Aza-*ortho*-xylylenes in Organic Synthesis

Krzysztof Wojciechowski[a]

Keywords: Cycloadditions / Heterocycles / Hydrogen transfer / Pericyclic reactions / Sigmatropic rearrangements

Aza-*ortho*-xylylenes (*ortho*-quinone methylene imines or 1-methylene-6-iminocyclohexa-2,4-dienes) are potential building blocks for the construction of heterocyclic systems. These reactive, non-isolable intermediates may be generated by a variety of procedures, such as cheletropic extrusion of SO_2 from benzosultams, [4+2] cycloreversion of 3,1-benzoxazin-2-ones, or by 1,4-elimination of various species (H_2O, R_2NH, HCl, HF) from 2-aminobenzyl derivatives. The aza-*ortho*-xylylenes enter into [4+2] cycloaddition reactions, producing condensed heterocycles. In numerous cases, aza-*ortho*-xylylenes undergo [1,5]-sigmatropic hydrogen shifts to afford 2-vinylaniline derivatives, while addition of nucleophiles to them gives rise to 2-aminobenzyl derivatives. The problem of stability and valence isomerization of benzazetidines to aza-*ortho*-xylylenes is discussed. A brief survey of methods of synthesis of precursors suitable for generation of aza-*ortho*-xylylenes is also included.

Introduction

1-Azadienes are useful tools for the construction of heterocyclic systems.[1] Some exceptional representatives of 1-azadienes are aza-*ortho*-xylylenes, also known as 6-methylenecyclohexa-2,4-dien-1-imines or *ortho*-quinone methylene imines.[2] These reactive, non-isolable species are potential building blocks for the construction of condensed heterocycles. The related *ortho*-xylylenes (1,2-quinodimethanes) have found numerous applications in the synthesis of condensed carbocyclic systems difficult to obtain by other synthetic methods; numerous reviews devoted to the chemistry of *ortho*-xylylenes have appeared in recent years.[3–9] Unlike that of *ortho*-xylylenes, which can be generated from a range of precursors (most conveniently by electrocyclic ring-opening in benzocyclobutenes[7,9] or cheletropic extrusion of SO_2 from 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides[6,10,11]), the chemistry of aza-*ortho*-xylylenes has been the focus of much less attention, largely due to the lack of convenient methods suitable for generation of these reactive species. Since the publication of our last review,[2] however, new and efficient methodologies for generating aza-*ortho*-xylylenes have been developed, allowing wider use of these reactive intermediates in organic synthesis. This review summarizes literature reports on the generation and reactions of aza-*ortho*-xylylenes, and gives a full account of our work on the applications of benzosultams as aza-*ortho*-xylylene precursors. Since it is difficult to separate the generation of aza-*ortho*-xylylenes from their further reactions, the generation of these reactive intermediates is directly followed in this presentation by their transformations. In addition, a brief survey of methods of synthesis of precursors suitable for generation of aza-*ortho*-xylylenes is included.

This review excludes numerous derivatives of five-membered heterocycles — such as imidazole, pyrazole, oxazole, indole, etc. — bearing exocyclic C=C and C=N bonds and which therefore might be viewed as heteroanalogs of aza-*ortho*-xylylenes. These compounds are often stable and do not exhibit the high reactivity typical of aza-*ortho*-xylylenes. In particular, they do not enter into [4+2] cycloadditions, unlike heteroanalogs of *ortho*-xylylenes, the high reactivity of which is driven by aromaticity recovery in five- and six-membered rings.[6,11,12] Reactions of condensed heterocycles

[a] Institute of Organic Chemistry Polish Academy of Sciences, ul. Kasprzaka 44/52, PO Box 58, 01-224 Warszawa 42, Poland
E-mail: kris@icho.edu.pl

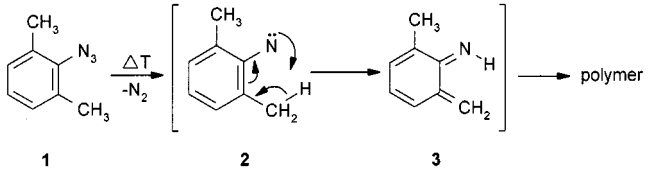
Dr. Krzysztof Wojciechowski, born in Warszawa in 1950, received his M.Sc. in 1974 and his Ph.D. in 1980 from the Technical University, Warszawa (with Prof. M. Mąkosza). In 1982 he was a postdoctoral fellow with Prof. M. J. O'Donnell at IUPUI (Indianapolis, USA) and in 1992 a JSPS fellow with Prof. Yoshihiko Ito (Kyoto University). Since 1979 he has been a research associate at the Institute of Organic Chemistry, Polish Academy of Sciences. In 1993 he completed his habilitation on the generation and reactions of aza-ortho-xylylenes and since 1998 he has been Associate Professor (Docent) at his mother institute. His research focuses on heterocyclic chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

  1434–193X/01/1019–3587 $ 17.50+.50/0

containing aza-*ortho*-xylylene fragments — such as 2,1-benzisoxazoles (anthranils), 2,1-benzisothiazoles, 2*H*-indoles, 2*H*-indazoles, etc. — are also beyond the scope of this survey.

The structure of aza-*ortho*-xylylene was proposed for the first time by Smolinsky,[13] for an intermediate **3** formed through a [1,4]-hydrogen shift in nitrene **2**, generated during the pyrolysis of 2,6-dimethylphenyl azide (**1**) (Scheme 1).



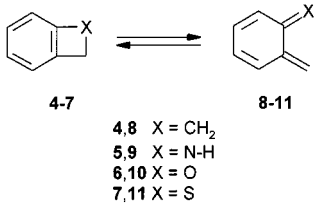
Scheme 1

The formation of aza-*ortho*-xylylene was proved experimentally some years later by Burgess and McCullagh,[14] who found a cycloaddition product of this intermediate, formed by thermal electrocyclic ring-opening in *N*-phenylbenzoazetine (Scheme 5, vide infra).

Discussion

Benzoazetines − Aza-*ortho*-xylylenes Valence Isomerization

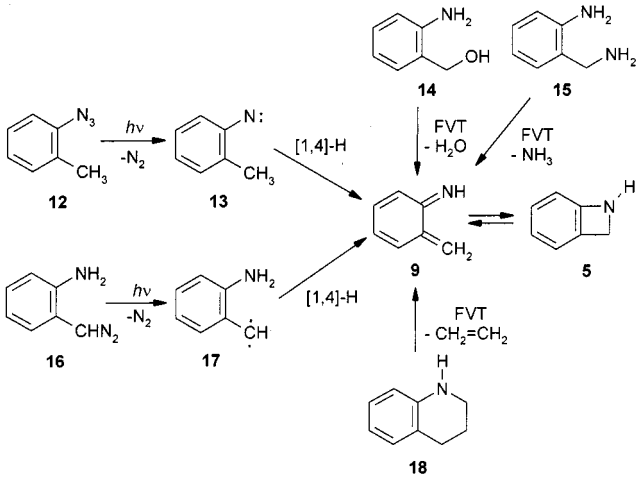
A fundamental problem in the chemistry of *ortho*-xylylenes and their oxy-, aza-, and thio- analogues is the valence isomerization of benzenoid **4**−**7** and *ortho*-quinoid systems **8**−**11** (Scheme 2).[15] In this process, an important role is played by two opposing factors: the strain of the four-membered ring in the aromatic form and the loss of aromaticity in the open quinoid system.[16,17] Rearomatization is thus the driving force in all reactions of *ortho*-xylylenes and their analogues.[16]



Scheme 2

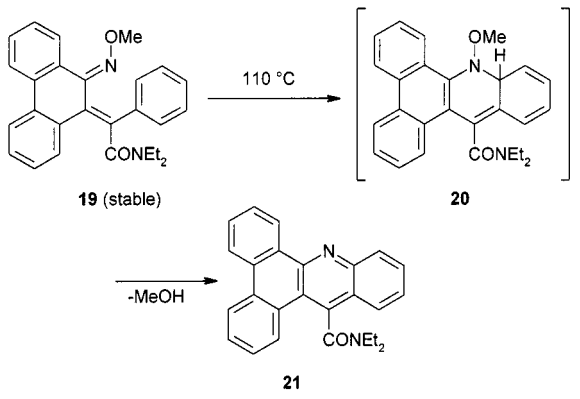
The valence isomerization of benzoazetine (**5**) and aza-*ortho*-xylylene (**9**) has been the subject of numerous theoretical studies.[15,18−21] The calculated relative stabilities of benzoazetine (**5**) and aza-*ortho*-xylylene (**9**) depend on the theoretical method used. Results of semiempirical MNDO calculations predict a higher stability for benzoazetine (**5**) than for aza-*ortho*-xylylene (**9**),[20] but results of AM1 calculations suggest the greater stability for the latter.[18] A thorough comparison of the results of calculations, semiempirical and ab initio, obtained at various theory levels has been performed by Sander et al.[18,19] Results of our ab initio calculations at the MP2 theory level suggest a higher stability for aza-*ortho*-xylylene (**9**) than for benzoazetine (**5**).[21] These calculations also confirm a strong tendency towards [1,5]-hydrogen shifts in *N*-methyl-aza-*ortho*-xylylene.[21] According to results of semiempirical AM1 calculations, the 6π electrocyclization of *N*-acyl-aza-*ortho*-xylylene to *N*-acyl-3,1-benzoxazine is more favorable than the 4π electrocyclization to *N*-acylbenzoazetine (Scheme 36, vide infra).[22] These calculations also predict higher stabilities than that of benzoazetine for both the (*E*) and the (*Z*) isomer of *N*-acylaza-*ortho*-xylylene.[22]

Numerous efforts to isolate and characterize aza-*ortho*-xylylenes have been made (Scheme 3). Ripoll et al. assigned the structure of aza-*ortho*-xylylene (**9**) to the yellow deposit, trapped at −196 °C, arising from the flash vacuum thermolysis (FVT) of 1,2,3,4-tetrahydroquinoline (**18**).[23] This compound was very unstable and at −100 °C it turned into a colorless polymeric material. The pyrolysates of 2-aminobenzyl alcohol (**14**) and 2-aminobenzylamine (**15**) behaved similarly.[23] [1,4]-Hydrogen shifts in nitrene **13**, generated from *ortho*-tolyl azide (**12**), and in 2-aminophenylcarbene (**17**), generated during the photochemical decomposition of 2-aminophenyldiazomethane (**16**), both produced aza-*ortho*-xylylene (**9**), which was trapped in an argon matrix.[18,19] An analogous [1,4]-hydrogen shift in the nitrene generated from 3,5-dimethyl-2-(9-fluorenyl)phenyl azide afforded an aza-*ortho*-xylylene, which electrocyclized to form condensed dihydroacridine.[24] The IR spectra of aza-*ortho*-xylylene (**9**) and benzoazetine (**5**) fit well with those predicted by theoretical calculations.[18]



Scheme 3

As mentioned, UV irradiation of the trapped **9** resulted in electrocyclization to benzoazetine (**5**).[18,19] It was concluded that the benzoazetine cannot arise from the direct thermolysis of any of the precursors, but can only be formed as a result of the secondary irradiation of aza-*ortho*-xylylene (**9**).[19] UV photoelectron spectroscopy (UV-PES) was used for detection of aza-*ortho*-xylylene and benzoazetine among the products formed during FVT of 2-aminobenzyl alcohol (**14**), 2-aminobenzylamine (**15**), and 1,2,3,4-tetrahydroquinoline (**18**).[20] No benzoazetine was detected by UV-PES among the products formed during the thermolysis of 2,1-benzisothiazoline 2,2-dioxide.[21]



Scheme 4

In particular cases, the additional stability provided by aromatic rings enables stable compounds containing the aza-*ortho*-xylylene fragment to be isolated.[25−27] The stable phenanthrene derivative **19** undergoes thermal electrocyclization followed by an elimination of methanol to produce dibenzoacridine **21** (Scheme 4).[25]

Preparation of Stable Benzoazetines

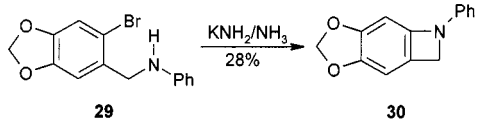
According to semiempirical calculations,[15] the stability of benzoazetine (**5**) should be between that of benzocyclobutene (**4**) and benzothiete (**7**) on one hand and that of benzoxete (**6**) on the other. Benzocyclobutene (**4**)[7,9] and benzothiete (**7**)[28] are stable under normal laboratory conditions, unlike benzoxete (**6**), which is an elusive species capable of being trapped and analyzed only in an argon matrix at 10 K.[29] Several methods for the preparation of benzocyclobutenes[7,9] and benzothietes[28] have been developed, enabling wide use of the *ortho*-xylylenes **8** and thia analogues **11** generated from them in organic synthesis. Numerous efforts have therefore been made to synthesize the benzoazetines **5**, which, if stable, might be convenient precursors of aza-*ortho*-xylylenes. These efforts have been only marginally successful.

N-Phenylbenzoazetine (**24**) was obtained as the main product of a photolytic extrusion of dinitrogen from 3-phenyl-4*H*-1,2,3-benzotriazine (**22**) (Scheme 5).[14] The four-membered ring is formed as the result of an intramolecular recombination of the initial biradical **23**. The benzoazetine **24** is relatively stable at ambient temperature; it undergoes thermal ring-opening in benzene at 30 °C (and more rapidly at 80 °C) to *N*-phenylaza-*ortho*-xylylene (**25**), which was trapped with aniline to give *N*-[(2-phenylamino)-benzyl]aniline.[14] The xylylene **25**, which can be generated at 200 °C, undergoes a [4+2] cycloaddition with *N*-phenylmaleimide (NPMI), resulting in the 1,2,3,4-tetrahydroquinoline derivative **26**.[14] We have used aza-*ortho*-xylylene generated from **24** in a Diels−Alder reaction with 1,4-naphthoquinone.[30] The initially formed cycloadduct **27** tautomerized on silica gel to give the more stable isomer **28**.

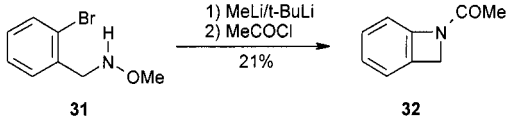
The *N*-phenylbenzoazetine derivative **30** was obtained in moderate yield by an intramolecular amination of the aryne formed from *N*-(2-halobenzyl)aniline (**29**) (Scheme 6).[31] The formation of benzoazetines is suppressed by a competitive addition of amide anion to the intermediate aryne,[31] or by a ring-closure of an ambident aniline anion, producing phenanthridines.[32]

Beak et al. obtained *N*-acetylbenzoazetine (**32**) in an intramolecular reaction of *N*-methoxy-2-bromobenzylamine (**31**), doubly lithiated with methyllithium and *tert*-butyllithium (Scheme 7).[33] No attempts to apply **32** as an aza-*ortho*-xylylene precursor were undertaken.

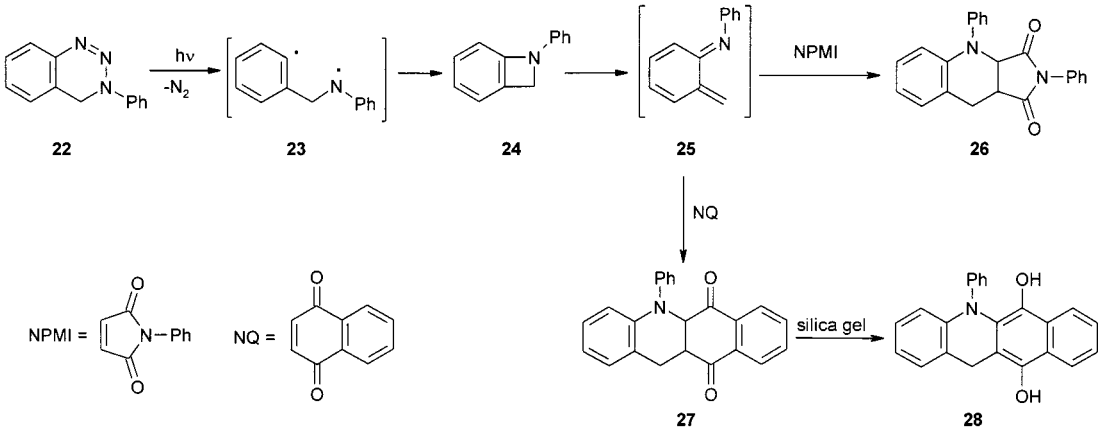
The stable 1-methylbenzoazetine (**66**) and 1,2-dimethylbenzoazetine (**65**) were obtained from the corresponding



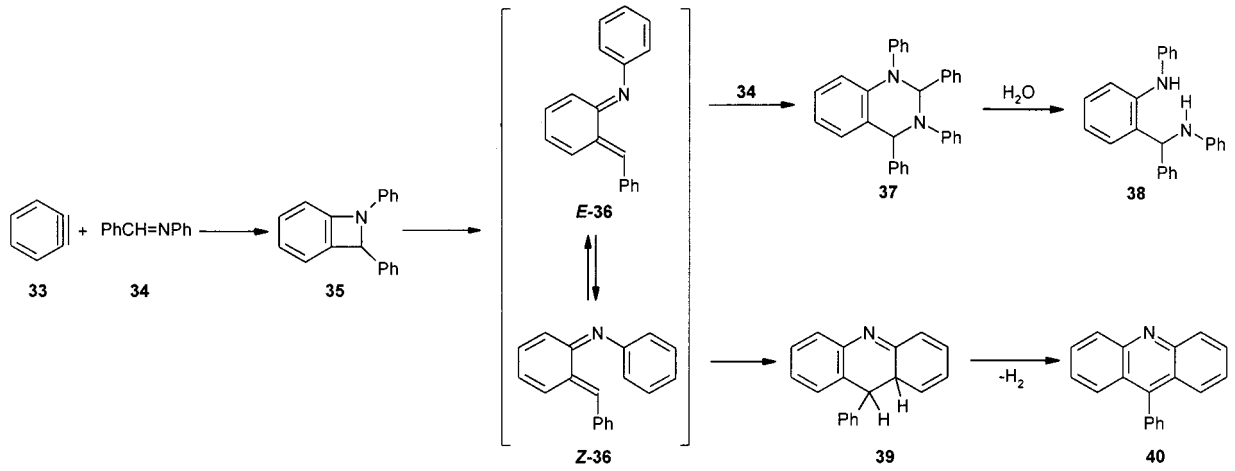
Scheme 6



Scheme 7



Scheme 5

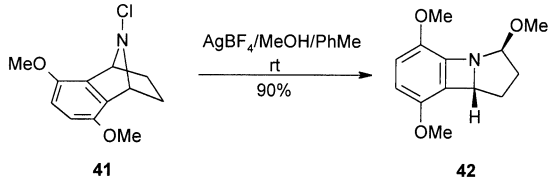


Scheme 8

benzosultams **54** and **62**, respectively[34] (vide infra, Scheme 16).

Yoshida et al.[35] and Storr et al.[36] attempted to isolate 1,2-diphenylbenzoazetine (**35**), formed in the [2+2] cycloaddition between benzylideneaniline (**34**) and benzyne (**33**) generated from 2-diazabenzoate (Scheme 8). These efforts were fruitless, but there was considerable evidence for the formation of benzoazetine **35** and its participation in further reactions. The initially formed adduct **35** underwent an electrocyclic ring-opening and the aza-*ortho*-xylylene **36** [(*E*) isomer] formed reacted with another molecule of Schiff base to give tetrahydroquinazoline (**37**), which then hydrolyzed to the diamine **38**. Dihydroacridine **39**, arising from electrocyclization of the (*Z*) isomer of aza-*ortho*-xylylene (*Z*-**36**), and fully aromatic 9-phenylacridine (**40**), resulting from dehydration of **39**, were also detected in this reaction.[36]

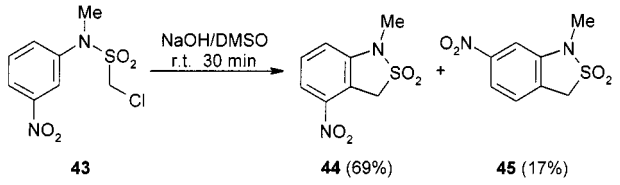
Surprisingly, the stable benzoazetine **42** derivative was obtained during a silver ion-mediated transformation of *N*-chloramine **41** (Scheme 9),[37,38] but was not recognized as an aza-*ortho*-xylylene precursor.



Scheme 9

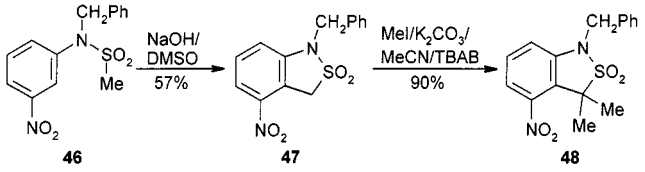
Synthesis of Benzosultams

Our interest in aza-*ortho*-xylylene chemistry was stimulated by earlier studies on the reactions between carbanions and aromatic nitro compounds, particularly the vicarious nucleophilic substitution of hydrogen (VNS).[39−41] We investigated intramolecular VNS reactions in *N*-alkyl-*N*-chloromethanesulfonyl-3-nitroanilines.[42,43] For example, the sulfonamide **43** in the presence of solid sodium hydroxide in dimethyl sulfoxide gives a mixture of 4- and 6-nitro-2,1-benzisothiazoline 2,2-dioxides **44** and **45**. For these compounds we proposed the simple name benzosultams (Scheme 10).



Scheme 10

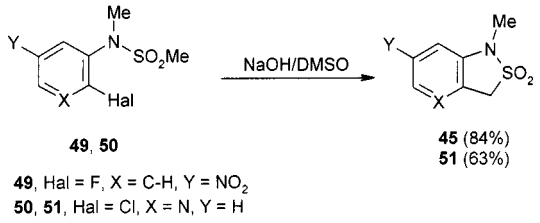
Alkanesulfonamides derived from *meta*-nitroanilines in the presence of sodium hydroxide in DMSO undergo intramolecular oxidative nucleophilic substitution of hydrogen (ONSH)[44−46] *ortho* to the nitro group and give benzosultams in moderate yields.[47−49] Benzosultam **47** was obtained from the sulfonamide **46** in 57% yield, for example (Scheme 11).[48]



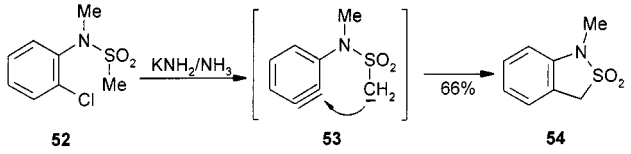
Scheme 11

An intramolecular aromatic nucleophilic substitution (S_NAr) of fluorine in sulfonamide **49** furnishes benzosultam **45** (Scheme 12).[48] Similarly, isothiazolo[4,3-*b*]pyridine 2,2-dioxide (**51**) can be obtained from 2-chloro-3-(sulfonylamino)pyridine (**50**).[50,51]

An aryne-mediated intramolecular substitution in 2-chloro-*N*-methyl-*N*-methanesulfonylaniline (**52**)[52,53] and (2-bromophenyl)methanesulfonamide (**57**)[54] results in



Scheme 12



Scheme 13

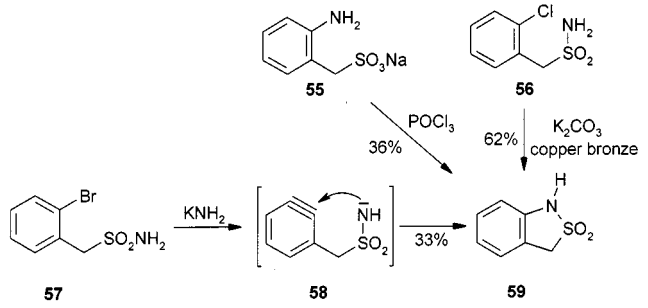
benzosultams **54** and **59**, respectively, via **53** and **58** (Scheme 13).

The simplest benzosultam (**59**) can also be obtained upon treatment of sodium (2-aminophenyl)methanesulfonate (**55**) with $POCl_3$ (36% yield)[55] or by cyclization of (2-chlorophenyl)methanesulfonamide (**56**) in the presence of K_2CO_3 and copper bronze (62% yield),[55] as shown in Scheme 14.

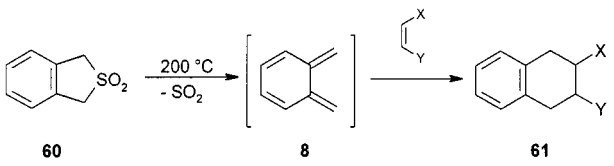
Further functionalization of the obtained *N*-alkyl-benzosultams by alkylation (Scheme 11),[51,56,57] nitroarylation,[49,51,56,58] and Knoevenagel condensation with aldehydes[56,59] provides the 3-substituted benzosultams.

Reactions of Aza-*ortho*-xylylenes Generated from Benzosultams

Benzosultams are structurally similar to 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**60**), which on heating undergoes thermal cheletropic extrusion of SO_2 to generate *ortho*-xylylene (**8**), which can be trapped with dienophiles to give the tetrahydronaphthalenes **61** (Scheme 15).[60] Compound **60** and its heteroanalogs bearing five- and six-membered heterocycles instead of the benzene ring are useful precursors of *ortho*-xylylenes[4,8] and their heteroanalogs.[6,12,61−64] The structural similarity of **60** to



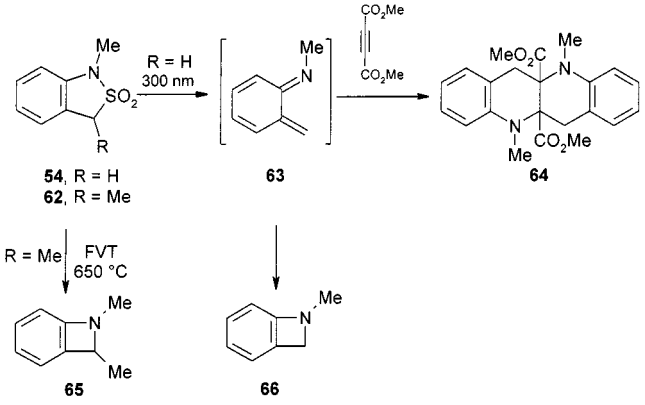
Scheme 14



Scheme 15

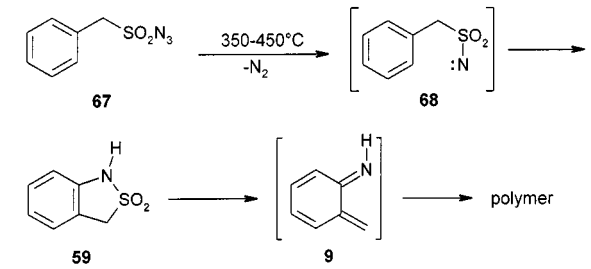
59 prompted us to employ benzosultams as precursors of aza-*ortho*-xylylenes.[65]

According to an earlier report,[34] the photolysis (300 nm) of 1-methyl-2,1-benzisothiazoline 2,2-dioxide (**54**) or flash vacuum thermolysis (FVT) of 1,3-dimethylbenzosultam (**62**) at 650 °C provides 1-methylbenzoazetine (**66**) or 1,2-dimethylbenzoazetine (**65**), respectively (Scheme 16). No attempts to apply the isolated benzoazetines **65** and **66** as aza-*ortho*-xylylene precursors were undertaken, although when the photolysis of **54** was performed in the presence of dienophiles, such as 3-chloroacrylic acid or dimethyl acetylenedicarboxylate, the **63** generated in situ entered into [4+2] cycloadditions, to give, for example, **64**.[34]



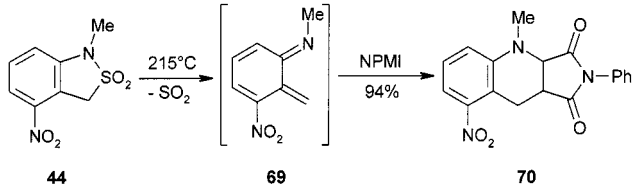
Scheme 16

The formation of aza-*ortho*-xylylene (**9**) was probably overlooked during a thermal decomposition (350−450 °C) of phenylmethanesulfonyl azide (**67**, Scheme 17).[54] Among the products of this reaction, small amounts (0.9−4.3%, depending on temperature) of benzosultam **59** were identified. Such a very low yield was probably due to instantaneous extrusion of SO_2 from the produced benzosultam **59**. Using GC-MS systems for fast screening of thermal reactions, we have found that the decomposition of benzosultams in the gas phase proceeds at 350−400 °C to a great extent.[66]



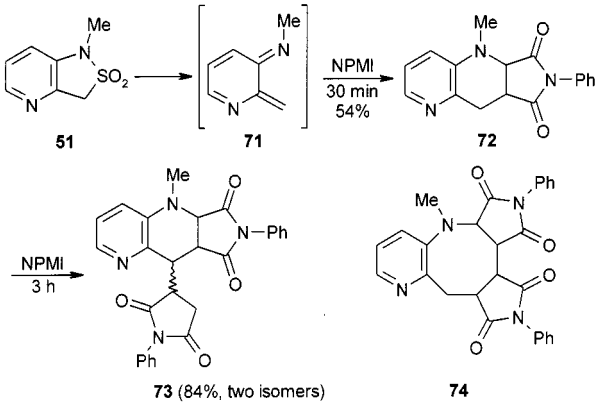
Scheme 17

The aza-*ortho*-xylylene **69**, generated from nitrobenzosultam (**44**) in boiling 1,2-dichlorobenzene (180 °C) or 1,2,4-trichlorobenzene (215 °C), enters into a [4+2] cycloaddition with *N*-phenylmaleimide (NPMI), producing the 1,2,3,4-tetrahydroquinoline derivative **70** (Scheme 18).[65,67]



Scheme 18

The pyridine analogue **71** of aza-*ortho*-xylylene, generated from pyridosultam **51**, enters into a Diels−Alder reaction with NPMI to give the tetrahydro[1,5]naphthyridine derivative **72** (30 min, 54% yield, Scheme 19).[50] Extended heating of the adduct in the presence of an excess of NPMI affords a mixture of two products **73** (total yield 84%, 1:1 ratio). Each of these products consists of two units of NPMI and one of diazaxylylene **71**. The compounds **73** are formed by a Michael addition of the originally formed tetrahydro[1,5]naphthyridine (**72**) to another molecule of NPMI. We originally assigned[50] the structure of pyridoazocine **74** to these compounds, but this was later called into question by Storr et al.,[12] whose similar structural assignment of 2:1 adducts of NPMI to pyrimidine analogue of *ortho*-xylylene[61,63] had also been withdrawn.[12] Reinvestigation of the structures of our bis adducts **73** confirmed Storr's suggestions.[68]



Scheme 19

The reaction between aza-*ortho*-xylylene **69** and 1,4-naphthoquinone (NQ) produces an unexpected spiro derivative **77**.[30] The plausible mode of formation of this product consists of a Diels−Alder reaction followed by a ring-opening of the cycloaddition product **75** to give **76**, followed by a final intramolecular Michael addition (Scheme 20). Similar five-membered spiro products have recently been observed in reactions between 1,4-benzoquinone and *N*-substituted enaminones.[69]

The reaction between azaxylylene **79**, generated from 3-phenylpyridosultam (**78**), and 1,4-naphthoquinone results in the tetracyclic derivative **82**.[30] The initially formed adduct **80** was oxidized, probably by an excess of the quinone used, to **81**, which then isomerized to **82** (Scheme 20).

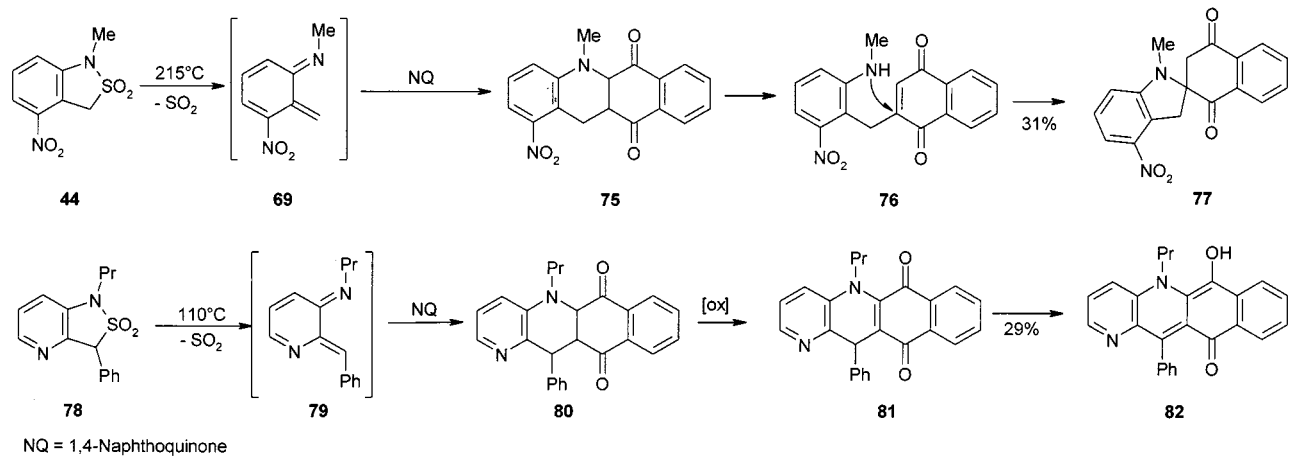
Aza-*ortho*-xylylenes generated from benzosultams and pyridosultams form [4+2] cycloaddition products with dialkyl maleates and fumarates,[67,68] but in lower yields. In the absence of a dienophile, the pyridine analogue **84** undergoes a [4+4] cycloaddition to afford the condensed diazocine **85** (Scheme 21).[50]

An intramolecular cycloaddition of the aza-*ortho*-xylylenes **88** and **89**, generated from benzosultams **86**[67] and pyridosultams **87**[50] bearing *N*-alkenyl substituents with terminal double bonds, is a very good tool for the construction of the condensed heterocyclic systems **90** and **91** (Scheme 22).

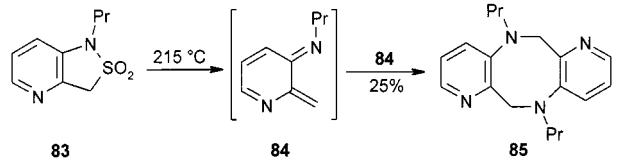
The courses of reactions of aza-*ortho*-xylylenes strongly depend on the interactions of the substituents present in the molecule. Particularly important are the configuration across the exocyclic C=N bond and *E*/*Z* isomerization. This problem was studied for N−H aza-*ortho*-xylylenes by Sander et al.,[18,19] who found the *E* isomer of **9** to be more stable.[18] *Z* isomers of *N*-alkyl-xylylenes undergo a [1,5]-hydrogen shift from the alkylimine group to the exocyclic methylene group, giving *ortho*-toluidine-derived Schiff bases.[67,70] We observed no influence of substituents on the [4+2] cycloadditions of aza-*ortho*-xylylenes generated from 4-, 5-, and 6-substituted benzosultams,[67] which in the presence of dienophiles give 1,2,3,4-tetrahydroquinoline derivatives in high yields. With azaxylylenes generated from 7-substituted benzosultams (7-methyl, 7-chloro, or 7-methoxy), no [4+2] cycloaddition was observed and imines such as **94** were formed by [1,5]-sigmatropic hydrogen shifts facilitated by steric interactions, forcing the substituent at the imine nitrogen to adopt the *Z* configuration, as demonstrated in Scheme 23 for the xylylene **93** formed from 1-benzyl-7-methyl-benzosultam (**92**).[67]

When steric interactions are weaker, as in the case of the 7-fluoro derivative, the reaction with *N*-phenylmaleimide gives the products arising from [4+2] cycloaddition and those resulting from [1,5]-hydrogen shifts.[67] Aza-*ortho*-xylylene **96**, with a fixed *E* configuration, gives the [4+2] cycloaddition product **97** in high yield (Scheme 24).[67] In aza-*ortho*-xylylenes generated from 4-, 5-, and 6-substituted benzosultams, the [1,5]-hydrogen shift to form imines is the dominant process in the absence of a dienophile.[67]

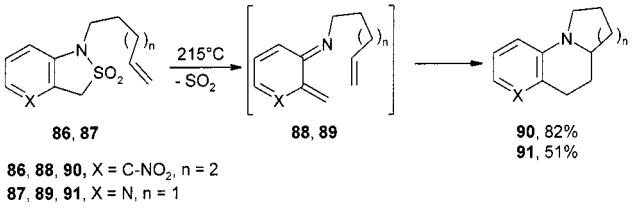
Aza-*ortho*-xylylenes generated from 3-alkylbenzosultams do not enter into [4+2] cycloadditions, but instead undergo [1,5]-sigmatropic hydrogen shifts to produce 2-vinylaniline derivatives.[51,57,71,72] This occurs even when aza-*ortho*-xylylenes are generated from 3-alkylbenzosultams bearing an alkyl chain with a terminal double bond suitable for intramolecular [4+2] cycloaddition, such as in **98**, which yields (via **99**) the aniline derivative **101** and not the cycloadduct **102** (Scheme 25).[57,71]



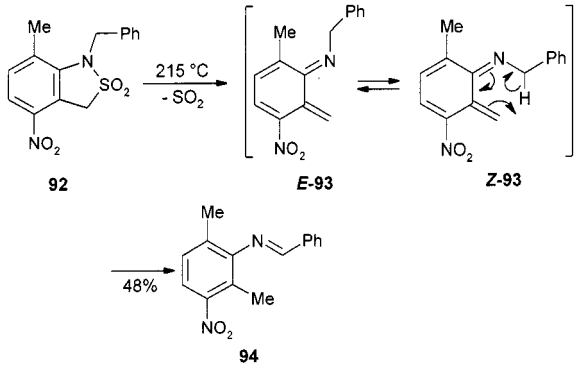
Scheme 20



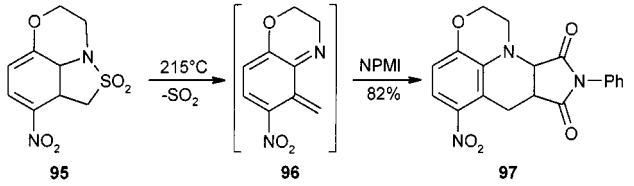
Scheme 21



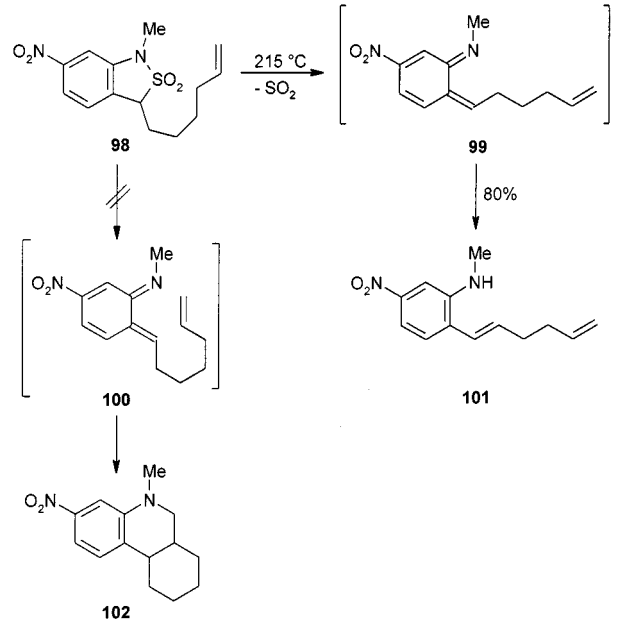
Scheme 22



Scheme 23

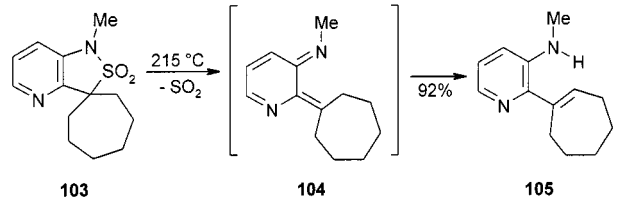


Scheme 24



Scheme 25

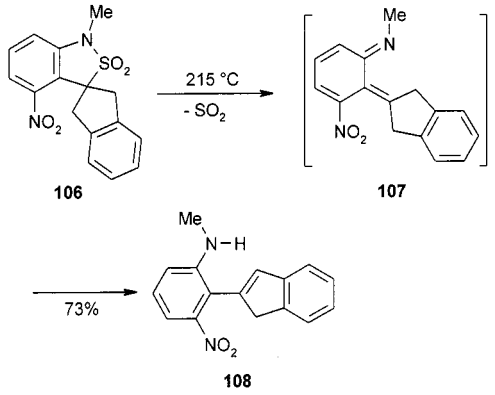
3-Amino-2-(cyclohepten-1-yl)pyridine (**105**) is formed in good yield as a result of a [1,5]-hydrogen shift in the diazaxylylene **104**, generated from 3,3-hexamethylenepyridosultam (**103**) (Scheme 26).[51] Analogous cyclopentene and cyclohexene derivatives are also available.[51]



Scheme 26

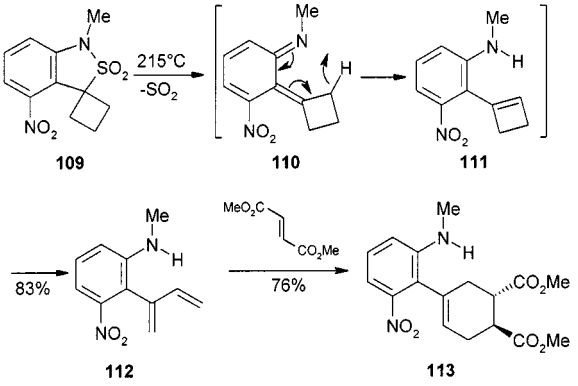
Similarly, indano-2-spiro-3-benzosultams such as **106** are readily transformed, via **107**, into the 2-arylindenes **108** in

high yields (Scheme 27).[72] The pyridine analogue of **106** gives the corresponding 2-(2-pyridyl)indene.[51]



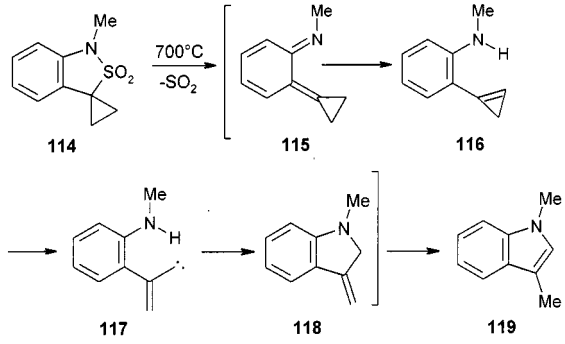
Scheme 27

A cascade of pericyclic transformations initiated by the thermal extrusion of SO_2 from 3,3-trimethylenebenzosultams such as **109**[57] and its pyridine analogue[51] can be classified as *domino reactions*.[73] A [1,5]-hydrogen shift in the xylylene **110** produces the cyclobutene derivative **111**, which, under the reaction conditions used, undergoes an electrocyclic opening of the four-membered ring to form the isolable 2-arylbuta-1,3-diene (**112**). In the presence of a dienophile (such as dimethyl maleate) the butadiene **112** enters into a Diels–Alder reaction, giving the 1-aryl-cyclohexene derivative **113** in good yield (Scheme 28).[57]



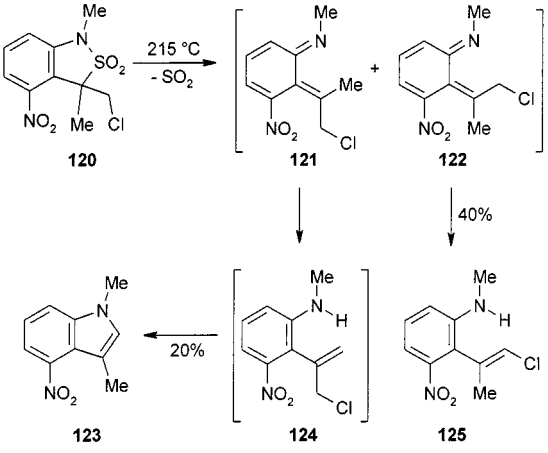
Scheme 28

The ease of extrusion of SO_2 from cyclobutanespirobenzosultams sharply contrasts with the reactivity of the cyclopropanespiro derivative **114**,[51] a potential precursor of arylcyclopropene **116**. Under standard conditions (refluxing 1,2,4-trichlorobenzene, 215 °C), the sultam **114** was reluctant to extrude SO_2, while in higher boiling solvents it produced an intractable mixture of tarry materials. Employing a pyrolytic oven attached to the GC-MS system, we have found that extrusion of SO_2 from **114** begins at about 400 °C and is complete at 700 °C, resulting in a complex mixture of products in which 1,3-dimethylindole (**119**) predominates. A plausible means of formation of indole is shown in Scheme 29. The extrusion of SO_2 is followed by a [1,5]-hydrogen shift and opening of cyclopropene **116** to give the vinylcarbene **117**, which then inserts into the N–H bond to give **118**. A final isomerization produces **119**.[74]



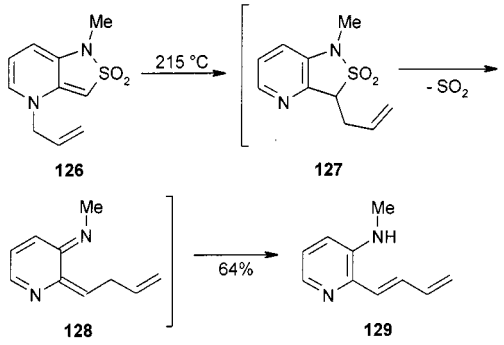
Scheme 29

Extrusion of SO_2 from 3-chloromethyl-3-methylbenzosultam (**120**) produces two isomeric aza-*ortho*-xylylenes **121** and **122**, which transform through [1,5]-hydrogen shifts into the allyl and vinyl derivatives **124** and **125**, respectively. The allyl derivative **124** cyclizes to indole **123** under the reaction conditions (Scheme 30).[57]



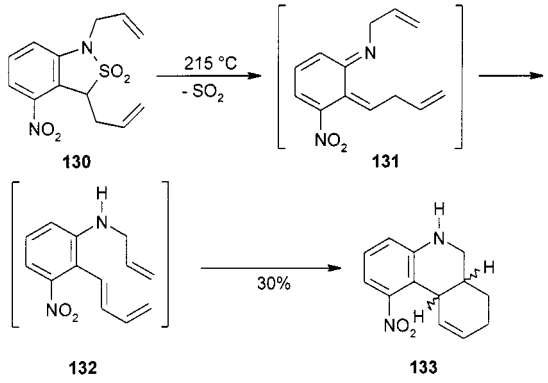
Scheme 30

A series of three consecutive pericyclic processes occurs when the 4-allyl-isothiazolo[4,3-*b*]pyridine derivative **126** is heated at 215 °C (Scheme 31).[75] A Cope rearrangement to the 3-allylsultam **127** is followed by a cheletropic extrusion of SO_2 to give **128**, and then by a [1,5]-sigmatropic hydrogen shift to afford 1-[2-(3-methylamino)pyridyl]buta-1,3-diene (**129**).



Scheme 31

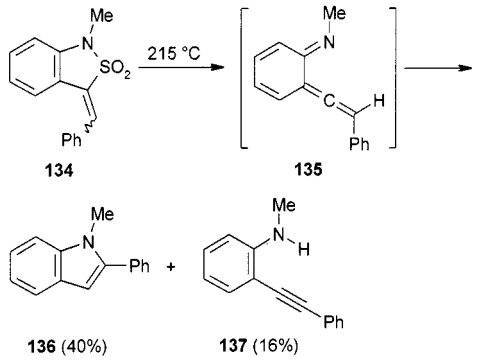
A similar series of pericyclic processes — cheletropic extrusion of SO_2, [1,5]-sigmatropic hydrogen shift, and intramolecular [4+2] cycloaddition — is involved in the thermally initiated transformation of 1,3-diallyl-4-nitrobenzosultam (**130**) into the condensed heterocycle 1-nitro-5,6,6a,7,8,10a-hexahydrophenanthridine (**133**), by way of **131** and **132** (Scheme 32).[57]



Scheme 32

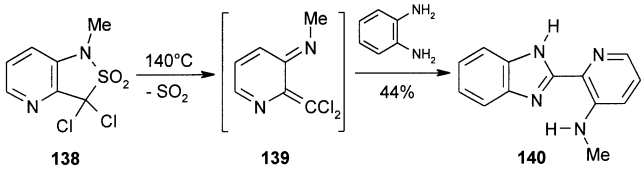
Some clues as to the susceptibility of benzosultams to SO_2 extrusion can be inferred from their electron ionization mass spectra.[65,67,74,76,77] Loss of SO_2 from the benzosultam molecular ion, resulting in the formation of an [M − 64] ion, is usually predominant. We proposed[77] two mechanisms for the elimination of SO_2 from the molecular ions of benzosultams: a) a concerted mechanism with simultaneous breaking of S−N and S−C bonds, and b) a stepwise mechanism in which the S−C bond is broken first. However, some exceptions have been found. In cyclobutanespirobenzosultams such as **109**, the elimination of ethylene by a [2+2] cycloreversion mechanism precedes the elimination of SO_2,[74] whereas in *N*-methoxymethylbenzosultams, a novel rearrangement resulting in elimination of formaldehyde was observed, for which we proposed a mechanism involving the presence of an ion-neutral complex.[78] In 1-alkyl-7-nitrobenzosultams, primary fragmentations involve the *N*-alkyl and nitro groups, resulting in elimination of carbonyl compounds.[79] The molecular ion of the cyclopropanespirobenzosultam **114** shows much more complex fragmentation patterns,[74] and the loss of SO_2 to produce [M − SO_2] proceeds only to a minor extent. The high stability of the molecular ion of **114** is probably due to a perturbation of the hybridization of C-3. Cheletropic extrusion requires sp^3 hybridization, a condition not met in the case of a strained cyclopropane ring.

3-(Arylmethylene)benzosultams, obtained from Knoevenagel reactions between the sultam and aromatic aldehydes, undergo slow extrusion of SO_2. The condensed xylylene **135**, generated from the 3-benzylidenesultam **134**, for example (Scheme 33), rearranges to 1-methyl-2-phenylindole (**136**) by electrocyclization followed by a [1,2]-hydrogen shift, and into the diarylacetylene **137** by a [1,5]-hydrogen shift.[59] The slow rate of extrusion of SO_2 is probably due to the sp^2 hybridization at C-3.



Scheme 33

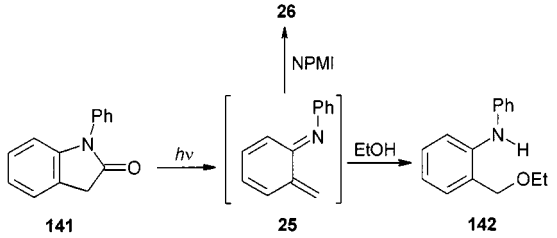
As in the case of aza-*ortho*-xylylenes generated from other precursors, those generated from benzosultams also enter into reactions with nucleophiles.[66] The dichloroxylylene **139**, generated from the 3,3-dichloropyridosultam **138**, does not undergo cycloaddition reactions.[68] In the presence of nucleophiles, the intermediate **139** enters into a Michael addition, resulting in the replacement of both chlorine atoms. The treatment of **139** with *ortho*-phenylenediamine, for example, produces 2-(2-pyridyl)benzimidazole (**140**) (Scheme 34).[68] Difluoroaza-*ortho*-xylylenes, generated by base-induced 1,4-elimination of HF from 2-(trifluoromethyl)anilines, react similarly, giving 2-arylbenzoxazoles or benzothiazoles with 2-aminophenol or 2-aminothiophenol.[80]



Scheme 34

Photodecarbonylation of Oxindoles

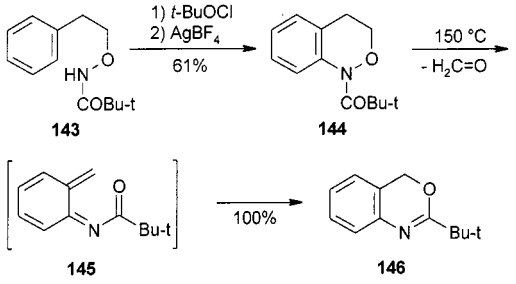
Unlike the benzosultam case, reports on the extrusion of carbon monoxide from structurally similar oxindoles are scarce.[18,19,81,82] Photodecarbonylation of 1-phenyloxindole (**141**) produces *N*-(phenyl)aza-*ortho*-xylylene (**25**), which enters into a [4+2] cycloaddition with *N*-phenylmaleimide to afford **26** (Scheme 35).[81,82] Photolysis of **141** in the presence of nucleophiles such as alcohols, amines, or 2-hydroxypyridine results in the corresponding 2-aminobenzyl ethers (such as **142**) and amines.[82] It is worth noting that 1-methyloxindole and 1,3-diphenyloxindole are stable under UV irradiation conditions,[81] but oxindole produces aza-*ortho*-xylylene at a very slow rate.[18,19]



Scheme 35

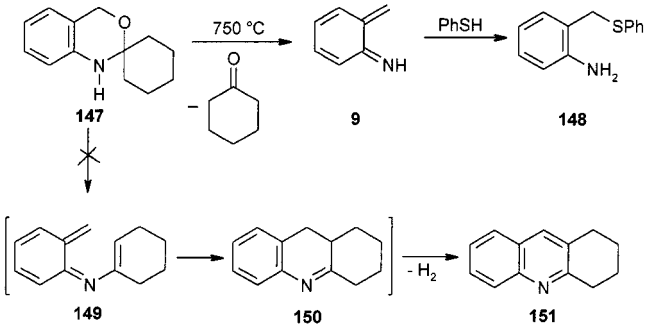
[4+2] Cycloreversion Reactions as Sources of Aza-*ortho*-xylylenes

There are a few reports of [4+2] cycloreversion processes producing aza-*ortho*-xylylenes. The FVT of 1,2,3,4-tetrahydroquinoline (**18**) with loss of ethylene[23] is shown in Scheme 3. *N*-Acyl-2,1-benzoxazines decompose thermally with a loss of formaldehyde.[22] For example, *N*-pivaloyl-3,4-dihydro-1*H*-2,1-benzoxazine (**144**), prepared from **143**, gives *N*-pivaloylaza-*ortho*-xylylene (**145**), which electrocyclizes to 2-(*tert*-butyl)-3,1-benzoxazine (**146**) in nearly quantitative yields (Scheme 36).[22] Attempts to trap the xylylene **145** with dienophiles, diethyl maleate, or maleic anhydride failed.[22]



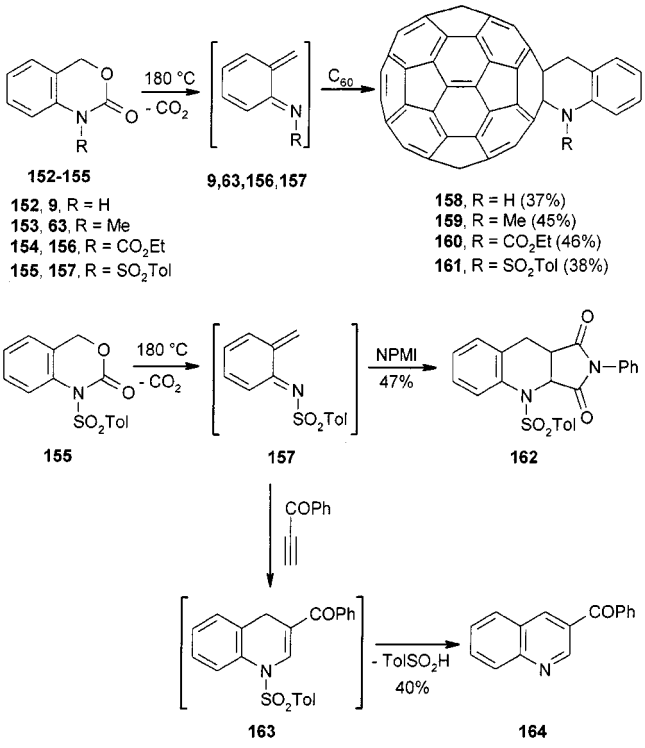
Scheme 36

3,1-Benzoxazines, readily available from 2-aminobenzyl alcohol and carbonyl compounds, undergo retro-Diels–Alder reactions under FVT conditions, as was shown by trapping of the intermediate **9** formed from 2,2-pentamethylene-3,1-benzoxazine (**147**) with thiophenol, to give the aniline **148** (Scheme 37).[83] This result contradicted an earlier report[84] that claimed formation of *N*-alkenylaza-*ortho*-xylylene **149** from **147** and its further electrocyclization through **150** to give the 2,3-disubstituted quinoline **151**.



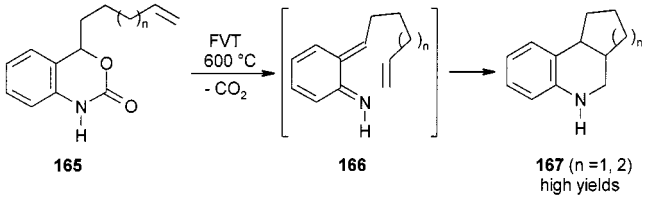
Scheme 37

The 3,1-Benzoxazin-2-ones **152**–**155**, obtained from 2-aminobenzyl alcohols and phosgene or ethyl chloroformate, are suitable precursors for the generation of aza-*ortho*-xylylenes **9**, **63**, **156**, and **157** by [4+2] cycloreversion with loss of carbon dioxide.[70,85–88] These xylylenes add to buckminsterfullerene C_{60} to give the fullerotetrahydroquinolines **158**–**161** in moderate yields (Scheme 38).[88] Addition of the *N*-sulfonyl xylylene **157** to NPMI gives *N*-sulfonyl-1,2,3,4-tetrahydroquinoline (**162**).[87] With alkynes, such as ethynyl phenyl ketone, the initial cycloadduct **163** eliminates toluenesulfinic acid, resulting in 3-benzoylquinoline (**164**).[87]



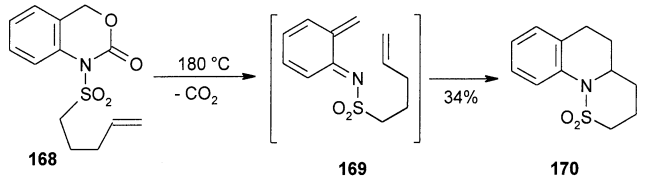
Scheme 38

Intramolecular [4+2] cycloadditions of azaxylylenes generated under FVT conditions from *N*-alkylbenzoxazin-2-ones bearing a terminal double bond in an alkyl substituent proceed in low yields.[70,85] Such xylylenes mostly undergo [1,5]-sigmatropic hydrogen shifts, giving imines. The aza-*ortho*-xylylenes **166**, generated under FVT conditions from the 4-alkenyl-3,1-benzoxazin-2-ones **165**, undergo intramolecular Diels–Alder reactions to give the condensed heterocycles **167** in good yields (Scheme 39).[86] This result sharply contrasts with those obtained from reactions of the similarly substituted aza-*ortho*-xylylene **99**, generated at lower temperatures from benzosultam **98**; this exclusively undergoes a [1,5]-sigmatropic hydrogen shift to afford the *ortho*-vinylaniline **101** (Scheme 25).[57,71] At the high temperatures applied for the FVT of **165** the C-substituent in xylylenes **166** probably adopts an *E* configuration favorable for [4+2] cycloaddition.



Scheme 39

An intramolecular Diels–Alder reaction of aza-*ortho*-xylylene **169**, generated from **168** and incapable of undergoing a [1,5]-hydrogen shift, gives the sultam **170** in moderate yield (Scheme 40).[87]



Scheme 40

1,4-Elimination Reactions Resulting in Aza-*ortho*-xylylenes

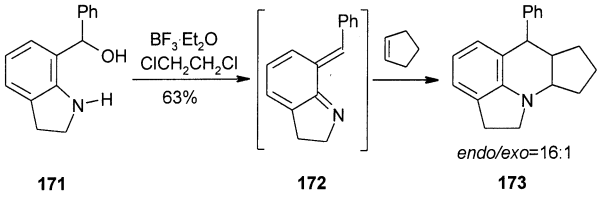
Aza-*ortho*-xylylenes may conveniently be obtained from various 2-aminobenzyl derivatives such as alcohols, amines, chlorides, and fluorides by 1,4-elimination of water, ammonia or amines, hydrogen chloride, and hydrogen fluoride, respectively. Depending on the precursor employed, such transformations can be executed under acidic, basic, or neutral conditions.

1,4-Elimination of Water from 2-Aminobenzyl Alcohols

One of the general methods in this category involves the 1,4-elimination of water from 2-aminobenzyl alcohols. These precursors are available by: a) classical reduction of *N*-alkyl- and *N*-arylanthranilic acids and their esters with lithium aluminum hydride, b) addition of aldehydes to *ortho*-lithiated anilines,[86] or c) *ortho*-hydroxyalkylation of anilines in the presence of dichlorophenylborane.[89–91]

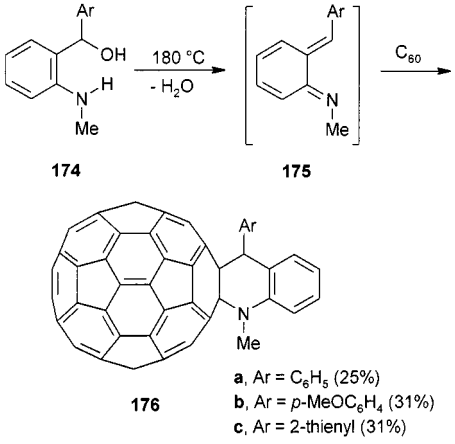
The 1,4-elimination of water from *ortho*-aminobenzyl alcohol **14** (Scheme 3) requires relatively harsh conditions. It proceeds under flash vacuum thermolysis (FVT) conditions and begins at about 400 °C. The simple aza-*ortho*-xylylene generated under FVT conditions has not found applications in organic synthesis, but has been the subject of spectral studies.[18–20][92] No intermolecular [4+2] cycloadditions of aza-*ortho*-xylylenes generated from *ortho*-aminobenzyl alcohols under FVT conditions are known, but numerous examples of intramolecular reactions under these conditions have been reported.[70,84–86] At lower temperatures (150–200 °C), the 1,4-elimination of water can be carried out with 2-(alkylamino)benzyl alcohols,[89,91,93] 2-(arylamino)benzyl alcohols,[89,93] and 2-(alkylamino)benzhydrols.[94] In the presence of Lewis acids[89,90,95] or under Mitsunobu reaction conditions[96] such 1,4-eliminations proceed smoothly at room temperature.

Lau et al. have developed methodologies for the generation of aza-*ortho*-xylylenes by the thermal[89,91] or Lewis acid-catalyzed[90,95] 1,4-elimination of water from *ortho*-aminobenzyl alcohols (Scheme 41, see also Schemes 42, 45, and 47). The *ortho*-quinone methide imines formed in these reactions undergo intermolecular and intramolecular cycloadditions to afford condensed heterocycles, with high levels of stereocontrol usually being observed. The indoline derivative **171**, for example, is transformed via **172** into the condensed heterocycle **173** upon treatment with cyclopentene.[95]



Scheme 41

Lau's procedure[91] has been recently applied with **175**, generated from **174**, for the first synthesis of the tetrahydroquinolinofullerenes[60] **176** (Scheme 42).[94]

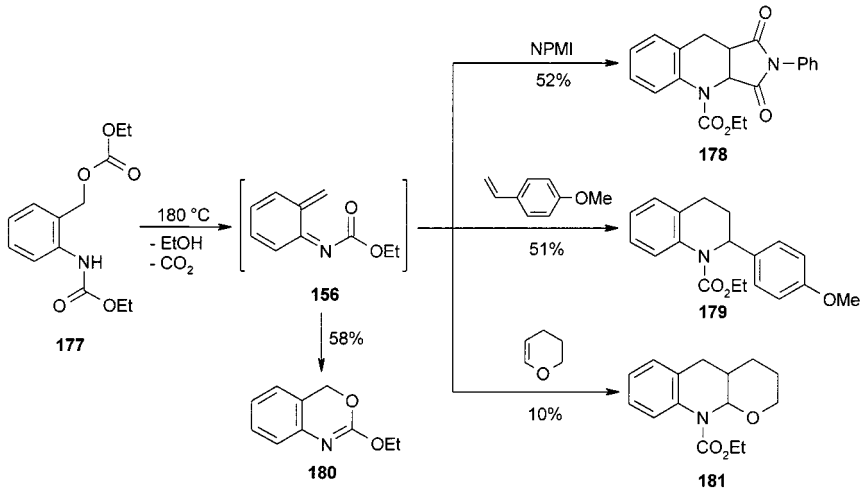


Scheme 42

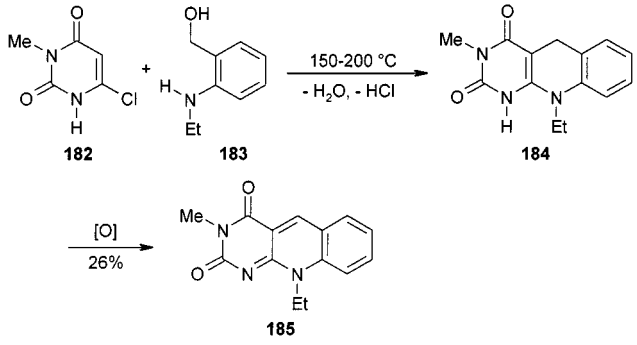
2-Ethoxycarbonylaminobenzyl ethyl carbonate (**177**) eliminates ethanol and CO_2 in boiling dichlorobenzene, and the *N*-(ethoxycarbonyl)aza-*ortho*-xylylene (**156**) formed undergoes a 6π electrocyclization to give 2-ethoxy-4*H*-3,1-benzoxazine (**180**) in 58% yield (Scheme 43).[97] With the dienophiles *N*-phenylmaleimide, styrenes, and 3,4-dihydro-2*H*-pyran, the intermediate **156** enters into [4+2] cycloadditions, affording the cycloaddition products **178**, **179**, and **181**, respectively, albeit in low yield in the last case.[97]

The participation of aza-*ortho*-xylylene in [4+2] cycloadditions has been implicated in the synthesis of the 5-deazaflavin derivative **185** from chlorouracil **182** and 2-(ethylamino)benzyl alcohol (**183**) via the dihydro derivative **184** (Scheme 44).[93]

An intramolecular Diels–Alder reaction of aza-*ortho*-xylylene **187**, generated from the amino alcohol **186**, in the presence of phenylboronic acid produces the tetracyclic azacannabinoid derivative **188**, with a *trans* junction in the formed ring (Scheme 45).[89] The diene **187** is also formed in this reaction, as a result of a [1,5]-sigmatropic hydrogen

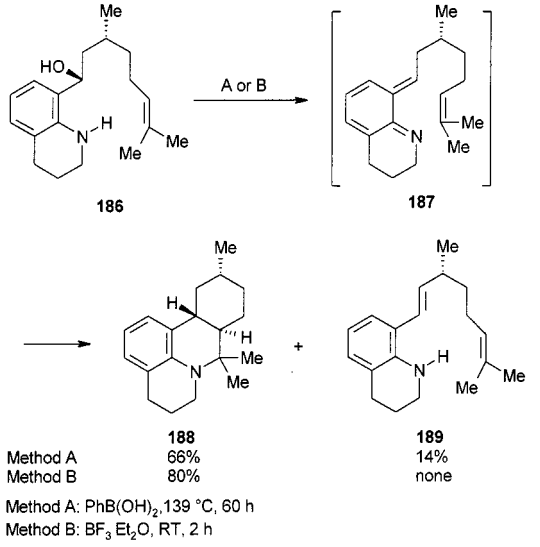


Scheme 43



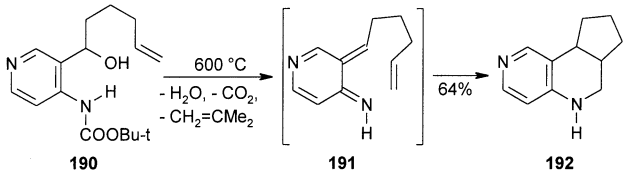
Scheme 44

shift in the xylylene **187** or the direct 1,2-elimination of water from the substrate **186**. With boron trifluoride–diethyl ether at room temperature, the cycloaddition product **188** was formed in 80% yield, and no elimination of water to give diene **189** was observed.[95]



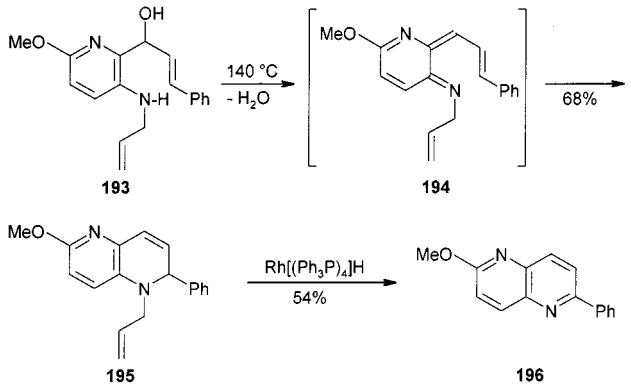
Scheme 45

The intramolecular Diels–Alder reactions of aza-*ortho*-xylylenes generated from *ortho*-aminobenzyl alcohol derivatives proceed smoothly. For example, the heteroanalog of aza-*ortho*-xylylene **191**, generated from the pyridine derivative **190**, cyclized to [1,6]naphthyridine **192** (Scheme 46).[86] The structurally similar aza-*ortho*-xylylene **99**, generated from benzosultam **98**, underwent only a [1,5]-hydrogen shift to produce the vinyl aniline **101** (Scheme 25).



Scheme 46

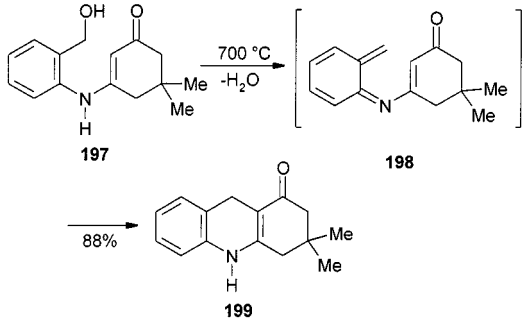
1-(2-Aminophenyl)allyl alcohols and their heteroanalogs **193** eliminate water in boiling xylene, and the intermediate xylylenes **194** thus created undergo electrocyclization reactions to give 1,2-dihydroquinolines (Scheme 47).[89,91] The obtained *N*-allyl-1,2-dihydroquinolines can easily be aromatized by deallylation. Dihydro[1,5]naphthyridine (**195**), for example, upon heating for extended periods of time (180 °C, 20 h)[90] or in the presence of tetrakis(triphen-



Scheme 47

ylphosphane)rhodium hydride in trifluoroacetic acid (85 °C, 4−20 h),[89,90] eliminates propylene to give the fully aromatized [1,5]naphthyridine **196**.

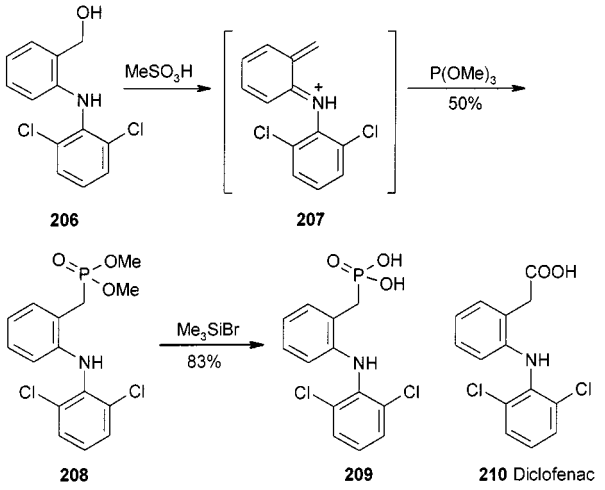
There are numerous examples of electrocyclization reactions of aza-*ortho*-xylylenes generated under FVT conditions from aminobenzyl alcohols.[70,85,86] 9,10-Dihydroacridine is formed during the electrocyclization of aza-*ortho*-xylylenes generated by FVT from 2-(phenylamino)benzyl alcohol and isomeric 2-aminobenzhydrol.[70] The electrocyclization of aza-*ortho*-xylylene **198**, derived from the amino ketone **197**, gives the acridine derivative **199** in high yield (Scheme 48).[70]



Scheme 48

Several examples of reactions between nucleophiles and aza-*ortho*-xylylenes generated from *ortho*-aminobenzyl alcohols under FVT conditions are known.[23,92] The intermediate **204** has been postulated in the synthesis of benzylamines such as **205** from 2-amino-6-methyl-3-nitrobenzyl alcohol (**200**) and secondary amines under Mitsunobu reaction conditions (triphenylphosphane/diethyl azadicarboxylate) (Scheme 49).[96] Under these conditions, no reactions between secondary amines and benzyl alcohol, 2-aminobenzyl alcohol, 3-nitrobenzyl alcohol, or 6-methyl-2-(dimethylamino)-3-nitrobenzyl alcohols took place, which supports the formation of intermediate **204** from **200**.[96] Similarly, 3,1-benzoxazin-2-one (**202**) in boiling piperidine undergoes ring-opening to form the carbamate **203**; this then eliminates piperidine and CO_2 to form the aza-*ortho*-xylylene **204**, which adds piperidine producing the amine **205** in good yield.[98]

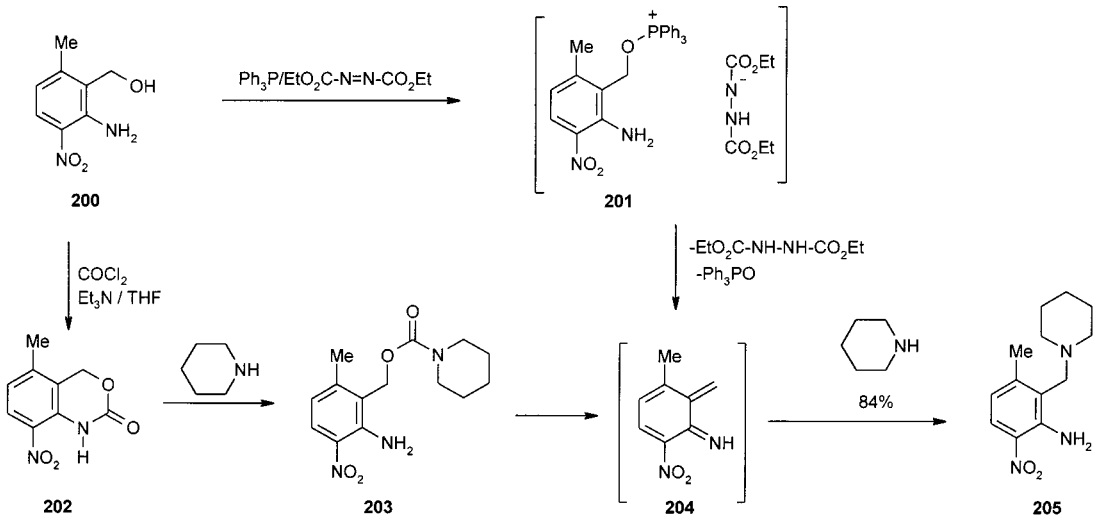
The presence of intermediate **207** has been postulated in the synthesis of the phosphonic acid analogue **209** of Diclofenac (**210**), obtained by an Arbuzov reaction between the aminobenzyl alcohol **206** and trimethyl phosphite (Scheme 50).[99] The reaction proceeds under mild conditions at room temperature in the presence of methanesulfonic acid. Hydrolysis of the phosphonate **208** to the acid **209** was achieved with trimethylsilyl bromide. No anti-inflammatory biological activity was detected in the obtained benzylphosphonic acid **209**.



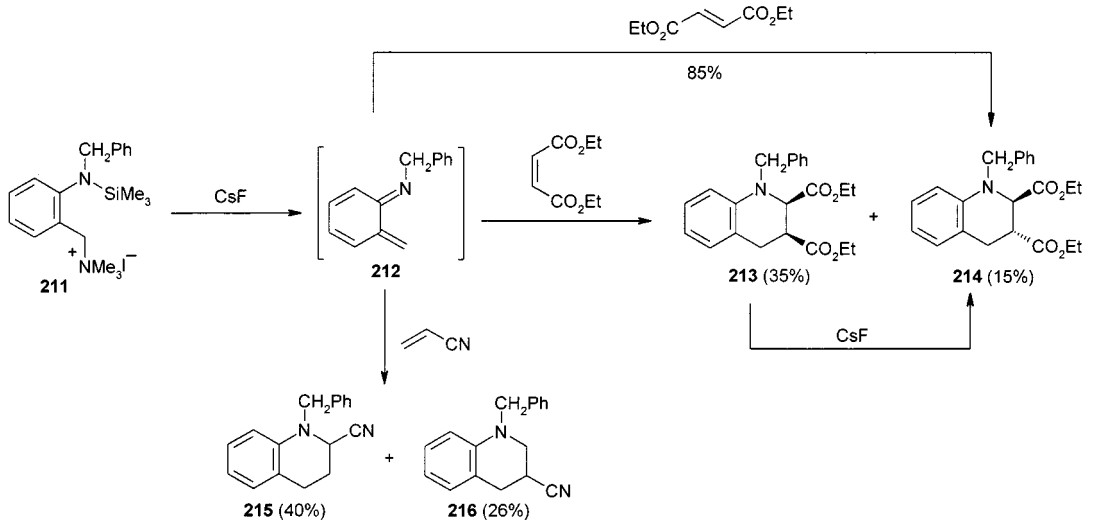
Scheme 50

1,4-Elimination of Ammonia and Alkylamines from 2-Aminobenzylamines

2-Aminobenzylamine derivatives behave similarly to the analogous benzyl alcohols, and eliminate amines under



Scheme 49



Scheme 51

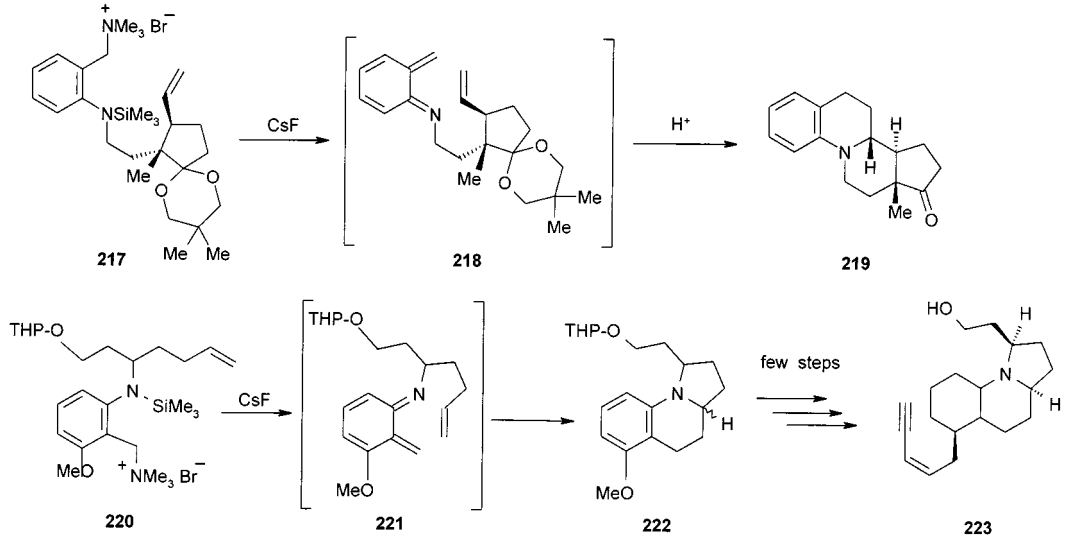
various conditions to form aza-*ortho*-xylylenes. Ripoll et al. described the formation of aza-*ortho*-xylylene (**9**) from 2-aminobenzylamine (**15**) under FVT conditions (Scheme 3).[23] Saegusa and Ito[100−104] developed a mild method for the generation of aza-*ortho*-xylylenes by a fluoride-ion-induced 1,4-elimination of trimethylamine from the *ortho*-[*N*-alkyl-*N*-(trimethylsilyl)amino]benzyltrimethylammonium salts **211**. This reaction proceeds satisfactorily in acetonitrile in the presence of cesium fluoride at 60 °C.[104] The *N*-alkyl intermediate **212** adds to dienophiles such as acrylonitrile and dimethyl maleate and fumarate, forming the expected cycloadducts **213**−**216** in good yields (Scheme 51).[104] The maleate *cis* adduct **213** slowly transforms in the presence of fluoride ions into the *trans* isomer **214**.

An intramolecular reaction employing this approach was used as the key step in the synthesis of the azasteroid 9-azaestra-1,3,5(10)-trien-17-one (**219**) from **217** via **218** (Scheme 52).[101] Analogously, the key intermediate **222** in the formal synthesis of gephyrotoxin **223**, a condensed pyrrolo[1,2-*a*]quinoline alkaloid, was obtained from **220** via **221** (Scheme 52).[103]

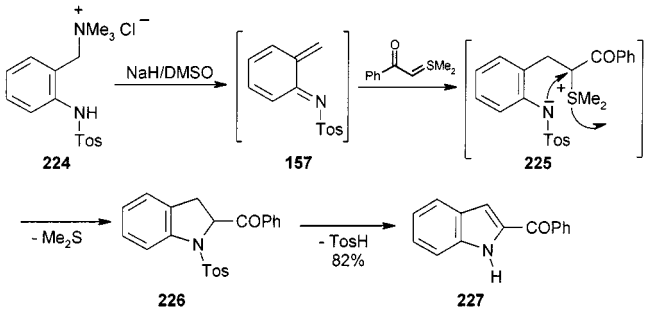
A similar 1,4-elimination mechanism, giving xylylene **157**, is apparently operative in the synthesis of the 2-substituted indoles **227** from the 2-(benzenesulfonylamino)benzylammonium salts **224** and sulfonium ylides,[105] although that possibility was overlooked by the authors. Addition of the ylide to xylylene **157**, followed by a cyclization of **225**, produces the indoline **226**, which aromatizes under basic conditions to indole **227** with elimination of toluenesulfinic acid (Scheme 53).

1,4-Elimination of HCl from 2-(Chloromethyl)aniline Derivatives

The simplest method for generating aza-*ortho*-xylylenes has recently been developed by Steinhagen and Co-

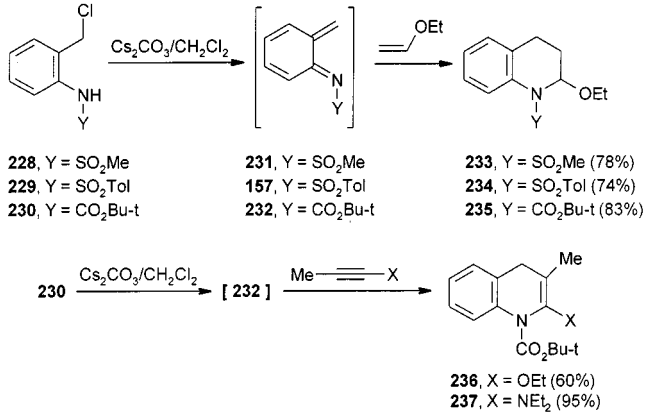


Scheme 52



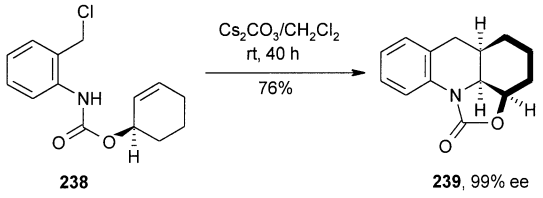
Scheme 53

rey.[106,107] Readily available *ortho*-(chloromethyl)aniline derivatives, amides, and sulfonamides **228**−**230** were subjected to a base-induced elimination of HCl with cesium carbonate. The generated *N*-acyl- and *N*-sulfonyl-aza-*ortho*-xylylenes **157**, **231**, and **232** added to π-electron-rich olefins such as vinyl ethers, 2,3-dihydrofuran, and ketene acetals, resulting in the formation of the 2-substituted tetrahydroquinolines **233**−**235** in good yields (Scheme 54).



Scheme 54

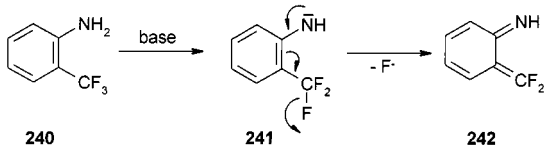
It is worth mentioning that this approach permits the addition of aza-*ortho*-xylylenes to π-electron-rich acetylenes such as *N*,*N*-diethyl-1-propynylamine or 1-ethoxyprop-1-yne, furnishing the 1,4-dihydroquinoline derivatives **236** and **237** (Scheme 54).[106] Intramolecular reactions proceed smoothly, as has been demonstrated in the synthesis of the chiral tetracyclic derivative **239** from the readily available precursor **238** (Scheme 55).[106,107]



Scheme 55

1,4-Elimination of HF from 2-(Perfluoroalkyl)anilines

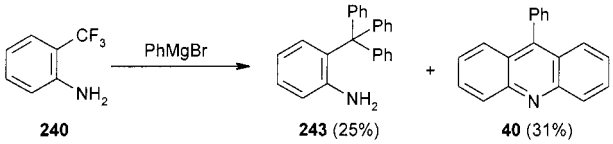
The trifluoromethyl groups in *ortho*- and *para*-(trifluoromethyl)anilines exhibit an enhanced activity towards nucleophilic attack.[108] Such derivatives are easily hydrolyzed to the corresponding 2- and 4-aminobenzoic acids in basic media, unlike the *meta* isomers, which are resistant to hydrolysis. It is believed that ionization of the amino group in **240** is followed by elimination of fluoride anion from **241**, resulting in the formation of the difluoro intermediate **242** (Scheme 56).



Scheme 56

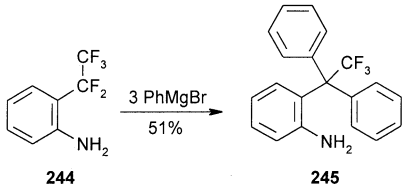
Strekowski et al. have developed a methodology for the generation of difluoro aza-*ortho*-xylylene **242** by a base-induced 1,4-elimination of hydrogen fluoride from 2-(trifluoromethyl)aniline (**240**). These reactive intermediates enter into numerous reactions, mostly additions of nucleophiles[80,109−116] and electrocyclizations.[117−122] The characteristic feature of these processes is the possibility of the recurrence of the elimination and addition steps, resulting in the complete replacement of the fluorine atoms in the final product. Despite all the efforts undertaken,[108] there are no reports on the participation of these intermediates in [4+2] cycloadditions. Only new developments in this area that have appeared since the publication of the last review[108] are described here.

All the fluorine atoms in 2-(trifluoromethyl)aniline (**240**) can be replaced by alkyl or aryl substituents by treatment with an excess of Grignard reagent.[111] On treatment with an excess of phenylmagnesium bromide, a series of elimination−addition reactions produces tetraphenylmethane (**243**) (Scheme 57). As a second product, 9-phenylacridine (**40**) is formed by electrocyclization of an intermediate diphenyl adduct.



Scheme 57

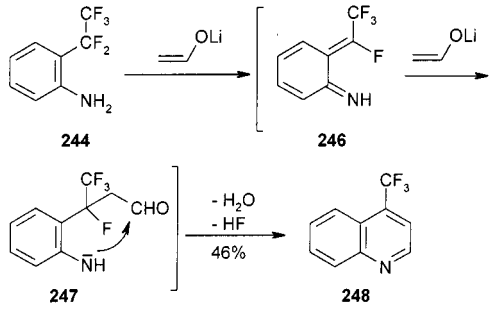
1,1,1-Triaryltrifluoroethane **245** was formed in good yields on treatment of 2-(perfluoroethyl)aniline (**244**) with phenylmagnesium bromide (Scheme 58).[109] 2-(Perfluoropropyl)aniline and 2-(perfluorobutyl)aniline react analogously, giving the corresponding triaryl perfluoroalkanes in 72 and 83% yields, respectively.[109]



Scheme 58

There are numerous examples of reactions between difluoro xylylenes and nucleophiles resulting in the formation of condensed heterocycles.[80,111,113–115,117] The treatment of ketone enolates with 2-(trifluoromethyl)anilines and heteroanalogs results in the formation of pyridine ring systems.[113–116]

2-(Perfluoroalkyl)anilines react with aliphatic aldehydes to give 4-(perfluoroalkyl)quinolines bearing a perfluoroalkyl chain one carbon atom shorter.[115,116] 2-(Perfluoroethyl)aniline (**244**), for example, treated with a fivefold excess of the lithium enolate of acetaldehyde, gives 4-(trifluoromethyl)quinoline (**254**) in 46% yield, via **246** and **247** (Scheme 59).[115]



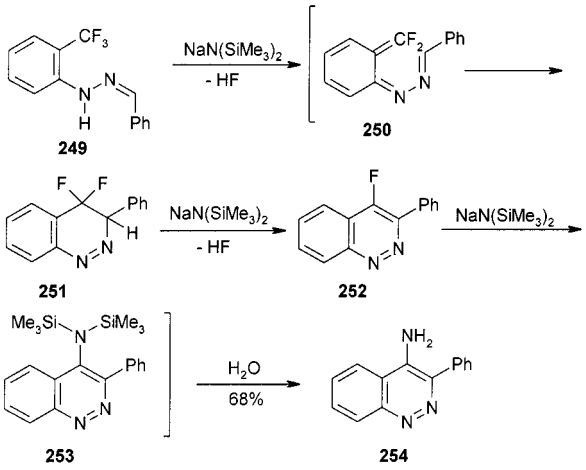
Scheme 59

The 1,4-elimination of HF from 2-(trifluoromethyl)phenylhydrazones of aromatic aldehydes, followed by electrocyclization of the intermediate trienes, gives 4-amino-3-arylocinnolines.[123] The benzaldehyde hydrazone **249**, for example, reacts with an excess of sodium hexamethyldisilylamide to give 4-amino-3-phenylcinnoline (**254**) in good yield, via **250**–**253** and after desilylation of **253** (Scheme 60).

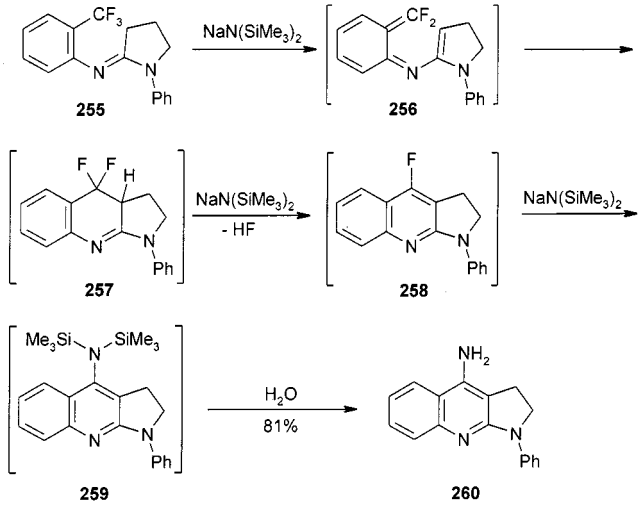
Similarly, the intermediate **256**, generated from the cyclic amidine **255**, transforms via **257**–**259** into the condensed quinoline **260** in good yield, as shown in Scheme 61.[121] Other five- and six-membered amidines react analogously.[121]

1,5-Elimination of HCl and R_2NH

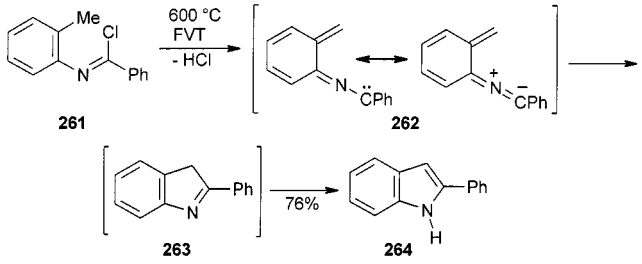
The 1,5-elimination of HCl from the imido chloride **261** under FVT conditions at 600 °C gives the cumulated xylylene **262**, which electrocyclizes via **263** to give 2-phenylindole (**264**) (Scheme 62).[124] In an analogous fashion, the imido chloride obtained from benzoyl chloride and 4-amino-2-methylpyridine cyclizes to give 2-phenyl-5-azaindole in 62% yield.[125]



Scheme 60

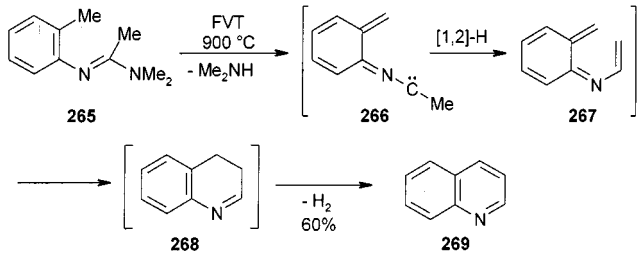


Scheme 61



Scheme 62

The 1,5-elimination of dimethylamine from the much more stable amidine **265** proceeds at higher temperatures (FVT, 900 °C) and gives the quinoline (**269**).[125] Under these conditions, the formed intermediate **266** undergoes a [1,2]-hydrogen shift to afford the *N*-vinyl xylylene **267**. Subsequent electrocyclization of **267** and dehydration of **268** produces quinoline (**269**) (Scheme 63).

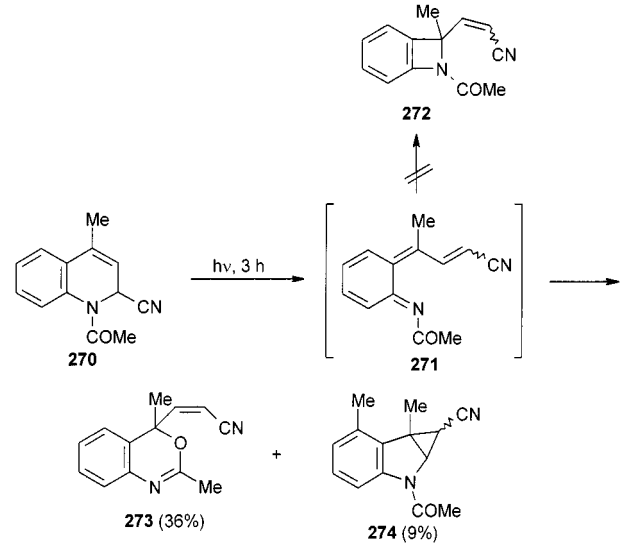


Scheme 63

Aza-*ortho*-xylylenes by Ring Opening of Heterocyclic Systems

There are a few known examples of the formation of aza-*ortho*-xylylenes through ring-opening reactions of heterocyclic systems other than benzoazetines. The Reissert compound **270**, upon irradiation in ethanol or diethyl ether, rearranges to *N*-acetylaza-*ortho*-xylylene **271**, which then electrocyclizes to 3,1-benzoxazine **273** (Scheme 64).[126] As a side-product, the tricyclic indole derivative **274** is formed. In the earlier report, the structure of phenylbenzoazetine **272** was erroneously assigned to the major product.[127]

The nitrene **276**, generated from thermally unstable 1-methyl-2-azidoindole (**275**), undergoes ring-opening to afford the cyanoxylylene **277** (Scheme 65), which can then be trapped by a range of dienophiles including dimethyl acrylate, acrylonitrile, dimethyl fumarate, dimethyl maleate, and (*E*)- and (*Z*)-but-2-ene, giving the corresponding tetrahydroquinolines.[128,129] No regioselectivity control or stereoselectivity control was observed in the reaction between **277** and acrylonitrile, which gave a mixture of all four *cis* and *trans* isomeric 2,4- and 3,4-dicyano-1-methyl-1,2,3,4-tetrahydroquinolines **278**−**281** in 82% total yield. The reaction between **277** and dimethyl fumarate gave the cyano diester **283** in 68% yield. The aziridine **282** was formed as a side product by a [1+2] cycloaddition between the unrearranged nitrene **276** and the fumarate.[128]

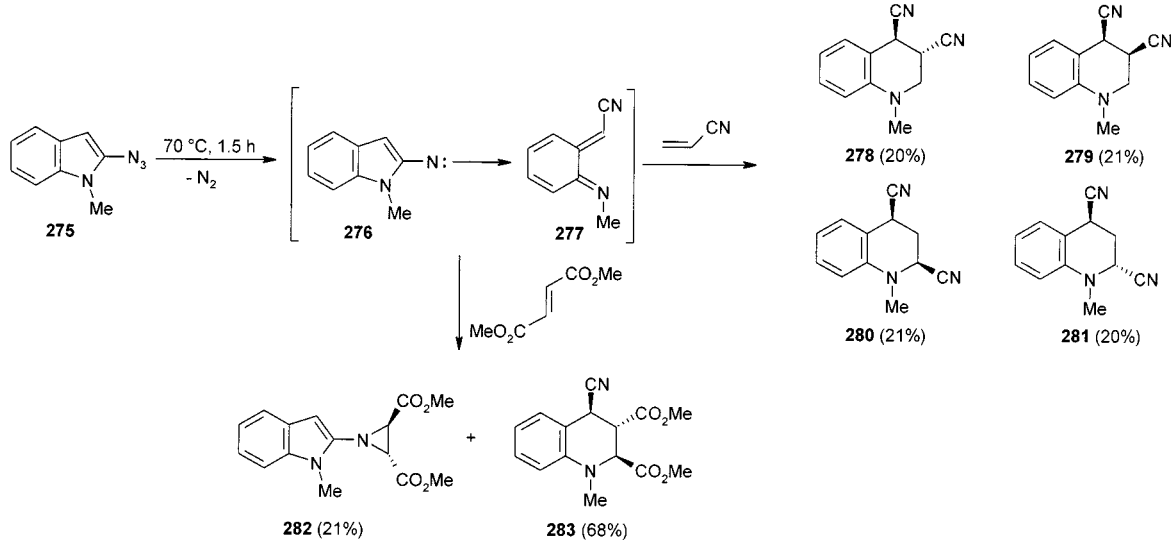


Scheme 64

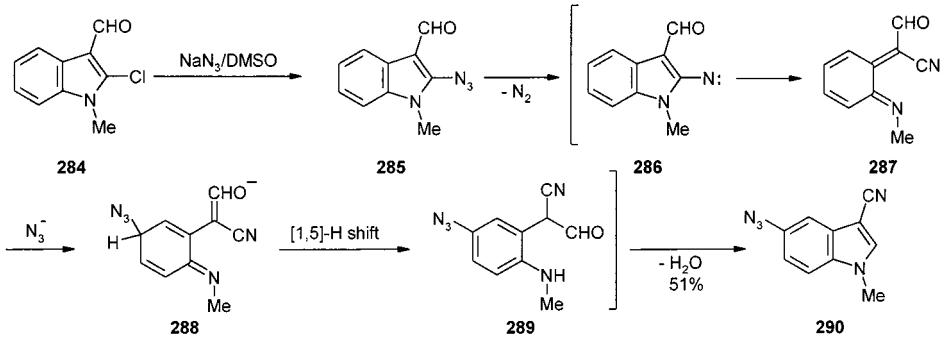
An analogous transformation of nitrene **286**, generated from the azide **285**, is a key step in the nucleophilic *tele*-substitution[130] of 2-chloro-1-methylindole-3-carbaldehyde (**284**) with azide anion, resulting in the formation of 5-azido-1-methylindole-3-carbonitrile (**290**) via **287**−**289** (Scheme 66).[131,132]

Conclusions

Aza-*ortho*-xylylenes have become intermediates of potential application in organic synthesis. The arsenal of methods used for the generation of these reactive intermediates is broadening. They can now be generated from easily available precursors under various conditions: by the practically neutral thermal extrusions of SO_2 from benzosultams or of CO_2 from 3,1-benzoxazin-2-ones, by a Lewis acid-mediated elimination of water from 2-aminobenzyl alcohols, or by a



Scheme 65



Scheme 66

base-induced elimination from 2-aminobenzyl chlorides and 2-aminobenzylammonium salts. This variety of procedures permits the construction of complex molecules, in particular condensed heterocycles, that are difficult to obtain by other known methods.

[1] J. Barluenga, M. Tomas, *Adv. Heterocycl. Chem.* **1993**, *57*, 1−80.
[2] K. Wojciechowski, *Pol. J. Chem.* **1997**, *71*, 1375−1400.
[3] E. Ciganek, *Org. React.* **1984**, *32*, 1−374.
[4] J. L. Charlton, M. M. Alauddin, *Tetrahedron* **1987**, *42*, 2873−2889.
[5] N. Martin, C. Seoane, M. Hanack, *Org. Prep. Proceed. Int.* **1991**, *23*, 237−272.
[6] T. S. Chou, *Rev. Heteroatom Chem.* **1993**, *8*, 65−104.
[7] P. Y. Michellys, H. Pellissier, M. Santelli, *Org. Prep. Proceed. Int.* **1996**, *28*, 545−606.
[8] J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199−3246.
[9] G. Mehta, S. Kotha, *Tetrahedron* **2001**, *57*, 625−659.
[10] R. A. Aitken, I. Gosney, J. Cadogan, *Prog. Heterocycl. Chem.* **1993**, *5*, 1−33.
[11] K. Ando, H. Takayama, *Heterocycles* **1994**, *37*, 1417−1439.
[12] S. J. Collier, R. C. Storr, *Prog. Heterocycl. Chem.* **1999**, *10*, 25−48.
[13] G. Smolinsky, *J. Org. Chem.* **1961**, *26*, 4108−4110.
[14] E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, *88*, 1580−1581.
[15] H. Kolshorn, H. Meier, *Z. Naturforsch., Teil A* **1977**, *32*, 780−782.
[16] M. Manoharan, F. D. Proft, P. Geerlings, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1767−1773.
[17] M. Manoharan, F. D. Proft, P. Geerlings, *J. Org. Chem.* **2000**, *65*, 7971−7976.
[18] J. Morawietz, W. Sander, M. Traubel, *J. Org. Chem.* **1995**, *60*, 6368−6378.
[19] W. Sander, J. Morawietz, *Tetrahedron Lett.* **1993**, *34*, 1913−1914.
[20] G. Pfister-Guillouzo, F. Gracian, A. Senio, M. Letulle, J.-L. Ripoll, *Tetrahedron Lett.* **1992**, *33*, 5753−5756.
[21] A. Chrostowska, F. Gracian, J.-M. Sotiropoulos, G. Pfister-Guillouzo, K. Wojciechowski, *Eur. J. Org. Chem.* **2000**, 313−318.
[22] S. A. Glover, K. M. Jones, I. R. McNee, C. A. Rowbottom, *J. Chem. Soc., Perkin Trans. 2* **1996**, 1367−1376.
[23] M. Letulle, P. Guenot, J.-L. Ripoll, *Tetrahedron Lett.* **1991**, *32*, 2013−2016.
[24] S. Murata, T. Sugawara, H. Iwamura, *J. Am. Chem. Soc.* **1985**, *107*, 6317−6329.
[25] V. H. M. Elferink, H. J. T. Bos, *J. Chem. Soc., Chem. Commun.* **1985**, 882−883.
[26] D. N. Nicolaides, K. E. Litinas, G. K. Papageorgiou, J. Stephanidou-Stephanatou, *J. Heterocycl. Chem.* **1991**, *28*, 139−143.
[27] D. N. Nicolaides, R. W. Awad, G. K. Papageorgiou, J. Stephanidou-Stephanatou, *J. Org. Chem.* **1994**, *59*, 1083−1086.
[28] H. Meier, *J. Prakt. Chem.* **1996**, *338*, 383−385.
[29] H. Tomioka, T. Matsushita, *Chem. Lett.* **1997**, 399−400.
[30] S. Kosiński, K. Wojciechowski, *Pol. J. Chem.* **1998**, *72*, 2546−2550.
[31] K. Krohn, D. Carboo, U. Puttfarcker, *Justus Liebigs Ann. Chem.* **1978**, 608−616.
[32] S. V. Kessar, B. Gopal, M. Singh, *Tetrahedron Lett.* **1969**, 71−72.
[33] P. Beak, G. W. Selling, *J. Org. Chem.* **1989**, *54*, 5574−5580.
[34] M. Lancaster, D. J. H. Smith, *J. Chem. Soc., Chem. Commun.* **1980**, 471−472.
[35] J. Nakayama, H. Midorikawa, M. Yoshida, *J. Chem. Soc. Jpn.* **1975**, *48*, 1063−1064.
[36] C. W. G. Fishwick, R. C. Gupta, R. C. Storr, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2827−2829.
[37] J. V. Davies, M. L. Durrant, A. Naylor, J. R. Malpass, *Tetrahedron* **1995**, *51*, 8655−8664.
[38] M. L. Durrant, J. R. Malpass, *Tetrahedron* **1995**, *51*, 7063−7076.
[39] M. Mąkosza, A. Kwast, *J. Phys. Org. Chem.* **1998**, *11*, 341−349.
[40] M. Mąkosza, K. Wojciechowski, *Liebigs Ann./Recueil* **1997**, 1805−1816.
[41] M. Mąkosza, *Synthesis* **1991**, 103−111.
[42] M. Mąkosza, K. Wojciechowski, *Tetrahedron Lett.* **1984**, *25*, 4791−4792.
[43] K. Wojciechowski, M. Mąkosza, *Synthesis* **1992**, 571−576.
[44] M. Mąkosza, K. Staliński, *Tetrahedron* **1998**, *54*, 8797−8810.
[45] M. Mąkosza, K. Staliński, *Chem. Eur. J.* **1997**, *3*, 2025−2031.
[46] M. Mąkosza, K. Staliński, *Pol. J. Chem.* **1999**, *73*, 151−161.
[47] Z. Wróbel, *Tetrahedron Lett.* **2000**, *41*, 7365−7366.
[48] K. Wojciechowski, *Pol. J. Chem.* **1992**, *66*, 1121−1124.
[49] K. Wojciechowski, *Synth. Commun.* **1997**, *26*, 135−144.
[50] K. Wojciechowski, S. Kosiński, *Tetrahedron Lett.* **1997**, *38*, 4667−4670.
[51] S. Kosiński, K. Wojciechowski, *Eur. J. Org. Chem.* **2000**, 1263−1270.
[52] J. F. Bunnett, T. Kato, R. R. Flynn, J. A. Skorcz, *J. Org. Chem.* **1963**, *28*, 1−6.
[53] J. A. Skorcz, J. T. Suh, R. L. Germershausen, *J. Heterocycl. Chem.* **1974**, *11*, 73−75.
[54] R. A. Abramovitch, R. R. Harder, W. D. Holcomb, *Heterocycles* **1987**, *26*, 2327−2330.
[55] D. Chiarino, A. M. Contri, *J. Heterocycl. Chem.* **1986**, *23*, 1645−1649.
[56] J. A. Skorcz, J. T. Suh, *J. Heterocycl. Chem.* **1972**, *9*, 219−222.
[57] K. Wojciechowski, *Tetrahedron* **1993**, *49*, 10017−10026.
[58] Z. Wróbel, K. Wojciechowski, *Pol. J. Chem.* **1992**, *66*, 1125−1129.
[59] K. Wojciechowski, *Molecules* **1996**, *1*, 51−56.
[60] K. C. Nicolaou, W. E. Barnette, P. Ma, *J. Org. Chem.* **1980**, *45*, 1463−1470.

[61] A. C. Tome, J. A. S. Cavaleiro, R. C. Storr, *Tetrahedron Lett.* **1993**, *34*, 6639−6642.
[62] L. A. White, P. M. O′Neill, B. K. Park, R. C. Storr, *Tetrahedron Lett.* **1995**, *36*, 5983−5986.
[63] A. C. Tome, J. A. S. Cavaleiro, R. C. Storr, *Tetrahedron* **1996**, *52*, 1735−1746.
[64] A. C. Tome, J. A. S. Cavaleiro, R. C. Storr, *Tetrahedron* **1996**, *52*, 1723−1734.
[65] K. Wojciechowski, *Synlett* **1991**, 571−572.
[66] W. Danikiewicz, K. Wojciechowski, M. Olejnik, *Tetrahedron Lett.* **1995**, *36*, 1099−1102.
[67] K. Wojciechowski, *Tetrahedron* **1993**, *49*, 7277−7286.
[68] S. Kosiński, Ph. D. Thesis, Institute of Organic Chemistry, Warszawa **2001**.
[69] U. Kuckländer, U. Lessel, *J. Prakt. Chem.* **2000**, *342*, 17−26.
[70] R. D. Bowen, D. E. Davies, C. W. G. Fishwick, T. O. Glasbey, S. J. Noyce, R. C. Storr, *Tetrahedron Lett.* **1982**, *23*, 4501−4504.
[71] I. R. Trehan, V. K. Jain, V. Seth, V. Singh, *Indian J. Chem.* **1993**, *32B*, 328−333.
[72] K. Wojciechowski, *Synth. Commun.* **1993**, *23*, 2415−2422.
[73] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136.
[74] W. Danikiewicz, K. Wojciechowski, S. Kosiński, M. Olejnik, *J. Mass Spectrom.* **2001**, *36*, 430−440.
[75] K. Wojciechowski, S. Kosiński, *Tetrahedron* **2001**, *57*, 5009−5014.
[76] W. Danikiewicz, K. Wojciechowski, R. H. Fokkens, N. M. M. Nibbering, *Org. Mass Spectrom.* **1993**, *28*, 853−859.
[77] W. Danikiewicz, K. Wojciechowski, R. H. Fokkens, N. M. M. Nibbering, *Rapid Commun. Mass Spectrom.* **1993**, *7*, 763−768.
[78] W. Danikiewicz, K. Wojciechowski, *Rapid. Commun. Mass Spectrom.* **1996**, *10*, 36−39.
[79] W. Danikiewicz, K. Wojciechowski, *Eur. Mass Spectrom.* **1997**, *3*, 55−65.
[80] A. S. Kiselyov, M. Hojjat, K. V. Aken, L. Strekowski, *Heterocycles* **1994**, *37*, 775−782.
[81] M. Fischer, F. Wagner, *Chem. Ber.* **1969**, *102*, 3486−3494.
[82] M. Fischer, *Chem. Ber.* **1969**, *102*, 3495−3499.
[83] S. J. Barker, G. B. Jones, K. R. Randles, R. C. Storr, *Tetrahedron Lett.* **1988**, *29*, 953−954.
[84] Y. Mao, V. Boekelheide, *J. Org. Chem.* **1980**, *45*, 1547−1548.
[85] I. Hodgetts, S. J. Noyce, R. C. Storr, *Tetrahedron Lett.* **1984**, *27*, 5435−5438.
[86] C. W. G. Fishwick, R. C. Storr, P. W. Manley, *J. Chem. Soc., Chem. Commun.* **1984**, 1304−1305.
[87] R. Consonni, P. DallaCroce, R. Ferraccioli, C. LaRosa, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1809−1814.
[88] M. Ohno, H. Sato, S. Eguchi, *Synlett* **1999**, 207−209.
[89] J. M. Wiebe, A. S. Caille, L. Trimble, C. K. Lau, *Tetrahedron* **1996**, *52*, 11705−11724.
[90] P. Zakrzewski, M. Gowan, L. A. Trimble, C. K. Lau, *Synthesis* **1999**, 1893−1902.
[91] D. Migneault, M. A. Bernstein, C. K. Lau, *Can. J. Chem.* **1995**, *73*, 1506−1513.
[92] P. d. Champlain, J. L. Luche, R. A. Marthy, P. deMayo, *Can. J. Chem.* **1976**, *54*, 3749−3756.
[93] X. Chen, K. Tanaka, F. Yoneda, *Chem. Pharm. Bull.* **1990**, *38*, 612−615.
[94] N. Martin, A. Martinez-Grau, L. Sanchez, C. Seoane, M. Torres, *J. Org. Chem.* **1998**, *63*, 8074−8076.
[95] A. S. Caille, L. Trimble, C. Berthelette, C. K. Lau, *Synlett* **1996**, 669−670.
[96] S. S. Nikam, B. E. Kornberg, M. F. Rafferty, *J. Org. Chem.* **1997**, *62*, 3754−3757.
[97] K. Nishiyama, H. Kubo, T. Sato, K. Higashiyama, S. Ohmiya, *Heterocycles* **1998**, *48*, 1103−1106.
[98] S. S. Nikam, P.-W. Yuen, B. E. Kornberg, B. Tobias, M. F. Rafferty, *J. Org. Chem.* **1997**, *62*, 9331−9334.
[99] B. Mugrage, C. Difenbacher, J. Somers, D. T. Parker, T. Parker, *Tetrahedron Lett.* **2000**, *41*, 2047−2050.
[100] Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 863−865.
[101] Y. Ito, S. Miyata, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1981**, *103*, 5250−5251.
[102] Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1981**, *103*, 476−477.
[103] Y. Ito, E. Nakajo, M. Nakatsuka, T. Saegusa, *Tetrahedron Lett.* **1983**, *24*, 2881−2884.
[104] Y. Ito, E. Nakajo, T. Saegusa, *Synth. Commun.* **1986**, *16*, 1073−1080.
[105] P. Dalla Croce, R. Ferraccioli, C. L. Rosa, *Heterocycles* **1996**, *43*, 2397−2407.
[106] H. Steinhagen, E. J. Corey, *Angew. Chem.* **1999**, *111*, 2054−2056; *Angew. Chem. Int. Ed.* **1999**, *38*, 1928−1931.
[107] H. Steinhagen, E. J. Corey, *Org. Lett.* **1999**, *1*, 823−824.
[108] A. S. Kiselyov, L. Strekowski, *Org. Prep. Proc. Int.* **1996**, *28*, 291−318.
[109] L. Strekowski, H. Lee, S.-Y. Lin, A. Czarny, D. V. Derveer, *J. Org. Chem.* **2000**, *65*, 7703−7706.
[110] R. L. Wydra, S. E. Patterson, L. Strekowski, *J. Hetrocycl. Chem.* **1990**, *27*, 803−805.
[111] L. Strekowski, S.-Y. Lin, H. Lee, J. C. Mason, *Tetrahedron Lett.* **1996**, *37*, 4655−4658.
[112] M. Hojjat, A. S. Kiselyov, L. Strekowski, *Synth. Commun.* **1994**, *24*, 267−272.
[113] L. Strekowski, A. S. Kiselyov, M. Hojjat, *J. Org. Chem.* **1994**, *59*, 5886−5890.
[114] A. S. Kiselyov, L. Strekowski, *Tetrahedron Lett.* **1994**, *35*, 7597−7600.
[115] L. Strekowski, S.-Y. Lin, H. Lee, Z.-Q. Zhang, J. C. Mason, *Tetrahedron* **1998**, *54*, 7947−7954.
[116] A. Czarny, H. Lee, M. Say, L. Strekowski, *Heterocycles* **1997**, *45*, 2089−2092.
[117] L. Strekowski, R. L. Wydra, M. T. Cegła, A. Czarny, D. B. Harden, S. E. Patterson, M. A. Battiste, J. A. Coxon, *J. Org. Chem.* **1990**, *55*, 4777−4779.
[118] S. E. Patterson, L. Janda, L. Strekowski, *J. Heterocycl. Chem.* **1992**, *29*, 703−706.
[119] L. Strekowski, S. E. Patterson, L. Janda, R. L. Wydra, D. B. Harden, M. Lipowska, M. T. Cegła, *J. Org. Chem.* **1992**, *57*, 196−201.
[120] L. Strekowski, R. L. Wydra, D. B. Harden, V. A. Honkan, *Heterocycles* **1990**, *31*, 1565−1569.
[121] L. Smith, A. S. Kiselyov, *Tetrahedron Lett.* **1999**, *40*, 5643−5646.
[122] A. S. Kiselyov, *Tetrahedron Lett.* **1999**, *40*, 4119−4122.
[123] A. S. Kiselyov, C. Dominguez, *Tetrahedron Lett.* **1999**, *40*, 5111−5114.
[124] C. W. G. Fishwick, K. R. Randles, R. C. Storr, *Tetrahedron Lett.* **1985**, *26*, 3053−3056.
[125] K. R. Randles, R. C. Storr, *Tetrahedron Lett.* **1987**, *28*, 5555−5558.
[126] M. Ikeda, S. Matsugashita, C. Yukawa, T. Yakura, *Heterocycles* **1998**, *49*, 121−126.
[127] M. Ikeda, M. S, F. Tabusa, H. Ishibashi, Y. Tamura, *J. Chem. Soc., Chem. Commun.* **1975**, 575−576.
[128] E. Foresti, M. T. D. Gioia, D. Nanni, P. Zanirato, *Gazz. Chim. Ital.* **1995**, *125*, 151−161.
[129] E. Foresti, P. Spagnolo, P. Zanirato, *J. Chem. Soc., Perkin Trans. 1* **1989**, 1354−1356.
[130] J. Suwiński, K. Świerczek, *Tetrahedron* **2001**, *57*, 1639−1662.
[131] K. Pluta, K. V. Andersen, F. Jensen, J. Becher, *J. Chem. Soc., Chem. Commun.* **1988**, 1583−1584.
[132] J. Becher, P. L. Joergensen, K. Pluta, N. J. Krake, B. Fält-Hansen, *J. Org. Chem.* **1992**, *57*, 2127−2134.

Received March 26, 2001
[O01144]