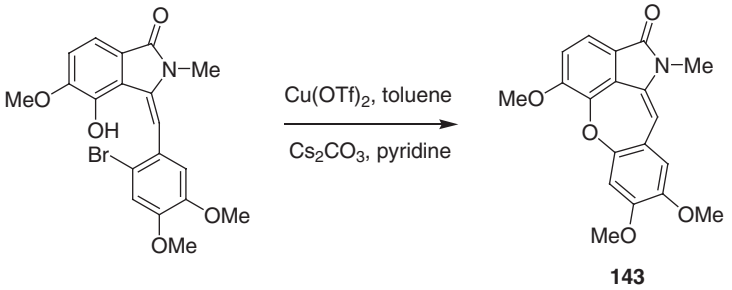
Several methods for the synthesis of indolo benzoxepines with the *peri*-fusion have been reported. A route to 3,4-fused indoles by two consecutive palladium-catalyzed reactions and an intramolecular Heck reaction followed by a reductive *N*-heteroannulation has been described (Scheme 27 (2005T3637)). In the case of the 1-butene **138a** (R = CH_2CH_2) the corresponding nitro oxepine **139** and indolo oxepine **140** are the products of the sequence. Reaction of the substituted vinyl styrene **138b** (R = *o*-C_6H_4) is more complex, giving an unseparatable mixture. Sequential reductive annulation results in a mixture of indolo benzoxepine **141** and dibenzo[*b,f*]oxocin-10-amine **142**.

A *peri*-fused system can be synthesized by diaryl copper-catalyzed ether coupling accomplished utilizing $(CuOTf)_2 \cdot PhMe$ in pyridine (Equation (21) (2004JOC4527)). This protocol produces several annulated ring systems and gives



Scheme 27

straightforward access to the natural product aristoyagonine **143**.



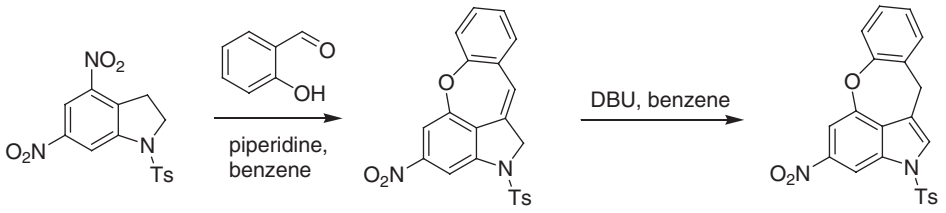
(21)

Alternative strategies to the aristoyagonine molecular structure (2002ARK62, 1996TL9357) and its synthetic analogs (1992JOC2029, 1990TL6247) have been reported.

1-Tosyl-4,6-dinitroindoline **144** undergoes under basic conditions condensation with salicylic aldehyde followed by intramolecular nitro group substitution to afford mono nitro compound **145** in 75% yield (Scheme 28 (2003RCB759)). Further refluxing in benzene in the presence of DBU gives isomerization product **146** in 82% yield.

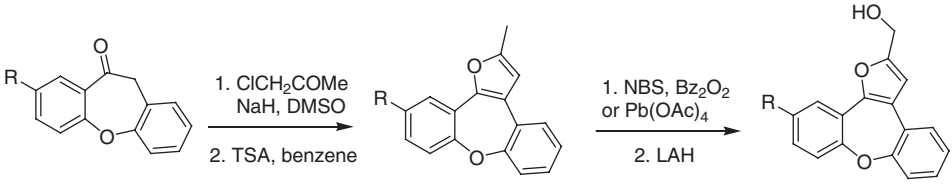
2.2.2 Benzoxepines with fused furan ring

The synthesis of these rings involves annulation of the furan ring onto the preformed benzoxepine core or intramolecular oxepine C–C bond formation of the furan precursors. Thus, 2-methyldibenzo[*b,f*]furo[2,3-*d*]oxepines **148** (R = H, Cl)



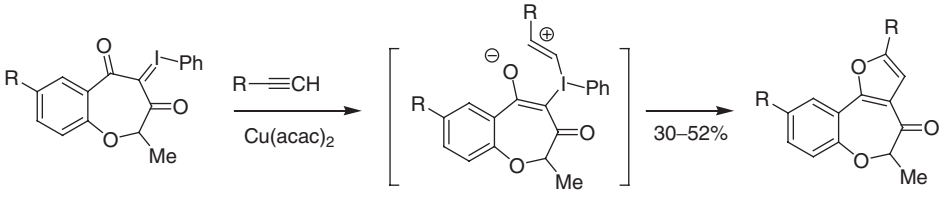
144 **145** **146**

Scheme 28



147 **148** **149**

Scheme 29



150 **151** **152**

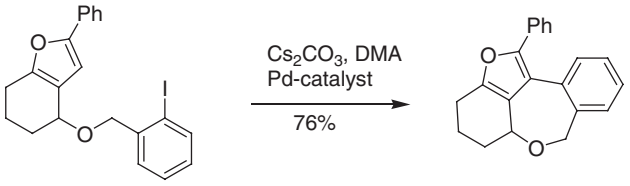
Scheme 30

are readily available by reaction of 11*H*-dibenzo[*b,f*]oxepine-10-ones **147** and chloroacetone through an intermediate diketone not shown (Scheme 29 (2006JHC749)).

Alternative furan ring fusion involves the reactions of phenyliodonium ylides of cyclic seven-membered *β*-diketones with alkynes. These processes lead under mild conditions to cyclization products **152**. The high regioselectivity can be explained by the formation of dipolar intermediate **151** favored by the predominant enolization of the carbonyl adjacent to phenyl ring. Terminal alkynes react in the similar fashion, although, in this case, mixtures of regioisomers have been reported due to steric hindrance in the intermediate enol (Scheme 30 (1993JOC4885)).

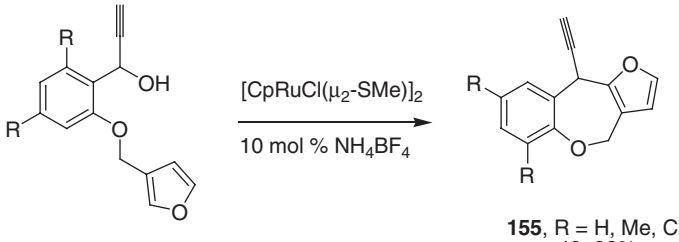
The next two examples illustrate intramolecular oxepine C–C bond formation of the furan precursors. Palladium catalyzed intramolecular arylation of **153**

affords furano oxepine **154** in good yield (Equation (22) (2005JOC7679)).



153 **154** (22)

Ruthenium catalyzed intramolecular propargylation leads to furobenzoxepines **155** in moderate to good yields (Equation (23), 2006EJO881).



155, R = H, Me, Cl
40–93% (23)

In a manner similar to that of 1-tosyl-4,6-dinitroindoline (see Scheme 28, Section 2.2.1), 4,6-dinitrobenzofuran undergoes condensation with salicylic aldehyde under basic conditions followed by nitro group substitution/cyclization to afford a mono nitro compound with *peri*-fusion of the benzofuran ring in 68% yield (2005CHE796).

2.2.3 Benzoxepines with fused thiophene ring

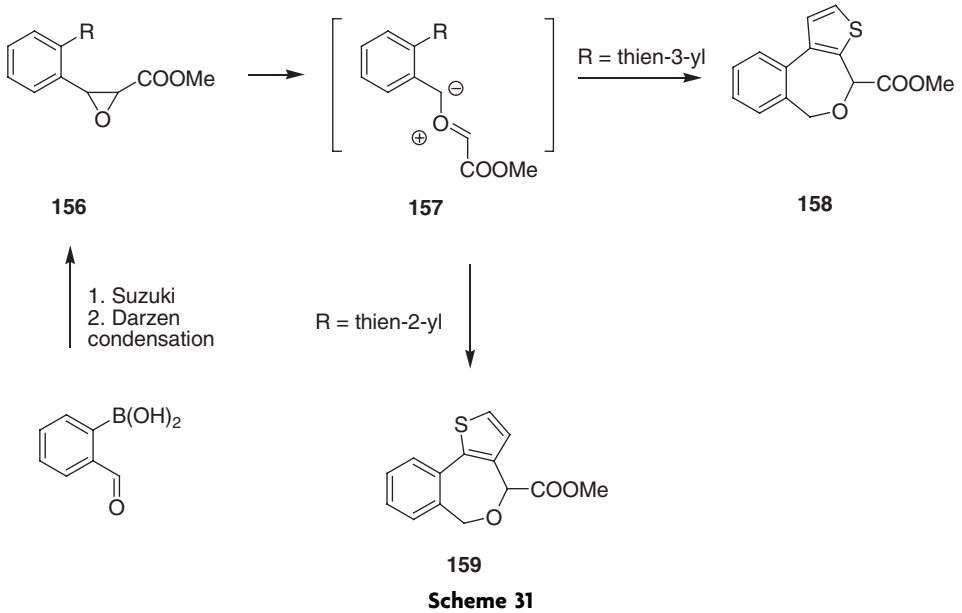
Flash vacuum pyrolysis of oxiranes **156**, accessible by a two-step procedure, results in carbonyl ylides **157**, conjugated with a diene system formed by benzene and heterocyclic substituents R. They further undergo 1,7-electrocyclization and subsequent 1,5-sigmatropic hydrogen shift to give oxepines **158** and **159** (Scheme 31 (1997JCS(P1)3025, 1996JCS(P1)515)).

Benzopyran **160** reacts with 2,3-dichloro-1,4-naphthoquinone by substitution of both chlorine atoms. The unstable primary adduct **161** undergoes ring expansion of oxirane **162** to produce thieno benzoxipine **163** in 70% yield (Scheme 32 (1994JCS(P1)2191)).

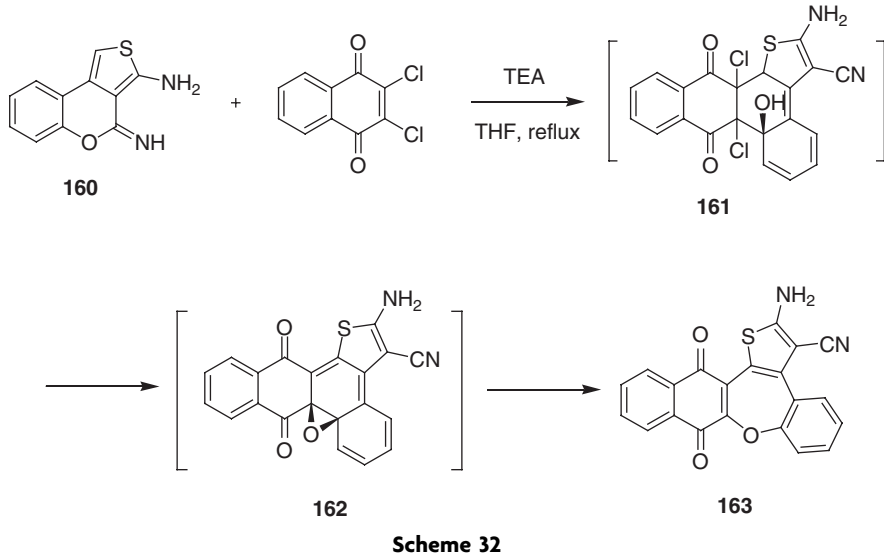
2.3 Benzothiepines

2.3.1 Benzothiepines with fused pyrrole ring

Chiral pyrrolo[*d*]thiepine **166** can be obtained efficiently in 63% yield starting from *N*-alkylated maleimide **164**. Successive Michael addition of phenethyl thiol and regioselective reduction are followed by spontaneous loss of hydrogen by *N*-acyliminium intermediates **165** and π-aromatic intermolecular α-amidoalkylation



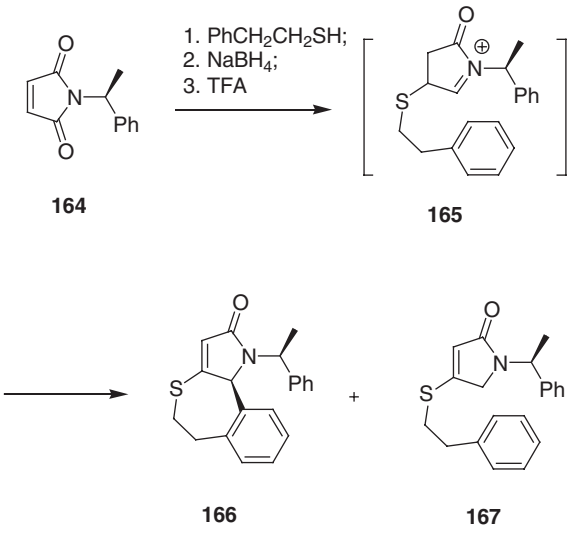
Scheme 31



Scheme 32

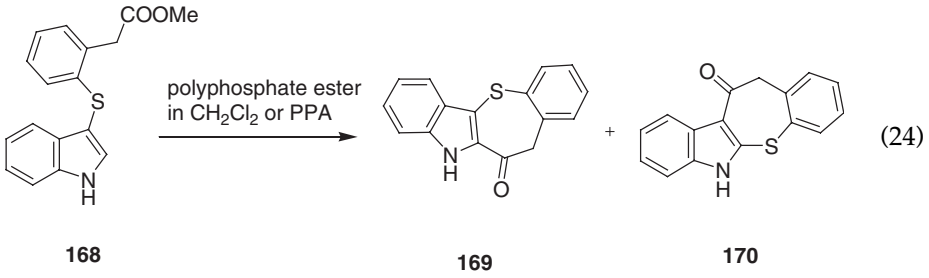
cyclization (Scheme 33). An alternative pathway, which involves isomerization of **165**, results in 22% of the open chain separable byproduct **167** (2001TL573).

2-(3-Indolylthio)phenylacetic acid **168** in 50% polyphosphate ester in methylene chloride at room temperature affords **169** as a major product in 65% yield. In hot polyphosphoric acid (PPA) cyclized **169** and **170** were formed in 15 and 21% yields, respectively, due to the partial isomerization. Heating in PPA for a prolonged period gives a 90% yield of **170** as a sole product of



Scheme 33

isomerization/cyclization (Equation (24) (1999JHC643)).



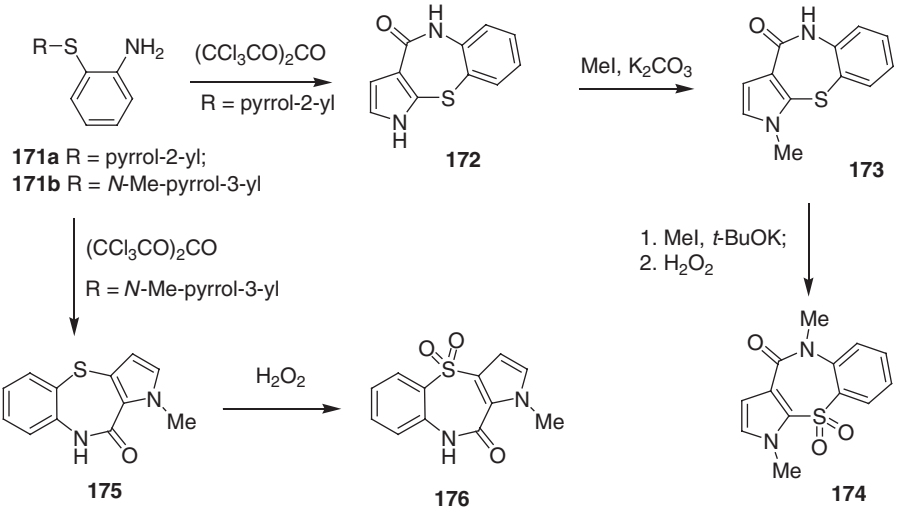
(24)

Treatment of substituted pyrrole **171a** (R = pyrrol-2-yl) with triphosgene and triethylamine leads to pyrrolo-benzothiazepine **172** in 35% yield (Scheme 34 (1994MI283)). Similarly, substituted pyrrole **171b** (R = *N*-Me-pyrrol-3-yl) produces pyrrolo-benzothiazepine **175**.

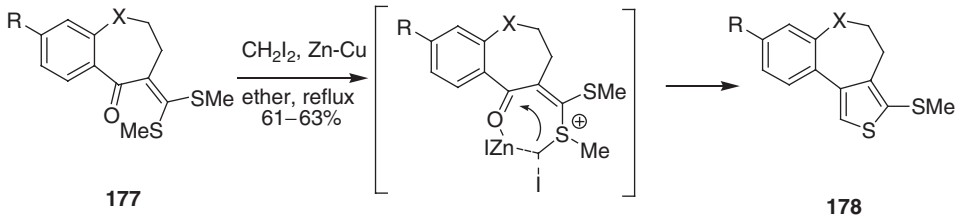
An indole ring can be fused to a benzothiepine *via* Fisher synthesis to give benzothiepino[5,4-*b*]indole (2006BMCL3233).

2.3.2 Benzothiepines with fused thiophene ring

Dithioacetals derived from heteropine **177** smoothly react with methylene iodide in the presence of a zinc–copper couple in refluxing ether to give the corresponding fused thiophenes **178**. The suggested mechanism involves formation of an ylide which undergoes intramolecular aldol-type condensation assisted by coordination of zinc with a carbonyl followed by demethylation of the *S*-methylthiophenium species (Scheme 35 (1989TL3093)).



Scheme 34



Scheme 35

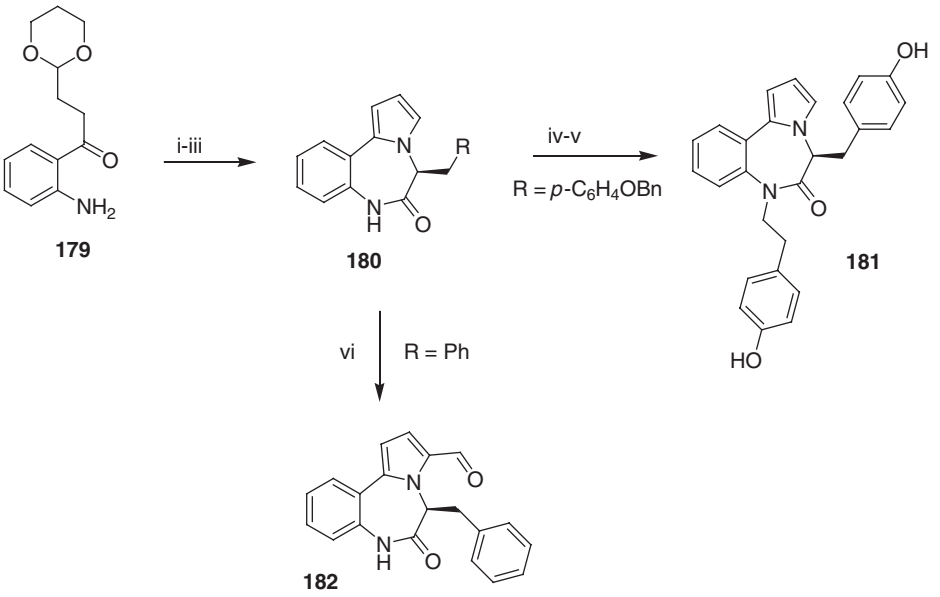
3. BENZOHETEROPINE RINGS WITH TWO HETEROATOMS ON THE HETEROPINE RING

3.1 Benzodiazepines

3.1.1 Benzodiazepines with fused pyrrole ring

The synthetic chemistry for these targets has been most extensively developed for benzopyrrolo[1,2]diazepines. It includes annulation of the pyrrole ring to a pre-formed benzodiazepine core, intramolecular cyclizations of non-cyclic precursors and 6 + 1 and 4 + 3 dicomponent cyclizations. Similar approaches have been reported for a few systems with other fusion modes, and they are surveyed at the end of each section.

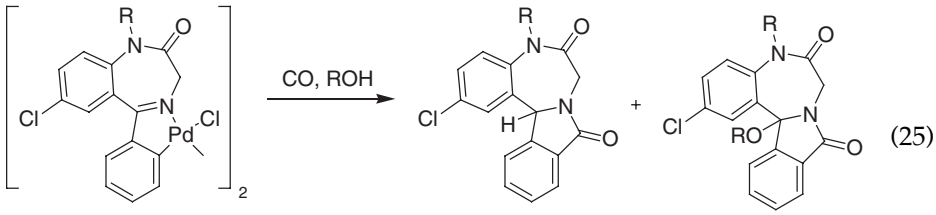
3.1.1.1 Annulation of the pyrrole ring. *o*-Aminoketone **179**, bearing the protected aldehyde moiety, can be smoothly reacted with substituted phenyl alanines and transformed into 1,4-benzodiazepinones **180** with a fused pyrrole ring (Scheme 36 (1992BMCL1639)).



i, BocNHCHRCOOH, NMM, *i*-BuOCOCl; ii, HCl (g), then 1N NaOH; iii, oxalic acid, H_2O; iv, $BrCH_2CH_2C_6H_4OBn$, DMF, NaH; v, $CHCl_3$, TMSI; vi, $POCl_3$, DMF

Scheme 36

The high-pressure carbonylation of dimeric palladium derivatives **183** (R = Me or cyclopropyl) in ethanol or methanol/chloroform leads in moderate yields to fused isoindoles **184** as mixtures with their alkoxy derivatives **185**, easily separated by flash chromatography (Equation (25) (1991JOM371)).

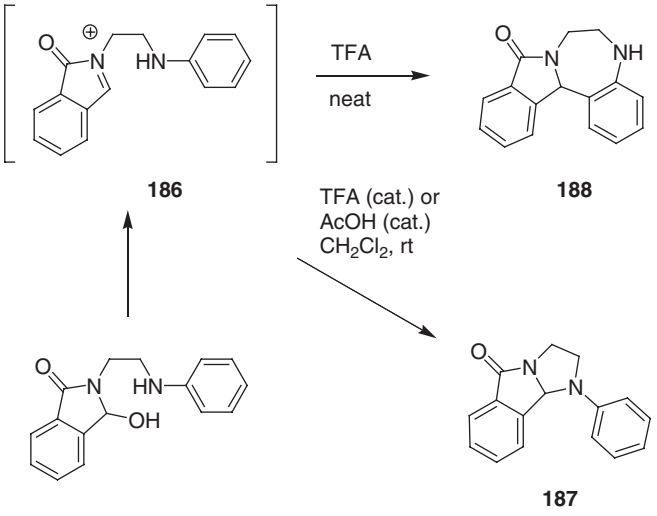


(25)

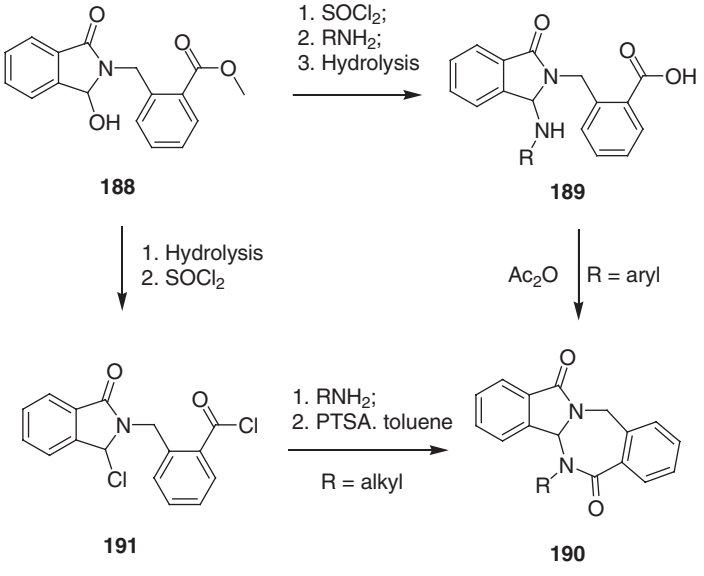
3.1.1.2 Intramolecular cyclizations. Intramolecular cyclizations of electron-rich chloroacetyl indoles leads to indolo[1,2-*d*][1,4]benzodiazepin-6-one **20** as a result of a side nucleophilic cyclization at the indole nitrogen (Equation (4), Section 2.1.1.1 (2005T5489)).

Imidazo[2,1-*a*]isoindolone **187** is the product of an intramolecular α-aza-amidoalkylation of *N*-acyliminium species **186**. Nevertheless, when the β-substituent is an aromatic moiety, a competing α-amidoalkylation takes place and isoindolo[1,4]benzodiazepine **188** is obtained under thermodynamic control (Scheme 37 (2004T11029)).

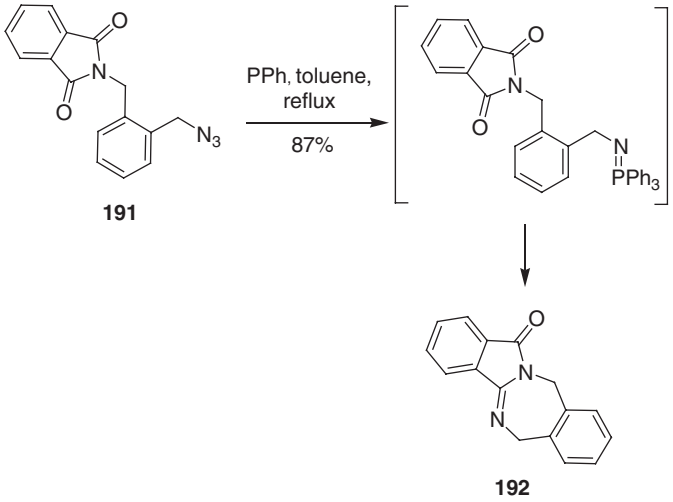
N-Aryl isoindolo[2,1-*b*][2,4]benzodiazepines **190** (Scheme 38, R = Ar) can be obtained by an intramolecular acylation of amino acids **189** in acetic anhydride (1998T1497).



Scheme 37



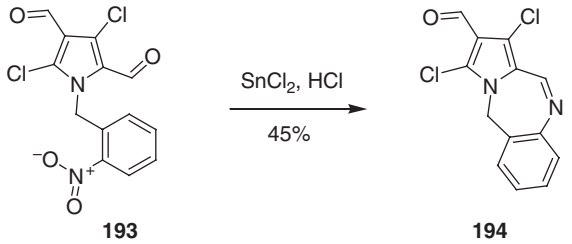
Scheme 38



Scheme 39

6,11-Dihydro-13*H*-isoindolo[2,1-*b*][2,4]benzodiazepin-13-one **192** has been reported as a product of the tandem Staudinger/aza-Wittig reaction of azidoimide **191** (Scheme 39 (1989CC602)).

Reduction of nitro derivative **193** with tin (II) chloride leads to aldehyde **194** in 45% yield (Equation (26) (2005T5831)).

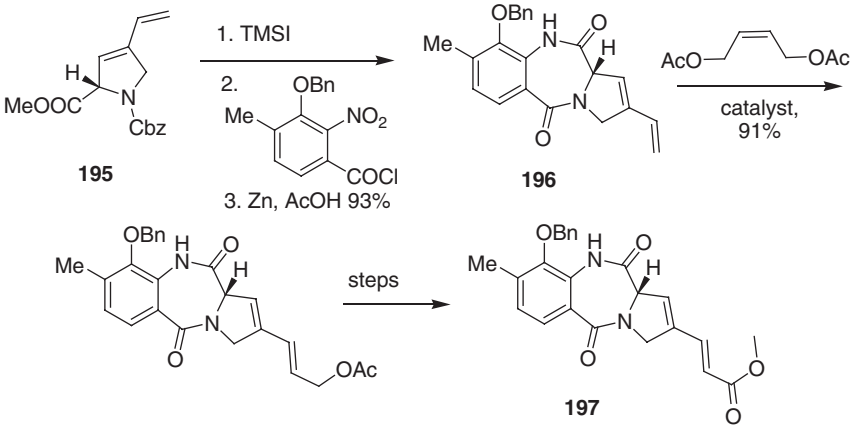


(26)

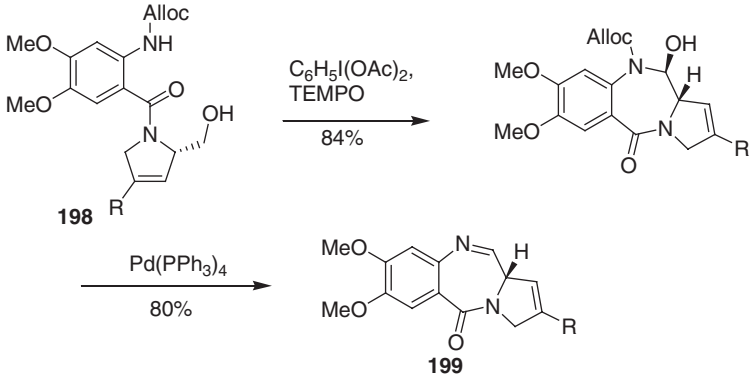
The precursor of (+)-anthramycin, pyrrolo-benzodiazepine **196**, can be synthesized by deprotection, acylation and reductive cyclization of pyrrolidine derivative **195**, obtained by enyne metathesis (Scheme 40 (2004T9649)).

Pyrrolo-benzodiazepine **199** with controlled stereochemistry has been prepared from the corresponding protected amino alcohol **198** in good yield (Scheme 41 (2003CC1688)).

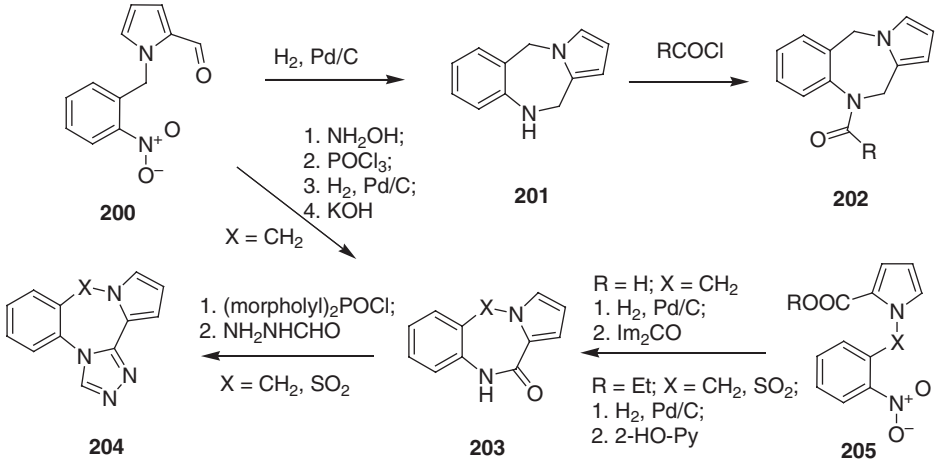
Reductive ring closure of 1-(2-nitrobenzyl)-2-pyrrole carbaldehyde **200** results in pyrrolo[2,1-*c*][1,4]benzodiazepine **201** (Scheme 42 (1999BMCL1737)). On the other hand, oxo derivative **203** can be synthesized starting from aldehyde **200** through a nitrile formation/cyclizations multistep sequence. The alternate synthetic strategy included reduction of the intermediate acid (R = H) or ester (R = Et) **205** followed by CDI or thermal cyclization (1992JHC1005).



Scheme 40

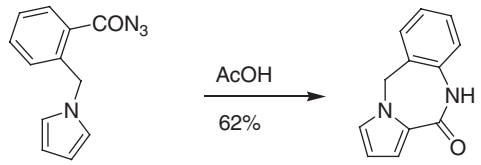


Scheme 41



Scheme 42

The pyrrole derivative of carbonyl azide **206** undergoes thermal Curtius rearrangement into isocyanate, which spontaneously cyclizes into pyrrolodiazepinone **207** (Equation (27) (1991JHC1911)).



(27)

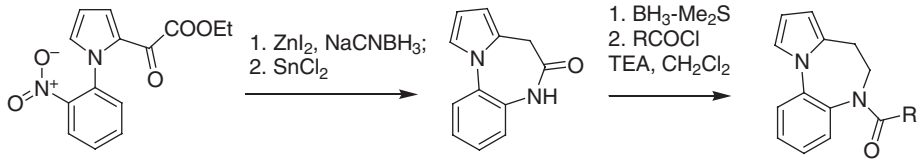
206 **207**

Ketoester **208** derived from 1-(2-nitrophenyl)-1*H*-pyrrole and ethyl oxalyl chloride can be selectively reduced at the keto group with zinc iodide and sodium cyanoborohydride. Further reduction of the nitro group and cyclization to lactam **209** has been accomplished by treatment with stannous chloride in refluxing ethanol (Scheme 43 (2003BMCL2195)).

Sequential Mannich reaction of ester **210a** or nitrile **210b**, alkylation and displacement of quaternary ammonium salt affords azides **211**. Further hydrogenation can be followed by intramolecular cyclization under basic conditions into pyrrolo-benzodiazepinone **212** (Scheme 44 (1994JHC1317, 1994S164)).

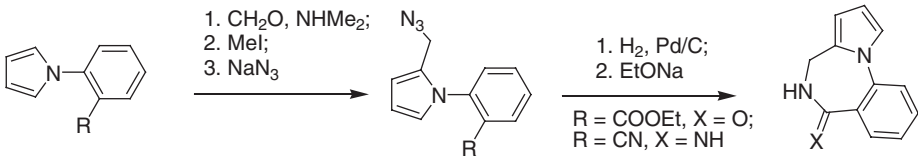
Aminomethyl substituted pyrrolo-benzdiazepine can be formed from the Cbz-protected precursor **214** and further reduced into tetrahydro derivative **215**. Alternatively, the unsubstituted ring in **217** has been synthesized by a Bischler–Napieralski method (Scheme 45 (1993JHC749)).

5,6-Dihydro-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]diazepin-4-one **220** is a product of reductive cyclizations of ester nitrile **219a** (R^1 = COOMe, R^2 = CN), while amido



208 **209** **202**

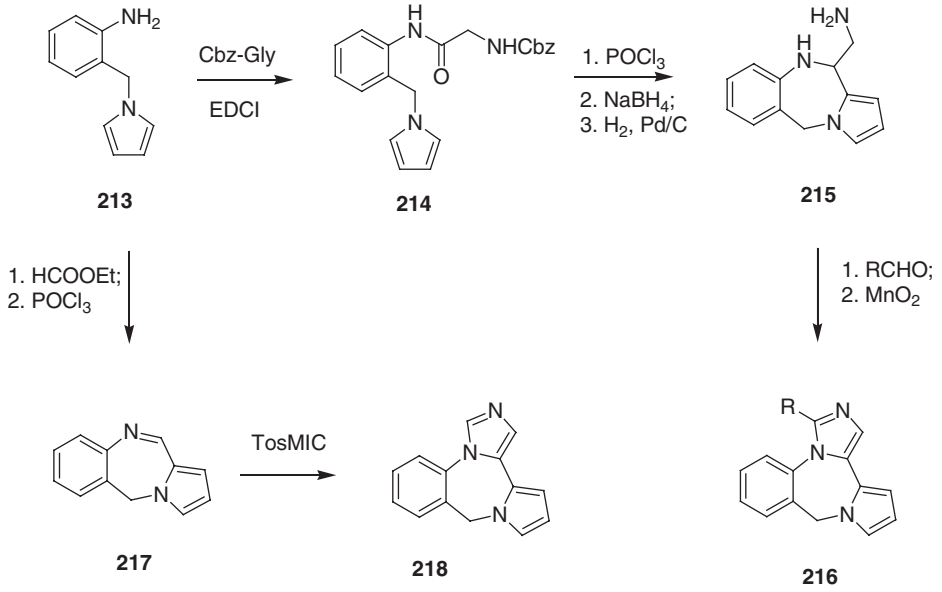
Scheme 43



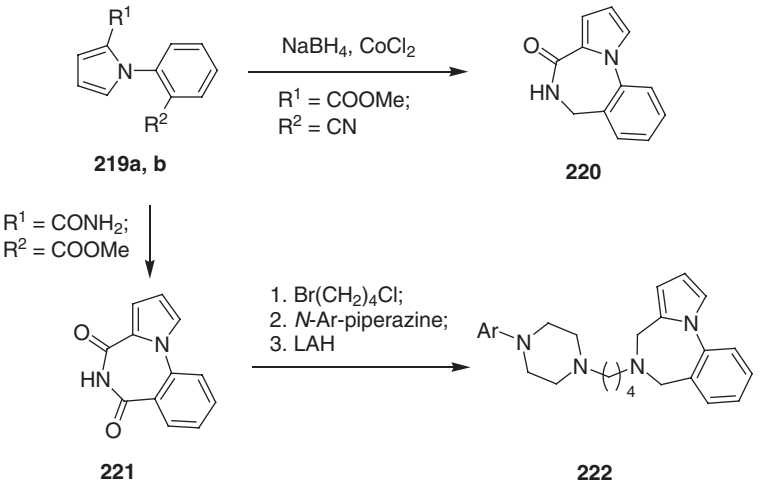
210a R = COOEt;
210b R = CN

211 **212a, b**

Scheme 44



Scheme 45



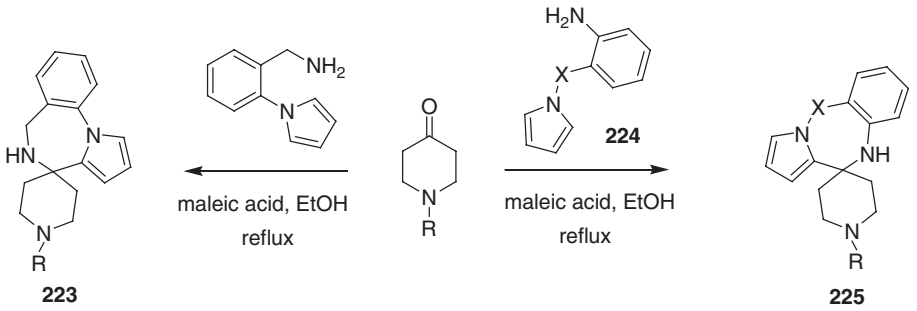
Scheme 46

ester **219b** ($R^1 = CONH_2$, $R^2 = COOMe$) can is cyclized into the corresponding benzodiazepine dione **221** (Scheme 46 (1993MI249)).

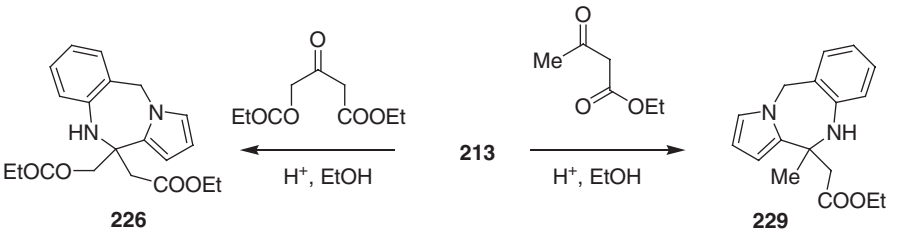
Intramolecular cyclization is the final step in the preparation of the scaffold for a 66-member C2-aryl pyrrolo[2,1-*c*][1,4]benzodiazepine library (2007JCC437).

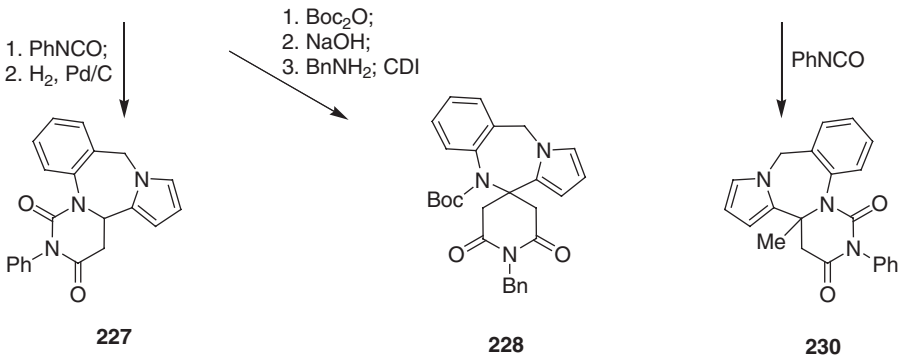
Solid-phase synthesis of a 210 member library of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones has been reported (2007JCC29).

3.1.1.3 6 + 1 cyclizations. A number of pyrrolo-benzodiazepines with the spiro piperidine moiety have been reported (Scheme 47 (1992JHC241)). Their synthesis included direct reaction of (2-(1*H*-pyrrol-1-yl)phenyl)methanamine with 4-piperidone or its *N*-substituted derivatives to afford spiro[piperidine-4,11′-pyrrolo[2,1-*c*][1,4]-benzodiazepines **223** in 55–79% yields. Alternatively, *ortho*-aminomethyl derivatives **224** under the same reaction conditions give 5′,6′-dihydrospiro[piperidine-4,4′-pyrrolo[1,2-*a*][1,4]benzodiazepines **225** (1990SC3537).

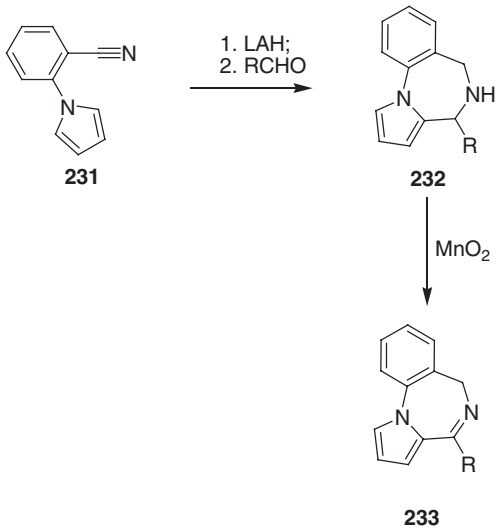


Scheme 47





Scheme 48

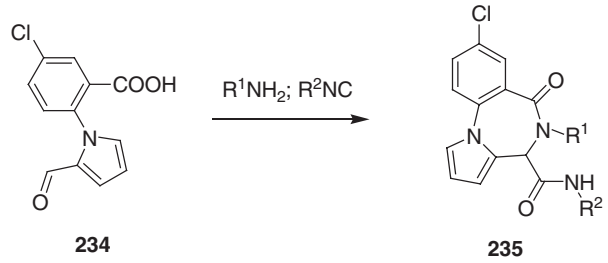


Scheme 49

Similarly, amine **213** affords carboxy substituted diazepine derivatives **226** and **229** from ethyl 3-oxo-4-(propionyloxy)butanoate and ethyl acetoacetate, respectively (Scheme 48 (1993JHC897)).

Tetrahydro pyrrolo-benzodiazepine **232** is a product of a two-step sequence starting from nitrile **231** (Scheme 49 (2005BMCL3453)).

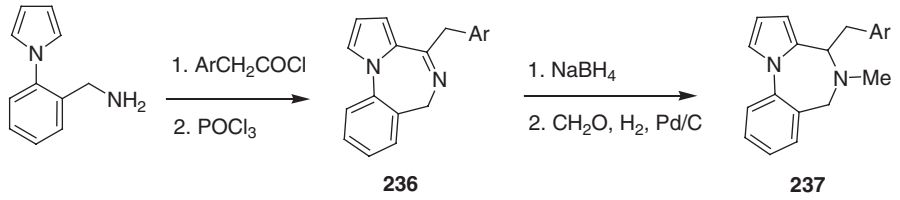
A multicomponent reaction of aldehyde acid **234** with isonitriles and amines in methanol at 40 °C leads to novel pyrrolo[1,2-*a*][1,4]diazepines **235** in 75–85% yields (Equation (28), 2005JOC1478).



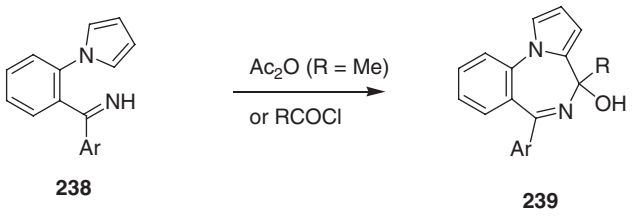
(28)

A Bischler–Napieralski intramolecular cyclization involving aryl acetyl chlorides in phosphoryl chloride affords 4-arylmethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines **236** (Scheme 50 (1995EJM593)).

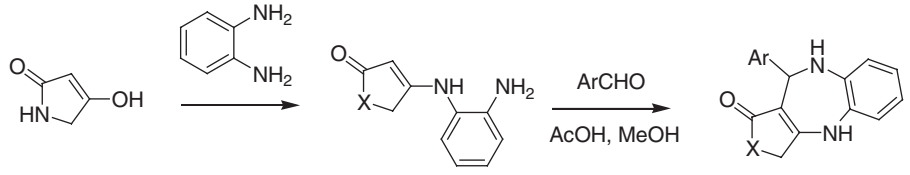
Direct acylation of imines **238** produces stable hydroxyl substituted pyrrolobenzodiazepines **239** (Equation (29) (1993TL1929)).



Scheme 50



(29)

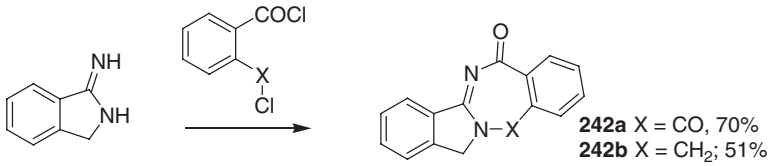


Scheme 51

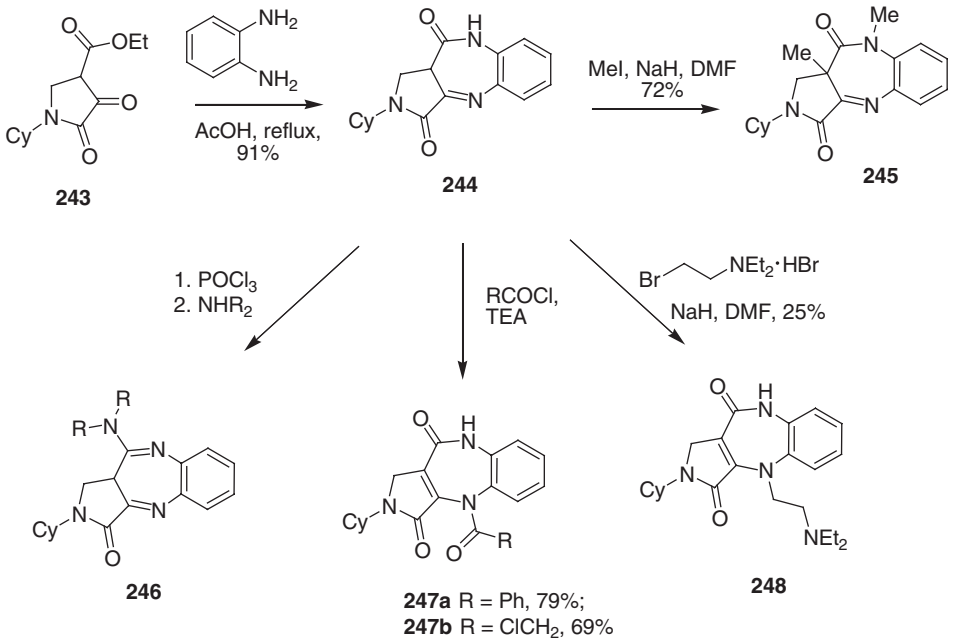
N-Alkyl isoindolo[2,1-*b*][2,4]benzodiazepines **190** (R = alkyl, Scheme 38, Section 3.1.1.2) are synthesized by an intramolecular *N*-acyliminium ion–amide reaction (1997TL2985, 1998T1497). Isothiocyanates **23** undergo under basic conditions in DMF ring closure by an intramolecular substitution between N1 of the pyrrole ring and isothiocyanate group to afford benzo[*f*]pyrrolo[1,2-*c*][1,3]diazepine-5-thiones **25** (Scheme 2, Section 2.1.1.1 (2005BMCL3220)).

A two-step route to tetrahydrobenzo[*b*]pyrrolo[3,4-*e*][1,4]diazepinone **241** (X = NH) starting from 4-hydroxy pyrrolone **240** has been reported (Scheme 51 (1991KFZ16)).

3.1.1.4 4 + 3 cyclizations. Isoindolo[2,1-*b*][2,4]benzodiazepin-6-ones **242** are easily accessible from isoindolin-1-imine and phthalic dichloride or *o*-chloromethyl benzoyl chloride (Equation (30) (1993PHA812)). The structural assignment of **242b** (X = CH_2) was based on NMR data and comparisons with those of known benzodiazepinones.



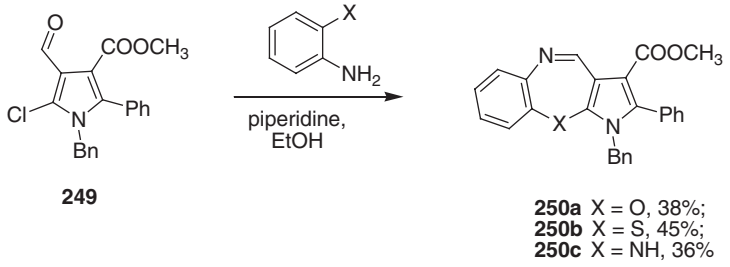
(30)



Scheme 52

Pyrrolo-benzodiazepine dione **244** can be obtained from the ketoester **243** in refluxing AcOH in high yield (Scheme 52 (1991ZOR1951, 1992CE649, 1996PHA548, 2005H2451)).

The diazepine with fused pyrrole ring **250c** is the product of the condensation of *ortho*-phenylenediamine with pyrrole carbaldehyde **249** in 36% yield (Equation (31) (2006T6018)).



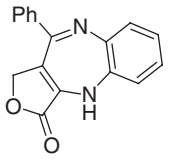
(31)

3.1.2 Benzodiazepines with fused furan ring

Reaction of 4-benzoyl-3-hydroxy-2(5H)-furanone with 1,2-phenylenediamine results in a low yield of diazepine **251** (Figure 3 (1991JHC1501)).

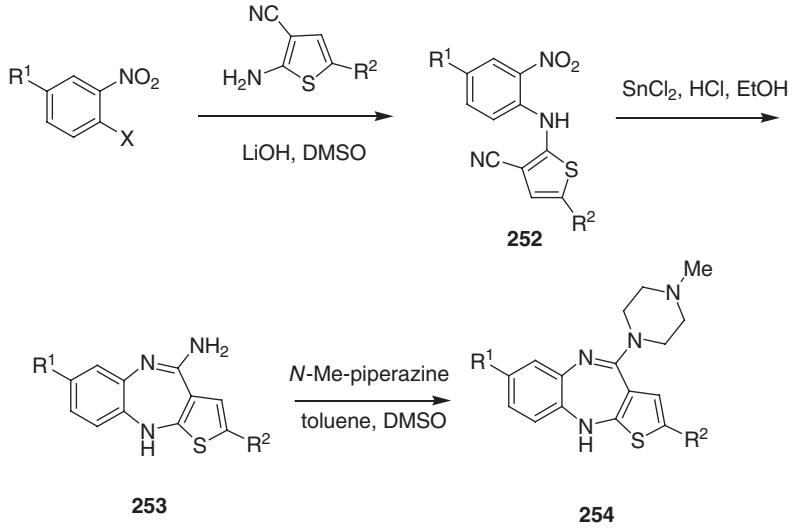
3.1.3 Benzodiazepines with fused thiophene ring

Thieno benzodiazepine **253** is available in two steps starting from *o*-nitro halobenzenes and a thieno amino nitrile through intermediate **252** (Scheme 53 (1997BMCL25)).



251

Figure 3



252 **253** **254**

Scheme 53

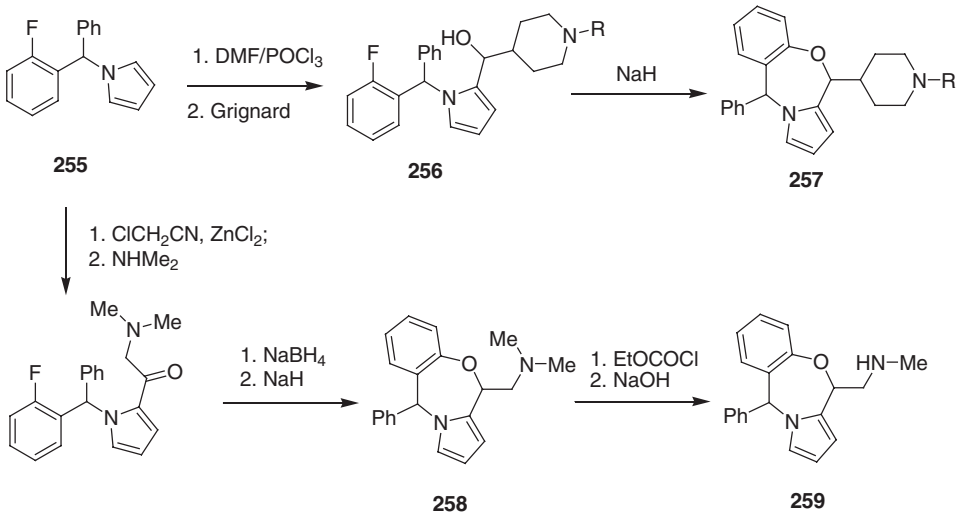
As for benzo[*b*]pyrrolo[3,4-*e*][1,4]diazepin-3(4*H*)-ones **241**, a fused thiophene (X = S) can be synthesized using a two-step reaction sequence (Scheme 51, Section 3.1.1.3 (1991CE495)).

3.2 Benzoxazepines

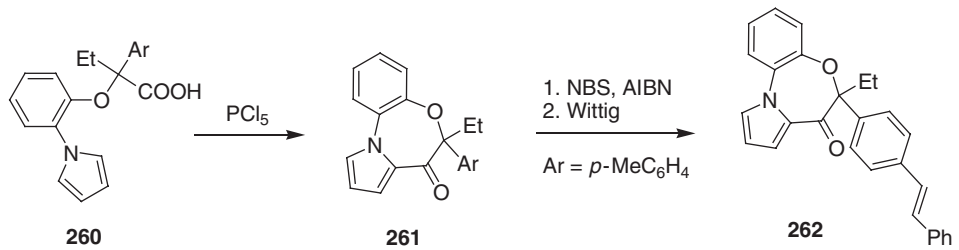
3.2.1 Benzoxazepines with fused pyrrole ring

3.2.1.1 Pyrrolo[1,2]oxazepines. Piperidine derivatives of pyrrolo-benzoxazepine **257** have been reported starting with Vilsmeier formylation of pyrrole **255**, followed by a reaction with Grignard reagents derived from *N*-substituted 4-chloropiperidine (R = Me, Bn). Resulting alcohol **256** undergoes cyclizations in the presence of sodium hydride (Scheme 54 (1993JHC177)). The corresponding dimethylamino derivative **258** can be constructed in the similar manner.

Benzopyrrolo[1,2]oxazepines **68** (X = O) can be obtained from the corresponding acids **67** by an intramolecular Friedel–Crafts acylation (Scheme 14, Section 2.1.1.5 (1996JMC3435, 2002JMC4276)). Similarly, pyrrolo-benzoxazepines **261** are accessible by intramolecular Friedel–Crafts cyclization of acids **260**



Scheme 54



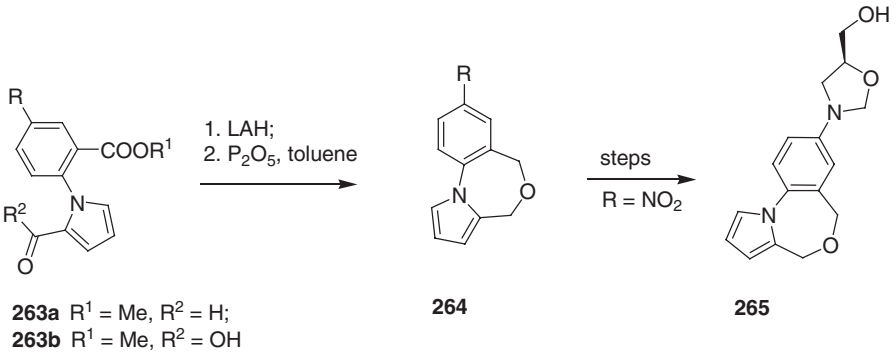
Scheme 55

(Scheme 55 (2005JMC7153, 1999JMC4462, 1996JMC2672)). This methodology was further extended to the derivatives of **261** substituted on the benzo ring (2005JMC4367).

One-step reduction of aldehyde and ester functions in intermediate **263a** ($R^1 = Me$, $R^2 = H$) results in a di-alcohol, which, when treated with P_2O_5, undergoes cyclization into oxazepine **264** (Scheme 56 (2005BMCL2515)). Similarly, this reaction sequence can start from monoester **263b** ($R^1 = H$, $R^2 = OH$ (2001JCS(P1)1039)).

N-(2-Hydroxymethylphenyl)pyrrole is prone to selective α-metalation with *n*-BuLi-potassium *tert*-butoxide. Trapping the formed anion with a variety of electrophiles and treatment of the crude products with silica gel in toluene results in pyrrolo-benzoxazepines **266** and pyrrolo-benzoxazepinone **267** (Scheme 57 (1994T2071)).

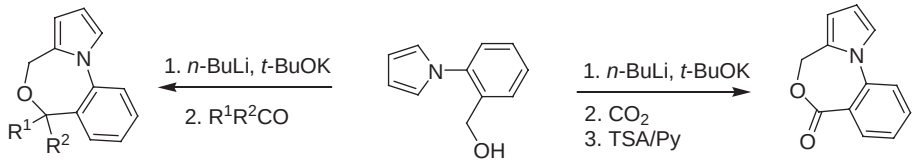
N-Phenylpyrrole generates a di-lithio derivative which after trapping with acetone and treatment with silica gel produces tetramethyl pyrrolo-benzoxazepine



263a R^1 = Me, R^2 = H;
263b R^1 = Me, R^2 = OH

264 **265**

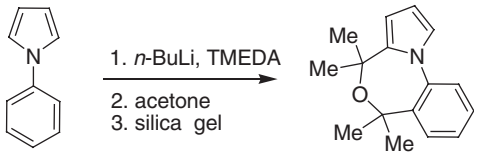
Scheme 56



266 **267**

Scheme 57

268 (Equation (32) (1993T10271)).

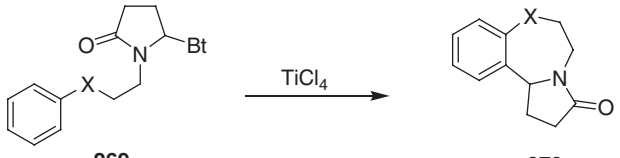


(32)

268

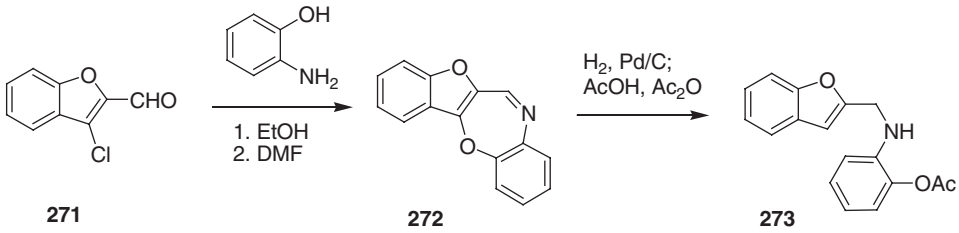
3.2.1.2 Pyrrolo-benzoxazepines with other fusion modes. As with diazepine, benzoxazepine with the fused pyrrole ring **250a** can be prepared by condensing *ortho*-amino phenol (X = O) with pyrrole carbaldehyde **249** in moderate yield (Equation (31), Section 3.1.1.4 (2006T6018)).

1-[2-Aryloxyethyl]-5-benzotriazolyl-2-pyrrolidinones **269** (X = O) and the corresponding isoindolinones (not depicted) undergo Lewis acid mediated cyclizations to 1,4-benzoxazepines **270** (X = O) (Equation (33) (2001JOC5590)).

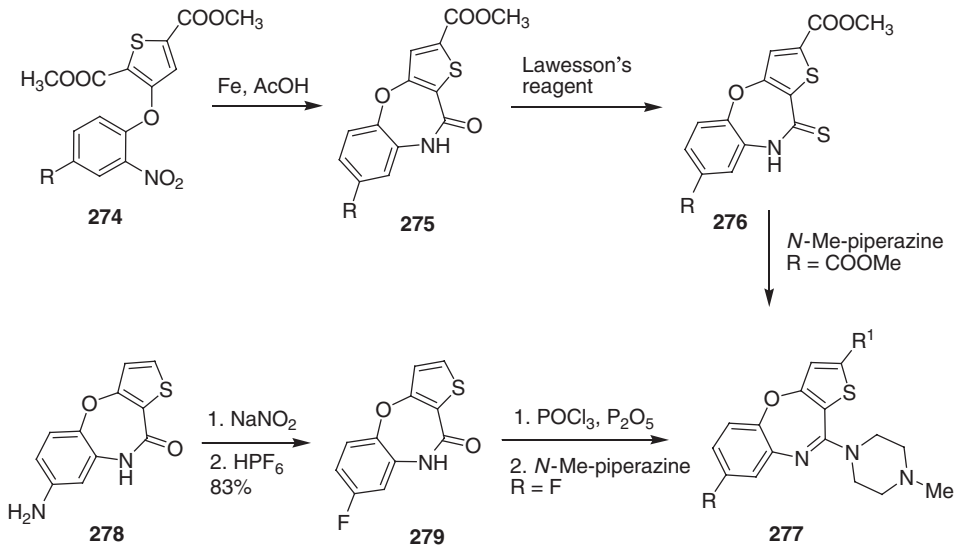


(33)

269 **270**



Scheme 58



Scheme 59

3.2.2 Benzoxazepines with fused furan ring

Benzo[*b*]benzofuro[2,3-*f*][1,4]oxazepine **272** is the sole product obtained from chloro aldehyde **271** and *o*-aminophenol (Scheme 58 (2001JHC383)).

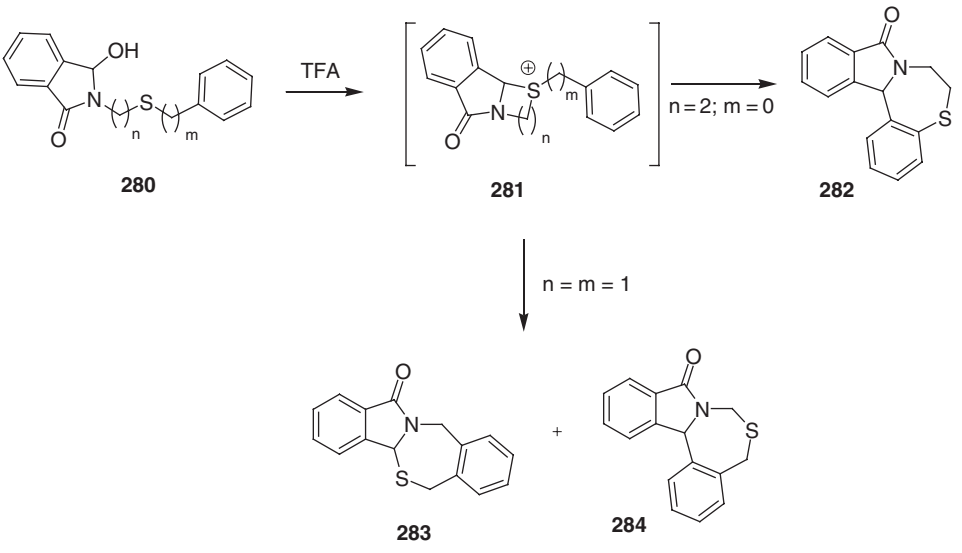
3.2.3 Benzoxazepines with fused thiophene ring

Nitro ester **274** undergoes reduction with iron in acetic acid to afford thieno benzoxazepine **275** (Scheme 59 (1994JHC1053)). An alternative route to **275** by the intramolecular formation of a C_{thiene}–O bond has been reported (2002JHC163).

3.3 Benzothiazepines

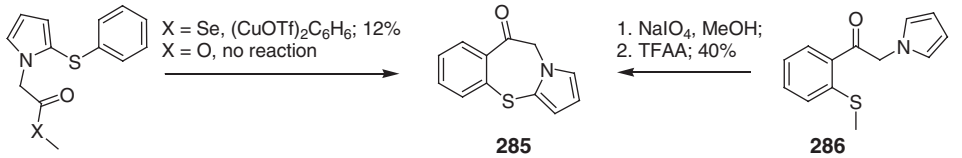
3.3.1 Benzothiazepines with fused pyrrole ring

3.3.1.1 Pyrrolo[1,2]thiazepines. Hydroxy lactam **280a** ($n = m = 1$), upon treatment with neat TFA at room temperature gives a 20:1 mixture of benzothiazepines **283** and **284** in overall 94% yield. In contrast, **280b** ($n = 2$, $m = 0$) produces



280 281 282 283 284

Scheme 60



285 286

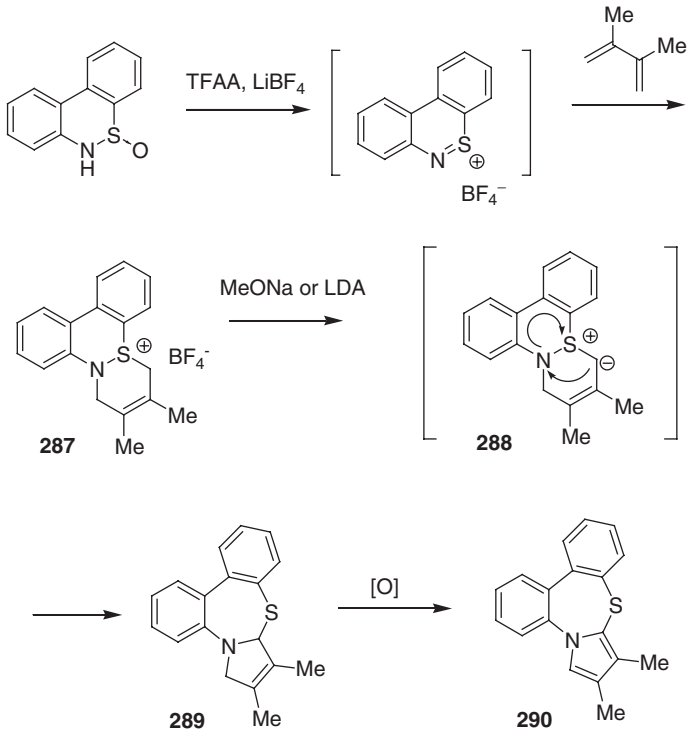
Scheme 61

benzo[1,4]thiazepine **282** in an excellent yield of 95% (Scheme 60 (2005EJO2758)). The regioselectivity of the process can be explained by the formation of the bicyclic onium intermediate **281**.

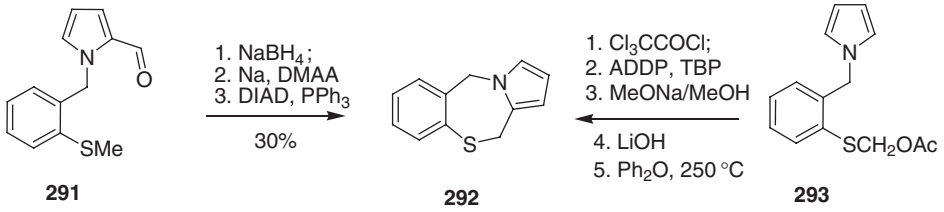
Intramolecular electrophilic cyclization of methyl selenoate gives only a 12% yield of benzo[*f*]pyrrolo[2,1-*b*][1,3]thiazepin-9(10*H*)-one **285**, while cyclization of an acetate derivative under a variety of the conditions failed (Scheme 61 (1998JMC3763)). An alternate route from pyrrole ketones **286** by oxidation and TFAA induced cyclization proved to be advantageous providing a 40% yield of **285**.

Treatment of cycloadduct **287**, obtained from a dibenzo thiazinylium intermediate and a diene, with base affords dibenzo[*d,f*]pyrrolo[2,1-*b*][1,3]thiazepine **290** in 58% yield. The proposed mechanism involves formation of ylide intermediate **288** which undergoes intramolecular rearrangement into dihydro derivative **289** and spontaneous oxidative aromatization (Scheme 62 (1999TL95)).

A new method for the preparation of pyrrolo[2,1-*c*][1,4]benzothiazepine **292** starting from aldehyde **291** with an intramolecular Mitsunobu cyclization in the last step has been reported (Scheme 63 (1999T1479)). A disadvantage of this procedure is the redox nature of the Mitsunobu reaction, which is responsible for a side oxidation of the thiol group and poor isolated yields of the product.



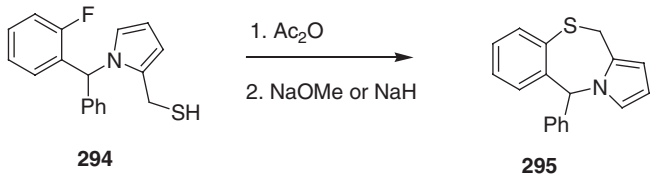
Scheme 62



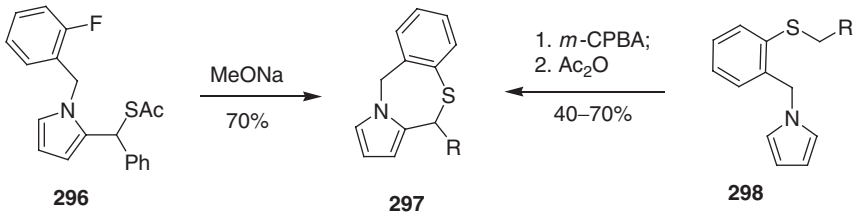
Scheme 63

The alternate route starting from **293** provides the target compound in improved 58% yield.

Preliminary acetylation of thiol **294** followed by a displacement step, using 2 equiv. of MeONa or NaH in DMF/benzene, gives tricycle **295** in 25% yield (Equation (34) (1996T7745)).



(34)



296 297 298

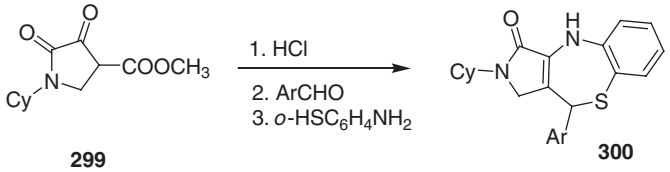
Scheme 64

Pyrrolo[2,1-*c*][1,4]benzothiazepine **297** (R = Ph) has been prepared by an intramolecular nucleophilic displacement of acetyl derivative **296** (Scheme 64 (1992H51)). The same compound and its aryl (R = Ar (1992H51)) and carboethoxy or cyano (R = COOEt or CN (1990H1291)) analogs can also be obtained by a Pummerer rearrangement-cyclization of sulfinyl precursor **298**.

Pyrrolo[1,2]thiazepine **68** (R = Ph; X = S) can be obtained from the corresponding acid **67** *via* an intramolecular Friedel–Crafts acylation (Scheme 14, Section 2.1.1.5 (1997EJM241, 1996JMC2672, 1994JMC4100, 1994JMC1427)).

3.3.1.2 Pyrrolo-benzothiazepines with other fusion modes. Thiazepine with fused pyrrole ring **250b** can be prepared by condensing *ortho*-amino thiophenol with pyrrole carbaldehyde **249** in moderate yield (Equation (31), Section 3.1.1.4 (2006T6018)).

Pyrrolo[3,4-*c*][1,5]-benzothiazepin-3-ones **300** are available from ketoester **299** by a three-step sequence which includes hydrolysis and decarboxylation, aldol condensation and cyclization with *o*-aminothiophenol (Equation (35) (1993CE773)).

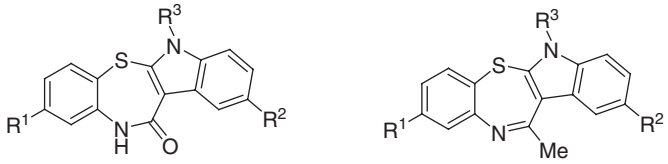


299 300 (35)

Two types of benzothiazepines with fused indole rings **301** and **302** (Figure 4) have been reported as products of a Fischer indole type synthesis (1993EJM659).

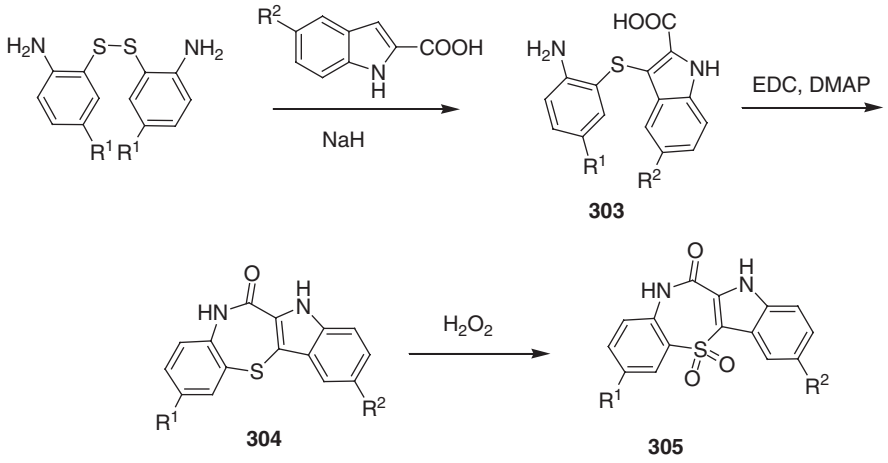
3-Arylthioindole-2-carboxylic acids **303**, obtained from aryl disulfides and indole-2-carboxylic acids, afford tetracyclic 5*H*-indolo-[3,2-*b*][1,5]benzothiazepin-6(7*H*)-ones **304** on treatment with EDC–DMAP (Scheme 65 (1998MI139)).

2*H*-Pyrrolo[3,4-*b*][1,5]benzothiazepine **307** can be obtained by thermal cyclization of pyrrole aminoester **308** (R = Et) in the presence of 2-hydroxypyridine (Scheme 66 (1998SC2517, 2005FES385)). An analogous transformation has been reported for the corresponding pyrrole amino acid **308** (R = H) (1990BCJ1617). Alternatively, dihydro analog **309** can be obtained starting from nitro ketone **306** by reductive cyclization (1998SC2517).



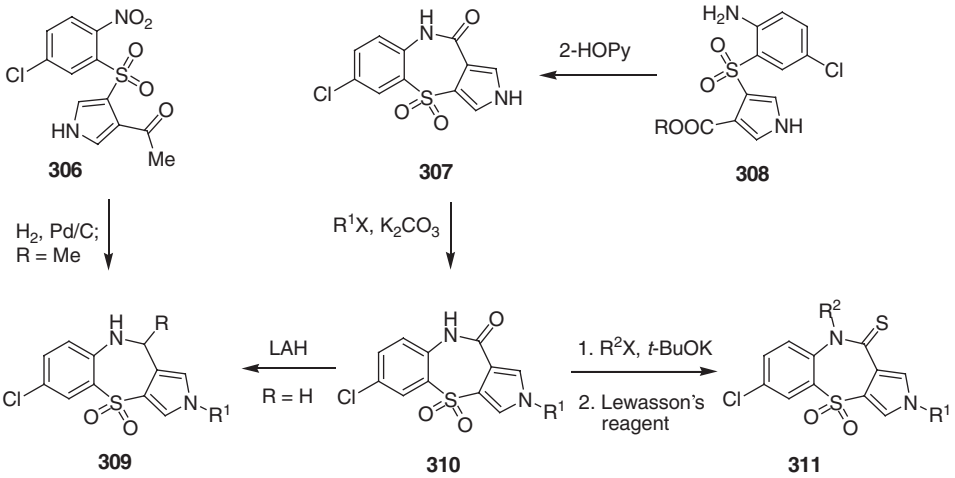
301 **302**

Figure 4



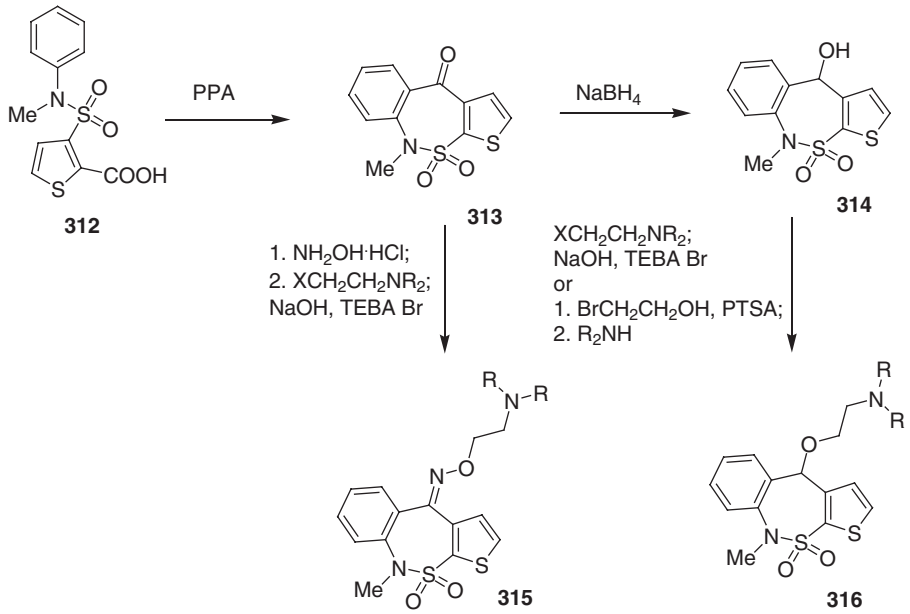
303 **304** **305**

Scheme 65



306 **307** **308** **309** **310** **311**

Scheme 66



312 313 314 315 316

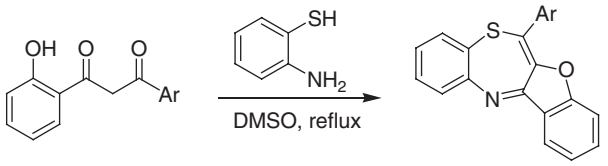
Scheme 67

Benzo[*c*]thieno[3,2-*f*][1,2]thiazepin-4(9*H*)-one **313** is the product obtained from acid **312** on dehydration (Scheme 67 (1997JHC1191, 1998PHA130, 1993JHC1509)). A similar transformation has been reported for the preparation of an isomeric to **313** benzo[*c*]thieno[3,4-*f*][1,2]thiazepin-10(5*H*)-one (not depicted in the Scheme).

1-[2-Arylthioethyl]-5-benzotriazolyl-2-pyrrolidinones **269** (X = S, Equation (33), Section 3.2.1.2) and the corresponding isoindolinones (not depicted) undergo Lewis acid mediated cyclizations to 1,4-benzothiazepines **270** (X = S) (2001JOC5590).

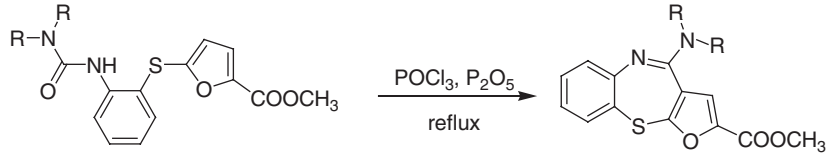
3.3.2 Benzothiazepines with fused furan ring

A convenient preparation has been reported for benzofuran annulated 2-phenyl-1,5-benzothiazepine derivatives **318** by oxidative cyclocondensation of phenolic diketones **317** with *o*-aminothiophenol in DMSO (Equation (36) (2000M393)).



317 318 (36)

Furobenzothiazepines **320** can be prepared by a Bischler–Napieralski method from ester ureas **319** (Equation (37) (1999JHC819)).



319 **320** (37)

3.3.3 Benzothiazepines with fused thiophene ring

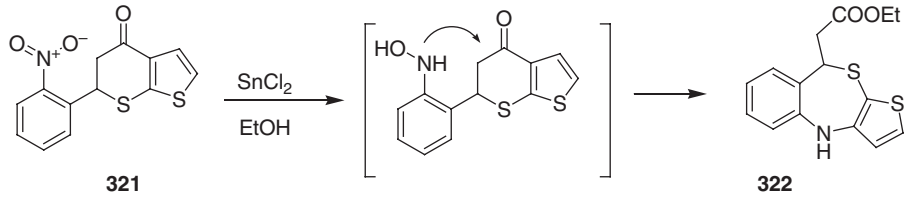
2-(2-Nitrophenyl)-thiochroman-4-one **321** upon treatment with $SnCl_2$ in ethanol does not give the expected aniline derivative. Instead, ethyl 5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin-11-ylacetate **322** is produced in high yield. The presumed mechanism involves addition of an hydroxylamine intermediate to the ketone carbonyl, followed by a tin-mediated pinacol-type rearrangement with preferred migration of the phenyl substituent and ethanolysis of the intermediate amide (Scheme 68 (2002JOC8662)).

Syntheses of benzo[*f*]thieno[3,2-*b*][1,4]thiazepin-9(10*H*)-one **323** (2001BMC1123) and thieno[3,4-*b*]-[1,4]benzothiazepine **324** (Figure 5 (1999JHC659)) start from the corresponding open chain amino acids.

4. SYSTEMS WITH MORE THAN TWO ATOMS ON THE HETEROPINE RING AND MISCELLANEOUS RING SYSTEMS

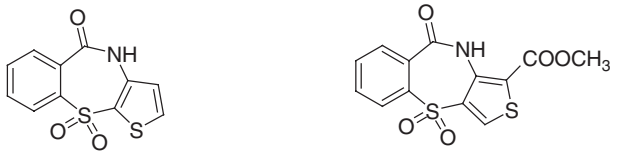
4.1 Benzotriazepines

Phthalimide **325** when refluxed with triethylphosphite yields iminophosphorane that further transforms into 5*H*-isoindolo[1,2-*b*][1,3,4]benzotriazepin-5-one **326**



321 **322**

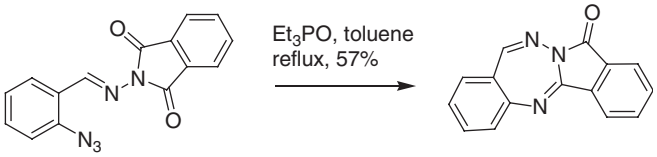
Scheme 68



323 **324**

Figure 5

in 57% yield (Equation (38) (1990TL6561)).

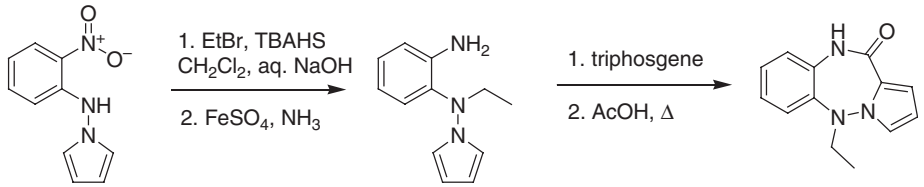


325 326 (38)

Pyrrolo[1,2-*b*][1,2,5]benzotriazepin-11-one **329** is the product of a sequence starting from *N*-(2-nitrophenyl)-1*H*-pyrrol-1-amine **327**. The pathway included alkylation, reduction of the nitro group, formation of the isocyanate from intermediate **328** and intramolecular thermal cyclization (Scheme 69 (2000JHC1539)).

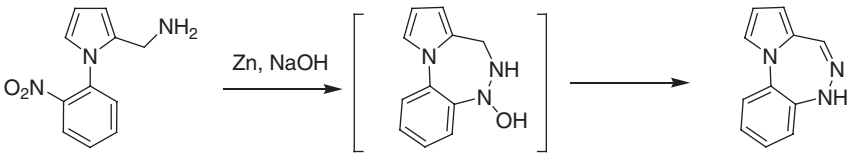
Similar to pyrrolo-benzodiazepines, pyrrolo-benzotriazepines **225** (X = NMe) with a spiro piperidine moiety have been reported (Scheme 47, Section 3.1.1.3 (1992JHC241)). Their synthesis included direct reaction of hydrazine **224** (X = NMe) with *N*-substituted 4-piperidones to afford **225** in 42–63% yields.

Reductive cyclization of nitro amine **330** with zinc in boiling aqueous sodium hydroxide afforded pyrrolo[2,l-*d*][1,2,5]benzotriazepine **332** in 30% yield. The proposed mechanism (Scheme 70) involves an intramolecular coupling between amino and *in situ* generated nitroso groups to give intermediate **331**. The latter loses water under the strongly basic conditions and azo intermediate (not shown on the scheme) further undergoes prototropic interconversion to cyclic hydrazone **332** (1996T10751).



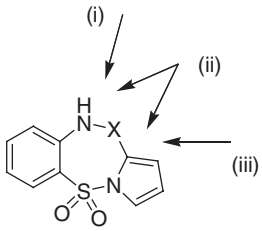
327 328 329

Scheme 69



330 331 332

Scheme 70



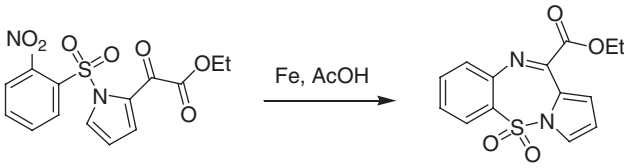
333

Figure 6

4.2 Pyrrolo-benzothiadiazepines

Syntheses of this class of compounds usually involve 1,2,5-thiadiazepine ring **333** (Figure 6) which is stable in the S-oxidized form and structurally represents cyclic pyrrole *N*-sulfonyl derivatives. Most of the synthetic strategies include formation of an $S–N_{pyrrole}$ bond in the early stages. A final cyclization step typically includes (i) intramolecular cyclization by creation of an N–X bond from a suitable pyrrole precursor or (ii) a 6 + 1 type cyclization that involves dielectrophilic species to form linker X and utilizes the nucleophilicity of the phenyl amino group and of the pyrrole ring at C2. Intramolecular processes with the formation of the $X–C2_{pyrrole}$ bond (iii) are rarer.

Reduction of nitro glyoxylic ester **334** with iron powder in acetic acid into pyrrolo-benzothiadiazepine **335** represents a type (i) intramolecular cyclization (Equation (39) (1996JHC2019)).



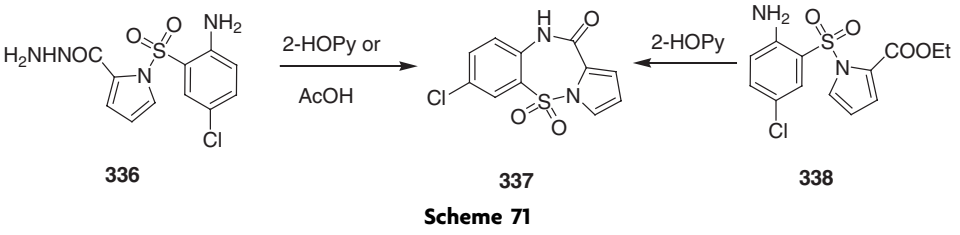
(39)

334 **335**

Formation of the similar pyrrolo-benzothiadiazepinone dioxide **337** from amino hydrazide **336** occurs with a loss of hydrazine when reacted with 2-hydroxypyridine or glacial acetic acid (Scheme 71 (2000H2163)). Similar rings can be synthesized starting from the corresponding esters **338** (1996BMC837, 1997FES323).

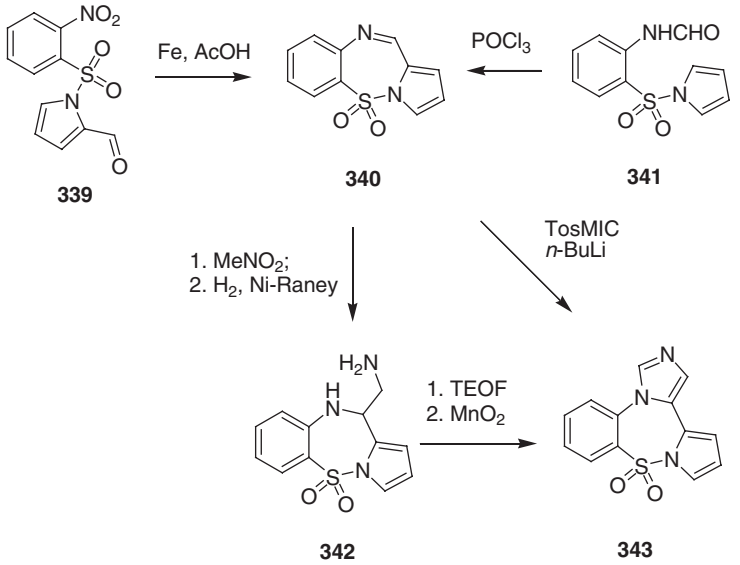
Fused cyclic system **340** can be obtained by type (i) reaction through the reduction of the nitro aldehyde intermediate **339** and its sequential cyclization in acetic acid. Alternate type (iii) process starts from the corresponding formamide **341** that can be cyclized with phosphorus oxychloride by a Bischler–Napieralski reaction (Scheme 72 (1994JHC1033)).

Another example of type (iii) intramolecular cyclization is the final step of a multistep synthesis of a series of substituted pyrrolo-benzothiadiazepines **344**



336 337 338

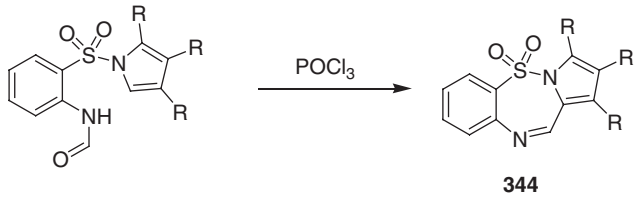
Scheme 71



339 340 341 342 343

Scheme 72

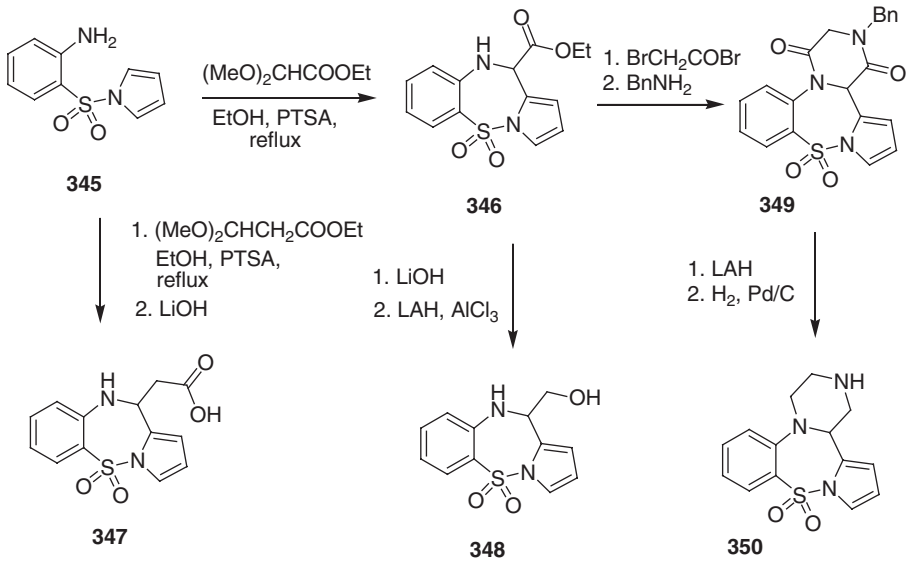
(Equation (40) (2004TL7553)).



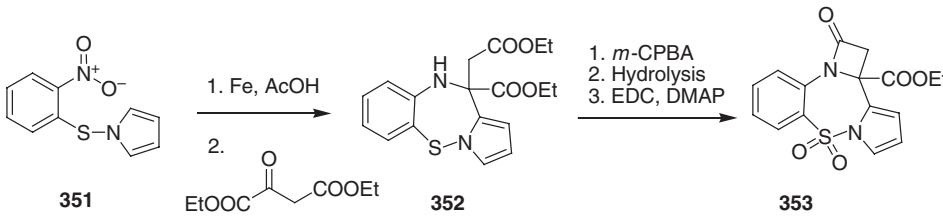
344 (40)

Type (ii) cyclizations are more common. Thus, acid derivatives of pyrrolo[1,2-*b*]-[1,2,5]benzothiadiazepine 5,5-dioxide **346** and **347** have been prepared from amino sulfonyl pyrrole **345** with acetal (2006JMC5840) or the semiacetal (1994JHC867) of ethyl glyoxalate or ethyl 2,2-diethoxy propionate (1996FES425) in the presence of PTSA catalyst in boiling absolute ethanol by a Pictet–Spengler type of reaction (Scheme 73).

Reduction of nitro derivative **351** followed by reaction with diethyl 2-oxosuccinate affords diester **352** (Scheme 74 (1994SC2685)).



Scheme 73



Scheme 74

As with pyrrolo-benzodiazepine (1992JHC1005), oxo derivative of pyrrolo-benzothiadiazepine **203** (X = SO_2) can be synthesized by the thermal cyclization of intermediate **205** (Scheme 42, Section 3.1.1.2 (1992SC1433)).

4.3 Miscellaneous ring systems

Several other types of rings related to the reviewed cyclic systems have been reported (Figure 7). Structurally similar, most are out of the scope of the current review although they give insight into the possible diversity. Most of the systems described in this section have been synthesized using the methods mentioned above and the reader is referred to the individual references for this information.

Syntheses of furano thiazepinones **354** by intramolecular Friedel–Crafts cyclizations have been reported (1995CPB2064). Examples of other benzoheteropines with fused five-membered rings include annulated oxazoles **355** (1993JOC4885), and pyrazoles **356** (1996AP352, 1997JHC1191, 1998PHA130, 2003FES1), as well as pyridines **357** (1995CPB2064) and **358** (1994JCS(P1)1193),

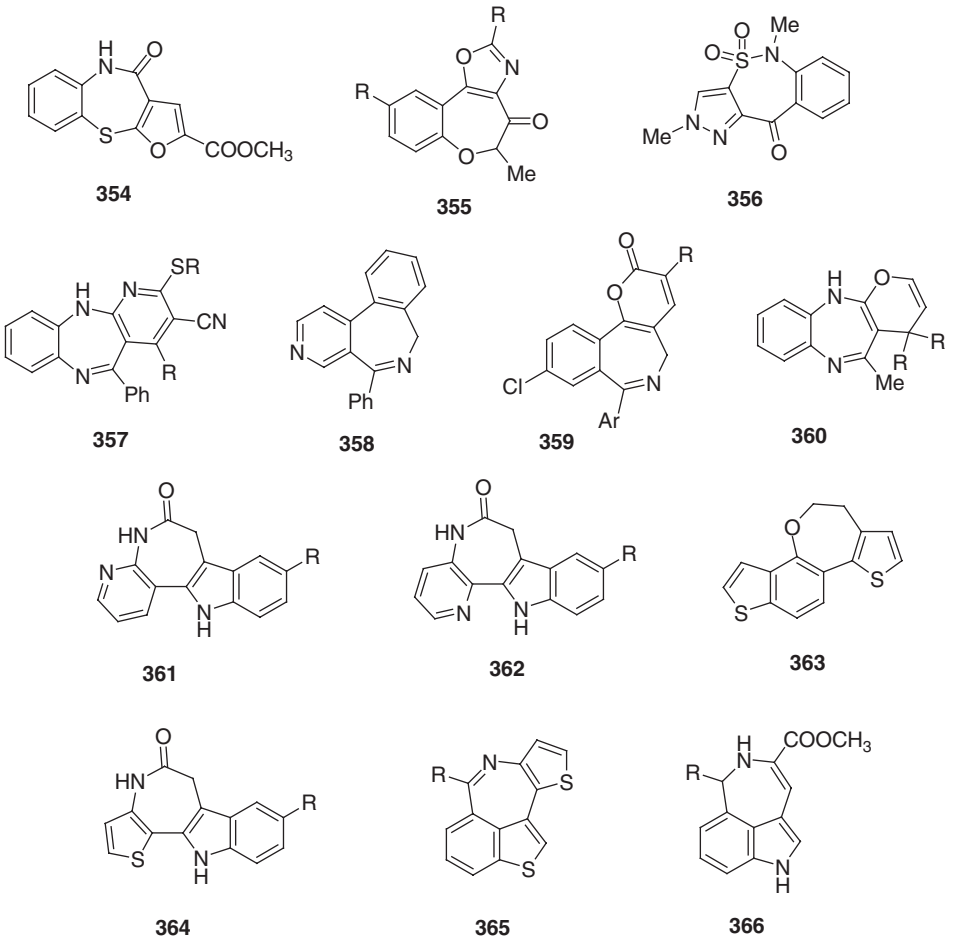


Figure 7

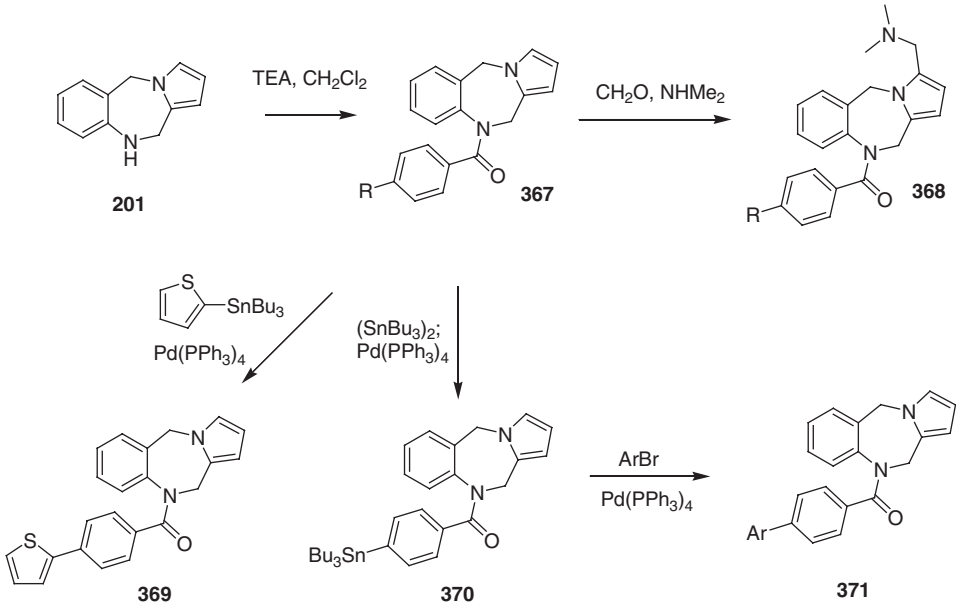
and pyrones **359** (1989JHC1299) and **360** (1999SC3561). Five-membered rings fused to cores other than benzoheteropines are represented by pyrido azepines **361** and **362** (2004BMCL413), and benzothiophene derivative **363** (1994JCR(S)295). Thieno[3′,2′:2,3]azepino[4,5-*b*]indol-5(4*H*)-one **364** (1992AP297, 2004BMCL413) as well as *peri* fused **365** (2002H1831) and **366** (2003H73) have been reported.

5. REACTIVITY OF BENZOHETEROPINES WITH FUSED FIVE-MEMBERED RINGS

5.1 Reactivity of the rings

5.1.1 Electrophilic attack on ring carbons

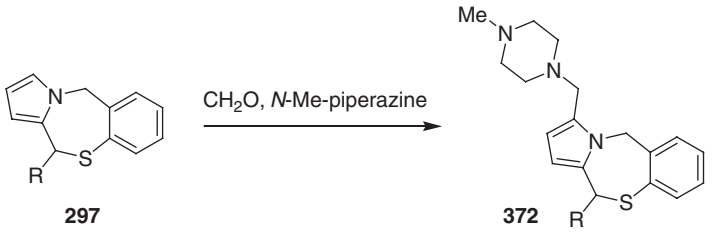
Electrophilic substitution on position 2 of pyrrolo[1,2]benzoheteropines is the most common example of this type of transformation. Thus,



Scheme 75

10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **367** undergoes reaction with formaline and dimethylamine in acetic acid (2005BMCL5003) or tetramethyl diaminomethane (2000BMCL783) to form dimethylaminomethyl derivatives **368** (Scheme 75). Similar reactions were performed using the corresponding secondary amines and paraformaldehyde to afford Mannich products in 60–80% yields (2000BMCL783).

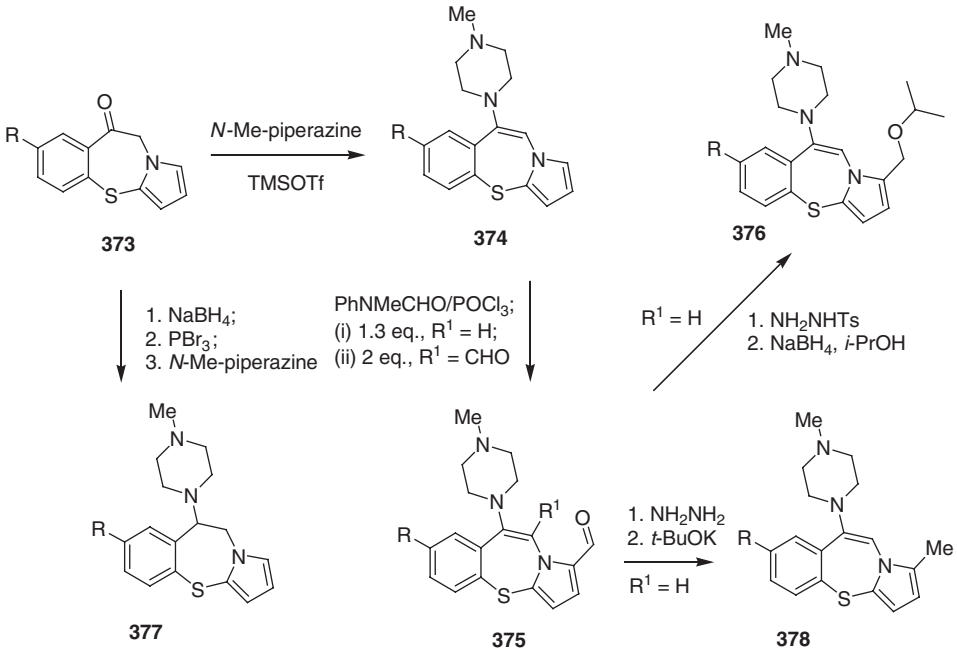
Reaction of phenyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **297** (R = Ph) with paraformaldehyde and 1-methylpiperazine dihydrochloride in methanol occurs on the 2-pyrrole position and affords Mannich product **372** (Equation (41) (1999JMC3334)).



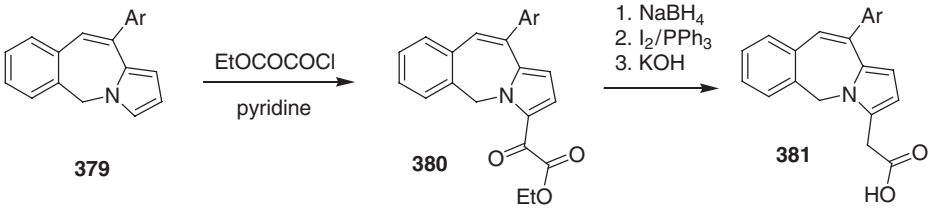
(41)

Analogous dimethylamino derivatives of this ring with different substitution patterns on the thiazepine ring have been reported (1996T7745).

Formylation of 5*H*-benzo[*f*]pyrrolo[1,2-*d*][1,4]diazepin-6(7H)-one **180** pyrrole ring with $POCl_3$/DMF is known (Scheme 36, Section 3.1.1.1 (1992BMCL1639)). Formyation of pyrrolo-benzothiazepine can be accomplished using $POCl_3$/PhNMeCHO (Scheme 76 (2004JMC143)). The monoaldehyde **375** (R^1 = H) is



Scheme 76



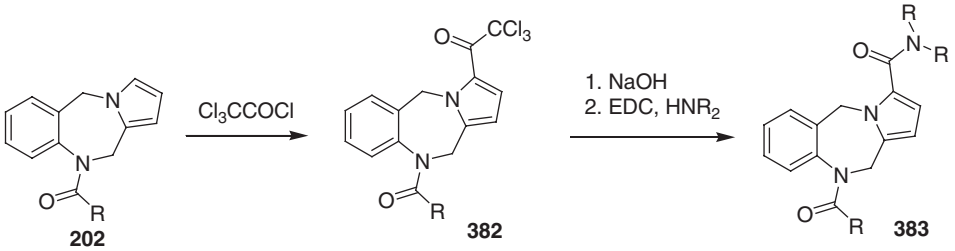
Scheme 77

prepared using 1.3 equiv. of the formylating agent, while exposure to 2 equiv. of the reagent provided the 1,10-diformylated derivative (R^1 = CHO).

Syntheses of a series of pyrrolo-benzazepine acetic acids **381** have been reported (Scheme 77 (1994MI385)). They include acylation of the core heterocycle with ethoxy oxalyl chloride in the first step to afford ketoesters **380**. This sequence can also be successfully applied to a pyrrolo-benzothiazepine ring system.

Reaction of 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines **202** with trichloroacetylchloride results in trichloromethyl keto derivatives **382** (Scheme 78 (2000BMCL783)).

An example of electrophilic substitution on position C2 of the fused furan has been reported for 8*H*-furo[3,4-*d*]dibenz[*b,f*]azepine, which reacts with *t*-butyl hypochlorite to afford a mono chlorinated furan ring product (1995H431).



Scheme 78

5.1.2 Electrophilic attack on ring heteroatoms

This kind of reactivity is usually limited to substitution on the nitrogen of benzazepine ring and the nitrogen of pyrrole (or indole) fused to the heteropine core.

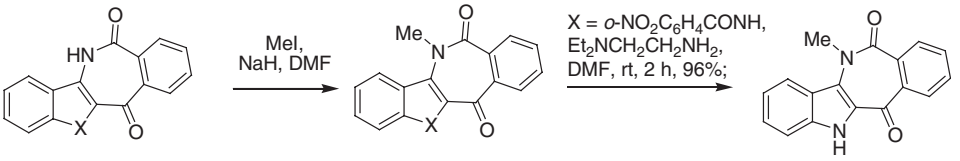
Electrophilic substitution of a pyrrolo-benzazepine depends on the nature of the electrophile, base and solvent and can be fine tuned. Thus, *N*-alkylation of indolo benzazepinones **41** (Scheme 8, Section 2.1.1.3 (1999JMC2909)) proceeds selectively on the azepinone nitrogen in THF in the presence of sodium hydride, while in acetone with potassium hydroxide it gives exclusively indolo N1 substituted products **44**. Acylation of this ring system with Boc anhydride gives a product substituted on both nitrogens in methylene chloride in the presence of DMAP. Application of large excess of the Boc_2O in NaH/THF leads to a tri-substituted product of N5, N12 and C7 alkylation (1999JMC2909).

Similarly, methylation of pyrrolo-benzothiazepines **172** (Scheme 34, Section 2.3.1 (1994MI283)) and **307** (Scheme 66, Section 3.3.1.2 (2005FES385)) with methyl iodide in acetone in the presence of potassium carbonate proceeds regioselectively and produces *N*-methyl pyrrole derivatives as sole products. Methylation on the thiazepine ring nitrogen requires stronger base, i.e. potassium *tert*-butoxide, to give dimethyl **174** and **311**, respectively.

Alkylation of pyrrolo-benzodiazepine dione **244** with methyl iodide occurs on both positions N9 and C10a, while reaction with 2-bromo diethylaminoethane leads to the low yield of the 4-substituted **248**. Acylations with benzoyl and 2-chloroacetyl chlorides are directed exclusively to position 4 to afford **247** (Scheme 52, Section 3.1.1.4 (1992CE649, 2005H2451)). Alkylation of 5*H*-benzo[*f*]-pyrrolo[1,2-*d*][1,4]diazepin-6(7H)-one with a substituted phenethyl bromide has been reported (Scheme 36, Section 3.1.1.1 (1992BMCL1639)).

Electrophilic substitutions of rings with a single *N*-nucleophilic site proceed smoothly. Thus, indolo benzazepine **36a**, protected on the indole ring, and benzoxepine **36c** are easily methylated on the benzazepine nitrogen (Scheme 79 (1991JHC379)).

Other examples of mono-alkylation include thieno azepinone **118** (Scheme 23, Section 2.1.3.3 (1999PHA645)), benzodiazepine dione **221** (Scheme 46, Section 3.1.1.2 (1993MI249)) and 7,12-dihydro-6*H*-[1]benzothiepino[5,4-*b*]indole (2006BMCL3233).



36a, c

384a X = *o*-$NO_2C_6H_4CONH$, 73%;
384b X = O, 73%

385

Scheme 79

The reactivity of *N*-nucleophilic sites of other fused heteropines towards acylating agents is similar to pyrrolo-benzazepines described at the beginning of this chapter. Pyrrolo[2,1-*c*][1,4]benzodiazepine **201** with acid chlorides (CH_2Cl_2/TEA, at room temperature) gives amide **202** (Schemes 42 and 43, Section 3.1.1.2 (1999BMCL1737) and (2003BMCL2195), correspondingly). Compounds **111** and **113** undergo smooth acylation on the azepine nitrogen with 4-(2-methylbenzoylamino)benzoic acid chloride to give amides (Scheme 22, Section 2.1.3.2 (1999BMCL1733)). 10,11-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **201** gives amides **367** by reacting with acid chlorides in the presence of triethylamine in methylene chloride (Scheme 75, Section 5.1.1 (2005BMCL5003, 1998JMC2442, 2000BMCL783)).

Reductive formylation of dihydro compounds derived from 4-arylmethyl pyrrolo-benzodiazepines **236** with formaldehyde in a Parr apparatus yields *N*-methyl **237** (Scheme 50, Section 3.1.1.3 (1995EJM593)).

Carboxy substituted diazepines **226** and **229** react with phenyl isocyanate to afford pyrimido diones **227** and **230**, correspondingly (Scheme 48, Section 3.1.1.3 (1993JHC897)). *N*-Hydroxymethylation on an indole ring annulated to benzazepinone, as well as formation of the corresponding carbamate and urea, has been described (2004MI1076).

5.1.3 Reactions with nucleophiles

Fusion of the imidazole ring to pyrrolo-benzothiadiazepine **340** can be achieved by straightforward TosMIC cycloaddition approach (Scheme 72, Section 4.2 (1994JHC1033)). An alternative sequence starts with the addition of nitromethane to the C–N double bond on the thiadiazepine ring, nitro group reduction and manganese oxide oxidation of the intermediate dihydroimidazole derived from amine **342** and triethyl ortho formate.

5.1.4 Reduction

The most general of this type of transformation is the reduction of lactam carbonyls on five- or seven-membered rings. Examples also include the reduction of C–C or C–N double bonds on the azepine ring. Therefore, reaction of a pyrrolidone carbonyl with $BF_3 \cdot O(C_2H_5)_2/BH_3 \cdot S(CH_3)_2$ provides tetracyclic benzo[*f*]pyrrolo[1,2-*a*]thieno[3,2-*c*]azepine **104a** in good yield (Scheme 20, Section 2.1.3.1 (2001H1519)). Lithium aluminum hydride is the usual reactant of choice for the reduction of a lactam carbonyl on an azepinone ring

(see Scheme 66, Section 3.3.1.2 and Scheme 46, Section 3.1.1.2 for examples (1998SC2517) and (1993MI249), correspondingly).

Reduction of the azepinone ring in **63** can be accomplished selectively. Thus, hydrogenation results in selective 1,4-reduction of the enone moiety and furnishes the corresponding saturated ketone **65**. Selective enone 1,2-reduction can be performed with *n*-BuLi–BH_3 to produce allylic alcohol **64**. Reduction with borohydride is non-selective and gives saturated hydroxyl compound **66** (Scheme 13, Section 2.1.1.5 (2000T9351)).

4-Arylmethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines **236** can be transformed with sodium borohydride to corresponding derivatives reduced at the imine double bond (Scheme 50, Section 3.1.1.3 (1995EJM593)).

Contrary to the stable azepines and diazepines, benzo[*b*]benzofuro[2,3-*f*][1,4]-oxazepine **272** undergoes ring cleavage under reductive conditions in the acetic acid/acetic anhydride to afford open chain acetoxy amine **273** (Scheme 58, Section 3.2.2 (2001JHC383)).

5.1.5 Oxidation

Oxidation on the sulfur atom of pyrrolo-benzothiazepine **175** (Scheme 34, Section 2.3.1 (1994MI283)), indolo benzothiazepine (Scheme 65, Section 3.3.1.2 (1998MI139)) and pyrrolo-benzothiadiazepine (Scheme 74, Section 4.2 (1994SC2685)) proceeds smoothly with hydrogen peroxide in acetic acid or with MCPBA to afford cyclic sulfones in good yields.

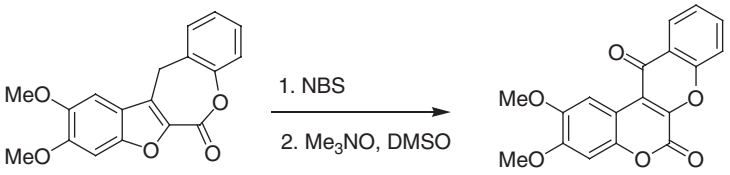
Treatment of the keto isomer of cryptoheptine with sodium ethoxide in ethanol leads to fast enolization followed by formation of 5-methylindolo[3,2-*b*]-[1]benzazepin-7(5*H*)-one **39** as an oxidation product (Scheme 7, Section 2.1.1.2 (2000JNP643)).

Tetrahydro pyrrolo-benzodiazepine **232** can be oxidized with manganese (IV) oxide to imino analog **233** (Scheme 49, Section 3.1.1.3 (2005BMCL3453)).

5.1.6 Intramolecular ring transformation reactions

This type of transformation usually involves contraction of a seven-membered ring into a thermodynamically more stable five- or six-membered ring.

Bromination of lactone **386** followed by oxidation with trimethylamine oxide in DMSO resulted in rearranged **387** in poor, 7% yield (Equation (42) (2001H91)).



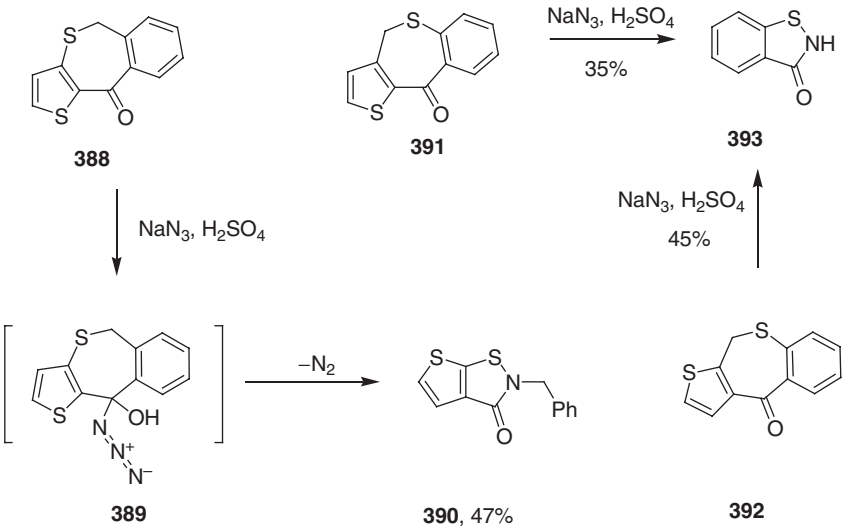
386 **387** (42)

Benzo[*e*]thieno[3,2-*b*]thiepin-10(5*H*)-one **388** under Schmidt conditions undergoes a ring contraction into 2-benzylthieno[3,2-*d*]isothiazol-3(2*H*)-one **390** through initial intermediate **389** by nitrogen loss and intramolecular nucleophilic

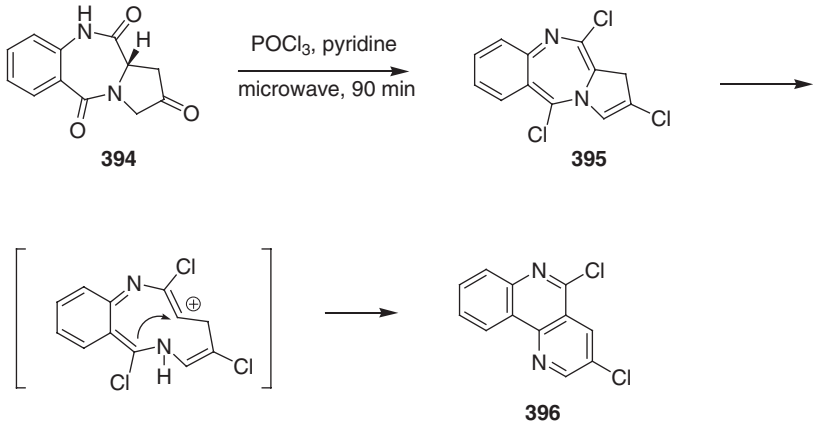
attack of the sulfur on the imminium nitrogen. Interestingly, a similar transformation for isomeric thieno thiepinones **391** and **392** is accompanied with the loss of the methylene thiophene moiety to produce benzo[*d*]isothiazol-3(2*H*)-one **393** (Scheme 80 (1991JHC1881)).

Hexahydro pyrrolo-benzdiazepinetrione **394** in boiling phosphorous oxychloride produces 3,5-dichlorobenzo[*h*][1,6]naphthyridine **396** as rearrangement product of trichloride **395** (Scheme 81 (2003JHC255)). The suggested mechanism includes thermal aromatization in the final step.

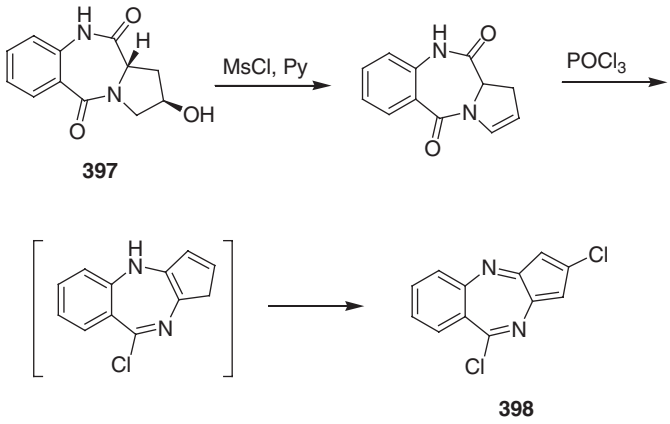
A similar transformation for hydroxyl derivative **397** requires initial dehydration with mesytyl chloride/pyridine followed by rearrangement to **398** (Scheme 82 (1997TL2271)).



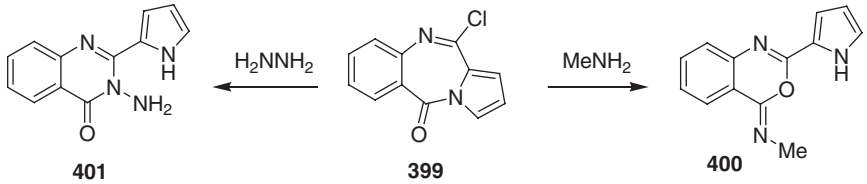
Scheme 80



Scheme 81



Scheme 82



Scheme 83

11-Chloropyrrolo[2,1-*c*]-[1,4]benzodiazepines **399** are readily accessible from 2-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepines in refluxing thionyl chloride. Further reaction with methyl amine gives imino benzoxazine **400**, while quinazoline **401** is the product of hydrazinolysis (Scheme 83). In contrast, reactions with dimethyl amine and ammonia lead to open chain products of diazepine ring cleavage on CO–$N_{pyrrole}$ bond (2001TL5183).

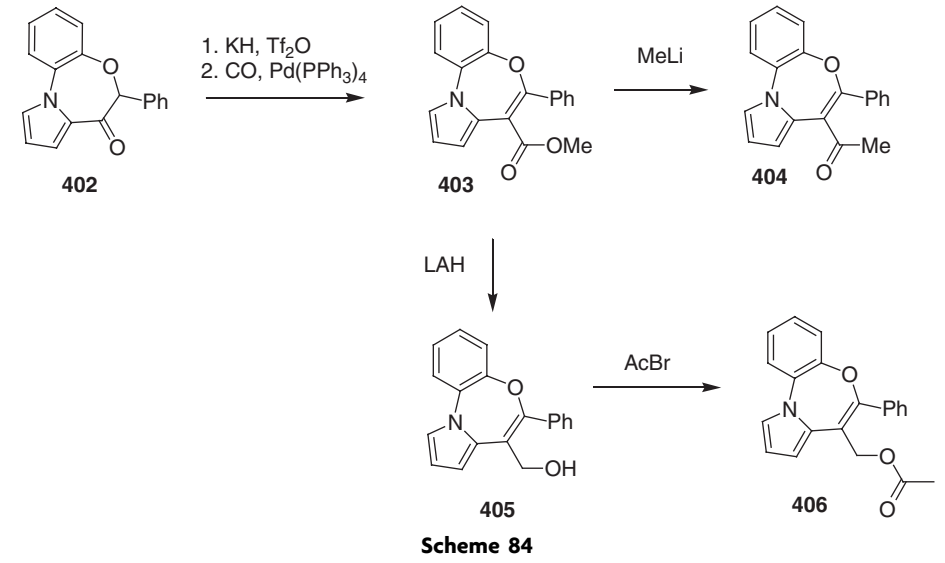
5.2 Reactivity of substituents

5.2.1 Reactivity of substituents attached to ring carbon atoms

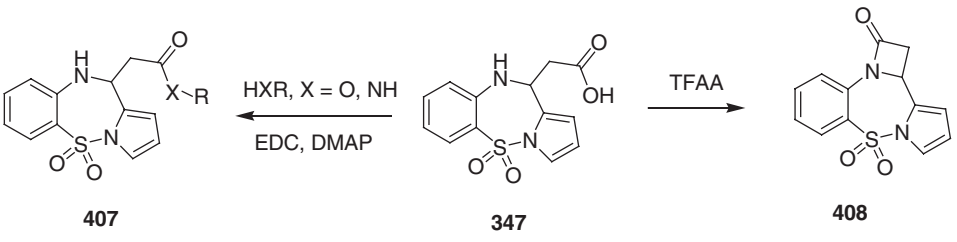
5.2.1.1 Alkyl groups and further carbon functional groups. *p*-Tolyl derivative of pyrrolo-benzoxazepine can be brominated with NBS and further submitted to a Wittig reaction to afford unsaturated **262** (Scheme 55, Section 3.2.1.1 (2005JMC7153)).

Trichloromethyl keto derivatives **382** (Scheme 78, Section 5.1.1) undergo hydrolysis with sodium hydroxide in aqueous THF to produce acids in overall yields of 60–70%. Coupling of the acids with amines leads directly to amides **383** in 80–90% yield (2000BMCL783).

Oxidation of the methyl group in position 2 of the 1,8-dioxadibenzo[*e*,*h*]azulene system proceeds smoothly resulting in aldehydes. Further LAH reduction gives alcohols **149** in 35–83% yields (Scheme 29, Section 2.2.2 (2006JHC749)).



Scheme 84

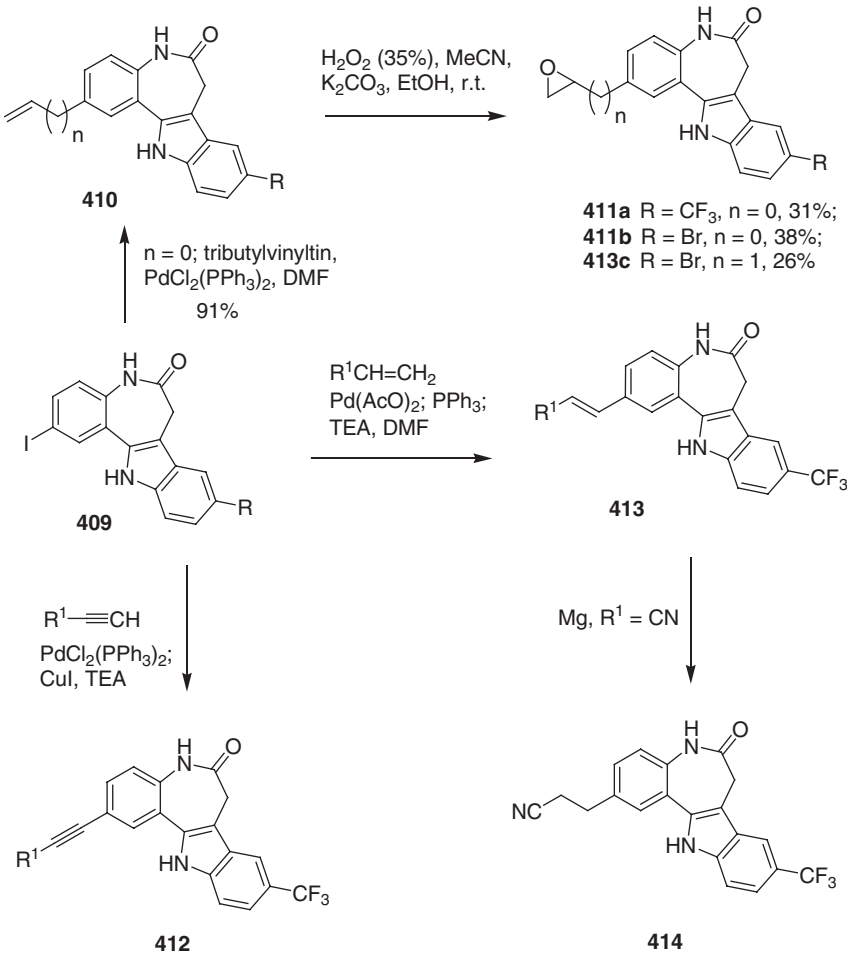


Scheme 85

The ester derivative of pyrrolo-benzoxazepine **403** (Scheme 84) has been transformed into ketone **404** with methyl lithium, while ester **406** was synthesized by esterification with acetyl bromide of alcohol **405**, prepared by LAH reduction of **403** (1996JMC3435).

Di-carboxy substituted diazepine **226** results in spiro **228** after Boc-protection, hydrolysis, CDI activation and imide formation (Scheme 48, Section 3.1.1.3 (1993JHC897)). The conjugated ester group of (+)-anthramycin derivative **197** can be constructed by cross-metathesis of pyrrolo-benzodiazepine **196** (Scheme 40, Section 3.1.1.2 (2004T9649)).

Lithium hydroxide hydrolysis of the ester of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide **346** afforded the acid, subsequently reduced with lithium aluminum hydride-aluminum chloride to alcohol **348** (Scheme 73, Section 4.2 (2006JMC5840)). Pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine acid **347** gives easy access to a variety of esters and amides **407**, while treatment with TFAA produces fused lactam **408** (Scheme 85 (1996FES425)).



Scheme 86

Diester **352** (Scheme 74, Section 4.2 (1994SC2685)) after the sulfur atom oxidation undergoes hydrolysis and intramolecular acylation to the pyrrolo-thiadiazepine **353** with a fused lactam ring.

Examples of transformations on the side-chains attached to a benzo ring have been reported. Epoxidation of the double bond in vinyl and allyl derivatives of paullone **410** can be achieved with a hydrogen peroxide/nitrile mixture (Scheme 86 (2005EJM655)). The saturated analogue **414** has been prepared upon refluxing the acrylonitrile **413** with magnesium turnings in methanol (2000BMCL567).

5.2.1.2 Amino and imino groups. Amino thieno benzoxepine **163** (Scheme 32, Section 2.2.3) can be smoothly transformed into the corresponding amides and urea (1994JCS(P1)2191). The dimethylamino substituted pyrrolo-benzoxazepine

258 gives mono methyl derivative **259** with ethyl chloro formate followed by basic hydrolysis of the intermediate carbamate (Scheme 54, Section 3.2.1.1 (1993JHC177)).

Amino methyl substituted pyrrolo-benzodiazepine **215** forms a cyclic aminal with aldehydes that can be further oxidized with MnO_2 to fused 3-substituted imidazole **216**. Alternatively, cyclic imine **217** can be submitted to TosMIC cyclization to afford unsubstituted 9*H*-benzo[*e*]imidazo[5,1-*c*]pyrrolo[1,2-*a*][1,4]-diazepine **218** (Scheme 45, Section 3.1.1.2 (1993JHC749)).

The amino group of 10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepin-4-amine **253** can be substituted with *N*-methyl piperazine by direct amination under thermal conditions (Scheme 53, Section 3.1.3 (1997BMCL25)).

7-Aminobenzo[*b*]thieno[2,3-*f*][1,4]oxazepin-10(9*H*)-one **278** forms 7-fluoro derivative **279** by a standard diazotation/fluorination procedure (Scheme 59, Section 3.2.3 (1992AF896, 2002JHC163)).

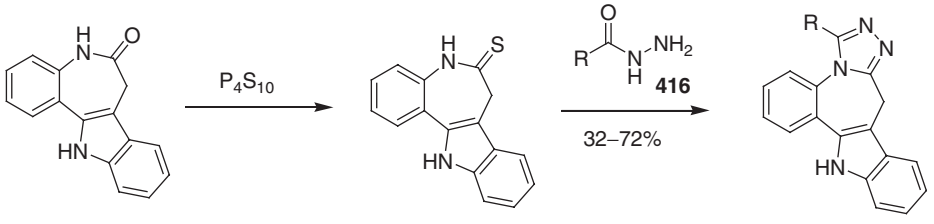
Elaboration of the nitro group in **264** ($R = NO_2$) has been reported and it leads, after multistep transformation, to alcohol **265** (Scheme 56, Section 3.2.1.1 (2005BMCL2515)).

An alternate route to fuse an imidazole to a pyrrolo-benzothiadiazepine includes side-chain nitro reduction and manganese oxide oxidation of the dihydroimidazole derived from amine **342** and triethyl *ortho* formate (Scheme 72, Section 4.2 (1994JHC1033)).

5.2.1.3 Hydroxy and oxo groups and other O-linked groups. Treatment of the potassium enolate of the pyrrolo-benzazepine and benzoxepine ketones **68** with the *N*,*N*-diethylcarbamyl chloride gives carbamates **69** (Scheme 14, Section 2.1.1.5 (2002JMC4276)). A similar modification has been reported for a benzopyrrolo[1,2]thiazepine (1997EJM241).

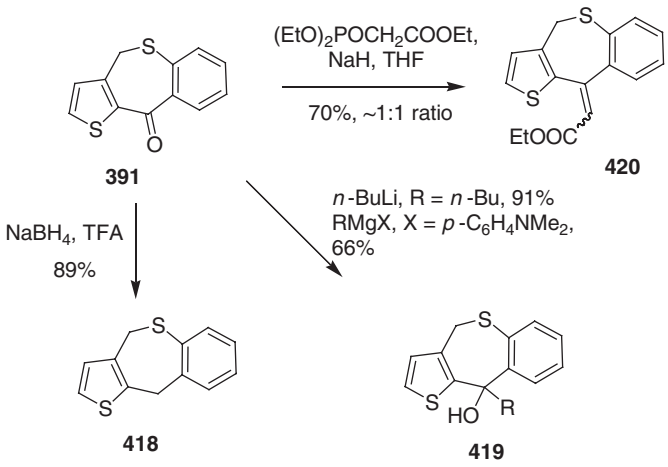
Reaction of indolo benzazepinone **27** with phosphorus pentasulfide yields 91% of the corresponding thione **415** (Scheme 87 (1993LA1141)).

Reduction of the keto group in naphtho derivative **115** with sodium borohydride results in 69% of the alcohol **116** (Scheme 23, Section 2.1.3.3 (1999PHA645)). Further triethylsilane reduction gives **117** in 67% yield. Synthesis of a series of pyrrolo-benzazepine and pyrrolo-benzothiazepine acetic acids (Scheme 77, Section 5.1.1 (1994MI385)) includes reduction of ketoesters **380** into corresponding hydroxyl esters, subsequent deoxygenation with iodine/PPh_3 and hydrolysis.



27 **415** **417**

Scheme 87



Scheme 88

The 1-isopropoxymethyl derivative of pyrrolo-benzothiazepine **376** can be obtained from aldehyde **375** through the tosyl hydrazone followed by reduction with sodium borohydride in 2-propanol. 1-Methyl substituted **378** is available from aldehyde **375** and hydrazine monohydrate followed by potassium *tert*-butoxide (Scheme 76, Section 5.1.1 (2004JMC143)).

Reduction of the keto group in thieno thiepinone **391** proceeds smoothly to give thiepine **418**. Reactions of the carbonyl group with strong nucleophiles give alcohols **419** in good yields. A Wittig–Horner reaction of **391** results in the substituted acrylic ester **420** as a separatable mixture of *E*- and *Z*-isomers formed in approximately a 1:1 ratio (Scheme 88 (1992JHC1789)).

Benzo[*e*]thieno[3,2-*b*]thiepin-10(5*H*)-one **388** can be smoothly reduced with sodium borohydride to the corresponding alcohol, which forms the chloro substituted compound under standard treatment with thionyl chloride (1991CPB2564). Dihydro derivatives of pyrrolo-benzothiazepine **377** have been reported starting from ketone **373** by a carbonyl reduction, bromination and amination sequence (Scheme 76, Section 5.1.1 (1998JMC3763, 2002JMC344, 2004JMC143)).

Treatment of the azepinone ring with TMS triflate followed by amination affords piperazine **83** (Scheme 16, Section 2.1.1.5 (2005JMC1705)). Likewise, benzothiazepines **374** can be prepared from ketones **373** with *N*-alkylpiperazines and *N*-methylhomopiperazine in the presence of trimethylsilyl triflate (Scheme 76, Section 5.1.1 (2002JMC344, 2004JMC143)).

Fusion of a 1,2,4-triazole ring to pyrrolo-benzodiazepine (1992JHC1005) and pyrrolo-benzothiadiazepine (1992SC1433) rings has been reported starting from oxo **203** and included formation of the phosphonic imidate with formyl hydrazine (Scheme 42, Section 3.1.1.2).

The lactam carbonyl of 2*H*-pyrrolo[3,4-*b*][1,5]benzothiazepinone **310** undergoes an *O*–*S* exchange with Lewasson's reagent to afford benzothiazepine thiones **311** (Scheme 66, Section 3.3.1.2 (2005FES385)).

Formation of thiolactam **276** and its direct amination with *N*-methyl piperazine (1994JHC1053) is one of the routes to piprerazines **277** (Scheme 59, Section 3.2.3 (1992AF896, 2002JHC163)). Alternatively, 7-fluorobenzo[*b*]thieno[2,3-*f*][1,4]oxazepin-10(9*H*)-one **279** undergoes chlorination and sequential amination to **277**.

The lactam moiety of pyrrolo-benzdiazepine dione **244** can be transformed into the corresponding cyclic imidoyl chloride and further reacted with anilines and aliphatic amines to afford amines **246** (Scheme 52, Section 3.1.1.4 (1996PHA548)).

Pyrrolo-benzoxazepine **402** (Scheme 84, Section 5.2.1.1) gives ester **403** through the triflate intermediate by reaction with carbon monoxide and methanol in the presence of tetrakis(triphenylphosphine)palladium **(**1996JMC3435).

Transformations on the keto group of benzo[*c*]thieno[3,2-*f*][1,2]thiazepin-4(9*H*)-one **313** and isomeric benzo[*c*]thieno[3,4-*f*][1,2]thiazepin-10(5H)-one (not depicted in the Scheme) include reduction with sodium borohydride to afford alcohol **314** and formation of oximes (Scheme 67, Section 3.3.1.2 (1997JHC1191, 1998PHA130)). The later can be further *O*-alkylated to 2-aminoethyl **315** (2003FES1, 1996AP352). Similarly, substituted 2-aminoethyl ethers **316** were synthesized using two alternative routes (2000JHC389).

5.2.1.4 S-Linked groups. Thiomethyl **43** with hydroxyl amine or hydrazine hydrate affords **45** by displacement of the thiomethyl group (Scheme 8, Section 2.1.1.3 (2006IC1945)).

Oxidation of a thiomethyl group in indolo azepines to a sulfoxide and a sulfone has been reported (2004AP486). Thione **415** with a variety of hydrazides **416** under thermal conditions (*n*-butanol, reflux) gives fused triazoles **417** in moderate to good yields as the products of a substitution/cyclization sequence (Scheme 87, Section 5.2.1.3 (1993LA1141)).

5.2.1.5 Halogen atoms. The introduction of side-chains on 9-trifluoromethyl-paullone **409** can be accomplished applying a Stille coupling (Scheme 86, Section 5.2.1.1 (2005EJM655)). Similarly, a Heck reaction of iodo **409** with terminal alkenes under standard conditions affords 2-substituted paullones **413** exclusively as *E*-isomers. The reaction of terminal alkynes with **409** in the presence of cuprous iodide and a palladium catalyst in triethylamine furnishes the 2-alkynyl-paullones **412** (2000BMCL567).

5.2.2 Reactivity of substituents attached to ring heteroatoms

5.2.2.1 Alkyl groups and further carbon functional groups. The *N*-2-nitrobenzoyl derivative of indolo benzazepine **384a** can be easily deprotected on the indole nitrogen by treatment with *N*,*N*-diethylaminoethylamine in DMF at room temperature (Scheme 79, Section 5.1.2 (1991JHC379)).

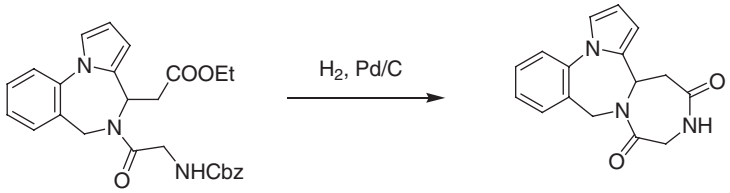
The iodo benzamide derivative of pyrrolo[2,1-*c*][1,4]benzodiazepine **367** (R = I, Scheme 75, Section 5.1.1) reacts with bis(tributyl)tin, lithium chloride and tetrakis(triphenylphosphine) palladium(0) in refluxing dioxane to yield the stannyl derivative **370**. The latter couples with substituted aryl bromides in the presence of

$(PPh_3)_4Pd(0)$ in boiling toluene to yield **371**. Similarly, **369** is accessible by a Stille coupling of **367** with 2-stannyl substituted thiophene (2005BMCL5003).

O-Debenzylation on the side-chain with TMSI to produce substituted benzo[*f*]pyrrolo[1,2-*d*][1,4]diazepinone **181** has been reported (Scheme 36, Section 3.1.1.1 (1992BMCL1639)).

The ester derivative of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine 5,5-dioxide **346** can be bromoacylated and further reacted with benzylamine and reduced to a four-ring system with an annulated piperazine ring (Scheme 73, Section 4.2 (1994JHC867)).

5.2.2.2 Amino, imino and other N-linked groups. Benzazepines **34** with acyl substituent on the azepine nitrogen are cleanly deprotected using NaOH in refluxing methanol (Scheme 5, Section 2.1.1.2 (1996TL4283)). Cbz-Protected ester **421** undergoes deprotection/cyclization by hydrogenation of the intermediate amide to furnish diazepino pyrrolo-benzodiazepinedione **422** (Equation (43) (1992JMC4533)).



421 **422** (43)

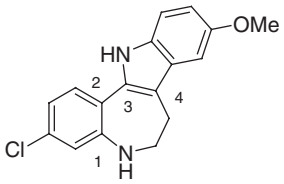
The *N*-4-chlorobutyl benzodiazepine dione **221** (Scheme 46, Section 3.1.1.2 (1993MI249)) gives the piperazine derivative after amination with *N*-methyl piperazine.

Condensation of substituted hydrazine **45** ($R = NH_2$, Scheme 8, Section 2.1.1.3) with 2-hydroxybenzaldehyde in methanol produces the corresponding hydrazone (2006IC1945).

6. PROPERTIES OF BENZOHETEROPINES WITH FUSED FIVE-MEMBERED RINGS

6.1 Theoretical methods

Semiempirical and molecular mechanics calculations have been widely used. Thus, conformation of indolo benzazepine **423** (Figure 8) with its conjugated benzo and indole rings has been studied by molecular mechanics (MMX force field). Its planarity was estimated from a calculation of dihedral angle $\tau_{1-2-3-4}$; the value of *ca.* 22° is due to strain as contributed by azepine ring. This characteristic was further compared to that of the open-chain and six-membered



423

Figure 8

analogs and to the experimental pK_a and *c*log*P* values (1994CPB1084, 1994EJM107).

Molecular mechanics calculations on two 6-arylpyrrolo[2,l-*d*][1,5]benzothiazepines (1995JMC4730) confirmed that binding to a mitochondrial benzodiazepine receptor depends on conformational strain as well as on specific repulsive interactions involving their side-chains.

Semiempirical molecular orbital calculations performed for a set of pyrrolobenzodiazepines using MNDO and AM1 were used for the interpretation of their mass-spectroscopic data (1996MI653).

6.2 Experimental methods

6.2.1 X-ray

Studies of the solid phase conformations of fused heteropines are useful for the prediction of their pharmacophore derived conformations. The crystal structure of 2,5-dimethyl-7-phenylsulfonyl-5,6-dihydroindolo[2,3-*c*]benzazepin-12-one has been reported (2005AX(E)o2410). This compound crystallizes with two independent molecules in the asymmetric unit, related by a non-crystallographic two-fold rotational axis. The two molecules differ in the relative orientations of the phenyl sulfonyl group and the indole ring. In both molecules the seven-membered ring adopts a distorted boat conformation. The molecular packing is stabilized by C–H$\cdots\pi$ and C–H$\cdots$O interactions.

Likewise, a boat conformation of the seven-membered ring has been reported for thieno benzodiazepines (2004AX(E)o66, 2003AX(E)o1367) and their hydrates and solvates (2005AX(E)o2720, 2004AX(E)o69). The benzene and thiophene systems, fused with the central 1,5-diazepine ring, are planar, and the dihedral angle between the planes of these two aromatic rings is 124.3(2)$^\circ$ for the methanol solvate and 118° for the methanol solvate hydrate (2004AX(E)o69, 2003AX(E)o1367).

X-ray structural data have identified the conformations responsible for receptor binding for a series of 6-arylpyrrolo[2,l-*d*][1,5]benzothiazepines (1995JMC4730). Crystal structures of methyl 12-methyl-12*H*-[3]benzoxepino-[1,2-*b*]indole-5-carboxylate **135** (1996JCS(P1)1767), benzoxepino[4,3-*b*]indole (1993AX(C)2126), and natural furobenzoxepine (1990JCR(S)114) have been reported.

6.2.2 Spectroscopic methods

NMR, UV and IR spectroscopies are routinely used for the characterization of the majority of reviewed systems and the reader is referred to the individual references for this information. The special cases of structure elucidation of a secondary metabolite of the Chinese drug Danshen (*Salvia miltiorrhiza* Bunge) by ^{1}H NMR (1990JOC3537) and of homocryptolepinone by HMQC, IDR-HMQC-TOCSY and HMBC experiments (1995JHC1631) are worth mentioning.

Mass spectrometry is suitable for the identification of pyrrolo-benzodiazepines and the differentiation of their isomers (1996MI653). A structural distinction can be made easily from their mass spectra or the metastable mass-analyzed ion kinetic energy (MIKE) spectra, produced by their molecular or most intense fragment ions. Established fragmentation pathways have been supported by MNDO and AM1 semiempirical calculations.

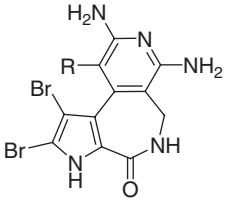
7. IMPORTANT COMPOUNDS AND APPLICATIONS

Heteropines with fused five-membered rings are structural blocks of valuable natural products and their synthetic analogs. Latonduines **424** A (R = H) and B (R = COOH) (Figure 9), two new alkaloids with pyrrolo-pyridoazepinone heterocyclic skeletons, have been isolated from the Indonesian marine sponge *Stylissa carteri* (2003OL2735).

Cyclic anhydride **425** is a secondary metabolite of the Chinese drug Danshen (*S. miltiorrhiza* Bunge) widely used to treat coronary heart diseases, particularly angina pectoris and myocardial infarction. This drug also has sedative and tranquilizing effects and is also being used to treat neurasthenic insomnia (1990JCR(S)114, 1990JOC3537).

Cularinoids are a group of isoquinoline alkaloids isolated from the plant families Fumariaceae, particularly the genus *Sarcocapnos enneaphylla*. Their distinguishing structural feature is a benzoxepine nucleus, and aristoyagonine **143** is the only example to date of a natural cularine alkaloid incorporating a five-membered lactam (1996TL9357, 2004JOC4527).

Homocryptolepinone **426** (Figure 10) was isolated from the extracts of the indigenous Ghanaian medicinal plant *Cryptolepis sanguinolenta* (1995JHC1631), as well as the alkaloid cryptoheptine **427** that was identified in other related



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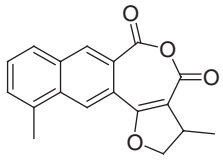
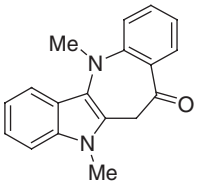


425

Figure 9



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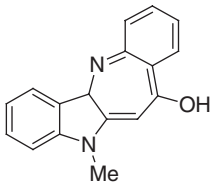

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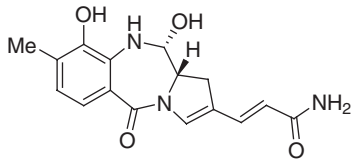

428

Figure 10

Cryptolepis species, extracts of which are used in traditional medicine in Central and West Africa (1996TL4283, 2000JNP643).

Benzoheteropines with fused five-membered rings represent bi-(hetero)aryl molecules that bind to many proteins and, therefore, are found in almost any therapeutic class. The broad scope of the biological activities of the reviewed class of heteropines is represented by analgetics (1989FES109, 1995EJM593), antibacterial (2005BMCL2515, 1993EJM659), antifungal (2005BMCL3453), antimalarial (1994EJM107), antihistaminic (1991CCC2482, 1994CCC667), and anti-inflammatory (1990FES817) agents.

Applications in psychopharmacology include antidepressants (1990FES1265, 1990FES7, 1992JMC4533, 1995CPB2064, 1996AP352, 1998PHA130, 2000JHC389, 2003FES1), antipsychotics (1992AF896, 1994MI845, 1997BMCL25, 1998JMC3763, 2002JMC344, 2003AX(E)o1367, 2004AX(E)o66, 2004AX(E)o69, 2004JMC143, 2005AX(E)o2410, 2005AX(E)o2720, 2005RJBC378, 2001JMC1603) and anxiolytics (1991KFZ16, 1992FES987, 1993MI249). The neurological drug class is represented by nootropics (1990SC3537), memory enhancing mitochondrial DBI receptor complex ligands (1992AG(E)1060, 1993JMC2908, 1994JMC1427, 1995JMC4730, 1996JMC3435, 1997EJM241, 2002JMC4276) and cerebrovascular agents (1991CPB2564).

(+)-Anthramycin **428** and related antitumor antibiotics are produced by *Streptomyces* species (1994CR433). Several other synthetic subclasses of antitumor agents (1993MI173, 1999PHA645, 2001BMC1123, 2005BMCL3220, 2005EJM655, 2006IC1945), including apoptotics (2001MI704, 2005JMC4367, 2006JMC5840) and CDK inhibitors (1999JMC2909, 2000BMCL567, 2002AP311, 2004AP486, 2004MI1076, 2005JCI1282, 2005MI541) have been reported.

Selective arginine vasopressin V_2 antagonists correct the fluid retention in congestive heart failure, liver cirrhosis, nephritic syndrome, central nervous system injuries, lung disease and hyponatremia (1998JMC2442, 1999BMCL1733, 1999BMCL1737, 2003BMCL2195, 2000BMCL695, 2000BMCL783, 2001PAC1401, 2002BMCL3081, 2004BMCL2747, 2004BMCL3363, 2005BMCL5003, 2006BMCL954).

Development of antiviral agents (2002EJM3) included HIV-1 non-nucleoside reverse transcriptase (1992BMCL1639, 1994MI283, 1996BMC837, 1996FES425, 1996JMC2672, 1997FES323, 1998MI127, 1998MI139, 1999JMC4462, 2000JHC1539, 2005FES385, 2005JMC7153) and HIV-1 integrase (1999JMC3334, 2002BMC4169, 2004BMCL1447, 2005JMC1496) inhibitors. These data have been further

summarized in a neural network computational model for *in silico* HIV-1 activity prediction (2006JMC1118).

Selective glycogen synthase kinase inhibitors (2004BMCL413), cardiovascular agents (1996JMC2922) and inhibitors of tubulin assembly (1996BCF251, 2000TL5853) of the fused benzoheteropine type have been reported.

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CHAPTER 2

Synthesis of Heteroannulated Azocine Derivatives

Leonid G. Voskressensky, Larisa N. Kulikova, Tatiana N. Borisova and **Alexey V. Varlamov**

Contents

Organic Chemistry Department, Russian Peoples Friendship University, 6, Miklukho-Maklaya Street, Moscow 117198, Russia

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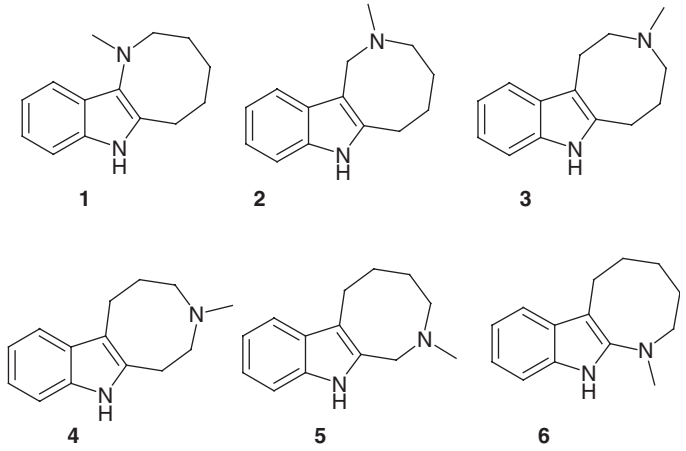
1. INTRODUCTION

The chemistry of heteroannulated azocines has not been explored in detail owing to the lack of efficient methods for their synthesis. The exception is azocinoindoles, which have been investigated extensively due to the host of alkaloids with an azocinoindole fragment in their structure.

2. HYDROGENATED AZOCINOINDOLES: NATURAL SOURCES, SYNTHESIS AND REACTIVITY

Theoretically, the existence of six isomeric azocinoindoles in which an azocine ring is annulated with a pyrrole fragment, is possible.

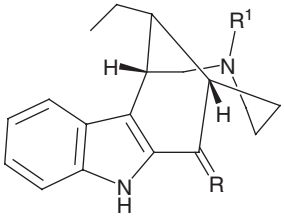


A large number of articles are devoted to various aspects of azocino[4,3-*b*]-indoles **2** chemistry. There are several publications on the synthesis and reactivity of the derivatives **3**, **4** and **5**. But, up to now, there has been no detailed work on azocinoindoles **1** and **6**.

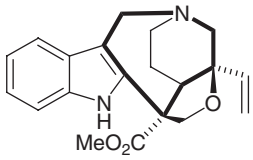
2.1 Natural alkaloids based on azocinoindoles

2.1.1 Alkaloids containing an azocino[4,3-*b*]indole fragment

The first papers on the extraction of alkaloids containing an azocinoindole fragment **2** and the elucidation of their structure go back to the 1950–1960s. Alkaloid uleine (**7a**), isolated (57HCA1189) from the roots and bark of the South-American *Aspidosperma ulei* tree contains an α-vinylindole fragment (59JA4433). Its structural analogs, dasycarpidone (**7b**) and nordasycarpidone (**7c**), also extracted from raw plant material (64E363), are assigned to the group of acetylindole alkaloids.



7a R=CH_2, R^1=Me
7b R=O, R^1=Me
7c R=O, R^1=H



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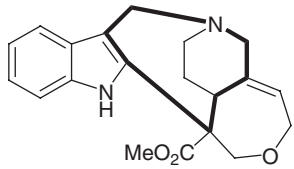

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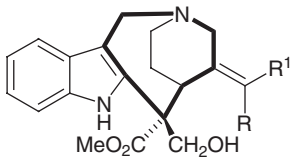
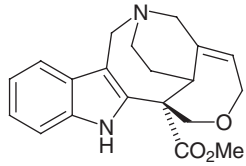
In succeeding decades reports on the extraction of these alkaloids from other plants have appeared (00MI208, 76P1093). Hydrogenated azocine fragments also can be found in the structures of some indole alkaloids of vallesamine, for example, angustilobine A (**8**) and angustilobine B (**9**), extracted from the leaves of *Alstonia angustiloba* (87JNP714, 89P1241).

Related alkaloids 19,20-Z-vallesamine (**10a**) and 19,20-E-vallesamine (**10b**) have been extracted from the leaves of *Alstonia scholaris* (87H(26)413), from the bark of *Tabernaemontana dichotoma* (85P2097) and from cell cultures *Tabernaemontana divaricata* (88MI393).



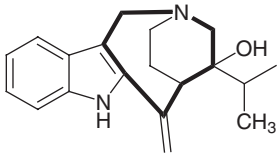
10a R=H, R^1=Me
10b R=Me, R^1=H



11

Alstonamine (**11**) – a pentacyclic alkaloid with a hydrogenated azocino[4,3-*b*]-indole fragment – has been isolated from the leaves of this plant (87P2139).

Brafouedine (**12**) and isobrafouedine (**13**), two alkaloids isolated in minor amounts from the bark of the rhizome of *Strychnos dintlagei* (86JNP452), and Epchrosine (**14**), a metabolite of cell cultures *Ochrosia elliptica Labill* (86MI147, 86MI381), have similar structures.



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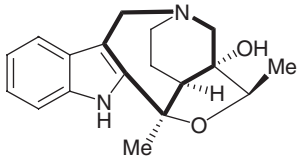

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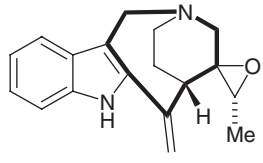
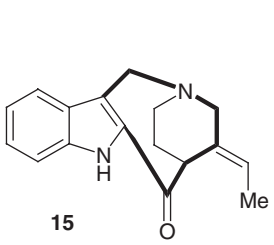


14

The related alkaloids ervaticine (**15**) and apparicine (**16a**) have been isolated from the leaves of *Ervatamia coronaria* (85H(23)2975) and from the wood of *Vallesia antillana* (77MI249), respectively. The latter exhibits high antibacterial activity. Subsequently, 16(S)-hydroxy-16,22-dihydroapparicine (**16b**) was isolated from the leaves of *T. dichotoma* (84JNP835).



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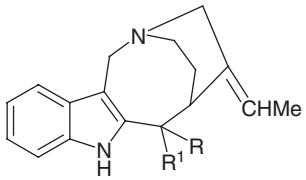
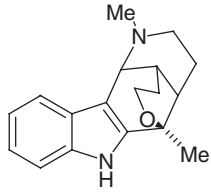


16a R′R^1- =CH_2
16b R=OH, R^1=Me



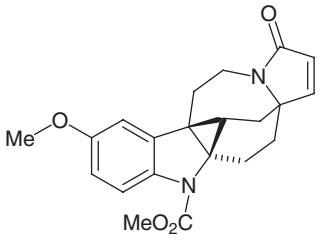
17

Gilbertin (**17**), isolated from the bark of *Aspidosperma gilbertii*, is assigned to another type of indole alkaloid (82TL5395).

The above structures are not the only examples of alkaloids containing the azocino[4,3-*b*]indole fragment but, only those most interesting from our point of view will be discussed here. More detailed information on the general topic can be found elsewhere (74MI219, 94CH(25)261).

2.1.2 Alkaloids with an azocinoindole fragment of different coupling

Only a few papers on the isolation of alkaloids with an azocinoindole fragment other than [4,3-*b*] coupling have appeared. Three indole alkaloids (lundurine A (**18**), lundurine B (**19**), lundurine C (**20**)) bearing the octahydroazocino[5,4-*b*]-indole fragment have been extracted from the leaves of *Kopsia tenuis*. Their structures have been established from spectral data (95TL759). All are tryptamine derivatives with an annulated cyclopentyl fragment.



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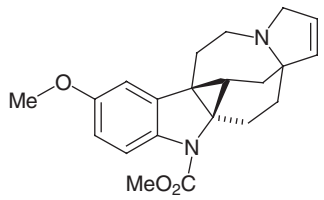

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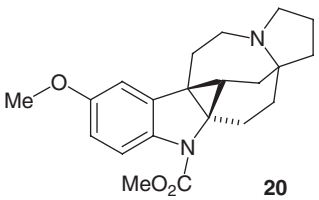

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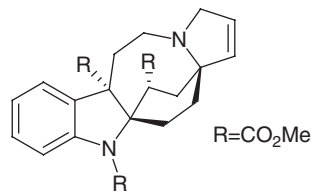
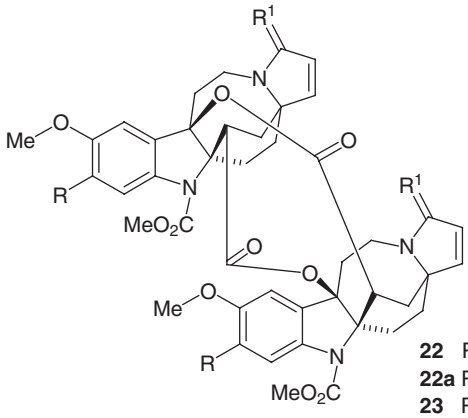


21

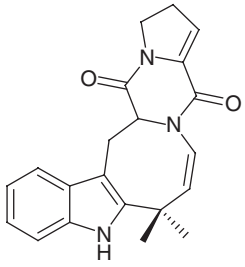
Alkaloid Lapidilectine A (**21**) has a basically similar carbon chain. A series has been isolated from the wood and leaves of *Kopsia lapidilecta*. (92TL2493, 93JNP1134).

Bis-indole alkaloids, Tenuisines A (**22**), B (**22a**) and C (**23**) were isolated from ethanol extracts of the leaves of *K. tenuis* later (96TL8811, 97T12661).



22 R=H, R^1=CH_2
22a R=OMe, R^1=CH_2
23 R=H, R^1=O

One of the indole diketopiperazines **24**, metabolite *Aspergillus Ustus* from mold spores forming in corn grains, has a pentacyclic structure with an azocino[5,4-*b*]indole fragment (73T107).



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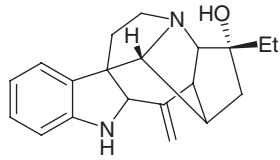
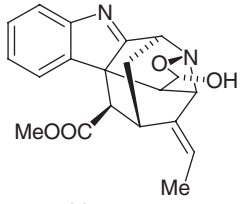


25

Pandine (**25**), bearing the azocino[5,4-*b*]indole fragment, has been isolated from *Pandaca caducifolia* (74TL3119). Its structure has been determined spectroscopically and corroborated by chemical transformations.

There are several publications on the isolation of indole alkaloids with the hydrogenated azocino[3,4-*b*]indole fragment from different plants. For example, nareline (**26**) (77HCA1419) and alschomine (**27**) (89CPB887, 90P3547) were extracted at different times from the leaves and wood of *A. scholaris*. Later, the isolation of derivatives **26** from other plants was reported (94P1737).



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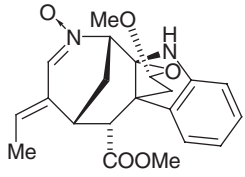
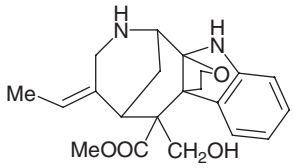


27

The alkaloid aspidodasycarpine (**28**), known since the 1960s (64TL3899), has been isolated from other plants in succeeding years (68P2045, 83JNP708). The nitrogen atom in its azocane fragment is not substituted, a phenomenon quite unique for this type of alkaloid.



28

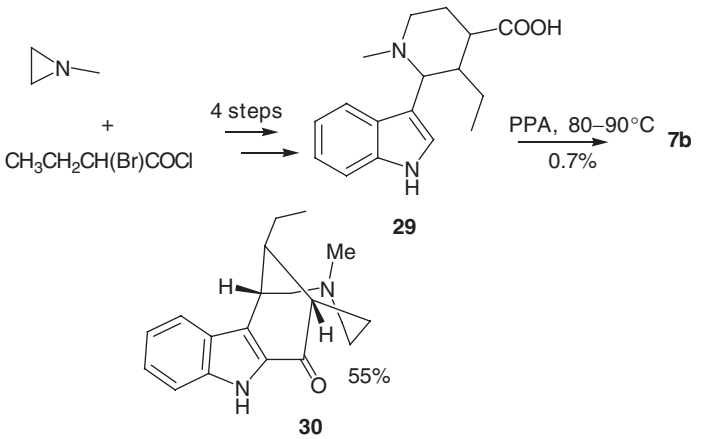
2.2 Synthesis of hydrogenated azocinoindoles

2.2.1 Synthesis of hydrogenated azocino[4,3-*b*]indoles

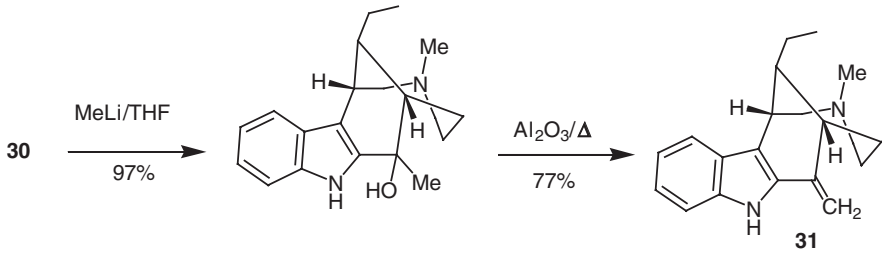
Most publications on the synthesis of hydrogenated azocinoindoles have involved attempts to synthesize known alkaloids and their derivatives. Early studies on the successful synthesis of racemic alkaloids uleine (**7a**) and dasycarpidone (**7b**) were conducted mainly in the 1960s. Dolby and Biere carried out acidic cyclization of indolyl-substituted amino acid **29** resulting in the formation of **7b** in poor yield. In the last stage they isolated epimer **7b** – (±) epidasycarpidone (**30**) with 55% yield (Scheme 1).

Using **30** as a starting material they also synthesized a racemic form of epimer **7a** – (±)epiuleine (**31**) (Scheme 2; 70JOC3843).

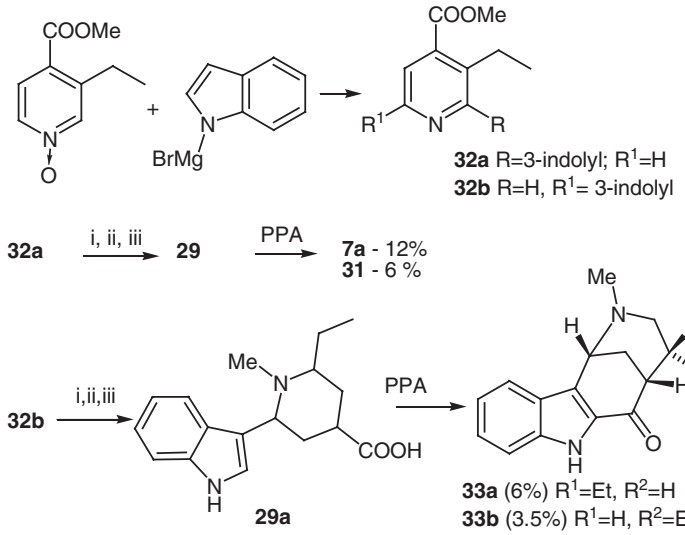
Kametani (71JOC1291) used a completely different approach to the synthesis of **29** (and correspondingly **7b**, **30** and **31**). The reaction between 3-indolylmagnesium bromide and 3-ethyl-4-carbomethoxypyridine N-oxide gave a mixture of 3-pyridylindoles **32a** and **32b**, separated chromatographically and converted into the corresponding methiodides with subsequent catalytic



Scheme 1



Scheme 2



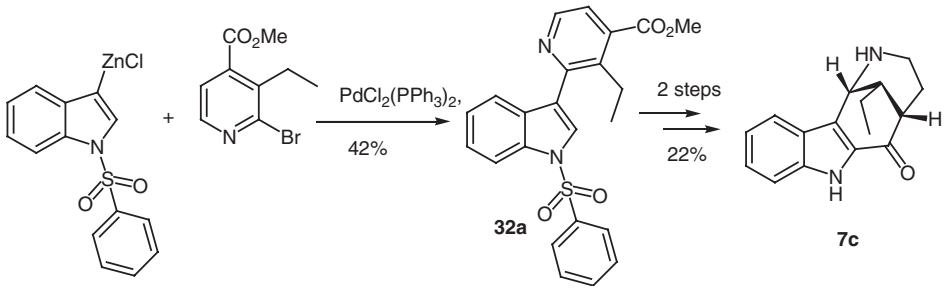
i: CH_3I/MeOH, reflux; ii: H_2/CH_3OH/Adams cat, iii: KOH/EtOH/H_2O, reflux, 3h

Scheme 3

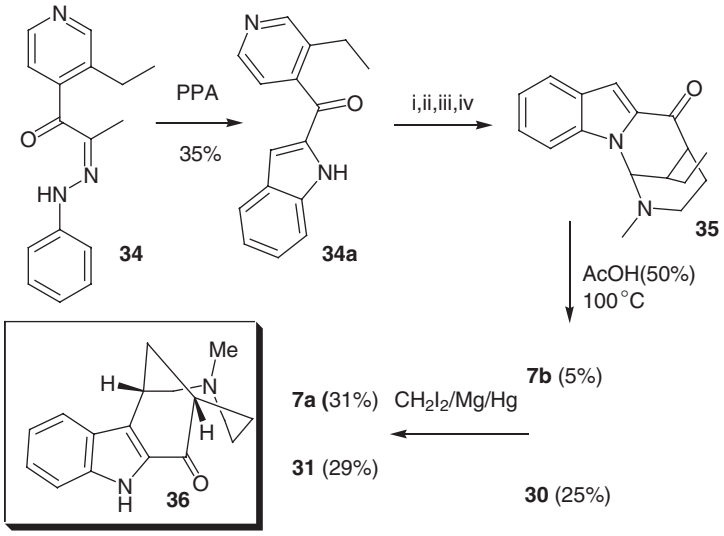
reduction and saponification to amino acid **29** and its isomer **29a**. On heating with polyphosphoric acid, the latter were converted into **7a** and **31** and their **33a** and **33b** isomers, respectively. The yields were not better than *ca*. 12% (Scheme 3).

Subsequently (71CPB1424), the same authors modified the synthesis, arriving at a better stereoselectivity and higher yield of the target product. Using heteroannulation with palladium catalyst to form intermediate **32a**, they obtained the corresponding azocinoindole **7c** in a high yield (Scheme 4; 97JOC3158).

About the same time a number of publications appeared on the complete synthesis of **7a**, **7b**, **30** and **31** using a different approach to build the alkaloid framework (Scheme 5; 68MI364, 68MI584, 69JCA(C)2738). Phenylhydrazone **34** under Fischer reaction conditions was converted into indole **34a** with subsequent successive transformations to pentacyclic derivative **35**. Its acid-initiated rearrangement led to the formation of **7b** and **30** in a ratio of 1:5. While **7b** and



Scheme 4



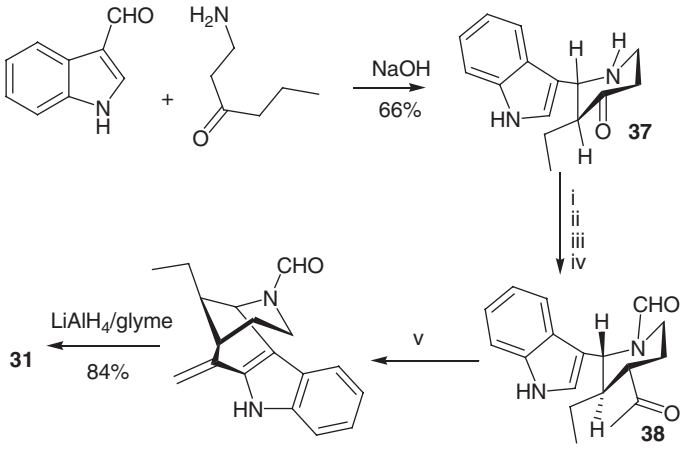
i: CH_3I, EtOH; ii: $NaBH_4$ (excess), MeOH,r.t, 2h, (yield 81%),
iii: MnO_2/CH_2Cl_2, r.t., 30 min., (yield 78%); iv: Na/DMSO/95 °C, 36h, (yield 30%)

Scheme 5

30 with methylene diiodide in the presence of magnesium amalgam gave uleine (**7a**) and epiuleine (**31**) correspondingly, a similar procedure gave (**36**)-de-ethyldasycarpidone.

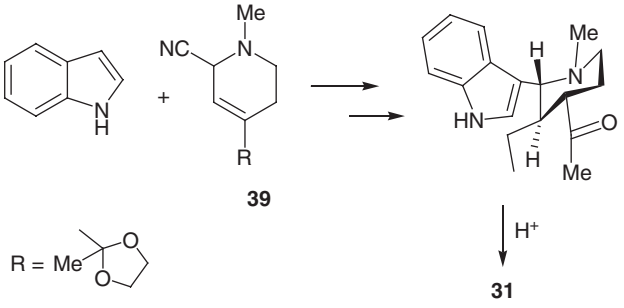
The first publications on the successful stereospecific synthesis of uleine (**7a**) and epiuleine (**31**) appeared in 1971 (71JA2492). Using **31** as an example, the key step lies in the formation of transoid piperidone **37**, whose conformational stability allows the subsequent transformations to be carried out stereoselectively (Scheme 6).

Later methods of stereoselective synthesis of alkaloids **30**, **31** and their derivatives differ mainly in the construction of the conformationally stable intermediate with a 3-(2-piperidyl) substituted indole fragment (type **38**). In the



i: $(CH_3CO)_2O$/HCOOH, r.t., yield 87%; ii: KCCK/THF –20 °C,13 h, yield 50%; iii: $Hg(CH_3COO)_2/CH_3COOH$, 2 days, yield 67%; iv: Li/liq.ammonia, yield 72%; v: BF_3xEt_2O, CH_2Cl_2, yield 70%

Scheme 6



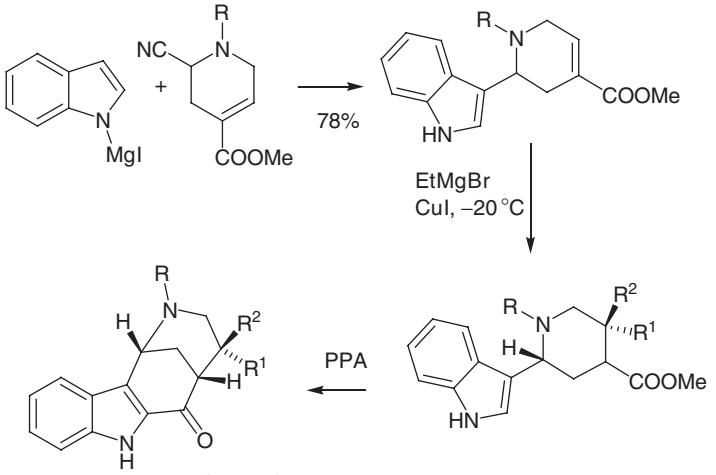
Scheme 7

publications (81TL331, 83T3683, 82JOC2435), the authors used acid-initiated condensation of 2-cyano-Δ-3-piperideines **39** with indole to achieve this result (Scheme 7).

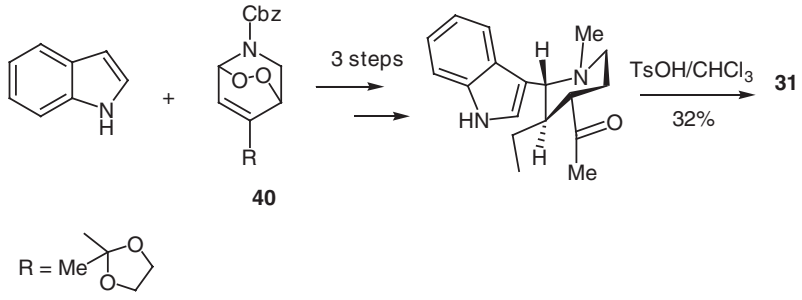
A similar approach, used for the synthesis of the isomeric alkaloids **33a** and **33b**, has been described in more recent work (85JOC1516, 89TL5659; Scheme 8).

In Ref. 80TL839, the main stage of the synthesis is the reaction of endoperoxide **40** with indole, initiated by tin chloride (II). The total yield of **31** is 10% (Scheme 9).

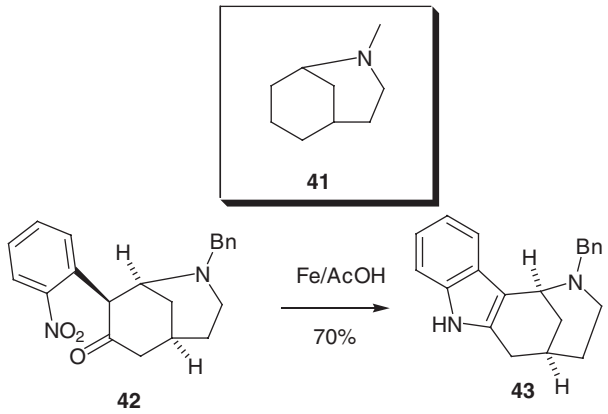
The derivatives of 2-azabicyclo[3.3.1]nonanes (morphane) (**41**) can also be used to build the framework of alkaloids with the azocino[4,3-*b*]indole fragment. 7-(2-Nitrophenyl)-substituted azabicyclononanone **42** obtained from *N*-benzylpiperidone-4 (seven stages, total yield (10%)) under the conditions of reductive cyclization has been converted into *N*-benzylhexahydroazocino[4,3-*b*]-indole **43** (Scheme 10; 88T2087).



Scheme 8



Scheme 9

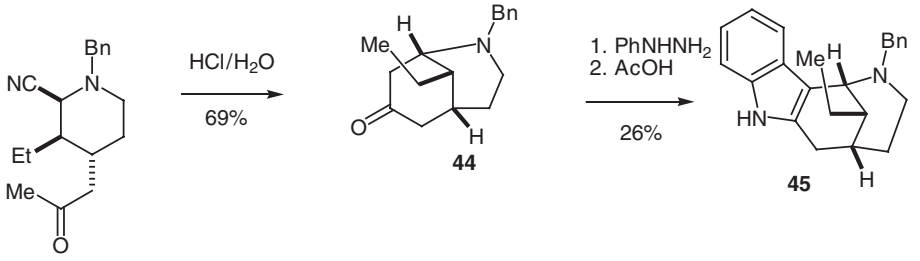


Scheme 10

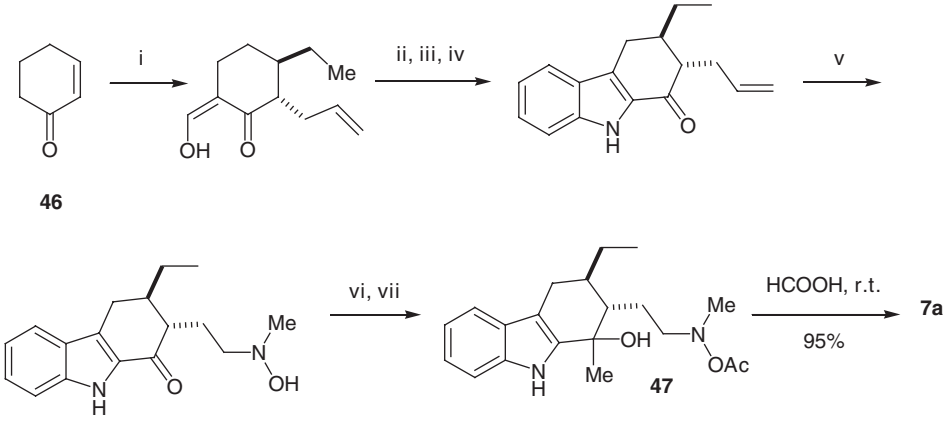
The Fischer indolization of bicycloketones of the morphane series often has been used for the synthesis of the corresponding azocinoindoles (89TL3841, 90TL2449, 92LA461). Thus, bicyclic ketone **44**, under Fischer conditions, has been transformed into azocinoindole **45** in moderate yields (94JOC3939; Scheme 11).

Blechert et al. have proposed a new effective approach to the synthesis of different indole alkaloids using cation domino reactions (95S592, 97AGE1474). The total yield of uleine (**7a**), produced on the basis of this concept, is 32%, which is quite unique in the synthesis of polycyclic indole alkaloids. Note that this is the total yield, starting from cyclohexenone **46**; the yield of the key step of the synthesis – the cyclization of carbazole **47** into **7a** is 95% (Scheme 12).

A more recent publication (96H(43)15) reports the synthesis of tetracyclic derivative azocino[4,3-*b*]indole **49** using an intramolecular aldol condensation of carbazole **48**. The possible elaboration of effective synthetic methods of the



Scheme 11



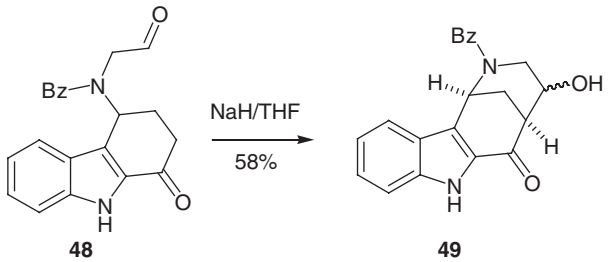
i: 1) a) EtMgBr, CuI, Me_2S, THF b) Allyl bromide, HMPTA, (yield 60%) 2)NaH, glyme, HCOOEt (yield 95%); ii: PhN_2Cl (yield 85%); iii: HCOOH (yield 86%); iv: NaOMe, MeOH, r.t, 12-14 d (yield 99%), v: 1)OsO_4, $NaIO_4$, MTBE, H_2O 2)MeNHOH, $NaCNBH_3$, *i*PrOH (yield 85%); vi: MeLi, THF, –20°C (yield 98%) ; vii: Ac_2O, pyridine, r.t. (yield 99%)

Scheme 12

starting compounds for this synthesis (00JHC11, 02JHC315) makes it appear promising (Scheme 13).

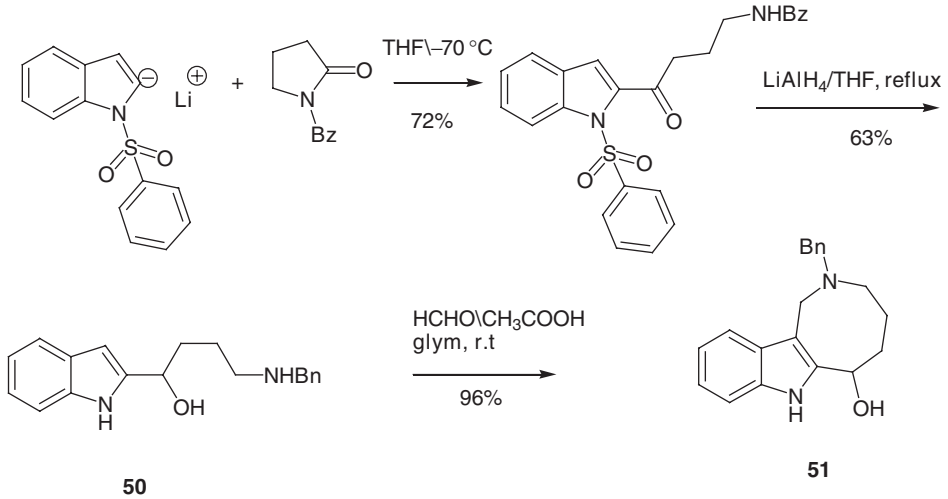
Other methods for the synthesis of indole alkaloids of the uleine type and related compounds are based on the use of 2-(1,3-dithian-2-yl)indoles (89TL6761, 93AQ(89)149, 94T6585, 95TL1693, 89H(29)2121, 96T3563), Friedel–Crafts intermolecular annulation of 2-indolylpiperidine-4-carboxylic acids (94TL7123), nucleophilic addition of indolyl-2-acetic acid esters to pyridine salts (94T5233) and intermolecular cyclization of 4-(indolylmethyl)piperidines catalyzed by mercury acetate (88H(27)2883, 85T1753). Enantiocontrolled syntheses have been used allowing optically active derivatives (97MI765, 95T10759, 00MI400, 03T1691) to be obtained. Further information can be found in the specialized paper (01MI(57)235).

In one of the few publications not directly connected with the synthesis of alkaloids, an original method for the formation of hexahydroazocino[4,3-*b*]-indoles using a Mannich intermolecular reaction of the corresponding 2-(*N*-*R*-aminobutyl)indoles **50** has been reported (Scheme 14; 87JCS(P1)1599).



48 **49**

Scheme 13



50 **51**

Scheme 14

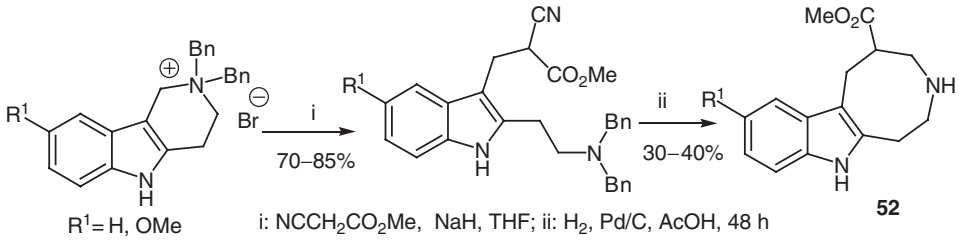
2.2.2 Synthesis of hydrogenated azocinoindoles of different couplings

In Ref. 95TL3511 the authors have suggested an ingenious method for hexahydroazocino[4,5-*b*]indoles **52** from readily available tetrahydro-γ-carbolines. In the first stage, a dibenzyl salt of the corresponding carboline is cleaved in the presence of methyl cyanoacetate and a strong base. This reaction is widely used in ''gramine'' chemistry.

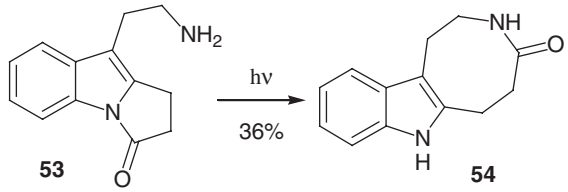
Reductive cyclization of the resulting β-cyanoethyl derivative followed by debenzylation leads to the formation of azocinoindole **52** (Scheme 15).

The preparation of azocino[5,4-*b*]indole **54** using photoisomerization of pyrrolo[1,2-*a*]indole **53** has been described (83T3657) giving the product in 36% yield (Scheme 16).

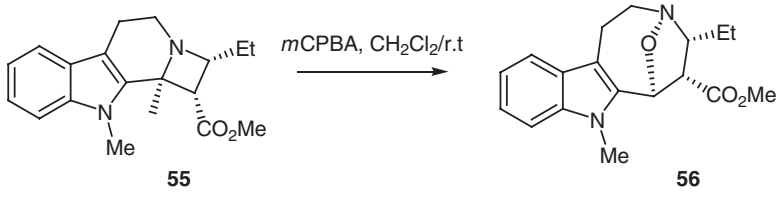
Epoxyhexahydroazocino[5,4-*b*]indole **56** (in the original paper mistakenly related to azocino[5,6-*b*]indoles) has been obtained in 60% yield by a Meisenheimer rearrangement of the N-oxide of azetopyrido[3,4-*b*]indole **55** (91CL1781; Scheme 17).



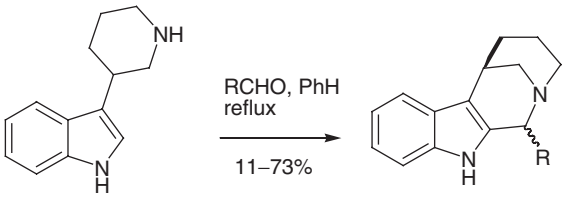
Scheme 15



Scheme 16



Scheme 17



57 58

Scheme 18

A number of azocino[3,4-*b*]indoles derivatives **58**, analogs of *β*-carbolines, have been synthesized by the Pictet–Spengler reaction using 3-piperidylindole **57** as the starting material (98TL1441, 01T2039). The products were isolated in various yields as mixtures of distereoisomers. The ratio of stereoisomers depended on the aldehyde used (Scheme 18).

2.2.3 Methods for the synthesis of azocino[4,5,6-*cd*]indoles

The first method for the preparation of tetrahydroazocino[4,5,6-*cd*]indoles was reported in 1966. In succeeding years, this reaction came to be known as the Witkop photocyclization.

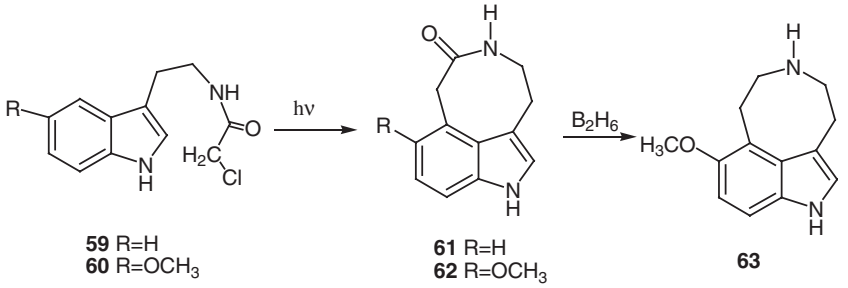
Azocino[4,5,6-*cd*]indoles **61** and **62** have been obtained from the corresponding *N*-chloroacetyl derivatives of tryptamine and melatonine with the help of photocyclization. Further, lactam **62** has been reduced to 8-methoxy-3,4,6,7-tetrahydro-1H,5H-azocino[4,5,6-*cd*]indole (**63**) under the action of B_2H_6 (69JMC(12)636; Scheme 19).

In succeeding years, the Witkop photocyclization has been widely used for the synthesis of similar compounds. For example, the dichloroacetyl derivative of tryptophane in the presence of sodium azide under the conditions of photocyclization (93JA813) produces 7-azidoazocinoindole **65** in 49% yield (Scheme 20).

The preparation of lactams **68** and **69** from the corresponding dichloramides **66** and **67** in acetonitrile under UV light in 43% and 42% yields, respectively, has been reported. But with dichloramide **67**, carried out under similar conditions in aqueous acetonitrile, in addition to the mixture of diastereoisomers of azocinoindole **70** (54%), azepinoindole **71** (25%) was also obtained (92JCS(P1)823, 92JCS(P1)797; Scheme 21).

When aqueous acetonitrile was used as solvent for the dichloroacetyl derivative of tryptophane **66** under Witkop cyclization conditions, two products were also obtained: azocino[4,5,6-*cd*]indole **68** in 16% yield and lactone **72** in 46% yield. Thereafter, in the reduction of major lactone **72** by sodium borohydride, 7-hydroxy-7-isopropylazocinoindol-4-yl-methanol **73** (42%) and a mixture of lactone diastereomers **74** in the ratio 1:1 (35%) were produced (Scheme 22).

The authors have shown that changing the hydroxyl group in the 8-position to an azide group causes transformation of the azocine ring into azocinoindole **75** under UV light. This leads to the exocyclic amine **76** and the product of azocine fragment enlargement, diazonino[4,3,2-*cd*]indole **77** (Scheme 23).

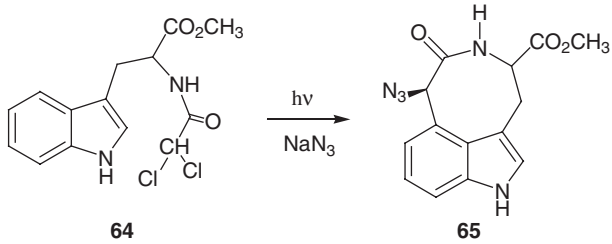


59 R=H
60 R=OCH_3

61 R=H
62 R=OCH_3

63

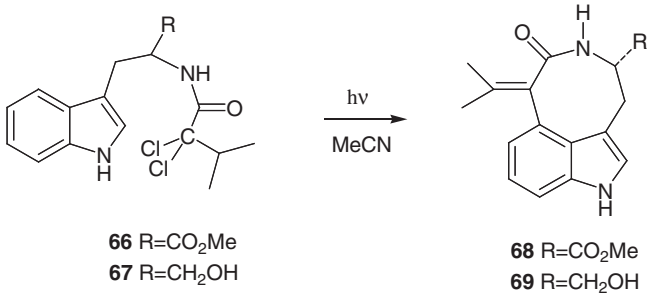
Scheme 19



64

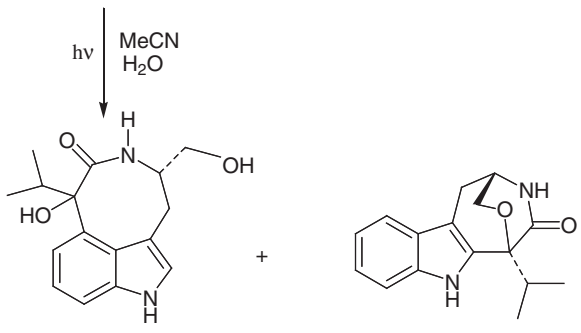
65

Scheme 20



66 R=CO_2Me
67 R=CH_2OH

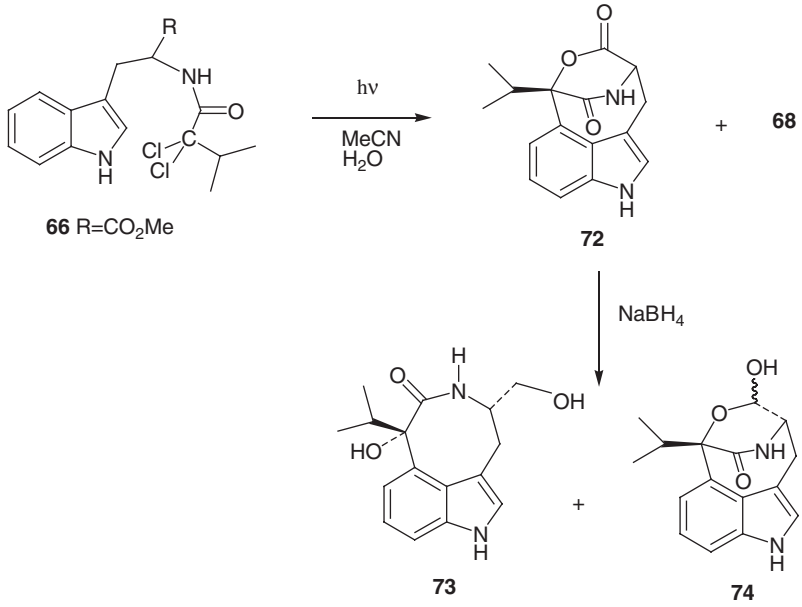
68 R=CO_2Me
69 R=CH_2OH



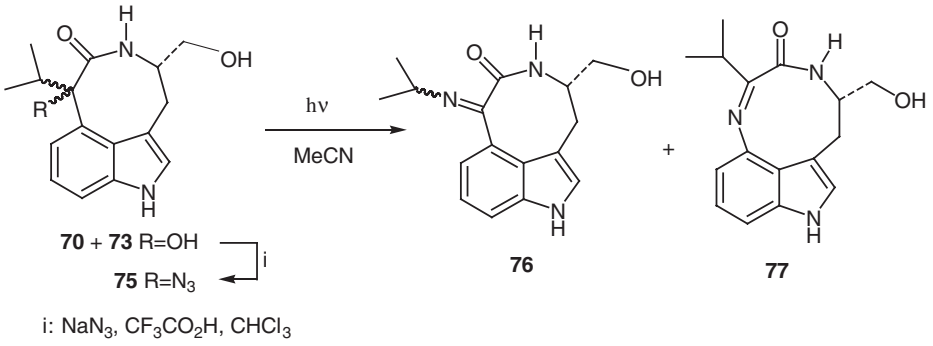
70

71

Scheme 21



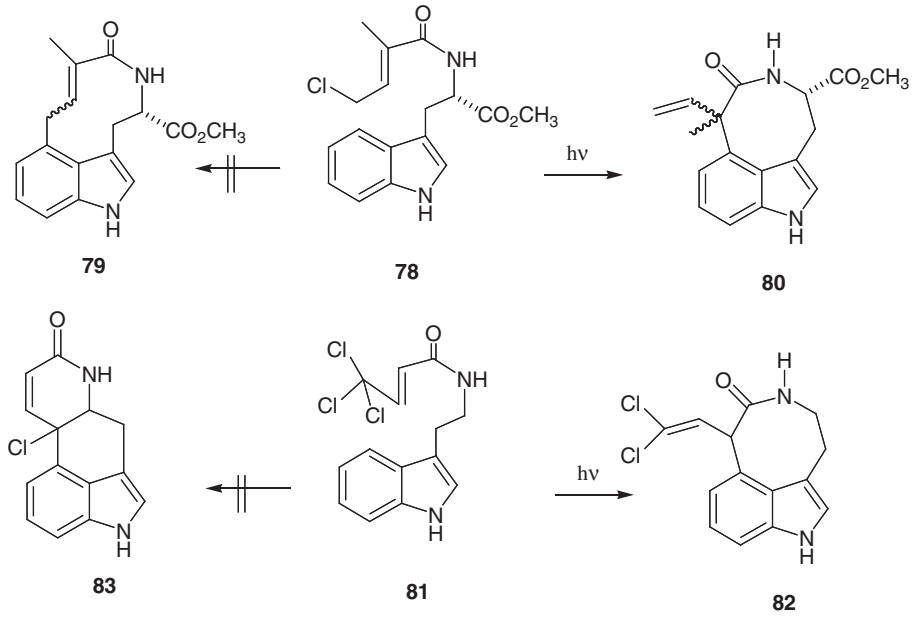
Scheme 22



Scheme 23

Anderson and Lavton in 1977 described vinyl modification of the Witkop cyclization to give azecino[4,5,6-*cd*]indole **79** from tryptophane **78**. But later it was proven that the product was, indeed, azocino[4,5,6-*cd*]indole **80** (99TL8443). The same photocyclization has been used for trichlorobutenamide **81** with the resulting formation of azocinoindole **82** instead of the expected **83** (Scheme 24).

A multi-stage synthesis of azocino[4,5,6-*cd*]indoles has been suggested (03MI3519). From 4-bromoindole (**84**) with the help of successive transformations (among them the Vilsmeier–Haack reaction, Henry nitroaldole condensation, lithium aluminum hydride reduction and insertion of an allyl fragment), indole **85** has been produced in 18% yield. The cyclization of the latter on palladium



Scheme 24

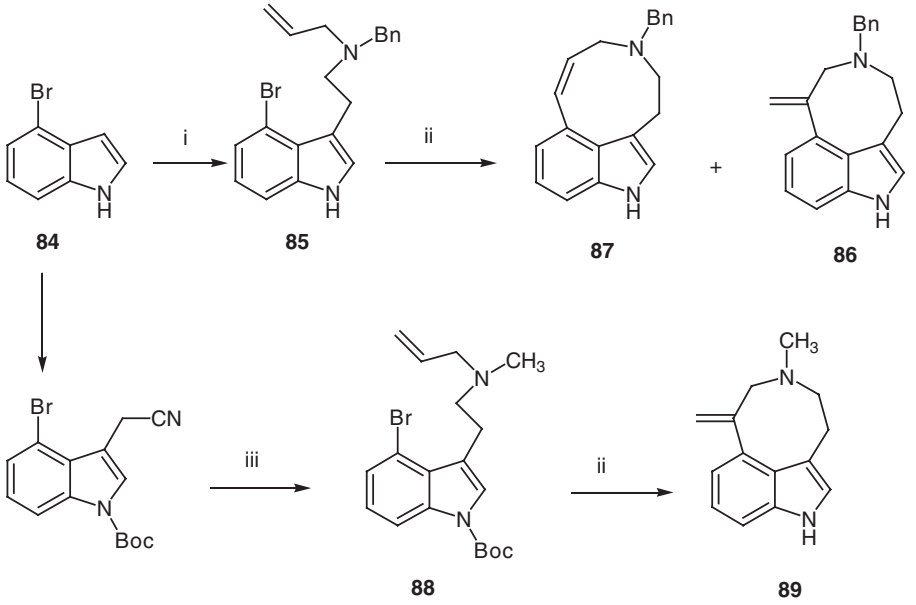
catalyst gives **86** and **87** with eight- and nine-membered rings. The alternate method, which includes cyanomethylation, *N*-Boc-protection and further reductive amination, leads to the formation of indole **88** in 28% yield, which under further cyclization produces azocinoindole **89** (30%) (Scheme 25).

2.3 Reactivity of hydrogenated azocinoindoles

One of the main reasons for investigating the reactivity of azocinoindoles is connected with the synthesis of pentacyclic indole alkaloids of the Strychnos group. In Refs. 98JOC7547, 90TL3453, 92JOC5792 and 85AQ277, *N*-(dimethylthio)ethyl and *N*-dimethoxyethyl derivatives of hexahydroazocino[4,3-*b*]indole **90**–**93** under the action of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) form pentacyclic compounds **94**. Their further reduction results in strychnine, tubopholine, tubopholidine and other analogs (Scheme 26).

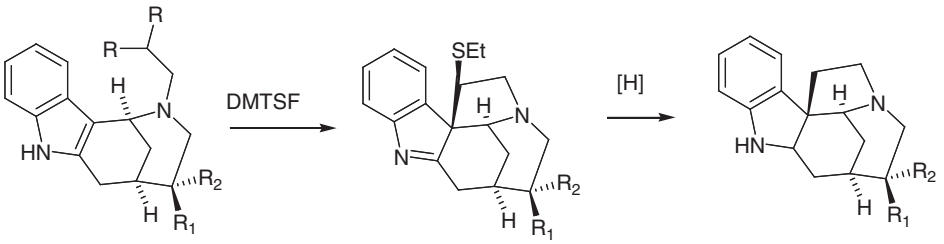
A different approach to the derivation of Strychnos-type pentacyclic alkaloids has been used (85T2557). Photocyclization of *N*-chloroacetyl derivative **99** takes place in position 4 of the indole core (but not in position 2, as expected) to form **100** (Scheme 27).

The rearrangement of hexahydroazocino[4,3-*b*]indole **101** into pyrrolo[3,2-*a*]-carbazole **102** under Wolff–Kishner reaction conditions is also described in the publication (Scheme 28; 84H(22)561). The reaction is a special case of cleavage of compounds related to gramine.



(i) $POCl_3$, DMFA; $MeNO_2$, NH_4OAc; $LiAlH_4$,THF; PhCHO, $NaBH(OAc)_3$, DCM-THF; AllylBr, MeCN.
(ii) 25 mol % $Pd(OAc)_2$, 55 mol % P(o-Tol)$_3$, NEt_3, MeCN
(iii) DIBALH, DCM; AllylNHMe, $NaBH(OAc)_3$, DCM.

Scheme 25



90 R=MeS, R_1=R_2=H
91 R=MeS, R_1=Et R_2=H
92 R=MeS, R_1=H R_2=Et
93 R=MeO, R_1=R_2=H

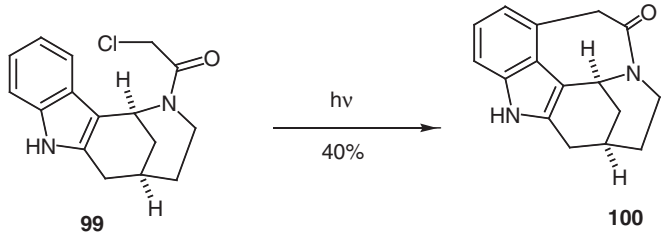
94

95 Tubofoline
96 Tubofolidine
97 19, 20-Dihydroakuamicine
98 Tubifoline

Scheme 26

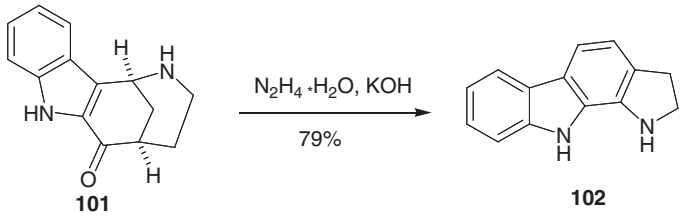
The acetate derivative of alkaloid uleine (**104**) obtained from its N-oxide **103** with acetyl chloride also undergoes cleavage by sodium borohydride, giving carbazole **105** in high yield (85LA2073; Scheme 29).

In the reduction of **7a** (83JNP206) it was shown that, on hydroboration only the expected hydroxymethyl derivative **106** is formed while the reduction in the presence of lithium aluminum hydride leads to the formation of a mixture of two derivatives **107** and **108** (Scheme 30).



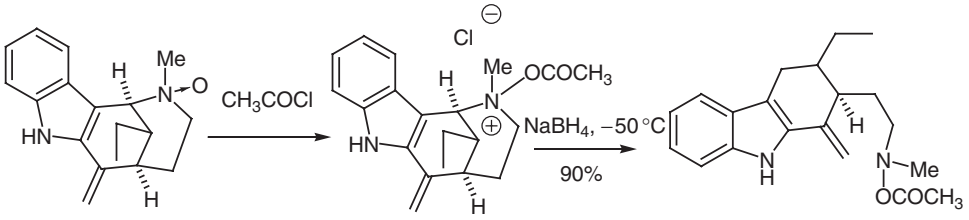
99 **100**

Scheme 27



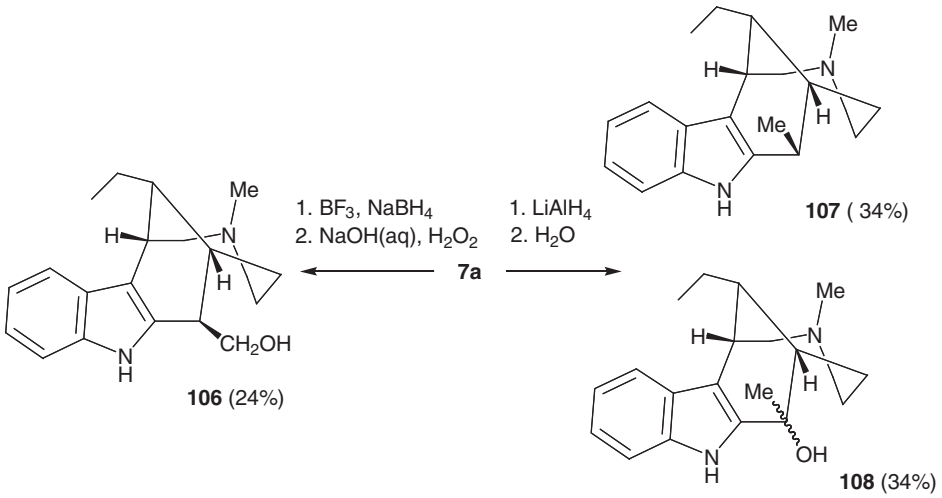
101 **102**

Scheme 28



103 **104** **105**

Scheme 29

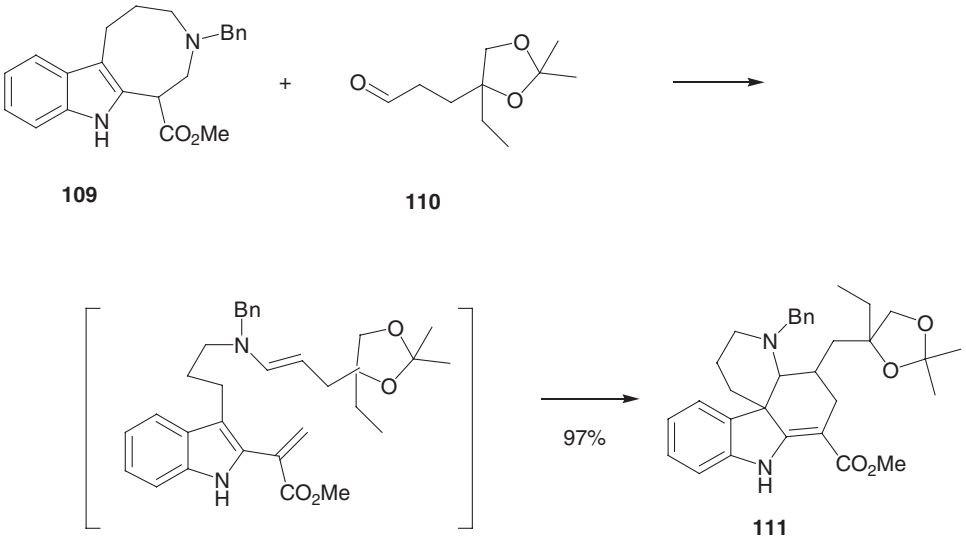


107 (34%)

106 (24%)

108 (34%)

Scheme 30



Scheme 31

In another publication by the same authors, the possible transformation of **7a** into **102** and **108** by different microorganisms was studied and confirmed (83JNP211).

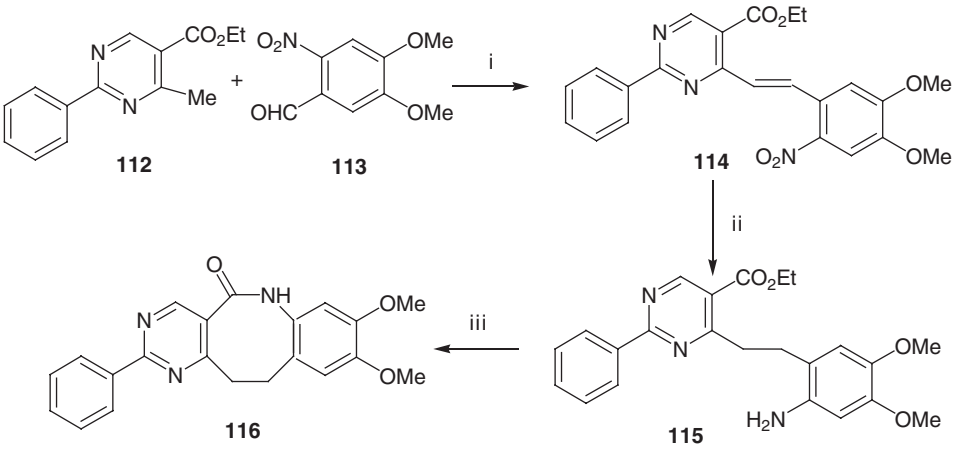
Unusual recyclizations of hexahydroazocino[4,5-*b*]indole derivatives under the action of aliphatic aldehydes have been described (01JOC5303). Thus, azocinoindole **109**, in the presence of aldehyde **110**, has been transformed into tetracyclic **111** in quantitative yield and isolated as a mixture of two diastereoisomers (Scheme 31).

The spectral characteristics of heterocycles examined in this paper are certain to be useful to chemists working in this field. Voluminous data on the NMR spectra of indole alkaloids containing the azocine fragment can be found in special publications (87MI377, 83JNP200).

3. SYNTHESIS OF PYRIMIDOAZOCINES

Only two examples of the synthesis pyrimidoazocines have been described. In Ref. 82JHC1257, a three-stage synthesis of a new heterocycle system, pyrimido[5,4-*c*]benz[1]azocine, has been proposed. Condensation of 4-methyl-2-phenyl-5-pyrimidincarboxylate (**112**) with 3,4-dimethoxy-6-nitrobenzaldehyde (**113**) led to the substituted alkene **114**, which, after catalytic hydrogenation of the nitro group on Raney nickel and subsequent intramolecular cyclization of product **115**, was converted into pyrimidobenz[1]azocine **116** (Scheme 32).

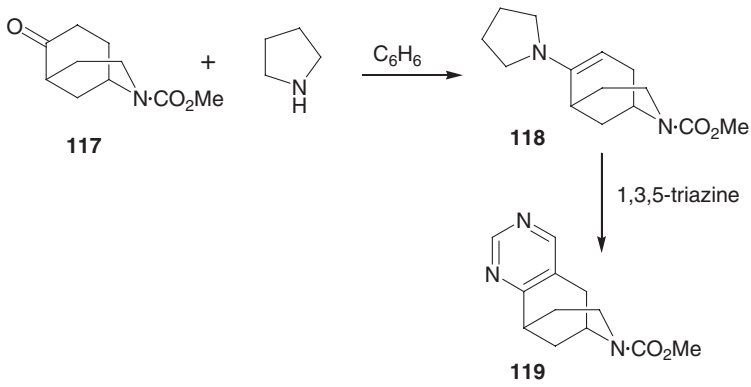
Pyrimidobenzomorphane **119**, has been obtained by [4+2] cycloaddition of enamine **118**, produced from the bicyclic ketone **117** and pyrrolidine, to 1,3,5-triazine (82TL4559; Scheme 33).



112 113 114 115 116

i: PhMe, pTSA, 44%
ii: H_2/Ni, 71%
iii: NaH, PhMe, 45%

Scheme 32

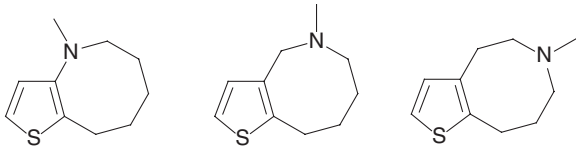


117 118 119

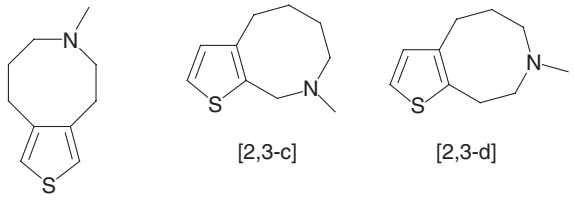
Scheme 33

4. SYNTHESIS OF HYDROGENATED THIENOAZOCINES

There are data on the synthesis of only six isomers of thienoazocines.

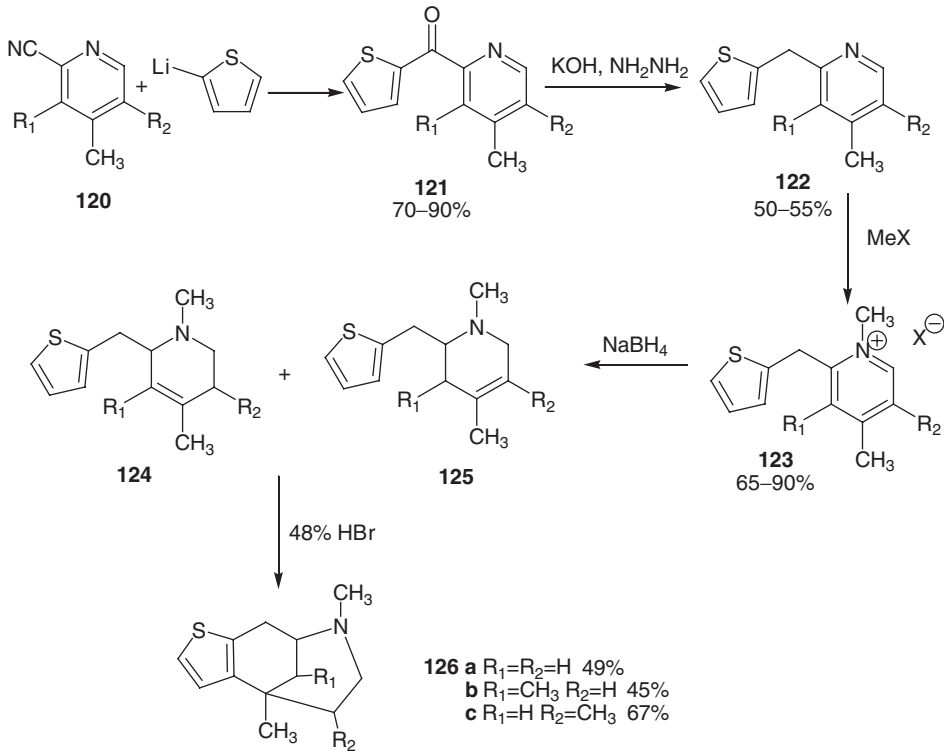


[3,2-b] [3,2-c] [3,2-d]

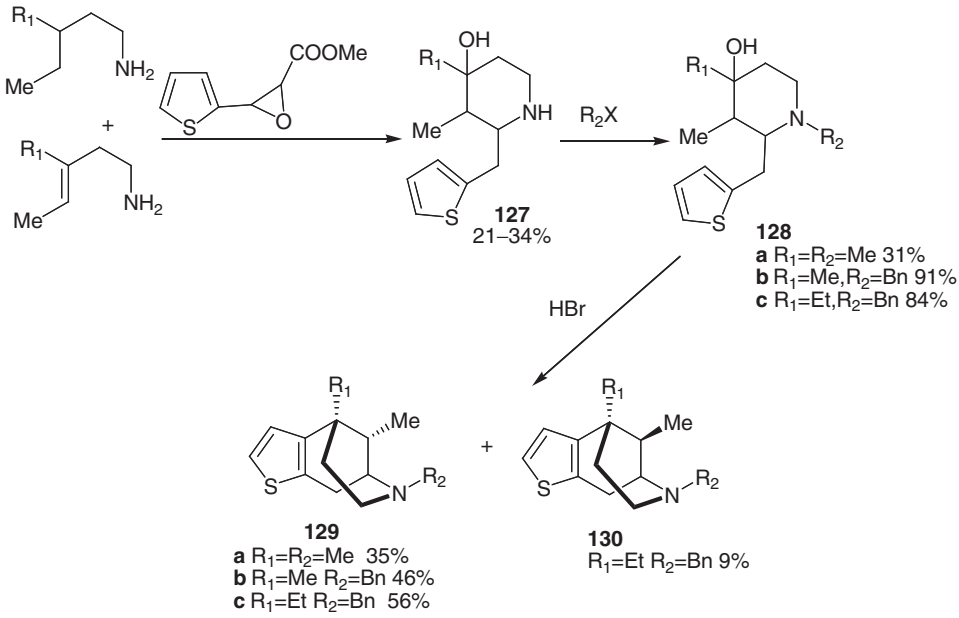


4.1 Synthesis of thieno[2,3-*d*]azocines

In recent years much attention has been paid to the synthesis of benzomorphane heteroanalogs in which a benzene ring has been replaced by a heteroaromatic one. Syntheses of substituted thieno[3,2-*f*]morphanes (derivatives of thieno[2,3-*d*]-azocine) described in Ref. 75JHC651 consists of the condensation of cyanopyridines **120** with 2-thienyllithium, reduction of the resulting ketones into thienylmethylpyridines, quaternization and reduction of the quaternary salts with sodium borohydride to form piperidines **124** and **125**. Intramolecular cyclization of the latter leads to the formation of thieno[2,3-*d*]azocines **126** (Scheme 34).



Scheme 34



Scheme 35

In (91H(32)107) the key stage of thieno[2,3-*d*]azocines **129** and **130** formation is the intramolecular cyclization of 2-thienylmethyltetrahydropyridines by HBr, resulting from dehydration of piperidols **128** (Scheme 35).

The synthesis of compound **135** (Scheme 12) includes the production of isoquinoline **132** *via* a Bischler–Napieralski reaction, its reduction and alkylation on the nitrogen atom followed by cyclization of *N*-alkyl derivatives **134** in the presence of acids (83JHC1477; Scheme 36).

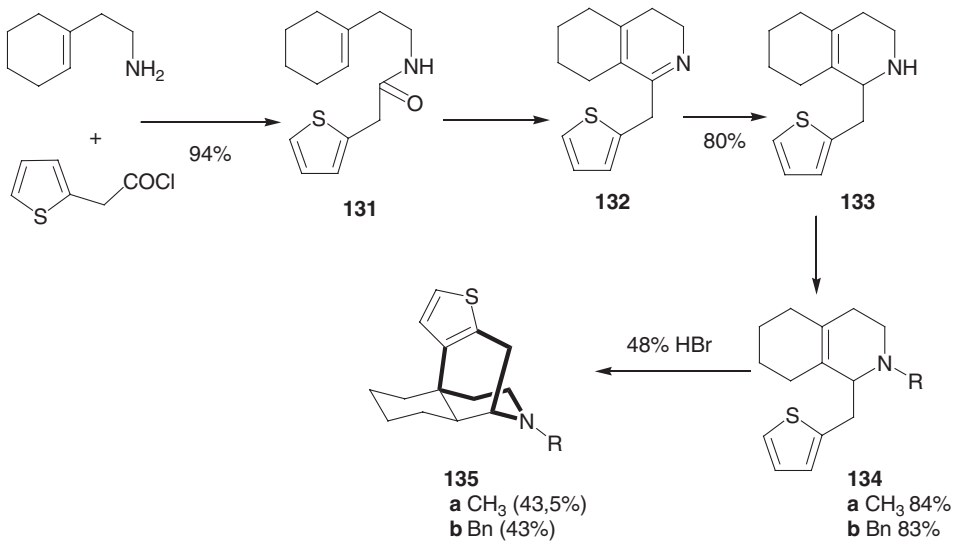
4.2 Synthesis of thieno[3,2-*d*]azocines

For the synthesis of isomeric thieno[3,2-*d*]azocines **138**, intramolecular cyclization of 2-thienyltetrahydropyridines **137** has been used (74JHC853; Scheme 37).

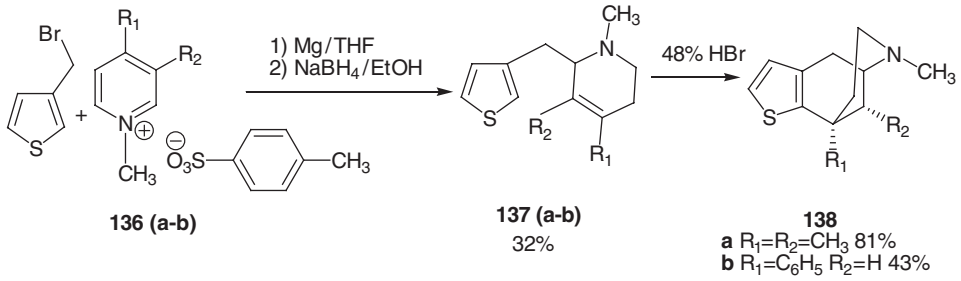
4.3 Synthesis of thieno[3,2-*b*]azocines

Esters of amino thienyldionic acids **140** served as starting compounds for the synthesis of thienoazocine **142** (76HCA104) produced in 87% yield by refluxing the hydrochloride of dicarboxylic acid **141**, first obtained by the ester **139** hydrolysis (Scheme 38).

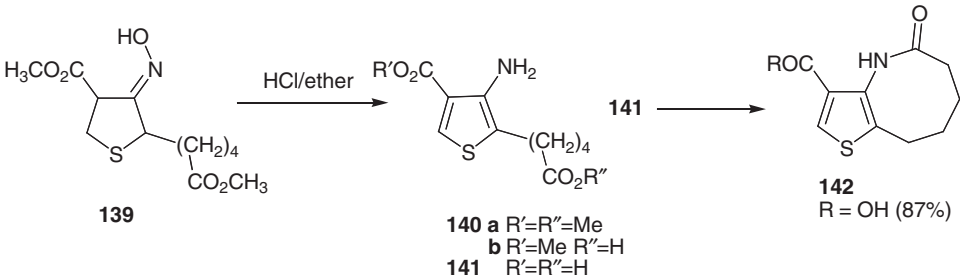
Thieno[3,2-*b*]azocines can also be produced (01JCS(P1)2774) from arylthioketene *S,N*-acetals **143** and trimethylsilyl ethers of enoles (Scheme 39).



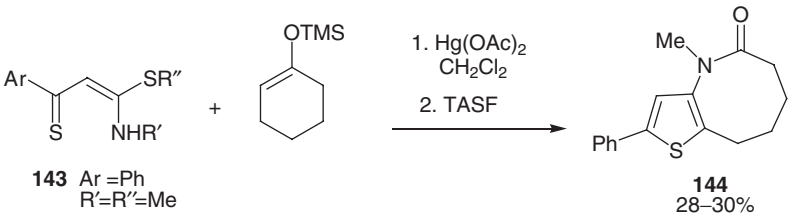
Scheme 36



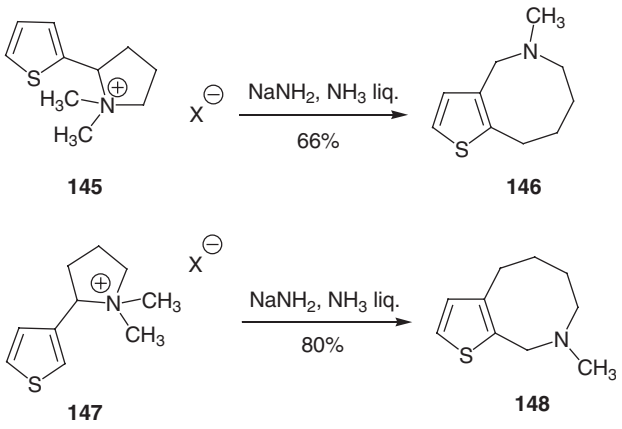
Scheme 37



Scheme 38



Scheme 39



Scheme 40

4.4 Synthesis of thienoazocines of different coupling

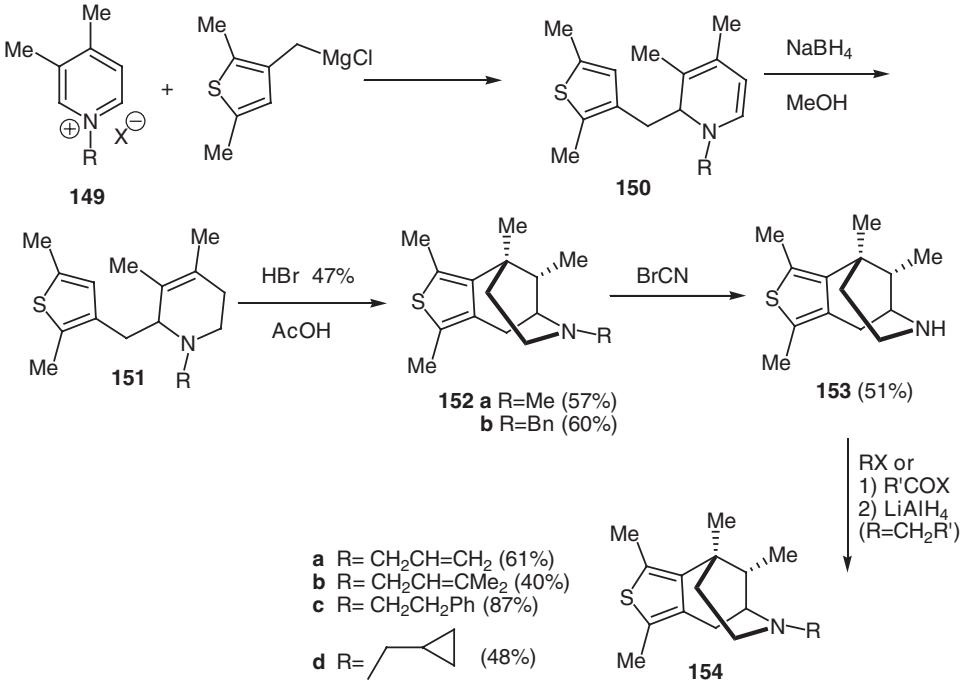
An effective method of hexahydrothieno[3,2-*c*]- and [2,3-*c*]azocines **146** and **148** syntheses involving a Sommelet–Hauser rearrangement of 1,1-dimethyl-2-(2- or 3-thienyl)pyrrolidine salts **145** and **147** under the action of $NaNH_2$ in liquid ammonia has been described (87SC935; Scheme 40).

Thieno[3,4-*d*]azocine (78JHC193) **152** is formed as a result of intramolecular cyclization of 2-thienyltetrahydropyridine **151** produced by the interaction of pyridine quaternary salts **149** and thienylmagnesiumbromide with subsequent reduction. Under the action of the cyanogenbromide thienoazocines **152** are converted into their NH derivatives **153**, subsequent alkylation allows the introduction of pharmacophoric substituents into the molecule (Scheme 41).

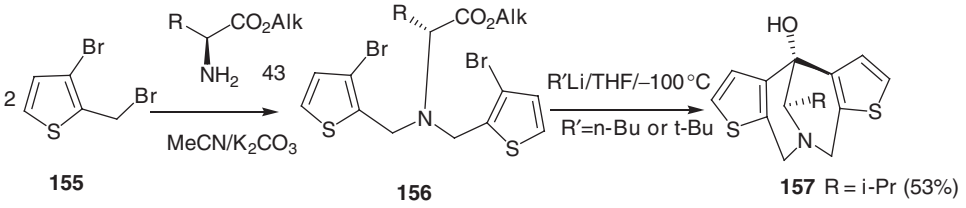
4.5 Synthesis of bisthienoazocines

The bisthieno[2,3-*c*:3′,2′-*f*]azocine **157** containing a bicyclic azocine fragment has been obtained for the first time by cyclization of *N*,*N*-bis-(thienyl-2-methyl)valine ester **156** with organolithium compounds (Scheme 42). Compound **156** has been formed by the alkylation of valine ester with thienylmethylbromide in acetonitrile in the presence of potash (98SL1355).

Maffrand (80H(14)321) has worked out the general strategy for the synthesis of bisthienoazocines with a bicyclic azocine fragment based on the



Scheme 41



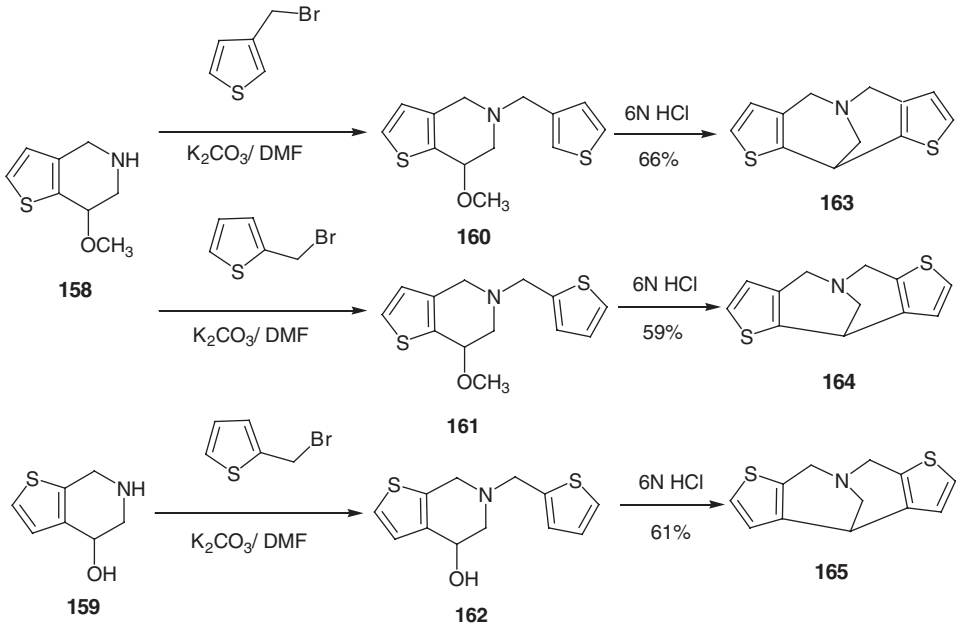
Scheme 42

thienomethylation of hydroxy- and methoxytetrahydrothieno[2,3-*c*]pyridines **158** and **159** and subsequent cyclization of *N*-thienomethyl derivatives **160–162** into azocines **163–165** (Scheme 43).

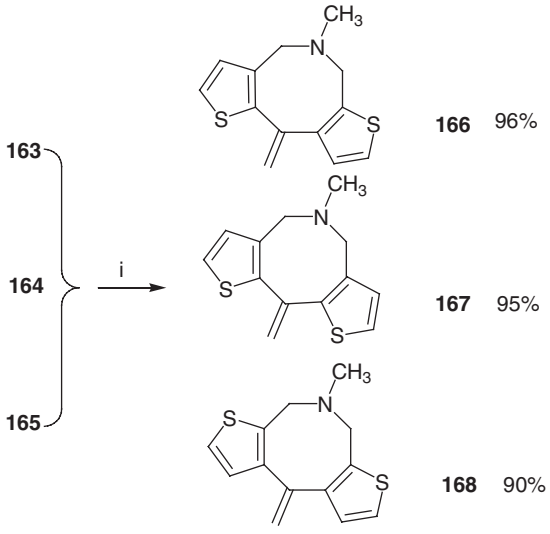
In a more recent paper (80H(14)325) quaternary salts were obtained from bisthienoazocines **163** and **164** and MeI or $(Me)_2SO_4$. Their interaction with bases under Hofmann conditions gave in all cases the corresponding vinyl derivatives **166–168** in high yields (Scheme 44).

5. SYNTHESIS OF HYDROGENATED THIENOBENZAZOCINES

One method for the synthesis of thienobenzazocines is bicyclization of *N*-thienylmethyl-*N*-arylmethylaminoethanal diethylacetal **169** with substituted aryl



Scheme 43



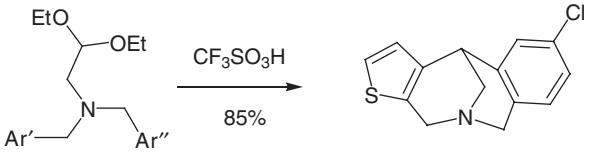
i- KOH 30%(MeOH), reflux, atm.N_2

Scheme 44

radicals in trifluoromethanesulfonic acid at room temperature. The corresponding thienobenzazocine **170** has been obtained in 85% yield (86CPB1888; Scheme 45).

The cyclization of aminoethanal acetal can be carried out in various acids. Thus, **171a–c**, produced by the alkylation of the corresponding N–H derivatives with *meta*-methoxy-substituted benzylhalides, transform into thieno[3,2-*d*][2]-benzazocines **172a–c** with 6N HCl (80H(14)321; Scheme 46).

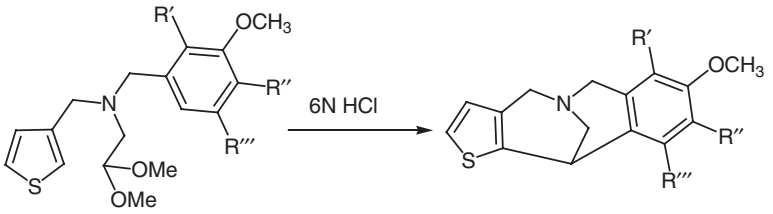
With compounds **173** and **159**, the above method gives thieno[2,3-*d*][2]benza-zocine isomer **176** (80H(14)321; Scheme 47).



169 **170**

Ar′ = 2-thienyl
Ar″ = p-Cl-Ph

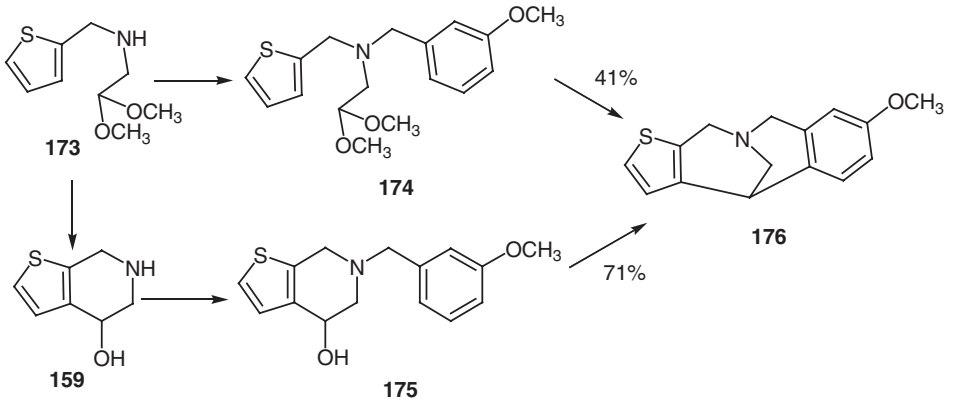
Scheme 45



172 (a-c)

171 a R′=R″=R‴=H
b R′=R‴=H R″=CH_3O
c R′=R″=CH_3O R‴=H

Scheme 46



Scheme 47

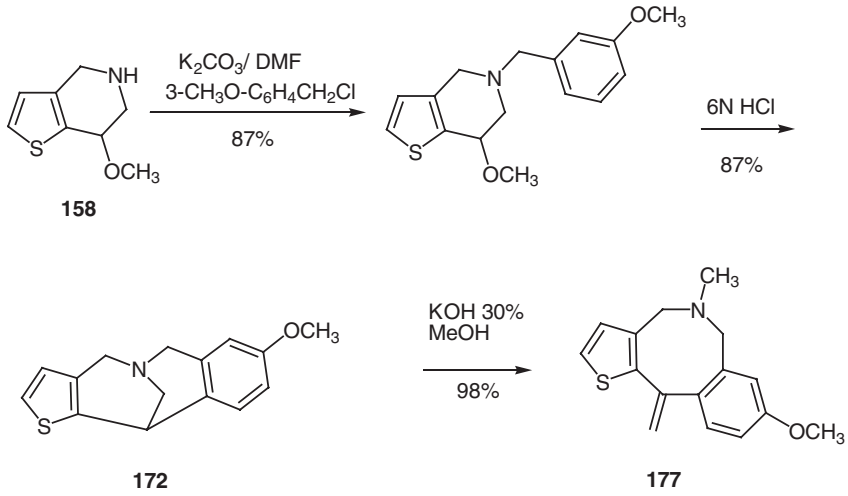
By an analogous scheme, thienobenzazocine **172** has been synthesized from methoxytetrahydrothienopyridine **158**, which undergoes further transformation into the vinyl derivative **177** under Hofmann conditions in quantitative yield (Scheme 48).

Thieno[3,2-*c*][1]benzazocines **179** and **180** have been obtained by Beckmann rearrangement of benzo[4,3]cyclohepta[1,2-*b*]thiophen-4-one oxime **178** (71HCA283; Scheme 49).

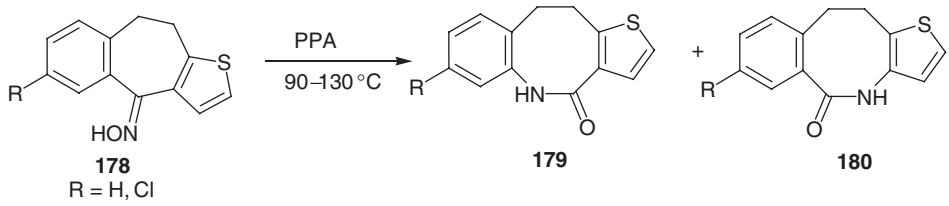
Thienobenzazocine **179** is formed regioselectively in 65–93% yield when the rearrangement is carried out in PPA or PPA in xylene. The use of H_2SO_4 or PCl_5 gives a mixture of regioisomers **179**:**180** in ratios from 90:10 to 60:40. The Schmidt reaction forms only thienobenzazocine **179** in 25–65% yield from benzo[4,3]-cyclohepta[1,2-*b*]thiophen-4-one **181** (Scheme 50).

The same thienobenzazocine **179** is produced in 65% yield when *O*-tosyloxime **182** is boiled in acetone (Scheme 50).

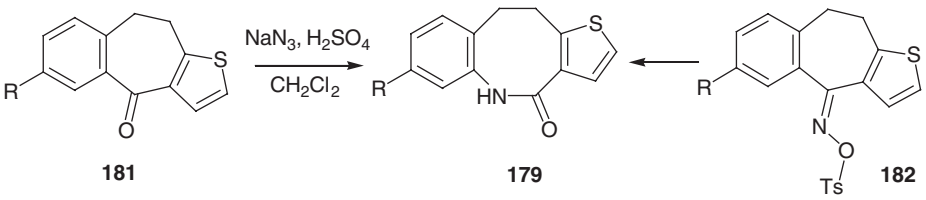
Azocine **183** can be synthesized in high yields by reduction of the carbonyl group in thienobenzazocine **179** by lithium aluminum hydride to a methylene group. *N*-Alkylation and *N*-acylation of azocines **179** and **183** carried out under



Scheme 48



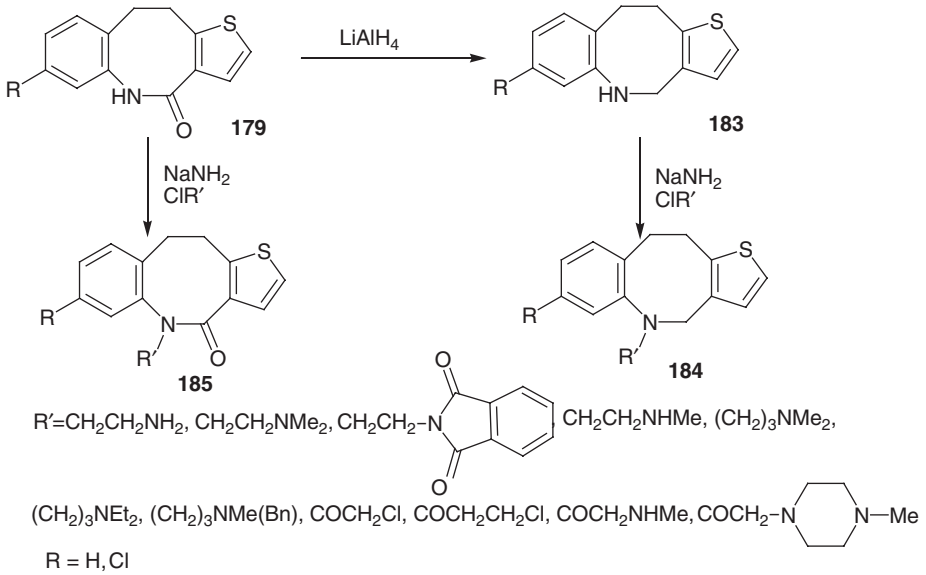
Scheme 49



181 **179** **182**

R = H, Cl

Scheme 50



179 **183** **185** **184**

R′=$CH_2CH_2NH_2$, $CH_2CH_2NMe_2$, CH_2CH_2–N(O,O), CH_2CH_2NHMe, $(CH_2)_3NMe_2$,

$(CH_2)_3NEt_2$, $(CH_2)_3NMe(Bn)$, $COCH_2Cl$, $COCH_2CH_2Cl$, $COCH_2NHMe$, $COCH_2$–N(piperazine)–N—Me

R = H, Cl

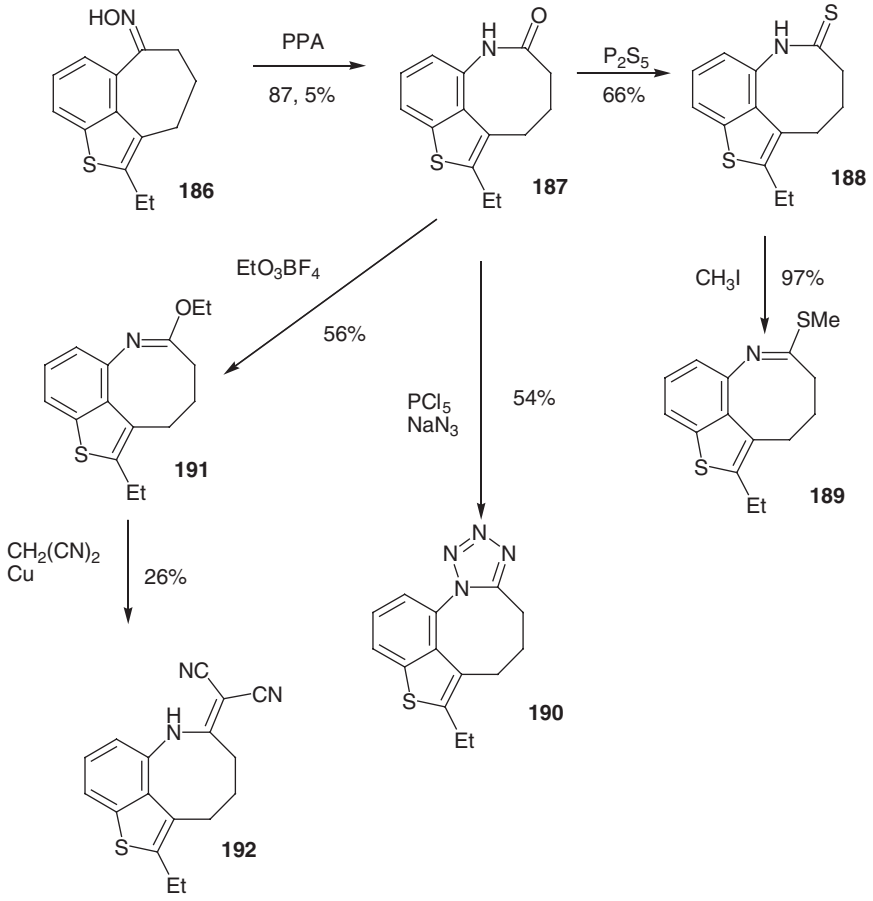
Scheme 51

the action of alkyl halides and chloroanhydrides in the presence of sodium amide, led to the formation of thienobenzazocines **184** and **185** (Scheme 51).

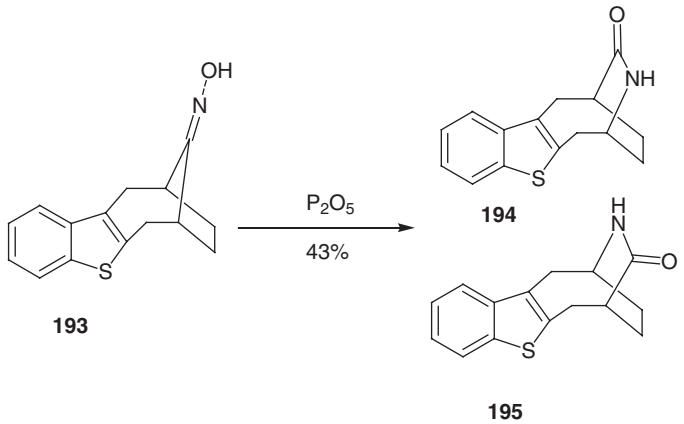
Thieno[4,3,2-*fg*]benz[1]azocine **187** is produced in high yield (79MI397) from oxime **186** by Beckman rearrangement in PPA. Transformations of amide and thioamide groups of azocines **187** and **188**, lead to derivatives **189–192**, as shown in Scheme 52.

6. SYNTHESIS OF HYDROGENATED BENZOTHIENOAZOCINES

A mixture of benzothieno[2,3-*d*]- and benzothieno[3,2-*d*]-azocines (**194** and **195**) is produced in 43% overall yield by the Beckmann rearrangement of the mixture of oxime isomers **193** with phosphorus pentoxide in dichloromethane (90JCS(P1)1083; Scheme 53).



Scheme 52



Scheme 53

7. SYNTHESIS OF FUROAZOCINES

Few publications are available on the synthesis of furoazocines.

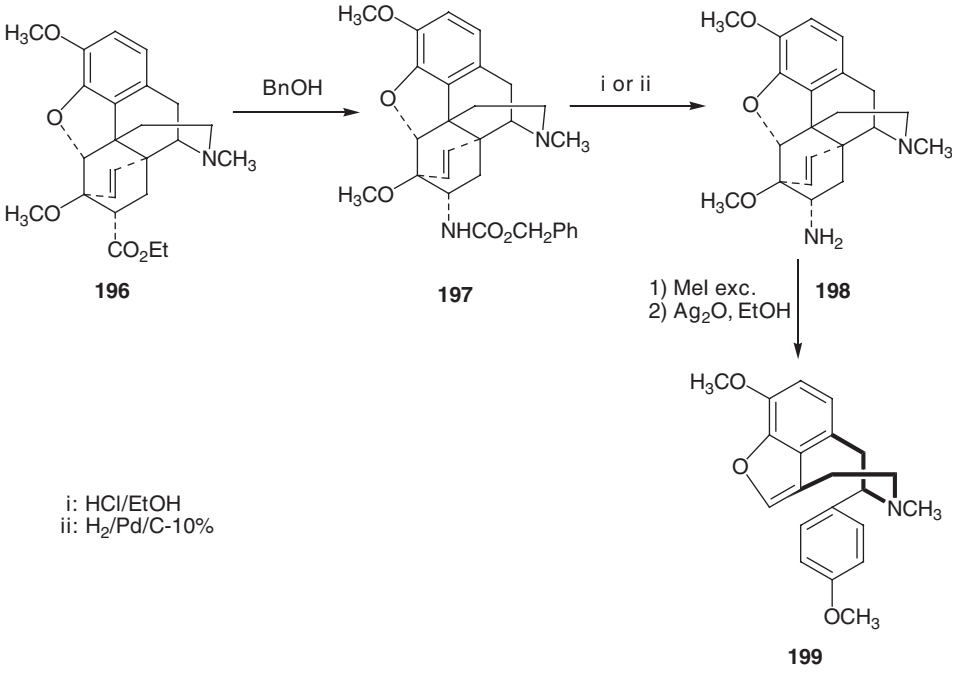
Curtius reaction of ester **196** in benzyl alcohol leads to benzylurethane **197**, which by hydrolysis and catalytic reduction gives amine **198** (72JCS(P1)878, 69JCS(C)2235). The primary amino group of compound **198** was converted into dimethylamino using the Eschweiler reaction, and then selectively quaterniz. Hofmann cleavage of this salt then leads to furo[4,3,2-*fg*]benzazocine **199** (Scheme 54).

Later reports (81JCS(P1)1969, 73JCA(CC)657) describe [3,2] sigmatropic rearrangements of bicyclic quaternary salt **200** into allene **201**, under the action of NaH in DMSO at room temperature. Allene **201** is converted into furoazocine **202** by prototropic rearrangement (Scheme 55).

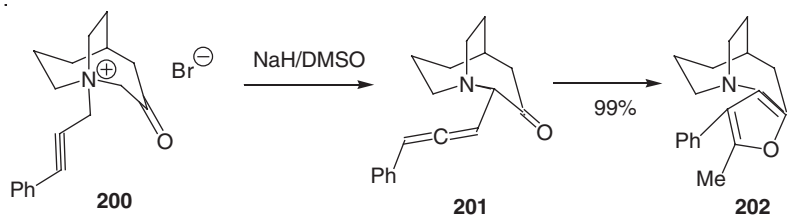
Cyclization (92ZN(B)1403) of 2-(*N*-pentenylaminopropyl)benzoquinone **203** in the presence of perchloric acid gives azocine perchlorate **204** (61%), from which azocine is isolated in 64% yield. The azocine ring closure takes place *via* nucleophilic addition of the enamine fragment to the benzoquinone ring (Scheme 56).

8. SYNTHESIS OF THIAZOLOAZOCINES

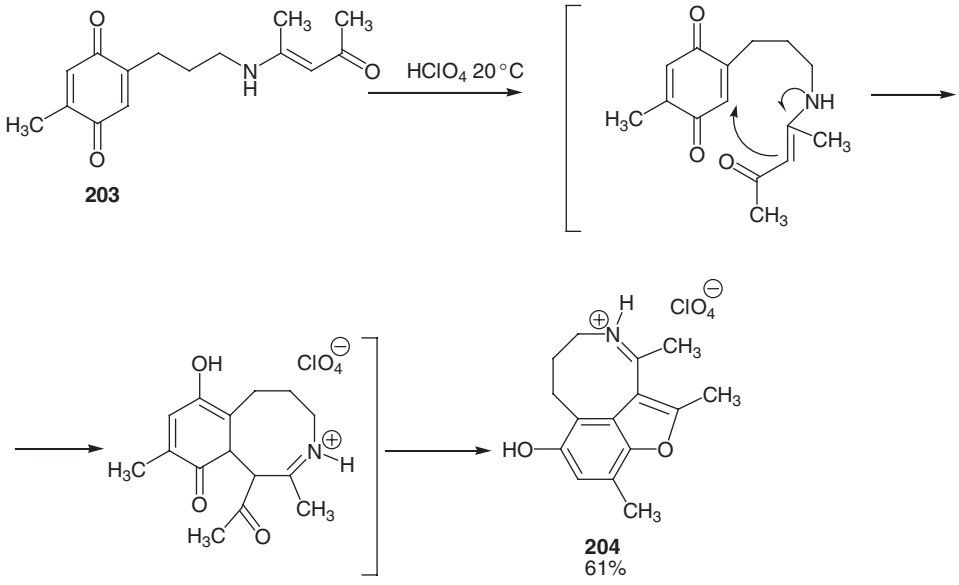
Cyclization of azocane 2-oxo-3-*p*-methoxybenzamide **205** with phosphorus pentasulfide gives thiazolo[5,4-*b*]azocine **206** (94JHC877; Scheme 57).



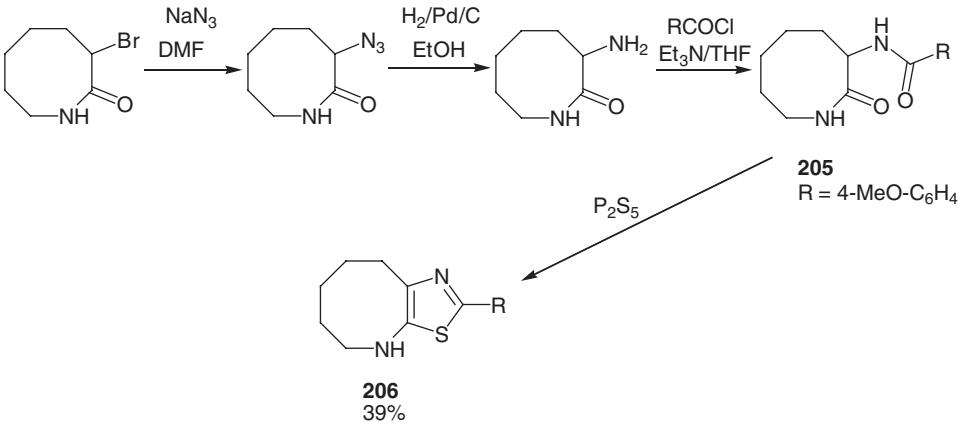
Scheme 54



Scheme 55



Scheme 56

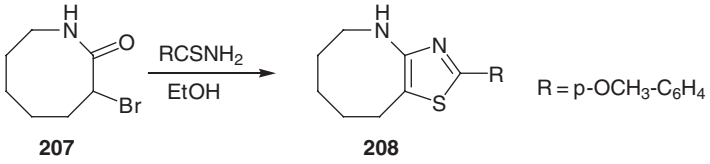


Scheme 57

Isomeric hexahydro[1,3]thiazolo[4,5-*b*]azocine **208** is formed in the reaction between 3-bromo-2-oxoazocane **207** and thioamide in ethanol (96CPB2070; Scheme 58).

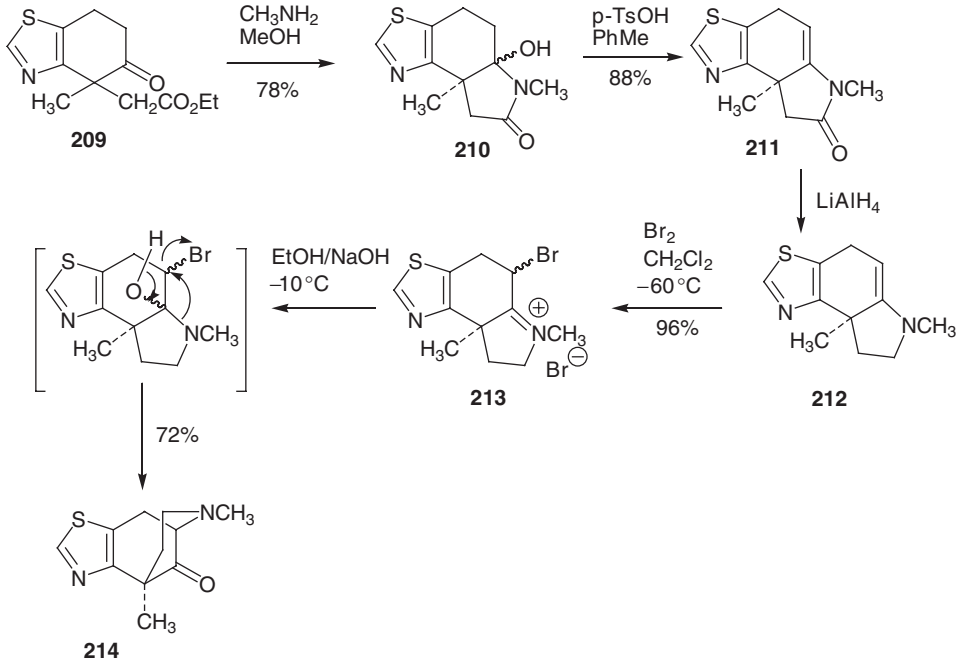
An ingenious multi-step synthesis of oxo[1,3]thiazolo[5,4-*f*]azocine **214** is based on the transformations of ethyl tetrahydro[1,3]benzothiazolyl acetate **209** (81CPB1780; Scheme 59). Under the action of methylamine, **209** cyclizes to thiazolo[4,5-*e*]indolone **210** which, through compounds **211** and **212**, converts into quaternary salt **213**. The key stage of the process is the efficient rearrangement of this salt into thiazoloazocine under the action of alcoholic base.

Wittig reaction of azocine **214** with triphenylmethylenphosphane gives methylene derivative **215**. In contrast, under Wolff–Kishner reaction conditions **214** was transformed into azocine **216a**. Catalytic hydrogenation of the methylene



207 **208**

Scheme 58



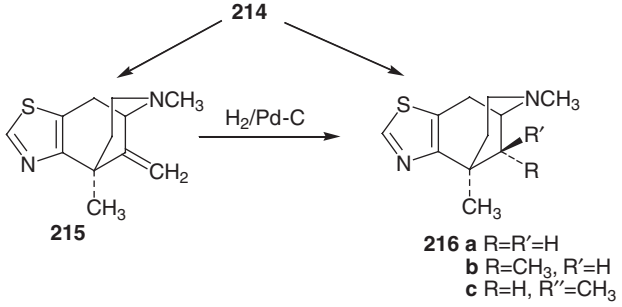
209 **210** **211** **212** **213** **214**

Scheme 59

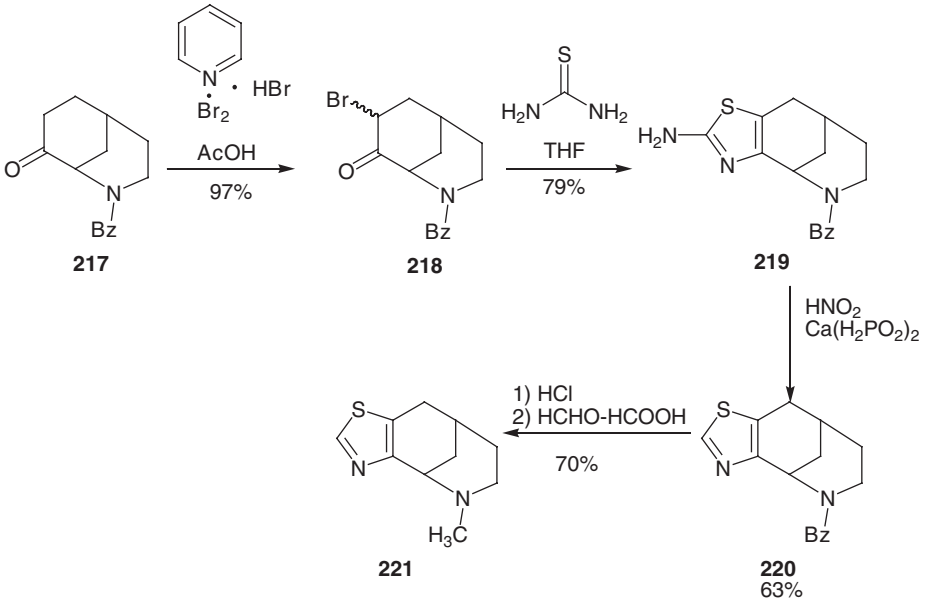
group of compound **215** leads to a mixture of thiazolo[5,4-*d*]azocines **216b,c** isomers in 75% yield (82CPB4378; Scheme 60).

2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-one (**217**) has been used for the synthesis of isomeric thiazolo[4,5-*c*]azocine **221** (83CPB2094). Bromination of **217** in the α-position by pyridinium dibromide hydrobromide and condensation of bromoketone **218** with thiourea leads to aminothiazoloazocine **219**. Successive deamination of **219**, the removal of *N*-benzoyl protection and methylation gives the target azocine **221** (Scheme 61).

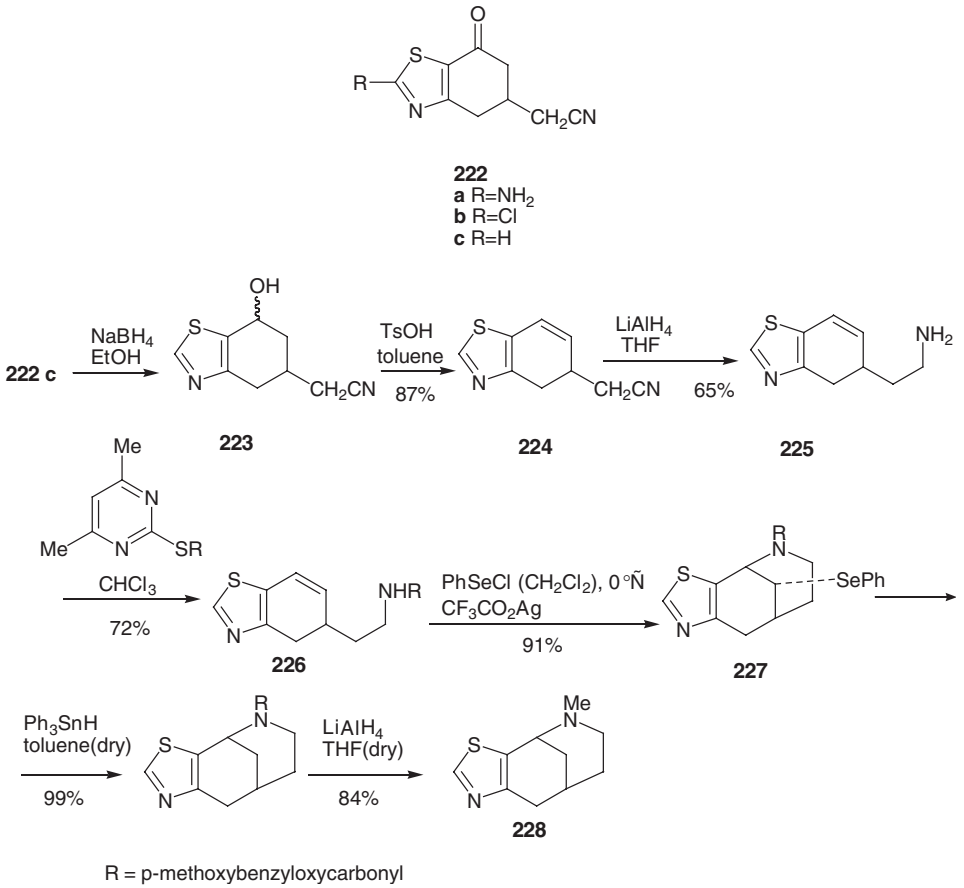
[1,3]Thiazolo[5,4-*c*]azocine **228** was synthesized from **222** (Scheme 62). The process includes reduction of the carbonyl group of **222**, dehydration of the alcohol **223** formed, reduction of the nitrile group, followed by the protection of



Scheme 60



Scheme 61

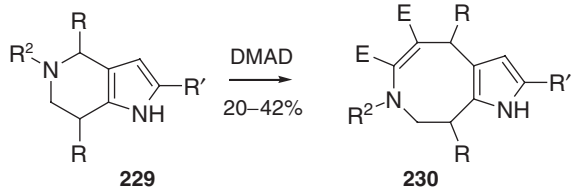


Scheme 62

the resulting amino group. *N*-Aryl-substituted dihydrobenzothiazole **226** is cyclized into thiazoloazocine **227** by benzeneselenenyl chloride. Successive deselenization of azocine **227** and reduction of the benzyloxycarbonyl group yield the target [1,3]thiazolo[5,4-*c*]azocine **228**.

9. TANDEM ENLARGEMENT OF THE SIX-MEMBERED RING IN HETEROANNULATED TETRAHYDROPYRIDINES UNDER THE ACTION OF ACTIVATED ALKYNES – A GENERAL METHOD FOR THE SYNTHESIS OF CONDENSED AZOCINES

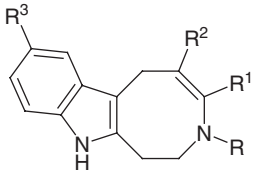
Tetrahydropyrrolo[3,2-*c*]pyridines **229** undergo enlargement of the six-membered ring by dimethylacetylene dicarboxylate (DMAD) in acetonitrile, yielding pyrrolo[2,3-*d*]azocines in moderate yield (02TL6767; Scheme 63).



229 **230**

R=Me or H, R′=H, $COCF_3$, CHO, R_2=Me or Bn, E=COOMe

Scheme 63



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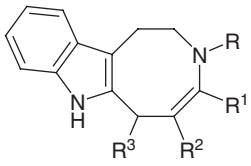

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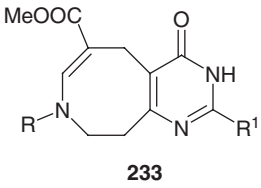

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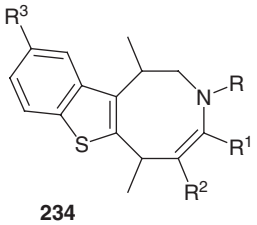

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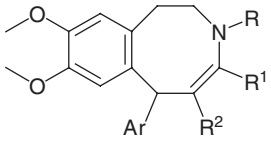


235

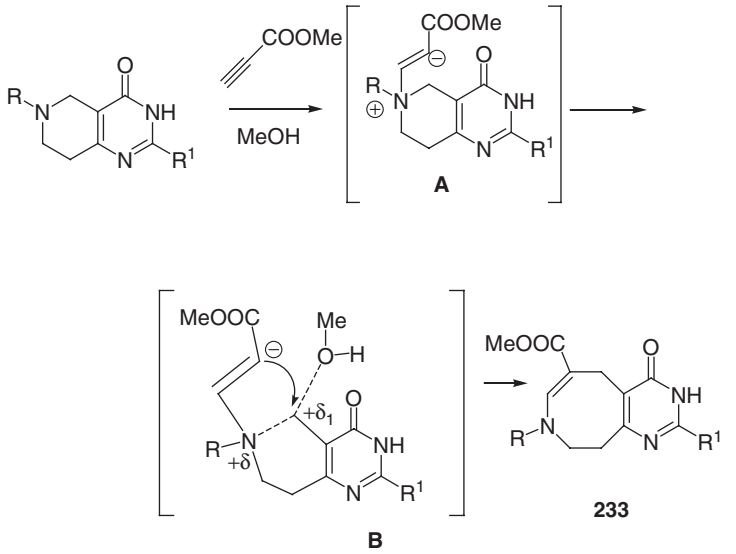
Scheme 64

This reaction was later used successfully for the synthesis of annulated azocines including tetrahydroazocino[4,5-*b*] **231** – and azocino[5,4-*b*]indoles **232** (04EJO(14)3128), tetrahydropyrimido[4,5-*d*]azocines **233** (06TL999), tetrahydrobenzo[*b*]thieno[3,2-*d*]azocines **234** (05CH944) and tetrahydrobenzo[*d*]azocines **235** (06TL4585; Scheme 64).

A plausible mechanism for the ring expansion (Scheme 65) proceeds *via* an intermediate zwitterion **A**, resulting from Michael addition of the tertiary nitrogen to the alkyne. Cleavage of the C(1)–N bond occurs *via* formation of the six-membered transition state **B** in which a molecule of alcohol facilitates the S_N reaction.

Some azocine derivatives, synthesized *via* this protocol, exhibited acetylcholinesterase (AChE) inhibitory activity (06MI7205).

Thus, hydrogenated heteroannulated azocines, while relatively little known, are of interest for potential biological activity and their synthesis has attracted attention.



Scheme 65

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CHAPTER 3

Metallacalixarenes: Organo-Inorganic Hybrid Molecular Architectures

Subodh Kumar, Navneet Kaur and **Harjit Singh**

Contents

1. INTRODUCTION

The application of the concept of molecular recognition, the cornerstone of biological operations invoking biomolecular interactions, when extended into the realm of design of abiotic receptors of synthetic origin provides molecular architectures of functional materials having catalyzing, sensing, conducting, stabilizing, transporting, etc. abilities (95MI1). Among three generations of synthetic receptors, calix[n]arenes **1**, a category of *m*-cyclophanes elaborating a cyclic array of aromatic phenolic rings joined at 1,3- positions by methylene bridges are marked for their ability to undergo structural diversifications and thereby display versatile binding characters. This uniqueness is characterized

Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

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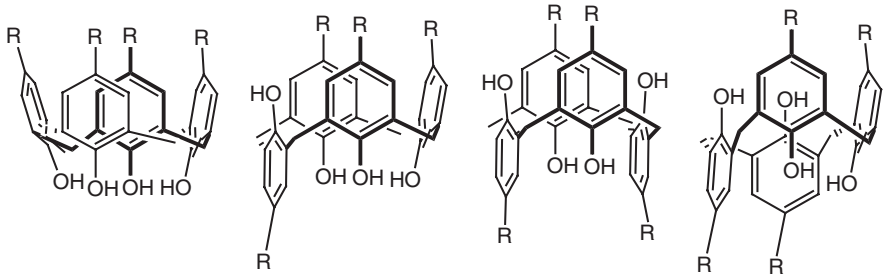
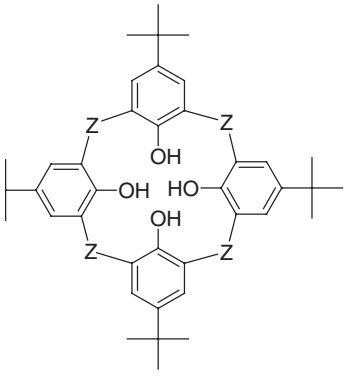


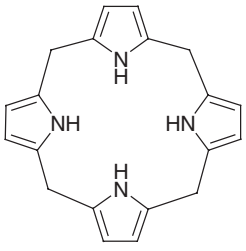
Figure 1 Conformations of calixarenes.

by: (i) a core of aromatic rings (π-electron rich cavity) providing π-cation, π–π, CH…π, etc. interactions, (ii) derivatization at rims generating varied possibilities of receptor designs capable of crown-type bindings, and (iii) tunability of the cavity with respect to its size ($n = 4, 5, 6,\ldots$), depth, and conformation such as a cone, partial cone, and 1,2-/1,3- alternate geometry (Figure 1, 98MI1). The replacement of phenolic unit(s) of calix[n]arenes by heterocyclic ring(s) constituting heterocalixarenes (e.g., **2** calix[4]pyrrole), further adds to their molecular recognition potential by enhancing an electron-rich (pyrrole) or imparting an electron-deficient (pyridine) cavity of π-electron character which can further be tuned by substitution and ring transformation reactions of the heterocyclic rings and by the influence of the heteroatom(s) (2005AHC67).

The replacement of methylene bridges of a calix[n]arene by heteroatom(s) and of appropriate heterocalixarene by metal species provides, respectively, heteracalix[n] arene (e.g. **3** thiacalix[4]arene) (2004JOC1675) and metallacalixarene **4** ($[Pt(en)UH\text{-}N1,N3]_4^{4+}$; UH = uracil monoanion and en = 1,2-diaminoethane) (2001CCR219). The latter constitutes a self-assembled product of the monomeric complex *cis*[(en)Pt(H_2O) (UH-*N1,N3*)]. Hence in the nomenclature 'metallacalixarene', it is presumed that for binding with a metallic specie, the organic linker would always be an appropriate heterocyclic ring and a metallacalixarene system would be a metal analog of a heterocalixarene.



1 Z = CH_2
3 Z = S



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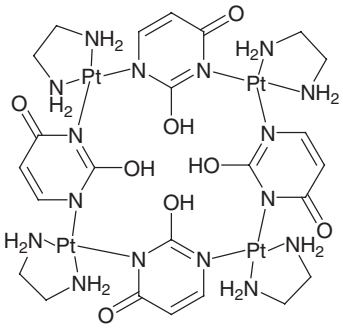


4

Structurally, metallacalixarenes constitute organo-inorganic hybrids where heterocyclic organic species with appropriately oriented donor nitrogens are linked in a self-assembled manner with inorganic metallic species to form functional entities which being positively charged can show anion-sensing ability. The presence of heterocyclic moieties and other functionalities (=O, OH, NHR etc.) can induce interactions with additional metal ions. Due to the presence of metal ions, these materials can possess magnetic, optical, catalytic, and structural properties intrinsic to the metal ions and the rigid voids enable the reversible absorption of gases such as nitrogen and ammonia (2001JA383, 2003POL3051). Moreover, as in heterocalixarenes, changes in organic linkers in metallacalixarenes, can induce a varied flexibility (geometry) and nuclearity (tri-, tetra-, hexameric etc.) influencing their interactive capability. Evidently, these structural features empower metallacalixarenes to provide a category of synthetic receptors which holds unique promise in the creation of newer functional materials.

In the comprehensive review on metallacalixarenes (2001CCR219, 99CCR653, 2005JSSC2436, 2002CCR199, 2003OM2166), in the absence of any rigorous nomenclature such as that in calixarenes (98MI1), the metallacalixarenes have been represented as their molecular units with an inbuilt provision for abbreviated heterocyclic component(s) with binding sites. Thus, the representation of **4** above indicates that four (en)Pt^{II} linkers are joined to four uracil moieties at their 1,3 positions to form the cyclic tetramer. For forming metallacalixarenes, 1,3-heterocycles having at least two angularly disposed ligating nitrogens (Figure 2) are employed and a prominent use has been made of nucleobases such as uracil, adenine, guanine, hypoxanthine etc. The model heterocycles 2,2′-bipyrazine and 4,7-phenanthroline having similar inbuilt angular ligating character have also been used. Thus metallacalixarenes derived from nucleobases and model heterocycles are categorized accordingly and discussed in separate sections. The presentation has also been titled and subtitled with respect to the various heterocyclic and/or metal component(s) used and the synthesis, structures, and binding characters of various metallacalixarenes formed from them have been elaborated.

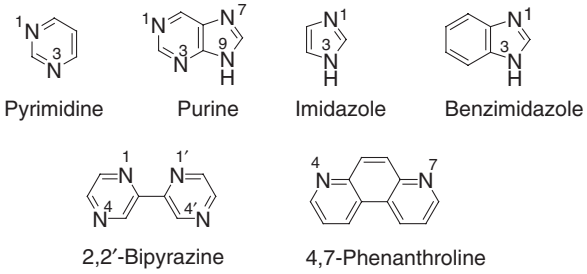


Figure 2 Structures of parent heterocyclic molecules used for elaborating metallacalixarenes.

2. METALLACALIXARENES DERIVED FROM NUCLEOBASES

2.1 General

Nucleobases have pyrimidine and purine (a combination of pyrimidine and imidazole) heterocyclic nuclei which have two ligating nitrogens placed in angular directions. The angular dispositions of pyrimidine, imidazole, and 1,7-purine nitrogens respectively being 120°, 150°, and 90° impart to these bases, heteroatom-induced endocyclic donor ability towards metals which drive self-assembly processes to form macrocyclic systems. The metallacalixarenes formed from nucleobases and various metal salts are discussed with respect to each base.

2.2 Metallacalixarenes based on pyrimidine nucleobases

Uracil based 'Pt Blues', *cis*-[(en)PtCl(UH-*N1*)] formed from (en)$PtCl_2$ and uracil (UH_2), on reaction with aqueous silver nitrate (81IC4326) gave [(en)Pt(UH-*N1*)H_2O]$^+$ which tetramerized to cyclic complex [(en)Pt(UH-*N1*,*N3*)]$_4^{4+}$ (**5**) and crystallized as its nitrate salt (92JCS(CC)1385, 94JA616). Though similar Pt^{II}, Pd^{II} based cyclic products derived from the nucleobases guanine (92JA10647, 89IC2067) and theophyline (88AGE1160) were already reported, a clear-cut analogy of such a self-assembled chemical entity with a classical calixarene was drawn by Lippert for the first time. He assigned these systems the nomenclature 'metallacalixarenes' (92JCS(CC)1385, 94JA616). This contribution has focused attention and visibility on this category of organo-inorganic hybrid receptor systems in which the metal-binding endocyclic sites are invariably nitrogens preferably *meta* oriented.

The abbreviation of a parent species shows the number of ionizable protons on nitrogen. On protonation or deprotonation the same abbreviation with increase or decrease in number of protons is given (Figure 3).

The tetranuclear product **5** in its X-ray structure depicts a 1,3-alternating arrangement in which oppositely placed uracil pairs have identical orientation with their O(2) groups on the same side. The hydrogen bonds between O(2)–O(4) of adjacent uracil units impart stability to this arrangement. In its crystals, tetranuclear cations are stacked producing a long channel and nitrate anions connect the cations *via* H-bonds involving NH_2 of (en). In solution **5** through rotation around a Pt–N bond by the uracil moiety through the annulus, achieves cone conformation **6** (^{1}H NMR, X-ray). This phenomenon is influenced both by

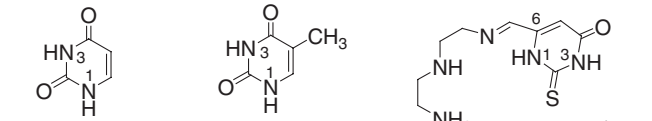


Figure 3 Structures of the pyrimidine nucleobases used in elaborating metallacalixarenes.

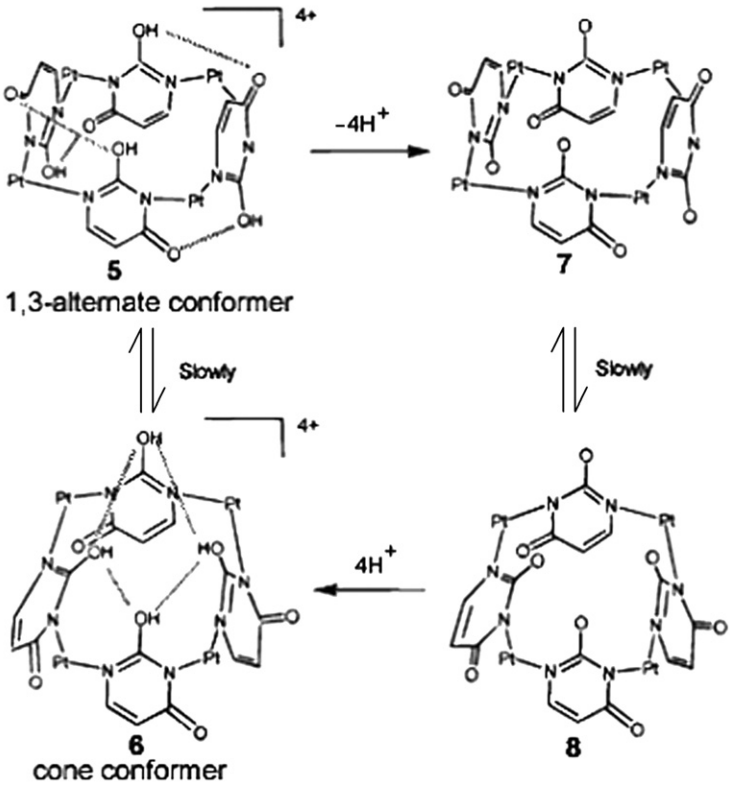


Figure 4 Effect of pH on conformational changes between **5** and **6**.

the pH and the presence of additional metal ions (Figure 4). In aqueous NaOH at pH 8, **5** forms its freely water-soluble alkali adduct **7** which on heating at 40 °C is partially (66%) converted to cone conformation **8**. This equilibrium is dependent on the nature of the base employed. Using $Mg(OD)_2$ 100% conversion to cone conformer **8** is observed. The adduct **8** on acidification affords **6** (cone conformation of **5**) where its four C(2)–OH units act as proton donors and acceptors as in classical calixarenes.

Despite its four-fold positive charge, metallacalixarenes **5** and **6** exhibit high basicity of the exocyclic O and react with metal cations in various stoichiometries depending on the nature of the metal ion and the original conformation of the metallacalixarene. 1,3-Alternate conformer **5** coordinates to four additional divalent metal ions to give octanuclear $[(en)Pt(U\text{-}N1,N3,O2,O4)CuCl(H_2O)_2]_4Cl_4$ (**9**) and $[(en)Pt(U\text{-}N1,N3,O2,O4)M(H_2O)_3]_4(SO_4)_4$ (**10**) (Figure 5) (M = **a**, Ni; **b**, Cu; **c**, Co; **d**, Zn) (97AGE1296, 2000EJI147). The X-ray structures of **9**, **10b**, and **10d** show that the 1,3-alternate conformation of **5** is retained in the octanuclear complexes. In each one of these complexes, the uracil ring binds with four metal centers and carries Pt^{II} at N(1), N(3) and M at O(2), O(4) of two adjacent dianionic moieties. The uracil rings at opposite side are not exactly parallel. The spatial disposition of the four heterometals in the molecular box is 1,3-alternate, with a

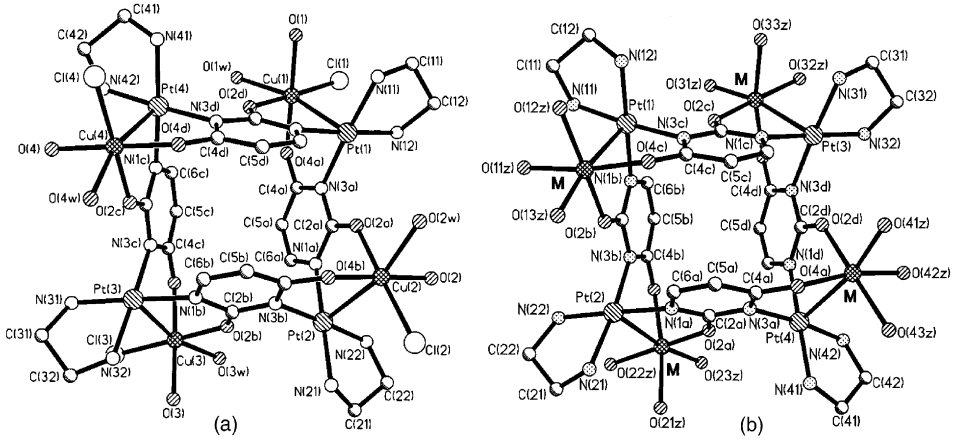


Figure 5 X-ray crystal structures of (a) [(en)Pt(U-*N1,N3,O2,O4*)CuCl$(H_2O)_2]_4Cl_4$ (**9**) and (b) [(en)Pt(U-*N1,N3,O2,O4*) M$(H_2O)_3]_4(SO_4)_4$ (**10**) (M = Cu^{II}, Zn^{II}). (Reprinted with permission from 2000EJI147, Copyright 2000, Wiley.)

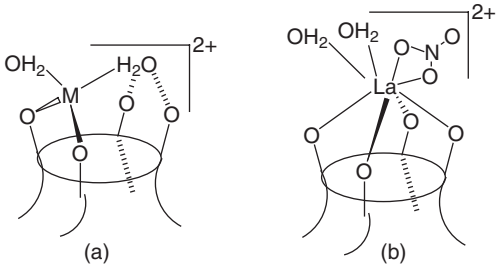


Figure 6 Schematic presentation of cone conformers of (a) **12** and (b) **13**.

displacement of ~1.9 Å from the plane defined by the four platinum centers. Similarly, 1,3-alternate conformer **5** with *cis*-$Pt^{II}(NH_3)_2$ and (en)Pt^{II} salts undergoes deprotonation of UH moieties to form $[(en)PtUPt(en)/(NH_3)_2]_4^{8+}$ which in the presence of an excess of NaCl or NaCN lose Pt units bound to O(4) and O(2). Despite the high thermodynamic stability of free $[Pt(CN)_4]^{2-}$, the platinum units bound to N(1) and (N3) are not dissociated.

In the presence of excess $AgNO_3$, **5** forms an octanuclear complex $[(en)Pt(UH)Ag]_4(NO_3)_8 \cdot 4H_2O$ (**11**), which from its partially resolved X-ray structure has been assigned a pinched cone conformation where four Ag^I centers bind to the uracil O(2) donor atoms of the four uracil monoanions. On addition of NaCl, all four Ag^I dissociate to give **6**.

However, the cone conformer of $[(en)Pt(UH\text{-}N1,N3)]_4^{4+}$, i.e. **6**, on addition of one equivalent of Zn^{II}, Be^{II}, or La^{III} salts undergoes deprotonation from four uracil units to form {$[(en)PtU]_4ZnSO_4$}(**12a**), {$[(en)PtU]_4Be$}$^{2+}$ (**12b**) and {$[(en)PtU]_4La$}$(NO_3)_3$ (**13**) (Figure 6) (99IC426). ^{1}H NMR and ESIMS show that in

the case of complexes **12a** and **12b**, the two exocyclic O atoms of the two base constituents are bridged by metal and the other two O are H-bonded *via* a coordinated water molecule thus stabilizing the cone conformation. In the case of **13**, the tetradendate binding of La^{III} to a cone conformer with nitrate anion binding at the *exo* side of the La^{III} has been suggested by ^1H NMR and mass spectral data (99IC426).

Metallacalixarenes **6** and **12** having a cone conformation are capable of binding with RSO_3^- (R = aliphatic or aromatic) anions in water. These associations arise due to a cooperative effect between well-structured hydrophobic cavities and electrostatic interactions between positively charged cavities and the anionic guest (99IC426). In **13**, coordination of La^{III} to the cone causes flattening of the cavity incapacitating it for guest inclusion. All complexes with 1,3-alternate conformations and Pt_4Ag_4 complex (**11**) having a pinched cone conformation, despite their high positive charge do not incorporate anions because of the narrowness of the inner cavity. In unique distinction from classical calix[4]arene which is isolated in a cone conformation, the uracil–Pt based metallacalixarene **5** is isolated in a 1,3-alternate conformation and has a high affinity for metal ions despite its positively charged nature. Its cone conformer **6** as well as its further derived positively charged complexes **12** bind anions also (99IC426). The host–anion complexation is maximized when the stability of the metalated species is optimized. Thus **12a** shows maximum interactions with anions at pH ~7.4 and remains stable between pH 3 and 8 and **12b** shows anion complexation only at pH < 5, a pH range in which **12b** is stable.

The *cis*-platin analog $[(dpk)PtCl_2]$, prepared by treating 2,2′-dipyridylketone (dpk) with K_2PtCl_4, on reaction with $AgNO_3$ and subsequently with uracil or thymine gave pentanuclear Pt^{II} complexes $[(dpk)_2(dpkOH_2)_3Pt_5(U)_3](BF_4)(NO_3)_3 \cdot 8H_2O$ (**14**), $[(dpk)_2(dpkOH_2)_3Pt_5(U)_3](PF_6)(NO_3)_3 \cdot 9H_2O$ (**15**), and $[(dpk)_2(dpkOH_2)_3Pt_5(T)_3](ClO_4)_2(NO_3)_2 \cdot 8H_2O$ (**16**). Here, the three dianionic nucleobases are bridged through three $Pt^{II}(2)$, $Pt^{II}(3)$, and $Pt^{II}(5)$ centers chelated to $(dpkOH_2)$ to form the trinuclear calix[3]arene segment (2004AGE1300). The other two Pt^{II} centers are coordinated to the oxygen atoms of nucleobases, the other potential metal-binding sites. $Pt^{II}(4)$ is bound through O(2) oxygens of nucleobases 'a' and 'b' and $Pt^{II}(1)$ is bound through O(4) oxygens of nucleobases 'a' and 'c' (Figure 7). As a result, the nucleobase 'a' coordinates to four Pt^{II} centers utilizing all N- and O- donor atoms and two other nucleobases 'b' and 'c' coordinate to three Pt^{II} centers (Figure 7).

The modified nucleobase H_2L^1, generated *in situ* from 2-thiouracil-4-aldehyde and diethylene triamine, undergoes self-assembly with $cobalt^{II}$ trifluoromethane sulfonate to form a tetrameric species $[Co(L^1)]_4^{4+}(CF_3SO_3)_4 \cdot 8H_2O$ (**17**) (Figure 8). In this complex four nitrogens including the N(1) of uracil are coordinated to one cobalt whereas the other uracil N(3) and S are bound to an adjacent Co^{III}. The cyclic tetramer constitutes a highly extended form of metallacalixarene where the uracil nitrogens are linked through Co^{III} (94JCS(CC)1773). It elaborates a columnar cavity at its centre with adjacent Co–Co separation of 5.54 Å.

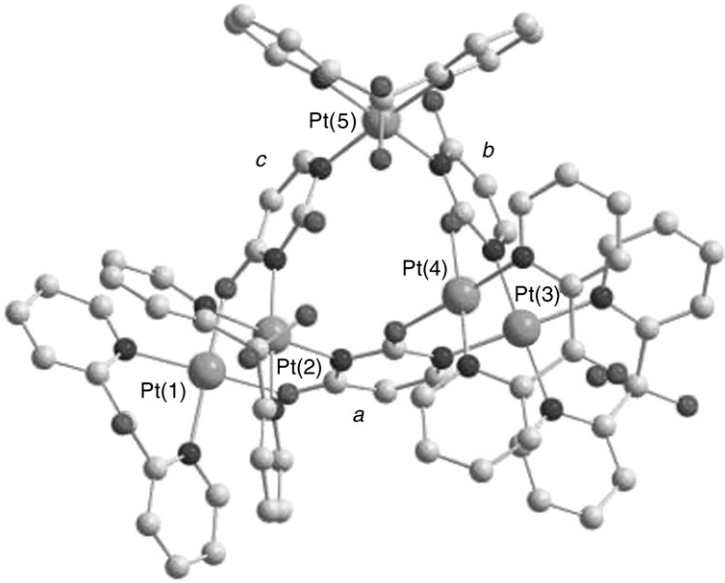


Figure 7 X-ray crystal structure of $[(dpk)_2(dpkOH_2)_3Pt_5(U)_3]^{4+}$ (**14**). (Reprinted with permission from 2004AGE1300, Copyright 2004, Wiley.)

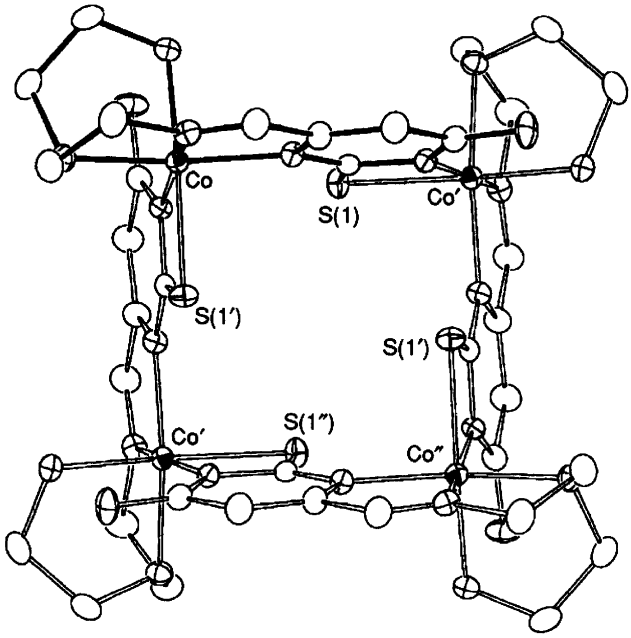


Figure 8 ORTEP diagram of $[Co(L^1)]_4^{4+}(CF_3SO_3)_4 \cdot 8H_2O$ (**17**). (Reprinted with permission from 94JCS(CC)1773, Copyright 1994, Royal Society of Chemistry.)

2.3 Metallacalixarenes based on purine nucleobases

Purine nucleobases having four inbuilt endocyclic nitrogens [N(1), N(3), N(7), N(9)] and additional exocyclic oxo, amino, or thione moieties at positions 2 and/or 6 (Figure 9) display versatile ligating abilities towards metal ions and generate a variety of new chemical entities. For forming metalla macrocycles, various combinations of two nitrogen sites mostly at positions 1,7; 7,9; 3,9 and in some cases even three nitrogen sites of purine bases react with metal salts, their complexes, or organometallics. However, further cooperative binding with additional exocyclic O, N, or S is also realized. Here, various modes of

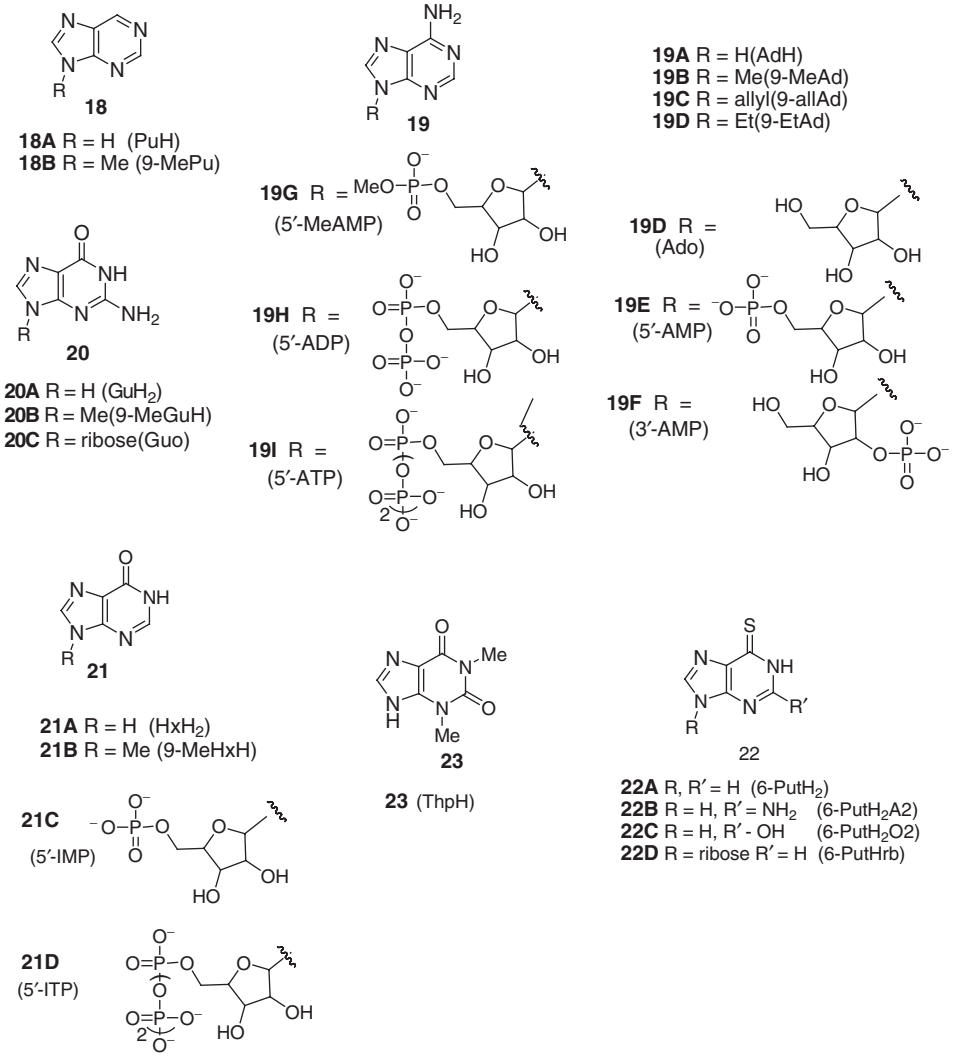


Figure 9 Structures of the purine nucleobases used in elaborating metallacalixarenes.

interactions of purine **18** (PuH), adenine **19** (AdH), guanine **20** (GuH_2), hypoxanthine **21** (HxH_2), 6-thiopurine **22** (6-$PutH_2$), theophylline **23** (ThpH) (Figure 9) with metal ions resulting in the formation of metallacalixarenes of varied nuclearity are detailed. With multiple possibilities of combinations of coordinating sites, the binding modes of purine bases and the nuclearities of their metallacalixarene products, depend mostly on the coordination geometries of the linker metals. Hence the presentation has been sub-classified in respect to metal coordinatives, discussed in the order Pt, Pt–Ag, or Pt–Hg, Pd, Ag, Cu, Cd, and Co and various organometallics.

2.3.1 Metal coordinatives

The reaction of the sodium salt of theophylline with $[Me_3Pt(H_2O)_3]_2SO_4$ (**24**) in water formed a trimeric product $[Me_3Pt(Thp\text{-}N7,O6;N9)]_3$ (**25**) (Figure 10a), m.p. 110 °C (79JCS(CC)324). This structure has been postulated on the basis of its ^1H NMR and osmometrically determined molecular weight. On refluxing K(Thp) and **24** in water, the product $[Me_3Pt(Thp\text{-}N7,O6;N9)]_6$ (**26**), m.p. > 215 °C, was formed. In its X-ray structure (Figure 10b), **26** revealed a hexameric metallacalixarene species in which Me_3Pt groups are coordinated in a *cis* fashion to N(7) and N(9) of the two neighboring thp monoanions. The interaction of O_6 of thp with Pt^{IV} completes its distorted octahederal coordination (88AGE1160).

6-Thiopurines **22A**–**22C** on reaction with $[(tacn)CoCl_3]$, in presence of sodium hydroxide, undergo deprotonation to produce initially monomeric $[(tacn)Co(\mathbf{22}\text{-}N,S)Cl]^+$ which on subsequent deprotonation undergo self-assembly to form trimeric and/or tetrameric complexes (Scheme 1). Whereas **22A** forms a mixture

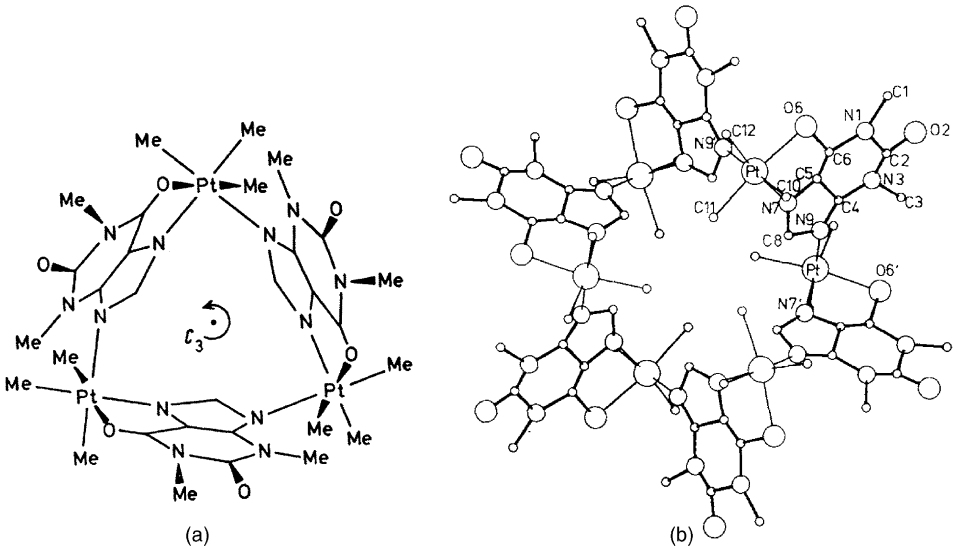
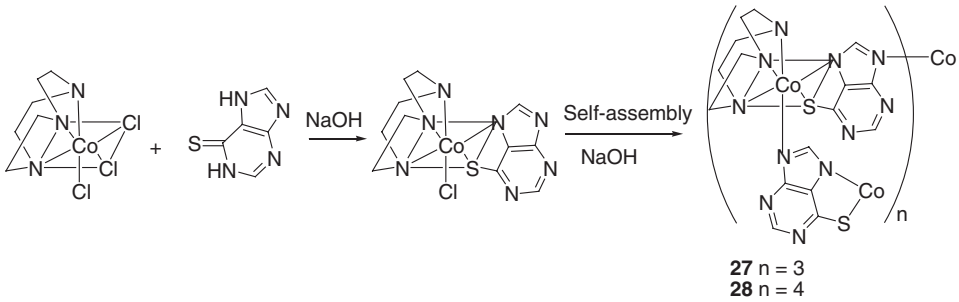


Figure 10 (a) The postulated structure of **25** (b) X-ray crystal structure of $[Me_3Pt(Thp\text{-}N7,O6;N9)]_6$ (**26**). (Reprinted with permission from 79JCS(CC)324, Copyright 1979, Royal Society of Chemistry; 88AGE1160, Copyright 1988, Wiley.)



Scheme 1 Synthesis of trimer **27** and tetramer **28**.

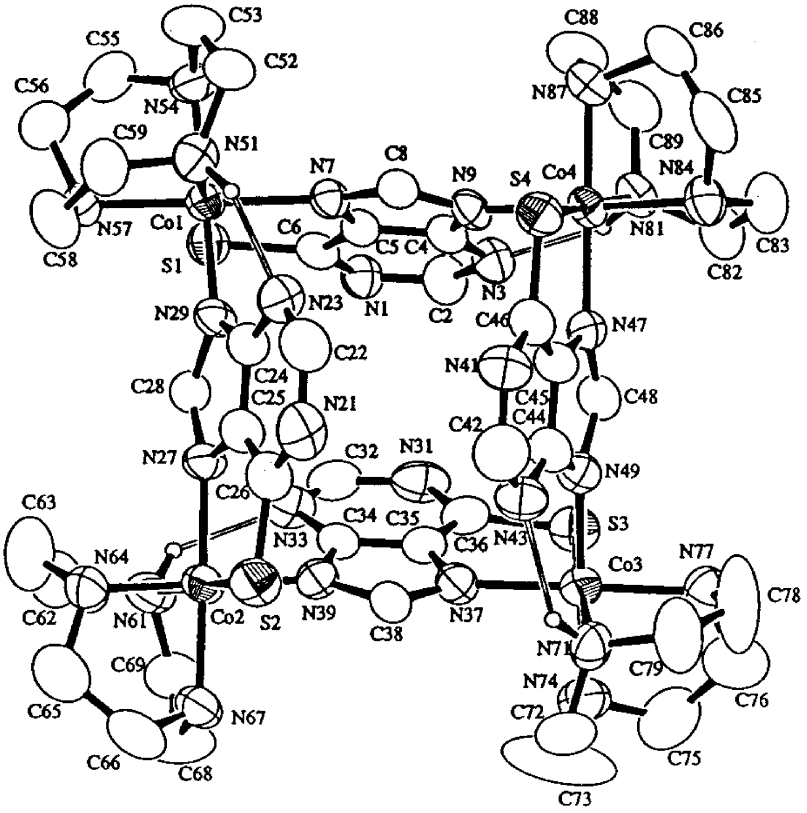


Figure 11 X-ray crystal structure of tetramer $[(tacn)Co(6\text{-put-}N7,S6;N9)]_4^{4+}$ (**28A**). (Reprinted with permission from 98IC5611, Copyright 1998, American Chemical Society.)

of trimeric $[(tacn)Co(6\text{-put-}N7,S6;N9)]_3^{3+}$ (**27**) and tetrameric $[(tacn)Co(6\text{-put-}N7,S6;N9)]_4^{4+}$ (**28A**) complexes, both **22B** and **22C** give tetrameric $[(tacn)Co(6\text{-putA2-}N7,S6;N9)]_4^{4+}$ (**28B**) and $[(tacn)Co(6\text{-putO2-}N7,S6;N9)]_4^{4+}$ (**28C**), respectively (98IC5611). The X-ray structures of **28A** (Figure 11) and **28B** reveal that all these thiopurines act as tridentate ligands *via* S, N(7), and N(9); where S and N(7) bind to one Co^{III} and are bridged to another Co^{III} through N(9).

In neutral aqueous solution, *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ reacts with 9-MeGuH (**20B**) to form a mixture of products from which a cyclic hexamer *cis*-$[(PMe_3)_2Pt(9\text{-}MeGu\text{-}N1;N7)]_6(NO_3)_6 \cdot 18H_2O$ (**29**) was crystallized (95IC1745). In the X-ray structure of **29** (Figure 12), six *cis*-$(PMe_3)_2Pt^{II}$ units are symmetrically bridged by deprotonated guanine ligands through their N(1) and N(7) atoms. The purine rings are alternately disposed above and below the mean plane passing through the metal atoms and the adjacent metal atoms are disposed alternately in two parallel planes separated by 0.34 Å.

Using metal entities such as *trans*-a_2PtCl_2 ($a = NH_3$ or CH_3NH_2) or Ag^I or $Hg(NO_3)_2$ displaying linear coordination geometries, metallacalixarenes having the same or mixed nucleobases as well as metal bridges have been reported. Lippert (98IC5044) crosslinked two cations *trans*-$[(NH_3)_2Pt(9\text{-}MeAd\text{-}N7)(9\text{-}MeGuH\text{-}N7)]^{2+}$ (**30**) by *trans*-$(CH_3NH_2)_2Pt^{II}$ through the N(1) position of 9-MeAd (**19B**) units to form U-shaped trinuclear *trans,trans,trans*-$\{(CH_3NH_2)_2Pt$

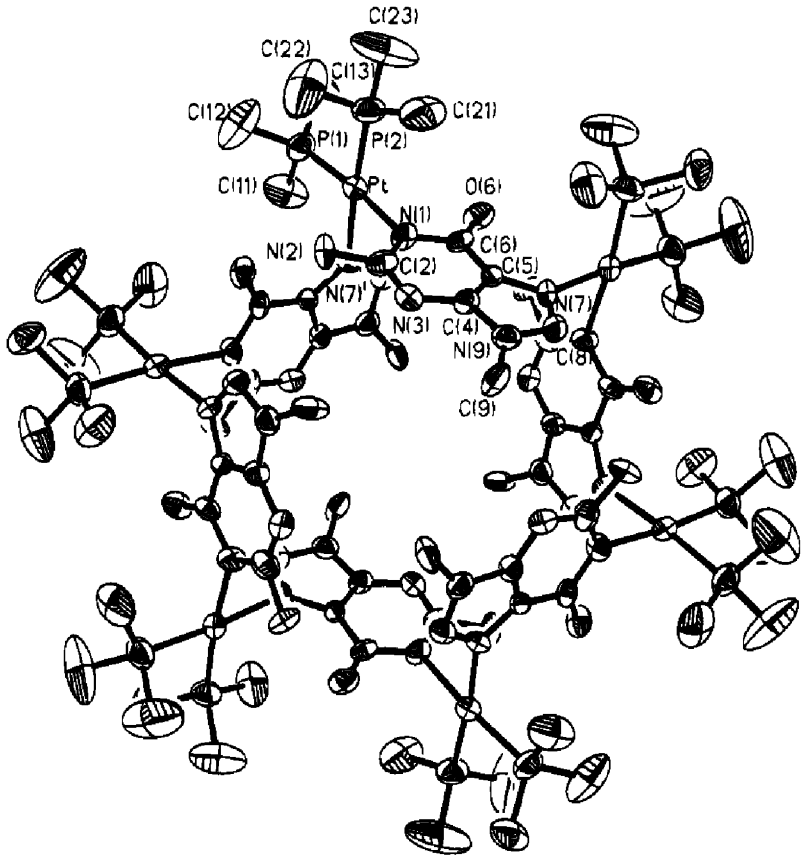
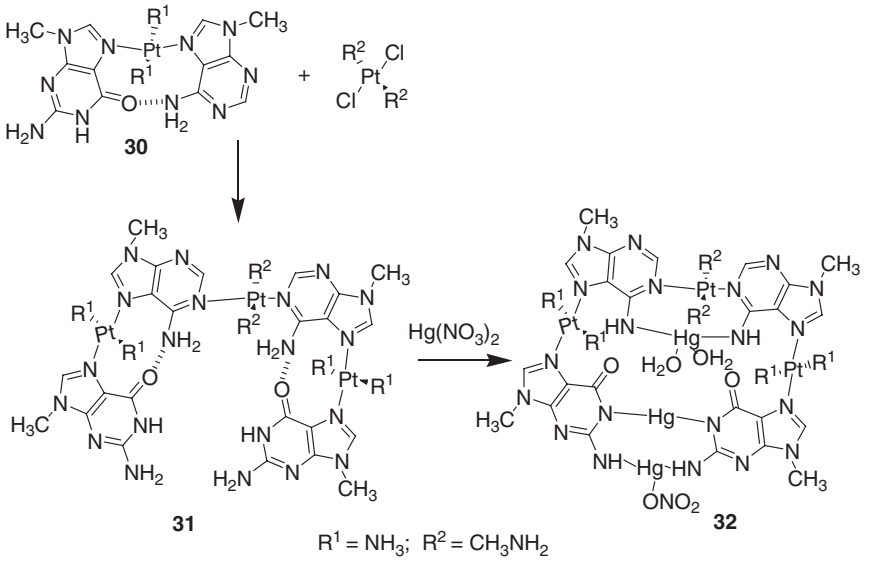


Figure 12 X-ray crystal structure of the cation of *cis*-$[(PMe_3)_2Pt(9\text{-}MeGu\text{-}N1;N7)]_6(NO_3)_6 \cdot 18H_2O$ (**29**). (Reprinted with permission from 95IC1745, Copyright 1995, American Chemical Society.)

(-9-MeAd-*N1;N7*)$_2$[$(NH_3)_2$Pt(9-MeGuH-*N7*)]$_2$}$(NO_3)_6 \cdot 6.25H_2O$ (**31**) (Scheme 2, Figure 13a). Intramolecular H-bonding between exocyclic N(6) and O(6) groups of the two purines remains as observed in the case of starting compound **30**. However, in solution, **31** exists in an equilibrium between U and S forms (^{1}H and



Scheme 2 Synthesis of **31** and **32**.

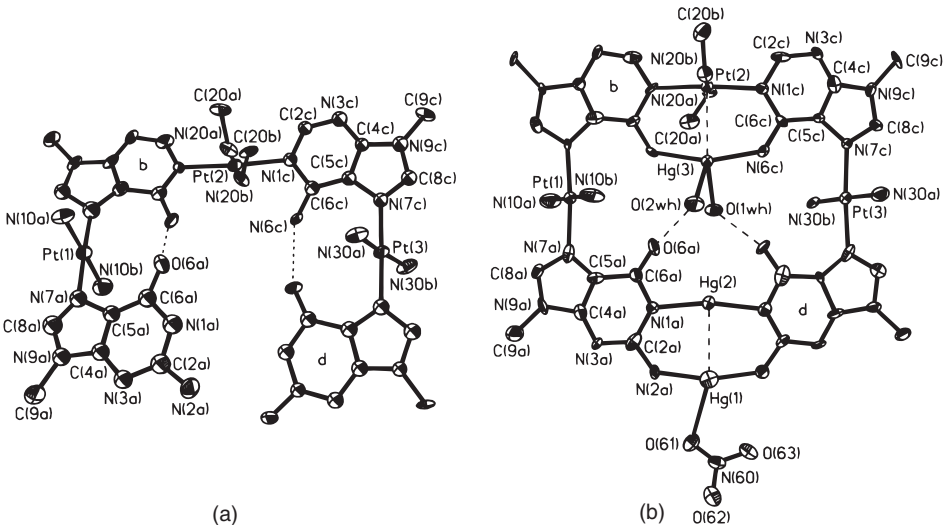


Figure 13 X-ray crystal structures of the cations of (a) *trans,trans,trans*-{$(CH_3NH_2)_2$Pt(-9-MeAd-*N1;N7*)$_2$ [$(NH_3)_2$Pt(9-MeGuH-*N7*)]$_2$}$(NO_3)_6 \cdot 6.25H_2O$ (**31**) and (b) *trans,trans,trans*-{$(CH_3NH_2)_2$PtHg$(H_2O)_2$ [(9-MeAd$^-$-*N1,N6;N7*)$(NH_3)_2$Pt(9-MeGu$^-$-*N1,N2;N7*)]$_2$Hg$_2$$(ONO_2)$} $(NO_3)_5 \cdot 13H_2O$ (**32**). (Reprinted with permission from 98IC5044, Copyright 1998, American Chemical Society.)

^{195}Pt-NMR data) with rotation about the Pt(2)–9-MeAd–N(1) bonds. Complex **31**, on reaction with $Hg(NO_3)_2$ in aqueous solution, formed quantitatively the mixed metallacalixarene *trans,trans,trans*-{$(CH_3NH_2)_2PtHg(H_2O)_2$[(9-MeAd$^-$-*N1,N6;N7*)$(NH_3)_2$Pt(9-MeGu$^-$-*N1,N2;N7*)]$_2Hg_2(ONO_2)$}$(NO_3)_5 \cdot 13H_2O$ (**32**) (Scheme 2, Figure 13b). In this process, the guanine undergoes di-deprotonation at N(1) and its *exo*-NH_2 and adenine undergoes deprotonation at its *exo*-NH_2 to form respective 9-MeGu$^-$ and 9-MeAd$^-$. One Hg^{II} crosslinks (with deprotonation) N(1) positions of two 9-MeGu$^-$ and two additional Hg^{II} ions ligate the exocyclic NH$^-$ of either two 9-MeGu$^-$ or two N-MeAd$^-$. Uniquely, here 9-MeGu$^-$ is linked through the three nitrogens N(1), N(2), and N(7) and this approach unlike self-assembly involves cyclometallation of a U-shaped precursor **31**. Ignoring the extra Hg^{II} ions bound to the exocyclic groups of nucleobases, nuclear three Pt^{II}, and one Hg^{II} bridges generate a molecular rectangle, a variant of molecular squares which utilize *cis* metal entities and colinearity of suitable ligands in their formation (98IC5044). ^{1}H and ^{195}Pt NMR studies also verify the cyclic structure in solution.

Another interesting mixed rectangular tetrameric metallacalixarene from 9-MeAd (**19B**), 9-MeHxH (**21B**), *trans*-$(NH_3)_2Pt^{II}$, and Ag^I involving pairwise N(1),N(7)–Pt^{II} and N(1),N(1)–Ag^I coordination is reported (2002SupC189). The complex *trans*-[$(NH_3)_2$Pt(9-MeAd-*N7*)(9-MeHxH-*N7*)]$(NO_3)_2 \cdot H_2O$ in the presence of $AgNO_3$ in aqueous solution undergoes deprotonation at N(1) of **21B** and the resulting specie undergoes cyclodimerization to form *trans*-[{$(NH_3)_2$Pt(9-MeAd-*N1;N7*)(9-MeHx-*N1;N7*) $\cdot$ Ag$(NO_3)(H_2O)$}$_2$Ag]$(NO_3)_3 \cdot 6H_2O$ (**33**) (Figure 14) which is further coordinated intermolecularly by Ag^I ions to form an infinite array of quartets. The water molecules are located between adjacent quartets and adopt a cyclic water hexamer structure in a chair conformation (2002SupC189).

9-Methylpurine (**18B**) and *trans*-[$(NH_3)_2$Pt(OH)Cl] $\cdot$ H_2O (**34**) in $HClO_4$ formed the 1:1 complex *trans*-[$(NH_3)_2$Pt(9-MePu-*N7*)Cl]ClO_4 (**35**), which in the presence of $AgNO_3$ through self-assembly provides a mixture of a molecular square [*trans*-{$(NH_3)_2$ Pt(9-MePu-*N1;N7*)}]$_4(ClO_4)_8 \cdot 6H_2O$ (**36**) and a molecular triangle [*trans*-{$(NH_3)_2$Pt(9-MePu-*N1;N7*)}]$_3(ClO_4)_6 \cdot 3H_2O$ (**37**) in 0.6:1 ratio (^{1}H NMR) (Scheme 3). By using sulfate anions as template, this ratio changes to 2.5:1 with an enhanced rate of formation of **36** and **37**. In the X-ray structures (Figure 15) of both **36** and **37**, the purine ligands and Pt^{II} atoms are essentially coplanar and the amine ligands are perpendicular to this plane. The tetramer **36** represents the first example of a true purine square with four metal entities at the periphery and alternate N(1),N(7) coordination. Both these compounds have affinity for sulfate anions which is more pronounced in case of **36** ($K_a = 7.2 \pm 1.2 \times 10^4\,M^{-1}$) than in **37** ($K_a = 9.9 \pm 0.6 \times 10^3\,M^{-1}$) (2006AGE147).

An unprecedented tetrameric metallacalixarene derived from a single nucleobase 9-allAd (**19C**) and a single intervening Ag^I ion and which is embedded in a unique polymeric network, [Ag(9-allAd-*N1;N3,N7*)]$_x(NO_3)_x$ (**38**), has recently been reported (2006JA400). The crystalline product **38**, obtained in a meticulously performed reaction of **19C** with $AgNO_3$ in 50% aqueous methanol, in its X-ray structure (Figure 16) revealed a distorted rectangle where four **19C**

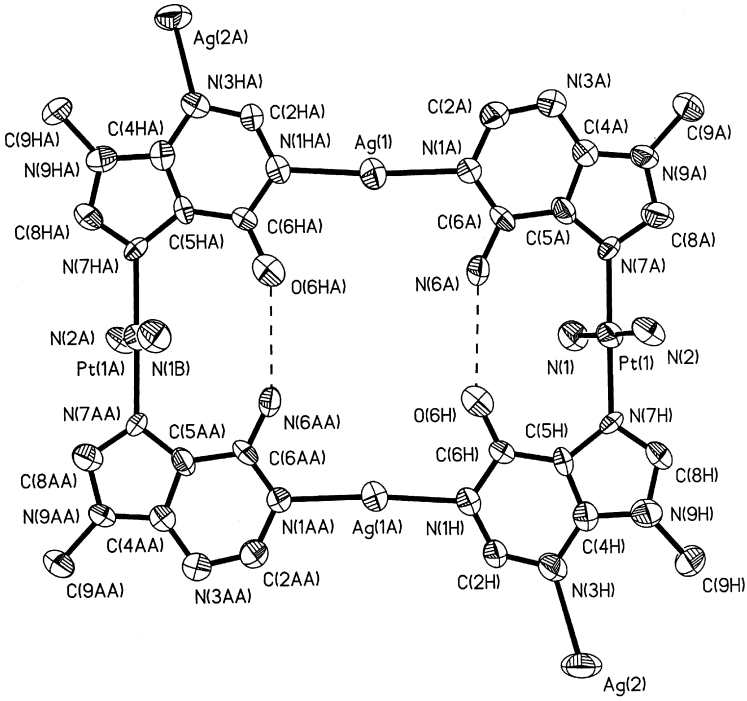


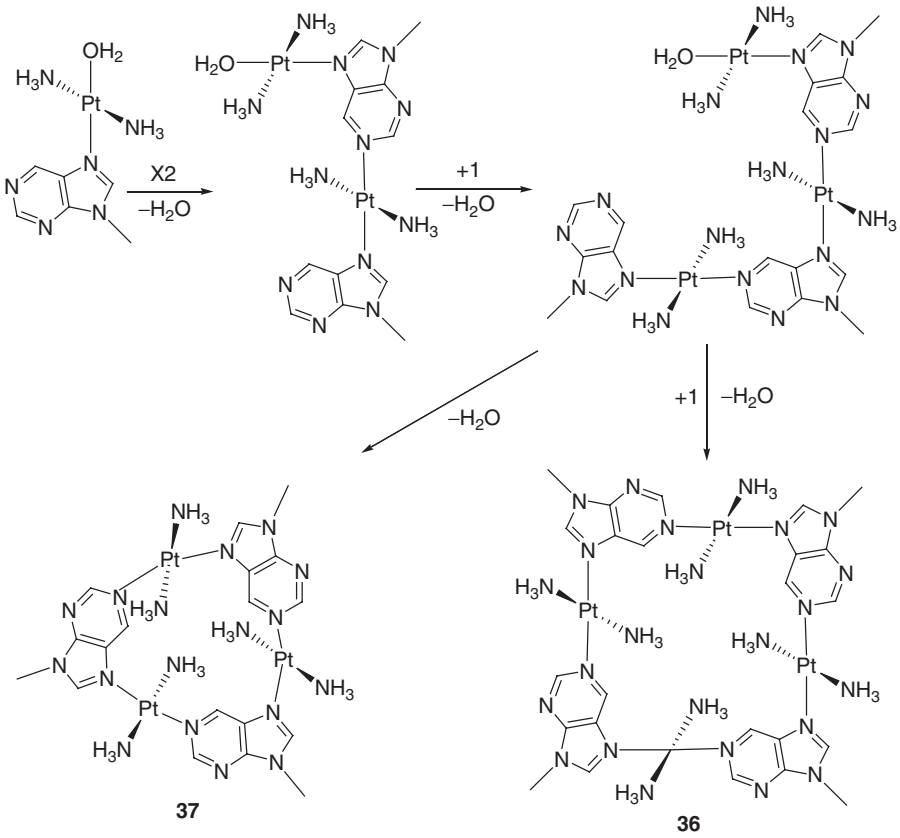
Figure 14 X-ray crystal structure of the cation of *trans*-[{$(NH_3)_2$Pt(9-MeAd-*N1;N7*)(9-MeHx-*N1;N7*)Ag$(NO_3)(H_2O)$}$_2$Ag]$(NO_3)_3 \cdot 6H_2O$ (**33**). (Reprinted with permission from 2002SupC189, Copyright 2002, Taylor and Francis Inc.)

molecules are linked to intervening Ag^I ions atoms consecutively through their N(7),N(1); N(7),N(3) sites. Each silver bridge is further tethered to an additional adenine unit through the third endocyclic nitrogen and thus is coordinated to three different endocyclic nitrogens N(1), N(3), and N(7) of three 9-allyladenine molecules (2006JA400), a rare case of the 3N coordination mode of a 9-substituted adenine.

The interactions of guanosine and its monophosphate with [(en)Pd$(NO_3)_2$] in D_2O, when spectrally monitored, supported the formation of tetrameric adducts having N7–Pd–N1 linkages between adjacent guanine rings (89IC2067). The formation of a similar adduct was noticed in the reaction of [(en)Pd$(NO_3)_2$] with inosine monophosphate. Hydrogen bonding from amino groups of en and phosphate groups stabilized these adducts (89IC2067).

The reaction of adenine and silver perchlorate in $HClO_4$ gave the first cyclic di-adeninium disilver perchlorate monohydrate [Ag_2(1-AdH_2^+-*N3;N9*)$_2$]$(ClO_4)_4 \cdot H_2O$ (**39**) which may be visualized as the smallest and earliest known dimeric metallacalixarene system (77IC2469). In the X-ray structure of **39** (Figure 17), silver bridging is evident at N(3) and N(9) sites and N(3)–Ag–N(9) angle is 164.1°.

Adenine (**19A**) (73IC1166, 69AX(B)1480, 71JCS(A)2167) and hypoxanthine (**21A**) (70AX(B)1609) have been found to react with Cu^{II} salts to form robust 3D systems which display a confluence of two dimeric metallacalixarenes bridged



Scheme 3 Synthesis of tetramer **36** and trimer **37**.

around Cu^{II}. Both nucleobases act as bidentate ligands and bind to Cu^{II} *via* their N(3) and N(9) nitrogens. In the X-ray structure of $[Cu_2(AdH\text{-}N3;N9)_4(H_2O)_2](ClO_4)_4$ (**40**) (Figure 18) formed from **19A** and copper perchlorate at pH 4, each Cu^{II} is surrounded by two N(3) and two N(9) atoms, one from each of the four different adenine molecules and one oxygen atom of a water molecule (73IC1166). Thus **40** represents a confluence of two dimeric metallacalixarenes having common Cu^{II} bridges, in which four nitrogen atoms coordinated to a given Cu^{II} are coplanar but the metal is displaced from that plane. The perchlorate anion and the lattice water molecules are held together in an intricate network of hydrogen bonds. Similar structures had earlier been proposed for $[Cu_2(Ad\text{-}N3;N9)_4(H_2O)_2]6H_2O$ (69AX(B)1480) and $[Cu_2(AdH\text{-}N3;N9)_4Cl_2]Cl_2 \cdot 6H_2O$ (71JCS(A)2167).

Hypoxanthine and copper chloride in aqueous HCl at pH 4 form $[Cu_2(HxH_2)_4Cl_2]_2Cl_2 \cdot 6H_2O$ (**41**) (70AX(B)1609), the X-ray structure of which is similar to its AdH analog **40**.

The reaction of monosodium salt of adenosine-5′-monophosphoric acid (**19E**) (AMP) with cadmium nitrate in the presence of nitric acid formed a binuclear

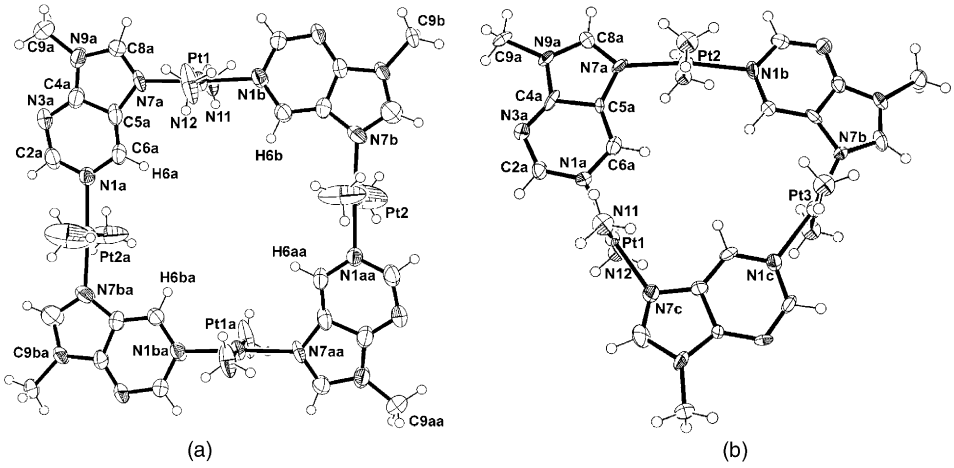


Figure 15 X-ray crystal structure of the cations of (a) [*trans*-{$(NH_3)_2$Pt(9-MePu-*N1;N7*)}]$_4$ $(ClO_4)_8 \cdot 6H_2O$ (**36**) and (b) [*trans*-{$(NH_3)_2$Pt(9-MePu-*N1;N7*)}]$_3$ $(ClO_4)_6 \cdot 3H_2O$ (**37**). (Reprinted with permission from 2006AGE147, Copyright 2006, Wiley.)

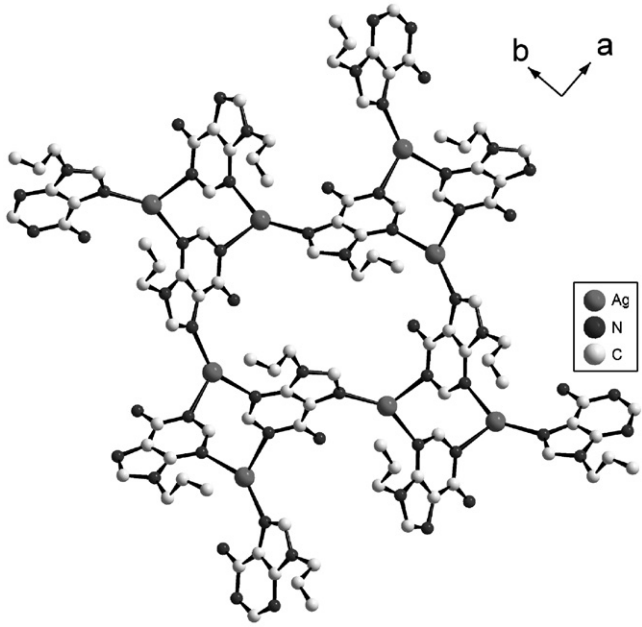


Figure 16 X-ray crystal structure of polymeric $[Ag(9\text{-allAd-}N1;N3,N7)]_x^{x+}$ (**38**). (Reprinted with permission from 2006JA400, Copyright 2006, American Chemical Society.)

complex $[Cd(AdH_2^+\text{-}N3;N9)(NO_3)_2 \cdot H_2O]_2(NO_3)_2$ (**42**). Its X-ray structure (Figure 19; 81IC356) shows water bridged nitrated cadmium atoms each of which is coordinated to the N(3) atom of one adenine moiety and to the N(9) of a centrosymmetrically related second adenine moiety. The water molecules in this

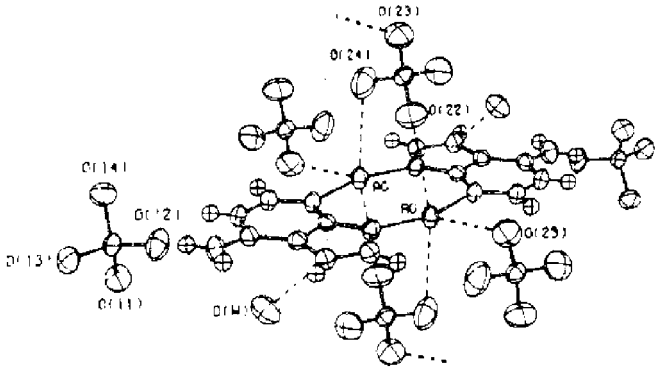


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Figure 17 X-ray structure of $[Ag_2(1\text{-}AdH_2^+\text{-}N3;N9)_2](ClO_4)_4 \cdot H_2O$ (**39**). (Reprinted with permission from 77IC2469, Copyright 1977, American Chemical Society.)

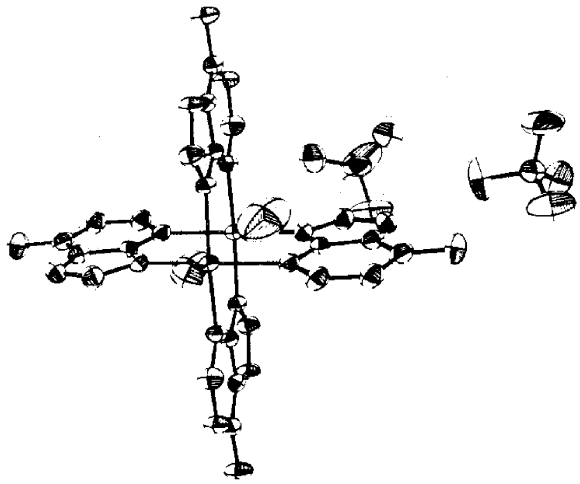


Figure 18 X-ray crystal structure of the cation of $[Cu_2(AdH\text{-}N3;N9)_4(H_2O)_2](ClO_4)_4$ (**40**). (Reprinted with permission from 73IC1166, Copyright 1973, American Chemical Society.)

structure serve as bridging ligands connecting two cadmium atoms. Each nitrate ion not bound to the metal is attached to the dimeric cation as a hydrogen bond acceptor and all hydrogens of the adenine ring as well as those of water molecules appear to participate in this network of hydrogen bonds.

A comparison of these nucleobase-derived metallacalixarenes with natural nucleobase-derived tetrands may be advisable. In the non-natural quartets formed by interconnection of uracil, purine or its derived nucleobases with coordinative metals, the cationic character lies on the metals in the periphery and anions are bound in the cavity. In natural tetrands of these nucleobases, the hydrogen bonds interconnect the bases and the structures are stabilized by a cation located in the centre whereas phosphate groups located in the periphery carry negative charge (2005AGE668). As against the existence of only natural

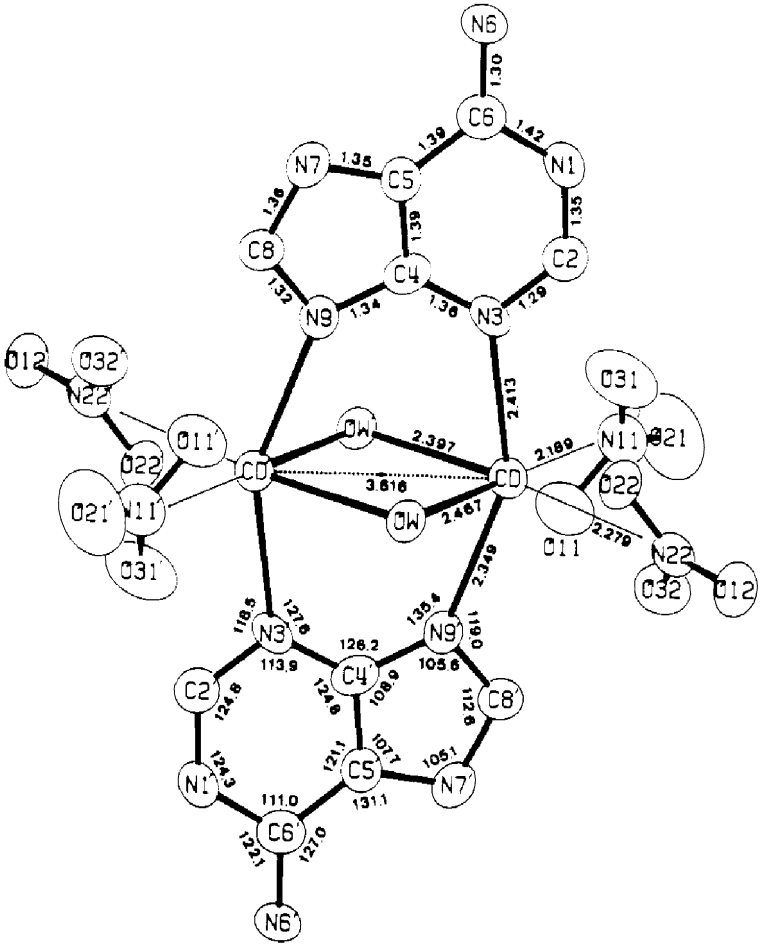


Figure 19 X-ray crystal structure of the cation of $[Cd(AdH_2^+\text{-}N3;N9)(NO_3)_2 \cdot H_2O]_2(NO_3)_2$ (**42**). (Reprinted with permission from 81IC356, Copyright 1981, American Chemical Society.)

quartets, metallacalixarenes with different nuclearity (dimer, trimer, hexamer etc.) are also realized in the non-natural mode.

2.3.2 Organometallics

The interactions of nucleobases with metal complexes as a consequence of the drug activity potential of the resulting products have been extensively investigated. In quite a few cases because of the availability of angular ligating profiles, the products have cyclic organo-inorganic hybrid structures constituting metallacalixarenes. In a similar manner, the use of organometallics in triggering self-assembly with appropriate nucleobases to constitute corresponding metallacalixarenes has been argued and investigated. Fish et al. (2003OM2166) pioneered these investigations and are responsible for initiating and advocating a focused attention of practitioners of organometallic chemistry towards this intriguing

new area of bioorganometallic chemistry. The reactions of Rh, Ru, and Ir based organometallics with nucleobases, reported so far, are detailed here in respect to the metallic linkers.

2.3.2.1 Rhodium organometallics. The water soluble (η^5-pentamethylcyclopentadienyl)-rhodium aqua complex $[Cp^*Rh(H_2O)_2(OTf)_2]_x$ (**43**) reacts with 9-MeAd (**19B**) in D_2O at pD 7.2 to form an unprecedented racemic trimeric metallacalixarene $[Cp^*Rh(9\text{-}MeAd^-\text{-}N1;N6,N7)]_3(OTf)_3$ (**44**) (Figure 20) (92JA10647). The X-ray structure of one of its enantiomers shows each Cp^*Rh^{III} bound to N(1) and N(6), N(7) of adjacent 9-MeAd monoanions. It displays a triangular dome like structure with three Cp^* groups stretching out from the top of the dome, three Me groups pointing to the bottom, three 9-MeAd planes forming the surrounding shell and three Rh^{III} cations embedded in the top of the dome. The formation of this 12-membered cyclic trimer is evidently triggered by the ability of the Cp^*Rh^{III} cation to act as an azaphile with a favorable geometry of N(1) poised to form the third bond to Cp^*Rh^{III} of an adjacent $[Cp^*Rh(9\text{-}MeAd^-\text{-}N1;N6,N7)](OTf)$ moiety.

The ^1H NMR spectrum of **44** shows the upfield shift of H(2) and downfield shift of H(8) signals of 9-MeAd moieties, as compared with the parent system. This parameter constitutes a convenient diagnostic tool for monitoring the formation and structural assignment of analogous trimeric cyclic metallacalixarene systems (92JA10647).

The reaction of **43** with adenosine (Ado) in H_2O at pH 7.1 provided a complex which could not be purified. Its ^1H NMR analysis showed it to be a mixture of two

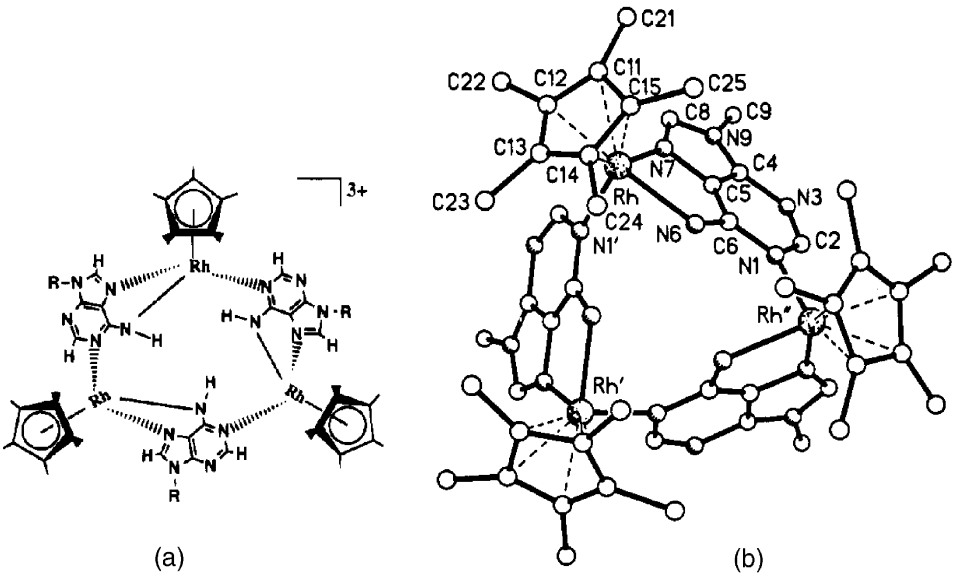


Figure 20 (a) Schematic presentation of **44** (R = Me) (b) X-ray crystal structure of the cation of $[Cp^*Rh(9\text{-}MeAd^-\text{-}N1;N6,N7)]_3(OTf)_3$ (**44**). (Reprinted with permission from 92JA10647, 95JA3631, Copyright 1992 and 1995, American Chemical Society.)

diastereomers of trimeric cyclic metallacalixarene [Cp*Rh(Ado$^-$-*N1;N6,N7*)]$_3$(OTf)$_3$ (**45**) (92JA10647, 96JA4993, 93IC4119). Similar reactions of **43** with 2′-deoxyadenosine and 2′,3′-dideoxyadenosine gave respective trimers **46** and **47** in good yields (95JA3631, 96JA4993). Adenosine 5′-monophosphate (**19E**, 5′-AMP) and **43** formed a mixture of mononuclear and dinuclear complexes and diastereomers of trimer in low yields (93IC4119). ^{1}H and ^{31}P NMR spectra of the mixture showed that 5′-P(O)$_2$═O group because of its competition with N(1) and NH(6) for Cp*Rh^{III} site significantly inhibited cyclic trimer formation. Further, the methylation of the 5′-phosphato group in **19G** (5′-MeAMP), mitigated such a competition and on reaction with **43** formed only the cyclic trimer [Cp*Rh(5′-MeAMP-*N1;N6,N7*)]$_3$(OTf)$_3$ (**48**) (93IC4119). On prolonged equilibration at pH 7.7, time-dependent ^{1}H NMR monitoring showed the enhancement of the ratio of diastereomers of **48** from 1:1 to 6:1. Such diastereoselectivity differences among **19D**, **19E**, and **19G** based trimers could be attributed to a more pronounced steric effect of the ester group on ribose which dramatically allowed resolution of one trimeric diastereomer in preference to the other to occur over time by equilibration between the two possible forms. The reaction of **43** with 3′-AMP (**19F**), a positional isomer of 5′-AMP formed mainly the cyclic trimer**,** and only a minor amount of a dimer (93IC4119). So both methylation of one of the oxygens of –P(O)$_2$═O or moving it away from N(7) and NH(6) prevented its competition for reaction at the Rh^{III} center and favored trimer formation. The trimer **46** has found utility as a new aqueous ^{1}H NMR shift reagent *via* a host–guest molecular recognition process by non-covalent π–π and hydrophobic interactions with a variety of water-soluble organic substrates (98JOC7151).

On ^{1}H NMR monitoring of the reaction of nicotine adenine dinucleotide (NAD$^+$), an important co-factor in enzymatic reactions, with **43** at pH 6, the formation of two unique diastereomeric cyclic trimeric metallacalixarene systems **49,** in a self-assembly mode, was evident (1999JOM(589)66). These products have a narrow stability range at pH 6 and decompose at lower or higher pH. The complex **49** was neither electroactive nor it was possible to convert it to the corresponding NADH-based system (1999JOM(589)66).

The molecular recognition ability of these unique adenine based organometallic metallacalixarene hosts for some biologically important guests has been extensively investigated using complexation induced ^{1}H NMR chemical shifts of both the guests and hosts, markedly in aqueous medium at pH 7.2 (96JA4993, 95JA3631). The cyclic trimers **44**–**48** recognize aromatic amino acids and several aliphatic amino acids with relatively long hydrophobic side chains by invoking π–π and/or hydrophobic host–guest interactions. It is further realized that molecular recognition of amino acids occurs inside the cavities of the hosts and hydrogen bonding, steric, conformational, and electronic factors also influence the recognition process (96JA4993, 95JA3631). In an intriguing study, in order to understand the role of water in the above molecular recognition modes, soft electrospray ionization mass spectrometry has been used to extend the same interactions in the gas phase for all the above hosts and guests (97CC2135). In a subtle comparison using L-tryptophan as the guest, it was found that just as in water, **46** was also the best host in the gas phase. The recognition process

here is found to occur predominantly *via* non-covalent π–π interactions whereas hydrophobic forces apparently remain weak or non-existent.

Guanosine (**20C**, Guo) reacted with **43** at pH 5.4 to provide a monomeric complex [Cp*Rh(Guo)(H_2O)(OH)](OTf) (92JA10647). The bonding differences between Ado and Guo for **43** reflect on the geometry of N(7) and exocyclic NH_2(6) positions for 5-membered ring chelate formation *via* a condensation reaction of the exocyclic NH_2(6) group with a reactive Cp*Rh hydroxyl species (92JA10647). In order to delineate the steric role of NH_2(2) and any role of the carbonyl group at C(6) and pH, the reactions of **43** with 9-ethylguanine and 9-methyl/ethylhypoxathine were studied. The reaction of 9-ethylguanine with *in situ* generated [Cp*Rh($MeOH)_3$]($OTf)_2$ formed [Cp*Rh(9-EtGu-*N7*)($CH_3OH)_2$] ($OTf)_2$, invoking exclusive N(7) binding. The lack of cyclic trimer formation even over a pH range (93IC4677) clearly implied a dominant steric role of the exocyclic NH_2(2) in inhibiting cyclic trimer formation.

9-Methylhypoxanthine (**21B**), like 9-ethylguanine also formed [Cp*Rh(N7-9-MeHxH)($CH_3OH)_2$]($OTf)_2$. Its N(7) coordination mode was verified by its X-ray structure. The ^{1}H NMR monitoring of its aqueous solution over a pH range showed that at pH 6.45, this complex changes to an unprecedented cyclic trimer $[Cp^*Rh(9\text{-}MeHx\text{-}N1;N7,O6]_3^{3+}$ (**50**) (Figure 21) (93IC4677) but it could not be isolated. It invoked (N7, O6) 5-membered ring formation, where the C6 carbonyl on 9-MeHx facilitated cyclometallation like C6-NH_2 of Ado (93IC4677). However, at pH 10.2 a dimer [{Cp*Rh[η^1(N1)-9-MeHx](μ-OH)}$_2$] was formed. Its X-ray structure displayed a unique N(1) binding mode for 9-MeHx and intramolecular hydrogen bonding between OH groups and O6 of nucleobase (95AGE1514).

The reaction of 9-ethylhypoxanthine with **43** at pH 6.1 formed the trimeric metallacalixarene [Cp*Rh(9-EtHx-*N1;N7,O6*)]$_3$($OTf)_3$ (**51**). Its X-ray structure

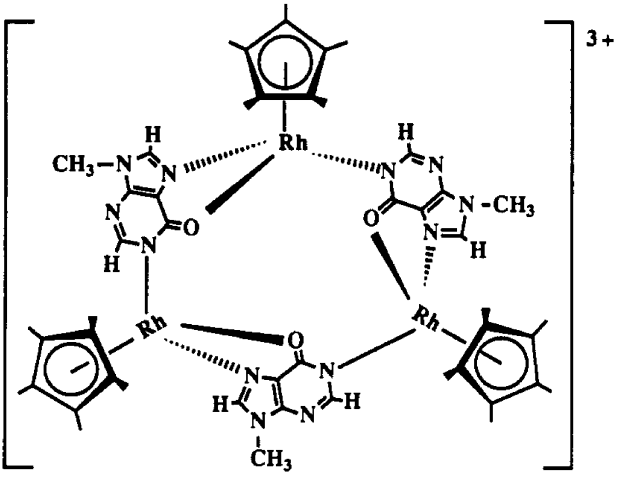


Figure 21 Solution phase structure of **50**. (Reprinted with permission from 93IC4677, Copyright 1993, American Chemical Society.)

displayed a triangular dome like cavity where three Cp* groups stretch out from the top of the dome, three ethyl groups point to the bottom, three hypoxanthine planes form the surrounding shell, and three Rh atoms are embedded on the top of the dome (95AGE1514).

The self-assembling reaction between **43** and 6-thiopurine ribose (**22D**, 6-PutHrb) having a ligating skeleton similar to adenosine except that NH_2(6) of adenosine is replaced by a thione group, forms a hexanuclear metallacalixarene system $[Cp^*Rh(6\text{-Putrb-}N1;N7,S6)]_6(CF_3SO_3)_6$ (**52**). Its X-ray structure reveals coordination by N(1) and N(7) of neighboring molecules of **22D** and the thione S binds Rh to form a five member chelate ring. Six Rh^{III} ions are crystallographically independent and six purine rings are arranged on the six planes of a cube, thus forming an unprecedented cubic cavity. Three ribose groups collect together towards each side of the longest cubic diagonal (2001AGE2268).

2.3.2.2 Ruthenium organometallics. Adenine (**19A**) and $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ (**53**) in a 2:1 molar reaction in aqueous solution formed a tetrameric product $[(\eta^6\text{-}C_6H_6)RuCl(AdH\text{-}N7;N9)]_4Cl_4$ (**54**). Its X-ray structure showed an N(7), N(9) bridging mode of adjacent adenine ligands. In the reaction of 6-methylaminoadenine (6-MeAdH) with **53** in methanol in the presence of sodium methoxide, analogous metallacalixarene $[(\eta^6\text{-}C_6H_6)RuCl(6\text{-MeAd-}N7;N9)]_4$ (**55**) was formed (93ICA15) (Figure 22).

The reaction of $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ (**56**) with adenine in water formed the tetrameric system $[(\eta^6\text{-}p\text{-cymene})Ru(Ad\text{-}N6,N7;N9)]_4(CF_3SO_3)_4$ (**57**). In its X-ray structure (Figure 23a), **57** exhibits crystallographic S_4 symmetry and N(9) and N(6), N(7) bridging modes for the adjacent adenine ligands with Ru linkers. The observation of N(7), N(9) bridging in **54** and **55** suggests that initial displacement of N(9) proton by Ru linker fragment might be leading to enhancement of the basicity of the second imidazole nitrogen N(7). In the absence of any other suitable ligand, metallation of N(6) through formation of a 5-membered ring provides additional stabilization of N(7), N(9) binding (97ICA85). The N(6) metallation also causes an upfield shift (^{1}H NMR) of the adenine ring protons as compared with the free base. This unique N(9); N(6), N(7) binding mode prompted investigation of N(9) substituted adenine derivatives with Ru^{II} linkers.

Similar reaction of **56** with 9-EtAd (**19D**) formed a trinuclear system $[(\eta^6\text{-cymene})Ru(9\text{-EtAd}^-\text{-}N1;N6,N7)]_3(CF_3SO_3)_3$ (**58**) (97ICA85). Its X-ray structure (Figure 23b) showed that N(6),N(7) participate in formation of a five-member chelate ring and due to the non-availability of N(9), the N(1) of the adjacent nucleobase coordinates with Ru^{II} to form the trinuclear cation with N(1); N(6),N(7) bridging mode. A similar binding mode has been also observed in **44** (92JA10647). Trimer formation is accompanied by dramatic chemical shifts in H(2) (downfield) and H(8) (upfield) protons of 9-EtAd moiety in **58** in comparison to free **19D**. The ^{1}H NMR monitoring of the progress of the reaction also provides conclusive evidence for similar formation of trimeric adenosine complex $[(\eta^6\text{-}C_6H_6)Ru(Ado^-)]_3(CF_3SO_3)_3$ (**59**) from reaction of **56**, adenosine, and $Ag(CF_3SO_3)$ (97JCS(DT)2191).

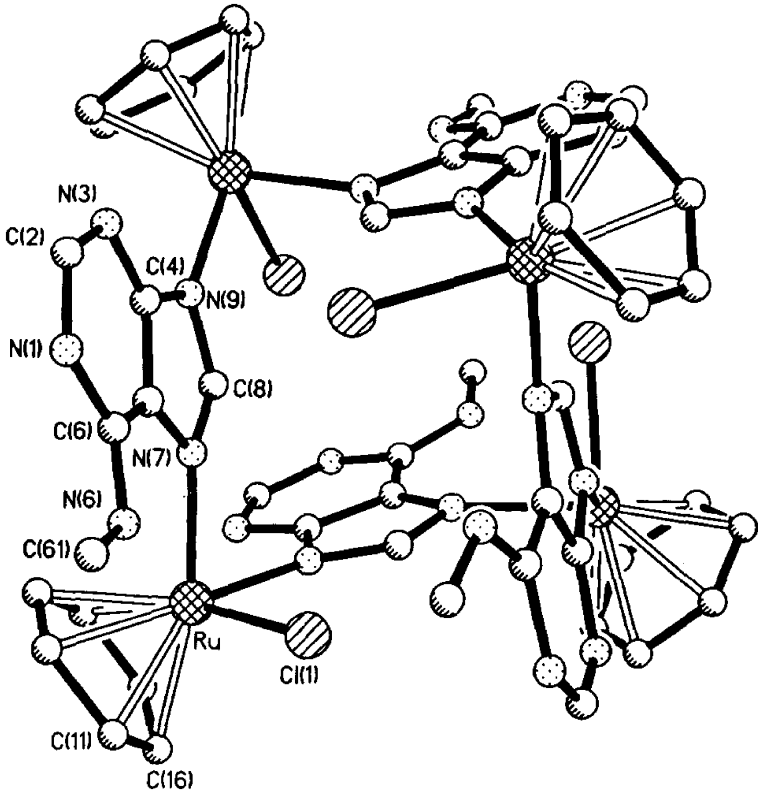


Figure 22 X-ray crystal structure of $[(\eta^6\text{-}C_6H_6)RuCl(6\text{-}MeAd)]_4$ (**55**). (Reprinted with permission from 93ICA15, Copyright 1993, Elsevier.)

In reactions of (η^6-arene)Ru^{II} fragments with nucleotides, macrochelation involving additional bindings with phosphate oxygens could compete with cyclic self-assembled oligomer formation. The reaction of $[(\eta^6\text{-}p\text{-cymene})Ru(Me_2CO)_3]^{2+}$ with 5′-H_2AMP in acetone gave $[(\eta^6\text{-}p\text{-cymene})Ru(5'\text{-HAMP})]_3(CF_3SO_3)_3$ which on slow evaporation of its aqueous solution formed crystals of $[(\eta^6\text{-}p\text{-cymene})Ru(5'\text{-AMP-}N1;N6,N7)]_3 \cdot 7.5H_2O$ (**60**) (97JCS(DT)2191). The X-ray structure (Figure 24) of its $Ru_sRu_sRu_s$ diastereomer established a pronounced degree of conformational flexibility in the sugar and phosphate residues. In the ^{1}H NMR monitored reaction of $[Ru(\eta^6\text{-}C_6H_6)(D_2O)_3]^{2+}$ with 5′-AMP (**19E**), in the pH range 3.30–9.18, the predominant formation of cyclic trimers of the type $[(\eta^6C_6H_6)Ru(5'\text{-AMP-}N1;N6,N7)]_3$ invoking N(1); N(6), N(7) binding of adjacent adenosine molecules was evident (97JCS(DT)2191). In contrast to 5′-AMP, cyclic trimers were not observed in more strongly acidic solution for equilibrium system $[(\eta^6\text{-}C_6H_6)Ru(5'\text{-ATP})]^{2-}$ and constituted minor species even at neutral or higher pH values. ^{31}P NMR confirmed that macrochelates constitute the dominant species in acidic solution. Time-dependant ^{1}H NMR studies for $[(\eta^6\text{-}C_6H_6)Ru(5'\text{-ADP})]^-$ indicated that initial macrochelation of this nucleotide was followed by cleavage of the β-phosphate group and formation of cyclic trimers of 5′-AMP.

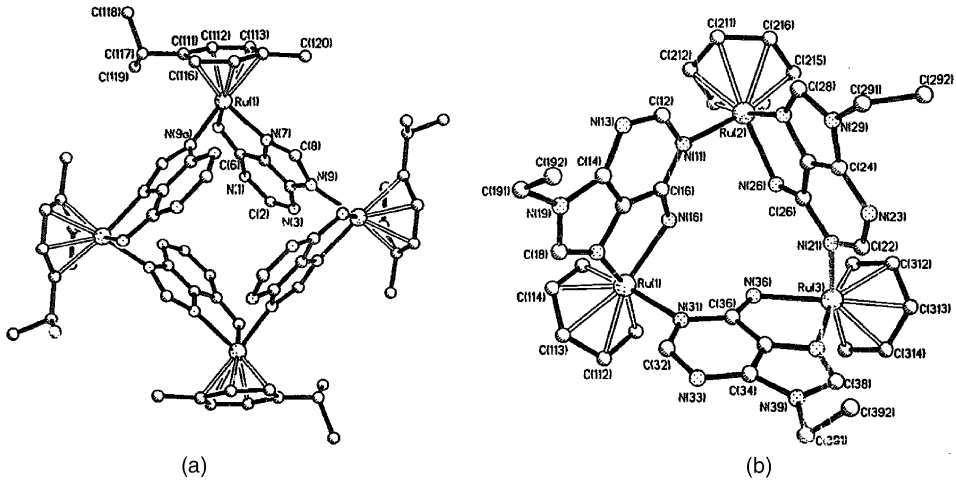


Figure 23 X-ray crystal structure of the cation of (a) $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{Ad-}N6,N7;N9)]_4(CF_3SO_3)_4$ (**57**) (b) $[(\eta^6\text{-cymene})\text{Ru}(9\text{-EtAd}^-\text{-}N1;N6,N7)]_3(CF_3SO_3)_3$ (**58**). (Reprinted with permission from 97ICA85, Copyright 1997, Elsevier.)

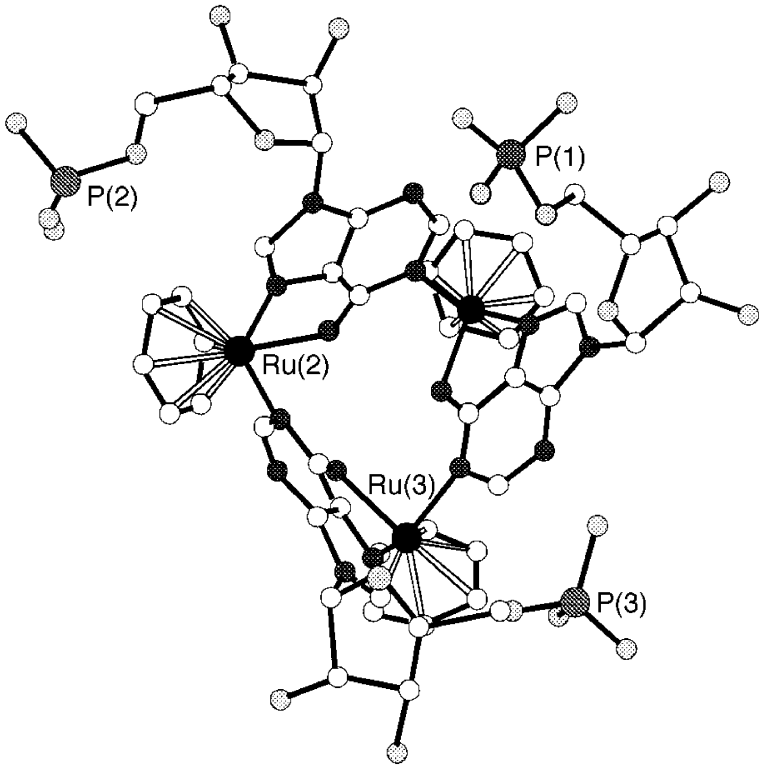


Figure 24 X-ray crystal structure of $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(5'\text{-AMP})]_3 \cdot 7.5H_2O$ (**60**). (Reprinted with permission from 97JCS(DT)2191, Copyright 1997, Royal Society of Chemistry.)

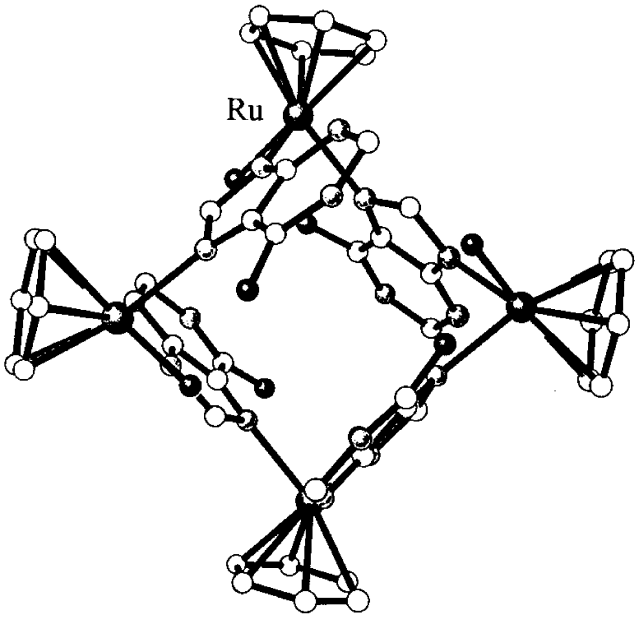


Figure 25 X-ray crystal structure of the cation of $[(\eta^6\text{-}C_6H_6)Ru(HxH\text{-}N7;N9)(H_2O)]_4$ $(CF_3SO_3)_4$ (**61**). (Reprinted with permission from 2000ICA115, Copyright 2000, Elsevier.)

In the ^1H NMR monitored reactions of guanosine 5′-mono, di and triphosphates with $[Ru(\eta^6\text{-}C_6H_6)(D_2O)_3]^{2+}$ between pH 3.69 and 8.38, formation of only 1:1 and 2:1 complexes and macrochelates involving N(7) and oxygens of phosphate groups have been realized (97JCS(DT)2191).

Hypoxanthine (HxH_2) and $[(\eta^6\text{-}C_6H_6)Ru(H_2O)_3](CF_3SO_3)_2$ reacted to form tetrameric metallacalixarene $[(\eta^6\text{-}C_6H_6)Ru(HxH\text{-}N7;N9)(H_2O)]_4(CF_3SO_3)_4$ (**61**). Its X-ray structure (Figure 25) showed N(7), N(9) binding of adjacent HxH molecules to the Ru^{II} bridge (2000ICA115). It revealed crystallographic S_4 symmetry and participation of exocyclic HxH oxygens in intramolecular hydrogen bonds to the coordinated water ligands.

2.3.2.3 Iridium organometallics. The reactions of $[Cp^*Ir(H_2O)](CF_3SO_3)_2$ (**62**) with adenine (**19A**) and 9-ethyladenine (**19D**) gave respective tetra and trinuclear products $[Cp^*Ir(Ad\text{-}N9;N6,N7)]_4(CF_3SO_3)_4$ (**63**) and $[Cp^*Ir(9\text{-}EtAd^-\text{-}N1;N6,N7)]_3$ $(CF_3SO_3)_3$ (**64**). In their X-ray structures (Figure 26a and b) (2000ICA115) the former exhibits an N(9); N(6),N(7) coordination mode for the bridging adenine ligands and the latter an N(1); N(6),N(7) binding pattern of adjacent 9-EtAd molecules. In these metallacalixarenes again, in the ^1H NMR spectra, substantial upfield and downfield shifts respectively for purine H(2) and H(8) are diagnostic of cyclic oligomerization. Equimolar equilibrium systems of **62** with **19E** and **19I** showed exclusive formation of analogous diastereomeric trimers in the pH range 3.5–9.0.

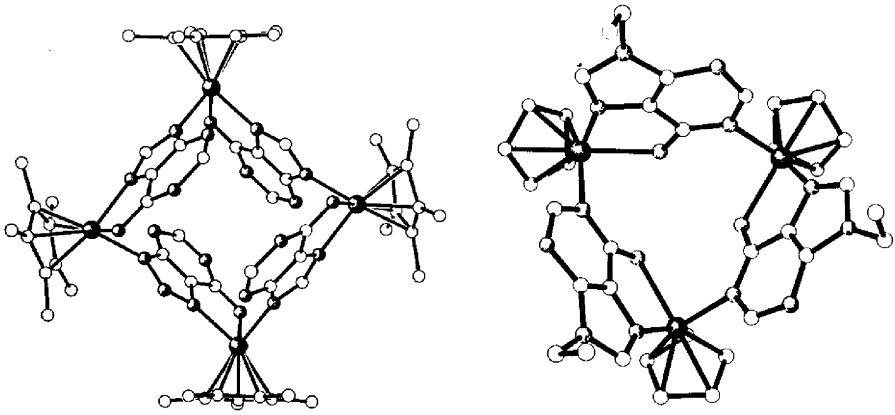


Figure 26 X-ray structure of the cation of (a) $[Cp^*Ir(Ad\text{-}N9;N6,N7)]_4(CF_3SO_3)_4$ (**63**) (b) $[Cp^*Ir(9\text{-}EtAd\text{-}N1;N6,N7)]_3(CF_3SO_3)_3$ (**64**). (Reprinted with permission from 2000ICA115, Copyright 2000, Elsevier.)

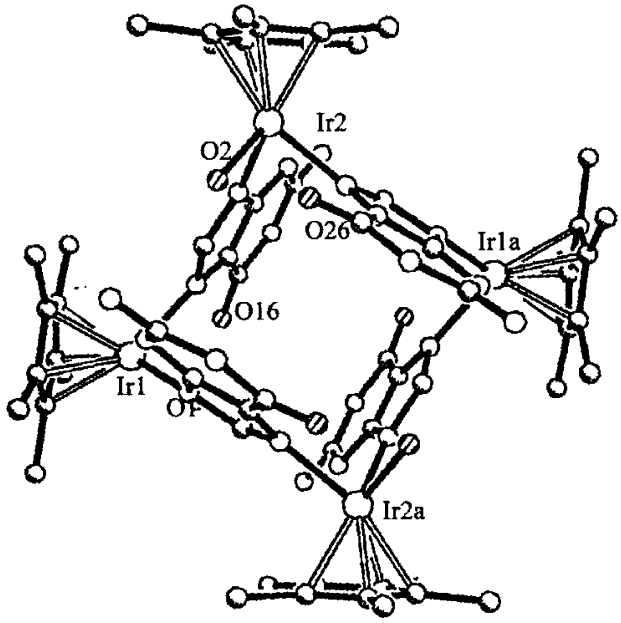


Figure 27 X-ray structure of the cation of $[Cp^*Ir(GuH)(H_2O)]_4(CF_3SO_3)_4$ (**65**). (Reprinted with permission from 2000ICA115, Copyright 2000, Elsevier.)

The reactions of **62** with guanine (GuH_2) and hypoxanthine (HxH_2) provided respective tetramers $[Cp^*Ir(GuH\text{-}N7;N9)(H_2O)]_4(CF_3SO_3)_4$ (**65**) and $[Cp^*Ir(HxH)(H_2O)]_4$ $(CF_3SO_3)_4$ (**66**) in which O(6) participated only in outer-sphere coordination through O6–H–O interactions to the water ligand. The N(7),

N(9) coordination mode of adjacent molecules of GuH in **65** has been confirmed by its X-ray structure (Figure 27) (2000ICA115).

In weakly acidic equilibrium systems of **62** and 5′-IMP (**21C**) or 5′-ITP (**21D**), two cyclic, presumably trimeric oligomers with respectively N(1); N(7),O(6) (**67**) and N(1); N(7), O (H_2O) (**68**) binding patterns of adjacently placed nucleobases were present in an approximately 1:1 ratio. The phosphate coordination was absent in the case of this Ir species in the presence of purine nucleoside 5′-triphosphate (2000ICA115).

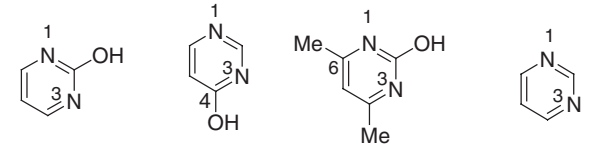
6-Thiopurine ribose (**22D**) reacted with **62** to form cyclic hexameric complex $[Cp^*Ir(6\text{-Putrb})]_6(CF_3SO_3)_6$, similar to **52** (2001AGE2268).

3. METALLACALIXARENES DERIVED FROM MODEL HETEROCYCLES

3.1 General

Simulation of the self-assembly reactions of nucleobases and appropriate metallic components in structurally simpler heterocyclic models elaborating similar structural set-up of two appropriately oriented binding sites would provide a broader perspective to this approach of generating new metallacalixarene-based chemical architectures of relevance in devising functional materials. Evidently, the first choice was pyrimidine and imidazole systems as these are constituents of nucleobases. However, heterocyclic systems such as 2,2′-bipyrazine and 4,7-phenanthroline also elaborate two angularly placed coordinating nitrogens. The reactions of these four categories of heterocycles with various metallic components are detailed here.

3.2 Metallacalixarenes based on pyrimidines



The deoxyuracil derivatives-2-hydroxypyrimidine (**69**) (2-pymoH), 4-hydroxypyrimidine (**70**) (4-pymoH), 4,6-dimethyl-2-hydroxypyrimidine (**71**) (2-dmpymoH), and pyrimidine (**72**) (pym), shown here as the minor tautomer, have provided metallacalixarenes having closer resemblance to classical calixarenes, as compared with those obtained from uracil. The reactions of $[(en)M(H_2O)_2](NO_3)_2$ ($M = Pd^{II}$ and Pt^{II}) with 2-pymoH in water gave tetranuclear metallacalixarenes $[(en)Pd(2\text{-pymo-}N1;N3)]_4(NO_3)_4$ (**73**) and $[(en)Pt(2\text{-pymo-}N1;N3)]_4(NO_3)_2$ (**74**) (2000IC2301). As compared with uracil-based systems, the appearance of one set of resonances for each of pyrimidine H, in their ^1H NMR spectra showed fast

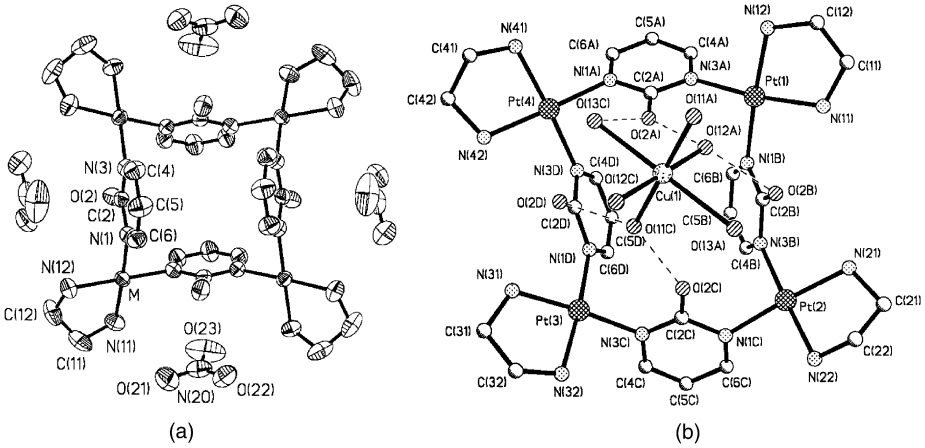


Figure 28 (a) X-ray structure of complexes **73** and **74** (M = Pd^{II} or Pt^{II}) (b) perspective view of the interaction between $[Cu(H_2O)_6]^{2+}$ and a tetranuclear $[(en)Pt(2\text{-pymo-}N1;N3)]_4^{4+}$ in **75**. (Reprinted with permission from 2000IC2301, Copyright 2000, American Chemical Society.)

rotation around M–N bonds and rapid conformational changes in solution. In the solid state, X-ray structures display a 1,3-alternate arrangement of 2-pymo residues (Figure 28a) where nitrate anions are H-bonded through en NH_2 and their stacking produces long channels. Metallacalixarenes **73** and **74**, despite their high positive charge, are unable to include anions, as the cavity is too small [C5–C5 separation of ~4.3 Å] to permit the inclusion of guest molecules.

In contrast to $[(en)Pt(UH\text{-}N1,N3)]_4^{4+}(NO_3)_4$ (**5**), there is no evidence of the interaction (^{1}H NMR) of either soft (Pt^{II}, Pd^{II}) or hard (Na^{I}, Ba^{II}, La^{III}) metal ions with **73** or **74**, which could be attributed to the low basicity of 2-oxo oxygens of pyrimidine residues. The recrystallization of **73** from ~1 M $HClO_4$ gave the adduct $\{[(en)Pt(2\text{-pymo-}N1;N3)]_4(ClO_4)_4\}_2 \cdot [H_{20}O_8](ClO_4)_4$ in which $HClO_4$ does not protonate the oxygens of 2-pymo residues and $[H_{20}O_8]^{4+}$ $(ClO_4)_4$ is sandwiched between two tetranuclear cations as a result of multiple H-bonding interactions with the oxo surface of two metallacalix[4]arenes. Again, a pinched-cone conformation of the 2-pymo residues is realized. Metallacalixarene **74** and $Cu(ClO_4)_2 \cdot 6H_2O$ formed 2:1 adduct, $[(en)Pt(2\text{-pymo-}N1;N3)]_4(ClO_4)_4\}_2 \cdot [Cu(H_2O)_6](ClO_4)_2 \cdot 9H_2O$ (**75**) (Figure 28b) in which Cu^{II} does not coordinate directly to the oxo surface of the metallacalix[4]arene but interacts strongly through H-bonding between the water molecules coordinated to the Cu^{II} center and the oxo-surfaces of the two metallacalix[4]arene **74** units. As a consequence, the 1,3-alternate conformation of **74** switches to a pinched cone conformation (2000IC2301) in which two 2-pymo residues are too close (C5–C5 separation of 3.63(3) Å), while the other two 2-pymo residues are 10.45(3) Å apart, making it unsuitable for inclusion of a guest molecule.

The conformationally flexible metallacalixarene $[(en)Pd(2\text{-dmpymo})]_4^{4+}$, formed by self-assembly of 2-dmpymoH and $[(en)Pd(H_2O)_2]^{2+}$, reacts with $Gd(NO_3)_3$ in aqueous solution to form $\{Gd(NO_3)_2(H_2O)[(en)Pd(2\text{-dmpymo-}N1;N3)]_4\}^{5+}(NO_3)_5 \cdot 8H_2O$ (**76**). Its X-ray structure (Figure 29) shows that the

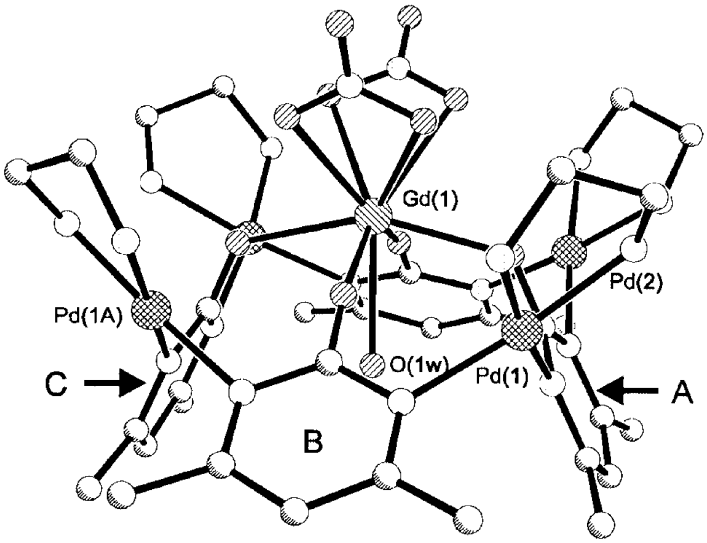


Figure 29 X-ray structure of the cation of $\{Gd(NO_3)_2(H_2O)[(en)Pd(2\text{-dmpymo-}N1;N3)]_4\}(NO_3)_5 \cdot 8H_2O$ (**76**). (Reprinted with permission from 2000CC235, Copyright 2000, Royal Society of Chemistry.)

large-sized Gd^{III} is bound to four oxygens of 2-dmpymo moieties and all the 2-dmpymo residues are oriented in the same direction affording a cone conformation with 7.82(2) Å and 10.64(2) Å separation between two opposite 2-dmpymo residues (2000CC235). The water molecule coordinated to the Gd^{III} center and included in the metallacalixarene cavity, alters the hydrophobic character of the cavity and allows the inclusion of an additional water molecule and a nitrate anion inside the cavity.

The 1:1 reactions between $[(R,R\text{-dach})Pd(H_2O)_2]^{2+}$ or $[(S,S\text{-dach})Pd(H_2O)_2]^{+2}$ with 2-pymoH, 4-pymoH, and 2-dmpymoH provided corresponding enantiopure tetrameric metallacalixarenes of general formula $[(R,R\text{-}/S,S\text{-dach})Pd(2\text{-pymo-}N1;N3)]_4(NO_3)_4 \cdot 14H_2O$ (**77a**/**77b**) (Figure 30a); $[(R,R\text{-}/S,S\text{-dach})Pd(4\text{-pymo-}N1;N3)]_4(NO_3)_4 \cdot 12H_2O$ (**78a**/**78b**); $[(R,R\text{-}/S,S\text{-dach})Pd(2\text{-dmpymo-}N1;N3)]_4(NO_3)_4 \cdot 10H_2O$ (**79a**/**79b**) (2003CEJ4414). In the case of reactions with 2-dmpyoH, the crystallizations from dilute solutions gave respective metallacalix[6]arenes $[(R,R\text{-}/S,S\text{- dach})Pd(2\text{-dmpymo-}N1;N3)]_6(NO_3)_6$ (**80a**/**80b**) (Figure 30b). On ^1H NMR monitoring of the self-assembly process, the formation of **80a/80b** could also be noticed along with their respective tetrameric species. Also, on heating above 60 °C, **80a/80b** underwent conversion to the entropically favored tetrameric products **79a/79b**. Thus it has been possible to engineer the size and functionalization of the metallacalixarenes by appropriate choice of the reaction conditions and pyrimidine derivatives.

Tetranuclear **77–79** and hexanuclear **80** systems, in their X-ray structures, show respective 1,3 and 1,3,5 alternate arrangements and the latter was folded because of the hydrophobic interactions between methyl protons and 2-dmpymo

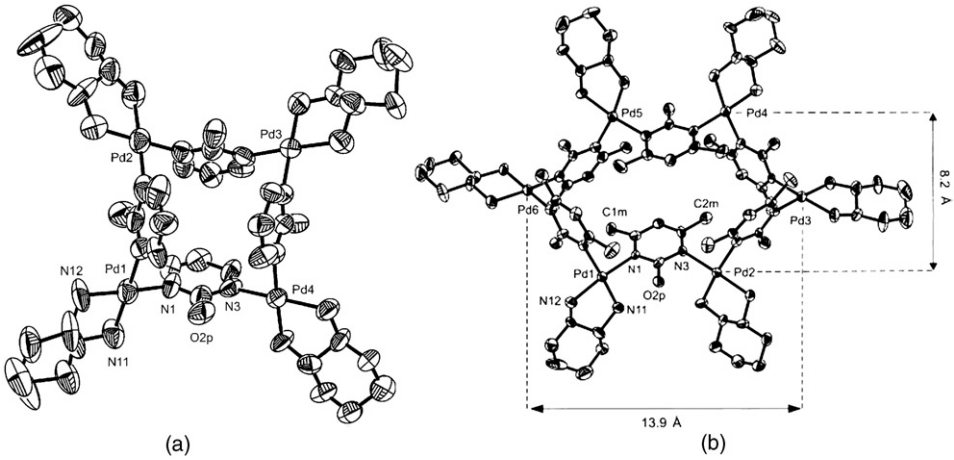
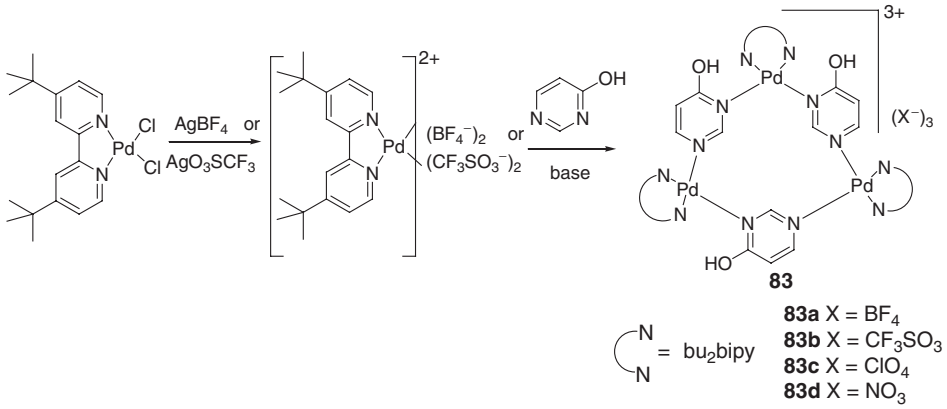


Figure 30 X-ray crystal structure of the cation of (a) [(*S,S*-dach)Pd(2-pymo-*N1;N3*)]$_4$ $(NO_3)_4 \cdot 14H_2O$ (**77b**) (b) [(*S,S*-dach)Pd(2-dmpymo-*N1;N3*)]$_6$ $(NO_3)_6$ (**80b**). (Reprinted with permission from 2003CEJ4414, Copyright 2003, Wiley.)

π- electrons. Both **77a** and **77b** on co-crystallization with $NaNO_3$ and $La(NO_3)_3$ gave {Na[(dach)Pd(2-pymo-*N1;N3*)]$_4$}$(NO_3)_5$ (**81**) and {La[(dach)Pd(2-pymo-*N1;N3*)]$_4$}$(NO_3)_7$ (**82**). In **81**, two hydrated Na^I ions were found in the asymmetric units composed of two crystallographically independent tetranuclear cations. Only one of the two Na^I ions was bound directly to one exocyclic pyrimidine oxygen atom of parent 1,3- tetramer **77**. **77a** and **77b** on reactions with lanthanum salts gave adducts and implied a 1,3-alternate to cone conformational change during complexation. In contrast, the non-formation of adducts of La^{III} with **78** and **79** could be attributed to the sterically hindered rotation about the Pd–N bonds between bulky methyl substituents and dach. Only **79a** and **79b** showed selective molecular recognition of adenosine 5′-monophosphate among adenosine, guanosine, thymidine, and cytidine 5′-monophosphates. These results point to the possibility of employing metallacalixarenes as selective metal-based DNA-binding drugs (2003CEJ4414).

In a unique self-assembly process, $[Pd(bu_2bipy)(thf)_2]BF_4^-/CF_3SO_3^-$ reacted with 4-pymoH under basic conditions to form trimeric products [(bu_2bipy)Pd(4-pymo-*N1;N3*)]$_3X_3$ (**83a**) (X = BF_4), **83b** (X = CF_3SO_3) (2002IC3967) (Scheme 4). On reaction with tetrabutylammonium perchlorate/nitrate, **83a** provided **83c**/**83d**. The steric bulk of the bu_2bipy chelating ligand probably forced the Pd to form a trimer as in the case of chelation with dach where the tetrameric product was formed (2000IC2301). In solution phase (^{1}H NMR), the presence of six resonances in the aromatic region, two in the *t*-butyl region for the bu_2bipy ligand showed non-equivalence of the two pyridyl rings. These signals along with three resonances for 4-pymo ligands were consistent with structure **83a**.

In the X-ray structure of **83a**, each of the three Pd^{II} centres is bound to four nitrogen atoms adopting a slightly distorted square planer coordination geometry (Figure 31) and an almost perfect equatorial triangle with 5.88 Å edges.



Scheme 4 Synthesis of metallacalixarenes **83**.

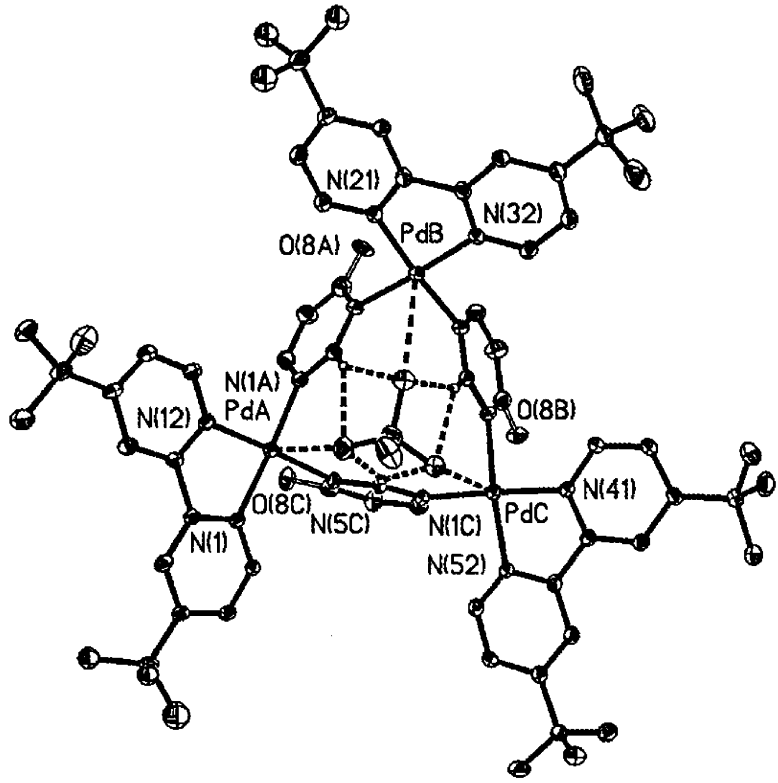


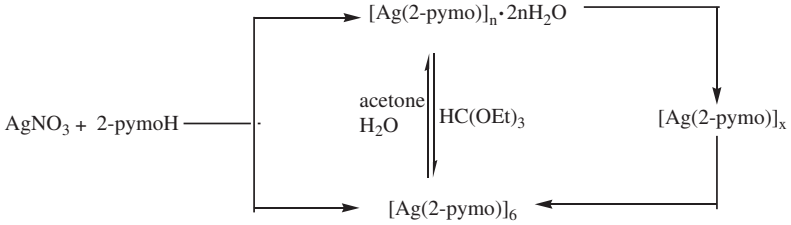
Figure 31 X-ray crystal structure of the cation of $[(bu_2bipy)Pd(4\text{-}pymo\text{-}N1;N3)]_3\ (BF_4)_3$ (**83a**). (Reprinted with permission from 2002IC3967, Copyright 2002, American Chemical Society.)

The 4-pymo rings are placed in the same direction (*syn*, *syn*, *syn*) at angles of 68.7°, 69.8°, and 68.7° with respect to the Pd_3 plane to form the cone conformation of the metallacalix[4]arene **83a** whereas related trimers formed from imidazolate and benzimidazolate ligands have the *syn*, *anti*, *anti* conformation (99AGE669, 92JCS(CC)321). The bowl formed by the three 4-pymo residues of **83a** is too small to accommodate guest molecules but the opposite side of the bowl, the open cavity defined by the $[(bu_2bipy)Pd]^{2+}$ residues, can accommodate one of the three tetrafluoroborate anions with three of the fluorine atoms directed towards the cationic Pd^{II} centers.

In addition, three fluorine atoms also form weak C–H…F H-bonds with three C(2)–H groups of the 4-pymo residues. The ^1H NMR titrations of **83a** with various anions have revealed that weakly binding anions such as HSO_4^-, NO_3^-, ClO_4^-, and $CF_3SO_3^-$ bind in the open cavity on the opposite side of the cone cavity of the **83a** whereas strongly binding anions $H_2PO_4^-$, CH_3COO^-, Cl^-, Br^- cleave **83a** (2002IC3967).

The combinations of pyrimidine endocyclic N (120°) with linear metal fragments mostly form polymeric materials but formation of tetra and hexameric metallacalixarenes have also been reported (2005JSSC2436). The reaction of 2-pymoH with $AgNO_3$ in acetonitrile in the presence of Et_3N gave hexameric metallacalixarene [Ag(2-pymo-*N1*;*N3*)]$_6$ (**84**). It also has been obtained from zig-zag polymeric $[Ag(2\text{-pymo})]_\infty \cdot 2\infty H_2O$ (**85**) either by thermal treatment or by its reaction with $HC(OEt)_3$ (97IC5648). The reversibility of the latter process has been realized by quantitative formation of **85** on stirring **84** in wet acetone (Scheme 5). XRPD analysis reveals non-planarity of the six 2-pymo ligands about the hexagonal Ag_6 with dihedral angles between adjacent 2-pymo rings of about 20 or 70°. Apparently the large cavity in the center of the hexamer is occupied by the tails of non-planar molecules.

Another hexagonal system [Cu(2-pymo-*N1*;*N3*)]$_6$ (**86**) has been identified in the grooves of polymeric $[Cu(2\text{-pymo-}N1;N3)]_\infty$ formed from $[Cu(MeCN)_4]BF_4$ and 2-pymoH (**69**) (98AGE3366). However, the reactions of CuY_2 [Y = Cl, NO_3, $(SO_4)_{1/2}$] with **69** in the presence of MX (M = NH_4, CH_3NH_3, Li, K, Rb; X = ClO_4, BF_4, PF_6) gave highly crystalline materials of formula $[Cu(2\text{-pymo-}N1;N3)_2](MX)_{1/3}(H_2O)_{4/3}$ (**87**). In **87,** Cu^{II} ions are coordinated to four nitrogen donor atoms of four different 2-pymo moieties, each one symmetrically bridging two Cu centers (2001JA383). In this way, tetranuclear and hexanuclear molecular boxes analogous to calix[n]arenes ($n = 4$, 6) along with planar hexanuclear



Scheme 5 Reversibility between various $[Ag(2\text{-pymo})]_x$ derivatives.

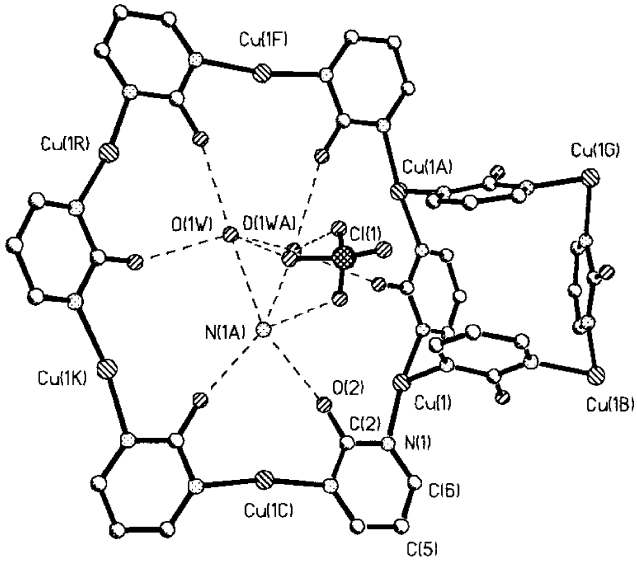


Figure 32 The X-ray crystal structure of a segment from **87** · NH_4ClO_4 polymer framework. (Reprinted with permission from 2001JA383, Copyright 2001, American Chemical Society.)

molecular hexagons are generated. These three structural motifs are interlocked to give a highly symmetric three dimensional framework that acts as a host for NH_4ClO_4. The $[Cu(2\text{-pymo})_2]_\infty$ framework in **87** · NH_4ClO_4 (Figure 32) accounts for ~80% of the total volume in the unit cell and the remaining ~20% is filled with NH_4 and ClO_4 ions and water molecules. The pores of 8.1 Å diameter are defined by planar $[Cu_6(2\text{-pymo-}N1;N3)_6]$ molecular hexagons and contain an NH_4 cation and two water molecules. Each of these pores connects two cavities of ~14 Å diameter in which two ClO_4 anions are included.

Organo-inorganic molecular architecture **87** elaborates rich host–guest chemistry. The facile exchange of ammonium in **87** · NH_4ClO_4 with Li^I, Na^I, K^I, and Rb^I on treatment with aqueous solutions of perchlorates gave respective **87** · $MClO_4$ clatharates. However, exchange of NH_4^+ with Cs^I, alkaline earth and lanthanides could not occur. Nitrogen sorption at 77 K by empty host **87** reveals its microporous nature with BET surface area of 200 $m^2 g^{-1}$. Hydrated **87** loses water on heating and when exposed to moist air regenerates the original hydrated material. Likewise, **87** · NH_4ClO_4 loses ammonia upon heating, giving the corresponding activated acidic material **87** · $HClO_4$ which upon exposure to gaseous ammonia regenerates **87** · NH_4ClO_4. Similarly, 3D polymeric $[Cu(4\text{-pymo-}N1;N3)_2 \cdot nH_2O]_\infty$ framework, formed from 4-pymoH and CuX_2 in the presence of NH_3, reversibly absorbs N_2 and water vapors with minimal structural changes (2003POL3051).

In a skillfully performed reaction of pyrimidine (**72**) with $AgNO_3$, $[Ag(Pym\text{-}N1;N3)]_4(NO_3)_4$ (**88**) was formed. Its X-ray crystal structure shows tetrameric cyclic self-assembly forming supramolecular 1:1 Ag^I:pyrimidine squares [3.8 × 3.8 Å] which exist in planar sheets with each square face to face stacked

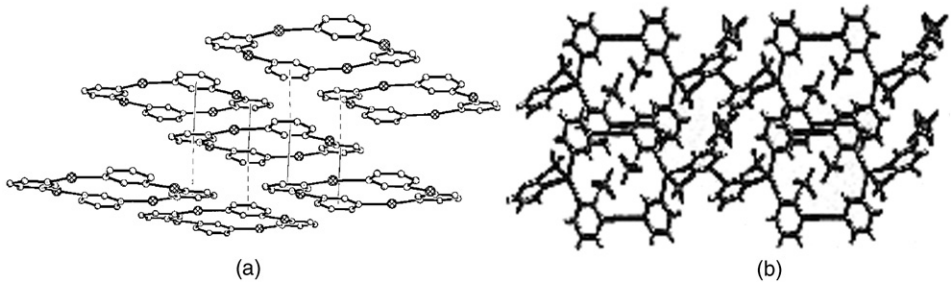


Figure 33 (a) The supramolecular squares of **88** showing face-to-face stacking to six other squares. (b) The supramolecular structure of **89** with vertically cross linked pym units. (Reprinted with permission from 98CC215, Copyright 1998, Royal Society of Chemistry.)

to six other squares (Figure 33a). The nitrate ions are inside the open channel structure which facilitates the exchange with other anions (98CC215). The crystals of **88** on suspending in methanolic $NH_4\,^{99}TcO_4$ underwent exchange of nitrate ions with TcO_4^-. The crystallization of $AgClO_4$ with Pym gave 1D coordination polymer $[Ag_{2.5}(Pym\text{-}N1;N3)_3][ClO_4]_{2.5}$ (**89**), having supramolecular squares similar to **88** but these squares are crosslinked by a dimeric pymo unit vertically in a stair case fashion (Figure 33b).

3.3 Metallacalixarenes based on imidazoles and benzimidazoles

The imidazole ring, an ubiquitous ligand in chemical and biological systems, has two angularly disposed ligating nitrogen atoms (150°) and reacts with appropriate metal complexes or organometallics in a self-assembled manner to form corresponding metallacalixarenes. Thus $[Cu(ImH)_2(OAc)_2]$, obtained *in situ* from imidazole (ImH) and $Cu(OAc)_2$, on reaction with 1,4,7-trimethyl-1,4,7-triazacyclononane (L^2) followed by treatment with sodium perchlorate formed an imidazolate bridged trinuclear complex $[(L^2)_3Cu_3(Im\text{-}N1;N3)_3](ClO_4)_3$ (**90**), a Cu^{II} analogue of calix[3]imidazole (93IC888). In its X-ray structure (Figure 34a), each Cu^{II} is placed at the corner of an equilateral triangle with the Cu–Cu separation of 5.92 Å and is coordinated to N(1) and N(3) of adjacently placed nearly planar imidazoles and three nitrogens of the cyclic amine (92JCS(CC)321). On replacing the tricyclic amine L^2 with 1,4,7-triazacyclononane (L^3), the same reaction provided the tetranuclear system $[(L^3)_4Cu_4(Im\text{-}N1;N3)_4](ClO_4)_4 \cdot 2H_2O$ (**91**). Its X-ray structure (Figure 34b) showed that the four Cu^{II} ions lie in a plane and form an approximate parallelogram with sides 5.89 Å and 5.99 Å (93IC888). These complexes are of interest from a magneto structural and a bio modeling standpoint. The complex **90** constitutes a first-generation model for the active site of ascorbate oxidase and both **90** and **91** display antiferromagnetic character.

Using benzimidazole (BzimH) as the non-linear bridging motif, luminescent platinum(II) trimeric systems $[Pt(thpy)(Bzim)]_3$ (**92**) and $[Pt(bzqn)(bzim)]_3$ (**93**) have been synthesized from sodium benzimidazolate and luminescent

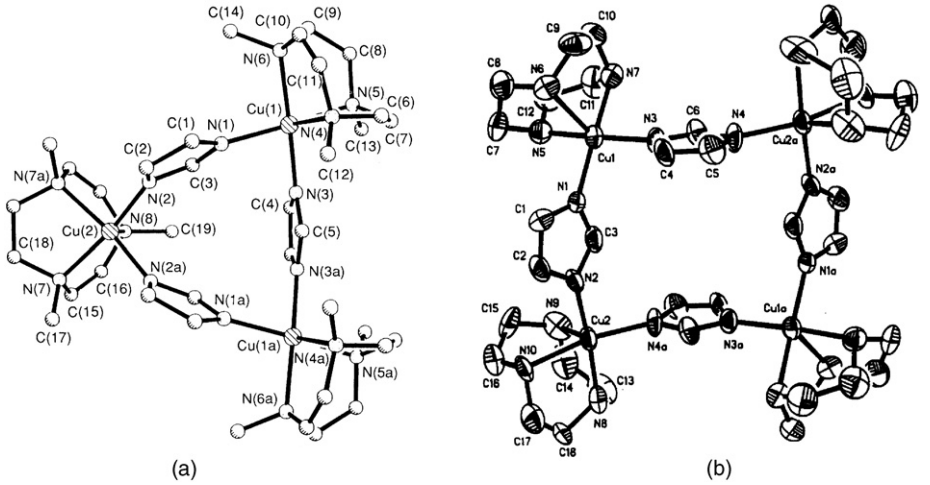


Figure 34 X-ray crystal structures of cations of (a) $[(L^2)_3Cu_3(\text{Im-}N1;N3)_3](ClO_4)_3$ (**90**) (b) $[(L^3)_4Cu_4(\text{Im-}N1;N3)_4](ClO_4)_4 \cdot 3H_2O$ (**91**). (Reprinted with permission from 92JCS(CC)321, Copyright 1992, Royal Society of Chemistry; 93IC888, Copyright 1993, American Chemical Society.)

cyclometalated Pt^{II} precursors [Pt(thpy)(thpyH)Cl] and $[n\text{-}Bu_4N][Pt(bzqn)Cl_2]$, respectively (99AGE669). The trimeric nature of **92**, consisting of alternating thpy vertices and benzimidazole edges has been confirmed by X-ray crystallography (Figure 35). The bzim groups are oriented in *syn*, *anti*, *anti* (two-up, one-down) fashion to create a partial cone conformation. From the mean plane through the Pt atoms, the angle to the *syn* bzim units is 60°, while the inclination of the *anti* one is 77°.

In the above synthetic approaches, monomers undergoing self-assembly have been generated *in situ* only. In an alternate approach, preformed monomeric Cu^{II} complexes of multidendate Schiff base ligands containing imidazole, stabilized as protonated species and having potential donor–acceptor character, act as self complementary building blocks and under basic conditions through coordination of the imidazolate nitrogen of one unit to Cu^{II} ion of the adjacent unit, generate Cu^{II} analogs of calix[4]imidazole (2002CCR199). Here, an appropriate choice of bulky ligands such as $L^{4–8}$ (Figure 36) imposing steric restrictions to facilitate cyclic self-assembly is evident. In the monomeric copper complexes with one donor and one acceptor sites per molecule, the assembly structure is easily predictable but in the case of multiple donor and/or acceptor sites, such a prediction could be difficult.

The mononuclear Cu^{II} complex $[Cu(HL^4)Cl]ClO_4$, formed from 4-formylimidazole, *N,N*-dimethyl-propane-1,3-diamine, $CuCl_2 \cdot H_2O$ and $NaClO_4$, on treatment with Et_3N formed $[(CuL^4)_4](ClO_4)_4$ (**94**) (93JCS(DT)2157). Its X-ray structure (Figure 37) shows a cyclic tetranuclear molecule in which each imidazolate nitrogen atom coordinates axially to the Cu^{II} ion of the adjacent unit.

The reactions of $CuCl_2 \cdot 2H_2O$ with Schiff bases HL^{5a} and HL^{5b} gave monomeric complexes $[Cu(HL^{5a})Cl_2]$ (**95**) and $[Cu(HL^{5b})Cl_2]$ (**96**) as light green

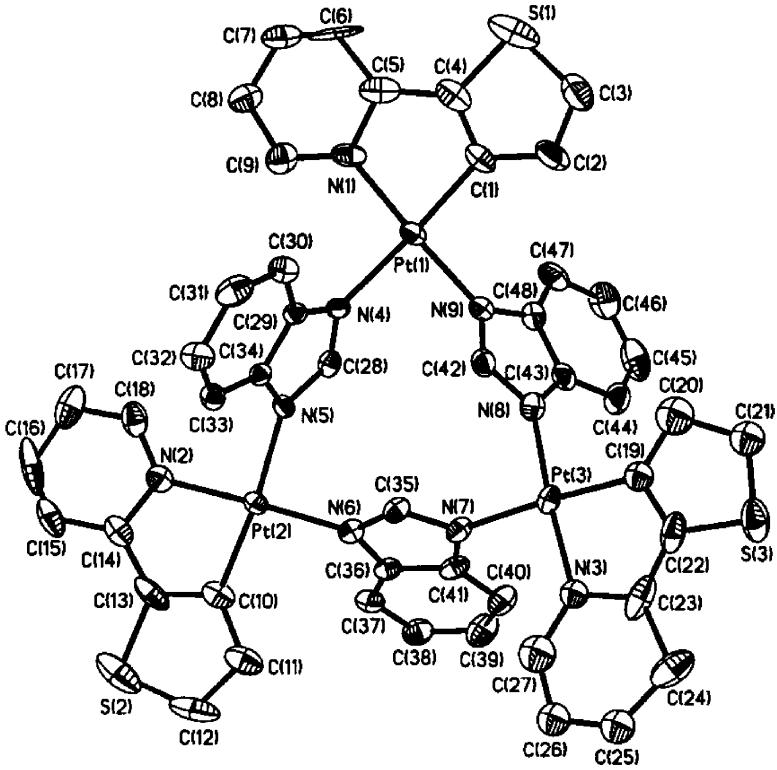


Figure 35 X-ray structure of [Pt(thpy)(bzim)]$_3$ (**92**). (Reprinted with permission from 99AG669, Copyright 1999, Wiley.)

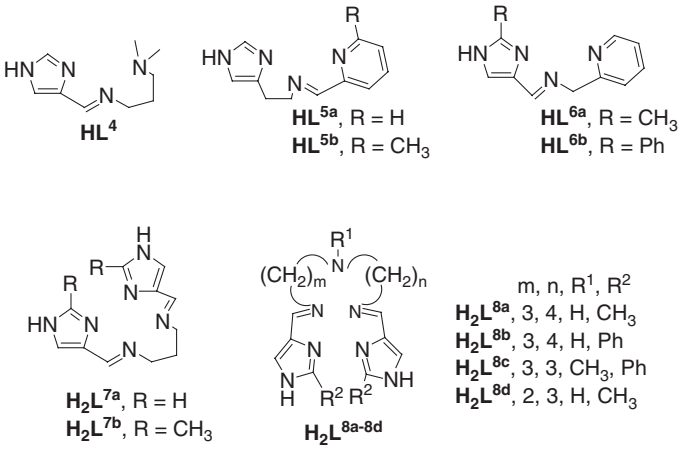


Figure 36 Structures of ligands L^4–L^8.

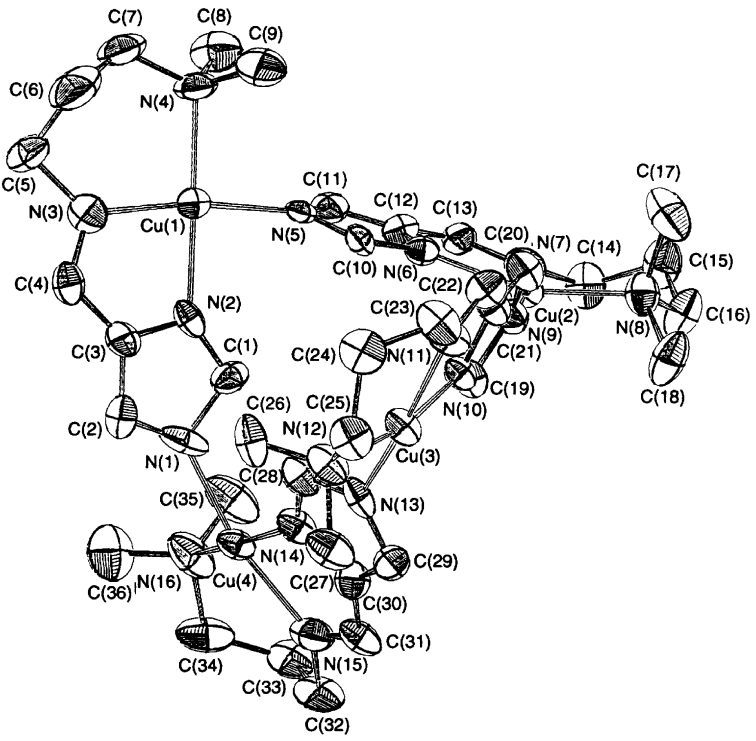
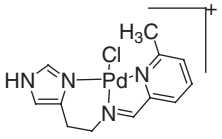


Figure 37 X-ray structure of the cation of $[(CuL^{4})_4](ClO_4)_4$ (**94**). (Reprinted with permission from 93JCS(DT)2157, Copyright 1993, Royal Society of Chemistry.)

crystals. The complex **95** on sequential treatment with sodium hydroxide and sodium perchlorate through self-assembly formed tetrameric metallacalixarene $[\{Cu(L^{5a})\}_4]^{4+}$ (**97**). On using **96**, having a 2-methyl group on a pyridine unit, a blue-coloured hexameric metallacalixarene, $[\{Cu(L^{5b})\}_6](ClO_4)_6$ (**98**) was formed and clearly indicated the role of steric bulk on the ligand in determining the nuclearity of the self-assembled system (2002CCR199). On treatment with HCl, **98** showed a visibly reversible interconversion to **96**. Its X-ray structure shows a tubular shape with a cylindrical cavity (radius ~4 Å). A constriction in the middle of the cylindrical cavity delineates two half-cavities (97AGE1860).

The protonated monomeric Pd^{II} complex $[Pd(HL^{5b})Cl]Cl$ (**99**), formed in a manner similar to that of **96**, on treatment with NaOH and $NaClO_4$ formed the self-assembled deprotonated cyclic tetramer $[\{Pd(L^{5b})\}_4](ClO_4)_4$ (**100**) (97AGE1860). Thus, the metal ion also determines the nuclearity of the oligomeric species through its coordinative requirements.



99

The monomeric copper complexes **101** and **102** obtained from 2-aminoethylpyridine, 2-Me (L^{6a})/Ph (L^{6b})-4-formylimidazole and $CuCl_2$, again constitute modular building units able to induce self-assembly *via* formation of metal-imidazolate coordination bonds. On treatment with base, **101** and **102** respectively gave $[Cu_4(L^{6a})_4](ClO_4)_4$ (**103**) (Figure 38a) and $[Cu_6(L^{6b})_6](ClO_4)_6$ (**104**) (Figure 38b) which could be converted to $[Cu_6(L^{6b})_6](PF_6)_6$ (**105**). Their structures have been confirmed through X-ray structural analysis and FAB-MS spectra (99IC1165). It may be seen that as in the case of the pyridine unit in L^5, the substitution profile of the imidazole unit in L^6, also tunes the nuclearity of self- assembled structures. The cyclic structures of **103**, **104** (Figure 38b) reveal that 2-imidazolate substituents of adjacent modular units orient themselves in directions opposite to each other resulting in face-to-face disposition of substituents of alternating units imposing steric repulsion, also evident in space filling models. Thus a hexanuclear structure is more favorable in the case of **104** having phenyl substituents.

The monomers $[Cu(H_2L^{7a})]NO_3$ (**106**) and $[Cu(H_2L^{7b})Cl]NO_3$ (**107**) obtained by 2:1 condensations of corresponding 4-formylimidazole with 1,4-diaminobutane and copper salts, in their X-ray structures reveal a bent butterfly shape imposing non-equivalence of two imidazoline moieties (98IC3553). On base induced self-assembly, **106** having unsubstituted imidazoles formed an infinite zig-zag chain but **107** having 2-methylsubstituted imidazoles gave cyclic product $[Cu(HL^{7b})]_4(NO_3)_2Cl_2 \cdot 1.25H_2O$ (**108**) which could also be further deprotonated. The difference in these modes of self-assembly has been explained due to the non-equivalence of two imidazoles with respect to their deprotonation process

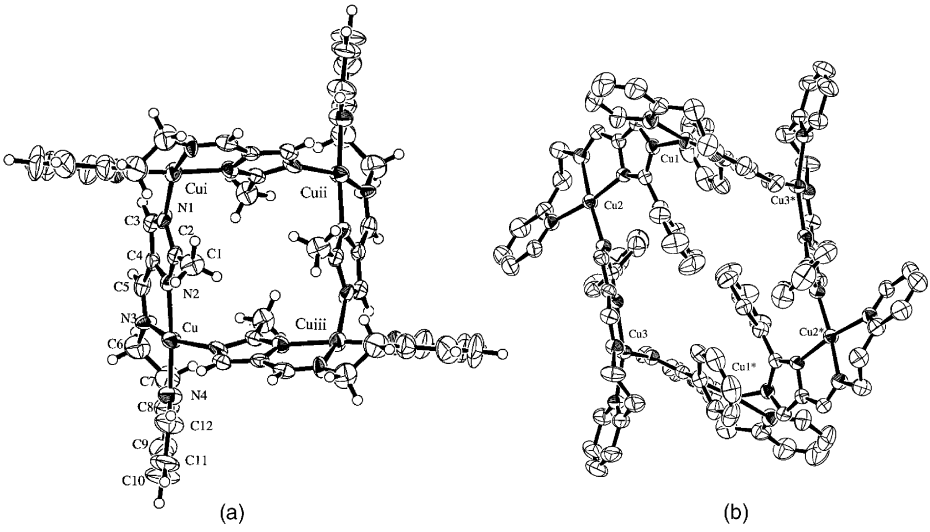


Figure 38 X-ray crystal structures of the cations of (a) $[Cu_4(L^{6a})_4](ClO_4)_4$ (**103**); (b) $[Cu_6(L^{6b})_6](ClO_4)_6$ (**104**). (Reprinted with permission from 99IC1165, Copyright 1999, American Chemical Society.)

and thereby oligomerization. In its X-ray structure, **108** (Figure 39) consists of an imidazolate-bridged cyclic tetranuclear molecule described as a molecular square with two nitrate and two chloride anions and water molecules (98IC3553).

The strand-type protonated complexes $[Cu(H_2L^{8a–d})](ClO_4)_2 \cdot xH_2O$ of pentadendate Schiff-base ligands containing two imidazole groups were synthesized from appropriate triamine cap, 4-formylimidazole derivative and $CuCl_2$ (99IC3513). The monodeprotonated copper complexes of $HL^{8a–c}$ contain one imidazole and one imidazolate groups per unit and are clockwise or anticlockwise enantiomorphs due to the spiral arrangement of the ligand around the Cu^{II} ion. These function as chiral building components for self-assembly process resulting from the formation of hydrogen bonds between the imidazole and imidazolate groups of adjacent units to yield 1D zigzag-chain structures. In a unique manner, $[Cu(H_2L^{8d})]^{2+}$ complex on deprotonation forms $[Cu(HL^{8d})_4](ClO_4)_4 \cdot 16H_2O$ (**109**) (Figure 40) where four $[Cu(HL^{8d})]$ units are bridged into a tetranuclear cyclic structure. The most interesting feature of **109** is the formation of a hexahydropyrimidine ring derived from the parent ligand H_2L^{8d} involving base induced partial dissociation of the secondary amine followed by its attack on an imine carbon resulting in ligand rearrangement to a

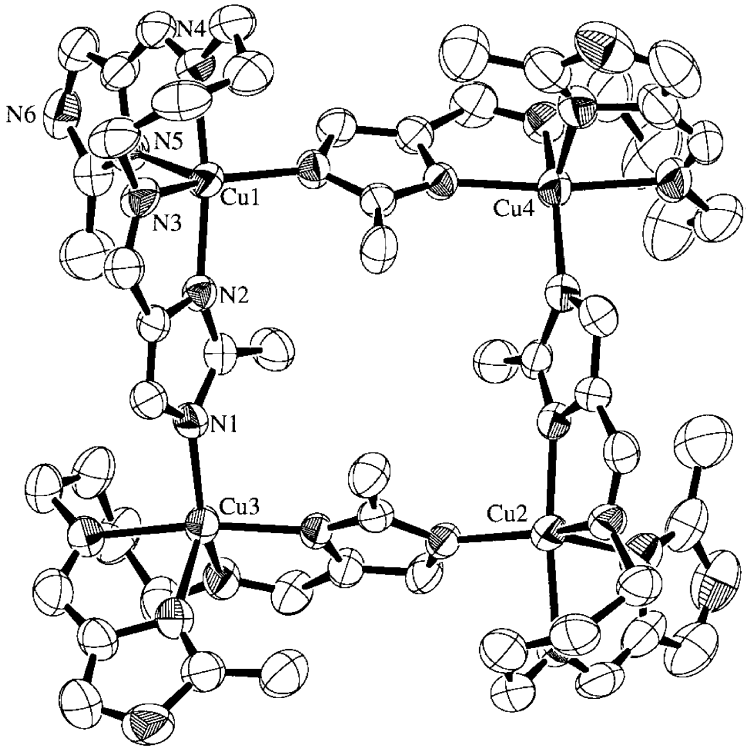


Figure 39 X-ray crystal structure of the cation of $[Cu(HL^{7b})]_4(NO_3)_2Cl_2 \cdot 1.25H_2O$ (**108**). (Reprinted with permission from 98IC3553, Copyright 1998, American Chemical Society.)

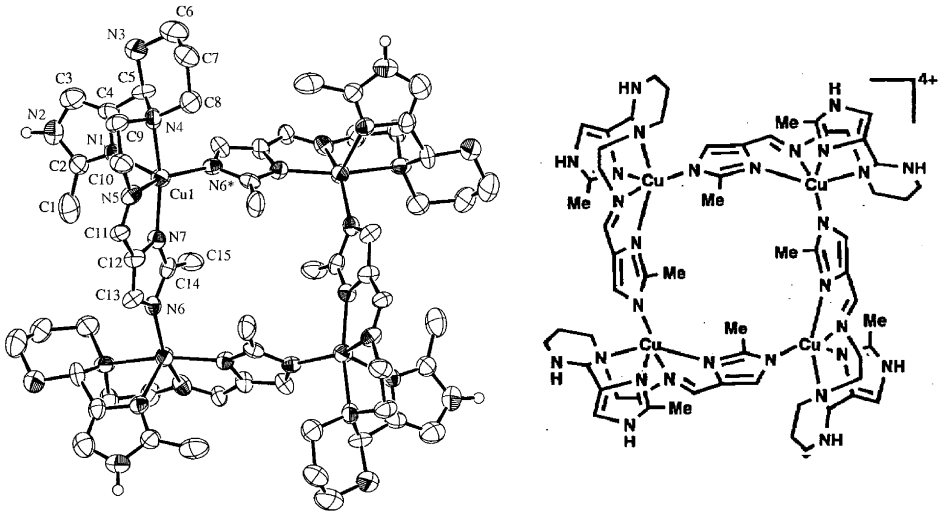


Figure 40 X-ray crystal structure of (a) the cation of $[Cu(HL^{8d})_4](ClO_4)_4 \cdot 16H_2O$ (**109**) and (b) a schematic presentation of **109**. (Reprinted with permission from 99IC3513, Copyright 1999, American Chemical Society.)

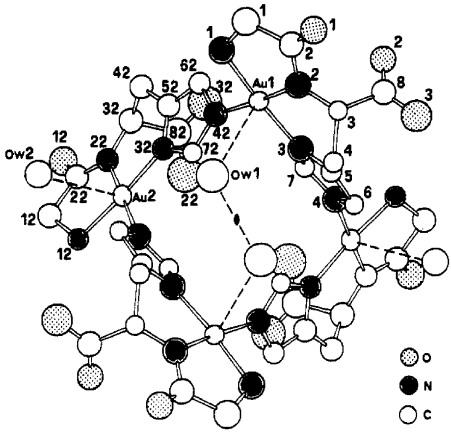


Figure 41 X-ray crystal structure of $[Au(Gly\text{-}L\text{-}His)]_4$ (**110**). (Reprinted with permission from 92IC1983, Copyright 1992, American Chemical Society.)

hexahydropyrimidine ring. Thus while mononuclear precursor $[Cu(H_2L^{8d})]$ is pentacoordinated, the ligand in **109** is tetradentate.

The mononuclear complex $[Au(gly\text{-}L\text{-}his)Cl]Cl \cdot 3H_2O$ formed from $H[AuCl_4]$ and gly-L-his · HCl at pH 1.5–2, unlike all other cases where alkaline conditions are essential for oligomerization, readily forms the cyclic tetramer $[Au(Gly\text{-}L\text{-}His)]_4$ (**110**) at pH 6–7 (92IC1983). In the X-ray structure of **110** (Figure 41), each Au^{III} is surrounded by the three nitrogen donor set as in the

precursor and a fourth nitrogen of the deprotonated imidazole ring and four water molecules interact both inside and outside the molecule.

Imidazole-4-carboxylic acid ($ImacH_2$) (**111**) on reaction with $[Cp^*RhCl_2]_2$ in the presence of Ag_2O as base formed a metallacalixarene $[Cp^*Rh\text{-}(Imac\text{-}N1;N3,O4)]_4$ (**112**). Its ^1H NMR is highly symmetrical and single crystal X-ray structure (Figure 42, Scheme 6) reveals it as a tetrameric self-assembly in which the two-fold deprotonated ligands bridge the Cp^*Rh fragments. Overall, the complex displays S_4 symmetry and the 5-membered N, O- chelate ring is nearly planar (2004IC1609).

In a different complementary approach, a self-assembled monomeric bridged dicopper(II) cation **114**, formed from bpimH (**113**) and Cu^{II}, on condensation with bidentate imidazolate formed the tetranuclear metallacalixarene

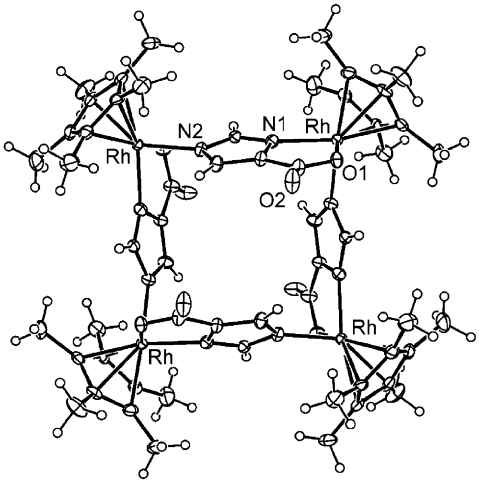
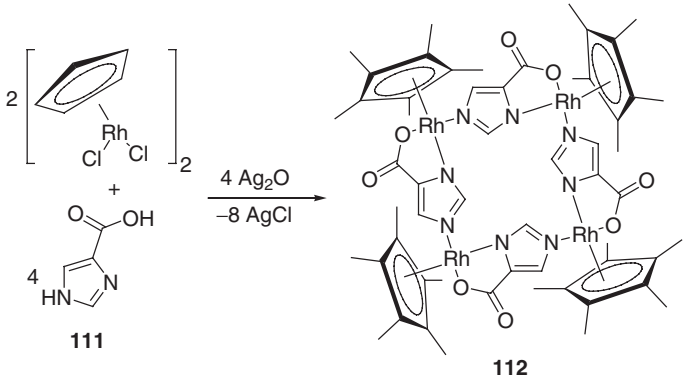
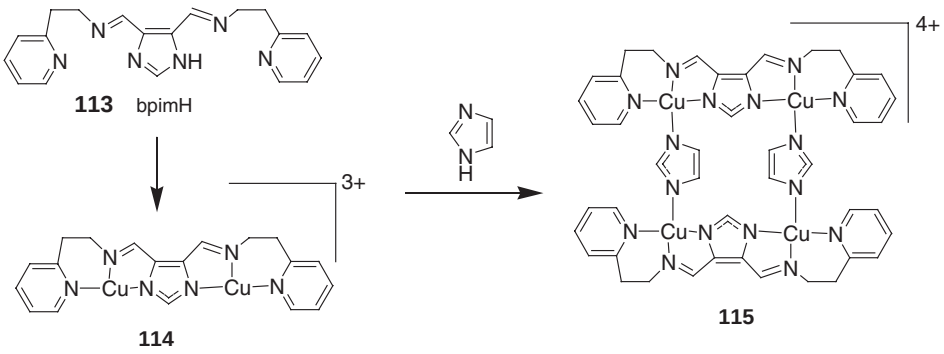


Figure 42 X-ray structure of $[Cp^*Rh\text{-}(Imac\text{-}N1;N3,O4)]_4$ (**112**). (Reprinted with permission from 2004IC1609, Copyright 2004, American Chemical Society.)



Scheme 6 Synthesis of $[Cp^*Rh\text{-}(Imac\text{-}N1;N3,O4)]_4$ (**112**).



Scheme 7 Synthesis of metallacalixarene $[Cu_2(bpim)(Im\text{-}N1;N3)]_2(NO_3)_4 \cdot 4H_2O$ (**115**).

$[Cu_2(bpim)(Im\text{-}N1;N3)]_2$ $(NO_3)_4 \cdot 4H_2O$ (**115**) (Scheme 7). Here, two sets of alternately placed imidazole nuclei are in different environments. Metallacalixarene **115** is unstable at both high and low pH but **114** is stable in pH range 3.5 to 11.5 (81IC2933).

3.4 Metallacalixarenes derived from 2,2′-bipyrazine and 4,7-phenanthroline

Some flexible organic ligands with at least two angularly disposed binding nitrogen donors react with metal salts to generate monomeric species having structural prerequisites for undergoing cyclic self-assembly. 2,2′-Bipyrazine (bpz) and 4,7-phenanthroline (4,7-phen) constitute two such species and have been used to create metal bridged cyclic oligomers in which organic ligands are not strictly 1,3- or *meta* linked as in calixarenes. But due to similarity of their structural set-up with calixarenes, these oligomers have been termed as metallacalixarenes (2005JSSC2436). The synthesis, structures, and anion interactions of these systems are elaborated here.

3.4.1 Metallacalixarenes based on 2,2′-bipyrazine

2,2′-Bipyrazine (bpz), through rotation around its C(2)–C(2′) bond elaborate *cis* and *trans* conformers. *Cis*-bpz on reaction with $(en)Pd^{II}$ formed only a mononuclear chelate $[(en)Pd(bpz\text{-}N1;N1')](ClO_4)_2$ (**116**) (98AGE119, 2000JA1381) but with $(en)Pt^{II}$ mainly *via* N(4),N(4′) metal coordination formed a unique trimeric cyclic system $[(en)Pt(bpz\text{-}N4,N4')]_3(NO_3)_6$ (**117**), alongwith a minor amount of $[(en)Pt(bpz\text{-}N1,N1')](NO_3)_2$ (**118**). The former, on prolonged heating in water quantitatively gave **118** (2000JA1381). ^1H NMR of metallacalixarene **117** revealed a number of interconvertible conformations in solution but crystallized in only an all *trans* rotamer. The formation of two types of structures with all *trans* and all *cis* conformations of bpz ligands have been triggered by the nature of the counter anion. In the X-ray structure of $[(en)Pt(bpz\text{-}N4,N4')]_3(NO_3)_2(PF_6)_4$ (**117a**) (Figure 43), cations with an all *trans* conformation and an all *cis* conformation

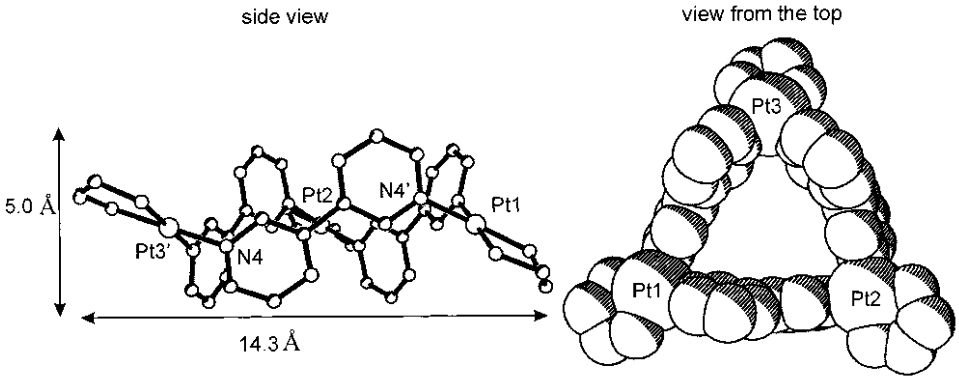


Figure 43 X-ray crystal structure of the cation of $[(en)Pt(bpz\text{-}N4,N4')]_3(NO_3)_2(PF_6)_4$ (**117a**). (Reprinted with permission from 2000JA1381, Copyright 2000, American Chemical Society.)

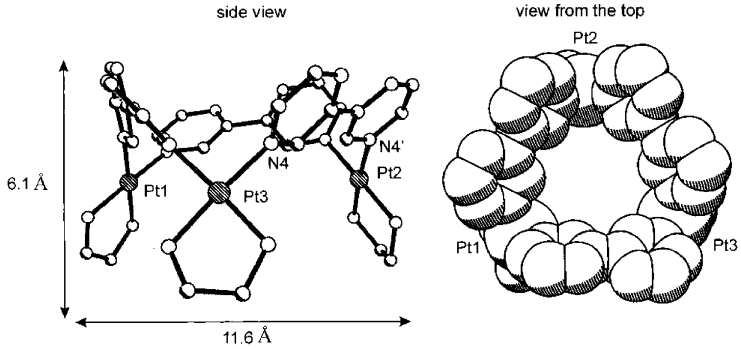


Figure 44 X-ray crystal structure of the cation of $[(en)Pt(cis\text{-}bpz\text{-}N4,N4')]_3(NO_3)_2(ClO_4)_4 \cdot 2H_2O$ (**117b**). (Reprinted with permission from 2000JA1381, Copyright 2000, American Chemical Society.)

of bpz ligands crystallize side-by-side. The three Pt atoms linked through N(4) atoms form an approximately equilateral triangle. In $[(en)Pt(cis\text{-}bpz\text{-}N4,N4')]_3(NO_3)_2(ClO_4)_4 \cdot 2H_2O$ (**117b**) (Figure 44), one of the bpz ligands is roughly planar while the other two are more strongly twisted. The structure of **117b** looks more like a vase or a double cone, when the en ligands are considered (2000JA1381).

The anions interact differently in both *cis* and *trans* isomers of bpz-based metallacalixarenes **117a** and **117b** and these interactions may be responsible for stabilizing or even inducing a particular rotamer structure (2000JA1381). In all *trans* rotamers **117** and **117a**, NO_3^- lies outside the cavity of the triangle and has no interaction with the metallacalixarene but in rotamer **117a** having both NO_3^- and PF_6^- anions, PF_6^- lies within the cavity (2000JA1381). In the all *cis* isomer **117b**, both NO_3^- and ClO_4^- anions are bound in the cavity with NO_3^- lying approximately in the Pt_3 plane revealing Pt…O interactions and ClO_4^- lies above the Pt_3 plane. The all *cis* triangles in both **117a** and **117b** behave as versatile hosts

for anions, incorporating trigonal planar NO_3^-, tetrahedral ClO_4^-, and octahedral PF_6^- and even a combination of both NO_3^- and ClO_4^- anions (2000JA1381).

Metallacalixarene **117** readily chelated with $(en)Pd^{II}$ to generate a hexanuclear Pt_3Pd_3 complex [(en)Pt(*N4;N4′*-bpz-*N1;N1′*)Pd(en)]$_3(NO_3)_4(PF_6)_8$ (**119**) (99AGE168, 2000JA 1381). Its X-ray structure reveals that while the three Pt atoms form an equilateral triangle, the Pd triangle at the rim is irregular and larger. In a similar way a Pt_6 vase has been formed from **117** and $[(en)Pt(H_2O)_2]^{2+}$. In contrast, hexanuclear [{(en)Pd(*N4,N4′*-bpz-*N1,N1′*)Pd(en)}$_3$]$(NO_3)_4(PF_6)_8 \cdot 5H_2O$ and [{(en)Pd(*N4;N4′*-bpz-*N1;N1′*)Pt(en)}$_3$]$(NO_3)_7(PF_6)_5 \cdot 9.75H_2O$ have been obtained by reactions of **116** and **118** with $[(en)Pd(H_2O)_2]^{2+}$ (2000JA1381). However **116**, on reaction with *trans*-$(NH_3)_2Pt^{II}$ forms an isomeric Pd_3Pt_3 complex [{(en)Pd}$_{2.5}$(*N1;N1′*-bpz-*N4;N4′*)$_3${$(NH_3)_2$Pt}$_3$]$(ClO_4)_6(NO_3)_5 \cdot 5H_2O$ (**120**) in which Pt^{II} links N(4),N(4′) and Pd^{II} binds N(1),N(1′) (99CC675). In the X-ray structure of **120** (Figure 45), both the Pd_3 and Pt_3 triangles are close to equilateral with Pd–Pd and Pt–Pt distances being 13.5 and 7.6 Å.

Metallacalixarene **119** simultaneously encapsulates both NO_3^- and PF_6^- anions, the nitrate being in the centre of the Pt_3 triangle with its oxygens pointing to acidic Pt^{II} atoms and PF_6^- is located in the centre of the antiprism on top of the nitrate ion (99AGE168). It is also a receptor for many other anions but binds SO_4^{2-} strongly and also encapsulates ClO_4^- in the center of the cation and aggregates in the solid state in such a way as to form long channels containing a string of ClO_4^- ions (99CC675).

In the reactions of **117b** with silver salts, higher nuclearity products $[(\mathbf{117b})_2Ag_2]^{14+}$ with molecular formula [{(en)Pt(*N4;N4′*-bpz-*N1;N1′*)}$_3$$AgNO_3$]$_2$ $(NO_3)_8(PF_6)_4 \cdot 15.5H_2O$ (**121**) and $[(\mathbf{117b})_2Ag_3]^{15+} \cdot AgNO_3$ with molecular

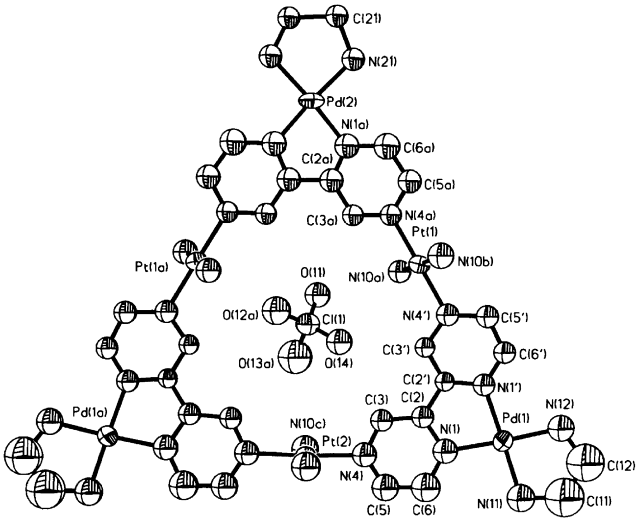


Figure 45 X-ray structure of the cation of [{(en)Pd}$_{2.5}$(*N1;N1′*-bpz-*N4;N4′*)$_3$${(NH_3)_2Pt}_3$](ClO$_4$)$_6$ $(NO_3)_5 \cdot 5H_2O$ (**120**). (Reprinted with permission from 99CC675, Copyright 1999, Royal Society of Chemistry.)

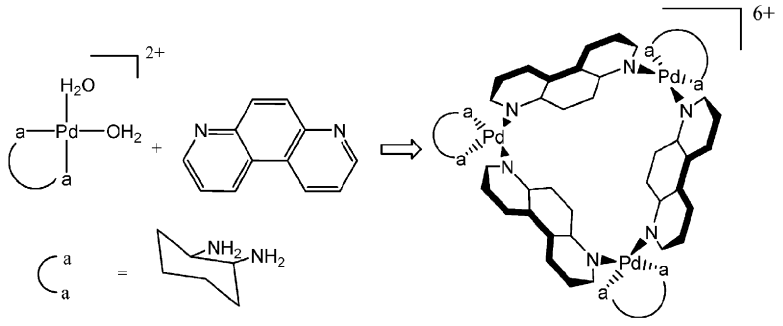
formula $[\{(en)Pt(N4;N4'\text{-bpz-}N1;N1')\}_3(AgNO_3)1.5]_2(NO_3)_{12}AgNO_3 \cdot 22H_2O$ (**122**) have been formed by respective bridging of two Pt_3 triangles with two and three silver ions *via* N1, N1′ positions (2000JA1381). The container complex **122** represents the inorganic version of an organic carceplex and has both one Ag^I cation and five nitrate anions incorporated in its interior.

3.4.2 Metallacalixarenes based on 4,7-phenanthroline

On the basis of its geometrical coordination requirements, 4,7-phenanthroline (phen) constitutes a ligand which can be considered as an extended pyrimidine ring. The cyclic self-assembled metallic systems based on phen and designated as metallacalixarenes have been obtained and their interactions with anions have been studied.

Trimeric metallacalixarenes $[(en)Pd(phen)]_3(NO_3)_6$ (**123**) and $[(en)Pt(phen)]_3(NO_3)_6$ (**124**) have been formed from phen and $[(en)Pd/Pt(NO_3)_2]$ (2003AGE686) (Scheme 8). In its X-ray structure, **123** reveals a calix[3]arene bowl with a cone conformation in which the three $[(en)Pd]^{2+}$ bridges of the phen backbone constitute an almost equilateral triangle which in aqueous solution binds sulfate ion more strongly than nitrate ion (2003AGE686). The reactions of [(*R,R*- and *S,S*-dach)$Pd(NO_3)_2$] and 4,7-phenanthroline in aqueous media formed trinuclear cyclic species $[(R,R\text{-dach})Pd(phen\text{-}N4;N7)]_3^{6+}$ (**125**) and $[(S,S\text{-dach})Pd(phen\text{-}N4;N7)]_3^{6+}$ (**126**) (2004DT1563). The X-ray structure of **125** confirms its trinuclear nature with N(4), N(7) bridging mode. The suitability of the extended aromatic nature of phen for π–π interactions and the rigid cone arrangements in the molecular vases of **123**, **124**, and **125** with upper ring opening of *ca*. 8.5 Å facilitated inclusion of mononucleotide guest molecules. Nucleotides induced decomposition of these metallacaliarenes gave acyclic adducts of the type $[a_2Pd(phen)(mononucleotide)]^+$ (2004DT1563).

For modulation of the size and shape of these metallacalixarene cavities, combinations of various pyrimidine and phen ligands have been used to form heterotopic metallacalixarenes. The multicomponent reactions of 3:1:2 mixture of $[(en)Pd^{II}]$, pyrimidine, and phen preferably formed heterotopic trimeric species $[(en)_3Pd_3(L\text{-}N1;N3)(phen\text{-}N4;N7)_2]^{5+}$ (**127**) (L, **a** = 2-pymo, **b** = 2-mpymo,



Scheme 8 Schematic formation of phen-based trimeric metallacalixarenes **123–126**. (Reprinted with permission from 2004DT1563, Copyright 2004, Royal Society of Chemistry.)

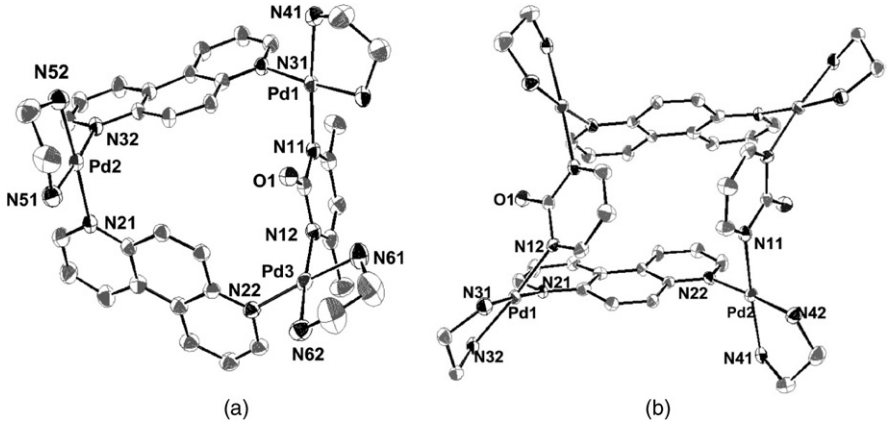


Figure 46 X-ray structures of the cations of (a) $[(en)_3Pd_3$ (2-dmpyo-*N1;N3*)(phen-*N4;N7*)$_2]^{5+}$ $(NO_3)_5$ (**127c**) and (b) $[(en)_4Pd_4$(2-pymo-*N1;N3*)$_2$(phen-*N4;N7*)$_2]^{6+}(NO_3)_6$ (**129**). (Reprinted with permission from 2004DT2780, Copyright 2004, Royal Society of Chemistry.)

c = 2-dmpymo) and not the homotopic species. Heterotopic metallacalixarenes **127** were also obtained by the reaction of a 3:8 mixture of homotropic systems [(en)Pd(phen-*N4;N7*)]$_3(NO_3)_4$ (**123**) and [(en)Pd(L-*N1;N3*)]$_4(NO_3)_4$ (**128**) (2004DT2780). In its X-ray structure (Figure 46a), **127c** reveals an irregular triangle exhibiting a pinched-cone conformation.

The reaction of a 2:1:1 mixture of $[(en)Pd]^{2+}$, 2-pymo, and phen formed the tetranuclear metallacalixarene $[(en)_4Pd_4$(2-pymo-*N1;N3*)$_2$(phen-*N4;N7*)$_2]^{6+}$ (**129**). Its X-ray structure (Figure 46b) shows a 1,3- alternate conformation with alternately placed pymo and phen moieties and the metal ions constituted the vertices of a parallelogram, rather than those of a rectangle. The reaction of a 3:4 mixture of homotropic species **128** (L = 2-pymo) and **123** formed hexanuclear metallacalixarene $[(en)_6Pd_6$(2-pymo-*N1;N3*)$_4$(phen-*N4;N7*)$_2]^{8+}$ (**130**) (2004DT2780). The host–guest interaction studies of these metallacalixarenes showed their ability to interact with both cationic as well as with anionic species (2004DT2780).

4. CONCLUSIONS

This account of an infant discipline of metallacalixarenes, the metallo-version of heterocalixarenes and a unique category of organo-inorganic hybrid systems elaborates many of their distinctive features with respect to other synthetic receptors. Their metallic components are primarily responsible for the multifold positive charge of the species which visibly constitute attractive hosts for anions so significant in biological reactions. The intrinsic magneto-electrical and structural contribution of metals could impart in metallacalixarenes such unusual features in target functional materials. An abundant use of nucleobases in their designs which is bye and large non-existent in parent heterocalixarenes points to

their relevance in mimicking supramolecular phenomenon in biological systems. Despite their positively charged nature, depending upon their heterocyclic component profiles, metallacalixarenes also interact with metal cations. As against the existence of nucleobase derived natural tetrands stabilized by a central metal ion, analogous metallacliaxrenes having desired metal components, nuclearity, and thereby cavity size compatible for even bigger biological anions, can be formed. Such unusual features evidently open up new vistas of research aimed at newer materials. But it calls for a focused and multifaceted collaborative approach coordinating design, synthesis and evaluation work. That only four model heterocycles have so far been used in evolving metallacalixarenes, points to the lack of awareness amongst practitioners of heterocyclic chemistry. It is hoped that their involvement in the exploration of this interfacial area will prove increasingly fruitful.

LIST OF ABBREVIATIONS

AdH	Adenine
Ado	Adenosine
5′-ADP	Adenosine-5′-diphosphate
9-AllAd	9-allyladenine
3′-AMP	Adenosine-3′-monophosphate
5′-AMP	Adenosine-5′-monophosphate
5′-ATP	Adenosine-5′-triphosphate
bpz	2,2′-bipyrazine
bu_2bipy	4-(*t*-butyl)-2,2′-bipyridine
BzimH	Benzimidazole
bzqnH	7,8-benzoquinoline
Cp^*	η^5-pentamethylcyclopentadienyl
dach	1,2-diaminocyclohexane
2-dmpymoH	4,6-dimethyl-2-hydroxypyrimidine
dpk	2,2′-dipyridylketone
en	1,2-diaminoethane
9-EtAd	9-ethyladenine
GuH_2	Guanine
Guo	Guanosine
HxH_2	Hypoxanthine
$ImacH_2$	Imidazole-4-carboxylic acid
ImH	Imidazole
5′-IMP	Ionosine-5′-monophosphate
5′-ITP	Ionosine-5′-triphosphate
9-MeAd	9-methyladenine
5′-MeAMP	Adenosine-5′-monophosphate methyl ester
9-MeGuH	9-methylguanine
9-MeHxH	9-methylhypoxanthine
9-MePu	9-methylpurine

2-MpymoH	4-methyl-2-hydroxypyrimidine
NAD^+	Nicotine adenine dinucleotide
phen	4,7-phenanthroline
PuH	Purine
6-PutH_2	6-thiopurine
6-PutH_2A2	2-amino-6-thiopurine
6-PutH_2O2	2-hydroxy-6-thiopurine
6-PutHrb	6-thiopurine-9-ribose
pym	Pyrimidine
2-pymoH	2-hydroxypyrimidine
4-pymoH	4-hydroxypyrimidine
T	Thymine dianion
tacn	Triazacyclononane
TH	Thymine monoanion
TH_2	Thymine
thf	Tetrahydrofuran
ThpH	Theophylline
thpyH	2(2′-thienyl)pyridine
U	Uracil dianion
UH	Uracil monoanion
UH_2	Uracil

ACKNOWLEDGEMENT

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CHAPTER 4

Sulfur Monochloride in the Synthesis of Heterocyclic Compounds ☆

O.A. Rakitin and **L.S. Konstantinova**

Contents

1. INTRODUCTION

Sulfur chlorides are important reagents in organic synthesis (1982AHC55, 1998MI145, 1999JPR99, 2006EJO849). Many are known S_nCl_2 ($n = 1$–12); some

☆ Dedicated to the late Professor Charles W. Rees – our teacher and coworker.

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

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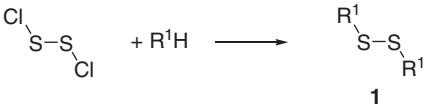
can be isolated (1969ZAAC241, 1972ZN(B)1006, 1984JOC1043, 1996ZAAC1594). Only two, sulfur dichloride (SCl_2) and sulfur monochloride (S_2Cl_2), are commercially available. However, sulfur dichloride is unstable and has to be purified before using (B-2001MI). Sulfur monochloride is sufficiently stable and can be kept in dark bottles resulting in slight decomposition giving small amounts of sulfur chloride and sulfur.

Sulfur monochloride shows versatile reactivity. It is an extremely powerful chlorinating agent for perchlorination of aromatic compounds (1960JA4294, 1992JOC5712), yet chemists rarely use it because there are many other chlorinating agents which allow higher yields. The sulfurating ability of sulfur monochloride is more important. Many inorganic sulfur reagents can be prepared from it (see e.g., 1991ZN5, 1996ZAAC557, 1994ZAAC632). However, both the chlorinating and sulfurating ability of sulfur monochloride can take place simultaneously and this diminishes its value as a sulfurating agent. Numerous attempts have been undertaken to prepare a sulfurating reagent (Scheme 1) with carbon, nitrogen, oxygen or sulfur leaving groups to replace the chlorine atom (1978JA1222, 1990SL473, 1998TL2467, 2001JOM173, 2002TL499 and many others).

But these disulfides **1** do not substitute for sulfur monochloride, and so S_2Cl_2 has ranked among the best sulfur transfer reagents in inorganic and organic chemistry since its discovery in the late 1800s (1860LA266).

Sulfur monochloride plays an important role with its ability to cyclize organic substances into a heterocyclic ring. The main feature of this reagent appears to be the addition of two sulfur atoms inserted between carbon–carbon or carbon–heteroatom bonds to produce heterocycles with two bound sulfur atoms. Yet, often it adds one, three, four, five, six and even more sulfur atoms, sometimes bonded together, sometimes not. These syntheses cannot be explained only by disproportioning of sulfur monochloride into sulfur dichloride and sulfur followed by the generation of higher sulfur chlorides (Scheme 2), as explained (1978JA1222). The role of S_2Cl_2 seems to be crucial.

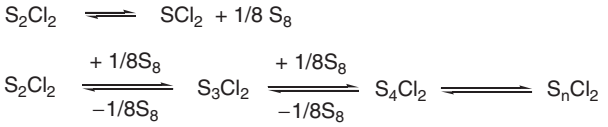
The results of most of the reactions (heterocycle ring size and yield) discussed in this review depend largely on conditions (solvent, temperature and conversion time)



1

R^1 = Ar, NR^2_2, OR^2, SR^2

Scheme 1



Scheme 2

as well as on activating compounds (most often tertiary amines) added to the reaction mixture.

Few general mechanisms can explain the full variety of heterocyclic syntheses, and therefore we will give special attention to mechanistic explanations even when they have not been proven.

This review is divided into sections depending on the quantity of sulfur atoms in the formed heterocycle. We have examined all the literature data for the last 150 years up to March 2007, including the latest achievements concerning 1,2,3-dithiazoles fused with other heterocycles. We do not discuss the Herz reaction since it is well known and has been reviewed (1957CRV1011).

A few reviews on the synthesis of heterocycles with sulfur chlorides have been published (1998MI145, 1999JPR99, 2006EJO849). They do not give the full scope of the reactivity and synthetic utility of sulfur monochloride.

2. HETEROCYCLES WITHOUT SULFUR ATOMS

Semicarbazones **2** were converted into their corresponding mono-, di- and trisubstituted 2,4-dihydro-1,2,4-triazol-3-ones **3** (Scheme 3; 1986JHC881).

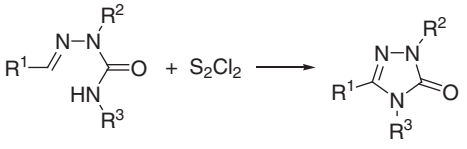
The reaction was carried out in refluxing acetic acid and ethyl acetate; triazolones **3** were isolated in good yields (Table 1).

Thiosemicarbazone **4** reacted in a similar manner to give 1,2,4-triazole-3-one **5** in good yield (1986JHC881), whereas at lower temperature (40 °C), unexpectedly, 2-methylamino-5-phenyl-1,3,4-thiadiazole **6** was isolated in low yield (Scheme 4).

The proposed mechanism includes the addition of sulfur monochloride to the N–H bond of semicarbazone or thiosemicarbazone with the formation of an N–S–S–Cl intermediate followed by its cyclization into the triazole or thiadiazole ring with the extrusion of two sulfur atoms and HCl.

1,3,4-Oxadiazoline-2-thione **7** was obtained in low yield from 2-benzoyl-1, 1-dimethylhydrazine and sulfur monochloride by similar process (1967JCS(C)2636). 1,1,4,4-Tetramethyltetrazane **8** was the major product (Scheme 5).

The addition of one equivalent of sulfur monochloride to two equivalents of 2-aminocinnamates **9** in chlorobenzene followed by brief refluxing produced diethyl 2,5-diaryl-3,4-pyrroledicarboxylates **10** in 36–52% yields (1984JOC4780). The mechanism was described and expected intermediates **11** and **12** were isolated under less stringent conditions (see Section 3.3; Scheme 6).

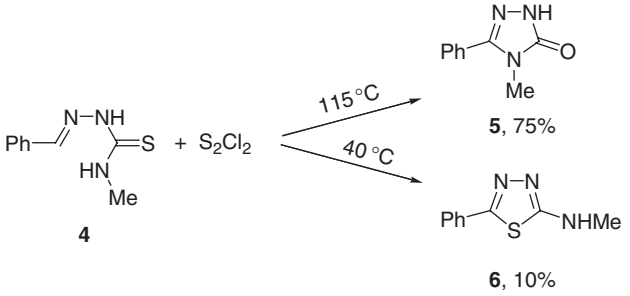


2 **3**

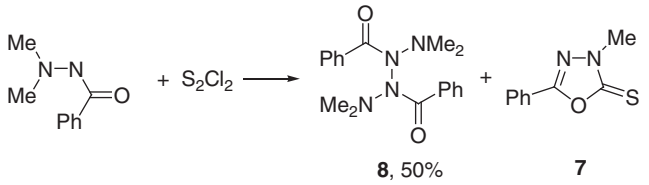
Scheme 3

Table 1 Yields and melting points of 2,4-dihydro-1,2,4-triazol-3-ones

R^1	R^2	R^3	Yield (%)	Mp (°C)
Ph	H	H	62	323
4-MeC_6H_4	H	H	64	334
4-ClC_6H_4	H	H	51	380 (dec)
2-HOC_6H_4	H	H	70	330
Ph	Ph	H	32	234–236
Ph	Ph	Et	52	80
Ph	Ph	Pr^n	54	82
Ph	Ph	Bu^n	68	70
Ph	Ph	Ph	72	221
Ph	Ph	3-$NO_2C_6H_4$	68	160
4-MeC_6H_4	Ph	2,5-$Cl_2C_6H_3$	81	161–162
4-$MeOC_6H_4$	Ph	Ph	80	174
4-ClC_6H_4	Ph	Ph	68	188



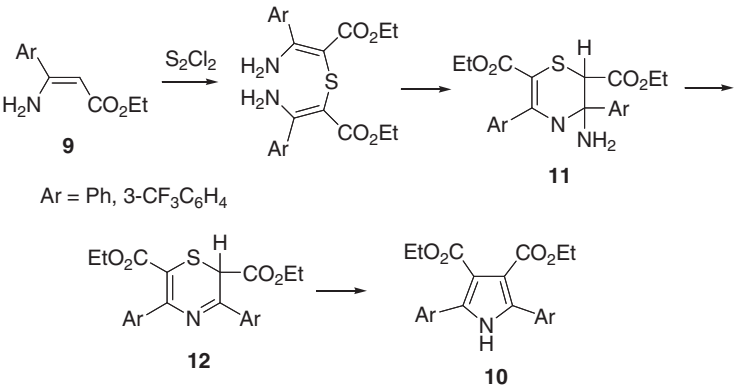
Scheme 4



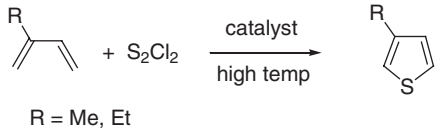
Scheme 5

3. HETEROCYCLES WITH ONE SULFUR ATOM

Sulfur monochloride can add one sulfur atom to a molecule and these transformations usually suggest the extrusion of sulfur dichloride or another sulfur atom with contraction of the heterocycle to a more stable (often heteroaromatic) ring.



Scheme 6



Scheme 7

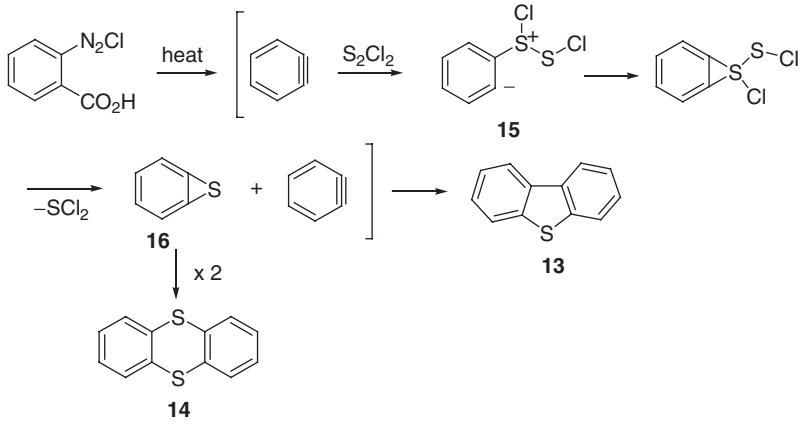
3.1 Thiophenes

Compounds with double and triple bonds react with sulfur monochloride to cyclize into a thiophene ring. The most vigorous method for preparing thiophenes is a reaction of 2-alkylbuta-1,3-dienes with sulfur monochloride at high temperature in the presence of a catalyst (1989JPP01066179, 2005CNP1583741; Scheme 7). Yields are moderate. Surprisingly, in this case, sulfur monochloride did not act as a chlorinating agent.

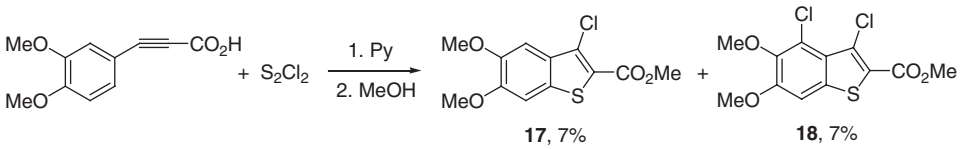
Benzyne generated from 2-carboxybenzenediazonium chloride reacted with sulfur monochloride to give dibenzothiophene **13** (8–10%) and thiantherene **14** (26–35%) (1989SUL83). A mechanism involving the addition of sulfur monochloride to benzyne with the formation of betaine **15** followed by the elimination of SCl_2 to afford benzothiirene **16** and a further reaction with another benzyne molecule or dimerization to thianthrene **14** is given in Scheme 8.

3-(3,4-Dimethoxyphenyl)prop-2-ynoic acid reacted with sulfur monochloride in the presence of pyridine to give low yields of substituted 1-benzothiophenes **17** and **18** (1979AJC833; Scheme 9).

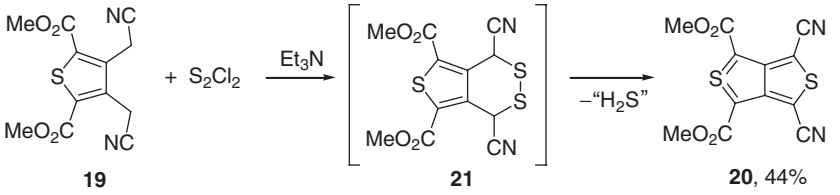
A thiophene ring can also be produced from two methylene groups. Here 2,5-dicarbethoxy-3,4-dicyanomethylthiophene **19** reacted with sulfur monochloride to give tetrasubstituted thieno[3,4-*c*]thiophene **20** in moderate yield (2002JOC2453). A mechanism for the thiophene **20** formation was proposed and 1,2-dithiine derivative **21** was likely to be an intermediate (Scheme 10) because sulfur monochloride gave higher yields of **20** than SCl_2. At the next step (**21**→**20**), sulfur monochloride apparently acted as an oxidant.



Scheme 8



Scheme 9

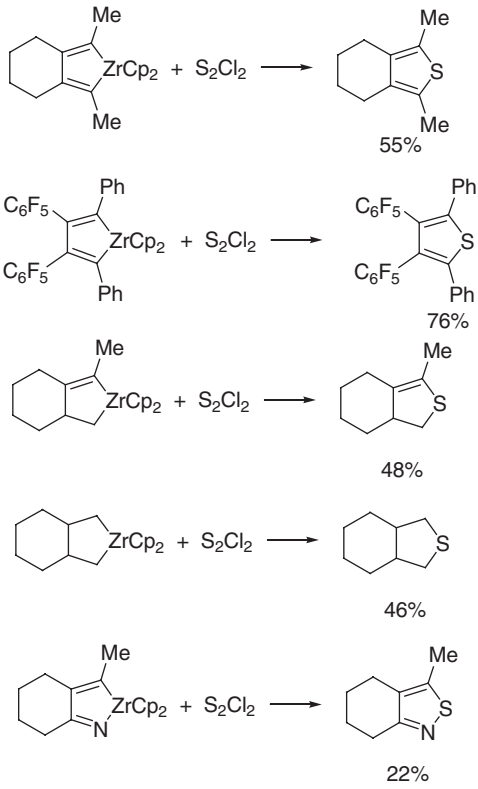


Scheme 10

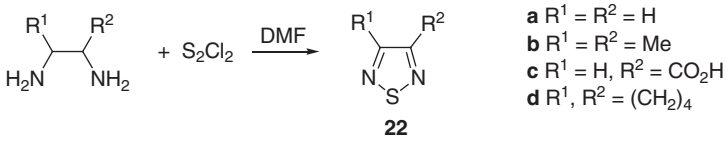
A variety of zirconium metallocycles was used to produce thiophenes, its dihydro and tetrahydro derivatives and also *iso*thiazoles (1994JA1880, 2003JA4199) through their reactions with sulfur and selenium halides. Surprisingly, higher yields were obtained with sulfur monochloride as compared to SCl_2, although one sulfur was added to the metallocycle molecule (Scheme 11). The reaction conditions were mild (1 h at 25 °C) and yields ranged from moderate to high.

3.2 1,2,5-Thiadiazoles

An overall strategy for the synthesis of 1,2,5-thiadiazoles from the acyclic N–C–C–N grouping and sulfur monochloride was proposed in 1967 (1967JOC2823). The N–C function could vary over oxidation levels of amine, imine, cyanide, oxime and nitroso derivatives. Aliphatic and aromatic compounds having these functionalities in many combinations reacted with sulfur monochloride to form appropriately substituted or fused 1,2,5-thiadiazoles. Based on this model, a large



Scheme 11

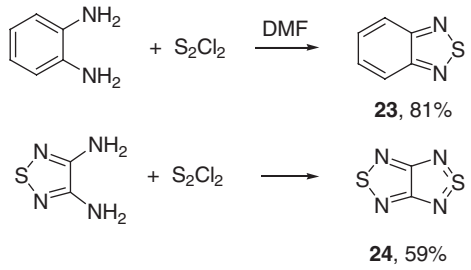


Scheme 12

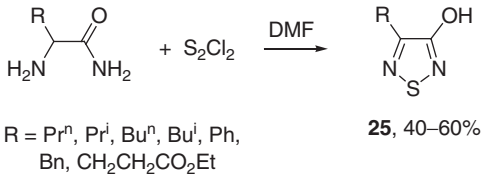
number of readily available acyclic and aromatic compounds serve as starting materials, including 1,2-diamines, α-aminoamidines, α-aminonitriles, alkyl cyanoformamidates, heterocyclic *o*-nitrosoamines, α-nitrosonitriles, α-dioximes and cyanogen. One sulfur atom is added because of the inherent stability of aromatic 1,2,5-thiadiazoles which is the driving force for their formation (1967JOC2823). Yields vary from 30% to 90%.

3.2.1 From 1,2-diamines

Ethylenediamine and some of its 1,2-dialkyl derivatives are easily transformed into the corresponding 1,2,5-thiadiazoles **22** with sulfur monochloride in DMF at room temperature (1967JOC2823; Scheme 12).



Scheme 13



Scheme 14

In the presence of $FeCl_3$ and chlorine, ethylenediamine dihydrochloride formed 3,4-dichloro-1,2,5-thiadiazole (74%) (1989DDP271425).

Aromatic and heteroaromatic *o*-diamines were also converted in high yields to fused thiadiazoles **23** and **24** under the same conditions (Scheme 13; 1967JOC2823, 1975JOC2749).

2-Aminoacid amides are suitable synthons for transformation to 3-hydroxythiadiazoles **25** (1967JOC2823, 1984WOP8402525) in moderate yields (Scheme 14). Clycinamide gave 4-chloro-1,2,5-thiadiazol-3-ol (1993JPP05140133) in a reaction with sulfur monochloride.

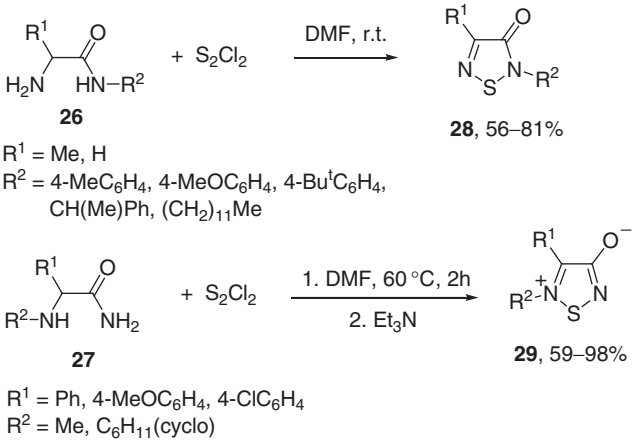
Sulfur monochloride and N^1- (**26**) or N^2- (**27**) substituted amides of 2-aminoacids afforded different 1,2,5-thiadiazole derivatives: 1,2,5-thiadiazol-3(2*H*)-ones **28** (1979NLP7712033, 1992CHP680220, 1994JPP06306063) and mesoionic 1,2,5-thiadiazolium-3-olates **29** (1981JCS(P1)1033; Scheme 15).

3.2.2 From ethyl oxamimidate and 2-aminoacetamidine

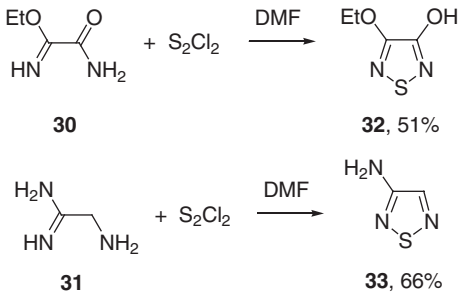
Compounds containing an α-aminoimidate fragment (HN═C–C–NH_2) as in ethyl 2-amino-2-oxoethanimidoate **30** and 2-aminoethanimidamide **31** reacted with sulfur monochloride to give, respectively, 4-ethoxy-1,2,5-thiadiazol-3-ol (**32**) and 3-amino-1,2,5-thiadiazol (**33**) (1967JOC2823; Scheme 16). Yields were moderate.

3.2.3 From aminonitriles

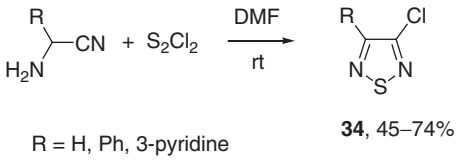
α-Aminonitriles are a convenient starting material for the preparation of 1,2,5-thiadiazoles. The amine must be primary and bear at least one α-hydrogen atom. Thus, treatment of unsubstituted α-aminonitrile and its aromatic and heterocyclic derivatives with sulfur monochloride in DMF at room temperature



Scheme 15



Scheme 16

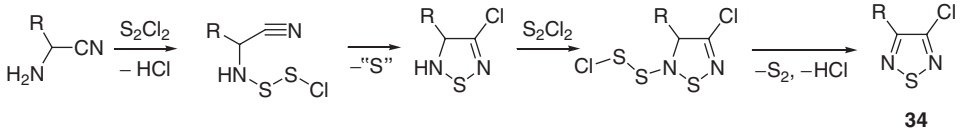


Scheme 17

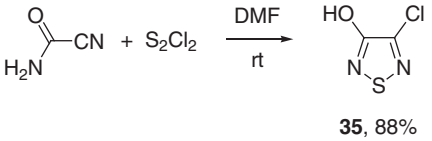
afforded 3-chloro-1,2,5-thiadiazoles **34** in moderate yields (1967JOC2823, 1995WOP9505174, 1999JMC1999; Scheme 17).

A mechanism for 1,2,5-thiadiazole formation was proposed in the 1960s (1967JOC2823) and seems to be reliable; this includes the formation of the *N*-chlorodithio intermediate followed by chlorination of the nitrile function, ring closure, addition of the second molecule of sulfur monochloride and formation of the heteroaromatic 1,2,5-thiadiazole cycle (Scheme 18).

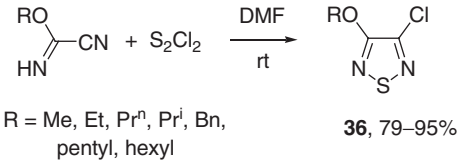
Similarly, 1-cyanoformamide can be converted into 4-chloro-1,2,5-thiadiazol-3-ol **35** upon treatment with sulfur monochloride (1967JOC2823; Scheme 19).



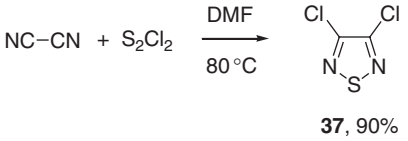
Scheme 18



Scheme 19



Scheme 20



Scheme 21

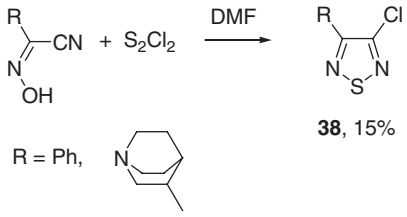
3.2.4 From nitriles and oximes

Treatment of cyanoimidates, easily obtained from cyanogen and alcohols in the presence of triethylamine, gave with sulfur monochloride the corresponding 4-chloro-1,2,5-thiadiazoles **36** in good-to-moderate yields (1967JOC2823, 1998JMC379; Scheme 20).

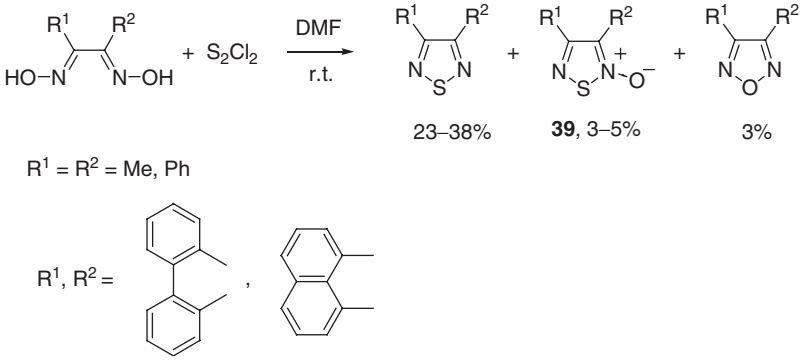
Cyanogen itself is reported to react smoothly with sulfur monochloride to form 3,4-dichloro-1,2,5-thiadiazole **37**. The reaction was not exothermic and was readily run by passing cyanogens into an S_2Cl_2 solution in dimethylformamide at 80 °C (1967JOC2823; Scheme 21).

Cyanooximes are less desirable starting materials for the synthesis of 1,2,5-thiadiazoles. Yields of 3-chloro derivatives **38** were low (1967JOC2823, 1992WOP9203433; Scheme 22).

The reaction of α-dioximes with sulfur monochloride is usually complex and leads to a mixture of various heterocycles including 1,2,5-thiadiazoles, their *N*-oxides **39** and sometimes 1,2,5-oxadiazoles (1967JOC2823, 1970JOC1165). Yields are low (Scheme 23).



Scheme 22



Scheme 23

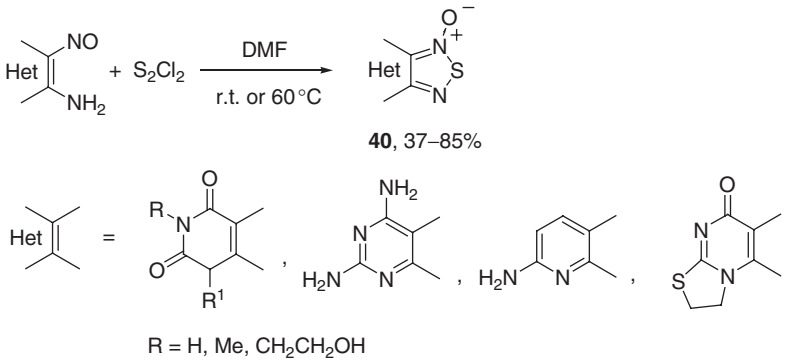
3.2.5 From *o*-aminonitrosoheterocycles

o-Aminonitrosoheterocyclic compounds were used in a selective synthesis of fused 1,2,5-thiadiazole *N*-oxides by a reaction with sulfur monochloride. Various nitrogen and sulfur–nitrogen heterocycles were employed and the yields varied from excellent to moderate (1996KGS997, 1998KGS1130, 2005ZOB493; Scheme 24). The reaction was carried out using both aromatic and non-aromatic heterocycles, yet it is difficult to predict how this method will work for particular classes of heterocyclic compounds. Although no information on the conversion mechanism was cited, it is easy to imagine the addition of sulfur monochloride to the amino group with the formation of an N–S–S–Cl derivative followed by the extrusion of hydrogen chloride and sulfur and the generation of the 1,2,5-thiadiazole-*N*-oxide ring.

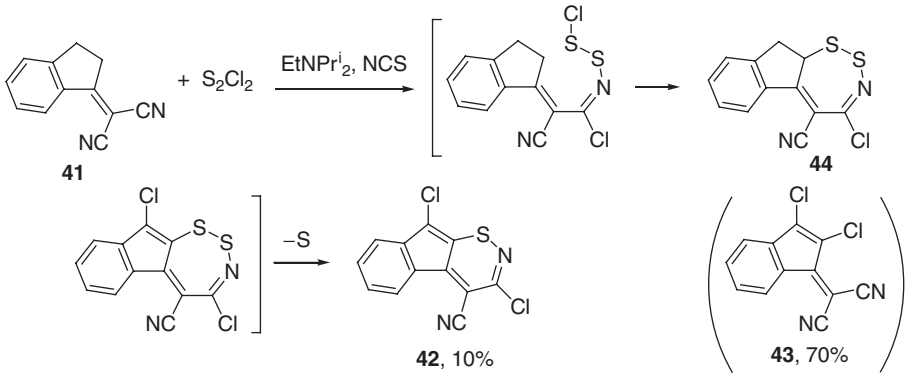
3.3 1,2- and 1,4-Thiazines

The reaction of 3-aminocinnamates **9** with sulfur monochloride leading to tetrasubstituted pyrroles **10** (see Section 2) can be stopped at the formation of 2*H*-1,4-thiazines **12** by the inverse addition of sulfur monochloride to compound **9**. Yields of thiazines **12** may reach 58–77% (1984JOC4780; see Scheme 6).

Treatment of dicyano compound **41** with sulfur monochloride, *N*-ethyldi*iso*-propylethylamine and *N*-chlorosuccinimide in tetrahydrofuran at 0 °C for 3 days led to condensed 1,2-thiazine **42** in low yield (10%) together with polychlorinated



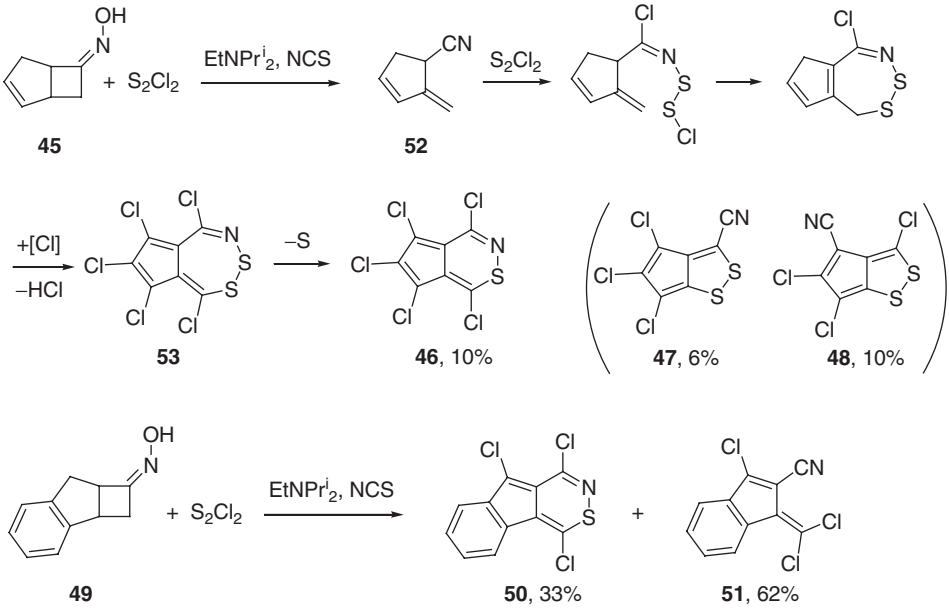
Scheme 24



Scheme 25

derivative **43** as the main product (70%) (1999JCS(P1)1023). A reasonable pathway for the conversion of dicyanide **41** into thiazine **42** includes the sulfur monochloride addition to the nitrile bond followed by cyclization onto an activated allylic position yielding either dithiazepine **44** or directly, with a loss of sulfur, the thiazine ring. A standard chlorination–dehydrochlorination process followed by the sulfur extrusion gave planar and formally aromatic product **42** (Scheme 25).

Cyclobutanone oxime **45** reacted with the same mixture to give cyclopenta-1,2-thiazine **46** in low yield together with two other unexpected 10-π pseudoazelenes **47** and **48** (1996JOC9178). Benzo derivative **49** of oxime **45** afforded analogous benzo product **50** together with methylenoindene **51** in high yield. The simplest mechanism for oxime **45** conversion into 1,2-thiazine **46** could involve an initial ketoxime fragmentation of the abnormal (second-order) Beckmann type, presumably induced by sulfur monochloride. Cyclobutane ring opening would give nitrile **52** that could react through the S_2Cl_2 addition to the nitrile with further cyclization and give a seven-membered dithiazepine ring which, by a dehydrogenation and chlorination sequence, would give fully



Scheme 26

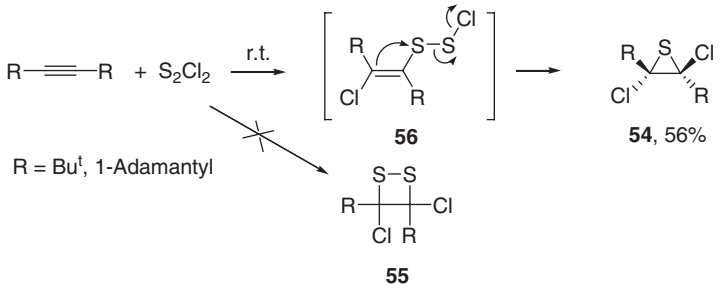
chlorinated product **53**. This is formally a 12-π system that upon the electrocyclization of the seven-membered ring to a fused 6-3 system followed by sulfur loss would give thiazine **46** (Scheme 26).

3.4 Other heterocycles with one sulfur atom

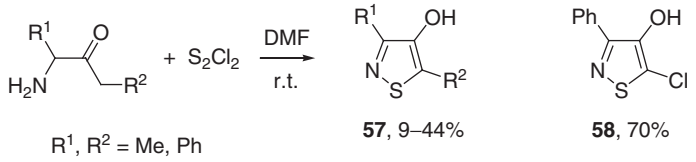
Three-, five-, six- and seven-membered heterocycles containing one sulfur atom, except for those described above, can be obtained from various organic substances and sulfur monochloride.

Unexpectedly, treatment of di-*tert*-butyl- and di-1-adamantylacetylenes with sulfur monochloride afforded dichlorothiiranes **54** in good yields (2002HAC424). Expected 1,2-dithietanes **55** were not formed even as trace amounts. The initial step might be the addition of sulfur monochloride to the acetylenes to produce adduct **56**. The preferred configuration of **56** might be as shown in Scheme 27 in order to avoid steric repulsions between the bulky substituent R and the S–C group. As a result, exclusive three-membered ring formation gives thiirane **54** with sulfur atom elimination (Scheme 27).

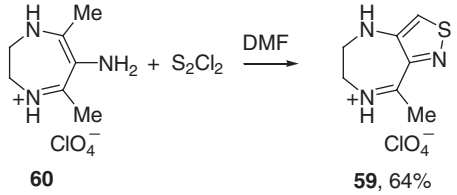
A series of five-membered heterocycles with two and three heteroatoms were synthesized. 4-Hydroxy*iso*thiazoles **57** were prepared from α-amino ketones with sulfur monochloride (1968BCJ959). Polar solvents, especially *N*,*N*-dimethylformamide, were preferable (Scheme 28). In a similar reaction of 1-amino-1-phenyl-2-propanone with sulfur monochloride 5-chlorinated *iso*thiazole **58** was obtained in high yield.



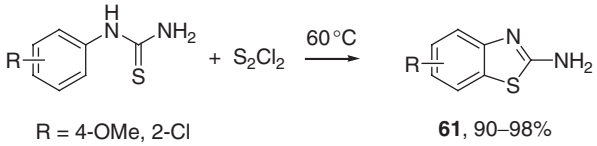
Scheme 27



Scheme 28



Scheme 29



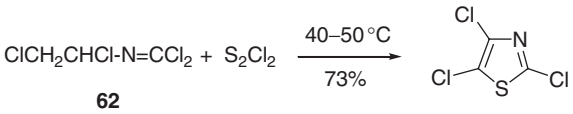
Scheme 30

Condensed *iso*thiazole **59** was isolated from *o*-aminomethyldiazepin **60** and sulfur monochloride (1996KGS997; Scheme 29).

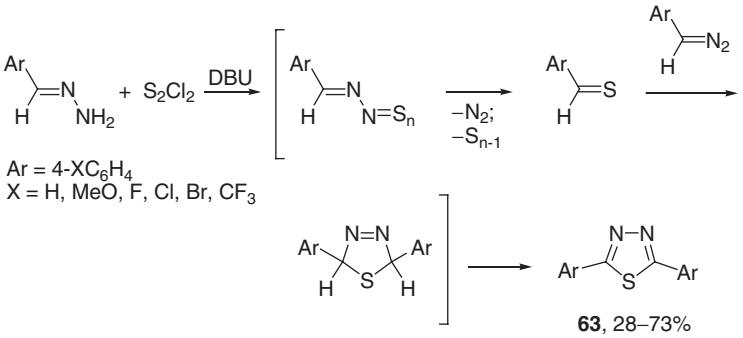
Substituted 2-aminobenzothiazoles **61** can be prepared from *N*-arylthioureas with sulfur monochloride (1976DEP2601700). Yields are almost quantitative (Scheme 30).

2,4,5-Trichlorothiazole was generated using **62** with sulfur monochloride (1976DEP2451632; Scheme 31).

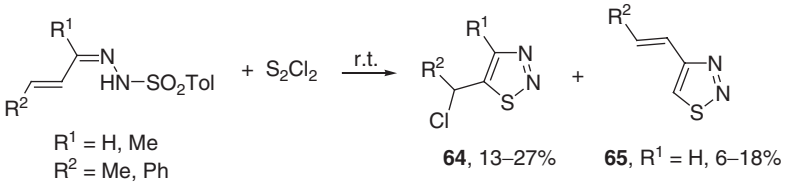
Hydrazones are useful materials for the synthesis of thiadiazoles. Benzaldehyde hydrazone and its derivatives substituted in the aromatic ring with sulfur monochloride in the presence of DBU gave 2,5-diaryl-1,3,4-thiadiazoles **63** in



Scheme 31



Scheme 32



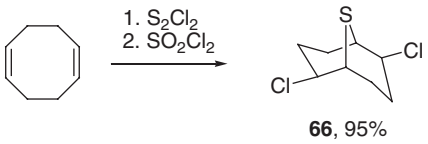
Scheme 33

moderate-to-good yields (2004S1929). The mechanism included the formation of arenecarbothialdehydes by a nucleophilic attack of hydrazone at S_2Cl_2 affording unstable *N*-thionitrosoimine followed by extrusion of nitrogen, and independent production of diazoalkane by the oxidation of the hydrazone with S_2Cl_2. Finally, the reaction between the two intermediate molecules led to corresponding 1,3, 4-thiadiazoline which was then oxidized to thiadiazole **63** (Scheme 32).

1,2,3-Thiadiazoles **64** and **65** can be prepared in good yields from *α,β*-unsaturated *p*-tolylhydrazones (1981G289). The reaction is not regioselective and usually gives a mixture of two isomers (Scheme 33).

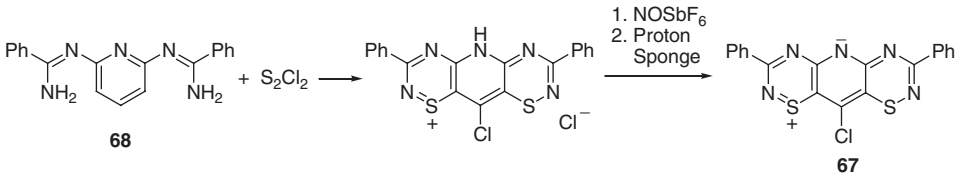
Treatment of 1,5-cyclopentadiene with sulfur monochloride and then with sulfuryl chloride provided high yields of 2,6-dichloro-9-thiabicyclo[3.3.1]nonane **66** containing a six-membered tetrahydrothiopyran ring (2006MI212). The formation of thiopyran **66** is assumed by the authors to be the result of the reversible elimination–addition of SCl_2, which is in equilibrium with sulfur monochloride, and of the high thermodynamic stability of **66** relative to the other monomeric and oligomeric sulfur dichloride addition products (Scheme 34).

Resonance-stabilized bis-thiadiazinylpyridine **67** can be prepared from bifunctional amidine **68** and sulfur monochloride followed by treatment of



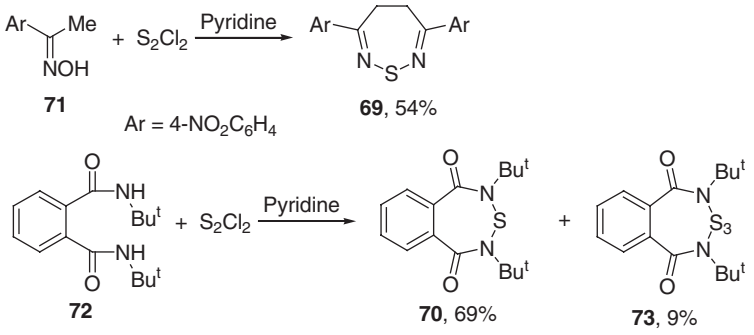
66, 95%

Scheme 34



68

Scheme 35



71 **69**, 54%

72 **70**, 69% **73**, 9%

Scheme 36

the insoluble chloride with $NOSbF_6$ and Proton Sponge (2005CC1218; Scheme 35).

Structurally similar seven-membered dihydro-1,2,7-thiadiazepine **69** and 1,2,7-thiadiazepan-3,6-dione **70** were obtained by an unexpected dimerization of acetoxime **71** (1997BSB605) and a ring closure of dicarboxamide **72** (1995CC1449). Curiously, the reaction of sulfur monochloride containing two sulfur atoms in both cases led to the insertion of one sulfur atom to the seven-membered ring or three sulfur atoms to the by-product **73** in the second reaction, but not two sulfurs (Scheme 36).

4. HETEROCYCLES WITH TWO SULFUR ATOMS

Heterocycles with two sulfur atoms obtained from sulfur monochloride, for example, 1,2-dithioles, 1,2,3-dithiazoles and 1,2-dithiines, are the most anticipated compounds because they are obtained by a direct insertion of two sulfur atoms during heterocyclic molecule construction. But even in that case some

unexpected transformations, such as the formation of an adjacent heterocyclic ring, may accompany the main process.

4.1 1,2-Dithioles

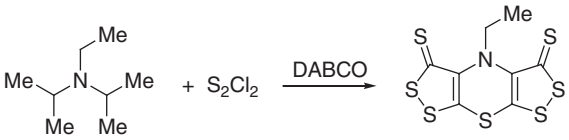
4.1.1 From *iso*propylamines

This approach to the synthesis of 1,2-dithioles from tertiary *iso*propylamines was discovered and elaborated by Charles Rees and coworkers in the late 1990s and in the beginning of this century. They commenced when *N*-ethyldi*iso*propylamine (Hünig's base), having been initially used as an ''inert'' base, was found to react with sulfur monochloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) to give an unexpected and novel multisulfur–nitrogen system – bis[1,2]dithiolo[1,4]thiazine **74** (1997AG(E)281). In this one-pot conversion of Hünig's base into tricycle **74,** 14 *iso*propyl C–H bonds were replaced by 10 C–S and 2 C–C double bonds, while the ethyl group remained intact. This is a striking example of high selectivity between primary and secondary *N*-alkyl groups in a competitive reaction (Scheme 37).

Other bis[1,2]dithiolo[1,4]thiazines **75** and **76** can be also selectively obtained by the reaction of Hünig's base with sulfur monochloride through the addition of oxygen donors such as cyclopentadienylacetic or formic acid (1998JOC2189; Scheme 38).

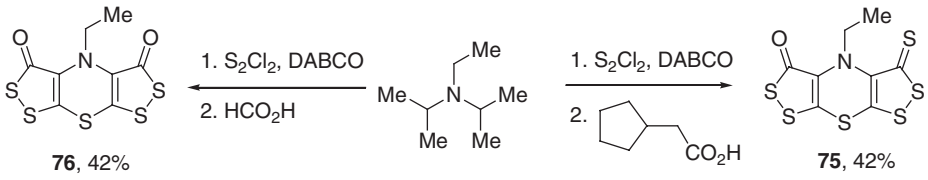
When the reaction of Hünig's base with sulfur monochloride was performed in boiling chlorobenzene, the corresponding bis[1,2]dithiolopyrroles **77–79** were formed by sulfur extrusion from intermediates **74–76** (Scheme 39).

The transformation of Hünig's base into bis[1,2]dithiolo[1,4]thiazines **74–76** and pyrroles **77–79** requires some 15 or so separate reaction steps, as estimated, from the formation of dithiole rings. A mechanistic pathway for the formation of all products was proposed (1998JOC2189; Scheme 40). The first step was the oxidation of the *iso*propyl group in Hünig's base by S_2Cl_2 (or its reactive complex with DABCO) to give more stable iminium ion **80**, as generally occurs in the



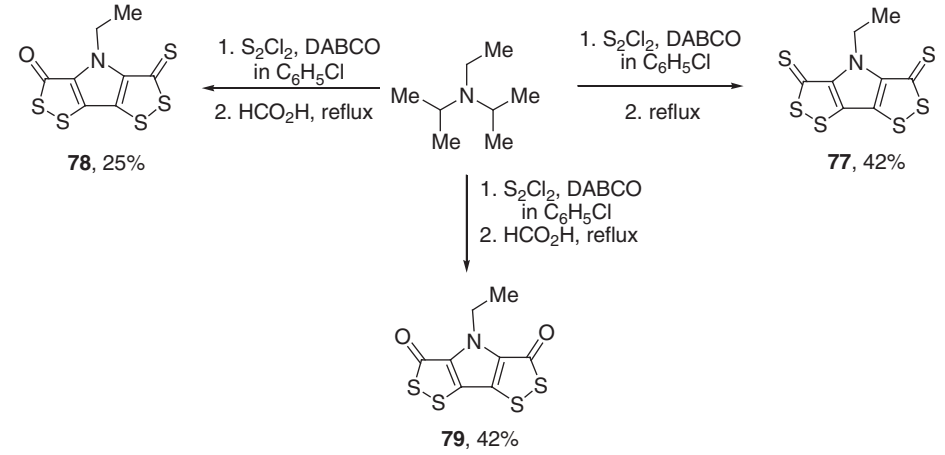
74, 40%

Scheme 37

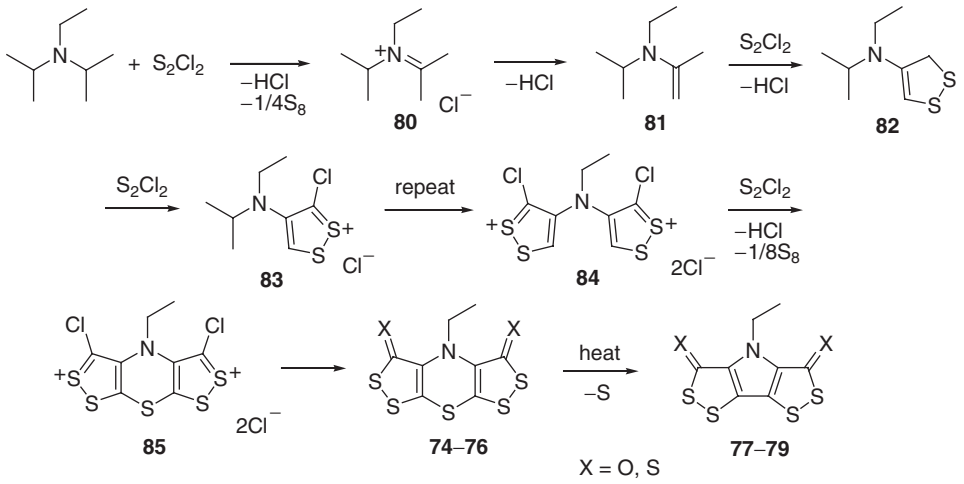


76, 42% **75**, 42%

Scheme 38



Scheme 39



Scheme 40

oxidation of tertiary amines (1991COS221). Further deprotonation of **80** gave enamine **81** which reacted with S_2Cl_2 to give 1,2-dithiole **82** which led to 3-chlorodithiolium salt **83**. The dithiolium ring in this compound is expected to be stable and the whole sequence could then be repeated to transform the other *iso*propyl group in a similar manner to give dithiolium salt **84**. This could cyclize to tricyclic species **85** by a further reaction with S_2Cl_2 with a loss of sulfur. 3,5-Dichloro-bis-dithiolium salt **85** presumably was the key intermediate and reacted with sulfur and oxygen nucleophiles to give heterocycles **74–79**.

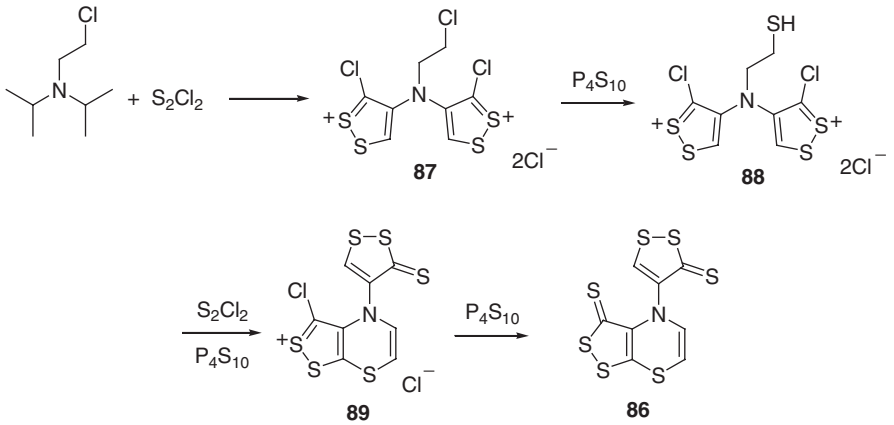
With a view to furthering the investigations of the substituted di*iso*propylamines reaction with sulfur monochloride, Rees and coworkers synthesized a number of tricyclic bis-dithiolothiazines (1999JOC5010, 2000JCS(P1)3421), including the parent members.

Treatment of *N*-(2-chloroethyl)di*iso*propylamine with sulfur monochloride in tetrahydrofuran followed by the addition of phosphorus pentasulfide with heating under reflux gave dithiolothiazine **86** (1999JOC5010). Bis-dithiolium salt **87**, which analogously formed disalt **84**, in the presence of P_4S_{10} gave intermediate **88** which could then cyclize to give partially saturated thiazine **89**, after further chlorination. Salt **89** converted into final product **86** with more P_4S_{10} (Scheme 41).

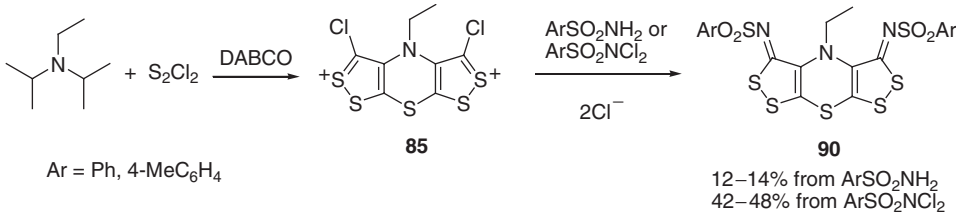
3,5-Dichloro-bis-dithiolium salt **85** obtained from *N*-ethyldi*iso*propylamine, S_2Cl_2 and DABCO in chloroform at room temperature reacted with arenesulfonamides and their *N*,*N*-dichloro derivatives with the formation of *N*,*N*′-bis(arylsulfonyl)-dithiolothiazine diimines **90** in modest yields (2001JCS(P1)2409; Scheme 42).

The reaction of Hünig's base, sulfur monochloride and toluene-*p*-sulfonhydrazide under the same conditions is more complex and gives monohydrazone **91** in low yield (2001JCS(P1)2409; Scheme 43).

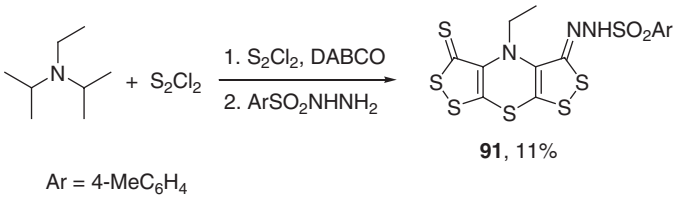
The reaction of *N*-alkyldi*iso*propylamines with sulfur monochloride and DABCO, deficient with respect to S_2Cl_2, prevented the formation of the 1,4-thiazine ring and led apparently to salts **84** which were then chlorinated by excess S_2Cl_2 and next treated with formic acid to give *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **92** together with the corresponding bis-dithiolothiazines **76**, although in low yields (1999JCS(P1)2237; Scheme 44).



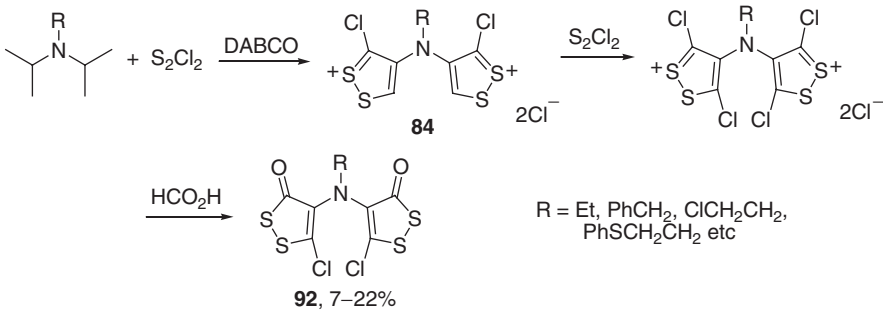
Scheme 41



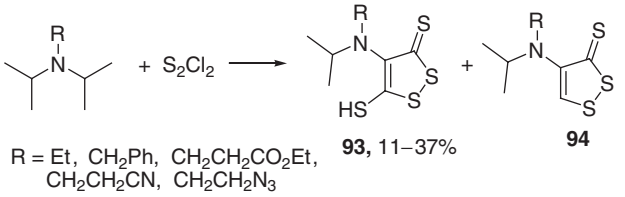
Scheme 42



Scheme 43



Scheme 44

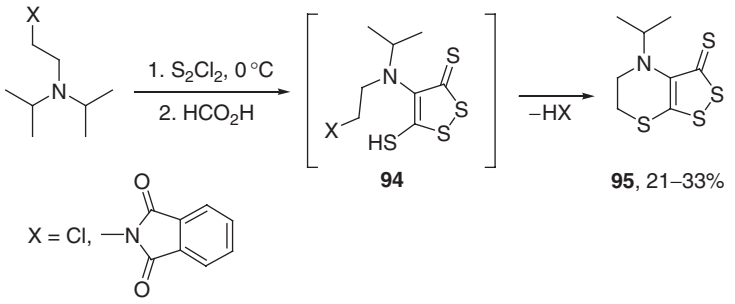


Scheme 45

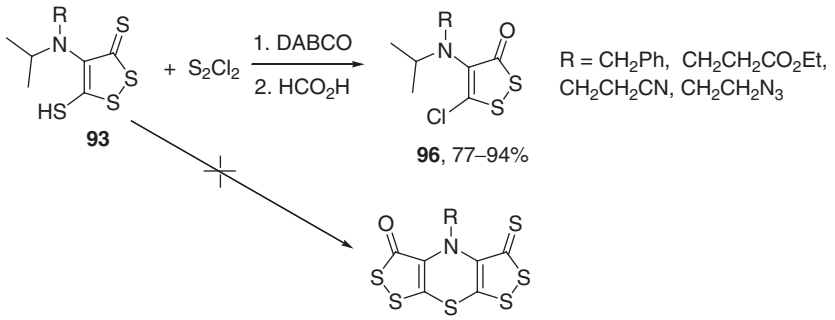
In all the reactions discussed in this section, both *iso*propyl groups were transformed into a 1,2-dithiole ring. When *N*-alkyldi*iso*propylamines and sulfur monochloride were mixed in chloroform in the absence of another base, that is, DABCO, two monocyclic dithiole-3-thiones **93** and **94** were isolated. 5-Mercapto derivative **93** was the main product in all the cases examined (2001MC165, 2006RCB143; Scheme 45).

Two other *N*-substituted di*iso*propylamines (R = CH_2CH_2Cl and CH_2CH_2Phth) in the same reaction gave dithiolothiazine **95** which had apparently resulted from the HCl or phthalimide extrusion from 5-mercapto-1,2-dithiole-3-thiones **94** (Scheme 46).

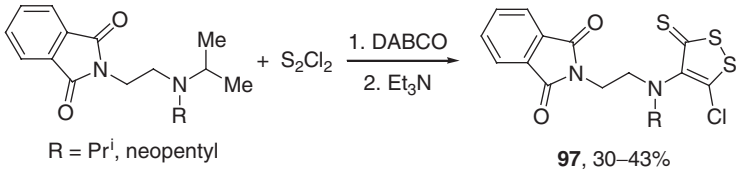
5-Mercaptodithiole thiones **93** were treated with sulfur monochloride and DABCO under conditions for the synthesis of tricyclic bis-dithiolothiazines from substituted di*iso*propylamines (see Scheme 38). Unexpectedly, in all the cases 5-chloro-1,2-dithiole-3-ones **96** were formed in high yields (2006RCB143; Scheme 47).



Scheme 46



Scheme 47

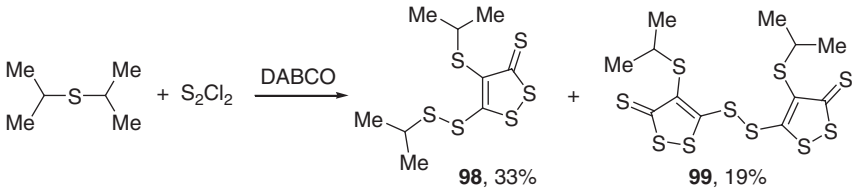


Scheme 48

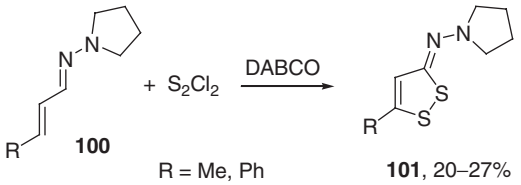
5-Chlorodithioles **96** can also be prepared from a reaction of *N*-alkyldi*iso*propylamines, sulfur monochloride and DABCO followed by the addition of formic acid (2001MC165).

Structurally similar 5-chloro-1,2-dithiole-3-thiones **97** were obtained upon treatment of *N*-(2-phthalimidoethyl)-*N*-alkyl*iso*propylamines with sulfur monochloride and DABCO and a final reaction with triethylamine (2003OL929). The stability of thiones **97** is explained by the dipole–dipole interaction between the electron-rich 1,2-dithiole-3-thione ring and electron-poor phthalimido groups (Scheme 48).

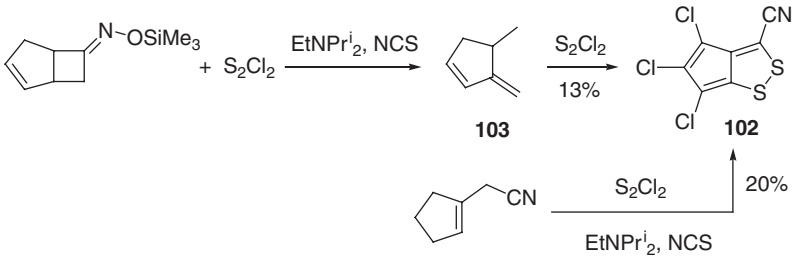
The reaction of di*iso*propyl sulfide with sulfur monochloride and DABCO afforded 1,2-dithiolo-3-thiones **98** and **99** (1999JOC4376). Dithiole ring formation had been assumed to be similar to that produced from tertiary di*iso*propylamines. However, in the case of di*iso*propyl sulfide only one *iso*propyl group was



Scheme 49



Scheme 50



Scheme 51

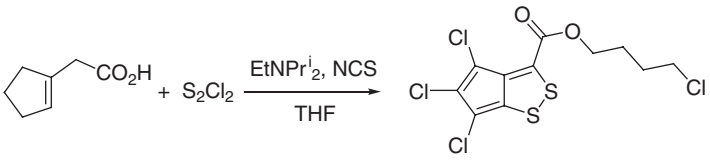
activated by the initial sulfide atom; this activation was suppressed when *iso*propyl sulfide was bonded to a dithiolthione group (Scheme 49).

4.1.2 From other sources

A general strategy for the synthesis of 1,2-dithioles is the addition of two sulfur atoms to the CH═CH–CH– group; also, non-ethylenic CH groups should be activated. Elemental sulfur is obviously the best reagent although sulfur monochloride is sometimes used.

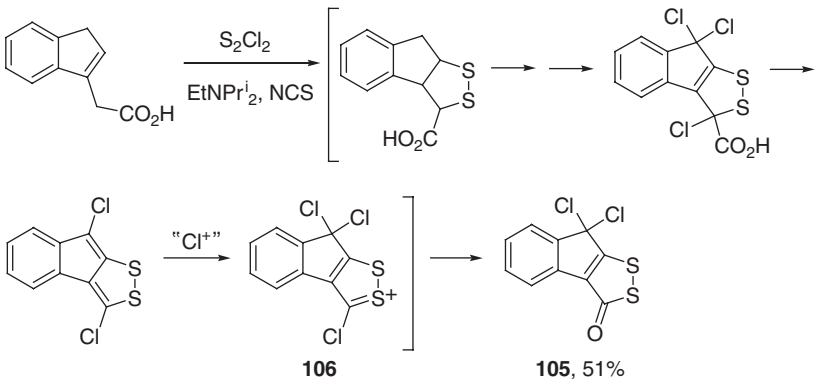
Treatment of α,β-unsaturated hydrazones **100** with sulfur monochloride gave 3-imino-1,2-dithioles **101** in low yields (1985ZC400; Scheme 50).

1-(Cyanomethyl)cyclopentene reacted with sulfur monochloride, Hünig's base and *N*-chlorosuccinimide to form perchlorinated cyclopenta-1,2-dithiole **102** (1996JOC9178). The same product was obtained from *cis*-bicyclo[3.2.0]hepten-6-one oxime, and in that case its formation was explained by the initial abnormal Beckmann rearrangement of the oxime to cyanide **103** followed by cyclization, extensive chlorination and dehydrochlorination (Scheme 51).



104, 22%

Scheme 52



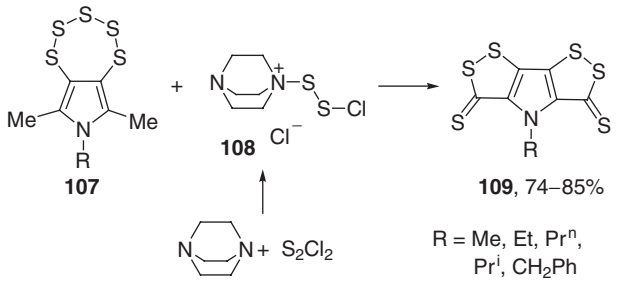
106 **105**, 51%

Scheme 53

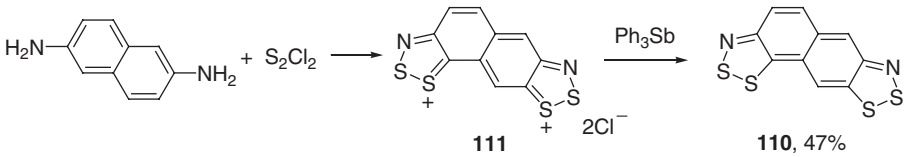
Cyclopentenylacetic acid when treated with sulfur monochloride, Hünig's base and *N*-chlorosuccinimide in tetrahydrofuran gave trichlorocyclopenta[1,2]-dithiole ester **104**, a product of heterocyclic ring formation, chlorination and dehydrochlorination and, unexpectedly, the conversion of the acid in THF into its 4-chlorobutyl ester (1999JCS(P1)1023; Scheme 52).

Under the same conditions indenylacetic acid afforded four crystalline products, the major being tricyclic 1,2-dithiolone **105** (1999JCS(P1)1023). While the indenylacetic acid conversion into **105** was not predicted, a pathway to it can be easily envisaged (Scheme 53) based on the demonstrated propensity of sulfur monochloride, NCS and Hünig's base to form 1,2-dithiole rings with activated allylic systems followed by extensive chlorination–dehydrochlorination that resulted in fully unsaturated and chlorinated products. This suggests acid group loss caused by decarboxylation and, probably, the formation of 3-chloro-1,2-dithiolium chloride **106** which then reacts with some external oxygen nucleophile.

Pentathiepinopyrroles **107** react with complex **108** obtained from sulfur monochloride and DABCO to give bis(dithiolo)pyrroles **109** in high yields (2005OL5725). Although pentathiepin rings and methyl groups are normally unreactive toward S_2Cl_2–DABCO at room temperature, pyrroles **107** react in an extensive cascade sequence. Presumably, the electron-releasing pyrrole nitrogen activated **107** to attack either the pentathiepin ring or a methyl group by the electrophilic reagent (Scheme 54).



Scheme 54



Scheme 55

4.2 1,2,3-Dithiazoles

4.2.1 From amines

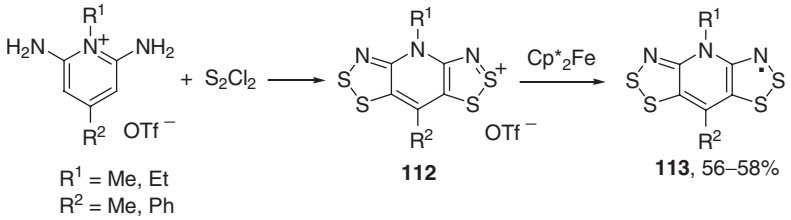
A synthesis of benzofused 1,2,3-dithiazolium (Herz) salts by the action of sulfur monochloride on arylamines is the best-known synthesis of this class. Although it has been known for over 80 years (1922DEP360690), it is still in use. This chemistry was reviewed (1957CRV1011) and therefore here we describe the synthesis of heteroannulated 1,2,3-dithiazolium salts and new achievements in their preparation.

Bis(1,2,3-dithiazoles) represent a new and potentially valuable class of heterocycles. A notable development is the ''double Herz condensation'' of 2,6-diaminonaphthalenes with sulfur monochloride which afforded naphtho-bis[1,2,3]dithiazole **110** after reduction of di-Herz salt **111** with triphenylantimony (1998CC1939; Scheme 55).

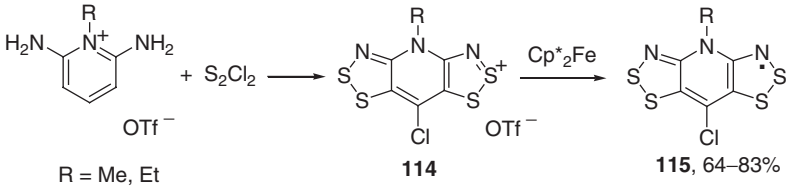
Double Herz condensation of *N*-alkylated 2,6-diaminopyridinium salts with sulfur monochloride is an effective procedure for the preparation of bis[1,2,3]dithiazolopyridinium salts **112** (2004CM1564) that were readily reduced to the corresponding dithiazolyl radicals **113** by decamethylferrocene (Scheme 56).

When 4-unsubstituted pyridinium salts were used, simultaneous chlorination accompanies the dithiazolium rings formation to give chlorinated salts **114** and radicals **115** after reduction in high yields (2002CC2562, 2003JA14394; Scheme 57).

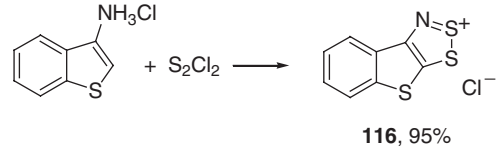
A few examples of the Herz reaction are known where the amino group is in the heterocyclic (thiophene) ring and thienodithiazolium salt **117** may be formed even if the carboxy group is in the *ortho*-position to the amino group in the heterocycle substituted by the dithiazole ring (1976KGS1355, 1979KGS447; Scheme 58).

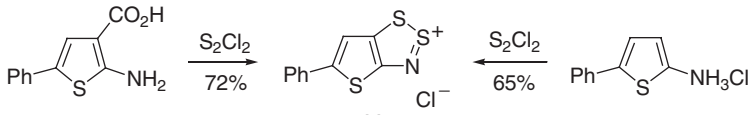


Scheme 56

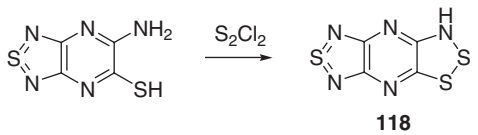


Scheme 57





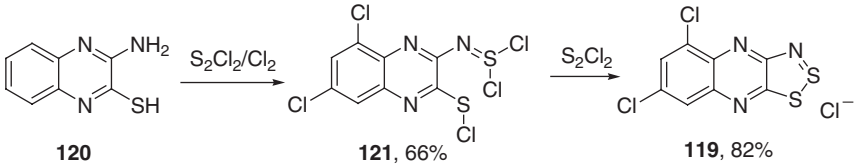
Scheme 58



Scheme 59

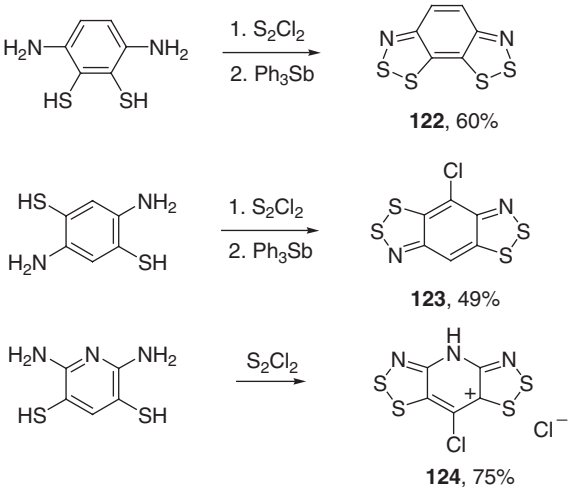
A series of condensed 1,2,3-dithiazoles were prepared by Oakley and coworkers from *o*-aminoaromatic and heterocyclic thiols and S_2Cl_2. This approach is more beneficial than a common Herz reaction that fails when applied to some aromatic amines, especially to phenylenediamines (1999JA969; Scheme 59).

A two-step synthesis of quinoxaline-1,2,3-dithiazolium chloride **119** utilized quinoxaline aminothiol **120** and a mixture of sulfur monochloride and chlorine with further treatment of intermediate **121** with S_2Cl_2 (2001CJC1352; Scheme 60).



120 **121**, 66% **119**, 82%

Scheme 60

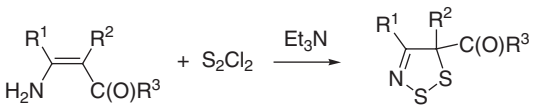


122, 60%

123, 49%

124, 75%

Scheme 61



R^1, R^2 = $(CH_2)_3$, $(CH_2)_4$, R^3 = OEt
R^1 = Me, Ph, R^2 = Me, R^3 = Me, OEt

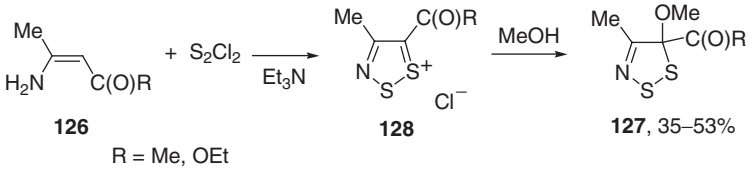
125, 35–83%

Scheme 62

A great advantage of this method is the synthesis of bis(1,2,3-dithiazoles) from diaminodithiols (1997JA12136, 1999CM164, 2000JA7602). Reduction of radical cations formed with Ph_3Sb led to neutral heterocycles **122** and **123** as air-stable crystalline solids (Scheme 61).

Activated enamines are expected to be useful precursors for 1,2,3-dithiazoles. In fact, the reaction of *β*-ketoenamines with sulfur monochloride gave 5*H*-1,2,3-dithiazoles **125** *via* intramolecular cyclization of an intermediate *N*-thiosulfinylamine with the possibility of its isolation (1981H803, 1981BCJ3541; Scheme 62).

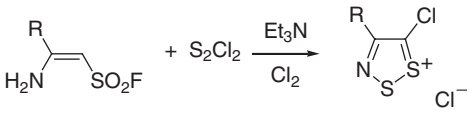
Treatment of enamines **126** with sulfur monochloride and methanol afforded 5-methoxydithiazoles **127** in moderate yield. Remarkably, the reaction without methanol under the same conditions gave no products. The formation of



126 **128** **127**, 35–53%

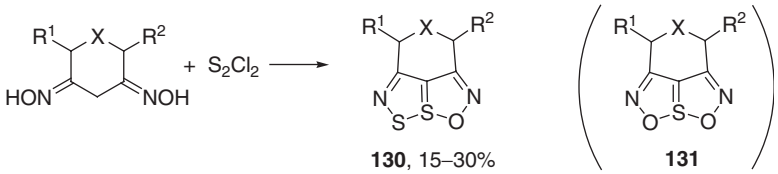
R = Me, OEt

Scheme 63



R = $H(CF_2)_5$, C_3F_7 **129**, 68–71%

Scheme 64



130, 15–30% **131**

X = CH_2, CHMe, CM_2, CHPh, CH(2-furyl), CH(2-thienyl), S, S(O), SO_2
$R^1 = R^2$ = H, Me, Ph

Scheme 65

dithiazoles **127** can be explained as a methanolysis of the intermediate dithiazolium salt **128** (Scheme 63).

Dithiazolium salts **129** were successfully isolated in the reaction of fluorinated enamines with sulfur monochloride; yields were high (1993ZOR491; Scheme 64).

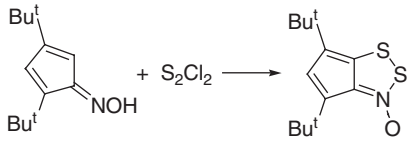
4.2.2 From oximes

A synthesis of annulated oxadithiadiazapentalene **130** can be achieved by the cyclization of 1,3-dioximes with sulfur monochloride. Moderate yields were accompanied by a small amount of dioxathiadiazapentalene **131**. Although yields of pentalenes **130** were from low to moderate, it still is the most convenient route to all known compounds of this class (1979BSF199, 1984USP4440564, 1985JPP62036388, 1985JCS(P2)1797; Scheme 65).

The single known *N*-oxide of 1,2,3-dithiazole **132** was isolated from cyclic oxime **133** and sulfur monochloride (1985TL189; Scheme 66).

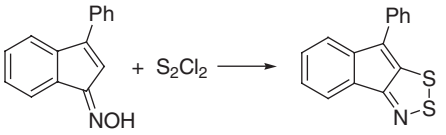
In other reactions, 1,2,3-dithiazole *N*-oxides were proposed as intermediates which underwent deoxygenation. Thus, 1-oximino-3-phenylindene formed 1,2,3-dithiazole **134** (1992JHC639, 1993JCS(P1)769; Scheme 67).

This reaction was extended further to cyclopentenone and cyclopentanone oximes (Scheme 68). The greatest improvement in the syntheses was the use of *N*-ethyldi*iso*propylamine (Hünig's base) that led to the highest yields of



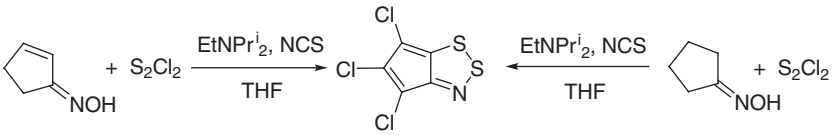
133 **132**

Scheme 66



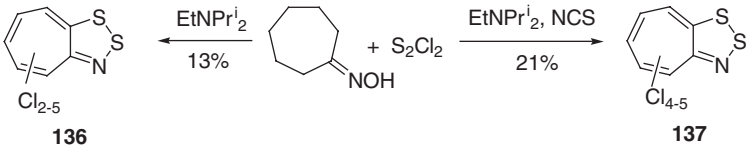
134, 60%

Scheme 67



135, 25%

Scheme 68



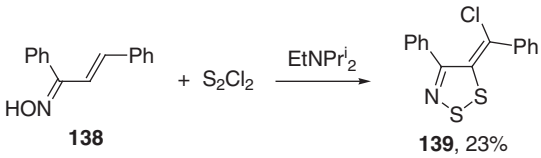
136 **137**

Scheme 69

dithiazoles **134** (80%) and **135** (25%). The introduction of chlorine atoms into the five-membered ring, for example, dithiazole **135**, demonstrated a chlorinating capacity of sulfur monochloride and its role as an oxidant in the case of cyclopentanone and cyclopentenone oximes. Multiple chlorination, dehydrochlorination and oxidation steps in the formation of **135** suggest a complex multistage mechanism which makes the reaction sensitive to reaction conditions and may be responsible for lower yields. Where the carbon ring is protected with substituents (Schemes 66 and 67), chlorination is prevented.

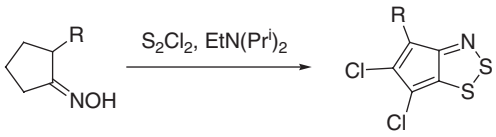
A reaction with seven-membered cyclic oximes proceeded similarly to give cyclopenta-1,2,3-dithiazoles **136** and **137** (1993JCS(P1)769; Scheme 69). For chlorination, up to 15 equivalents of sulfur monochloride were used and polychlorination was assisted by *N*-chlorosuccinimide.

A similar reaction gave dithiazole **139** (Scheme 70) with acyclic α,β-unsaturated oxime **138**.



138 **139**, 23%

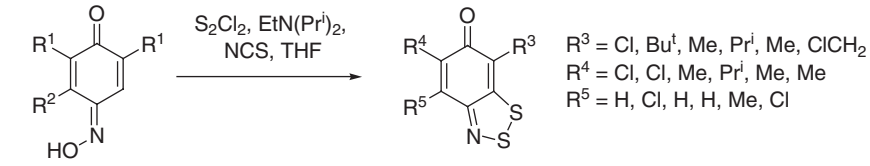
Scheme 70



R = CH_2CH_2CN

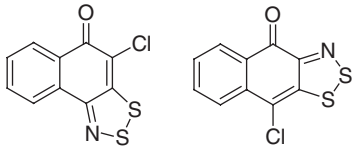
140, 47%

Scheme 71



R^1 = H, Cl, Bu^t, Me, Pr^i, Me
R^2 = H, H, H, H, H, Me

141



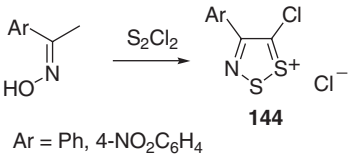
142 **143**

Scheme 72

Cyclopenta-1,2,3-dithiazole **140** was formed through a reaction of 2-substituted cyclopentanone oximes and S_2Cl_2 (Scheme 71; 2001CC403). Exhaustive chlorination accompanied this reaction as in the case of other cyclopentadithioles (see above).

6*H*-1,2,3-Benzodithiazol-6-ones **141** were prepared from *p*-benzoquinone-4-oximes, S_2Cl_2, *N*-ethyldi*iso*propylamine and NCS (1998T223; Scheme 72). Some ring chlorination occurred and 2,6-substituents were retained in the products except for the *tert*-butyl group, which was replaced by chlorine. 1,4-Naphthoquinone 4-oxime and 1,2-naphthoquinone 2-oxime similarly gave dithiazole derivatives **142** and **143** (1998T223).

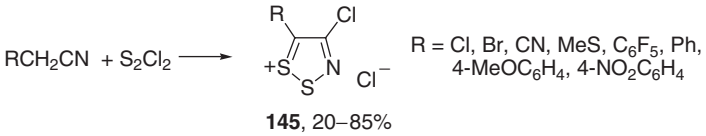
A possible synthesis of the extensively studied 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) analogs (see next section) was found in the reaction of acetophenone oxime and its 4-nitro derivative with S_2Cl_2 (1994H1827, 1997BSB605; Scheme 73).



144

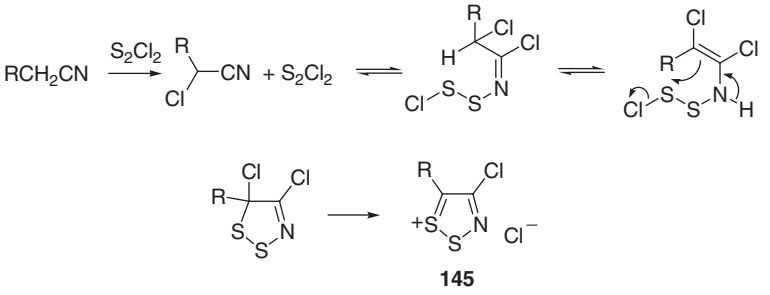
Ar = Ph, 4-$NO_2C_6H_4$

Scheme 73



145, 20–85%

Scheme 74



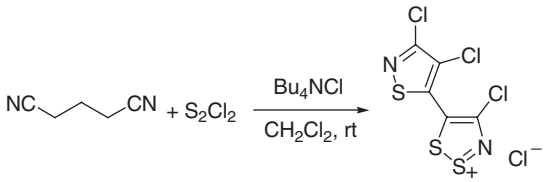
145

Scheme 75

4.2.3 From nitriles

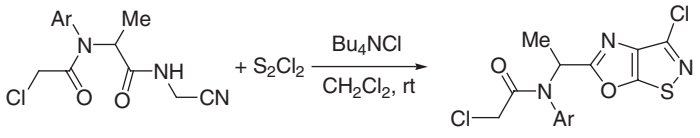
An extensively studied and highly important 1,2,3-dithiazole – 4,5-dichloro-1,2,3-dithiazol-1-ium chloride (Appel salt) **145** (R = Cl) – was first prepared by Appel and coworkers in 1985 by chlorination of chloroacetonitrile by sulfur monochloride in dichloromethane (1985CB1632) and it has been the most convenient procedure to date. Appel salt can be obtained also by prolonged chlorination of acetonitrile itself, or by the sulfur monochloride reaction with ethylamine; the yields and experimental conditions were not disclosed (1985PS277). Recently, a series of mono-substituted acetonitriles were converted to 5-substituted-4-chloro-1,2,3-dithiazolium chlorides **145** (1999CC531, 2005MI346; Scheme 74). Where the 5-substitutent was not a good leaving group, chloride salts were converted into the corresponding perchlorates sufficiently stable to be characterized.

Various mechanisms can be envisaged for the conversion of substituted acetonitriles into dithiazolium salt **145**, yet no firm evidence has been given. The first step could be the chlorination of acetonitrile by sulfur monochloride, as demonstrated for acetonitrile itself (1985CB1632) and for phenylacetonitrile (1939ZOK1329). This could be followed by sulfur monochloride addition to the cyano group, cyclization and ionization (Scheme 75).



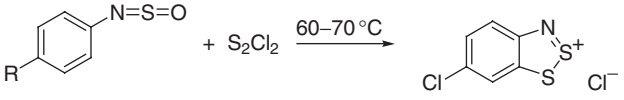
146, 78%

Scheme 76



148 **147**

Scheme 77



R = Cl, Br, I, NO_2 **149**, 15–35%

Scheme 78

Glutaronitrile reacted with sulfur monochloride to afford *iso*thiazolyldithiazolium chloride **146** by an unknown mechanism (2002CC1872; Scheme 76).

Bicyclic oxathiadiazapentalene **147** was prepared from acetonitrile derivative **148** with sulfur monochloride under the same conditions (1981USP4260624; Scheme 77).

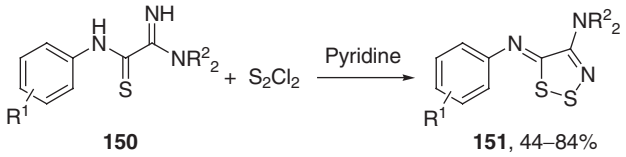
4.2.4 From other sources

6-Chloro-3*H*-1,2,3-benzodithiazolium chloride **149** can be prepared from *p*-substituted *N*-sulfinylanilines and sulfur monochloride when the substituent R is a good leaving group (1967RRC427; Scheme 78).

N′-Arylthiocarbamoyl-*N*,*N*-dialkylamidines **150** are useful intermediates for many heterocyclic systems (1996T8413), one being a reaction with sulfur monochloride that led to dithiazoles **151** (Scheme 79).

4.3 1,2- and 1,4-Dithiines

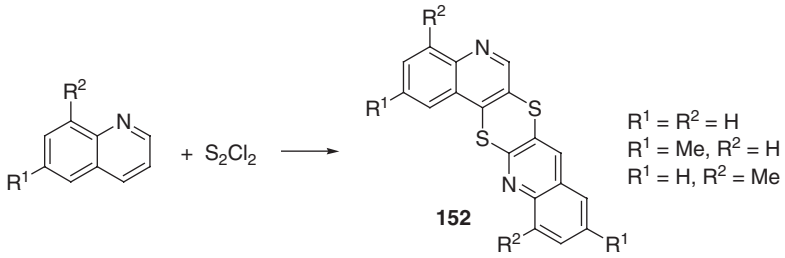
The synthesis of 1,4-dithiines from arenes and heteroarenes has been known for more than 100 years. The reaction of quinoline and sulfur monochloride gave dithiodiquinoline **152** ($R^1 = R^2 = H$) (1896JPR340). The structure of such compounds has been correctly identified only recently (1976PJC785, 1997JCR(S)435; Scheme 80).



150 **151**, 44–84%

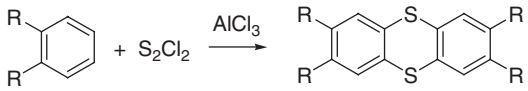
R^1 = 3-NO_2, 4-NO_2, 4-Cl, 4-Br, 4-Me, 4-OMe
R^2 = Et, Pr, Bu, allyl

Scheme 79



152

Scheme 80



R = H, OMe, OEt **153**, 10–90%

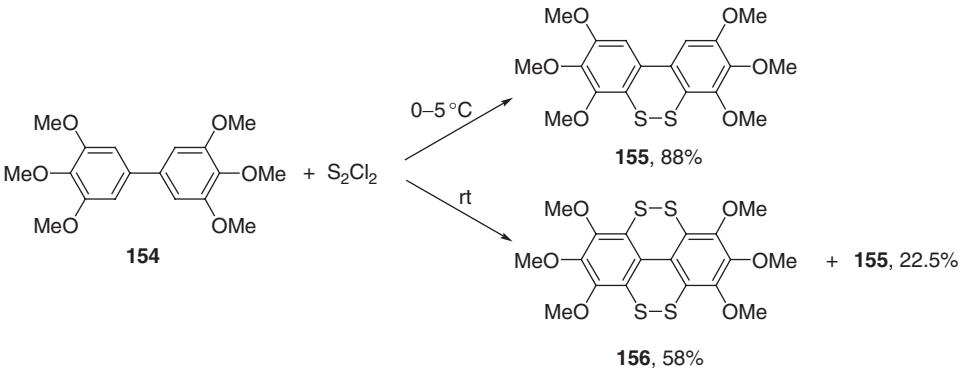
Scheme 81

The preparation of thianthrene **153** (R = H) from benzene, sulfur monochloride and aluminum chloride is the most inexpensive and simple method (1921LA265, 1956JA2163, 1976DEP2549435), also used for the preparation of other thianthrenes **153** (1972JCS(P1)1687; Scheme 81).

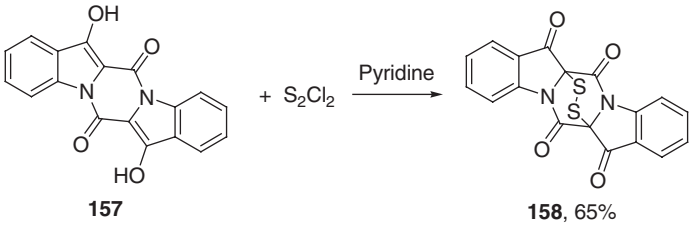
Only two examples of the 1,2-dithiine synthesis from biphenyls are known (1996NJC1031), although this transformation is the expected one. Dibenzodithiin **155** was formed in a reaction of 3,3′, 4,4′, 5,5′-hexamethylbiphenyl **154** with sulfur monochloride at low (0–5 °C) temperature. At room temperature the main product was bis[1,2]dithiine **156**. Surprisingly, monodithiine **155** did not convert to bisdithiine **156** after treatment with S_2Cl_2, and this probably implies that the addition of two sulfur monochloride molecules to biphenyl **154** took place simultaneously (Scheme 82).

4.4 Other heterocycles with two sulfur atoms

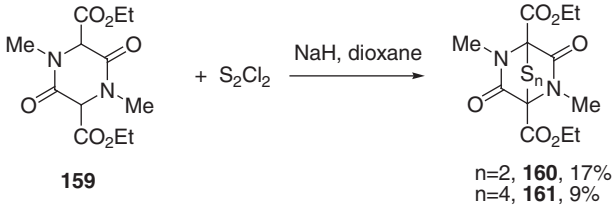
The insertion of two sulfur atoms between two carbons separated by one or two other atoms is an expected process, albeit examples of these transformations are few.



Scheme 82



Scheme 83



Scheme 84

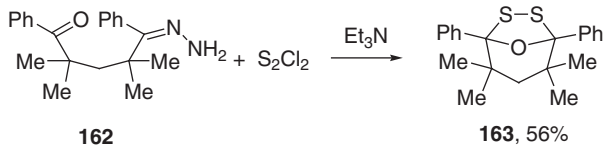
Pyrazinodiindole **157** reacted with sulfur monochloride and pyridine to give *epi*-dithio derivative **158** (an aromatic analog of arantins) (1977JOC948; Scheme 83).

A similar transformation of piperazindione **159** led to disulfide **160** and tetrasulfide **161**, also isolated in somewhat lower yield (1971TL3127; Scheme 84).

Another interesting reaction is the formation of *epi*-dithiooxaanthracenones from alkylydene-bisphenols (1988HCA1101).

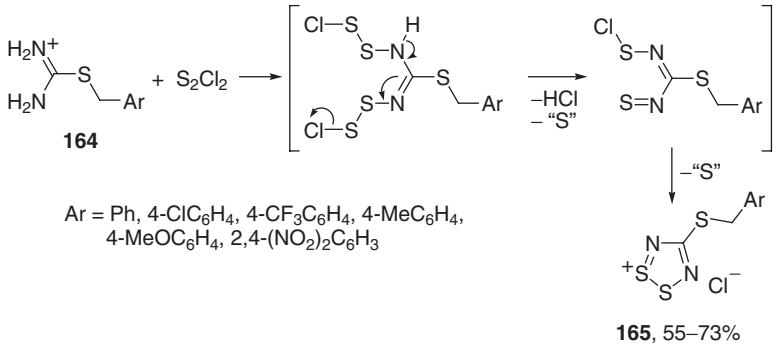
Bicyclic 1,3,4-oxadithiolane **163** – a rare ozonide analog in which two oxygen atoms are replaced by two sulfur atoms – was obtained by intramolecular cyclization of monohydrazone **162** with sulfur monochloride in the presence of triethylamine. No mechanism was given (1992CC7; Scheme 85).

1,2,3,5-Dithiadiazolyl radicals are considered to be organic molecular magnets and conductors and therefore chemists display increasing interest. Treatment of



162 **163**, 56%

Scheme 85



164

Ar = Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,4-$(NO_2)_2C_6H_3$

165, 55–73%

Scheme 86

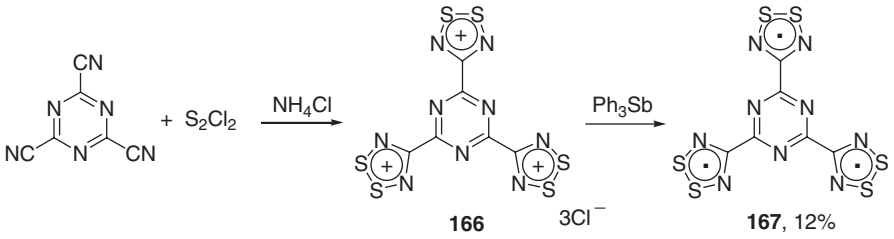
S-benzyl-*iso*-thiuronium chlorides **164** with sulfur monochloride provides a convenient method for preparing *S*-benzyl-1,2,3,5-dithiadiazolium chlorides **165** (2002ARK224). Based on the formation of similar products from amidines and guanidines with sulfur dichloride, the authors proposed a mechanism which included the addition of two S_2Cl_2 molecules to amidine **164** followed by HCl and sulfur extrusion (Scheme 86).

The preparation of tris(1,2,3,5-dithiadiazolyl)-1,3,5-triazine **166** was achieved through treatment of tricyanotriazine in refluxing sulfur monochloride in the presence of excess ammonium chloride. Reduction of the trication with triphenylantimony yielded triradical **167** (1993IC1554; Scheme 87). Interestingly, the usual strategy for the preparation of 1,2,3,5-dithiadiazolyls through amidines and their analogs failed.

A new class of sulfurated heterocycles – dithiadiazaphospholidine *S*-oxides **170** – was obtained by treatment of phosphonic diamide **168** with sulfur monochloride; its precursor heterocycle **169** was detected in the mixture. However, it was found to be susceptible to oxidation and only *S*-oxide **170** was isolated (1995CC1449; Scheme 88).

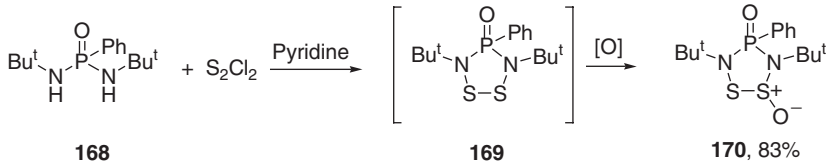
5. HETEROCYCLES WITH THREE SULFUR ATOMS

Non-symmetric isomers of benzotrithiadiazepine **173** were prepared by 1:1 condensation of azathienes **171** with sulfur monochloride followed by intramolecular *ortho*-cyclization of intermediate **172** (2001CC1774). In the case of *meta*-substituted



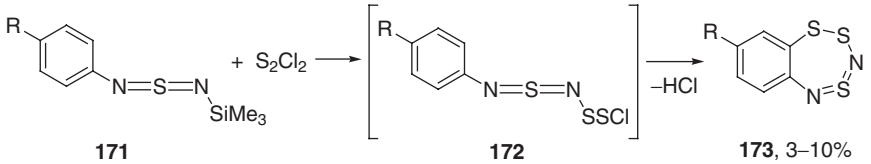
166 **167**, 12%

Scheme 87



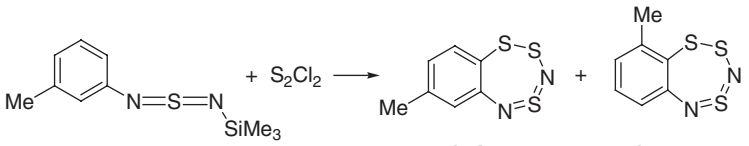
168 **169** **170**, 83%

Scheme 88



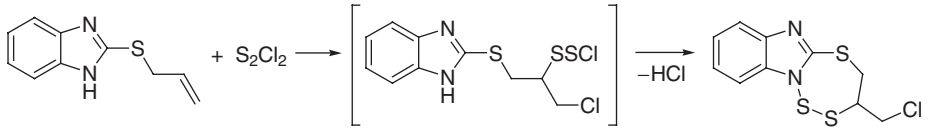
171 **172** **173**, 3–10%

R = H, Br



171, R = 3-Me **174**, 4.5% **175**, 2.5%

Scheme 89



176 **177** **178**, 30%

Scheme 90

precursor **171** (R = 3–Me), cyclization was not regioselective and led predominantly to 7-methyl substituted derivative **174** (Scheme 89).

2-Allylthiobenzimidazole **176** reacted with sulfur monochloride to give trithiazepinobenzimidazole **178** (2002MI317). The formation of intermediate **177** by S_2Cl_2 addition to the double allylic bond was proposed (Scheme 90).

6. HETEROCYCLES WITH FOUR SULFUR ATOMS

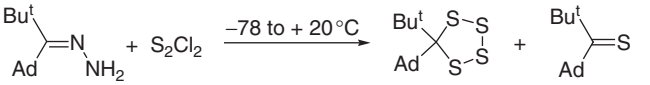
Heterocycles containing four consecutive sulfurs and one or two carbons, or two S–S bonds separated by carbon atoms are commonly prepared.

A reaction of sterically hindered hydrazone **179** with sulfur monochloride led to disubstituted tetrathiolane **180** in low yield together with 1-adamantyl-*tert*-butyl thioketone **181** as the main product (1996CC2681; Scheme 91).

If a diluted solution of dithiole **182** and sulfur monochloride in ether were mixed at low temperature, tetrathiane **183** was formed in low yield (1995JOC8056). The precipitation and purification of the final product were achieved by cooling the mixture to −78 °C (Scheme 92).

Bis-titanocene complex **184** reacted with one equivalent of sulfur monochloride to give intermediate mono-titanocene **185** which, upon treatment with ethane-1,2-disulfenyl chloride, transformed to bicyclic sulfur–carbon heterocycle **186** (1991CB2141; Scheme 93).

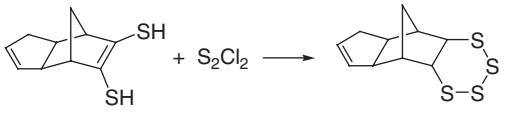
An unusual seven-membered diazaphosphatetrathia heterocycle (**190)** containing a chain of four sulfur atoms was obtained using diaryl or dialkyl phenyl phosphonamide **187** with sulfur monochloride in the presence of pyridine base (1993CC1684). A mechanism of the formation of **190** remains unclear but **190** was possibly formed *via* expected disulfide **188** which might be in equilibrium with bis(thionitroxide) **189** and the latter, in turn, could then further react with S_2Cl_2 (Scheme 94). The extension sulfur chain was explained by the S_2Cl_2 addition and



179 **180**, 5.5% **181**, 46%

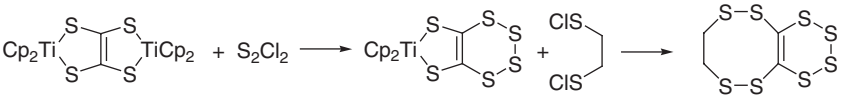
Ad = 1-adamantyl

Scheme 91



182 **183**, 10%

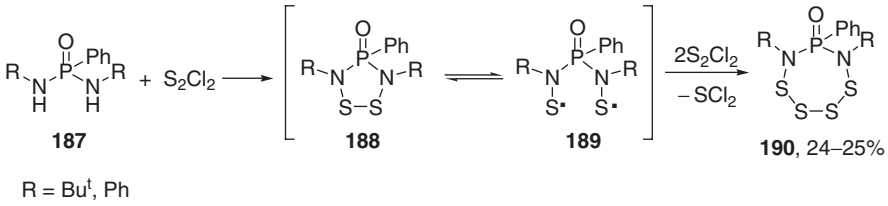
Scheme 92



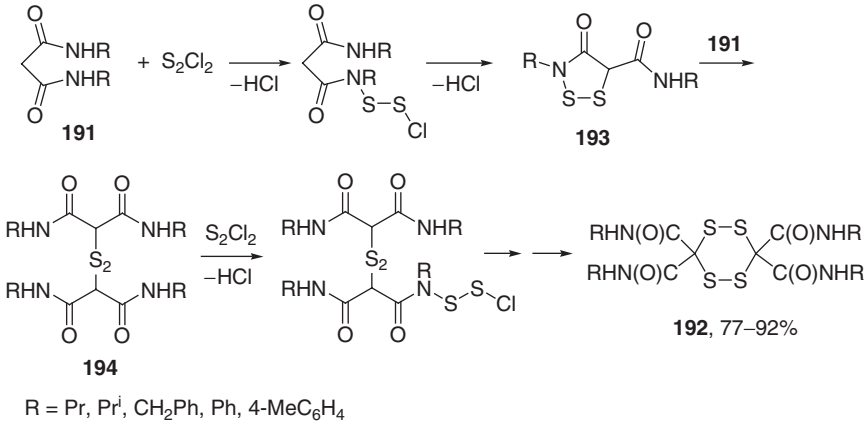
184 **185** **186**, 20%

Cp = cyclopentadienyl

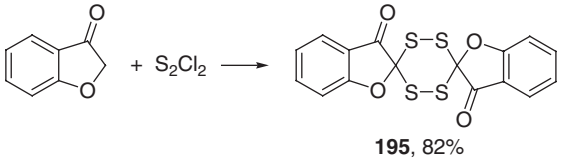
Scheme 93



Scheme 94



Scheme 95



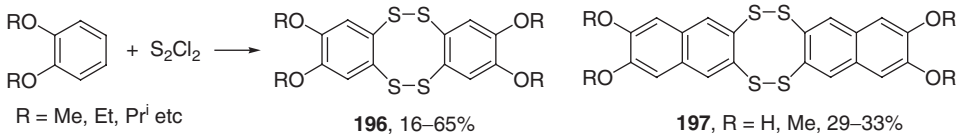
Scheme 96

SCl_2 loss, similar to how it was explained for the formation of pentathiepins (2005OBC3496) (see Section 7.1).

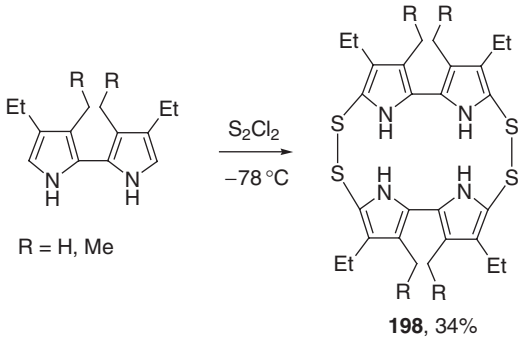
Although the first report on the reaction of sulfur monochloride with compounds containing active methylene groups had been published more than 120 years ago (1885CB2090), correct structures of the isolated products were proved only 28 years ago (1980CJC1233). The reaction of *N*,*N*′-dialkyl- and diaryl-malonodiamides **191** with sulfur monochloride gave symmetrically substituted 1,2,4,5-tetrathianes **192** (Scheme 95).

The reaction was apparently initiated by *N*-sulfenylation and the possible intermediate formation of 1,2,3-dithiazolidine **193** followed by the addition of the second diamide molecule with the formation of disulfide **194** and a final rearrangement to tetrathiane **192**.

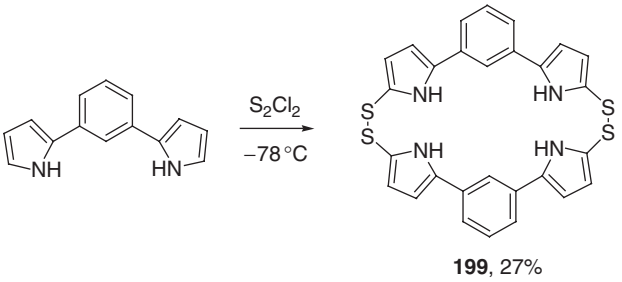
Tetrathiane **195**, similar in structure, was prepared by treatment of 3(2*H*)-benzofuranone with sulfur monochloride (1996T1961; Scheme 96).



Scheme 97



Scheme 98

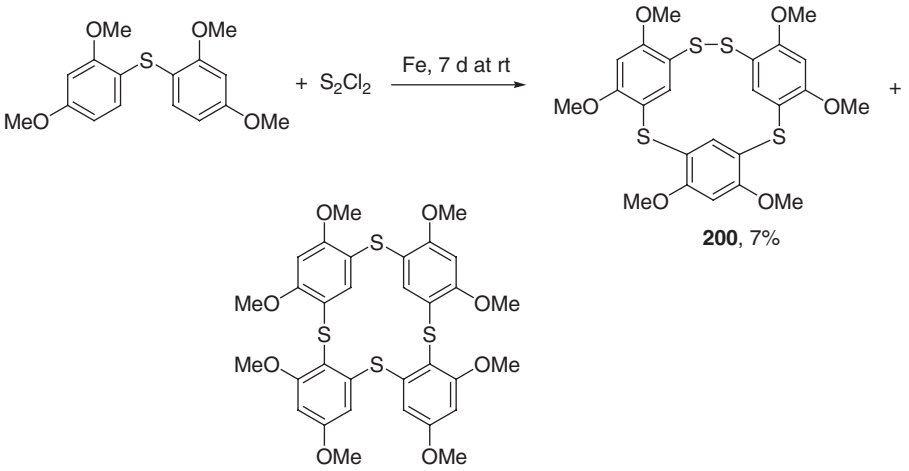


Scheme 99

Other heterocyclic compounds containing four sulfur atoms – tetrathiocines **196**, **197** – were synthesized from activated aromatic compounds, in particular 1,2-dialkoxybenzenes or 2,3-dialkoxynaphthalenes, and sulfur monochloride in acetic acid in fairly good yields (1989PS111; Scheme 97). Biphenyl **154** treated with S_2Cl_2 under the same conditions yielded 1,2-dithiines (see Section 4.3).

A reaction of α,α′-free pyrroles under argon at −78 °C with sulfur monochloride furnished disulfide-linked oligopyrrolic macrocycles **198** and **199** (2005CC2122; Schemes 98 and 99). It is noteworthy that S_2Cl_2 under the identical reaction conditions may lead to products containing sets of three sulfur atoms (see Section 8). These systems bear an important analogy to known carbon-linked oligopyrrole macrocycles. They or their putative congeners may play a role as ligands in cation complexation or as receptors for anion recognition.

An iron-catalyzed reaction between bis(2,4-dimethoxyphenyl)sulfide and sulfur monochloride in dilute chloroform led to a mixture of metacyclophanes in



Scheme 100

low yield. Tetrathiacyclophanes with three (**200**) or four (**201**) phenyl rings were the major products (1981JCS(P1)718; Scheme 100).

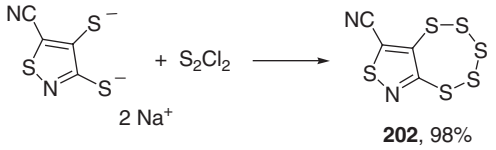
7. HETEROCYCLES WITH FIVE SULFUR ATOMS

7.1 1,2,3,4,5-Pentathiepins

One of the simplest routes to pentathiepins is a reaction of 1,2-dithioles or their salts with sulfur monochloride. There are few examples where the starting material is dithiol salt (1980JOC5122, 1994IC4537, 1995T2533, 1999AM758; Schemes 101–104). Isothiazolopentathiepin **202** was generated almost quantitatively (1980JOC5122); with hexalithium hexamercaptobenzene, the combined product yield was also very high but the major product was tristrithiole **204** (1995T2533). Only one pentathiepin ring was built (**203**), trithiole rings being more preferably formed in this situation.

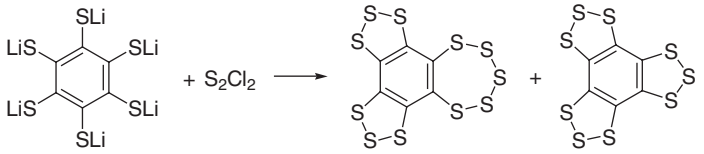
Further examples of this reaction where a dithiolate is generated *in situ* are shown in Schemes 105–111 (1981USP4275073, 1985JA3871, 1993JOC4522, 1993JA7017, 1994JOC5955, 1994MI101, 1995JA7261, 2001CC403).

An unusual synthesis of pentathiepins fused to another heterocyclic ring was discovered recently by Rees and coworkers (2002CC1204). Treatment of nucleophilic heterocycles such as pyrroles and thiophenes and their tetrahydro derivatives with sulfur monochloride and a base (usually 1,4-diazabicyclooctane, DABCO) provided a simple one-pot synthesis of condensed mono- and bis-pentathiepins, sometimes in surprisingly good yields (2005OBC3496). *N*-Methylpyrrole and its 2-chloro and 2,5-dichloro derivatives all gave the same dichloropentathiepin **214a** (Scheme 112).



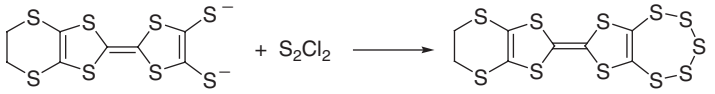
202, 98%

Scheme 101



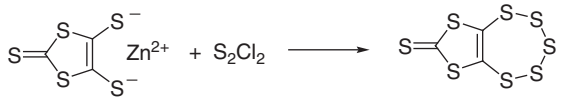
203, 20% **204**, 74%

Scheme 102



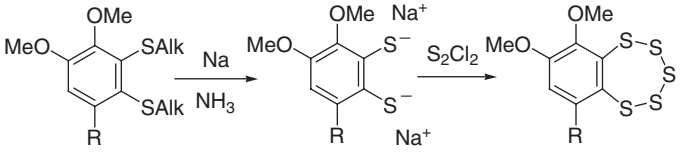
205, 27%

Scheme 103



206, 58%

Scheme 104

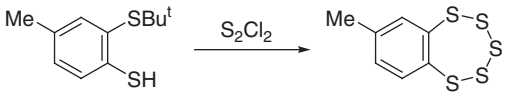


207

$R = CH_2CH_2NHC(O)OCH_2CH_2SiMe_3$ Alk = **a** Pr^n, 28%
b Bu^n, 47%

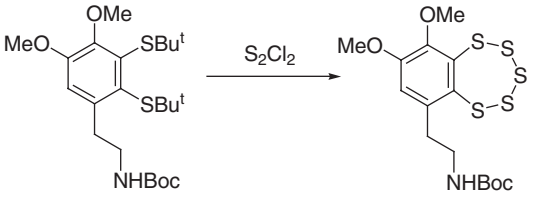
Scheme 105

N-Methyl-, *N*-ethyl, *N*-*iso*propyl- and *N*-*tert*-butyl-pyrrolidines, which are readily available from the reaction of dichloro- or dibromobutanes and their corresponding amines, all gave *N*-alkyl dichloropentathiepinopyrroles **214** as the main products in low-to-moderate yield (16–31%). Additionally,



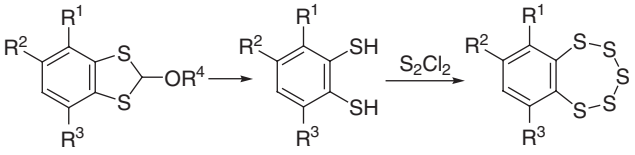
208, 86%

Scheme 106



209, 59%

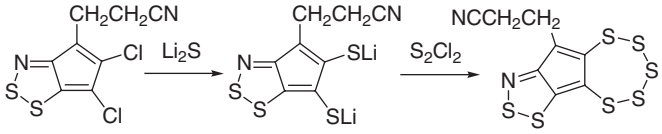
Scheme 107



210

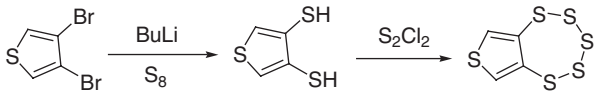
a $R^1 = R^2 = R^3 = H$, $R^4 = Bu$
b $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Bu$
c $R^1 = R^2 = OMe$, $R^3 = CH_2CH_2NHBoc$, $R^4 = CH_2CH_2CMe_2$

Scheme 108



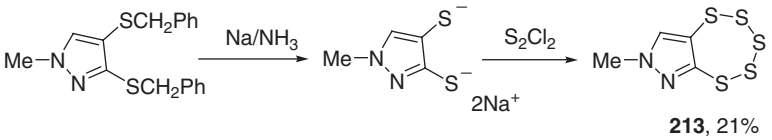
211

Scheme 109



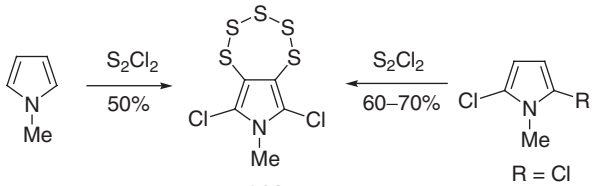
212, 2%

Scheme 110



213, 21%

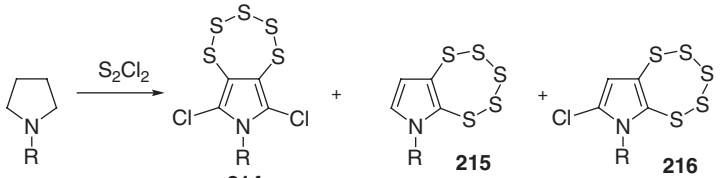
Scheme 111



214a

R = Cl
R = H

Scheme 112



214

a R = Me 31%
b R = Et 29%
c R = Pr^{i} 16%
d R = Bu^{t} 31%

215
R = Me, 5%

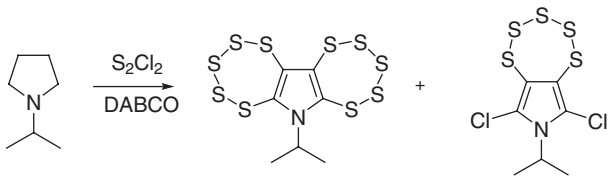
216
R = Et, 23%

Scheme 113

N-methylpyrrolidine gave a small amount (5%) of unchlorinated compound **215** with the pentathiepin ring fused across the 2,3-pyrrole bond and *N*-ethylpyrrolidine gave a higher percentage (23%) of product **216** fused similarly to the former but chlorinated in the free α-position of the pyrrole (Scheme 113).

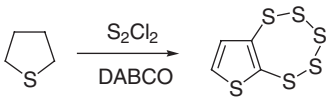
*N-Iso*propylpyrrolidine gave an unexpected mixture of two pentathiepins with the *N-iso*propyl groups remaining intact, dichloromonopentathiepin **214c** and bispentathiepin **217** (Scheme 114). The latter, a yellow oil, is believed to be the first bispentathiepin reported (2004CRV2617).

Thiophene gave a mixture of oligomers without pentathiepin products; apparently the ring is very reactive toward S_2Cl_2 and about a half of its hydrogen atoms, judging from NMR spectra, appeared to be substituted by sulfur. A reduced ratio of S_2Cl_2 and DABCO did not improve the situation but simply afforded similar oligomers in lower yield. Tetrahydrothiophene gave pentathiepin **218** and the yield increased as the S_2Cl_2–DABCO mixture was reduced from a sixfold excess (24%) to a fourfold excess (39%) (Scheme 115), which suggests



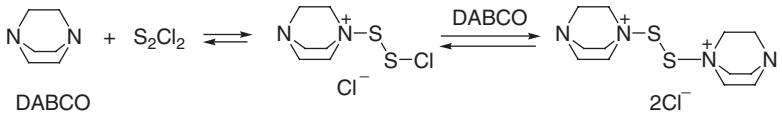
217, 31% **214c**, 16%

Scheme 114



218, 39%

Scheme 115



DABCO **219** **220**

Scheme 116

a possible conversion of **218** to a mixture of oligomers; indeed in a blank experiment, **218** reacted with S_2Cl_2 to give such a mixture.

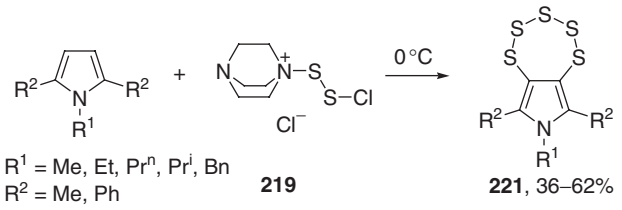
Too little is known about the nature of these reactions, although possible overall reaction pathways, including dehydrogenation of tetrahydroaromatics, chlorination and sulfuration of aromatics and their conversion into SSCl derivatives, and the pentathiepin ring formation, were proposed.

Other aromatic heterocycles, such as indoles and furan, did not yield pentathiepin products under these conditions. Also, where there was more than one site for fusion of the new polysulfur ring, these reactions were not regioselective and were sensitive to the nature of the heterocycle and conditions (2005OBC3496, 2004MC91). Recently it was found that a mixture of equimolar amounts of S_2Cl_2 and DABCO in chloroform, stored for 48 h at 0 °C or 1 h at room temperature before use, formed complexes **219** (1:1 mixture of S_2Cl_2 and DABCO) and **220** (1:2 mixture of S_2Cl_2 and DABCO) (2004MC91; Scheme 116).

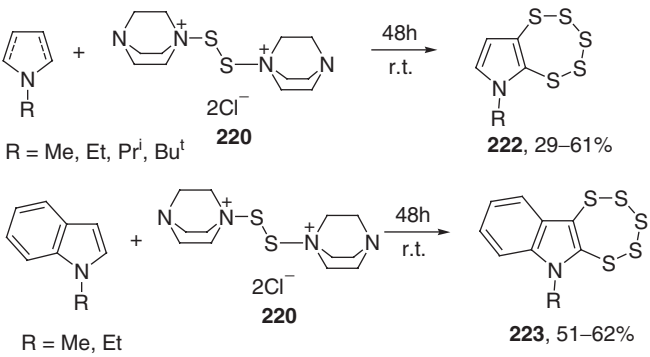
These complexes could exhibit different reactivities, since **219** is a potential Cl^+ and ^+S–SCl source and could be an electrophilic chlorinating and sulfurating agent, while **220** should react only as the latter.

A reaction of *N*-alkyl-and *N*-phenyl-2,5-disubstituted pyrroles with complex **219** at 0 °C gave the best yields of the corresponding pentathiepins **221** under conditions which include treatment with non-premixed sulfur monochloride and DABCO and with complex **220** (2005OL5725; Scheme 117).

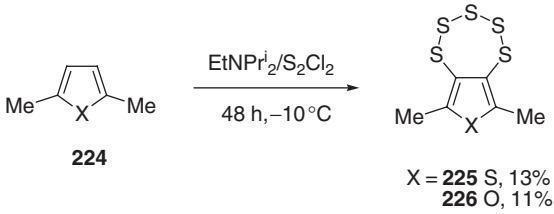
Treatment of *N*-alkyl-pyrrolidines and -indoles with a fivefold excess of complex **220** in chloroform for 48 h at room temperature gave regioselectively



Scheme 117



Scheme 118



Scheme 119

N-alkyl-1,2,3,4,5-pentathiepinopyrroles **222** and indoles **223** in moderate yields (2004MC91; Scheme 118).

Even milder conditions were used for the preparation of thienopentathiepin **225** and pentathiepinofuran **226** from the corresponding heterocycles **224** (2006MC289). These heterocycles with sulfur monochloride and *N*-ethyldi*iso*propylamine at low (−10 °C) temperature gave pentathiepins **225** and **226** although in low yields (Scheme 119).

The various, complex, cascade reactions described above converted simple saturated and aromatic heterocycles into polycyclic pentathiepins and their chlorinated and rearranged derivatives; this strikingly illustrates the extensive reactivity of S_2Cl_2 and its complexes with bases, particularly DABCO. This reactivity encompassed dehydrogenation of tetrahydroaromatics, chlorination and sulfuration of aromatics and their conversion into SSCl derivatives,

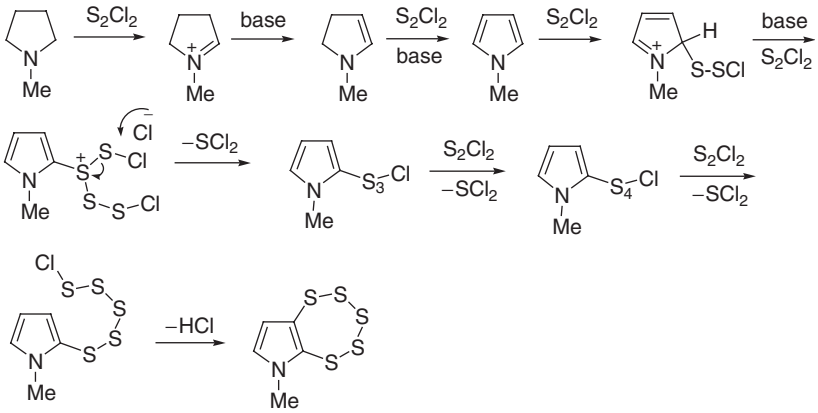
pentathiepin ring formation and pentathiepin-to-pentathiepin rearrangements. It was also proposed that $–S_nCl$ chains could be extended to give $–S_{(n+1)}Cl$ chains by the S_2Cl_2 addition and SCl_2 loss and, ultimately, the thermodynamically stable (2004CRV2617) pentathiepin ring. A typical mechanism is presented in Scheme 120 (2005OBC3496).

Sulfur monochloride was successfully used for the preparation of pentathiepino-fused poly(*N*-methylpyrrole) from the corresponding polymer (2005MI345).

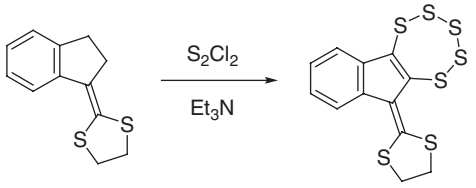
With triethylamine in toluene, S_2Cl_2 converted indane derivative **227**, probably activated by the enedithio group, into pentathiepin **228** in low yield (1974JCS(P1)447; Scheme 121).

More curious and unexpected reactions were observed when complex **219** was heated with triethylamine often used as an "inert" base in many reactions with sulfur monochloride. Thienopentathiepin **229** (30%) together with heptathiocane **230** (10%) were produced; their polysulfur rings had the anticipated chair and crown conformations, respectively (2003OL1939; Scheme 122).

Similar reactions were observed with other tertiary *N*-ethylamines though in lower yields. Despite rather low yields in most instances, the products were prepared in one pot and from cheap starting materials. The thiophene ring of **229** was built from two ethyl groups with a new C–C bond established between two formally unactivated methyl groups; the pentathiepin ring was fused onto

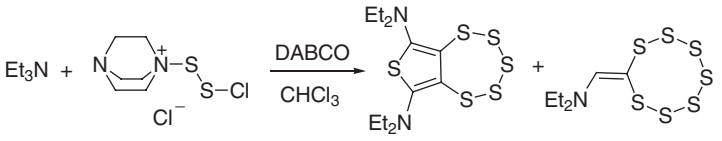


Scheme 120



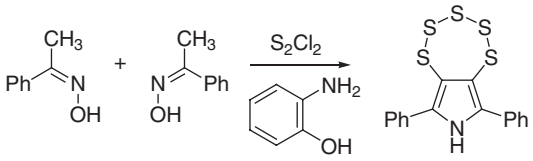
227 **228**, 14%

Scheme 121



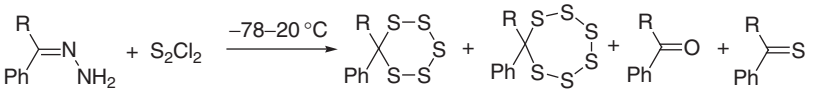
219 **229**, 30% **230**, 10%

Scheme 122



231, 2%

Scheme 123



R = 1-adamantyl, Bu^t, Ph

232, 4–11% **233**, 3–7% 15–63% 15–63%

Scheme 124

thiophene as in the above transformations (see Schemes 112–115, 117–120). Mechanisms were proposed.

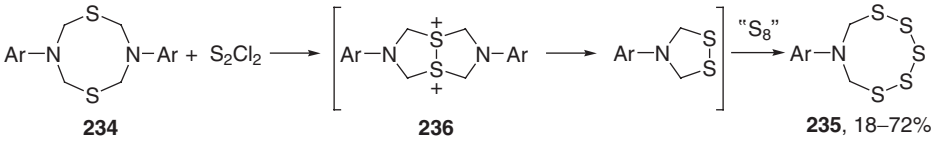
Pyrrolopentathiepin **231** was found as a minor by-product in a curious and completely unexpected reaction of acetophenone oxime and sulfur monochloride in the presence of pyridine and *o*-aminophenol (1997BSB605; Scheme 123). A possible mechanism was suggested.

7.2 Other heterocycles with five sulfur atoms

Treatment of hydrazones derived from 1-adamantyl phenyl ketone, pivalophenone and benzophenone with sulfur monochloride gave pentathianes **232** and hexathianes **233** along with the corresponding ketones and thioketones as the main products (1997H255; Scheme 124).

Surprisingly, under these conditions di-*tert*-butyl ketone hydrazone afforded 1,1-di-*tert*-butyltetrathiolane in very low yield (2%) (see similar reaction in Scheme 91).

A reaction of dithiadiazocanes **234** with sulfur monochloride gave a novel macrocyclic polysulfide, 1,2,3,5,7-pentathiocanes **235**, in moderate-to-high yields (2002CL90). The NMR monitoring of this reaction suggested that a plausible route involved the formation of an oxidative transannular S–S bond in a thermally stable secondary species, a symmetrical dithiadication **236**, followed by



234 **236** **235**, 18–72%

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 125

subsequent removal of half of the product **236** by the attack of some nucleophiles derived from elemental sulfur formed from sulfur monochloride (Scheme 125).

8. HETEROCYCLES WITH SIX OR MORE SULFUR ATOMS

Hexathiaspirododecane **237** containing six sulfur atoms in the ring was prepared from titanocene complex **238** with sulfur monochloride (1996ZAAC1594). The structure of **237** had a chair conformation as identified by X-ray analysis (Scheme 126).

A new sulfurimide heterocycle with six sulfurs – octyl hexathiazepane **239** – was obtained from titanocene complex **240** in high yield (1998AG(E)492; Scheme 127).

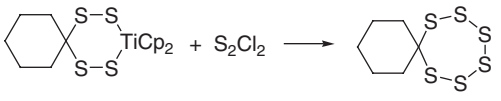
Sulfur monochloride reacted with another titanocene complex **241** to give nonasulfur imide **242**. The reaction proceeded smoothly at room temperature (1996AG(E)2537; Scheme 128).

Treatment of 3,4-diethylpyrrole with α,α'-free positions using sulfur monochloride under argon at $-78\,^{\circ}C$ gave macrocycle **243** where two pyrrole rings were linked by two chains of three sulfur atoms (2005CC2122; Scheme 129). The mechanism is unknown. However, it is noteworthy that under identical conditions sulfur monochloride gave products with a different number of bridging sulfur atoms depending on the pyrrole structure (see also Schemes 98 and 99).

Various aromatic compounds were intensively studied in reactions with sulfur monochloride to achieve macrocyclic multisulfur oligomers. A high-dilution methodology was usually used which often led to the selective formation of cyclic products. 1,4-Dialkoxybenzenes reacted with sulfur monochloride in the presence of Montmorrilonite-K catalyst to give macrocycles **244** in surprisingly moderate yields (1972JCS(P1)1687; Scheme 130). The structure of these compounds was confirmed by transformation to the corresponding dithiols or disulfonyl dichlorides.

The iron-catalyzed reaction of 1,3-dimethoxybenzene with sulfur monochloride in dilute chloroform gave two polysulfur heterocycles **245** and **246** with six sulfur atoms in the molecule, yields were very low (1979JCS(P1)1712; Scheme 131).

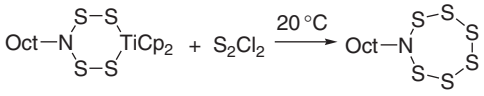
The structure of compounds **245** and **246** was confirmed by mass and NMR spectroscopy.



238 **237**, 51%

Cp = cyclopentadienyl

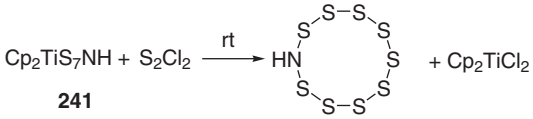
Scheme 126



240 **239**, 91%

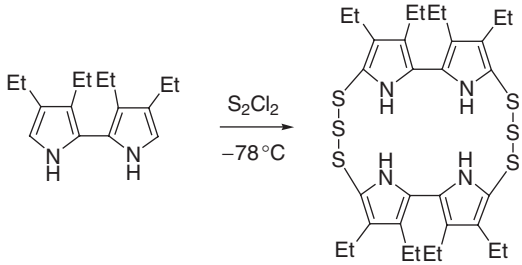
Cp = cyclopentadienyl

Scheme 127



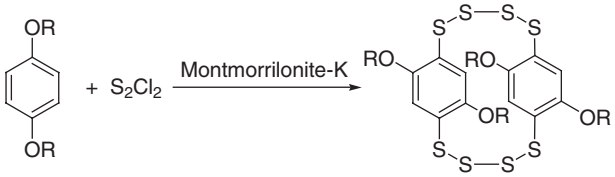
241 **242**, 54%

Scheme 128



243, 21%

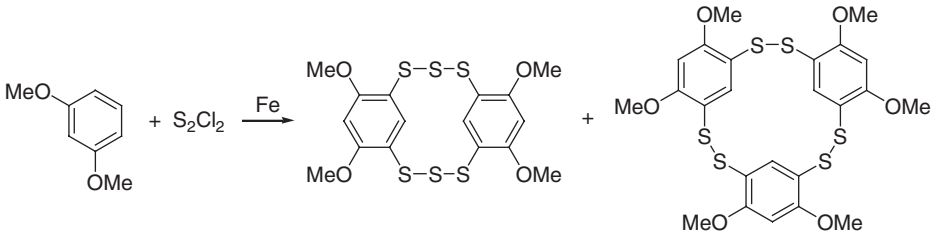
Scheme 129



R = Me, Et

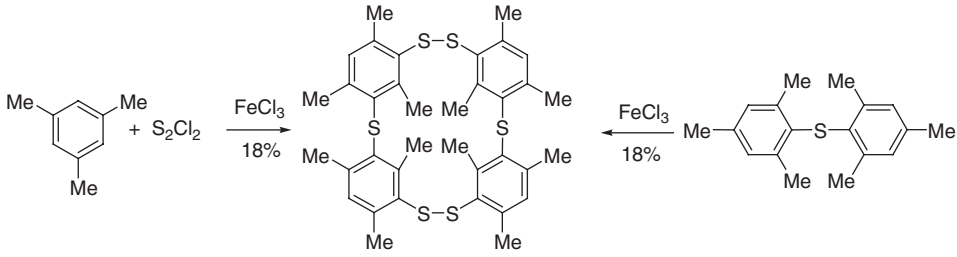
244, 52–59%

Scheme 130



245, 5% **246**, 1.5%

Scheme 131



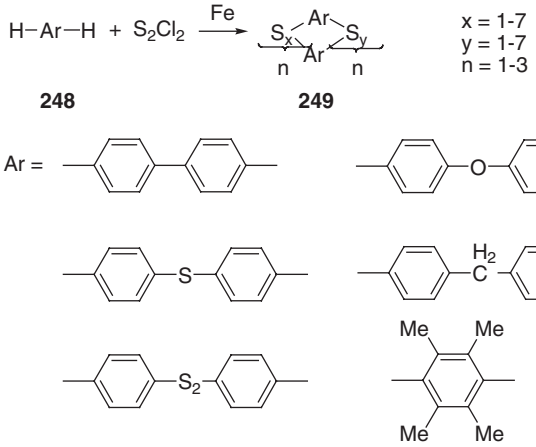
247

Scheme 132

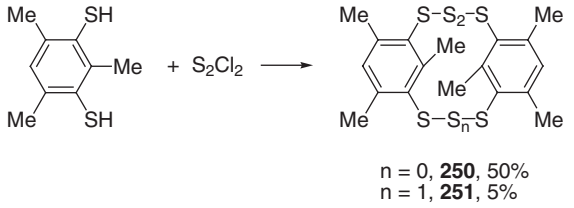
Treatment of mesitylene or dimesityl sulfide with sulfur monochloride led to the same polysulfur macrocycle **247**; yields in both cases were identical (1977T337; Scheme 132).

These investigations continue because these macrocyclic oligomers are promising reactive intermediates for the synthesis of high-performance linear aromatic polymers by ring-opening polymerization. Pseudo high-dilution conditions which were achieved by a slow addition of diphenyl derivatives **248** to the sulfur monochloride and iron powder catalyst led to a mixture of oligomers **249** in almost quantitative yield (1998MI6469, 2004MI735, 2004CNP1470511). MALDI-TOF mass-spectra showed that repeated cyclization units ranged from two to seven and a unit of the macrocyclic (arylene multisulfide) oligomers had from one to seven sulfur atoms (Scheme 133).

Polysubstituted benzene-1,3-dithioles are employed in the synthesis of polysulfur-bridged metacyclophanes. Surprisingly, the quantity of sulfur atoms inserted into the polycyclic ring may vary significantly. For example, when 4,6-dimethoxybenzene-1,3-dithiol was used in the reaction with sulfur monochloride, only one product with six sulfur atoms **245** was isolated (1979JCS(P1)1712). Mesitylene-2,4-dithiol gave two oligomers, an unsymmetrical hexathiametacyclophane **250** as the major product accompanied by minor amounts of higher homolog **251**. Compounds **250** and **251** were produced in equal yields by using sulfur dichloride instead of S_2Cl_2 (1980T3095; Scheme 134).



Scheme 133



Scheme 134

9. CONCLUSIONS

The reactions described show that sulfur monochloride is an important reagent for the synthesis of heterocycles with various numbers of sulfur atoms and even without sulfur. An important feature of this reagent is that it can add not only two sulfur atoms to the molecule, as might be expected, but also one, three, four, five or even more atoms, and the structure of the final compound often depends on its stability. Recent developments in the use of sulfur monochloride include the discovery of its ability to form complexes with organic bases and of the significant difference in reactivity of these complexes from S_2Cl_2. A selective synthesis of particular heterocycles requires accurate conditions (temperature, solvent, catalyst and base).

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SUBJECT INDEX