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CYCLOADDITION, RING-OPENING, AND OTHER NOVEL REACTIONS OF THIOPHENES[1]

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Abstract - *Synthetically useful reactions of thiophenes and benzo[b]thiophenes are reviewed in which the aromaticity of the thiophene ring is lost either permanently or temporarily, i.e. so-called "non-benzenoid" reactions. These include cycloaddition reactions with arynes, hetarynes, carbenes, nitrenes, olefins, acetylenes, ketones, and other substrates and various ring-opening reactions, e.g. of organometallic derivatives and 2-aminothiophenes. Also reviewed are C-2 protonation and reactions of thiophenes at the sulphur atom, e.g. alkylation. Brief reference is made to thiophene 1,1-dioxides and attention is drawn to other little-used reactions of thiophenes of potential synthetic usefulness, e.g. inverted reactivity of thienyl-lithium compounds.*

Contents:

1. INTRODUCTION

The following statement by Salo Gronowitz[2] appears in Janssen's book, published in 1967, on organosulphur chemistry:

> *"When I chose the title nonbenzenoid chemistry of thiophene, which is a rather diffuse term for this lecture, I think it was just in order to attract attention. It is just another protest against all the textbooks of organic chemistry which use the phrase that has been standard since Victor Meyer's days; that thiophene is very similar to benzene, although perhaps a little more reactive. Hartough[3] in his now ten-year old book on thiophene had already had enough of this oversimplification and stated that thiophene and benzene ought to be compared about as closely as a zoologist would compare the tortoise and the boa constrictor. They are in the same class but of widely separated species and I would like to add that it is thiophene which is the boa constrictor."*

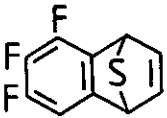
In contrast to benzene, the presence of sulphur in thiophene allows such "non-benzenoid" reactions to occur as desulphurisation, oxidation to thiophene 1,1-dioxides (which we refer to briefly later), and metallation in the 2-position. All of these synthetically useful reactions, together with tautomerism of derivatives, e.g. of hydroxythiophenes, which is not observed with the corresponding benzene derivatives, are covered adequately in the existing reviews on thiophenes.[2-6] However, in order to dispel once and for all the myths that still abound in books on heterocyclic chemistry that thiophene and its derivatives are particularly stable with respect to cycloaddition (involving only the ring) and ring-opening reactions, this review will concentrate on such reactions. Our treatment, which is not intended to be comprehensive, is aimed at promoting thiophenes as extremely versatile synthetically useful compounds.[7] We have referred also to analogous reactions of benzo[b]-thiophenes.[8]

2. CYCLOADDITIONS

Thiophenes undergo a variety of thermal and photochemical cycloaddition reactions to give a remarkable number of [2 + 2], [2 + 4], and other cycloadducts. The following account is classified according to the substrate. For detailed discussions of the mechanisms of these cycloaddition reactions the reader is referred to the original literature. Concerted Diels-Alder addition to thiophene and thiophene 1,1-dioxide has received a theoretical treatment.[9]

2.1 With Arynes and Hetarynes

The first successful cycloaddition reaction of the parent heterocycle was reported in 1966 by the Birmingham fluorine group,[10,11] who reacted tetrafluorobenzyne with thiophene in ether at 25°C and, after spontaneous extrusion of sulphur from the initial [2 + 4] cycloadduct (1), isolated a 40% yield of 1,2,3,4-tetrafluoronaphthalene.[12] Similar reactions occur between tetrafluorobenzyne and tetrachlorothiophene, to give a low yield of the perhalogenonaphthalene (2),[11] and between substituted polyfluorobenzynes and thiophene.[13,14] Initial attempts[10] to react benzyne with thiophene failed except under very high temperature gas-phase conditions.[15,16] However, Reinecke's group[17] have isolated naphthalene in up to 33% yield (see also ref.18) from a vacuum-sealed glass vial reaction of solid diphenyliodonium-2-carboxylate with thiophene at 220°C. Other products formed, including o-(2-thienyl)benzoic acid (3) (in up to 16% yield), suggest that the cycloaddition of benzyne and thiophene is prevented by faster reactions of thiophene with benzyne precursors. Also formed, by [2 + 3] cycloaddition, during the gas-phase reactions of benzyne with thiophenes are small amounts of benzo[b]thiophenes (Scheme 1; X = CH).[15,19] With monosubstituted thiophenes the unsubstituted side of the thiophene ring is usually attacked preferentially but, in the case of 2-methylthiophene, both sides are attacked.[19] A review of the reactions of benzyne with heterocycles, including thiophene, has been published recently[20] in which a critical account of the early work of Fields and Meyerson[15,16,21] is given. 2,3-Pyridyne reacts with thiophene to give products of insertion, quinoline (the product of [2 + 4] cycloaddition), and the thienopyridine (4; X = N) (Scheme 1), the product of [2 + 3] cycloaddition[22] and not a product of [2 + 2] cycloaddition to the C-S bond of thiophene, as claimed earlier.[16]



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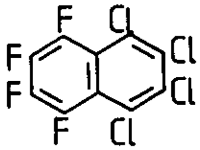

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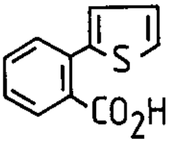
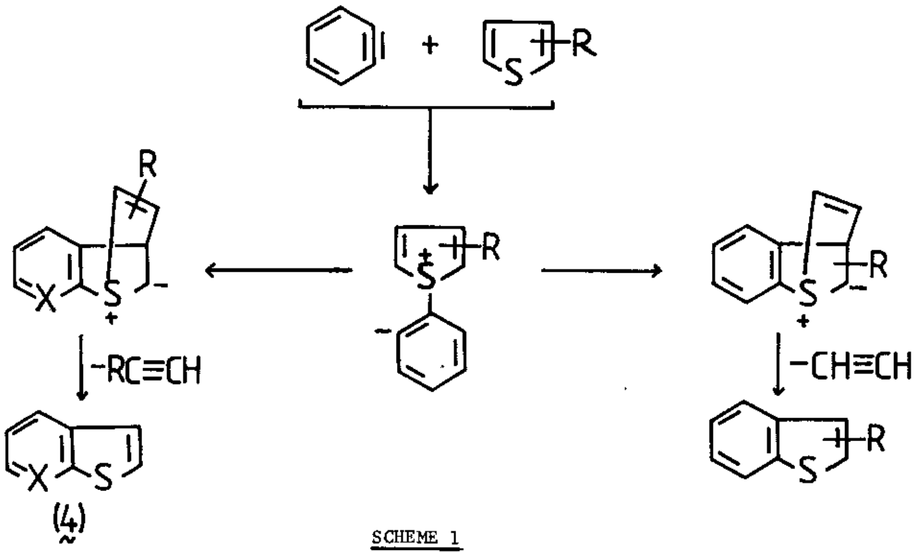
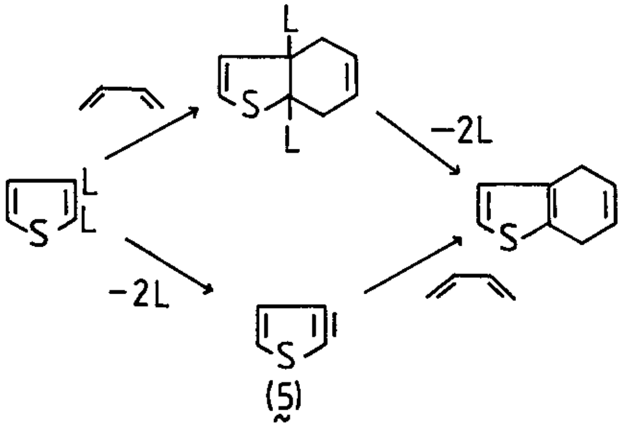


(3)

No attempt is made here to review the literature on the existence or otherwise of 2,3- or 3,4-thiophyne (or of 2,3-benzo[b]thiophynes) since this subject has been reviewed recently by Reinecke.[22] Noteworthy, however, is the fact that the same products (Scheme 2) can be formed either through the generation of a thiophyne, e.g. (5), or via a cycloaddition-extrusion sequence.



SCHEME 1

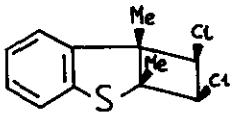


SCHEME 2

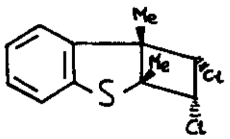
Nevertheless, 2,3-thiophyne (5) can be generated, e.g. by flash vacuum thermolysis (FVT) of thiophene-2,3-dicarboxylic acid anhydride, and made to react with thiophene, to give benzo[*b*]-thiophene (59% yield) after extrusion of sulphur from the initial adduct.[18,22]

2.2 With Olefins

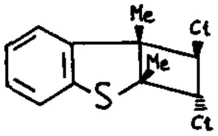
Thiophenes[23] and benzo[*b*]thiophenes[23-25] undergo sensitised (acetophenone or benzophenone) photochemical [2 + 2] cycloadditions with various halogeno-ethylenes to give mixtures of stereoisomers, e.g. with 2,3-dimethylbenzo[*b*]thiophene, *cis*- or *trans*-1,2-dichloroethylene give a mixture of the stereoisomers (6) - (9).[23] By contrast, the 1:2-adduct (12) arising from reaction of *NN'*-di-isopropyl-*NN'*-diphenyl-2,4-diaminothiophene (10) with acrylonitrile may be considered to arise *via* formation of the [2 + 4] cycloadduct (11) followed by cleavage of a C-S bond, attack of the



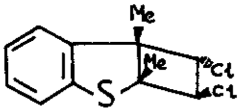
(6) cis, exo



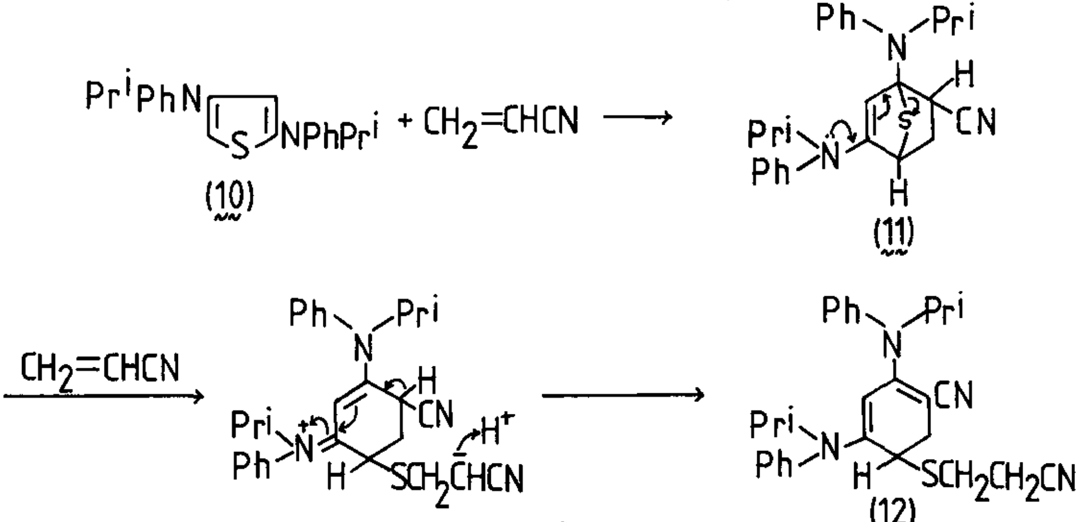
(7) cis, endo



(8) trans



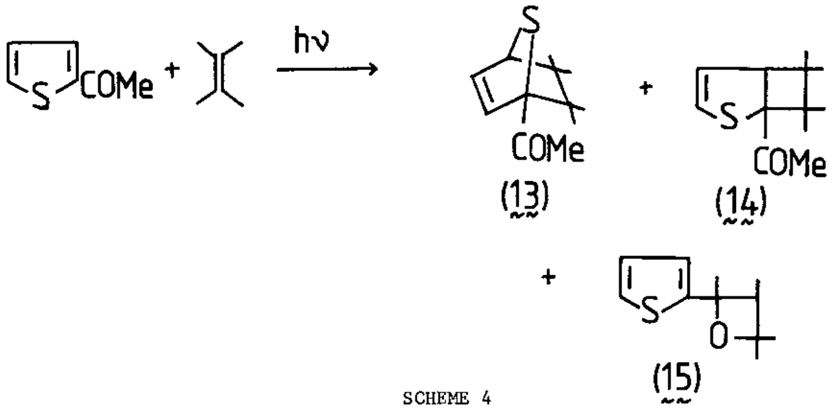
(9) trans



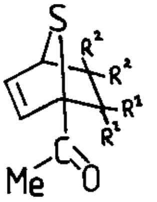
SCHEME 3

generated thiolate ion on a second molecule of acrylonitrile, and a final prototropic shift (Scheme 3).[26]

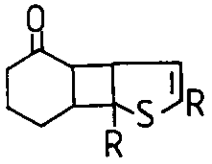
2-Acetylthiophene reacts with 2,3-dimethylbut-2-ene to give a mixture of the [2 + 4] cycloadduct (13) (Scheme 4) (38%), the [2 + 2] cycloadduct (14) (10%), and the oxetane (15) (11%) (see later).[27] Thiophene-3-carbaldehyde reacts more rapidly with this olefin to give (amongst other products) a small amount of a [2 + 2] cycloadduct analogous to (14).[28] With 2-acetylthiophene, 2-methylpropene (isobutene) reacts only by [2 + 4] cycloaddition, to give a mixture of the two possible isomers (16) and (17) together with a small amount of oxetane, whilst 2-aroylthiophenes react with olefins to give oxetanes (see later).[27] Cyclohexenone undergoes photochemical [2 + 2]



SCHEME 4



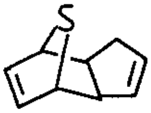
(16) R^1=Me,R^2=H
(17) R^1=H,R^2=Me



(18)

cycloaddition with thiophene or 2,5-dimethylthiophene.[29] With thiophene the yield of cycloadduct (18 ; R=H) is low (8%), the major product being olefin dimer whilst, with the dimethylthiophene, two stereoisomers of (18; R=Me) are obtained.

Under FVT conditions thiophene reacts with cyclopentadiene to give indene after extrusion of sulphur from the initial [2 + 4] cycloadduct (19).[18]



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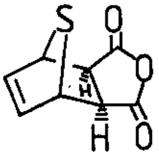

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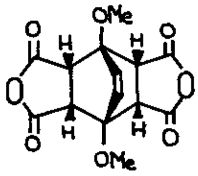

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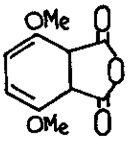

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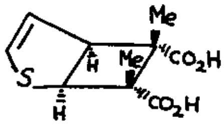

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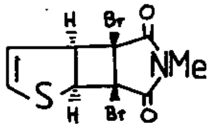
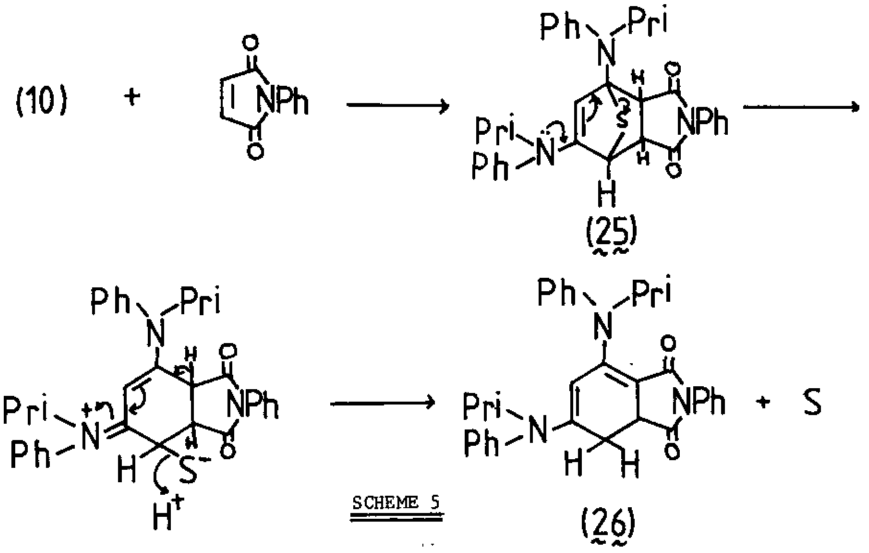


(24)

At 100°C and very high pressures thiophene undergoes [2 + 4] cycloaddition with maleic anhydride in dichloromethane to give the isolable 1:1-exo-cycloadduct (20) (37-47% yield).[30] 2,5-Dimethoxythiophene reacts differently with maleic anhydride in refluxing xylene, to give the 1:2-cycloadduct (21) (see also Section on cycloaddition reactions with other substrates).[31] In this case the initial [2 + 4] 1:1-cycloadduct loses sulphur to give the highly reactive diene (22). By contrast, [2 + 2] cycloadducts are formed on photolysis of mixtures of thiophene or methylthiophenes with 2-methyl- (citraconic) or 2,3-dimethylmaleic anhydride,[32-35] e.g. cycloadduct (23) is obtained from thiophene and dimethylmaleic anhydride. Benzo[b]thiophenes yield similar cycloadducts.[34-36] In some cases photosubstitution products are isolated as well as the cycloadducts. It is not clear whether the diacids are formed on work-up or during irradiation,[33-35] although anhydrides are isolable in some cases.[e.g.32]

Irradiation of a mixture of thiophene and dibromo-N-methylmaleimide gives an unstable [2 + 2] cycloadduct (24) which reacts with a further molecule of thiophene.[37] By contrast NN'-di-isopropyl-NN'-diphenyl-2,4-diaminothiophene (10) reacts with N-phenylmaleimide through formation of a [2 + 4] cycloadduct (25), cleavage of a C-S bond, and desulphurisation, to give the 1:1 cycloadduct (26).[26] In its reactions with acrylonitrile (Scheme 3) and 4-phenyl-1,2,4-triazoline-3,5-dione (Scheme 16) this diaminothiophene yields 1:2-cycloadducts with retention of sulphur.



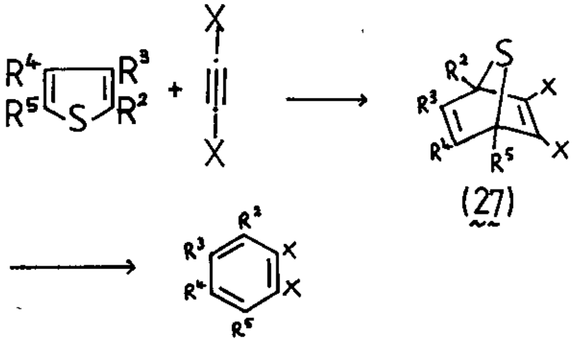
(25)

(26)

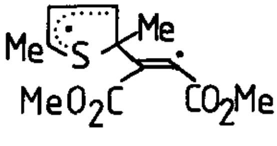
SCHEME 5

2.3 With Acetylenes

Various thiophenes are reported to undergo thermal [2 + 4] cycloaddition reactions with dicyanoacetylene,[38] dimethyl acetylenecarboxylate (DMAD), diphenylacetylene, or but-2-yne,[39] to give derivatives of benzene (Scheme 6; X = CN, CO_2Me, Ph, Me) after extrusion of sulphur from the initial [2 + 4] cycloadduct (27). At room temperature sensitised and non-sensitised photo-addition



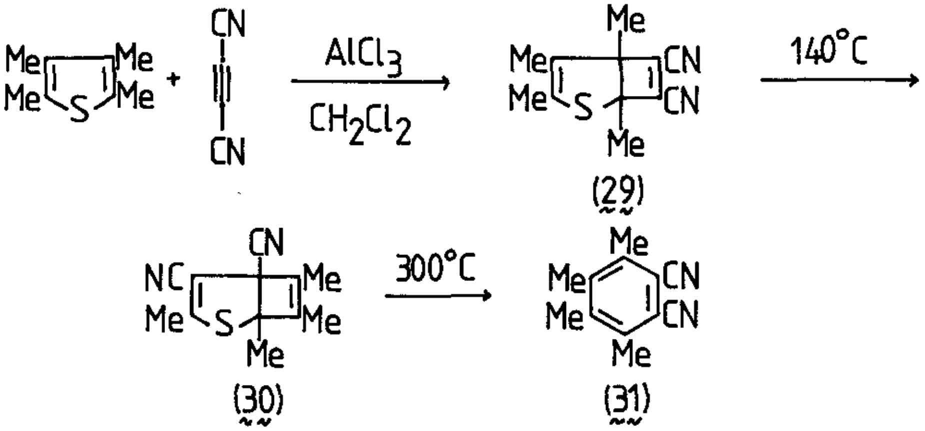
SCHEME 6



(28)

occurs to give the same products.[39] However, sensitised photo-addition is believed to occur via the formation of triplet-excited thiophenes and diradicals, such as (28), which undergo ring-closure either directly to the benzene derivative with simultaneous extrusion of sulphur or give initially the [2 + 4] adduct shown in Scheme 6.

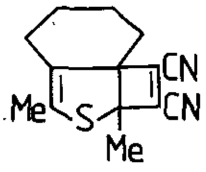
In the presence of aluminium chloride tri- and tetra-alkylthiophenes react with dicyano-acetylene in dichloromethane at room temperature or below ($0^{o}C$) via preferential [2 + 2] cycloaddition to give 2-thiabicyclo[3.2.0]hepta-3,6-diene-6,7-dicarbonitriles, e.g. (29; Scheme 7).[40-44]



SCHEME 7

Small amounts of benzene derivatives (e.g. 31) are isolated also, presumably formed via slower, competitive [2 + 4] cycloaddition (Scheme 6).[43,44] With unsymmetrical thiophenes, cycloaddition occurs on either thiophene double bond to give mixtures of [2 + 2] cycloadducts,[43,44] whilst 4,5,6,7-tetrahydro-1,3-dimethylbenzo[c]thiophene yields a [2 + 2] cycloadduct analogous to (29), namely (32), together with the product (33) of an "ene" reaction.[43,44] 2,5-Dimethylthiophene gives compound (34), which is formed by Friedel-Crafts alkylation of 2,5-dimethylthiophene by the initially formed [2 + 2] cycloadduct.[44]

At 110-140°C the [2 + 2] cycloadducts (Scheme 7) rearrange in high yields by a [3,3]antara,-



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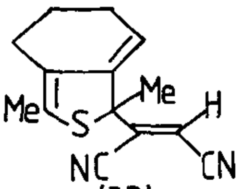

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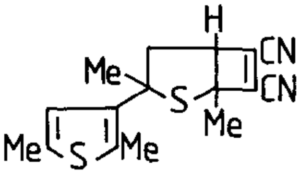
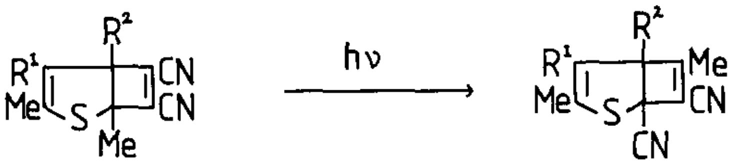


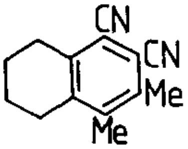
(34)

antara sigmatropic (Cope) rearrangement (the first to be reported for a 2-heterobicyclo[3.2.0]hepta-3,6-diene) to give an isomeric 2-thiabicyclo[3.2.0]hepta-3,6-diene, e.g. (29) → (30) (Scheme 7).[41-43,45] Irradiation of the initial [2 + 2] cycloadducts produces a different series of 2-thiabicyclo[3.2.0]hepta-3,6-dienes, (35) → (36).[43,45] All the 2-thiabicyclo[3.2.0]hepta-3,6-



(35) (36)

dienes (29,30,35 and 36) are converted thermally into phthalonitrile derivatives at 285-300°C, e.g. (30) → (31) (Scheme 7), probably via rearrangement to a thiepin followed by formation of a thia-norcaradiene (see later) and sulphur extrusion.[41-46] The [2 + 2] cycloadduct (32) was designed not to undergo a thermal Cope rearrangement and cannot undergo photochemical isomerisation by the mechanism which accounts for conversions such as (35) → (36). However, at 140°C, this cycloadduct (32) is more reactive than the analogous [2 + 2] cycloadducts, e.g. (29) (Scheme 7), and desulphurises, to give (37), with simultaneous formation of the sulphurated product (38).[43,46]



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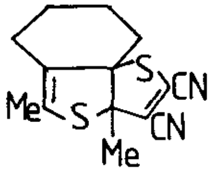
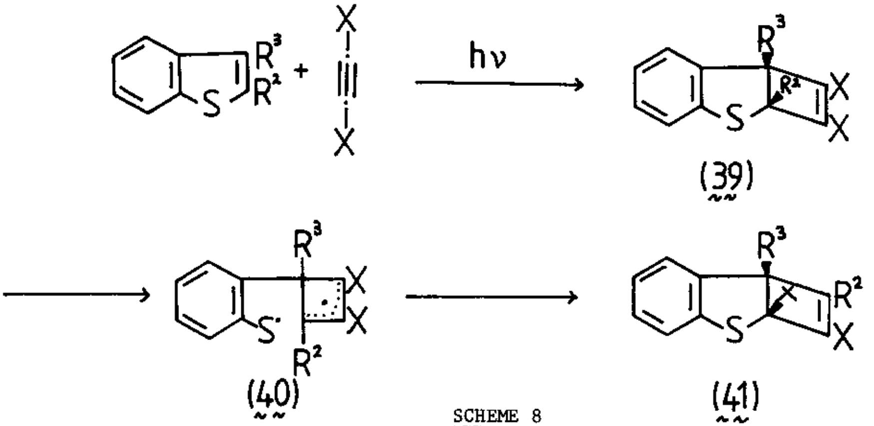
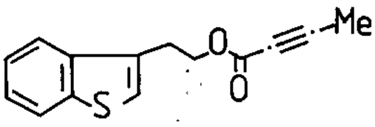


(38)

The products arising from irradiation of mixtures of benzo[b]thiophenes and acetylenes are dependent on the photolysis conditions. The initial [2 + 2] cycloadducts (39) are isolable but rearrange reversibly via an allylic diradical (40) to their isomers (41) (Scheme 8).[47] The benzo[b]-thiepin (42) and its 2-isomer undergo this reaction intramolecularly.[48] The rearranged products (41) are converted thermally into the corresponding naphthalene (43) probably via further rearrange-



SCHEME 8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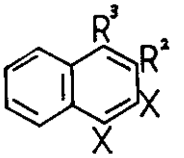
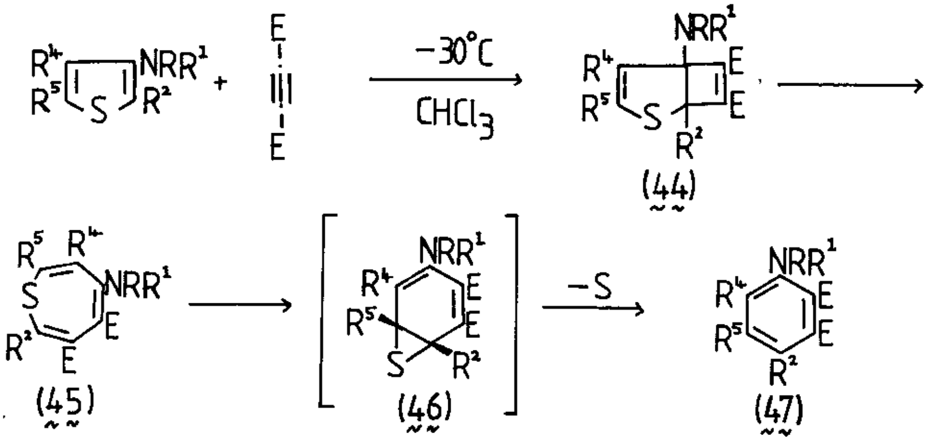

(43)

ment to an unstable benzo[b]thiepin followed by sulphur extrusion from a thianorcaradiene intermediate (see later).[47,48] Addition of unsymmetrical acetylenes to benzo[b]thiophenes appears to be highly selective.[47]

Reinhoudt's group in The Netherlands have successfully prepared monocyclic thiepins by cycloaddition of DMAD to several 3-(sec-amino)thiophenes in trichloromethane (Scheme 9).[43,49] Similar results are obtained in other relatively apolar solvents such as benzene, toluene, ether, or tetrachloromethane. At room temperature only amino-derivatives of dimethyl phthalate (47) are

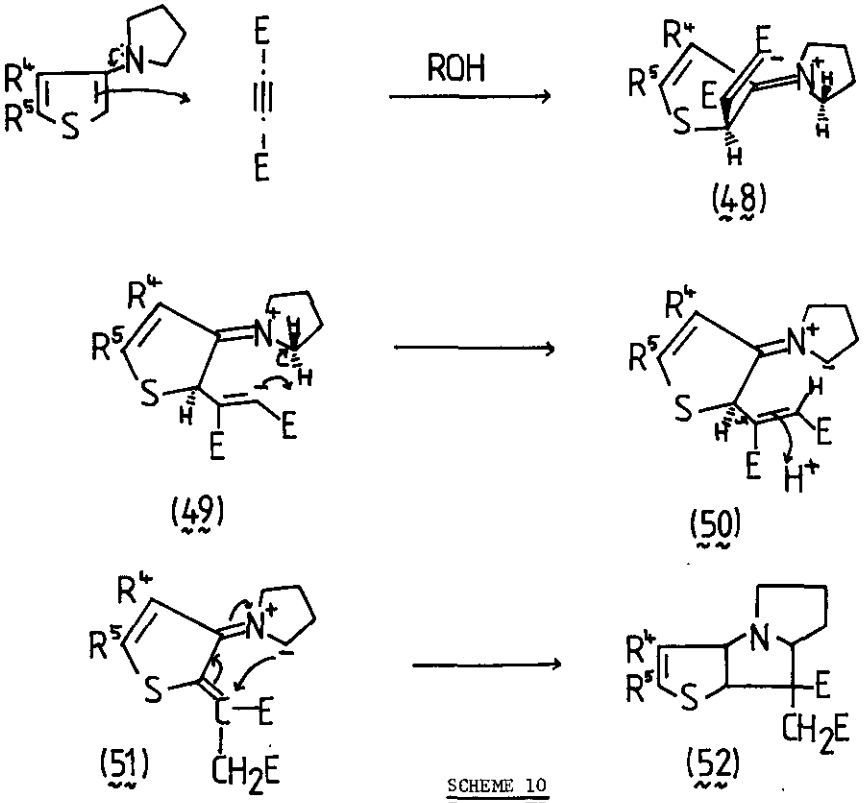


SCHEME 9

isolated but the monocyclic thiepins (45) are detectable at lower temperatures. The rate of isomerisation (44) → (45) is accelerated by the amino-substituent at the bridge-head. At room temperature the thiepins (45) readily lose sulphur via the intermediacy of a thianorcaradiene (46). Decomposition of the thiepins, (45) → (46) → (47), is retarded when R^5 = t-Bu (Scheme 9).[43,50]

Benzo[b]thiepins may be prepared similarly by reacting a 3-(sec-amino)benzo[b]thiophene with DMAD. They too lose sulphur to give naphthalene derivatives by a route analogous to that shown in Scheme 9 (R^4 and R^5 are a fused benzene ring in this case).[43,51]

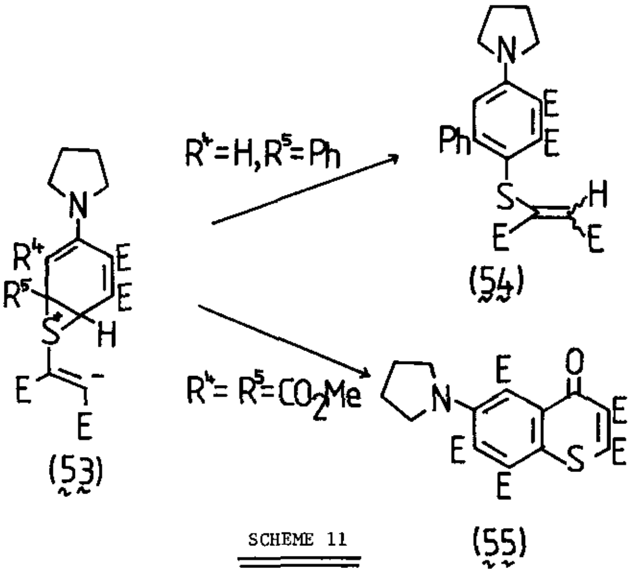
When 3-(sec-amino)-thiophenes or -benzo[b]thiophenes react with DMAD in polar protic (MeOH or n-BuOH) or aprotic (MeCN, $MeNO_2$) solvents (higher temperatures are necessary) the reaction takes a different course to that already described and thienopyrrolizines (Scheme 10) and other products are obtained.[43,50,52,53] The initial, rate-determining step is a nucleophilic attack by the



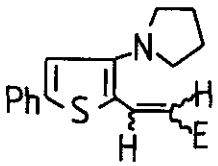
SCHEME 10

enamine on the acetylene, to give a tied ion-pair form (48) of a 1,4-dipolar intermediate. In apolar solvents this intermediate reacts by formation of a second σ-bond but, in polar solvents, rotation around the newly formed σ-bond occurs to give a solvent-stabilised, charge-separated ion-pair (49). This reacts further by a H-abstraction, as shown (Scheme 10), and the intermediate (50) produced undergoes a prototropic shift to give the conjugated 1,5-dipolar tautomer (51) which cyclises by a symmetry-allowed disrotatory electrocyclisation to the product (52).

2-Phenyl-4-(1-pyrrolidinyl)thiophene reacts with DMAD in acetonitrile at room temperature to give the pyrrolizine (52; R^4 = H, R^5 = Ph) (34% yield) but it also gives the E- and Z-isomers of the biphenyl (54) (26%) (Scheme 11).[50,52] The ratio of these two products is dependent on temperature. In methanol or nitromethane only the pyrrolizine (52; R^4 = H, R^5 = Ph) is obtained.[50,52]



SCHEME 11



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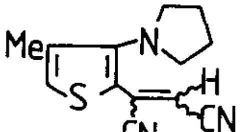

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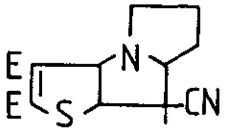


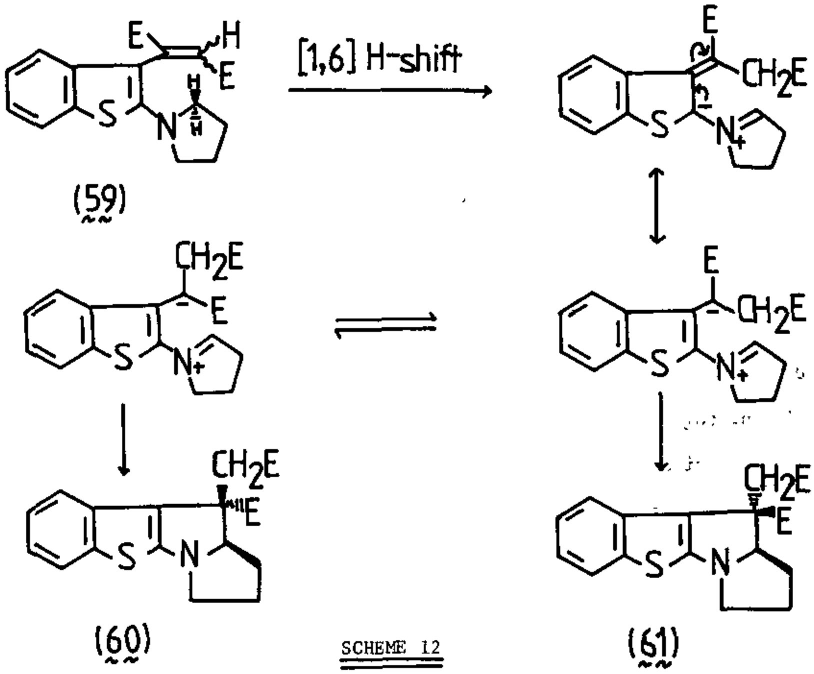
(58)

Dimethyl 4-(1-pyrrolidinyl)thiophene-2,3-dicarboxylate does not react with DMAD in either acetonitrile or nitromethane at room temperature but in the latter solvent (heated under reflux) it gives the thienopyrrolizine (52; R^4 = R^5 = E = CO_2Me) in detectable amounts, together with a biphenyl analogous to (54) as a mixture of its E- and Z-isomers (10% yield) and the benzothiopyranone (55) as the major product.[50,52] The formation of biphenyls arises through S-alkylation of the monocyclic thiepin (Scheme 11) by the DMAD before the captured intermediate (53) extrudes sulphur. Proton transfer and aromatisation then yields the biphenyl (e.g. 54). In intermediate (53; R^4 = R^5 = E = CO_2Me) an intramolecular nucleophilic attack by the carbanionic centre can occur on an adjacent ring ester carbonyl group leading through loss of a methoxyl group to the formation of the benzothiopyranone (55).[50,52]

2-Phenyl-4-(1-pyrrolidinyl)thiophene reacts with methyl propiolate, both in the absence of solvent and in methanol, to give only products (56) (E- and Z-isomers) of Michael-type addition.[50] A similar result is obtained when 3-methyl-4-(1-pyrrolidinyl)thiophene reacts instantaneously with dicyanoacetylene, even at -70°C; the product (57) is that of a Michael-type addition.[49]

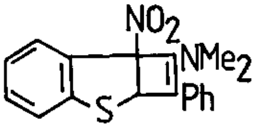
In contrast to the reactions of 3-(sec-amino)thiophenes with DMAD in apolar solvents dimethyl 4-(1-pyrrolidinyl)thiophene-2,3-dicarboxylate reacts with dicyanoacetylene in dichloromethane at -60°C to give the thienopyrrolizine (58).[50]

2-(1-Pyrrolidinyl)benzo[b]thiophene reacts with DMAD in methanol at room temperature to give a 3:1 mixture of the E- and Z-isomers of the Michael adduct (59).[54] When the E-isomer is heated in n-butanol it gives a 2:1 mixture of the pyrrolizines (60) and (61); in toluene, however, only pyrrolizine (61) is obtained. When the Z-isomer is heated in toluene neither isomerisation nor cyclisation occurs; in n-butanol, however, this isomer is converted into a mixture of the two pyrrolizines, (60) and (61).[54] The first step (Scheme 12) in these reactions is a concerted thermal antarafacial [1,6] H-shift, which is followed by a symmetry-allowed disrotatory 1,5-dipolar cyclisation. In the 1,5-dipole leading to (61) and/or (60) stereomutation can occur depending on structure, rate of cyclisation, and probably the polarity of the solvent, which explains why the E-isomer of (59) gives both pyrrolizines in n-butanol but only one in toluene.



SCHEME 12

Reinoudt's group have shown also that an electron-deficient thiophene ring will undergo [2 + 2] cycloaddition with an ynamine; e.g. 3-nitrobenzo[b]thiophene forms the cycloadduct (62) as the major product with 1-dimethylamino-2-phenylacetylene.[43,55]



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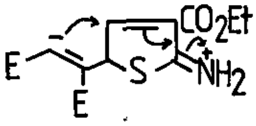

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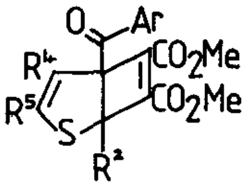

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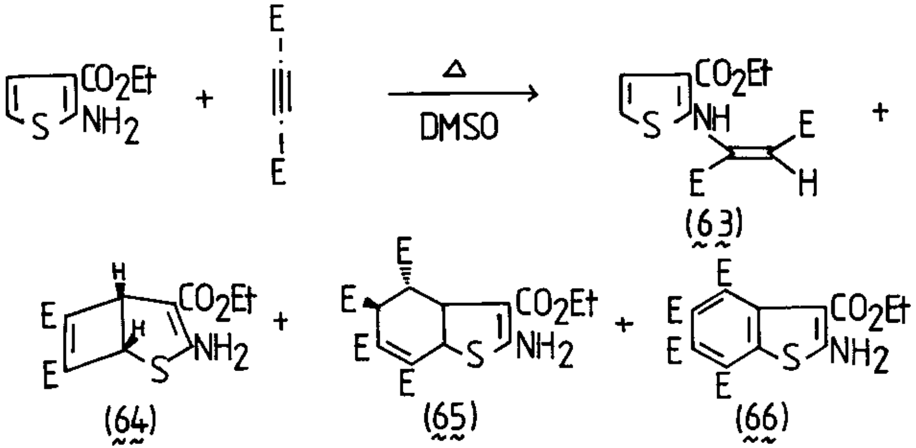


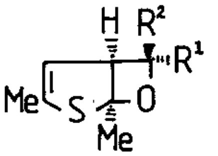
SCHEME 13

In hot DMSO ethyl 2-aminothiophene-3-carboxylate reacts with DMAD to give the product (63) of a Michael addition, together with a 1:1-cycloadduct (64) and two 1:2-adducts, (65) and (66).[56] Biere *et al.*[56] have rationalised the formation of these products by the intermediacy of the dipolar species (67) which can cyclise, as shown, to give the 1:1 adduct or react with a further equivalent of DMAD.

The initial unstable cycloadducts formed along with other products when mixtures of various 3-aroylthiophenes and DMAD are photolysed have been assigned the [2 + 2] structures (68) (see also next Section).[57]

2.4 With Ketones

2,5-Dimethylthiophene (but not other thiophenes) gives oxetanes as [2 + 2] cycloadducts with some ketones.[33,34,58,59] Unsymmetrical ketones yield both geometrical isomers, (69) and (70).



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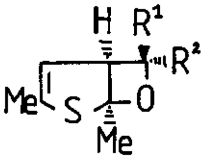
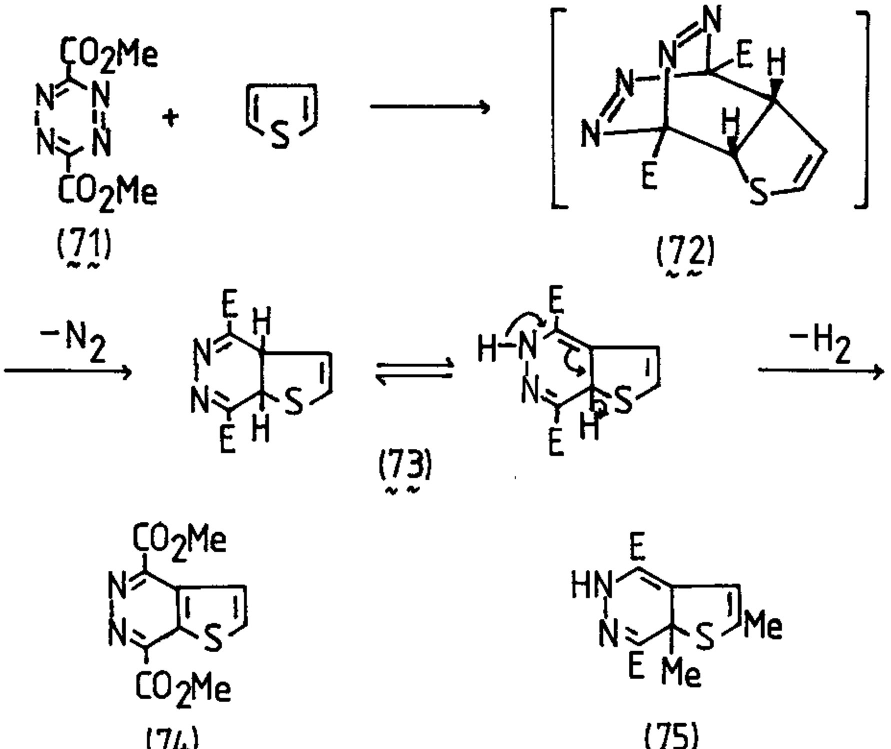


(70)

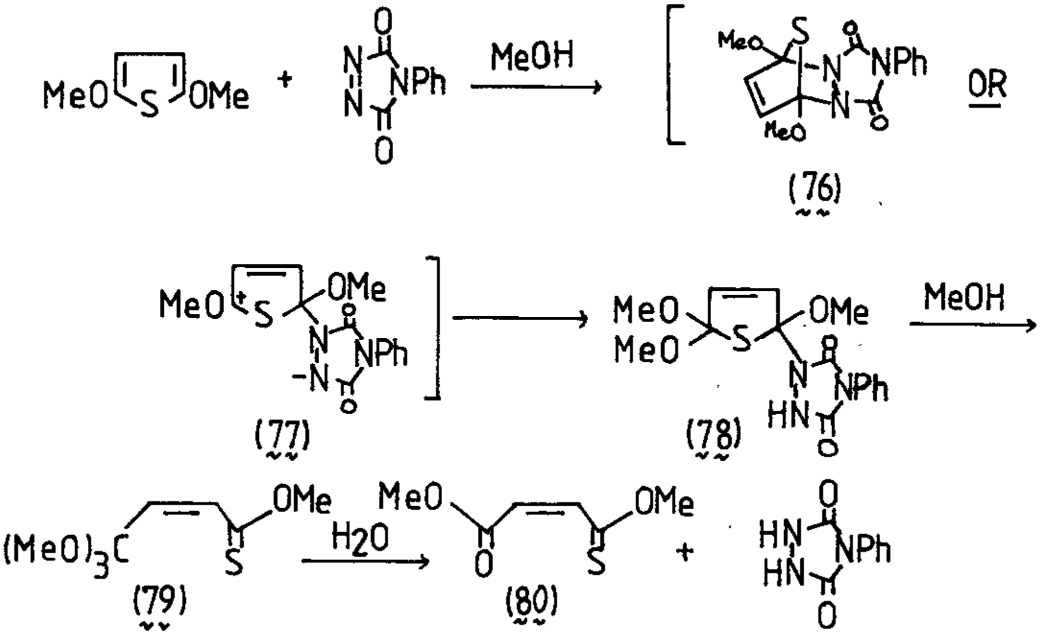
2.5 With Other Substrates

With the symmetrical tetrazine (71) thiophene gives the unstable [2 + 4] cycloadduct (72).[60] This loses nitrogen to give a tautomeric intermediate (73) which is oxidised to the isolable product (74) (Scheme 14). With 2-chlorothiophene the reaction occurs, but more slowly, whilst in the case of 2,5-dimethylthiophene the dihydro-derivative (75) is isolable.



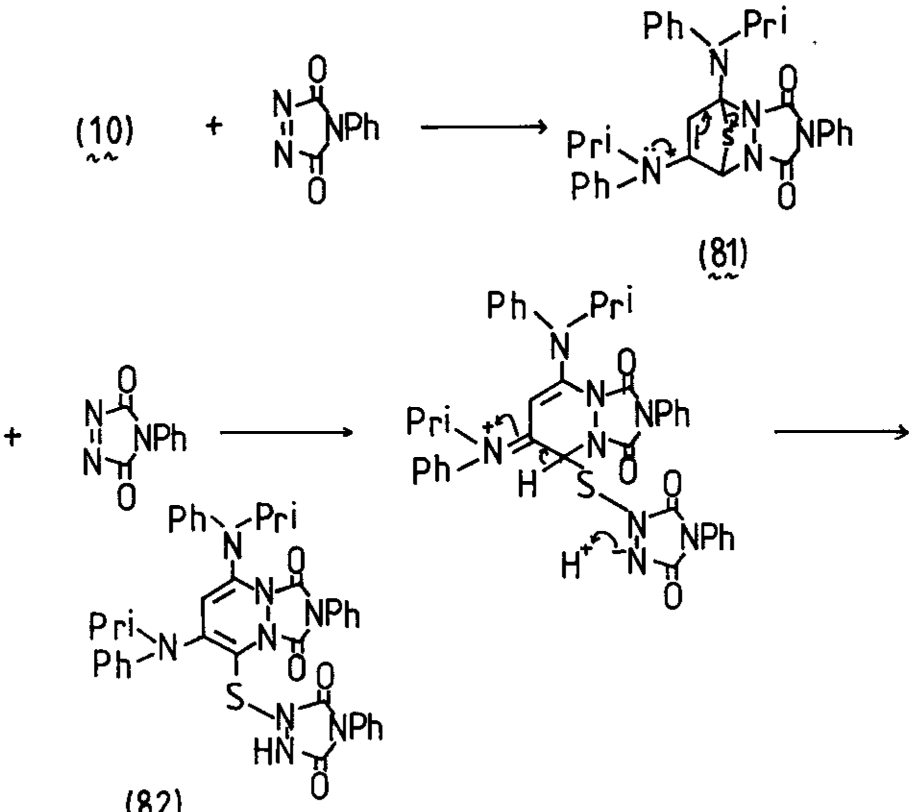
SCHEME 14

The first isolable product (78) (Scheme 15) in the reaction of 2,5-dimethoxythiophene with 4-phenyl-1,2,4-triazoline-3,5-dione in methanol may arise through solvolysis of either an initial



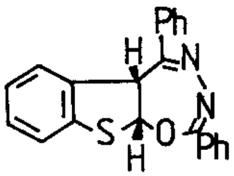
SCHEME 15

[2 + 4] cycloadduct (76) or the zwitterion (77).[61] It reacts further with methanol and the product (79) of oxidative cleavage of the thiophene ring is hydrolysed by water to the unstable olefin (80). A similar [2 + 4] cycloadduct (81) may be involved in the reaction of *NN'*-di-isopropyl-*NN'*-diphenyl-2,4-diaminothiophene (10) with 4-phenyl-1,2,4-triazoline-3,5-dione.[26] However, this reacts further by C-S bond cleavage, reaction of the generated thiolate ion with a second triazolinedione molecule, and a final prototropic shift, to give the 1:2-adduct (82) (Scheme 16).



SCHEME 16

Irradiation of 2,5-diphenyloxadiazole with benzo[*b*]thiophene yields the *cis*-fused oxadiazepine (83) amongst other products.[62] This cycloadduct is converted into the *trans*-fused [2 + 2] cycloadduct (84) on further irradiation through dissociation into starting materials. 2- and 3-Methylbenzo[*b*]-



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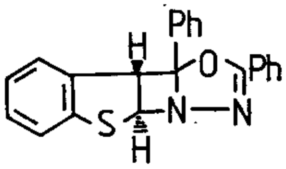
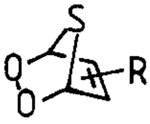


(84)

thiophene yield [2 + 2] cycloadducts similar to (84) but with cis-ring-fusion. In the presence of iodine, however, 3-methylbenzo[b]thiophene reacts to give the cis-fused regioisomer analogous to (84).[62]

The cycloadducts (85)[63-65] and (86)[64] have been postulated as the initial products of reaction of thiophenes and 4,5,6,7-tetrahydro-2,3-dimethylbenzo[b]thiophene, respectively, with singlet



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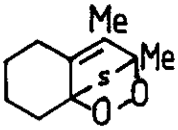

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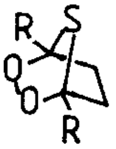
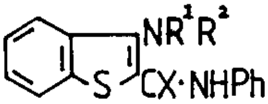


(87)

oxygen. Photo-oxygenation of 2,5-dialkylthiophenes in dichloromethane at low temperatures in the presence of a sensitiser followed by reduction of the initial adducts (85) with di-imine allows the reduced products (87) to be isolated.[66]

It is possible that the products (88; X = O or S) from reaction of a 3-(sec-amino)benzo[b]thiophene with phenyl isocyanate or isothiocyanate may arise via the intermediacy of a [2 + 2] cycloadduct (89) although an alternative mechanism has been proposed.[67]



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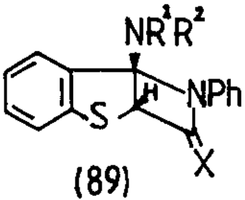
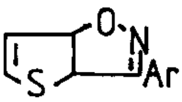


(89)

A 1,3-dipolar cycloaddition occurs between thiophene and 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide to give the 1:1-adduct (90) as the major product together with a lesser amount of the



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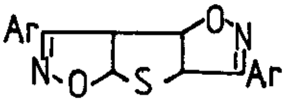

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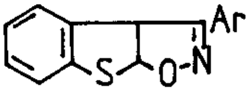
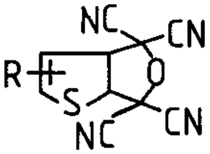


(92)

1:2-adduct (91).[68] The 1:1-adduct (90) reacts with this benzonitrile oxide to give the 1:2-adduct (91) and its regioisomer. By contrast, with thiophene, benzo[b]thiophene gives both the 1:1-adduct (92) and its regioisomer.[68] Similar 1:1- and 1:2-adducts are formed slowly between thiophene or benzo[b]thiophene and benzonitrile oxide (however, see ref.67) or mesitonitrile oxide.[69] Thiophene and benzonitrile oxide also give a 1:3 adduct. Frontier orbital calculations of the EH and MINDO/3 kind and comparisons with the regioselectivities of related systems allows elucidation of the observed regiochemistry.[69]

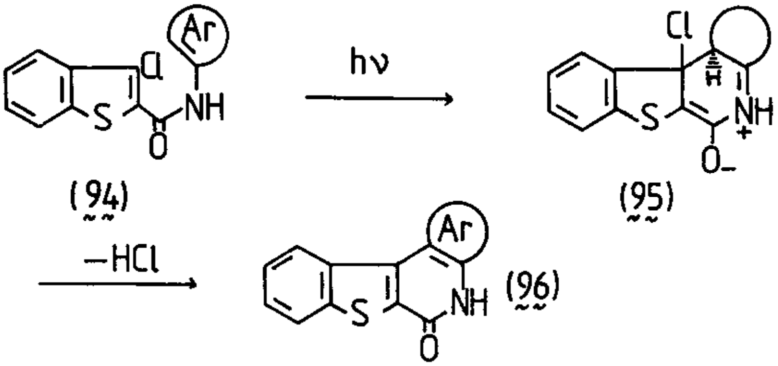
Thiophenes react with tetracyanoethylene oxide (TCNEO) to give the 1:1-cycloadducts (93).[70] Benzo[b]thiophenes react similarly. The mechanism of these reactions is not clear, although there



(93)

is evidence that TCNEO adds to olefins as a 1,3-dipole (formed by cleavage of the central C-C bond). Gronowitz and Uppström[70] found evidence that the initial attack on thiophenes is that of an electrophile.

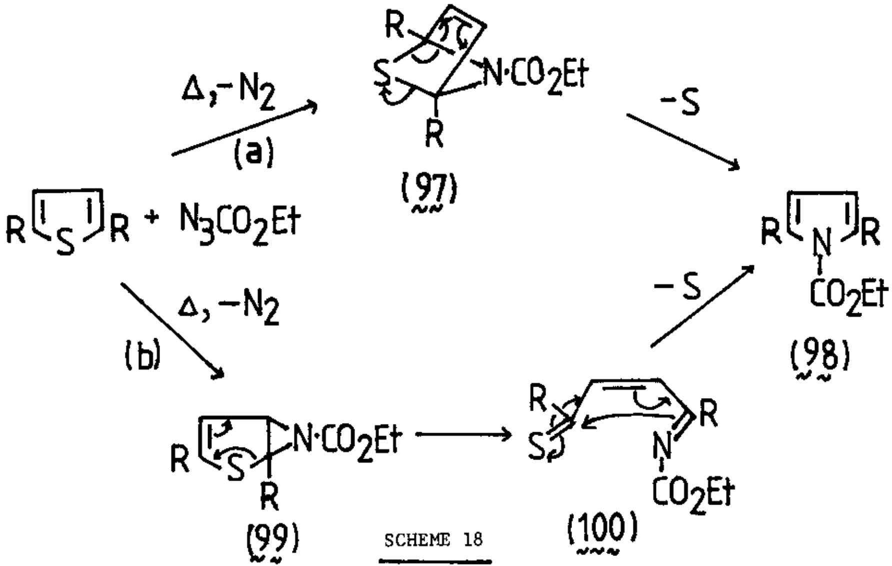
Intramolecular photoarylation of amides (94) derived from 3-chlorobenzo[b]thiophene-2-carboxylic acids to give compounds (96) is believed to proceed via intermediates (95) (Scheme 17).[71,72]



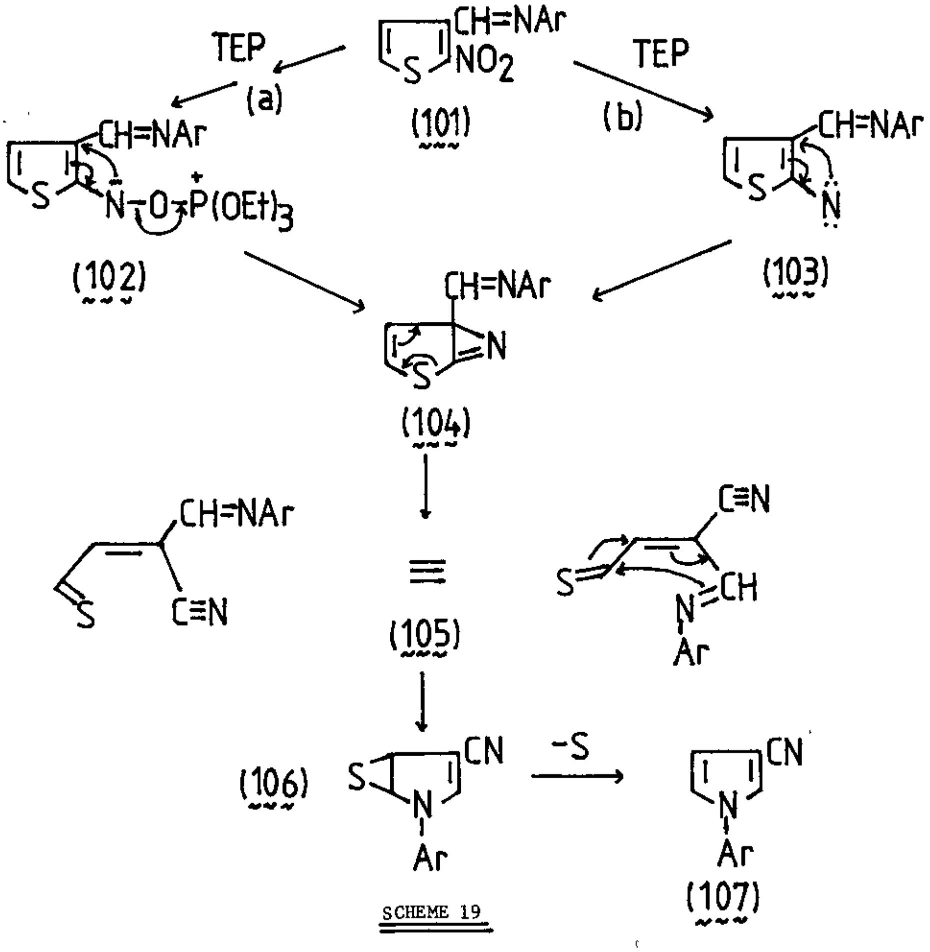
SCHEME 17

2.6 With Nitrenes and Carbenes

Thiophene and 2,5-dimethylthiophene are reported to be converted into pyrroles (98) on thermolysis with ethyl azidoformate by a mechanism (Scheme 18; path a) which involves the intermediacy of a [1 + 4] cycloadduct (97), but an alternative mechanism (Scheme 18; path b) is possible (see also the suggestion in refs. 4 and 73), involving concerted ring-opening of the [1 + 2] cycloadduct (99) and ring-closure of the product (100).[74] We[75] have reported a similar conversion of the Schiff's bases (101) of 2-nitrothiophene-3-carbaldehydes into pyrroles (107) (Scheme 19) in the presence of hot triethylphosphite (TEP) (cyclisation to thienopyrazoles also occurs). In our reported mechanism the key intermediates are the bicyclic azirines (104), which can undergo a concerted ring-opening reaction followed by ring-closure of the product (105), to give the pyrrole (107) after desulphurisation of intermediate (106). The key intermediates (104) may be formed via the intermediacy of a nitrene (103) or through the intermediacy of phosphorus

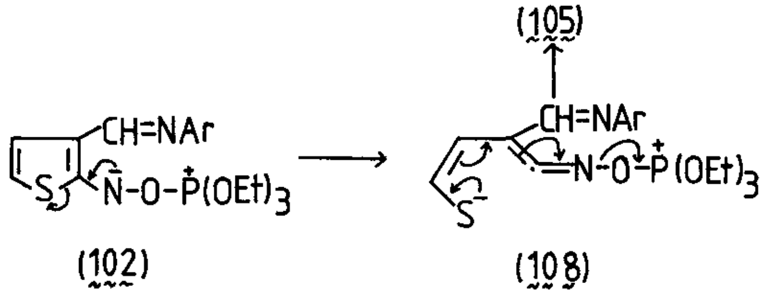


SCHEME 18



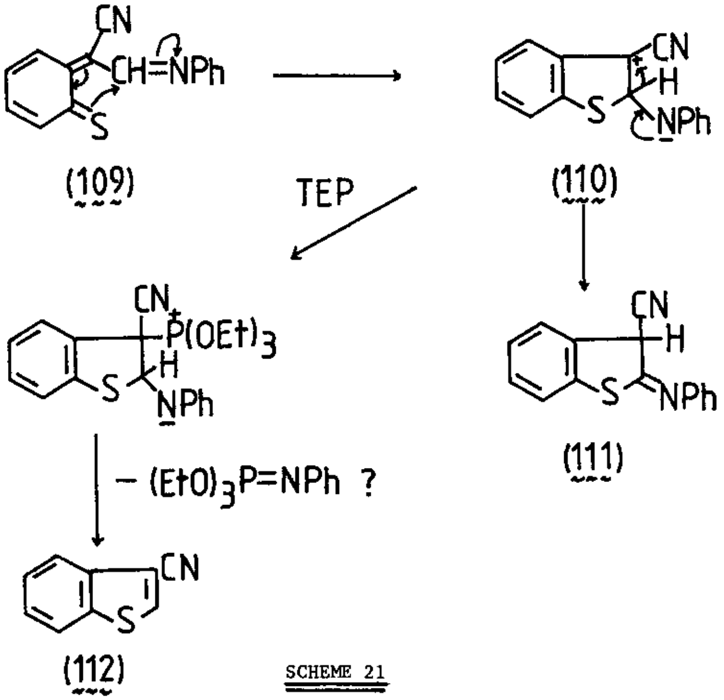
SCHEME 19

intermediates, e.g. (102). An alternative mechanism (see Section later on Ring-Opening of 2-Aminothiophenes) for the conversion (102) → (105) (Scheme 20) involves a concerted ring-opening of the phosphorus intermediate (102) followed by subsequent loss of triethylphosphate from the product (108).



SCHEME 20

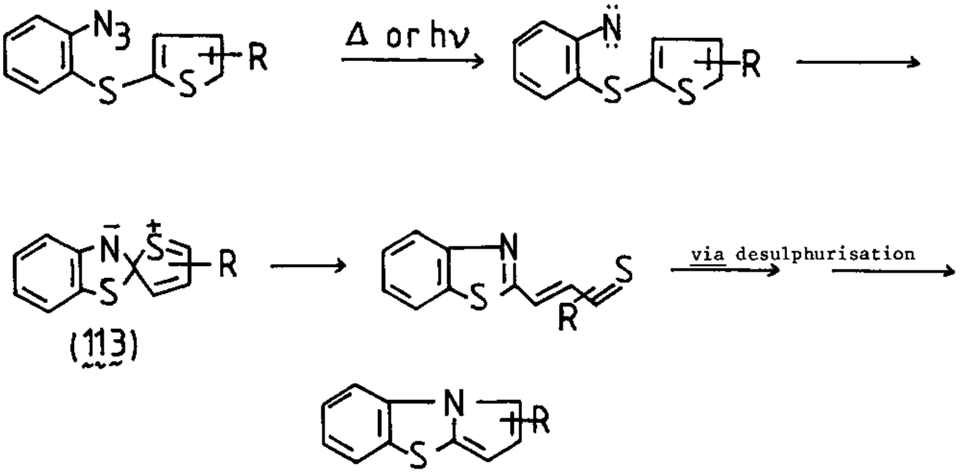
When the Schiff's bases of 2-nitrobenzo[b]thiophene-3-carbaldehyde are heated with TEP, the reaction follows a similar course initially (Scheme 21) but annelation prevents the ring-opened intermediate (109) from cyclising to give an intermediate analogous to (106) in Scheme 19.[76]



SCHEME 21

Instead, the carbenium ion (110) which results is trapped by the TEP and the product undergoes a Wittig-type elimination, to give benzo[b]thiophene-3-carbonitrile (112). When the corresponding azides are heated in diglyme the carbenium ions (110) rearrange to give nitriles (111) (Scheme 21).[76] The azides and the corresponding nitro-compounds also cyclise under the condition described to give varying amounts of benzothienopyrazoles.[76]

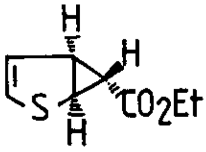
Although not involving an initial cycloaddition reaction, worth mentioning here are reactions of 2-(o-azidophenylthio)thiophenes[73] and 2-(o-azidobenzyl)thiophenes[77] which proceed via the



SCHEME 22

formation of a spiro-intermediate, in the former examples (113) (Scheme 22), with consequent loss of aromaticity in the thiophene ring; ring-opening of these intermediates is followed by a ring-closure to give the products (with[73] or without[77] desulphurisation).

Photolysis of a mixture of thiophene and ethyl diazoacetate gives the [1 + 2] cycloadduct (114) which is a useful intermediate for the synthesis of ethyl thiophene-3-acetate[78-80] and thiopyrylium.[81] Alkyl diazoacetates react similarly on thermolysis in the presence of a rhodium(II) catalyst.[80] Similar adducts are formed between thiophene and ethyl diazoacetoacetate[80]



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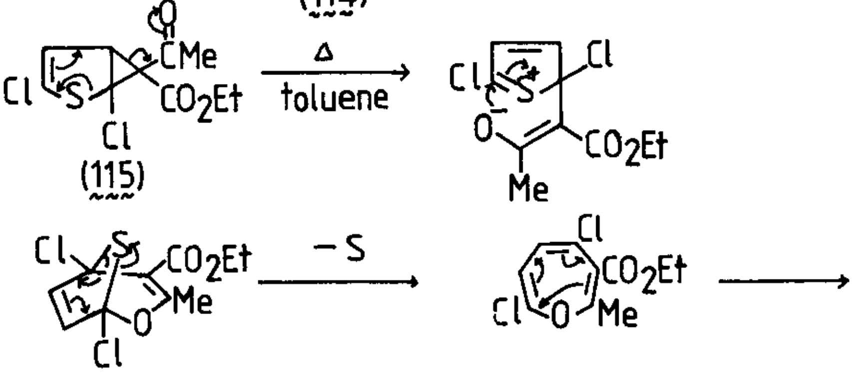

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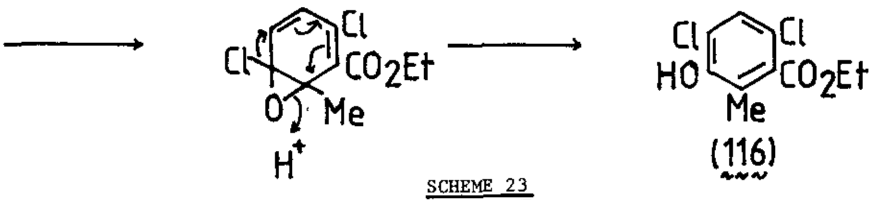
SCHEME 23 (cont.)

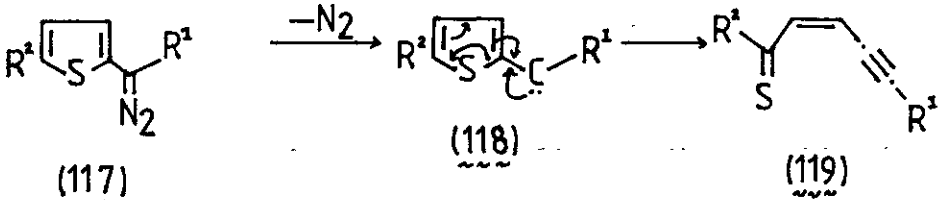


SCHEME 23

or diazomethane[82] and between 2,5-dichlorothiophene and ethyl diazoacetoacetate[83] (see also Section on Reactions at Sulphur). In the last case an adduct (115) is formed which rearranges by a novel mechanism (Scheme 23) to give a high yield of the substituted benzene (116).[83]

Benzo[b]thiophene reacts with ethyl diazoacetate to give a mixture of [1 + 2] cycloadducts arising by addition to the 2,3- and 4,5-double bonds of the heterocycle.[84-86]

Generation of the diazomethane derivatives (117) (Scheme 24) at high temperatures is followed by loss of nitrogen and fragmentation of the resulting carbenes (118), to give the unstable products (119), together with reactions between diazomethanes (117) and the carbenes (118), to give ethylene derivatives (major products) and nitrogen.[87]



SCHEME 24

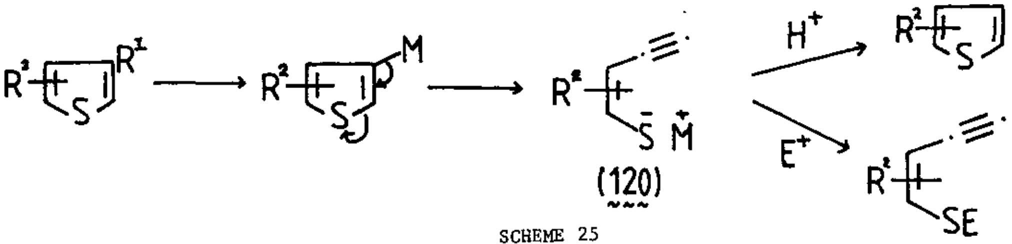
2.7 Thiophene 1,1-Dioxides

One of the few reactions (see later also) that occurs at the thiophene sulphur atom is oxidation. However, the products, thiophene 1-oxides and 1,1-dioxides, are no longer aromatic and their reactions are therefore outside the scope of this review.[88,89] Tetrachlorothiophene 1,1-dioxide appears to be a very useful compound for preparing a wide variety of useful systems.[90-92]

3. RING-OPENING REACTIONS

In one[93b] of their reviews[93] Gronowitz and Frejd classified base-promoted ring-opening reactions of five-membered aromatic heterocycles as follows:

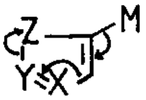
Ring-Opening of Type I (RO I). In this type of process a metal is introduced in position-3 of a thiophene (or other) ring by replacement of either hydrogen (metallation) or halogen (metal-halogen exchange), then a subsequent retrograde Michael reaction occurs to give a ring fission product (120) (Scheme 25), which can be trapped in the presence of a suitable electrophile. In the presence of acid a subsequent cyclisation reaction may occur instead.



(120)

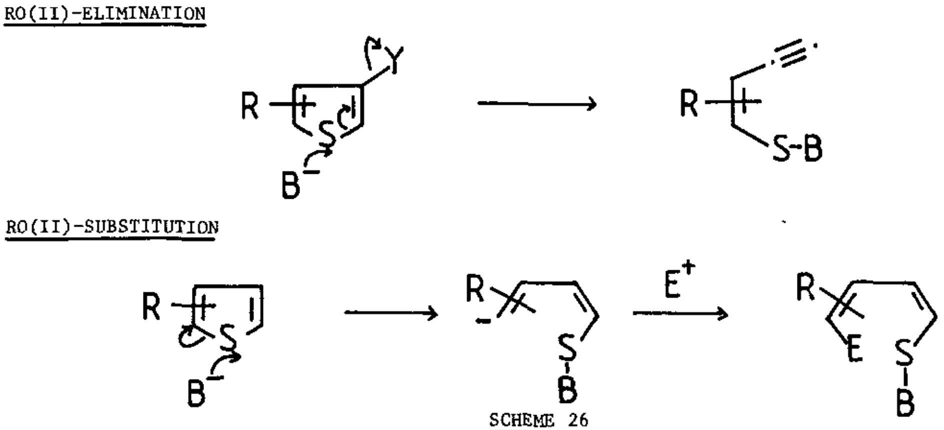
SCHEME 25

The alternative RO I reaction (121), involving extrusion of the fragment X≡Y, is not observed with thiophenes.



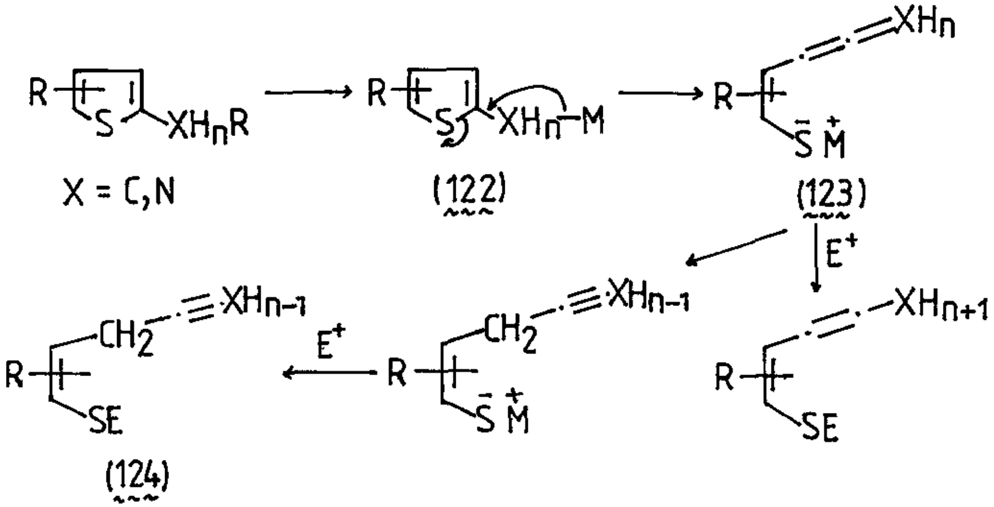
(121)

Ring-Opening of Type II (RO II). These may be sub-classified as RO II (elimination) or RO II (substitution) reactions, the difference being the presence or otherwise of a group, Y (Scheme 26), in the thiophene 3-position which can be eliminated. In RO II (substitution) reactions a carbanionic centre is generated and quenching with an electrophile is required. In both types of RO II reactions (and in contrast to RO I reactions) the products are dependent on the base used.



SCHEME 26

Ring-Opening of Type III (RO III). Removal of a proton from a side-chain or metal-halogen exchange between the metal and a halogen atom in the side-chain results in this type of process in the formation of an intermediate (122) (Scheme 27; X = C or N) which undergoes fission.



SCHEME 27

The product (123) can sometimes be trapped with a suitable electrophile but, in the presence of base, more often rearranges before trapping to give the product (124).

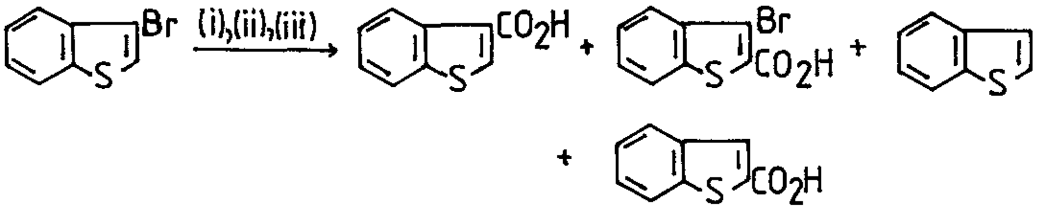
The best known reactions are those of type RO I; reactions of the RO II type have been discovered more recently. Although RO III reactions have been reported in the literature for some time, they have not been studied in detail.

Eliminative ring-fission reactions of the RO I and RO III types have been classified by Stirling[94] as endo:C=C:S:5 and exo:C=C:S:5 reactions, respectively. Because it is not possible to apply Stirling's classification procedure to RO II reactions we have used Gronowitz's classification procedure here.

4. RING-OPENING REACTIONS INVOLVING ORGANOMETALLIC DERIVATIVES

4.1 Ring-Opening of Type I (RO I)

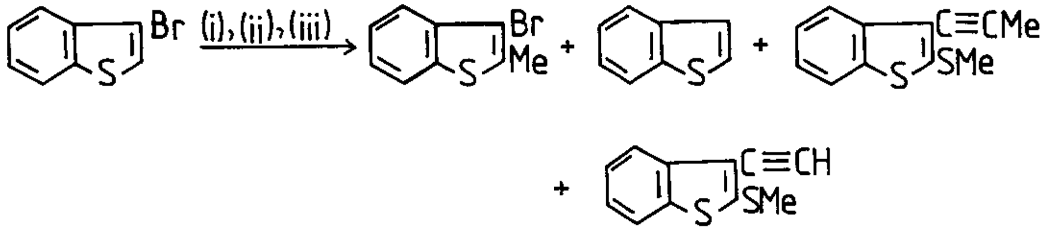
During a study of the reactions of 3-benzo[b]thienyl-lithium with various electrophiles[95] we reacted an ethereal solution of it with carbon dioxide. Although the corresponding 3-carboxylic acid could be obtained at low temperatures, the mixture of products shown in Scheme 28 was obtained



REAGENTS: (i) n-BuLi/0°C-R.T.; (ii) CO_2; (iii) H^+

SCHEME 28

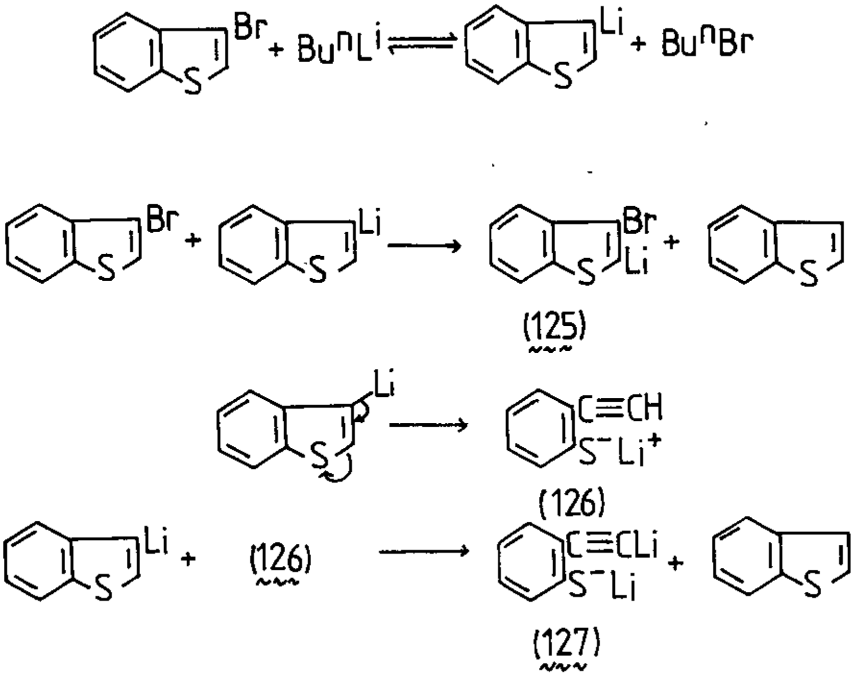
if this lithium compound was prepared by reaction of n-butyl-lithium with 3-bromobenzo[b]thiophene in ether at ambient temperature followed by carbonation. The same mixture was obtained after a reaction in THF, even at -70°C. Formation of benzo[b]thiophene-2-carboxylic acid and more benzo[b]thiophene than was expected by adventitious hydrolysis of the 3-lithiated compound with water were hard to explain initially.[95] Dissatisfied with carbon dioxide as the quenching reagent we changed to dimethyl sulphate, which gave the mixture of products shown in Scheme 29.[96,97] To account for



REAGENTS: (i) $nBuLi/Et_2O/20°C/1h$; (ii) Me_2SO_4; (iii) NH_4OH

SCHEME 29

these products we suggested the reactions shown in Scheme 30.[96,97] Methylation of lithium compounds

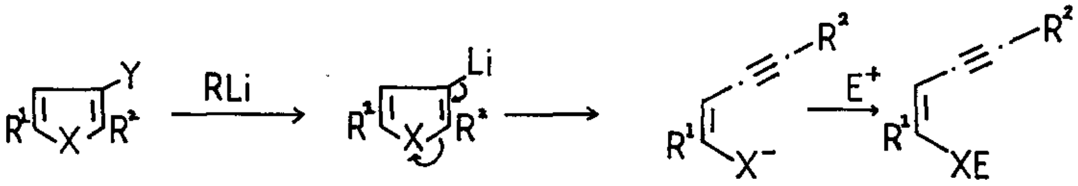


SCHEME 30

(125), (126), and (127) gives the methylated derivatives of Scheme 29, whilst carbonation of the

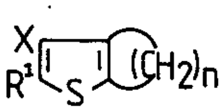
3-lithiated benzo[*b*]thiophene and lithium compound (125), gives two of the acids shown in Scheme 28. The third acid shown in Scheme 28 is formed by carbonation of lithium compound (127) followed by cyclisation of the product on work-up, which involves mineral acid (*cf*. Scheme 25). The sequence of reactions shown in Scheme 30 accounts also for the considerable amounts of benzo[*b*]-thiophene observed in our products. Other 3-benzo[*b*]thienyl-lithium compounds undergo RO I ring-opening reactions.[98]

In 1962, Moses and Gronowitz[99] observed the formation of "unsaturated aliphatic products" when handling 3-thienyl-lithium but did not realise what they were at that time. Following the isolation of acetylenic products arising from a 3-selenienyl-lithium compound[100] Gronowitz's group embarked on a detailed study of RO I reactions of this type. These reactions (Scheme 31) occur stereospecifically and the products (129) after alkylation of the intermediate anions (128) correspond to those of stereospecific and regiospecific addition of alkyl selenolates or thiolates to unsymmetrically substituted acetylenes. From trialkyl-substituted 3-thienyl-lithium compounds fully substituted vinyl acetylenic thioethers may be prepared which cannot be prepared by thiolate addition to diacetylenes, e.g. (130) → (131).[101] Macrocyclic alkylthiovinyl acetylenes, e.g. (132) from (133),[102] and acetylenic mixed ketene-thioacetals, e.g. (134; X = S) from (135; X = S),[103] and -seleno-acetals, e.g. (134; X = Se) from (135; X = Se),[103] may be prepared similarly. The scope and limitations of this synthetic method have been reviewed[93] and, consequently, we do not intend to go into detail here. The great advantage of this methodology lies in the aromatic nature of thiophene (or selenophene) which allows a wide variety of substituents to be introduced in a defined manner either by electrophilic substitution or by metallation and metal-halogen exchange reactions. One serious limitation of the method hitherto, namely that 3-thienyl-lithium derivatives with a free 2-position ring-open very slowly, has been overcome recently [104] by use of a 2-trimethylsilyl group. This allows the sequence of reactions shown in Scheme 32 to be accomplished,[104] together with the synthesis of some natural products, e.g. (136),[105] found in the plant genus *Anthemis*. Ring-opening of 3-thienyl-lithium compounds is subject to both electronic and steric effects created by substituents.[106] 2-*NN*-Dimethylaminomethyl-substituted 3-thienyl-

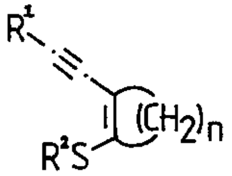


(128) (129)

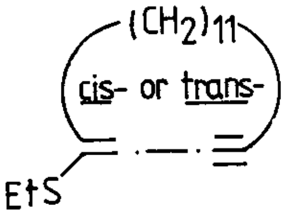
SCHEME 31



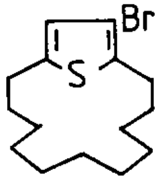
(130) (X = Br,I)



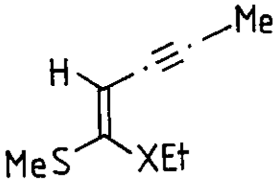
(131)



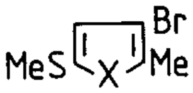
(132)



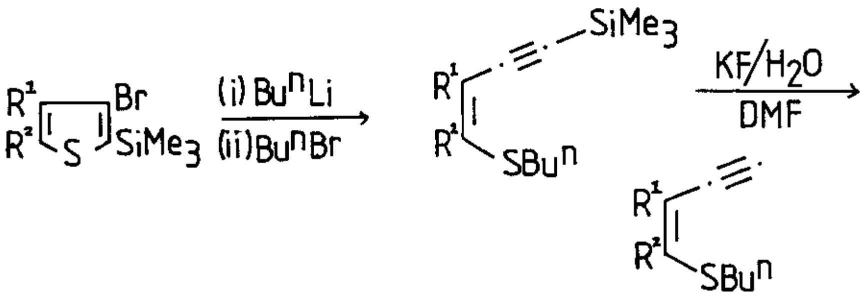
(133)



(134)

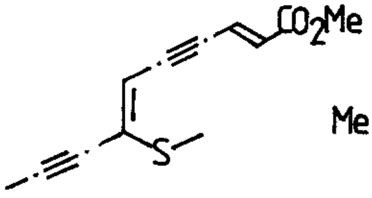


(135)

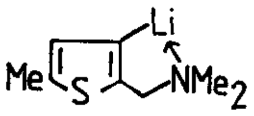


SCHEME 32

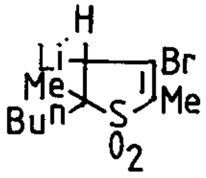
lithium compounds are stabilised by chelation, e.g. (137),[107] and a single chlorine atom or methoxyl group in the 2-position also appears to bestow stability on 3-thienyl-lithium compounds[106,108,109] although the presence of a second functional group of this type reverses this behaviour (see also Section on RO II reactions).[110,111] 2,5-Disubstituted 3-thienyl-lithium 1,1-dioxides also undergo



(136)



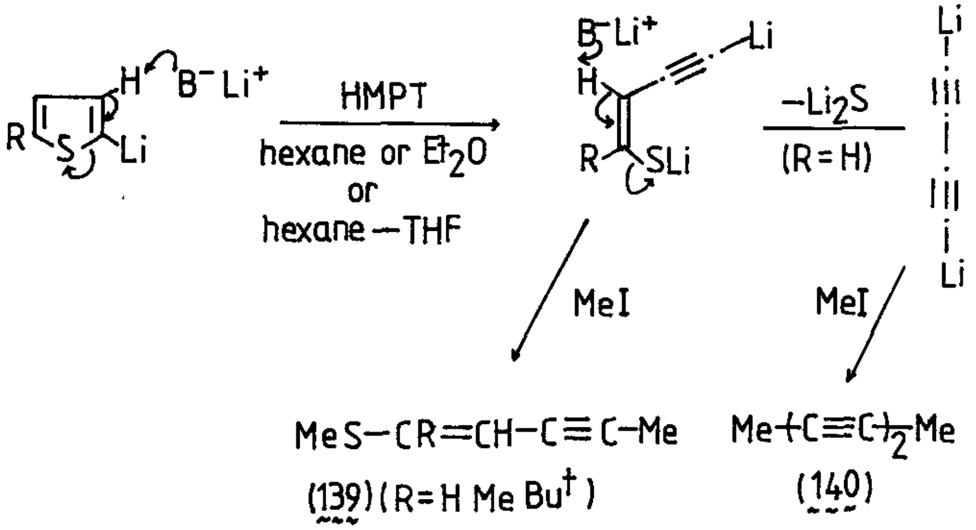
(137)



(138)

ring-opening reactions of the RO I type although, because the 3-bromo-compounds from which they are prepared are no longer aromatic, nucleophilic attack of the organolithium reagent in the 5-position can occur also, e.g. to give (138).[89,112] Metal-halogen exchange and subsequent ring-opening of the 3-lithiated compound is the preferred reaction when the 5-substituent in the starting thiophene is large (t-Bu) or when a bulky organolithium reagent (t-BuLi) is employed.

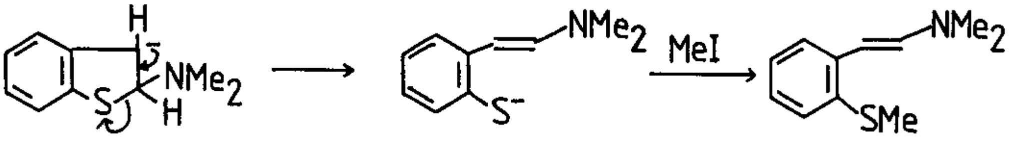
Gräfing and Brandsma[113] have shown that 2-thienyl-lithium (Scheme 33; R = H, Me, t-Bu) compounds can be made to undergo ring-opening reactions in the presence of hexamethylphosphoramide (HMPT) by the mechanism shown in Scheme 33. The amount of HMPT used is critical for ring-opening



SCHEME 33

to be observed; it solvates the lithium cation of the base (n-butyl-lithium or lithium di-isopropylamide), thus preventing further metallation of the ring. Addition of methyl iodide gives the enynesulphides (139). With thiophene as the starting material, when the mole ratio of n-butyllithium:thiophene exceeds 1.7, increasing amounts of hexa-2,4-diyne (140) are produced via a second proton-abstraction process (Scheme 33).[113] Under similar conditions 2,5-bis(methylthio)-

thiophene readily gives compound (139; R and terminal Me = SMe), presumably because the acidity of H-3 is increased.[113] The same product is obtained when lithium di-isopropylamide is used in a mixture of THF and HMPT and with sodamide in liquid ammonia.[113]

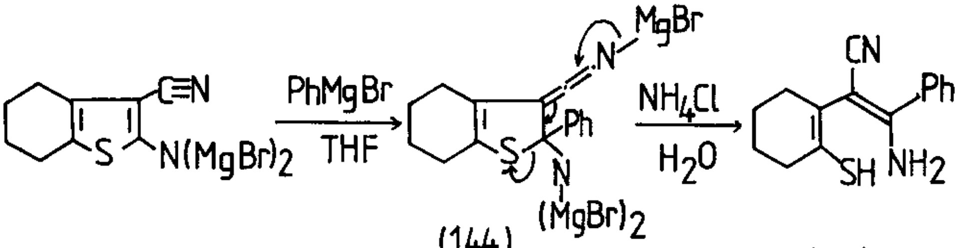


(141) (142)

SCHEME 34

A similar process is the ring-cleavage of benzo[b]thiophene with lithium dimethylamide in THF, which proceeds via the intermediate anion (141) to a product (142) that can be alkylated with methyl iodide (Scheme 34).[114]

When 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile is treated with phenylmagnesium bromide in THF it is converted via intermediates (143) and (144) (Scheme 35) into the ring-opened product (145).[115]

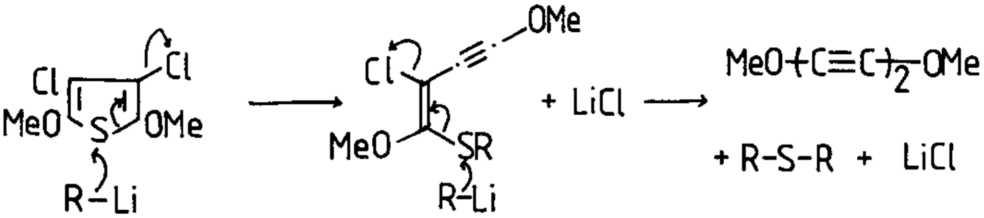


(143) (144) (145)

SCHEME 35

4.2 Ring-Opening of Type II (RO II)

A selenium atom is more susceptible to nucleophilic attack than a sulphur atom and this fact, together with the increased ring strain in selenophenes, makes these systems, especially those carrying electron-acceptor substituents such as chlorine, particularly prone to ring-opening by RO II mechanisms.[93] Few thiophenes have been reported to react in this way. However, 3,4-dichloro-

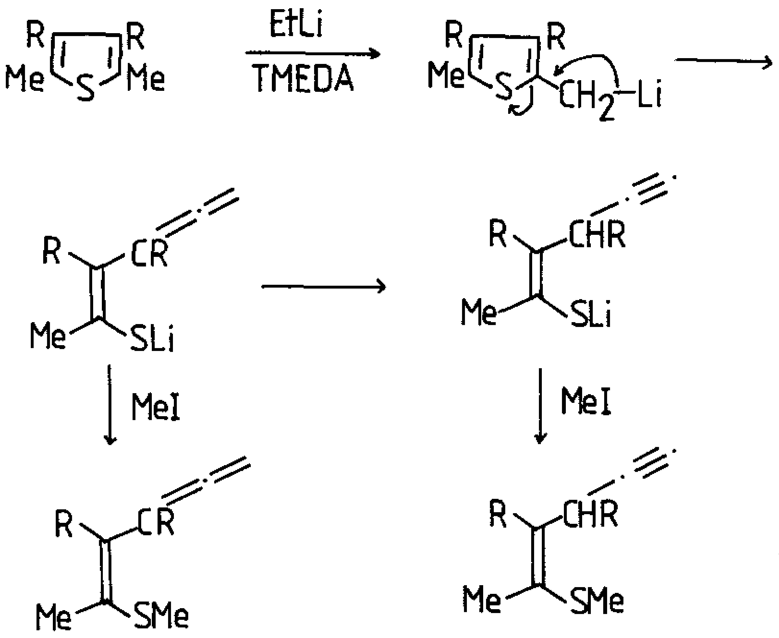


SCHEME 36

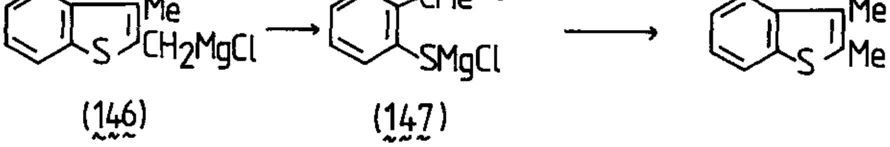
2,5-dimethoxythiophene probably undergoes such reactions with organolithium reagents, as shown in Scheme 36.[116]

4.3 Ring-Opening of Type III (RO III)

Gronowitz and Frejd[118] reported that 2,5-dimethyl- and 2,3,4,5-tetramethyl-thiophene undergo cleavage with ethyl-lithium in TMEDA via lateral metallation of the acidic methyl groups (Scheme 37). A mixture of allenes and acetylenes is produced following alkylation of the ring-fission products. The dimethyl compound also undergoes metallation in the 3-position.[118] Noteworthy is the ring-cleavage reaction of the Grignard compound (146) (Scheme 38); acidification of the product (147) (which can be trapped) gives 2,3-dimethylbenzo[b]thiophene.[119] Similar thiophene Grignard compounds rearrange instead of undergoing this ring-cleavage reaction.[93,119]



SCHEME 37

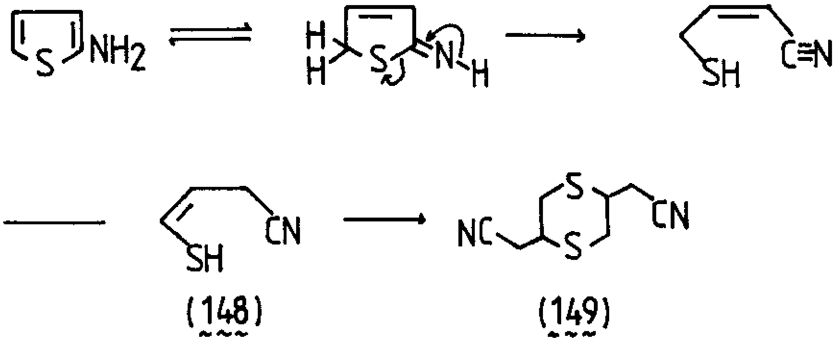


SCHEME 38

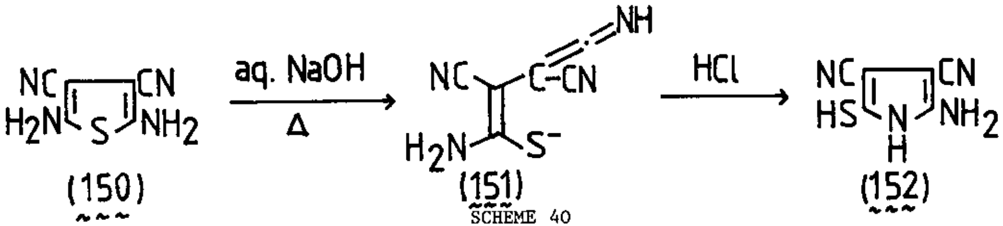
The reactions discussed in the next Section may be considered also as proceeding via a RO III-type mechanism.

5. RING-OPENING OF 2-AMINOTHIOPHENES

2-Aminothiophenes are well-known to be unstable. The parent compound appears to be able to undergo ring-opening as shown in Scheme 39, since in reactions of 2-aminothiophene with dimethyl acetylene-dicarboxylate, the dimer (149) of (148) has been isolated together with the expected addition product.[120] The diaminothiophene (150) can be rearranged in aqueous sodium hydroxide to the 2-aminopyrrole-5-thiol (152), presumably through the formation of intermediate (151) (Scheme 40).[121]



SCHEME 39

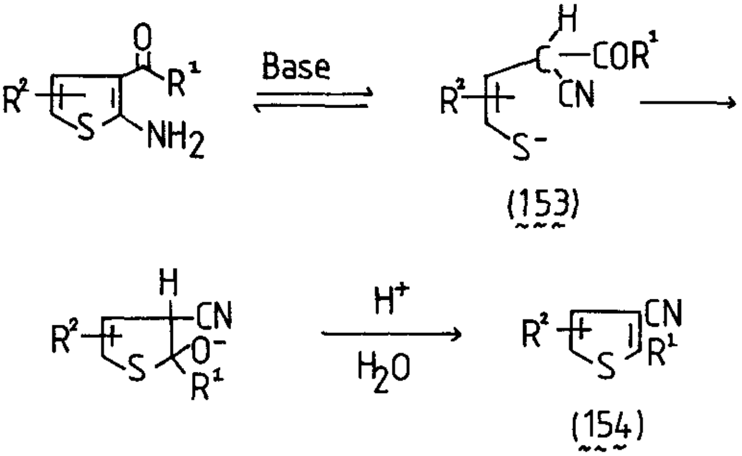


SCHEME 40

Usually, if an electron-withdrawing group is present in the 3-position of the 2-aminothiophene, it is able to capture the thiolate anion in the ring-cleavage product (153) (Scheme 41; R^1 = H, alkyl, or OEt) to give the thiophene-3-carbonitrile following acidification of the mixture.[115,122] With ethyl 2-aminothiophene-3-carboxylates, the products exist as thiolactones with alkyl substituents, but in the hydroxy form (154; R^1 = OH) with aryl or acyl substituents in the 5-position.

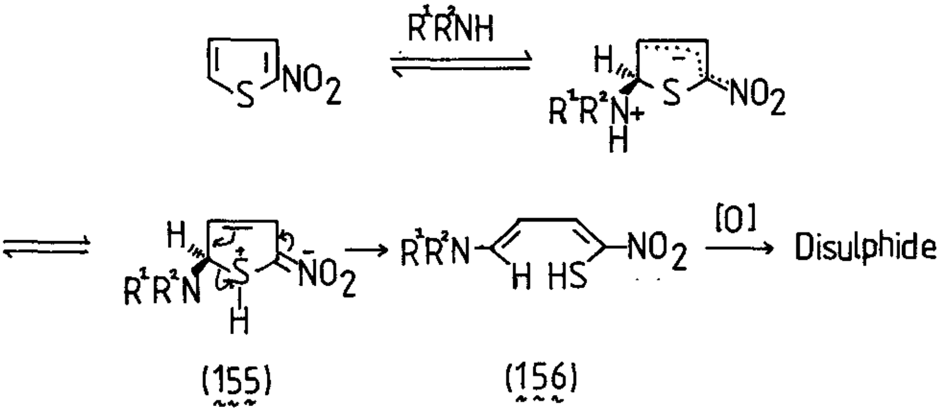
6. OTHER RING-OPENING REACTIONS

During the course of their extensive work on the nucleophilic substitution reactions of thiophenes an Italian group have isolated disulphides of the 4-dialkylamino-1-nitrobuta-1,3-dienes (156) by reaction of 2-nitrothiophene with various secondary amines in ethanol.[123] The reaction



SCHEME 41

proceeds (Scheme 42) by initial attack of the amine in the 5-position followed by a rapid proton

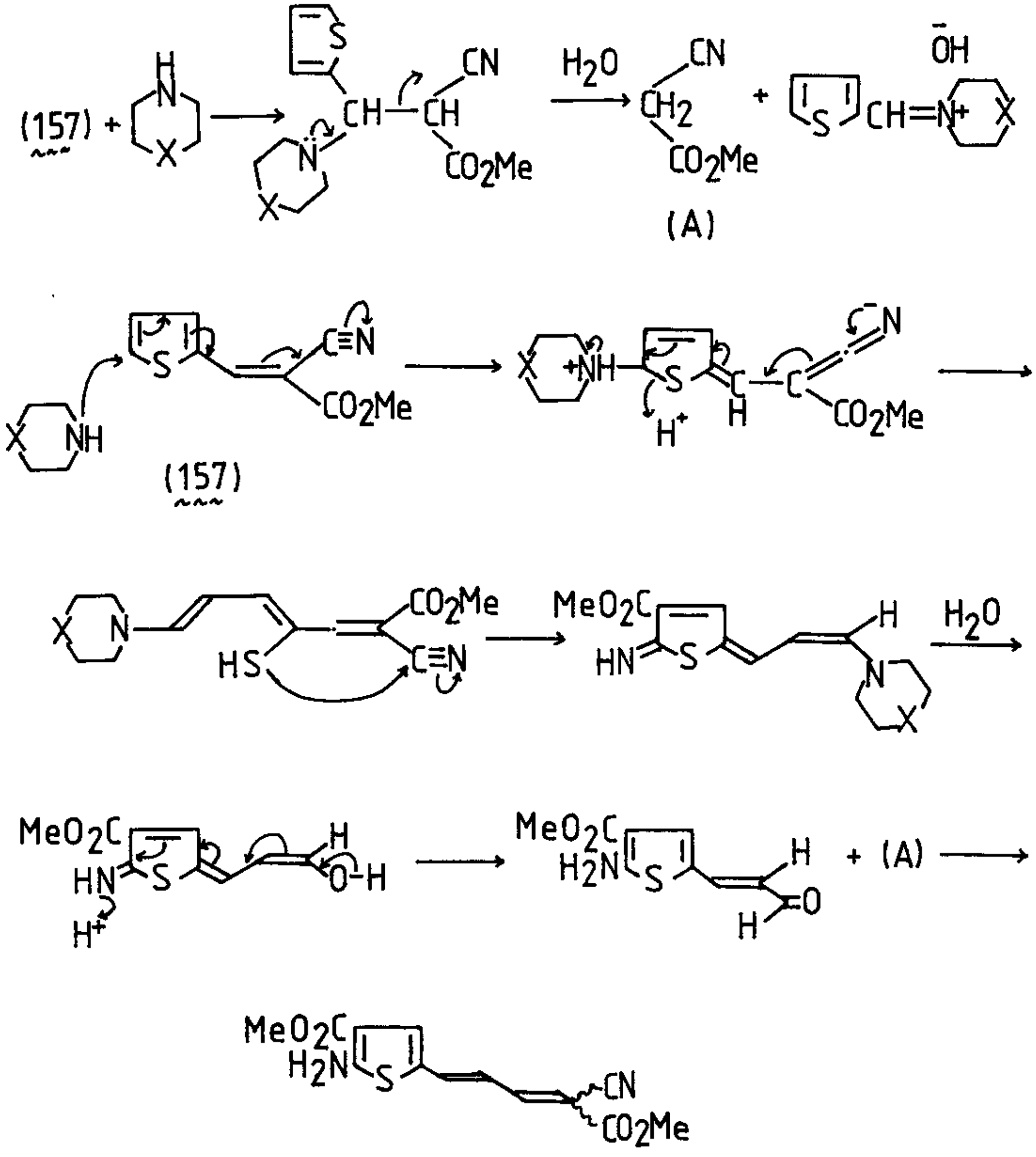


SCHEME 42

transfer and stereospecific ring-opening of the intermediate sulphonium-type intermediate (155). *3,4-Dinitrothiophene similarly undergoes ring-opening reactions* with various secondary amines, e.g. with piperidine it gives 2,3-dinitro-1,4-bis(piperidino)buta-1,3-diene.[124]

Initial attack of piperidine or morpholine at the 5-position of methyl α-cyano-β-(2-thienyl)-acrylate (157) is postulated as the first stage in one of the complex series of reactions (Scheme 43) leading to the formation of methyl 5-(5-amino-4-methoxycarbonyl-2-thienyl)-2-cyano-penta-2,4-dienoate (158).[125]

With alkali metal salts of secondary amines benzo[*b*]thiophene and its 3-methyl-derivative gives the corresponding 2-amino-2,3-dihydrobenzo[*b*]thiophene, presumably *via* nucleophilic attack at the

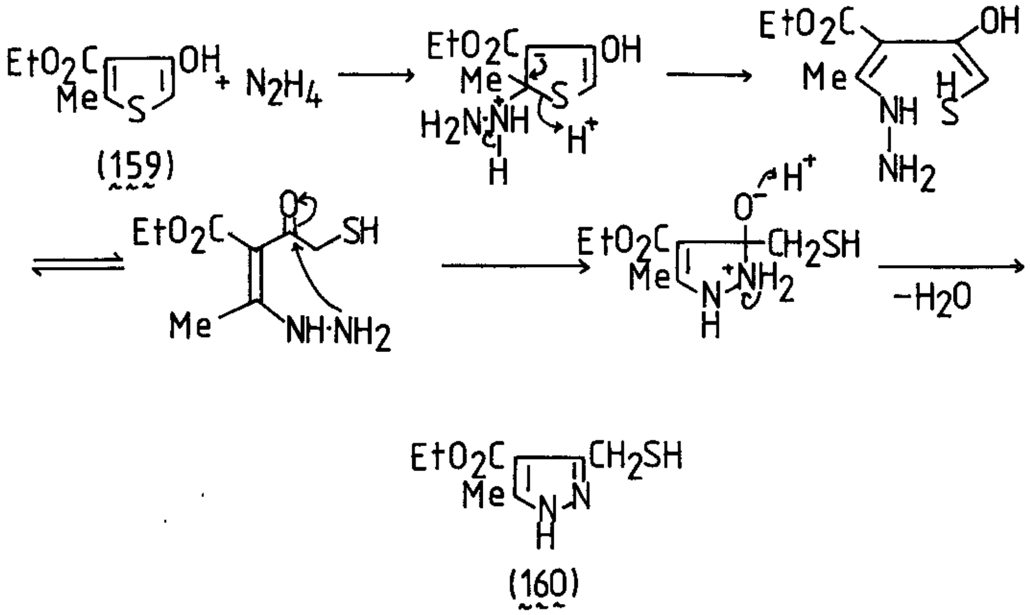


(158) (X = O, CH_2)

SCHEME 43

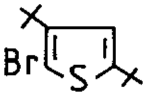
2-position followed by protonation of the resulting 3-carbanion by the excess of amine.[126] Similar reactions with low molecular weight primary amines result in fragmentation of the thiophene ring.[126]

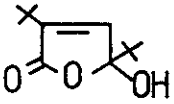
Hydrazine reacts with the thiophene (159) to give the pyrazole (160), presumably *via* an initial nucleophilic attack followed by the ring-opening/ring-closure sequence shown in Scheme 44.[127]



SCHEME 44

Bromination of 2,4-di-t-butyl-5-bromothiophene (161) using vigorous conditions (Br_2-AcOH-HNO_3-$AgNO_3$) converts it into the γ-lactone (162) via the first ring-opening of a thiophene to be reported.[128]


(161)


(162)

The reduction of thiophenes by alkali metals in liquid ammonia (Birch reduction) has been studied by Gold'farb's group in Russia.[129] Reduction of thiophene-2-carboxylic acids[5] in this way has attracted a lot of interest recently.[5,129-131] With an excess of lithium and an alcohol as a proton donor the product is a 5-mercaptopent-3-enoic acid[130] but careful control of the conditions allows 2,5-dihydrothiophene-2-carboxylic acids to be obtained in good yield.[131] Reduction of thiophenes with lithium in ammonia followed by hydrolysis provides a useful synthesis of variously substituted ketones.[5] Since these ring-opening reactions involve the intermediacy of an isolable, non-aromatic dihydrothiophene and because such process have been reviewed recently[5] we do not intend to comment further. Electrolytic oxidation of several thiophenes also leads to ring opened products.[132]

We referred before to the unusual oxidative ring-cleavage reaction of the thiophene ring in

2,5-dimethoxythiophene in the presence of 4-phenyl-1,2,4-triazoline-3,5-dione and methanol (Scheme 15).

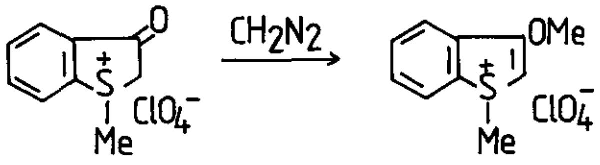
7. C-2 PROTONATION OF THIOPHENES

Several thiophenes are protonated directly at C-2 either in fluorosulphonic[133] or hydrofluoric acid[134] at low temperatures (e.g. -70°C), or in a mixture of hydrochloric acid, aluminium chloride, and dichloromethane.[135,136] Reduction of the resulting thiophenium salts (see also next Section) with triethylsilane yields the corresponding derivative of 2,3,4,5-tetrahydrothiophene.[136]

8. REACTIONS OF THIOPHENES AT THE SULPHUR ATOM

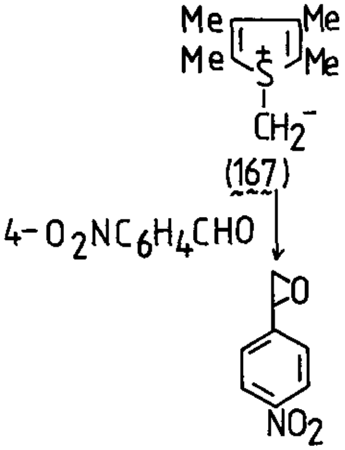
Alkylation at sulphur in thiophenes and benzo[b]thiophenes can be achieved with trialkyloxonium tetrafluoroborates,[137,138] alkyl halides in the presence of silver perchlorate or tetrafluoroborate,[135,137-139] alkyl fluorosulphonates,[138,139] O-methyldibenzofuranium tetrafluoroborate.[140] With methyl iodide and silver perchlorate 3-methoxybenzo[b]thiophene yields the salt (163) which gives the benzo[b]thiophenium salt (164) with diazomethane,[141] whilst salts (165; X = PF_6 or ClO_4) have been synthesised by intramolecular cyclisation of 4-(3-methyl-2-benzo[b]thienyl)butyl iodide with silver hexafluorophosphate or perchlorate.[142]

The physical and chemical properties of S-alkyl-thiophenium and -benzo[b]thiophenium salts indicate a loss of aromaticity in the thiophene ring.[138,139] Consequently irradiation of S-alkylthiophenium salts gives high yields of the isomeric thiophenium salts (166) (see also previous Section).[133] S-Alkylthiophenium salts do not appear to undergo Diels-Alder reactions[139] although they are strong alkylating agents.[138] 1,2-Dimethylthiophenium iodide appears to undergo a ring-opening reaction.[138] Semi-empirical calculations (Pople CNDO/2) of barriers to pyramidal inversion have been made for S-alkylthiophenium cations which agree in some cases with experimental observations.[143]

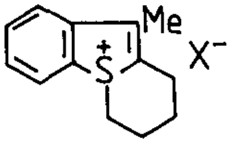


(163)

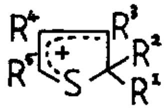
(164)



(168)

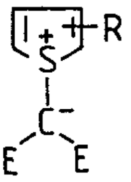


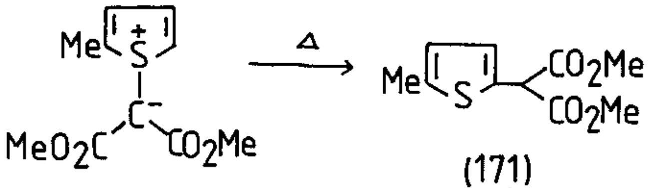
(165)



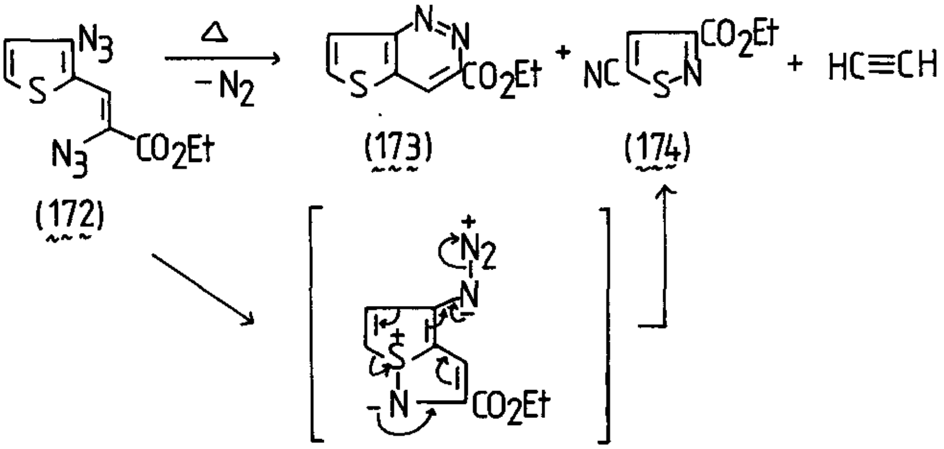
(166)

The thiophenium methylide (167) is formed when 1,2,3,4,5-pentamethylthiophenium hexafluorophosphate is treated with n-butyl-lithium.[139] With p-nitrobenzaldehyde it yields the epoxide (168). Similar ylides (169) are formed when thiophenes (or benzo[b]thiophenes) react with esters of diazomalonic acid under photochemical conditions[144] or in the presence of rhodium catalysts.[80,145,146] These ylides undergo a thermal rearrangement, e.g. (170) → (171).[146]


(169)


(170) (171)

The 3-azidothiophene (172) loses nitrogen and yields the thienopyridazine (173), isothiazole (174), and acetylene on pyrolysis in toluene or xylene; the isothiazole is thought to arise via intermediate (175) which collapses, as shown (Scheme 45).[147]

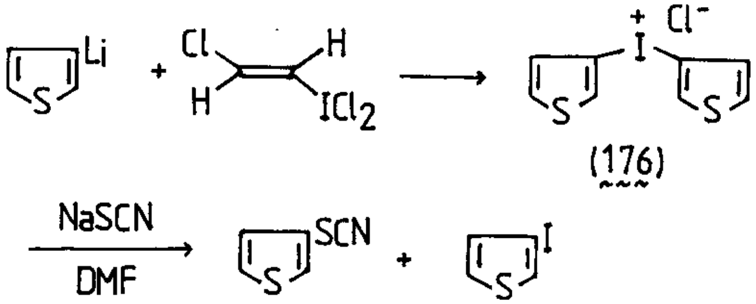

(172) (173) (174) (175)

SCHEME 45

9. INVERTED REACTIVITY OF THIENYL-LITHIUM COMPOUNDS

The synthesis of thiophenes by reactions of 2-(and 3)thienyl-lithium compounds with various electrophiles is well-known. Less well-known, however, is the reaction of these lithium compounds with trans-chlorovinyl iodosodichloride, which yields iodonium salts, e.g. (176) in Scheme 46, capable of reaction with nucleophiles.[93,148-152]

Finally, in connection with lithiated thiophenes, mention should be made of the synthesis of polylithiated thiophenes,[153] e.g. tetralithiothiophene, since little use has been made of these

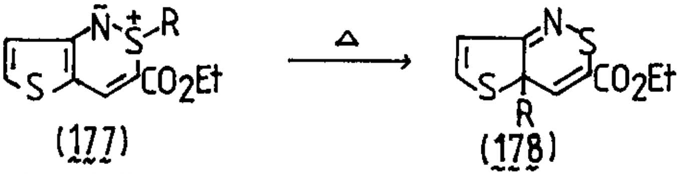


SCHEME 46

compounds in synthesis.

10. MISCELLANEOUS REACTIONS

A [1,4]-shift of the sulphur substituent (R = Me or Ph) occurs when the ylides (177) are heated, to give products (178) in which the aromaticity of the thiophene ring has been lost.^{154}



Low yields of pyrroles are obtained on irradiation of thiophenes in primary amines, e.g. n-propylamine, possibly by the intermediacy of a thioaldehyde or thioketone (Scheme 47) or by the mechanism shown in Scheme 48.^{155}

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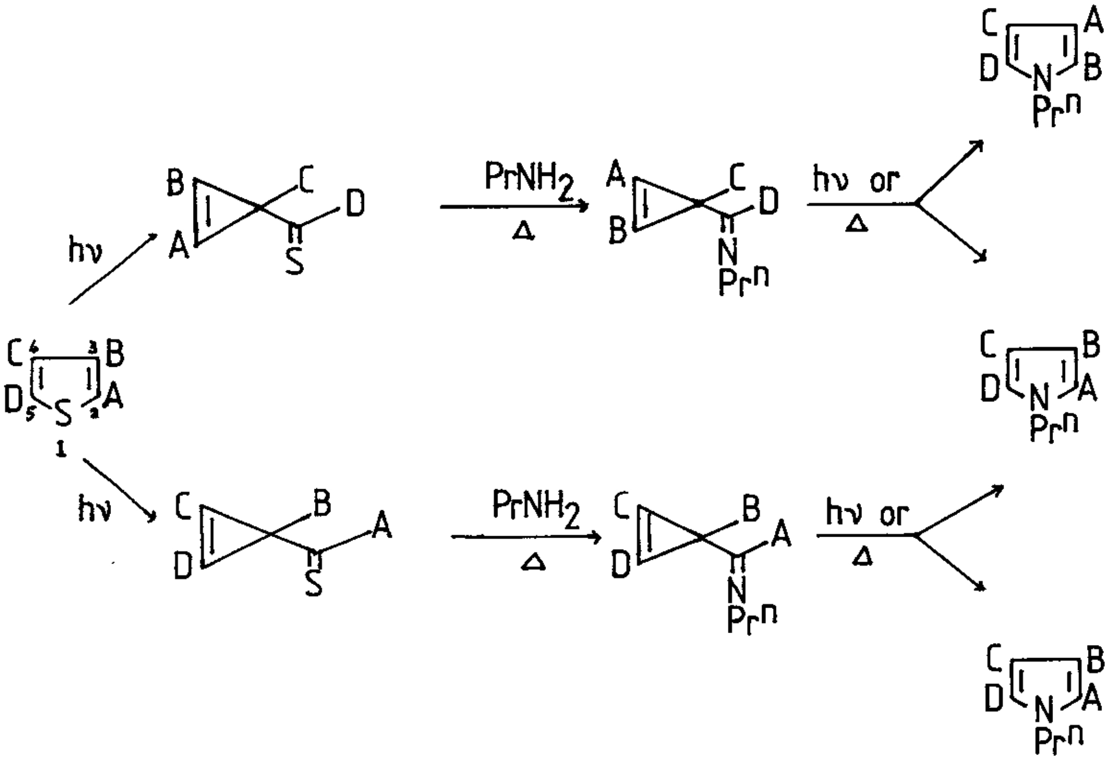
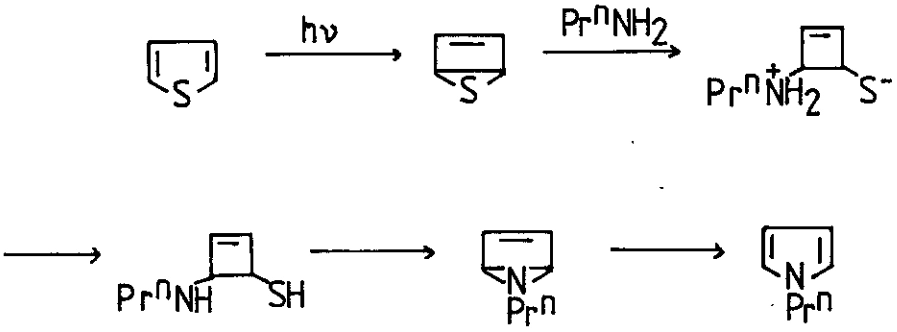


SCHEME 47



SCHEME 48

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