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Ibrahim A. El-Sakka[a]; Nasser A. Hassan[b]
[a] Department of Chemistry, Faculty of Science, Menoufia University, Shebin El Kom, Egypt [b] National Research Centre, Dokki, Cairo, Egypt

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REVIEW

Synthetic uses of thionyl chloride

IBRAHIM A. EL-SAKKA† and NASSER A. HASSAN*‡

†Department of Chemistry, Faculty of Science, Menoufia University, Shebin El Kom, Egypt
‡National Research Centre, Dokki, Cairo, Egypt

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1. Introduction

Synthetic organic chemistry involves specially designed reagents which are readily generated and used for further exploitation. An important example of such a reagent is thionyl chloride. An enormous number of reports on the utility of this reagent have been published. The emphasis of this review is placed on the literature published since a previous review in 1980 [1], which dealt mostly with the reactions of active methylene compounds.

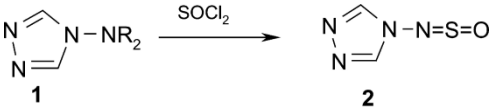
In this review we deal also with *O*- and *N*-nucleophiles. Patents have in general been ignored to keep the bulk of this review manageable.

2. Reaction with nitrogen nucleophiles

Thionyl chloride reacts with amines, imines, hydrazines, and related compounds to give open-chain or heterocyclic compounds.

2.1 *With amines*

Reaction of 4-amino-1,2,4-triazole **1a** or its bis(trimethylsilyl) derivative **1b** with thionyl chloride gave 4-(sulfinylamino)-1,2,4-triazole **2** [equation (1)] [2].



1 **2** (1)

a: R = H (55%)
b: R = $Si(CH_3)_3$ (77%)

*Corresponding author. Email: nasserabdelhamid@hotmail.com

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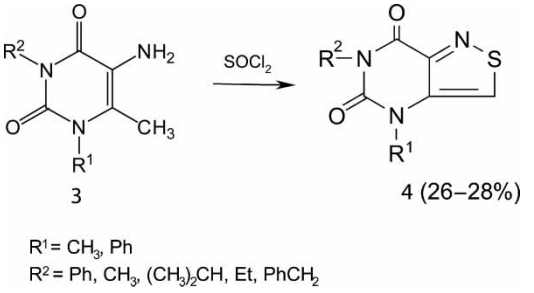
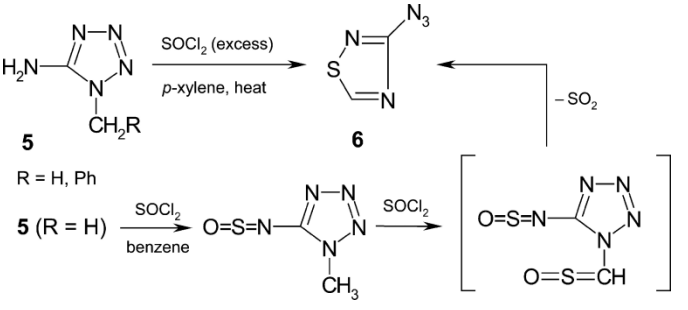
Aminouracils **3** reacted with thionyl chloride to yield isothiazolopyrimidines **4** [equation (2)] [3].



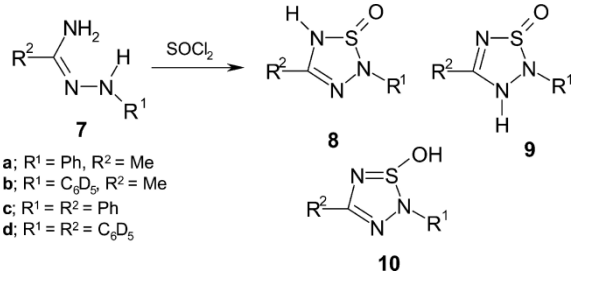
(2)

Heating of some 1-alkyl-5-aminotetrazoles **5** with thionyl chloride gave 3-azido-1,2,4-thiazoles **6** in a reaction involving the 5-(sulfinylamino)tetrazole as an intermediate (Scheme 1) [4].



SCHEME 1

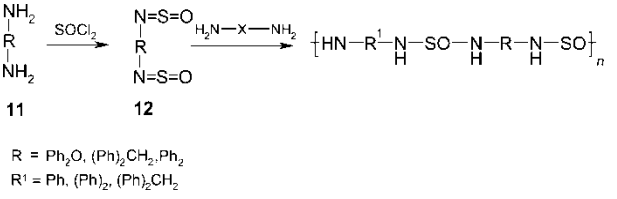
Substituted amidrazones **7** react with thionyl chloride in the presence of pyridine to give the corresponding 1,2,3,5-thiatriazole derivatives as the main products. These compounds can exist in various tautomeric forms, *e.g.*, as 2,5-dihydro- **8**, 2,3-dihydro-1,2,3,5-thiatriazole 1-oxide **9**, or 2*H*-1,2,3,5-thiatriazol-1-ium hydroxide [5]. The last form can, more likely, exist as structure **10** [equation (3)]. The tautomeric form in the crystal was established by X-ray structure determination of compound **8c**, which clearly revealed a 2,5-dihydro structure [equation (3)] [4].



(3)

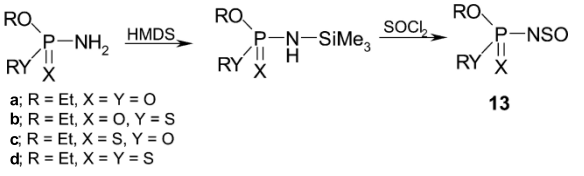
Monomers with two sulfinylimine functionalities have been reported. They react with appropriate aromatic diamines to give a new class of polymers having the sulfurous diamide

(-HN-SO-NH-) functional group in their backbone [equation (4)] [6].



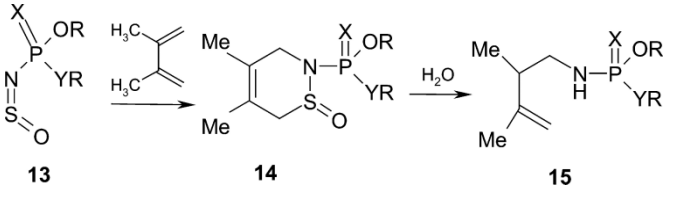
(4)

N-(Trimethylsilyl)amidophosphoric acid *O*,*O*-diethyl esters reacted with thionyl chloride to afford the *N*-sulfinyl compounds **13** [equation (5)].



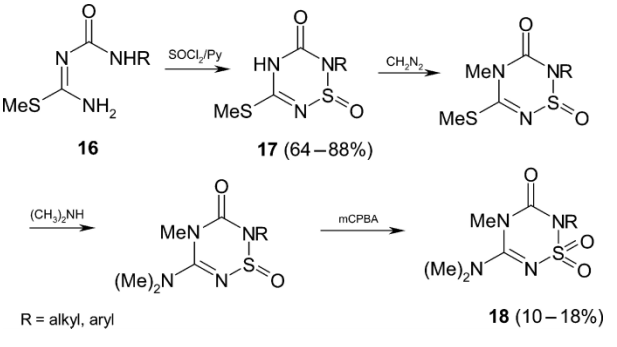
(5)

Compounds **13** were used in cycloadditions with 2,3-dimethylbutadiene to give *N*-phosphorylated 3,6-dihydro-1,2-thiazine 1-oxides **14** together with the open-chain *N*-phosphorylated 2,3-dimethylbut-3-enylamides **15** as by-products [equation (6)] [7].



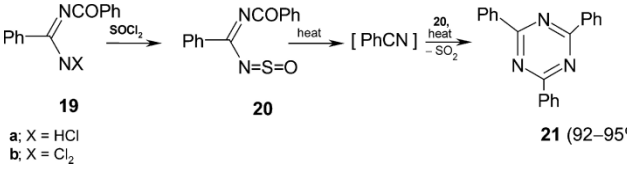
(6)

Treatment of 1-carbamoyl-2-methylisothioureas **16** with thionyl chloride gave the thiatriazinone oxides **17**, which were *N*-methylated with diazomethane, further treated with Me_2NH, and finally oxidized with *m*-chloroperoxybenzoic acid to give dioxides **18** [equation (7)] [8].



(7)

The 1,3,5-triazine **21** was obtained by reaction of the benzoylbenzamidine **19** with excess of thionyl chloride. The reaction takes place *via* the formation of sulfinylamine **20** [equation (8)].

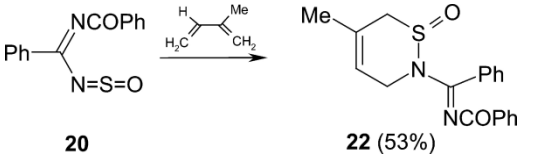


19 **20** **21** (92–95%)

a; X = HCl
b; X = Cl_2

(8)

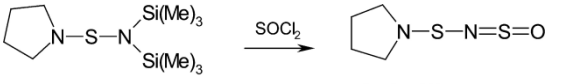
In the presence of pyridine, intermediate **20** was formed and decomposed with the formation of **21** when heated in benzene or CCl_4. The structure of **20** was confirmed by its conversion into stable adduct **22** through reaction with isoprene [equation (9)] [9].



20 **22** (53%)

(9)

Sulfoxylic diamides **23** and **24** were treated with thionyl chloride to give the *N*-sulfinyl derivatives **25** and **26**, respectively [equations (10) and (11)] [10].



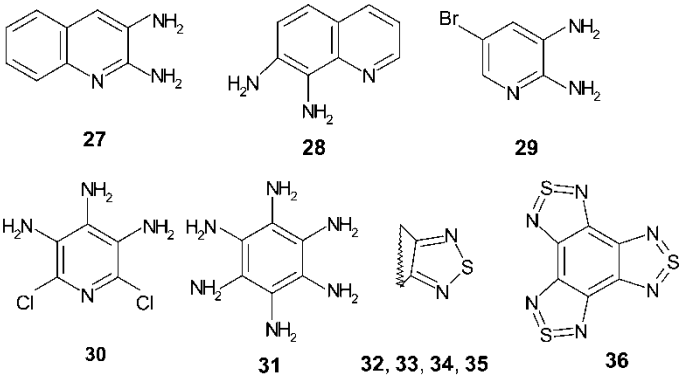
23 **25** (54%)

(10)

24 **26** (52%)

(11)

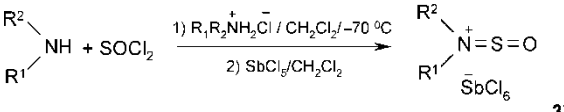
Thionyl chloride reacts with *o*-diaminoarenes **27–31** to give fused thiadiazolo derivatives **32–36** respectively (Scheme 2) [11–13].



SCHEME 2

N-Alkyl-*N*-sulfinylalkanaminium salts are useful reagents for dialkylamino-group transfer and in cycloaddition reactions [14–16]. A simple method for the preparation of

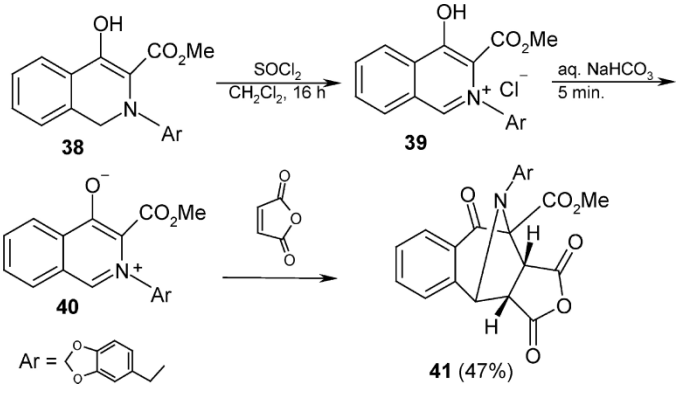
N-alkyl-*N*-sulfinylalkanaminium hexachloroantimonates **37a–d** has been reported [17] *via* reaction of dialkylamines with thionyl chloride.



a; $R^1 = R^2 = Et$ (75%)
b; $R^1 = R^2 = Me_2CH$ (71%)
c; $R^1R^2 = (CH_2)_5$ (71%)
d; $R^1R^2 = (CH_2)_2O(CH_2)_2$ (66%)

(12)

The addition of thionyl chloride to the dihydroisoquinoline **38** gave the isoquinolinium chloride **39**, which is readily converted into the corresponding ylide **40** upon treatment with $NaHCO_3$. This ylide undergoes simple 1,3-dipolar addition with dimethyl acetylenedicarboxylate, maleic anhydride, and acrylonitrile, respectively, to afford the corresponding benzocycloheptanone cycloadducts. Thus, addition of **40** to maleic anhydride gave adduct **41** (Scheme 3) [18].



SCHEME 3

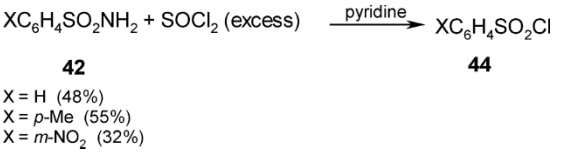
Reaction of *N′*-(4-nitrophenylsulfanyl)morpholine, *N*,*N′*-sulfanediylbismorpholine and *N*,*N′*-disulfanediylbismorpholine with thionyl chloride or sulfuryl chloride at 40 °C afford electrophilic chlorosulfenylating reagents, which add to the C=C bond of norbornene in high yields. Semiempirical quantum-chemical calculations and comparison of the relative reactivity of the sulfenylating complexes formed upon activation of arenesulfenamides by sulfur and phosphorus oxohalides were performed. The mechanism of these reactions has been discussed [19].

2.2 *With sulfonamides*

Arenesulfonamides **42** are well known to react with thionyl chloride to give the corresponding *N*-sulfinyl compounds **43**, which are useful reactive intermediates [equation (13)] [20–22].

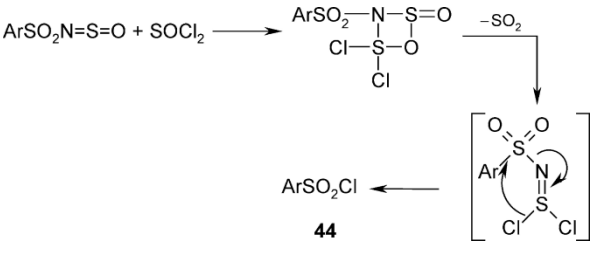
$$\underset{\mathbf{42}}{ArSO_2NH_2} + SOCl_2 \longrightarrow \underset{\mathbf{43}}{ArSO_2N{=}S{=}O} + 2\,HCl \qquad (13)$$

With more than one mole of thionyl chloride the corresponding arenesulfonyl chloride is produced [equation (14)] [23].



(14)

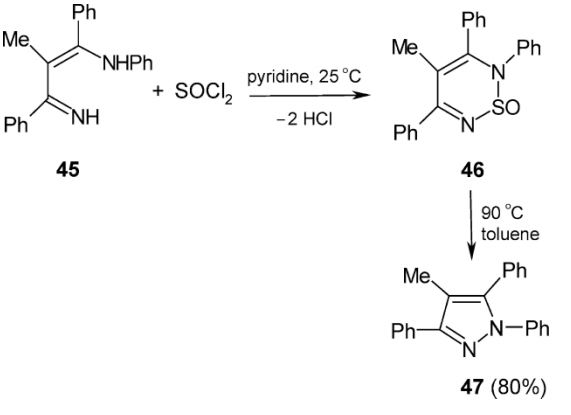
The mechanism of formation of **44** can be outlined as follows [equation (15)].



(15)

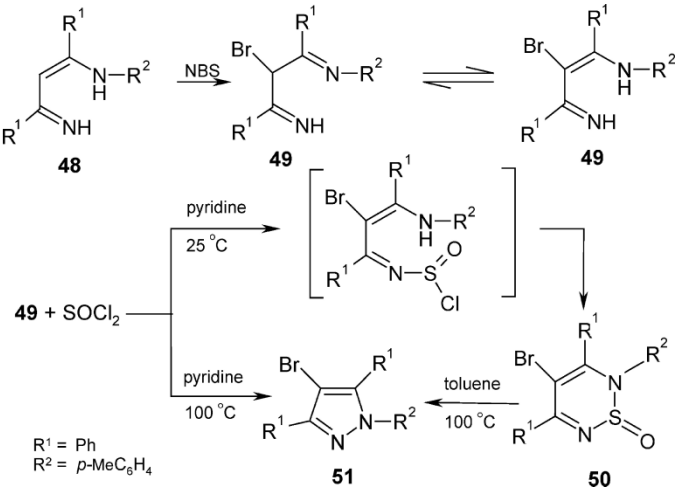
2.3 *With imines*

Thionyl chloride is one of the most common reagents used in the synthesis of heterocycles containing sulfur *via* condensation reactions [24]. Diimines, *e.g.* **45**, react with thionyl chloride, giving rise to 1,2,6-triazine *S*-oxides such as **46** in high yield. On heating, 3-pyrazoles **47** are obtained in high yield *via* thermal extrusion of SO [equation (16)] [25].



(16)

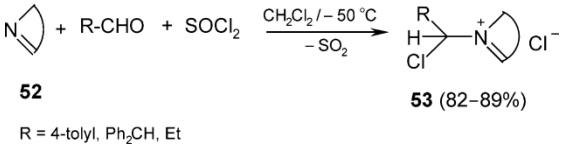
The monohalogenated diimine **49**, prepared by halogenation at the C_β-enaminic C-atom of the azabutadiene derivative **48**, underwent cyclocondensation with thionyl chloride in pyridine at 25 °C and at 100 °C to give 78% thiadiazine S-oxide **50** and 80% bromopyrazole **51**, respectively (Scheme 4) [26].



SCHEME 4

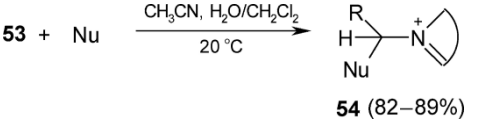
2.4 *Three-component reactions*

The three-component reaction of (un)substituted pyridine, 1-methylimidazole, or isoquinoline **52** with RCHO in the presence of thionyl chloride gave the corresponding azirenium chloride **53** [equation (17)].



(17)

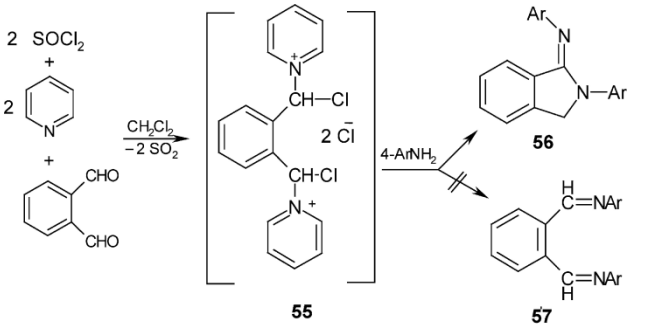
Substitution of **53** with some nucleophiles gave **54** [equation (18)] [27].



(18)

The (arylimino)isoindoles **56** can be synthesized by reaction of primary aromatic amines $ArNH_2$ (same R) with an azinium salt **55** obtained from thionyl chloride, pyridine, and benzene-1,2-dicarboxaldehyde [28]. Previous results [29,30] had shown that *N*-(1-halogenoalkyl)azinium halides react with primary amines to yield the

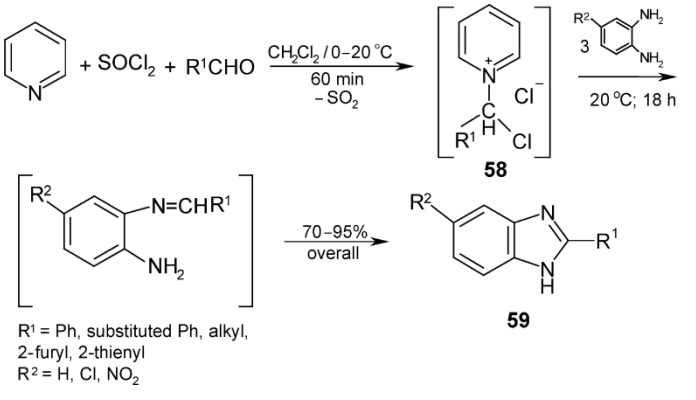
imines **57** [equation (19)].



(19)

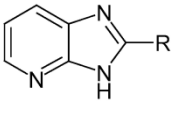
Ar = Ph (93%), 2-ClC$_6$H$_4$ (90%), 2-pyridyl (96%), 3 -O$_2$NC$_6$H$_4$ (95%), 3-pyridyl (92%), 4-methyl-2-pyridyl (90%)

N-(1-Halogenoalkyl)pyridinium halides **58** [30–33], prepared from pyridine, an aldehyde, and thionyl chloride, are advantageous precursors for the preparation of nitrogen heterocycles; *e.g.*, they react with *O*-phenylenediamine to give the 1*H*-benzimidazoles **59** (Scheme 5) [34].



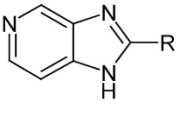
SCHEME 5

Similarly prepared are the imidazopyridines **60** and **61**.



60

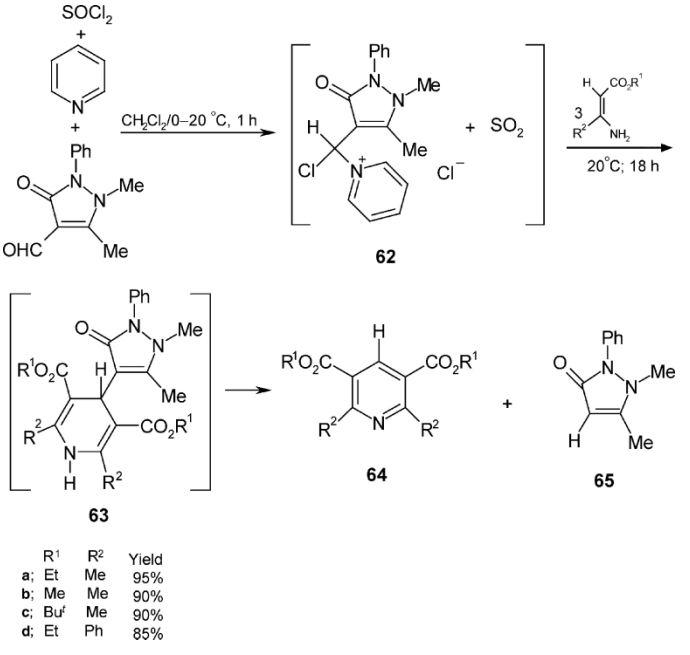
R = Ph, substituted Ph, 2-thienyl



61

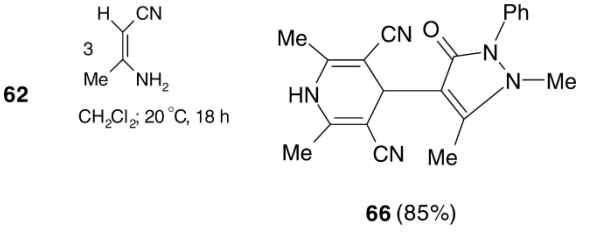
R = 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$

Under acidic conditions, Hantzsch-type 4-'antipyrinyl'-1,4-dihydropyridines **63** undergo elimination of the 4-substituent to yield the 4-unsubstituted pyridine **64** and the antipyrine **65** (Scheme 6) [35].



SCHEME 6

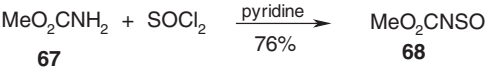
On the other hand, starting from **62** and 3-aminobut-2-enenitrile, the less hindered **66** was isolated, and no loss of the antipyrinyl moiety occurred [equation (20)]. Therefore, together with the formation of an aromatic pyridine, the driving force for the expulsion of the azole could be the relief of steric interaction [36] with the flanking ester group in intermediate **63**.



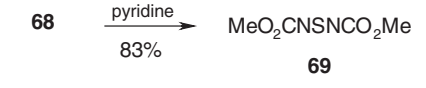
(20)

2.5 *With carbamates*

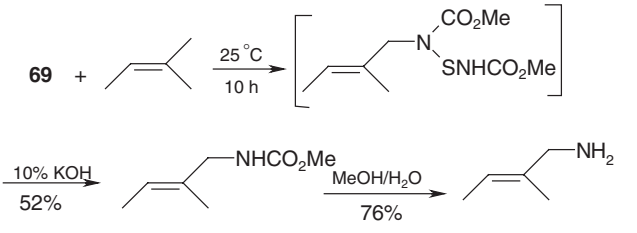
Methyl carbamate **67** reacts with thionyl chloride in pyridine to afford methyl *N*-sulfinylcarbamate **68** [equation (21)]. Even minute amounts of pyridine catalyze the conversion of **68** into *N*,*N*′-bis(methoxycarbonyl)sulfur diimide **69** [equation (22)], a reagent used for allylic amination [equation (23)] [37].



(21)

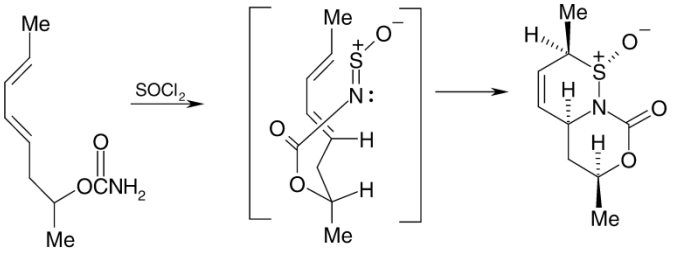


(22)



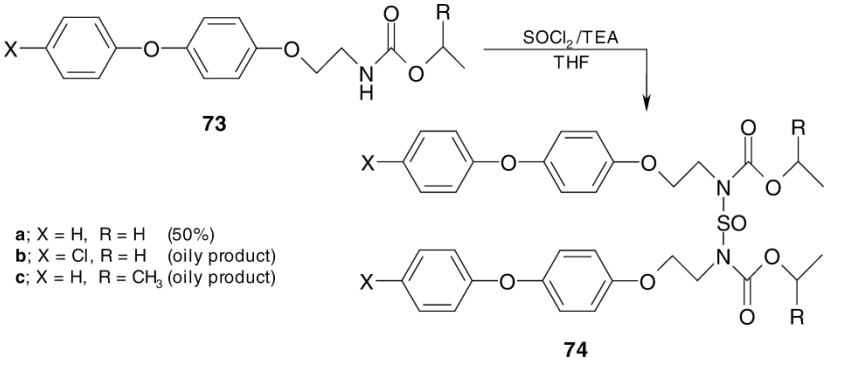
(23)

When carbamate **70** was treated with thionyl chloride/pyridine, a single Diels–Alder adduct **72** was formed *via* a stereoselective cycloaddition [equation (24)]. The structure and stereochemistry of this dihydrothiazine oxide was determined by single-crystal X-ray analysis [38].



(24)

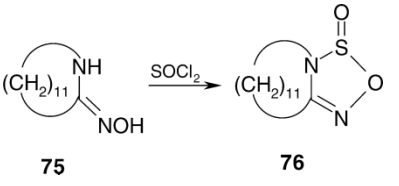
Sulfinylated derivatives of phenoxycarbamates have been prepared and evaluated for juvenile-hormone-mimicking activity. Thus, the carbamates **73** were treated with thionyl chloride to give the sulfinyl derivatives **74** [equation (25)] [39].



(25)

2.6 *With oximes*

Dehydration of aromatic as well as aliphatic aldoximes using a thionyl chloride–benzotriazole combination in dry dichloromethane proceeds smoothly at room temperature to give the corresponding nitriles in high yields (>90%) in short times (approx. 20 min) [40]. The cyclic aldoxime **75** reacted with thionyl chloride to yield the oxathiadiazoline S-oxide **76** [equation (26)] [41].



(26)

2.7 *With hydrazines and hydrazides*

1-Acyl-2-(*p*-tolylsulfonyl)hydrazines **77** react with thionyl chloride, giving the corresponding chloro derivatives **78** [equation (27)] [42].

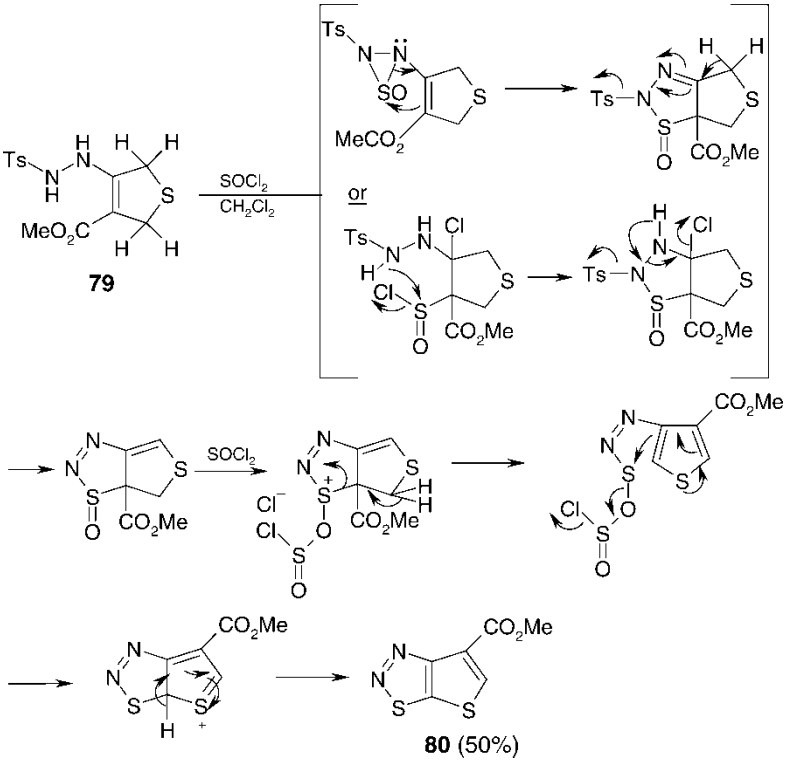
$$\underset{\textbf{77}}{\text{RCONHNHTs}} \xrightarrow{SOCl_2} \underset{\textbf{78}\ (10\text{–}60\%)}{\text{RC(Cl)=NNHTs}} \qquad (27)$$

R = Alkyl, aryl

This is in contrast to the reaction of **77** with S_2Cl_2, which leads to $N-N$ bond cleavage [equation (28)] [43].

$$\underset{\textbf{77}}{\text{RCONHNHTs}} \xrightarrow{S_2Cl_2} RCONH_2 + TsNH_2 \qquad (28)$$

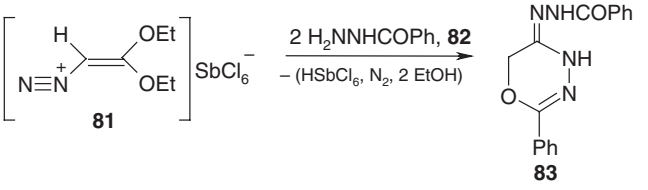
When the substituted hydrazide derivative **79** was treated with an excess of thionyl chloride in dichloromethane at room temperature for 8 h then thieno[3,2-*d*]-1,2,3-thiadiazole-6-carboxylic acid methylester **80** was obtained in 65% yield (Scheme 7) [45]. Although the synthesis of the same heterocyclic system has been reported by Paulmier [46], this approach is completely different from the previous one and gives a better yield [47].



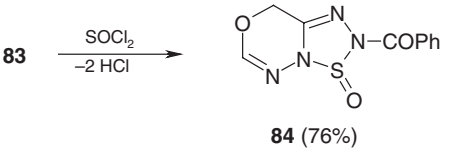
SCHEME 7

2.8 *With hydrazones*

The reaction of 2,2-diethoxyethene-1-diazonium salt **81** with the hydrazide **82** formed the oxadiazinone benzoylhydrazone **83** [equation (29)]. This was transformed by reaction with thionyl chloride to give **84** [equation (30)] [48].

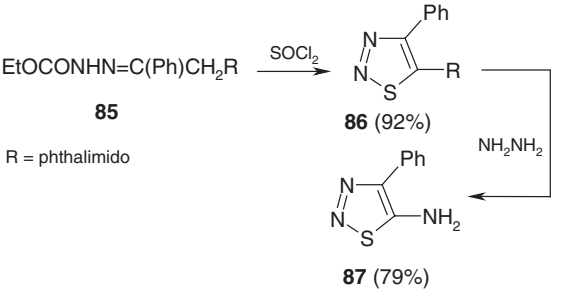


(29)



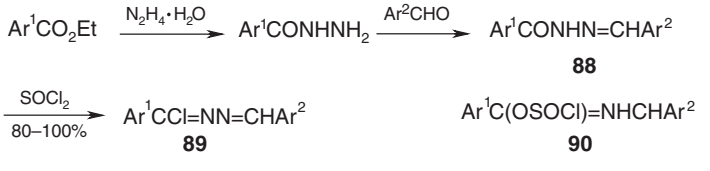
(30)

5-Aminothiadiazoles **87** have been prepared by treatment of 2-phthalimidoacetophenone ethoxycarbonylhydrazone **85** with thionyl chloride, to give **86**, followed by removal of the phthalimido group with hydrazine [equation (31)] [49].



(31)

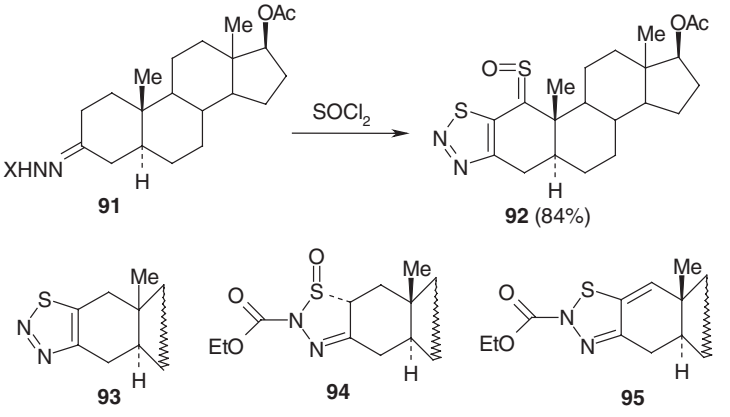
Reaction of thionyl chloride with the aroylhydrazones **88** gave the 1-chloro-1,4-diaryl-2,3-diazabutadienes **89**. This is consistent with a mechanism that involves decomposition of the intermediate chlorosulfite **90** (Scheme 8) [50].



SCHEME 8

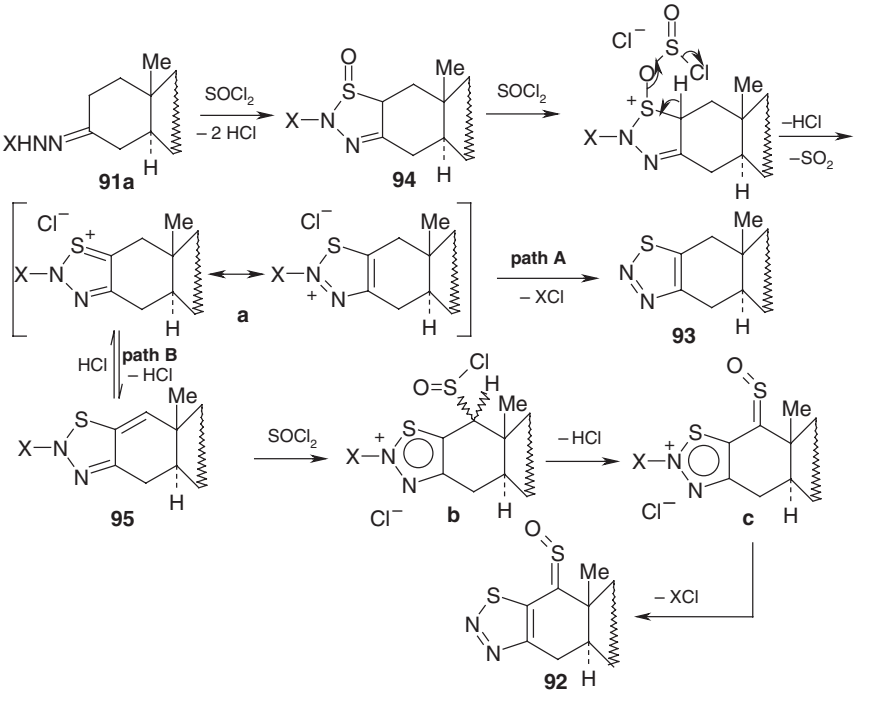
The reaction of 17β-acetoxy-5α-androstan-3-one (ethoxycarbonyl)hydrazone **91a** with neat thionyl chloride at 65 °C gave the thiadiazolethione *S*-oxide **92** in 84% yield. Under similar conditions the corresponding tosyl- and formyl-hydrazones afforded the thiazoles **93** and **94** in 84% and 85% yield, respectively, while the acetylhydrazone gave a mixture of both products. When **91** was treated with 2 equivalents of thionyl chloride at −20 °C, in addition to **92** and

93, the intermediates **94** and **95** were also isolated [equation (32)] [47].



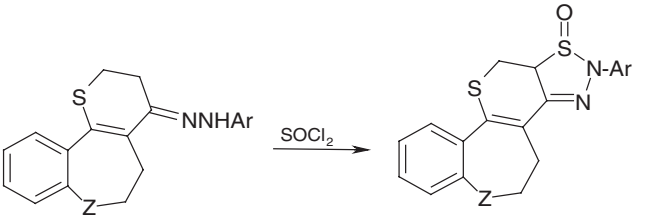
(32)

Based on the above and additional mechanistic studies, a mechanism for the formation of **92** and **93** from **91a** has been proposed (Scheme 9). The general behaviour of hydrazones with thionyl chloride is rationalized in the light of this mechanism.

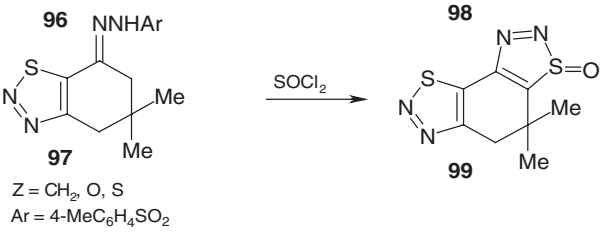


SCHEME 9

The thiazole derivatives **98** and **99** have been prepared from thionyl chloride and the tosylhydrazones **96** and **97**, respectively [equations (33) and (34)] [51].

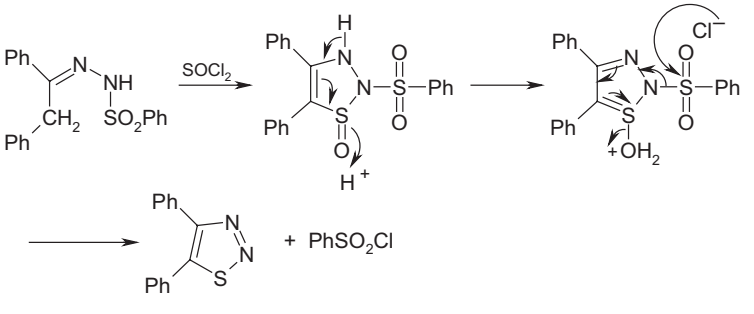


(33)



(34)

It has been reported [46] that thionyl chloride interacts with acyl hydrazones of the general stucture $R^1CH_2CR^2{=}NNH\text{-}X$ where X = CO_2Et, $COCH_3$, SO_2Ph, *etc.*, affording 1,2,3-thiadiazoles in good yields [equation (35)].



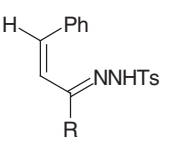
(35)

During an investigation of unsaturated *p*-tosylhydrazones [52], **100a** was treated with thionyl chloride and the side chain halogenated to yield the 1,2,3-thiadiazole **101**. The formation of **101** is easily explained by supposing that the necessary methylene group adjacent to the C=N bond is provided by the addition of hydrogen chloride (generated after the initial

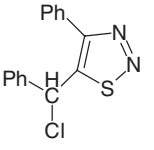
Table 1. Reaction of *p*-tosylhydrazones with thionydichloride

p-Tosylhydrazone	Time (*t*/min)	Product	Yield (%)
100a	45	**101**	40
100b	45	**102**	55
103	45	**105**	52
104	15	**106**	63
107a	15	**108a**	74
107b	30	**108b**	60
		109	26

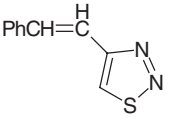
attack of thionyl chloride on the NH group) across the alkene double bond.



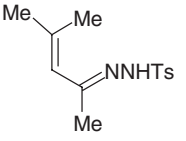
100a R = H
100b R = CH_3



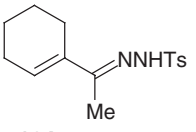
101 R = H



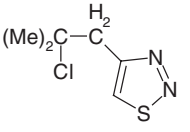
102



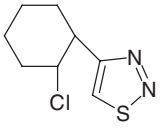
103



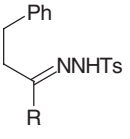
104



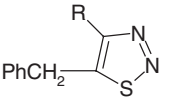
105



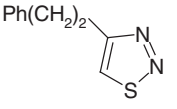
106



107a R = H
107b R = CH_3



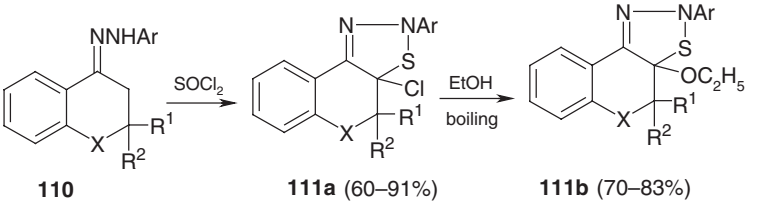
108a R = H
108b R = CH_3



109

If the azomethinic carbon is substituted with a methyl group as in the substrates **100b**, **103** and **104**, prepared from unsaturated ketones, the cyclization may occur without such a prior addition (Table 1). Addition of hydrogen chloride to the exocyclic C=C bond, after heterocyclic ring closure, is observed starting from substrates **103** and **104**, and β-chloroalkyl 1,2,3-thiadiazoles **105** and **106** are indeed isolated. This further transformation is not observed in the benzylideneacetone derivative **100b**, probably owing to the phenyl-alkene-thiadiazole conjugation. The corresponding saturated substrates **107a** and **107b** behave as expected. In the case of the ketone derivative **107b** a noteworthy ring closure with the methyl group is noted.

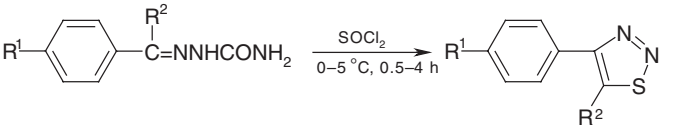
Some arylhydrazone derivatives **110** have been cyclized with thionyl chloride to give the chlorothiadiazoline derivatives **111a**. Surprisingly, the chlorine atom was found to undergo smooth nucleophilic substitution by boiling in absolute ethanol to give the corresponding ethoxythiadiazoline derivatives **111b** [equation (36)] [53].



110 **111a** (60–91%) **111b** (70–83%) (36)

a; X = CH_2 R^1 = CH_3, R^2 = C_2H_5 Ar = 4-$NO_2C_6H_4$
b; X = O R^1 = R^2 = CH_3 Ar = 4-$NO_2C_6H_4$
c; X = O R^1–R^2 = $(CH_2)_5$ Ar = 4-$NO_2C_6H_4$

Reaction of *p*-substituted acetophenone semicarbazones with thionyl chloride gave the corresponding thiadiazoles **112** [equation (37)] [54].

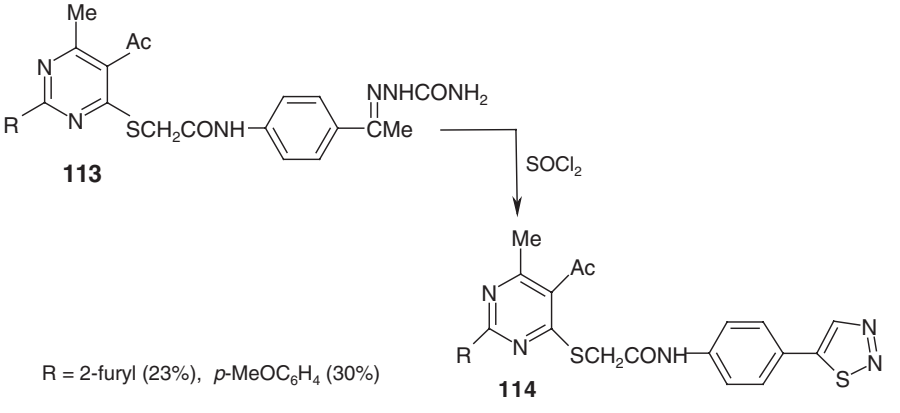


(37)

R^1 = H, Me, OMe, Cl, NO_2, Br, CN; R^2 = Me
R_1 = H, R^2 = CH_2Ph

112 (16–80%)

Some 1,2,3-thiadiazolopyrimidines **114** have been synthesized by cyclization of semicarbazones **113** with thionyl chloride [equation (38)] [55].



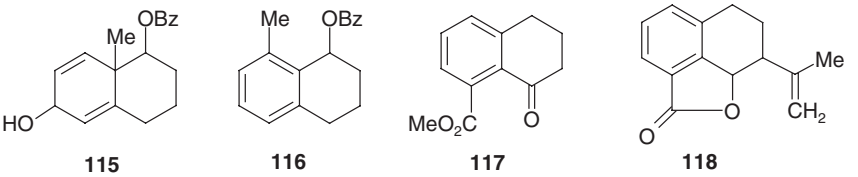
(38)

R = 2-furyl (23%), *p*-$MeOC_6H_4$ (30%)

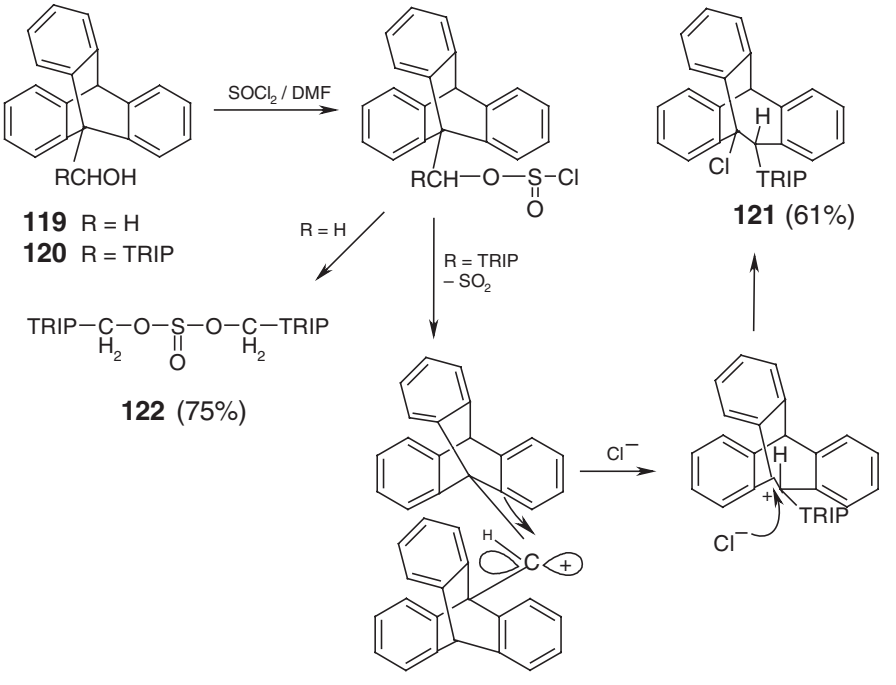
3. Reaction with *O*-nucleophiles

3.1 *With alcohols*

The cyclohexadienyl alcohol **115** on treatment with thionyl chloride and pyridine provided the tetrahydronaphthalene **116** whose transformation to the methoxycarbonyltetralone **117**, a key intermediate for platyphyllide **118**, has been accomplished in four steps [56].

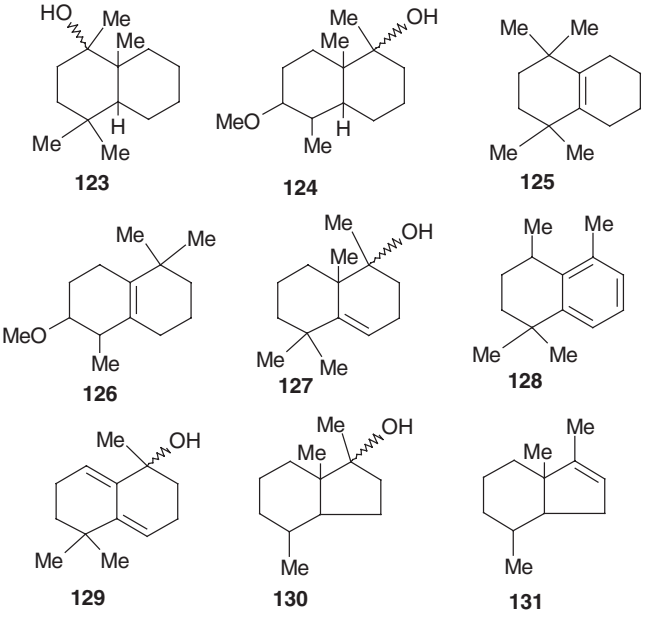


Reaction of the thionyl chloride–dimethylformamide reagent at 58 °C in deuteriochloroform with 1-triptycylcarbinol **119** and ditriptycylcarbinol **120** produced the sulfite ester **122** and the interesting rearranged compound 1-chloro-2-(1-triptycyl)tribenzobicyclo[3.2.2] nonatriene **121** respectively (Scheme 10) [57].



SCHEME 10

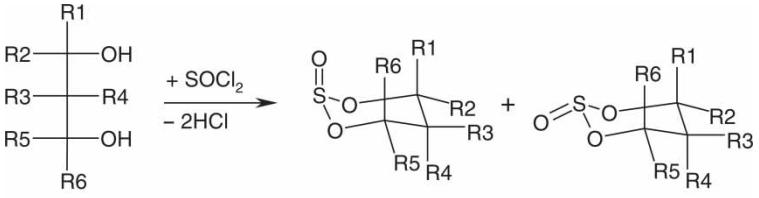
Tertiary alcohols **123** and **124** undergo rearrangement on treatment with thionyl chloride and pyridine, yielding **125** and **126** respectively. Alcohol **127** under similar treatment afforded a mixture of the tetrahydronaphthalene **128** and the hexahydronaphthalene **129**, whereas alcohol **130** suffered no rearrangement but produced olefins **131** [58].



Thionyl chloride is an efficient reagent for dehydration of tertiary alcohols. However, a number of tertiary alcohols undergo transformations with thionyl chloride, yielding unexpected products. These rearrangements are accompanied by aromatization, dehydrogenation, and migration of methyl groups and double bonds. In certain cases these transformations are accompanied by dimerization. The mechanistic interpretation of these transformations has been discussed briefly [59].

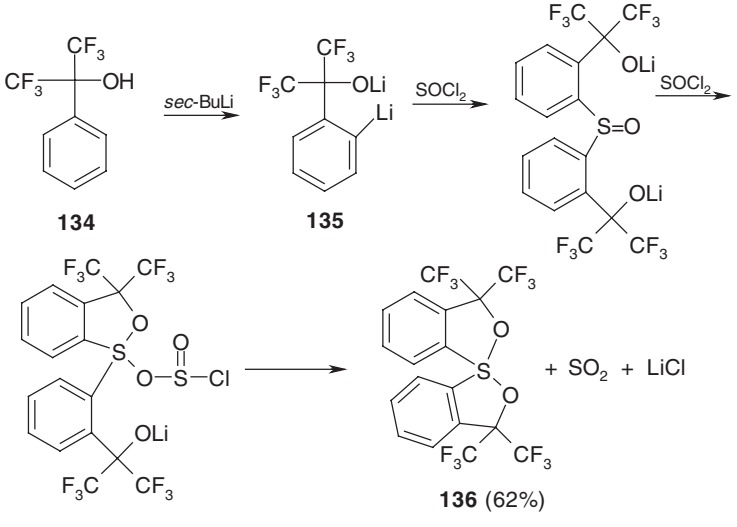
3.2 *With diols*

The 2-oxo-1,3,2-dioxathianes **133** have been synthesized by condensing alkane-1,3-diols **132** and thionyl chloride. The relative amounts of *SO* axial and *SO* equatorial isomers can be controlled by adding pyridine to the reaction mixture [equation (39)] [60].



132 **133a** **133e** (39)

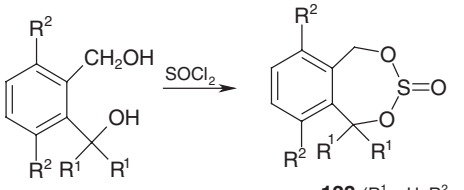
The dianion **135**, prepared from **134**, is a reagent for the simple introduction of a bidentate ligand which is particularly effective in stabilizing the higher co-ordination states of non-metallic elements. This reagent has been used to prepare a series of spiro compounds in which two of these ligands are attached to hypervalent sulfur. The reaction of **135** with excess of thionyl chloride gave the sulfurane **136** in higher yield (Scheme 11) [61].



134 **135** **136** (62%)

SCHEME 11

The dioxathiepines **138** and **139** were prepared by the action of thionyl chloride on 2,5-dimethyl-*o*-benzenedimethanol and α,α-dimethyl-*o*-xylene-α,α-diol, respectively [equation (40)].



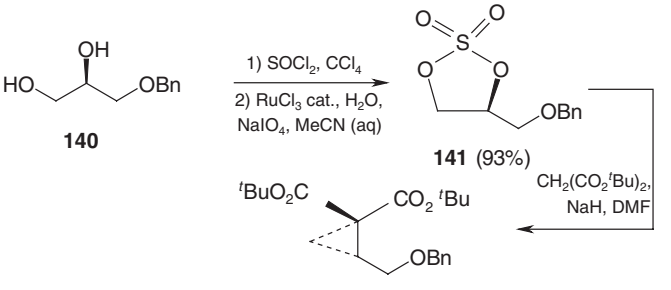
137

138 (R^1 = H, R^2 = Me) (25%)
139 (R^1 = Me, R^2 = H) (74%)

(40)

The conformations of **138** and **139** and their conformational inversion and inversion barriers were determined by ^{13}C and ^{1}H dynamic NMR (down to −148 °C). The IR spectra of **138** and **139** showed that the most stable conformations in 80:20 F_2CHCl–CD_2Cl_2 are 83% twist-boat and 17% chair with an axial *S*:*O* bond for **138**, and a twist-boat conformation for **139** [62].

The substituted glycerol **140** (Bn = benzyl) was treated with thionyl chloride and then oxidized with catalytic $RuCl_3$ to give a 93% yield of the cyclic sulfate **141**, which was treated with $Me_3CO_2CCH_2CO_2CMe_3$ in the presence of NaH to give a 76% yield of **142** [equation (41)] [63].



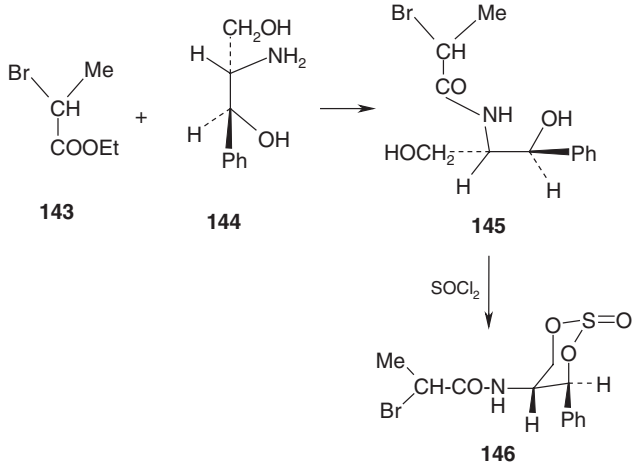
140

141 (93%)

142

(41)

The pair of crystalline diastereoisomers, (2′*R*,1*S*,2*S*)- and (2′*S*,1*S*,2*S*)-2-(2-bromopropanamido)-1-phenylpropane-1,3-diol **145a** and **145b** can easily be prepared from the corresponding bromo ester **143** and amino diol **144**. Compound **145b** was then converted with thionyl chloride into the diastereoisomer, (2′*S*,5*S*,6*S*)-5-(2-bromopropanamido)-6-phenyl-2-oxo-1,3,2-dioxathiane **146b** [equation (42)] [64].



143

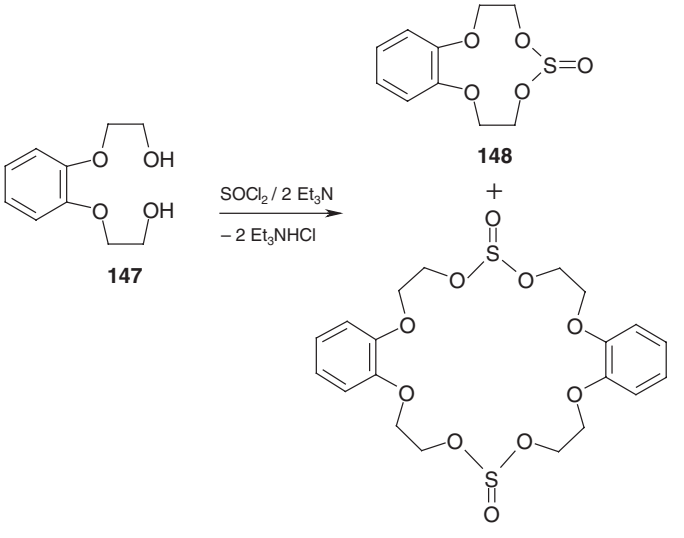
144

145

146

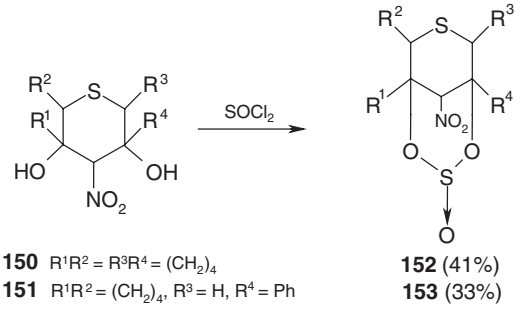
(42)

1,2-Bis-(2-hydroxyethoxy)benzene **147** reacts with thionyl chloride to give a mixture composed of **148** and the 22-crown ether **149** with one and two sulfinyl groups, respectively [equation (43)] [65].



(43)

On treatment of the nitroglycols **150** and **151** with thionyl chloride one obtains the corresponding cyclic sulfites **152** and **153**, which indicates a diaxial orientation of the hydroxy groups in the starting compounds [equation (44)] [66].

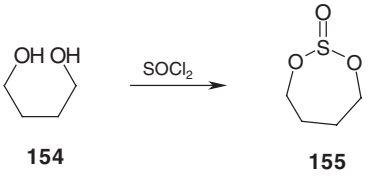


150 $R^1R^2 = R^3R^4 = (CH_2)_4$
151 $R^1R^2 = (CH_2)_4$, R^3 = H, R^4 = Ph

152 (41%)
153 (33%)

(44)

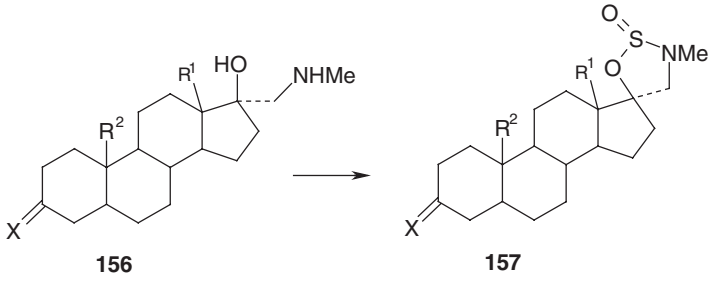
The seven-membered cyclic sulfite **155** has been prepared by reaction of butane-1,4-diol **154** with thionyl chloride in 50% yield [equation (45)] [67]. Compound **155** was used in cationic ring-opening polymerization.



154 **155**

(45)

3.3 *With amino alcohols*

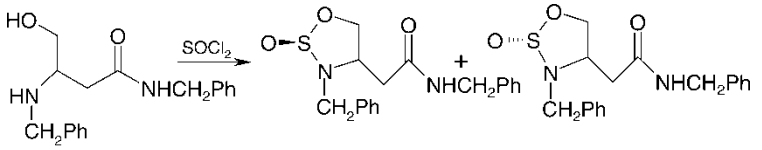


156 **157** (46)

Steroids **156** cyclize with thionyl chloride to give spiro-oxathiazolidine *S*-oxides **157** [equation (46)] [68].

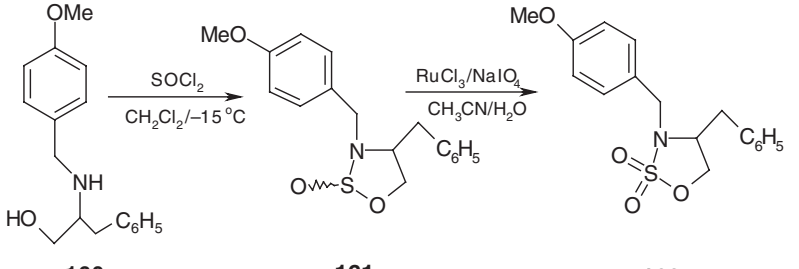
156, 157	R^1	R^2	X	Doppel-binding	Yield (%)
a	Et	–	CH_3O	2, 5 (10)	62
b	Me	–	CH_3O	2, 5 (10)	85
c	Me	–	CH_3O	1, 3, 5 (10)	73
d	Me	H	O	4	67
e	Me	Me	β-OH	5	67
f	Me	Me	β-CH_3O	5	89
g	Et	–	CH_3O	1, 3, 5 (10)	63

The reaction of *N*-benzyl-3-benzylamino-4-hydroxybutamide **158** with thionyl chloride resulted in formation of the oxathiazolidine oxide **159** [69]. The two sets of signals in the ^{1}H NMR spectrum of **159** may be explained by the presence of two configurational isomers, which is characteristic of heterocycles containing sulfoxide bonds [equation (47)].



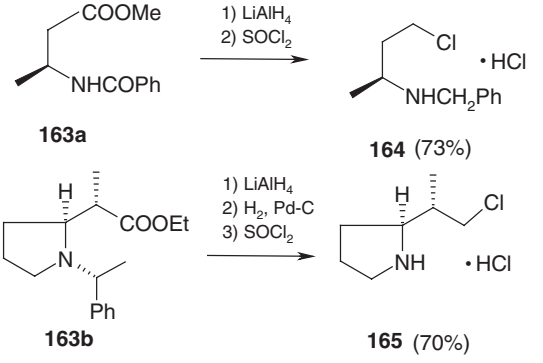
158 **159a** **159b** (47)

The cyclic sulfamate **161** has been prepared in 84% yield from the *N*-substituted 2-amino-3-phenylpropan-1-ol **160**. Oxidation with a ruthenium catalyst and periodate afforded **162** in 84% yield [equation (48)] [70].



160 **161** **162** (48)

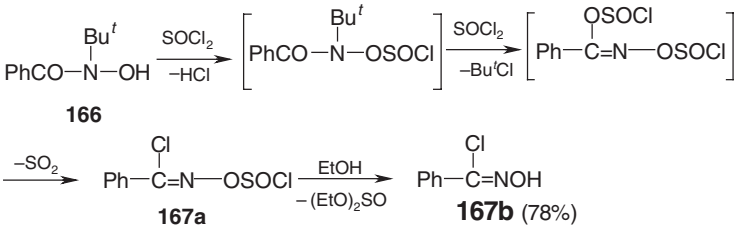
Chloroamine **164** and chloropropylpyrrolidine **165** were obtained from benzyamido ester **163a** and ester **163b** respectively by the action of thionyl chloride after reduction of the ester to the amino alcohols [equation (49)] [71].



(49)

3.4 *With hydroxylamines*

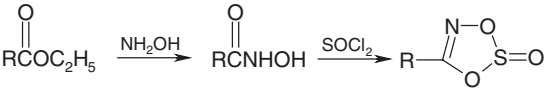
The reaction of *N*-benzoyl-*N*-*t*-butylhydroxylamine **166** with thionyl chloride in tetrachloromethane gave *O*-(chlorosulfinyl)benzohydroximoyl chloride **167a** as the main product. Upon treatment with ethanol the compound gave benzohydroximoyl chloride **167b** [equation (50)] [72].



(50)

3.5 *With hydroxamic acids*

Several cyclic sulfites **168** have been prepared by reaction of perfluoroaliphatic hydroxamic acids with thionyl chloride [equation (51)] [73].



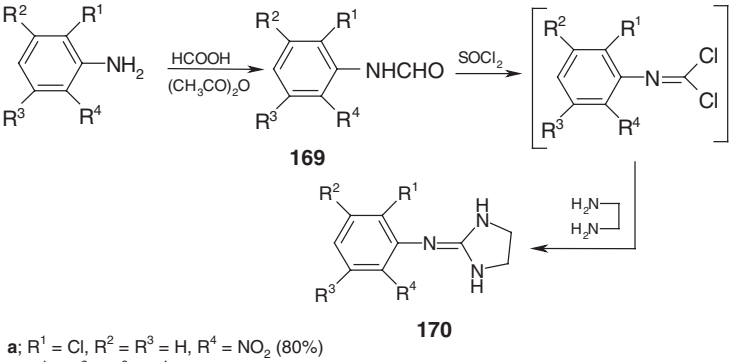
R = CF_3, C_2F_5 (51%), C_3F_7 (59%) **168**

(51)

3.6 *With formanilides*

The (chloronitrophenylimino)- and (tetrachlorophenylimino)-dihydroimidazole clonidine analogues **170a** and **170b** were prepared by treating the formanilides **169** with thionyl

chloride, followed by condensation with ethylenediamine [equation (52)] [74].



169

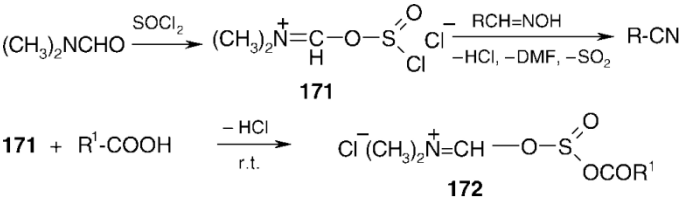
170

a; R^1 = Cl, R^2 = R^3 = H, R^4 = NO_2 (80%)
b; R^1 = R^2 = R^3 = R^4 = Cl (79%)

(52)

3.7 *With dimethylformamide*

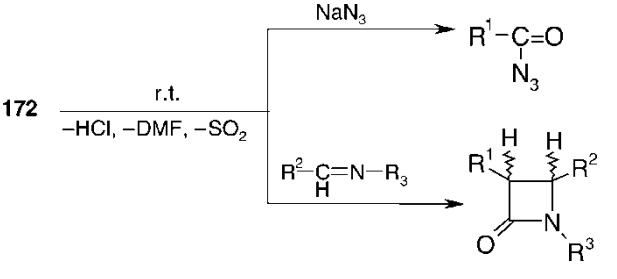
C-Chlorosulfinyloxy-*N*,*N*-dimethylmethaniminium chloride **171**, formed from thionyl chloride and dimethylformamide [equation (53)], is an efficient reagent for the synthesis of acyl azides from carboxylic acids and of nitriles from oximes. It is also highly efficient for the direct synthesis of β-lactams from carboxylic acids and imines, avoiding the use of acid chlorides [equation (54)] [75].



171

172

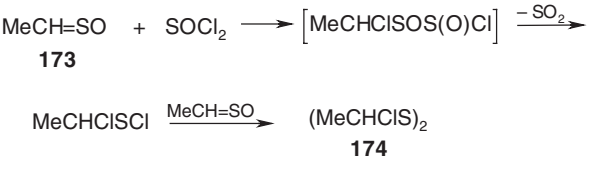
(53)



(54)

3.8 *With sulfines*

Treatment of sulfine **173** with thionyl chloride in $CFCl_3$ gave **174** in 52% yield via MeCHClSCl [equation (55)] [76].



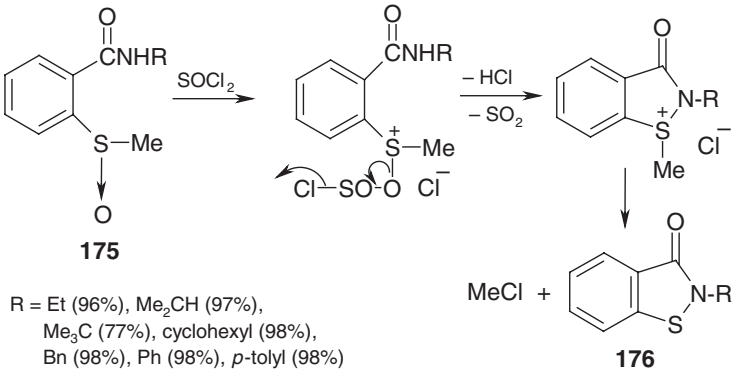
173

174

(55)

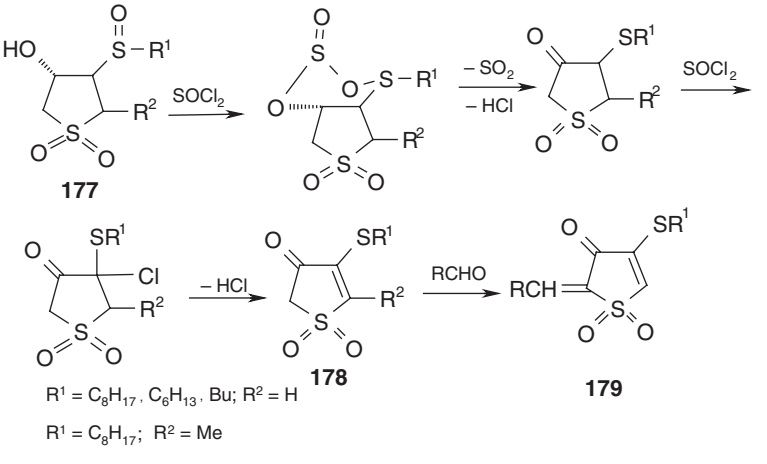
3.9 *With sulfoxides*

Cyclization of 2-(methylsulfinyl)benzamides **175** with thionyl chloride gave the corresponding 2-substituted 1,2-benzisothiazolones **176** [equation (56)] [77].



(56)

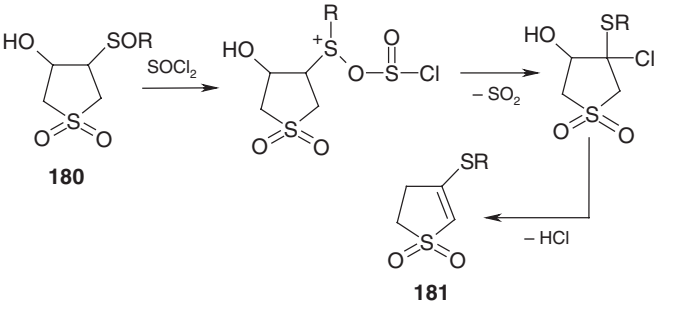
Treatment of the *trans*-hydroxy sulfoxides **177** with thionyl chloride gave, in 90–95% yield, ketones **178**. It can be supposed that in the reaction of the trans-isomer with thionyl chloride a favourable steric situation is created for the formation of a six-membered intermediate, the dissociation of which takes place with the release of SO_2 and HCl (Scheme 12).



SCHEME 12

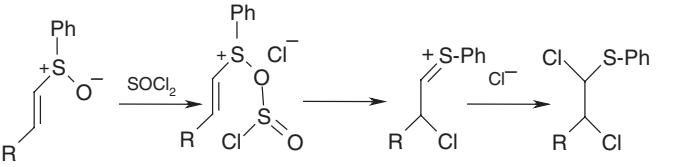
Compounds **178** ($R^1 = C_8H_{17}$, Bu; $R^2 = H$) were condensed with aldehydes (RCHO, R = Ph, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$) to give 85–90% yields of **179**. The aforementioned intermediate can probably not be formed in the reaction of the *cis*-isomers with thionyl chloride

and, unlike the *trans*-isomers, they react by the mechanism of the Pummerer reaction, giving sulfolenes **181** [equation (57)] [78].



180 **181** (57)

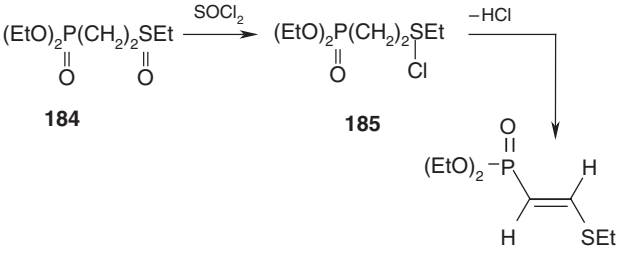
Treatment of alk-1-enyl phenyl sulfoxides **182** [79] with 5 equivalents of thionyl chloride [80] in dichloromethane at −5 to +25 °C for 30 min produced the α,β-dichloro sulfides **183** [equation (58)] [81]. This transformation is an example of a additive Pummerer rearrangement involving direct conversion of α,β-unsaturated sulfoxides into α,β-disubstituted sulfides.



182 **183** (85–95%) (58)

R = H, *n*-C_6H_{13}, Ph

The vinylphosphonate (*E*)-**186** is formed as a result of the Pummerer-type reaction between the β-(diethoxyphosphoryl) sulfoxide **184** and thionyl chloride at room temperature. The transiently formed Pummerer product **185** eliminates hydrogen chloride spontaneously and gives (*E*)-**186** as the final reaction product [equation (59)] [82].

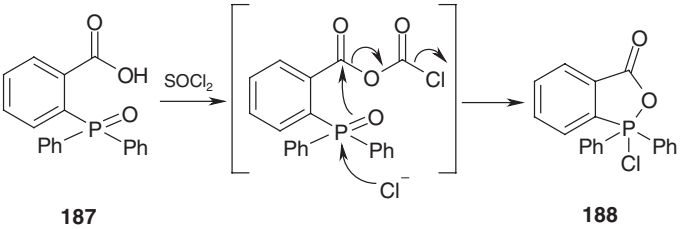


184 **185** (59)

The preparation of symmetrical diaryl sulfoxides from thionyl chloride and arenes catalyzed by trifluoromethanesulfonic acid (triflic acid) has been described. The reaction is characterized by its mildness, high yields, selectivity, and ease of work-up [83].

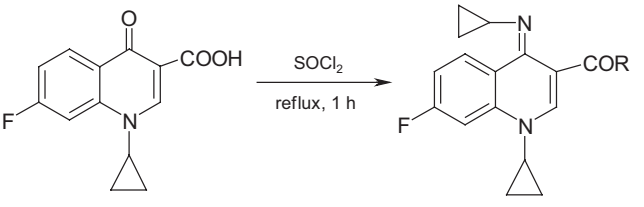
3.10 *With acids*

Treatment of 2-(diphenylphosphinoyl)benzoic acid **187** with thionyl chloride gave the corresponding (acyloxy)chlorophosphorane **188**. A mechanism involving attack of the phosphoryl oxygen at the carbonyl carbon was proposed [equation (60)] [84].



187 **188** (60)

Treatment of oxoquinolinecarboxylic acids with thionyl chloride and an aqueous solution of an amine or with thionyl chloride and dry amine yielded, instead of the oxoquinolinecarboxamide, the previously unreported 4-iminoquinolinecarboxylic acid and 4-iminoquinolinecarboxamide *via* a suspected acid chloride–hydrogen chloride complex intermediate. Thus, the cyclopropylquinolinecarboxylic acid **189** was treated with thionyl chloride at reflux for one hour and the resulting residue was treated with cold water containing NaOAc and cyclopropylamine to give a 16% yield of iminoquinolinecarboxamide **190** (R = cyclopropylamino) and an 82% yield of iminoquinolinecarbxylic acid **190** (R = OH) [equation (61)] [85].

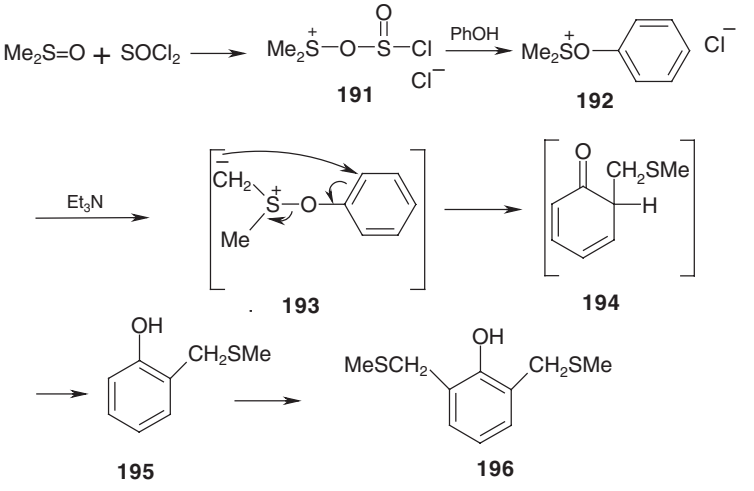


189 **190** (61)

The action of thionyl chloride on α-keto acids was revised. The reaction does not yield the corresponding γ-keto acyl chlorides, but instead efficiently produces γ-chlorobutyrolactones. The chemical properties of these products have been explored, along with some characteristic spectroscopic data [86].

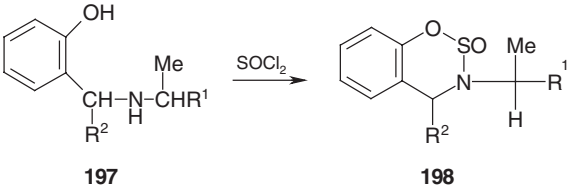
3.11 *With phenols*

Phenols were methylthiomethylated selectively in the *ortho* position by DMSO activated with thionyl chloride via a [2,3]-sigmatropic rearrangement of a sulfonium ylide **193**. The latter compound is formed by abstraction of a proton from the sulfonium salt **192**. The disubstituted product **196** seemed to arise from an exchange reaction between **195** and **192**, followed by a second [2,3]-sigmatropic rearrangement (Scheme 13) [87].



SCHEME 13

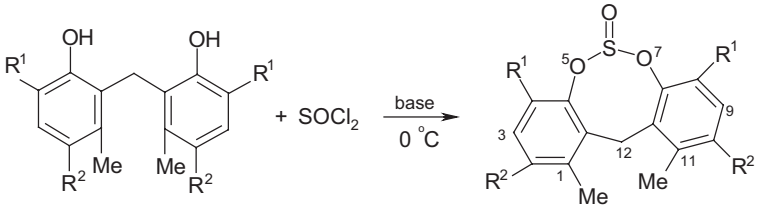
The benzoxathiazine 2-oxides **198** have been prepared in good yields by reaction of the aminophenols **197** with thionyl chloride [equation (62)] [88].



(62)

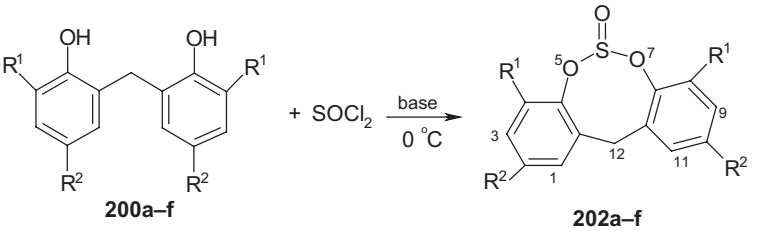
R^1 = Ph, 1-$C_{10}H_7$; R^2 = H, Me, Et, Bn

The dioxathiocines **201** and **202** have been prepared by condensation of the corresponding bisphenols **199** and **200**, respectively, with thionyl chloride [equations (63) and (64)] [89].



(63)

a; R^1 = Bu^t, R^2 = Me,
b; R^1 = Bu^t, R^2 = H,
c; R^1 = R^2 = Me



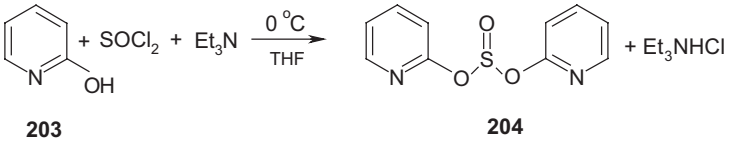
200a–f **202a–f**

a; R^1 = Bu^t, R^2 = Me, **d**; R^1 = R^2= Me,
b; R^1= R^2= Bu^t, **e**; R^1 = Me, R^2 = Bu^t,
c; R^1 = Bu^t, R^2 = H **f**; R^1 = Me, R^2 = H

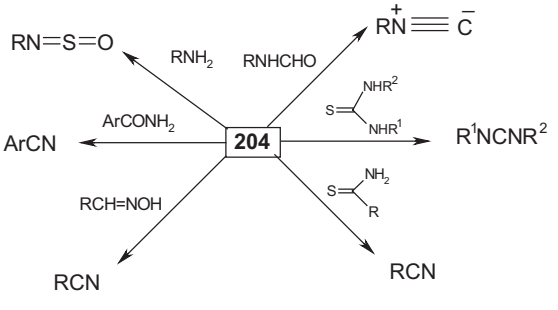
(64)

3.12 *With 2-hydroxypyridine*

Di-2-pyridyl sulfite **204** is a useful reagent for the preparation of *N*-sulfinylamines, nitriles, isocyanides, and carbodiimides in high yields under essentially neutral conditions by sulfinylation of amines, dehydration of amides or aldoximes, and dehydrosulfurization of thioureas or thioamides (Scheme 14). Di-2-pyridyl sulfite is conveniently prepared in high yield by reaction of thionyl chloride with 2 molar equivalents of 2-hydroxypyridine **203** and triethylamine in tetrahydrofuran at 0 °C [90].



203 **204**

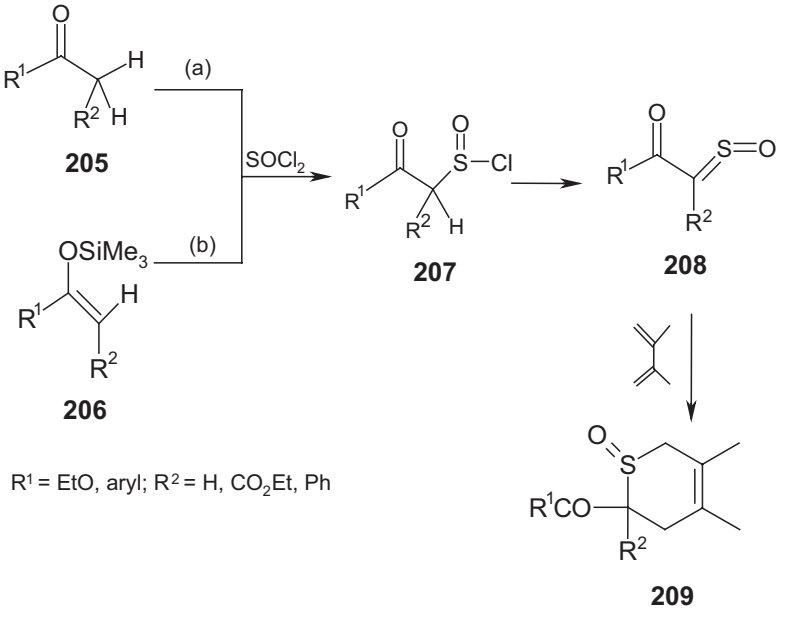


SCHEME 14

4. Reaction with *C*-nucleophiles

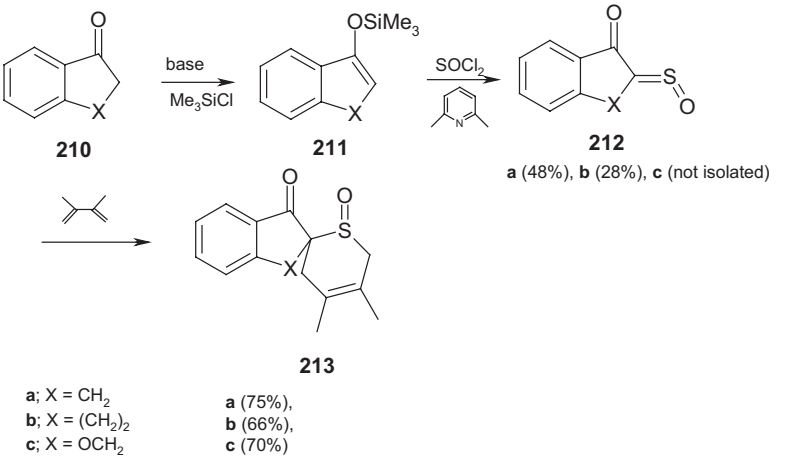
4.1 *Reactions via sulfines*

The reaction of some α-methylene ketones **205** with thionyl chloride leads to α-oxo sulfines **208** provided the ketone is sufficiently enolized. The reaction of trimethylsilyl enol ethers **206** is a more efficient and versatile method for the synthesis of α-oxo sulfines **208**. Isolation of **208** is only possible by crystallization from the reaction mixture. If this is not possible, the sulfines **208** can be trapped by cycloaddition with 2,3-dimethylbuta-1,3-butadiene (Scheme 15) [91].



SCHEME 15

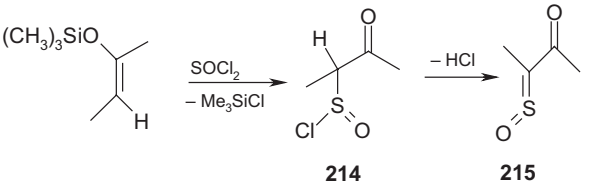
The silyl enol ethers **211** derived from indan-1-one, indan-2-one, α-tetralone, and chroman-4-one **210** reacted with thionyl chloride to give α-oxo sulfines **212**, which were isolated or trapped by a cycloaddition reaction with a diene to give the spiro adduct **213** (Scheme 16).



SCHEME 16

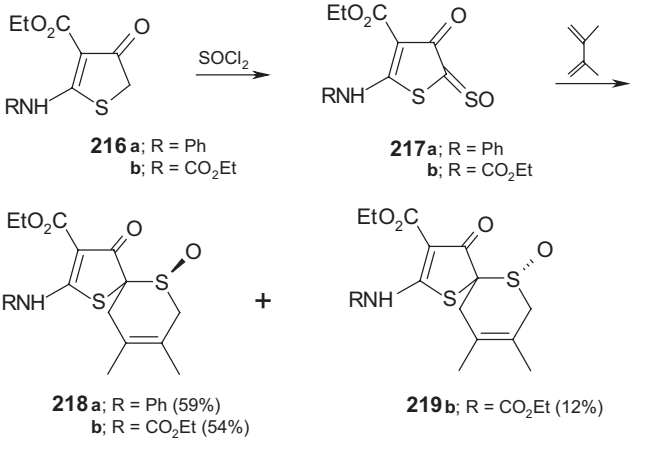
For these types of reactions it has been suggested [92] that a β-oxo sulfinyl chloride **214** [93,94] is formed first, which then eliminates hydrogen chloride to give the α-oxo

sulfine **215**. Probably, part of the silyl enol ether functions as a hydrogen-chloride-trapping agent [equation (65)].

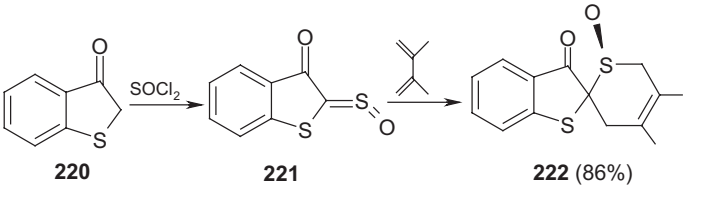


(65)

A re-investigation of the reaction of the dihydrothiophenes **216a** and **216b** with thionyl chloride confirmed that the sulfines **217** are involved by X-ray diffraction analysis of the Diels–Alder adduct **218a**. The corresponding reaction of dihydrothiophene **220** produced sulfine **221** [equations (66) and (67)] [95].

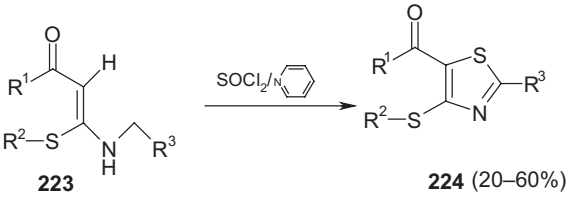


(66)



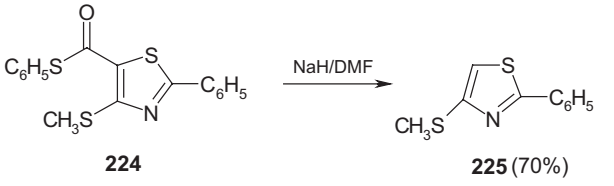
(67)

Cyclization of the keto ketene *S*,*N*-acetals **223** with thionyl chloride in pyridine gave the thiazoles **224** in 20–50% yield. Deacylation of **224** with NaH–DMF gave 70–72% yields of **225** [equations (68) and (69)].



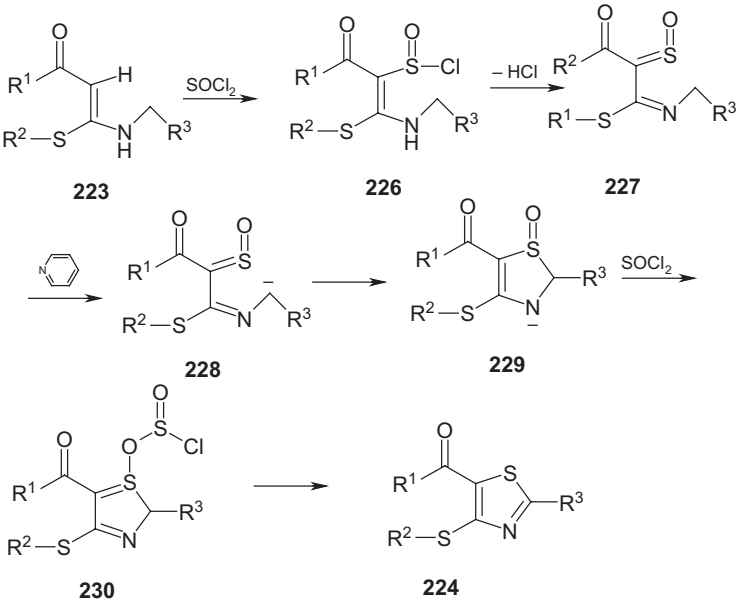
(68)

R^1 = Ph, *p*-tolyl. *p*-$MeOC_6H_4$, *p*-ClC_6H_4, Me
R^2 = Me, Et, $PhCH_2$
R^3 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, EtO_2C



224 **225** (70%) (69)

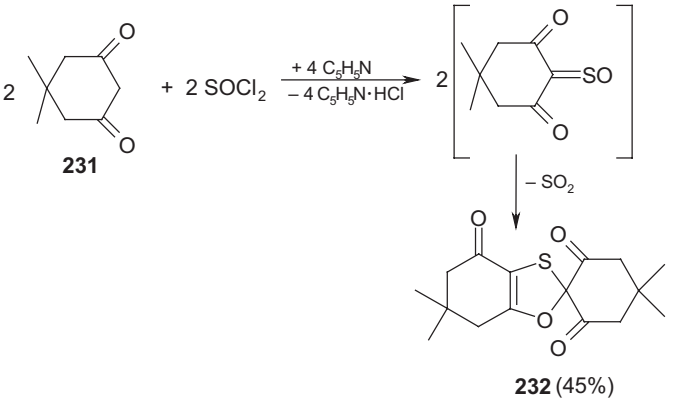
The mechanism of the formation of **224** from **223** appears to be similar to that proposed [96] for the reaction of 6-*N*-substituted 1,3-dimethyluracils with thionyl chloride to give thiazolo[4,5-*d*]pyrimidines. Sulfine intermediate **227** after proton abstraction undergoes cyclization *via* the anion **228** to form the corresponding thiazoline *S*-oxide **229**. Further reaction of **229** with thionyl chloride affords **224** *via* the Pummerer intermediate **230** (Scheme 17) [97].



223 **226** **227** **228** **229** **230** **224**

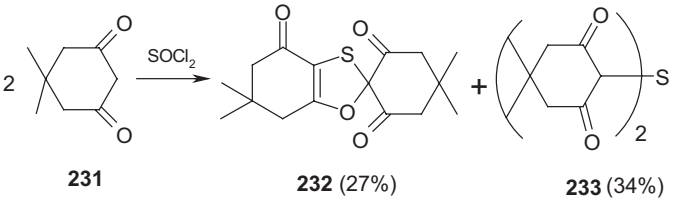
SCHEME 17

Reaction of dimedone **231** with thionyl chloride in the presence of pyridine gave the benzoxathiole derivative **232** [equation (70)].



231 **232** (45%) (70)

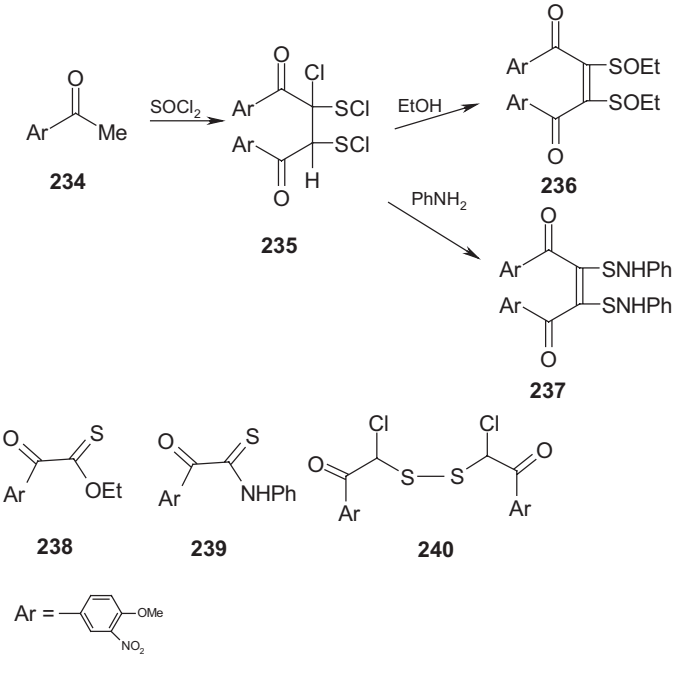
In the reaction of dimedone with thionyl chloride in the absence of base a mixture of **232** and the sulfide **233** was obtained [equation (71)] [98].



231 **232** (27%) **233** (34%) (71)

4.2 *Formation of sulfenyl chlorides*

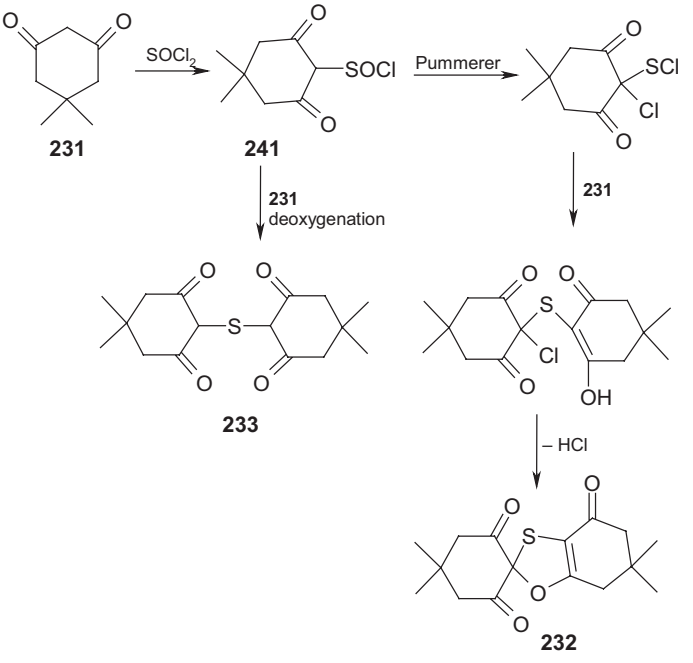
The intermediate bis(sulfenyl chloride) **235**, claimed [99] to be formed in the reaction of methyl ketones **234** with thionyl chloride, and the subsequent alcoholysis and aminolysis products **236** and **237** have been questioned. Based on spectral analysis, the more probable structures **238**, **239** and **240** for these products have been suggested (Scheme 18) [100].



SCHEME 18

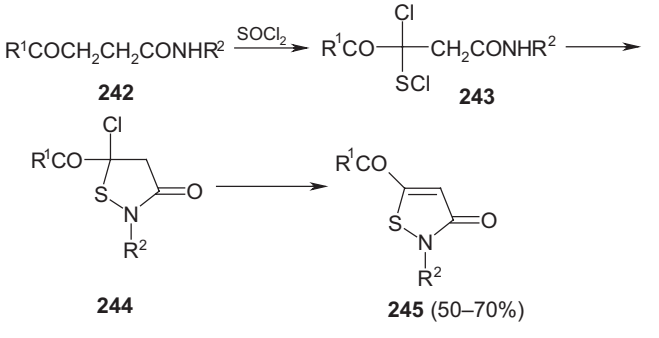
The reaction of dimedone **231**, with thionyl chloride gave, after a very short reaction period (1 hour), the interesting tricyclic product **232** [101], shown to be identical with the product obtained earlier by Koser and Yu [102]. A similar type of compound was obtained by Senning [103] from the reaction of an acyclic β-diketone, 1,3-diphenylpropane-1,3-dione, with thionyl chloride. A reasonable mechanism for the formation of **232** is the initial attack of thionyl

chloride at C-2, followed by a Pummerer rearrangement. The small amount of **233** formed in the reaction of **231** with thionyl chloride most likely results from attack on C-2 by the electrophile and subsequent reaction of the product **241** with a second molecule of dimedone (Scheme 19).



SCHEME 19

Reaction of the *N*-substituted 3-aroylpropionamides **242** with excess of thionyl chloride gave 2-substituted-5-aroylisothiazol-3(2*H*)-ones **245** [equation (72)] [104].

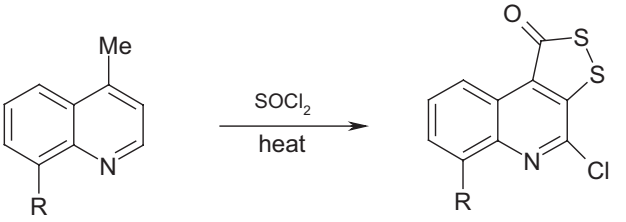


(72)

R^1 = Ph, R^2 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-HOC_6H_4
R^1 = *p*-$MeOC_6H_4$, R^2 = Me

A nucleophilic displacement reaction of the amide nitrogen on the sulfenyl chloride group of **243** would lead to ring closure to afford the heterocycle **244**. Elimination of hydrogen chloride then yields the isothiazol-3(2*H*)-one **245** [equation (72)].

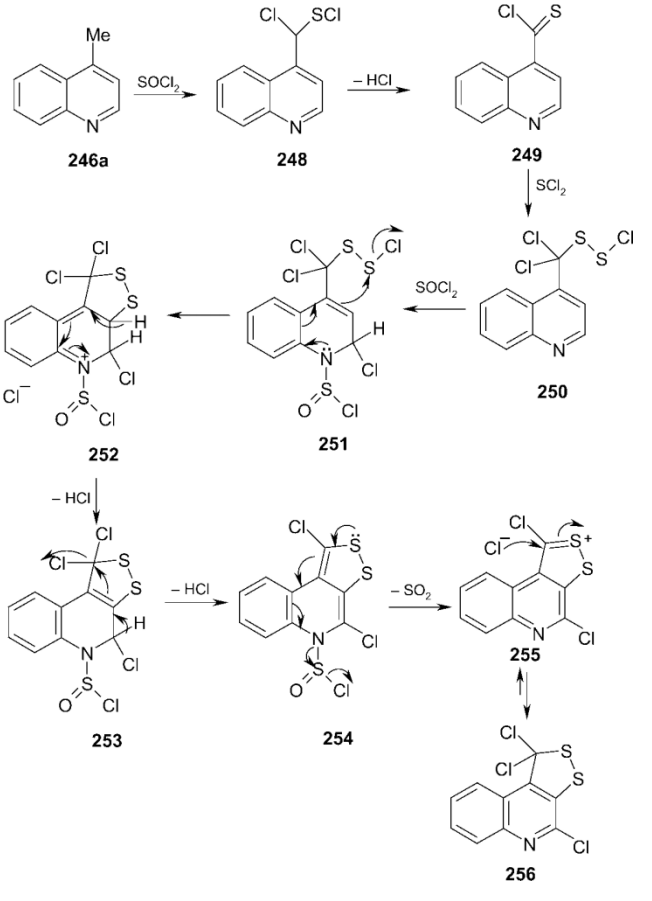
4.3 *Reaction with C-methyl heterocycles*



246a,b **247a,b**

a; R = H
b; R = CH_3

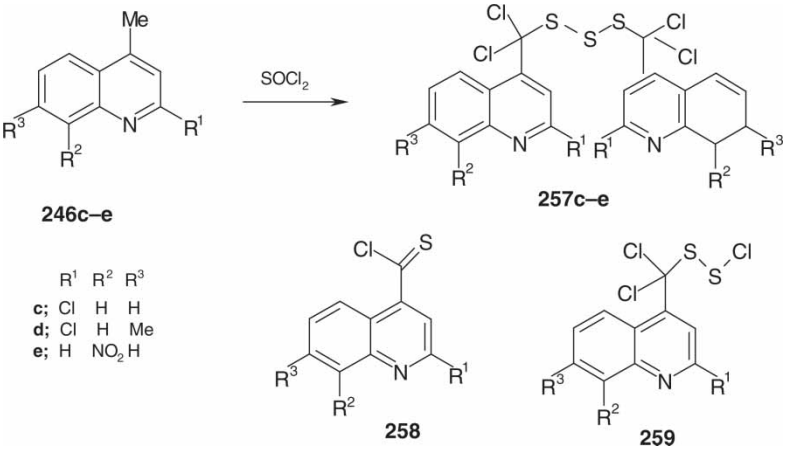
Reaction of 4-methyl- and 4,8-dimethyl-quinolines **246a,b** with excess of hot thionyl chloride gives the dithioquinolines **247a** and **247b** in 10% and 1% yield, respectively. It is believed that the primary product of the reaction of **246a** with thionyl chloride is dichloro derivative **256** (Scheme 20), which is then hydrolyzed to the observed product **247a**. A mechanism



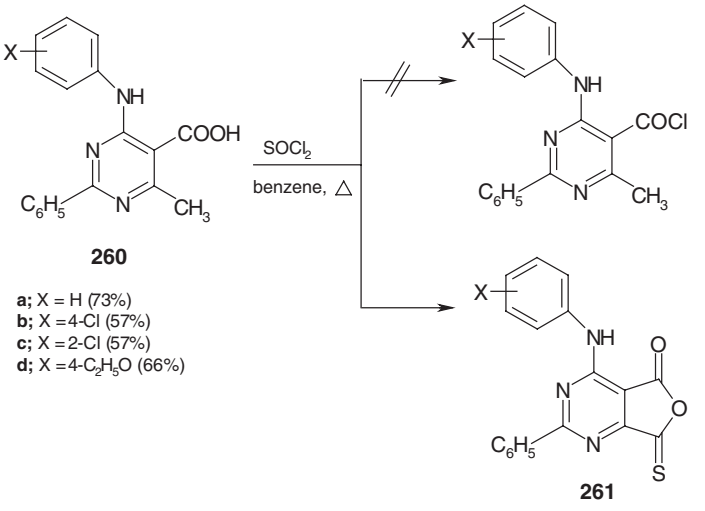
SCHEME 20

for the formation of **256** is proposed in Scheme 20. Sulfur chloride is produced by thermal decomposition of thionyl chloride.

When a chlorine atom was introduced into the 2-position of the starting materials, then a different type of product was obtained. Thus treatment of **246c** with hot thionyl chloride gave **257c**. Similarly, **257d** and **257e** were obtained from **246d** and **246e**. The mechanism of formation of the trisulfanes **257** probably follows the same initial pathway as that proposed for **247**. Instead of the intramolecular cyclization **251** → **252** (Scheme 20), the chlorodithianes **259** then add to a molecule of **258** giving the observed trisulfane **257** [105].

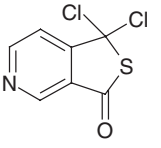


The pyrimidines **260** undergo an unusual reaction with thionyl chloride in boiling benzene to give 57–73% yields of the furopyrimidines **261**, presumably *via* a sulfine intermediate [equation (73)].



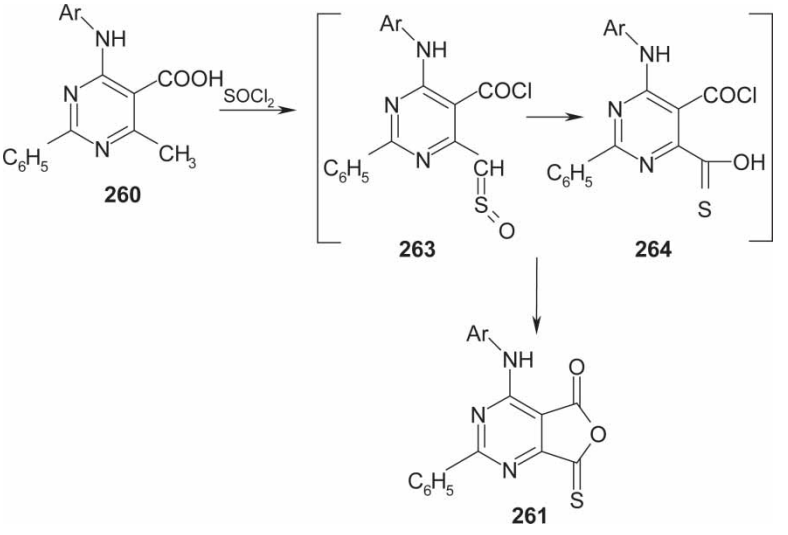
(73)

This is in contrast to the previously described reaction of 4-methylpyridine-3-carboxylic acid with thionyl chloride to afford a thiolactone with the thieno[3,4-*c*]pyridine structure **262** [106].



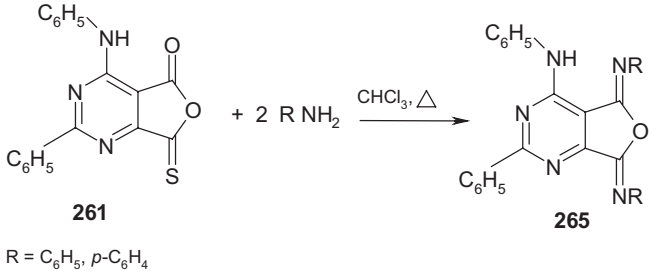
262

The mechanism of the formation of **261** may be understood in terms of an intermediate **263** *via* the thionic acid intermediate **264** [equation (74)].



(74)

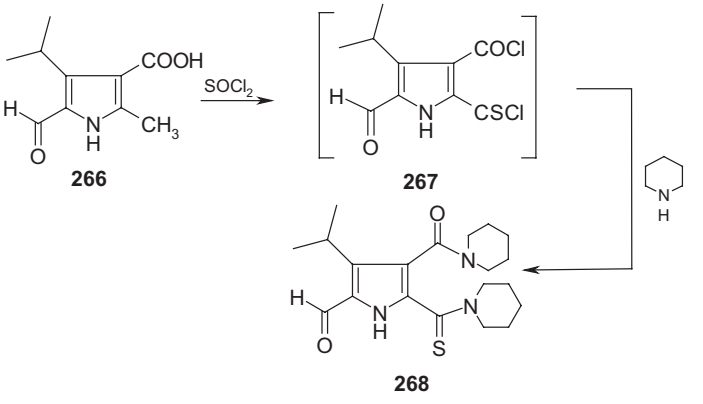
It should be noted that the generation of a sulfine *via* reaction of a methylene compound with thionyl chloride, followed by elimination of hydrogen chloride, was reported quite early [107]. The structure of **261a** was confirmed from microanalytical and spectral analyses, as well as by reaction with primary amines [equation (75)]. The resultant diimines **265** do not contain sulfur; an alternative thiophene structure similar to that of compound **262** can therefore be excluded [108].



R = C_6H_5, *p*-C_6H_4

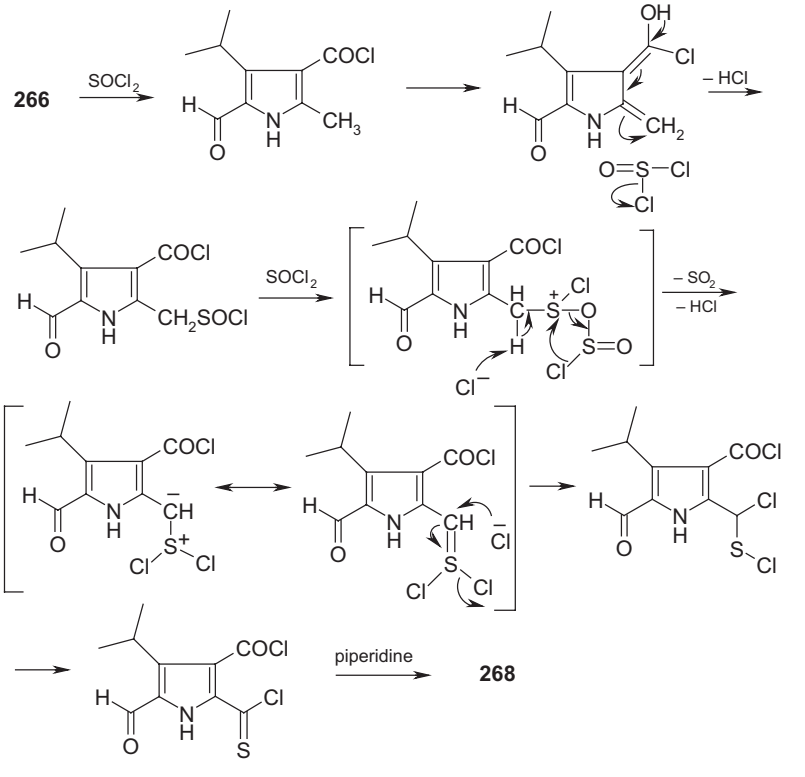
(75)

The 2-methylpyrrole derivative **266** has been converted into the thiocarboxamide **268** by being heated with thionyl chloride, followed by treatment of the crude product **267** with piperidine in toluene [equation (76)] [109].



(76)

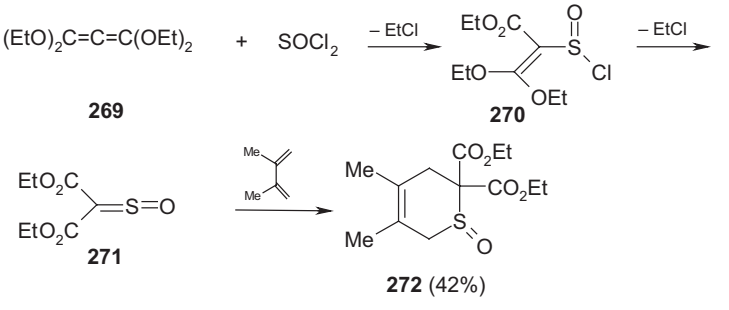
The data and the proposed mechanism of this reaction (Scheme 21) are consistent with earlier results obtained by Krubsack and Higa [110].



SCHEME 21

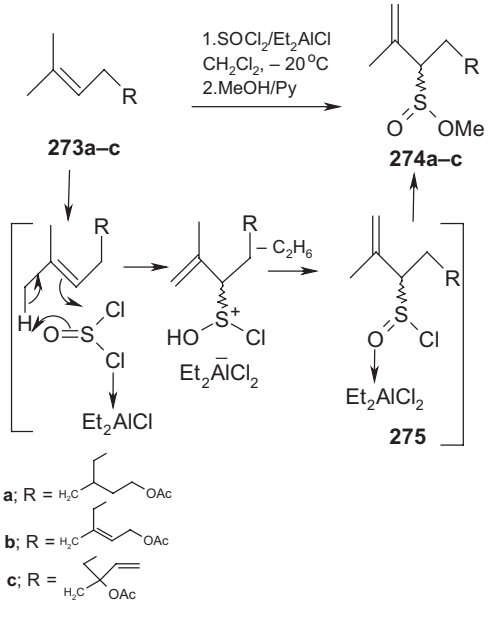
4.4 *Reaction with multiple bonds*

4.4.1 Addition. Tetraethoxyallene **269** reacts with thionyl chloride to afford diethyl thioxomalonate *S*-oxide **271**. The ketene acetal **270** is formed in the first step and then yields the heterocumulene **271** with spontaneous elimination of ethyl chloride [equation (77)]. Compound **271** was trapped with 2,3-dimethylbuta-1,3-diene to give the thiopyran oxide **272** [111].



(77)

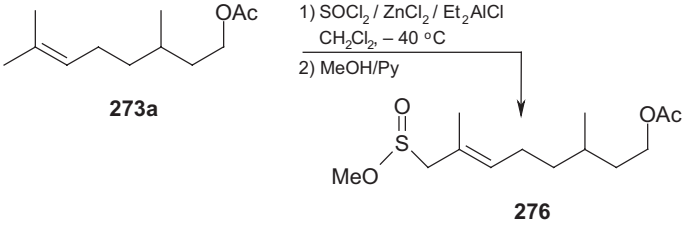
Trisubstituted methylalkenes **274a–c** can be prepared by the Et_2AlCl-catalyzed reaction of thionyl chloride with mono- and di-enes **273a–c**, followed by methanolysis of the intermediate alkyl sulfinyl chloride **275**. These reactions represent a new method for the terminal functionalization of linear isoprenoids (Scheme 22).



SCHEME 22

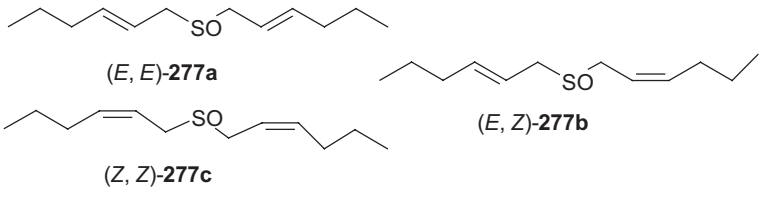
Quite unexpectedly, the linear allyl sulfinate **276** was isolated when the reaction of **273a** with thionyl chloride was conducted in the presence of 0.5 molar equivalent of Et_2AlCl and

3 molar equivalents of $ZnCl_2$. Allylic isomerization of an initially formed allylsulfinyl chloride **275a** may serve as a plausible explanation [equation (78)] [112].



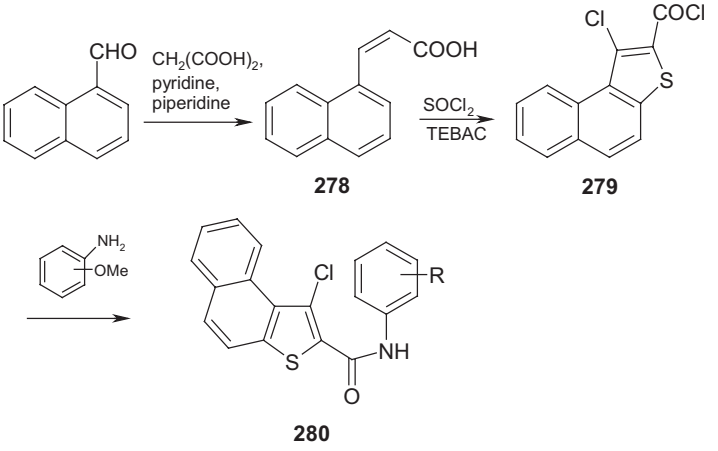
273a **276** (78)

Di(hex-2-enyl) sulfoxide **277** has been prepared by the reaction of hex-1-ene with thionyl chloride in the presence of stannic [tin(IV)] chloride. Thionyl chloride adds to hex-1-ene with subsequent dehydrochlorination. IR and NMR spectra revealed that **277** is formed in three isomeric forms (**277a,b,c**) in the proportions 8:2:3 [equation (79)]. The isomers were separated by fractional crystallization [113].



(*E*, *E*)-**277a** (*E*, *Z*)-**277b** (*Z*, *Z*)-**277c** (79)

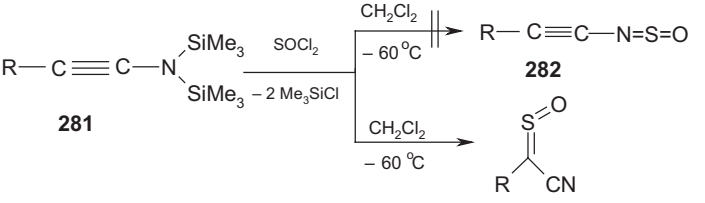
When 3-(1-naphthyl)propenoic acid **278**, prepared from naphthalene-1-carboxaldehyde and malonic acid, reacted with thionyl chloride in the presence of triethylbenzylammonium chloride (TEBAC), 1-chloronaphtho[2,1-*b*]thiophene-2-carboxyl chloride **279** was obtained in 30% yield. The reaction of **279** with *o*-, *m*- or *p*-anisidine afforded the corresponding carboxamide **280** [equation (80)] [114].



278 **279** (80)

280

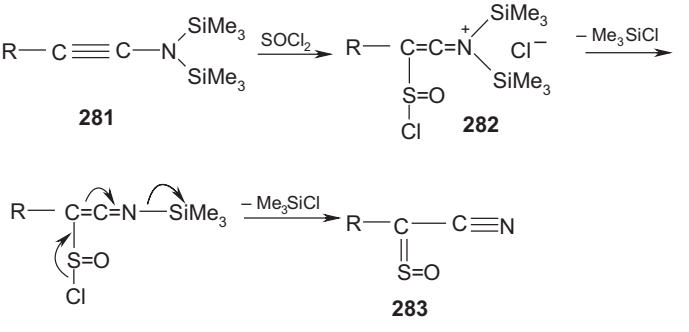
The reaction of *N*,*N*-bis(trimethylsilyl)ynamines **281** with thionyl chloride gave compounds **283** instead of **282** [equation (81)].



a; R = Ph
b; R = Bu^t
c; R = Pr
d; R = cyclohexyl

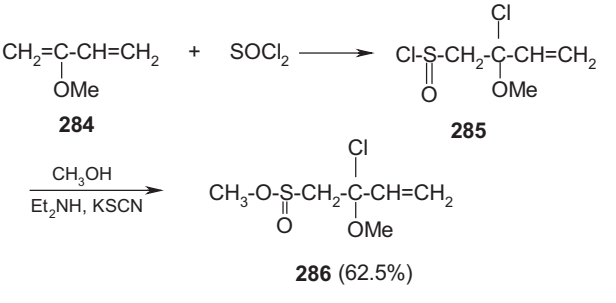
(81)

The suggested mechanism of formation of **283** from **281** is shown in equation (82) [115].



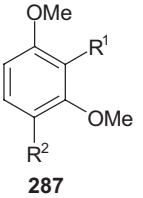
(82)

Thionyl chloride adds to the more nucleophilic 1,2-position of 2-methoxybuta-1,3-diene **284** to give a single product **285**. Sulfinate **286** is obtained if the more labile halogen is substituted by a methoxy group [equation (83)] [116].

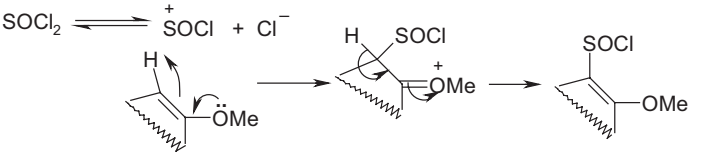


(83)

4.4.2 Substitution. Aromatic sulfinyl chlorides have been prepared in high yields by direct chlorosulfination of benzenes **287** with neat thionyl chloride at or below room temperature.

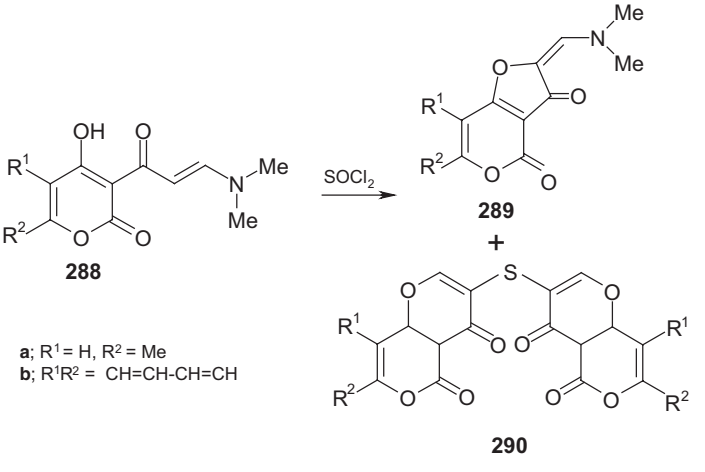


The mechanism of the reaction is suggested to be as shown in equation (84) [117].



(84)

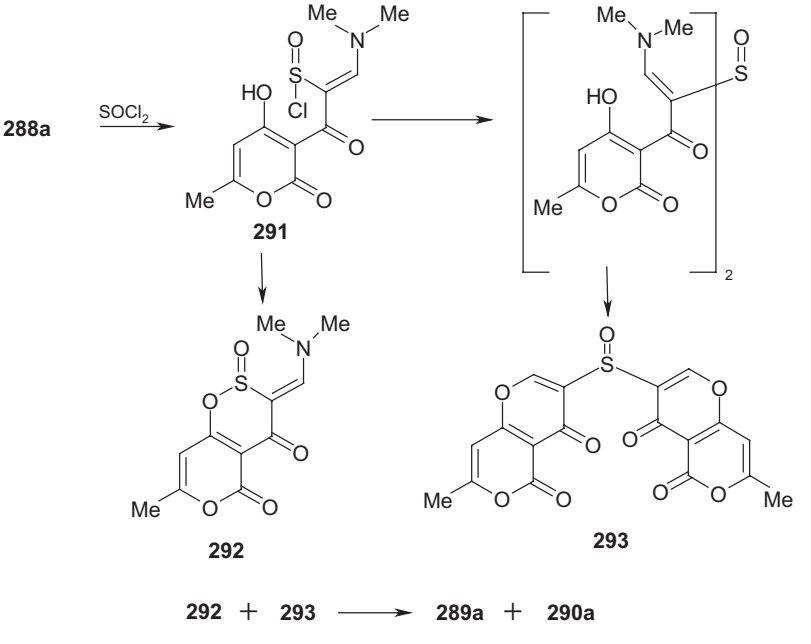
The enaminones **288** react with thionyl chloride to give the furopyrans **289** and the sulfides **290** [equation (85)].



a; R^1 = H, R^2 = Me
b; R^1R^2 = CH=CH-CH=CH

(85)

The following reaction mechanism was discussed (Scheme 23) [118].

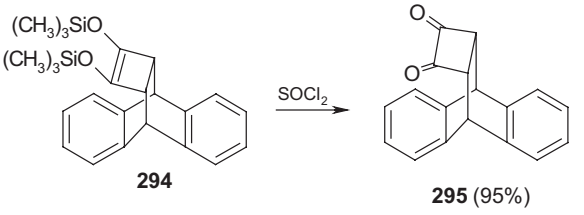


SCHEME 23

5. Miscellaneous

5.1 *Elimination*

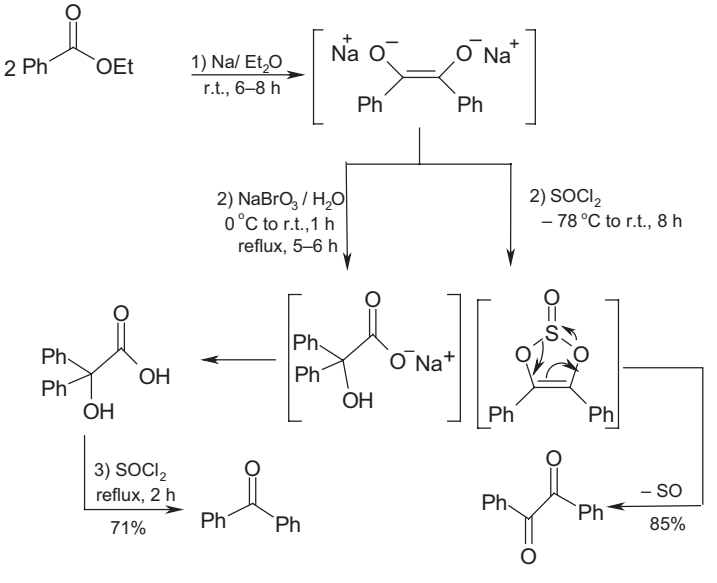
Cyclobutanoanthracenedione **295** has been prepared by elimination from the bis(trimethylsiloxy)cyclobutene derivative **294** in the presence of thionyl chloride [equation (86)] [119].



294 **295** (95%) (86)

5.2 *Formation of ketones from esters*

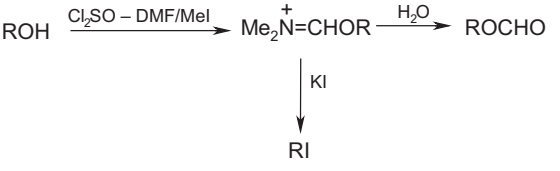
Thionyl chloride is widely used as a chlorinating agent, and is also useful in elimination and condensation reactions. Thionyl chloride is also a good oxidizing agent for *in situ*-formed sodium dienolates to yield 1,2-diketones, and serves as a convenient reagent to induce decarboxylation of α-hydroxy carboxylic acids to monoketones [120]. A convenient one-flask preparation of a series of symmetrical 1,2-diketones from esters has been reported using sodium metal-induced acyloin condensation, followed by reaction with thionyl chloride. Symmetrical monoketones were obtained when, after initial acyloin condensation, the reaction mixture was oxidized with aq. sodium bromate and then treated with thionyl chloride (Scheme 24).



SCHEME 24

5.3 *Formation of esters from alcohols*

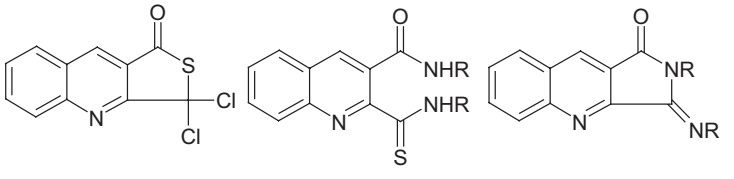
Primary and secondary alcohols are efficiently converted into the corresponding alkyl formates and iodides by reaction with thionyl chloride–DMF and in the presence of LiI and KI, respectively [equation (87)] [121].



(87)

5.4 *Oxidation*

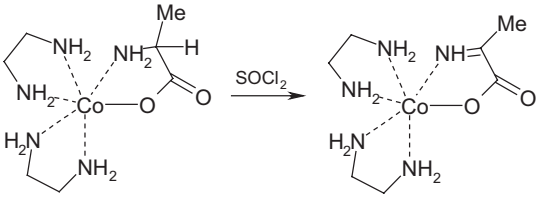
Oxidation of 2-methylquinoline-3-carboxylic acid with thionyl chloride afforded the thienoquinoline **296**; aminolysis of **296** with cyclohexylamine afforded diamide **296a** (R = cyclohexyl); aminolysis of **296** with isobutylamine also afforded the corresponding derivative **296b** (R = isobutyl) which slowly cyclized in $CHCl_3$ to the iminodihydropyrroloquinolinone **296c** (R = isobutyl). Aminolysis with $EtNH_2$ afforded the corresponding iminimide **296d** exclusively [122].



296 **296a** (R = cyclohexyl) **296b** (R = isobutyl) **296c** (R = isobutyl) **296d** (R = ethyl)

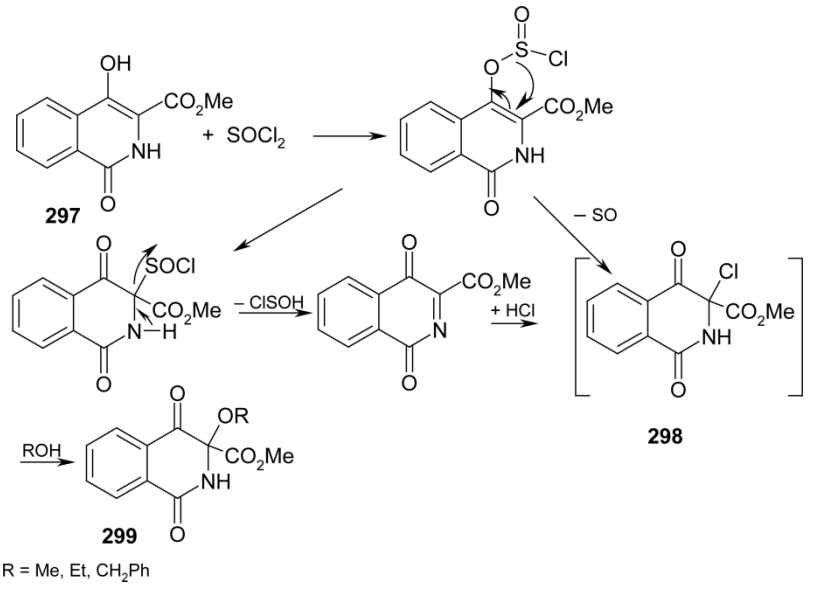
Oxidation of methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **297** with thionyl chloride gives an unstable intermediate **298**, which reacts with alcohols to give 3-alkoxy-1,4-dioxo-1,2,3,4-tetrahydroisoquinolines **299**. In this system, thionyl chloride was a convenient alternative oxidant to lead tetraacetate (Scheme 25) [123].

Amino acids chelated to cobalt are oxidized rapidly by thionyl chloride in DMF to give imines. Thus, the cobalt–alanine complex **300** has been oxidized with thionyl chloride in DMF to give the amino acid complex **301** [equation (88)] [124].



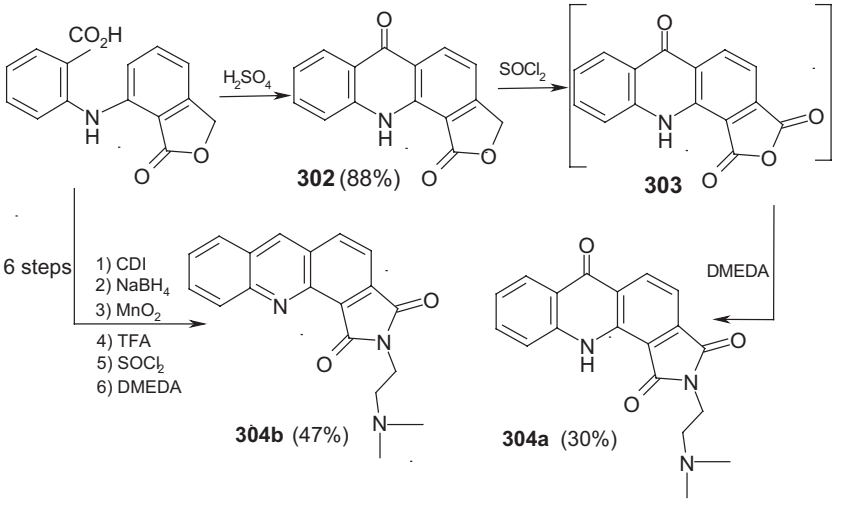
300 **301**

(88)



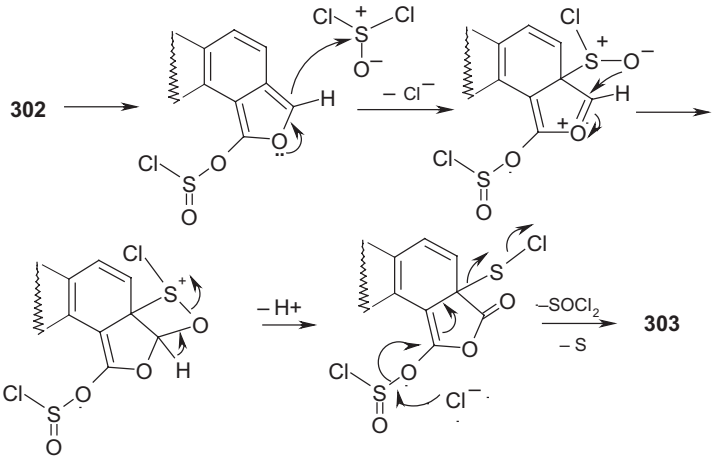
SCHEME 25

An unusual oxidation reaction was observed when the furoacridone **302** was treated with thionyl chloride. This unusual oxidation was found to be useful in the synthesis of 1,3-dihydro-2-[2-(dimethylamino)ethyl]-1,3-dioxopyrrolo[3,4-c]acridine **304**, a potent DNA topoisomerase II inhibitor [equation (89)] [125].



(89)

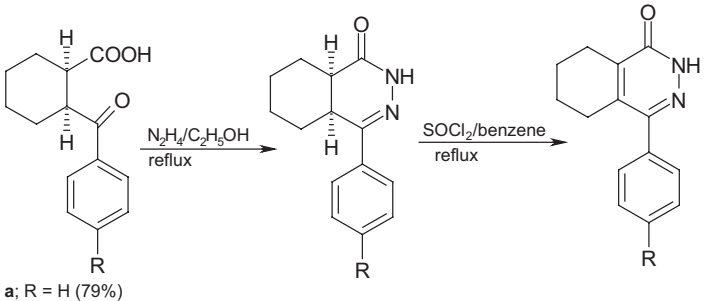
The mechanism of formation of **303** from **302** has been suggested as follows (Scheme 26).



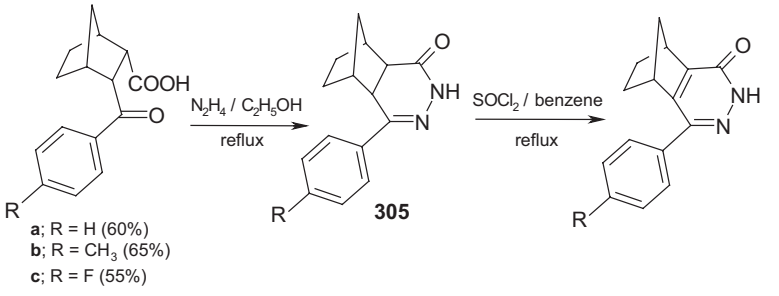
SCHEME 26

5.5 *Partial dehydrogenation*

A simple and convenient method has been reported [126] for the partial dehydrogenation of the cyclohexane- and trinorborane-condensed dihydropyridazinones **304** and **305** with thionyl chloride [equations (90) and (91)]. Relatively few publications are available concerning thionyl chloride as a dehydrogenating agent [127, 128]. The dehydrogenation process takes place during annulation. Chlorination, followed by elimination of hydrogen chloride, might be responsible for this transformation.



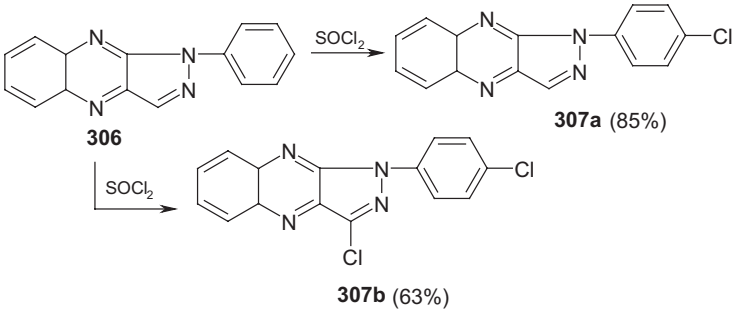
(90)



(91)

5.6 *Chlorination*

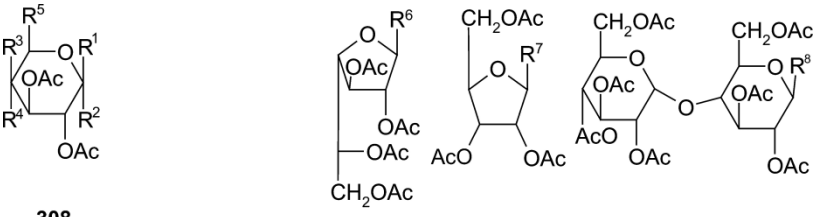
Chlorination of the pyrazoloquinoxaline **306** with thionyl chloride gives chloro derivatives **307a** and **307b** [equation (92)] [129].



(92)

The mechanism by which thionyl chloride acts as a chlorinating agent is not fully understood. One possible explanation is that thionyl chloride undergoes oxidation in the presence of atmospheric oxygen to sulfuryl chloride, which is a well known chlorinating agent for organic substances [130].

Reaction of the 1,2-*trans*-aldose per-acetates **308**, **309**, **310**, and **311** in CH_2Cl_2 with thionyl chloride–acetic acid gave 1,2-*trans*-per-*O*-acetyl-D-glycosyl chlorides **308** ($R^1 = Cl$), **309** ($R^6 = Cl$), **310** ($R^7 = Cl$), and **311** ($R^8 = Cl$), respectively, in good to excellent yields. The reaction is solvent dependent, no chloride being formed in THF or 1,2-dimethoxyethane. 1,2-*cis*-Aldose per-acetates **308** failed to undergo chlorination.



308

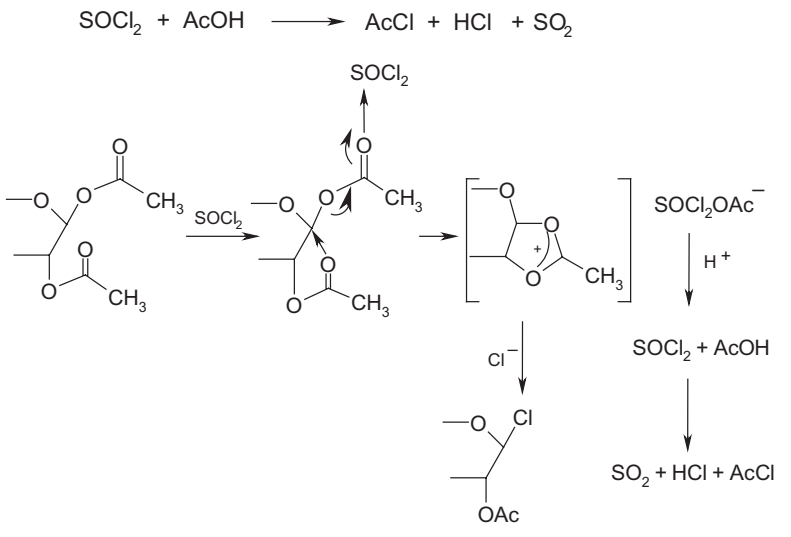
$R^1 = R^4 = OAc$,
$R^2 = R^3 = H$, $R^5 = CH_2OAc$;
$R^1 = R^3 = OAc$, $R^2 = R^4 = H$,
$R^5 = CH_2OAc$;
$R^1 = R^4 = OAc$,
$R^2 = R^3 = R^5 = H$

309 $R^6 = OAc$

310 $R^7 = OAc$

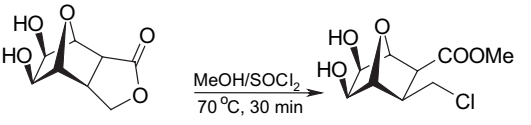
311 $R^8 = OAc$

These reaction sequences are probably initiated by the reaction of thionyl chloride with acetic acid to produce a mixture of acetyl chloride and hydrogen chloride, which, in combination with the remaining excess of thionyl chloride, acts as the effective reagent (Scheme 27) [131].

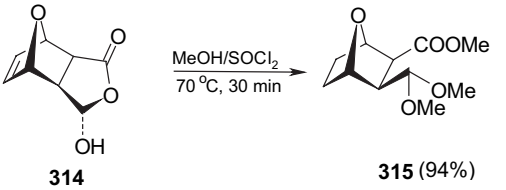


SCHEME 27

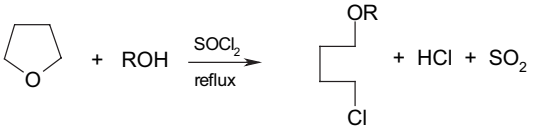
Mixtures of thionyl chloride and ROH (R = Me, Et, Pr, Me_2CH, allyl, propargyl) can be used advantageously for transformations of γ-butyrolactones, *e.g.* **312**, into the corresponding alkyl, allyl, and propargyl 4-chlorobutyrates, *e.g.* **313**; for the methanolysis of the unstable γ-hydroxy-γ-butyrolactone **314** into the corresponding methyl 4-oxobutyrate dimethyl acetal **315;** and for the synthesis of alkyl, allyl, and propargyl 4-chlorobutyl ethers **316** from tetrahydrofuran [equations (93)–(95)] [132].



312 **313** (91%) (93)



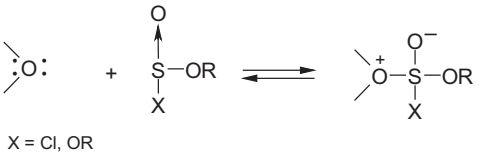
314 **315** (94%) (94)



316 (93–97%) (95)

Primary alcohols (ROH) react rapidly with thionyl chloride at 0 °C to generate first ROS(O)Cl and HCl, and then $(RO)_2SO + 2$ HCl [133]. It has not been ruled out yet that the chlorosulfites or/and dialkyl sulfites are responsible for the smooth reactions presented

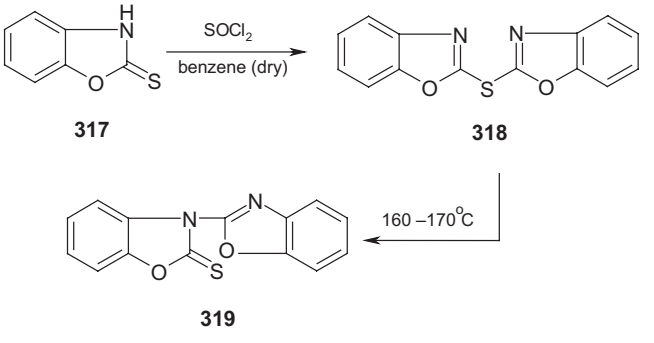
above. Because of the oxophilicity of the sulfites, these species compete favourably with HCl in assisting the opening of oxirane rings [equation (96)].



(96)

5.7 *Formation of sulfides*

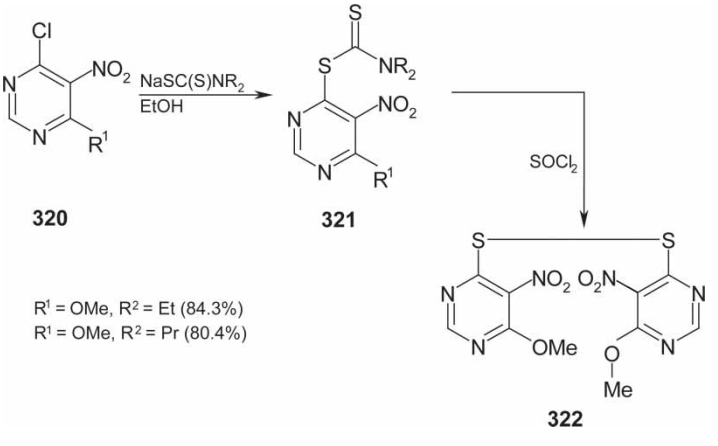
Treatment of benzoxazoline-2-thione **317** with thionyl chloride in dry C_6H_6 containing Et_3N gave a 75% yield of 2,2′-sulfanediylbisbenzoxazole **318**, which was also obtained in 85% yield from **317** and 2-chlorobenzoxazole. Heating **318** at 160–170 °C gave a 92% yield of the benzoxazolinethione **319** [equation (97)] [134].



317 **318** **319**

(97)

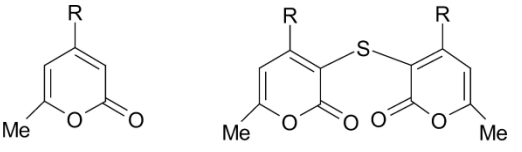
The dialkyldithiocarbamoyl derivatives **321** react with thionyl chloride in toluene to form the dipyrimidyl disulfide **322** [equation (98)] [135].



320 **321** **322**

(98)

Treatment of the lactone **323** with thionyl chloride at ambient temperature resulted in the formation of 3,3-bis-(4-hydroxy-6-methyl-2-oxopyran-3-yl) sulfide **324**, which could be converted into the bis: (methyl ether) **325** with dimethyl sulfate [136].

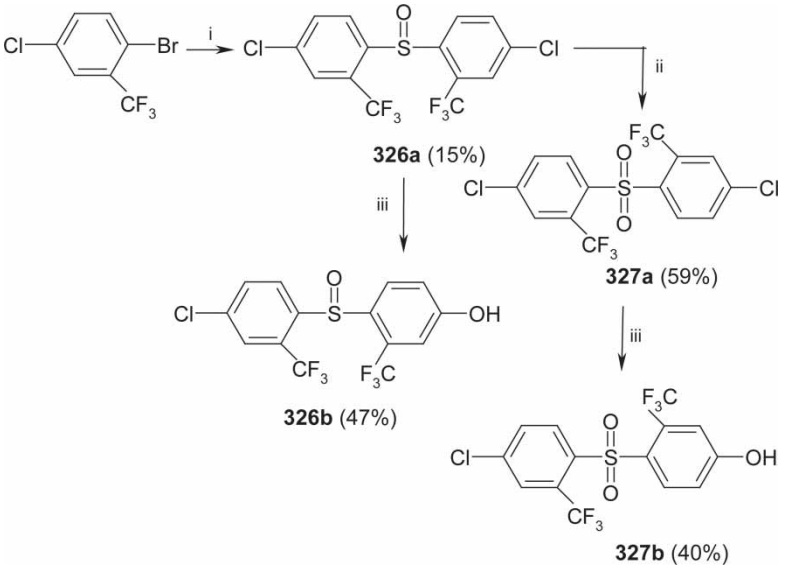


323 R = OH

324 R = OH
325 R = OMe

5.8 *Formation of sulfoxides and sulfones*

Bis-[4-chloro-2-(trifluoromethyl)phenyl] sulfoxide **326a** can be prepared from 2-bromo-4-chlorobenzotrifluoride and thionyl chloride and converted into the bis-[2-(trifluoromethyl)phenyl] sulfone **327a**, although the oxidation is remarkably difficult owing to the steric protection of the lone pair on sulfur by the CF_3 groups. Both the sulfoxide and the sulfone can be converted into the useful 4-chloro-4′-hydroxy monomers **326b** and **327b** by reaction with potassium hydroxide in aq. dimethyl sulfoxide at 120 °C (Scheme 28) [137].



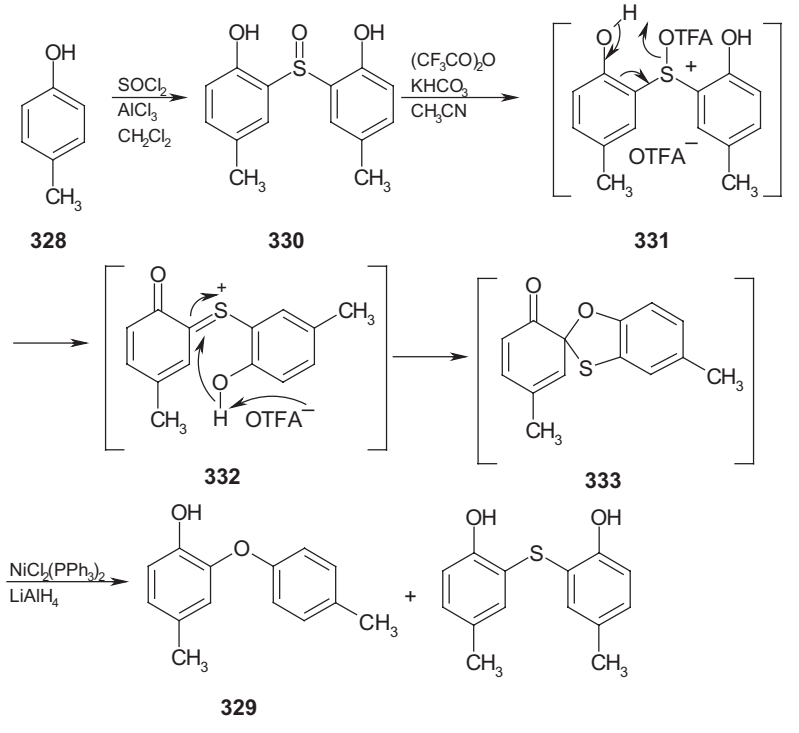
Reagents and conditions: (i) diethyl ether, Mg; then (at 0 °C) thionyl chloride, 19 h, H^+/H_2O; (ii) CrO_3, CH_3COOH, 100 °C, 24 h; (iii) KOH (2 mol. equiv.) in 85% aq. DMSO, 120 °C, 5 h, H^+/H_2O.

SCHEME 28

5.9 *Preparation of o-aryloxyphenols*

A simple two-step preparation of *o*-aryloxyphenols **329** has been described [138] in which the key step is the intramolecular trapping of an α-keto sulfonium salt **332**, prepared by Pummerer rearrangement of a symmetrical *o*-hydroxyaryl sulfide **331**, which in turn was prepared from sulfoxide **330** obtained from **328** in 95% yield (Scheme 29). Reduction of the

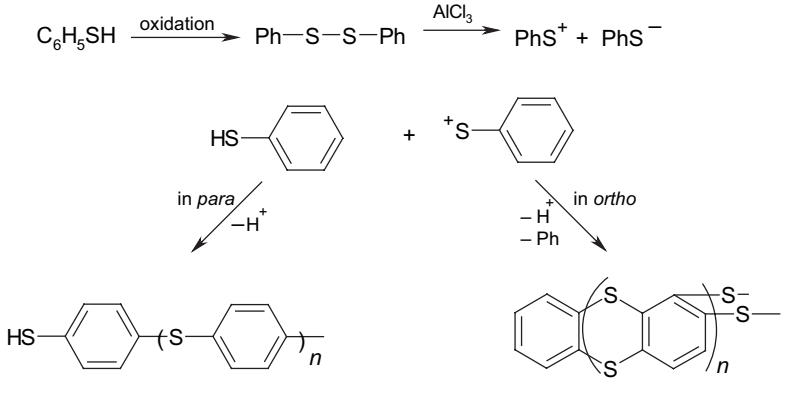
presumed intermediate **333** was achieved using the desulfurization reagent [139] prepared from $NiCl_2(PPh_3)_2$ and lithium aluminium hydride, to give the desired **329** in 38% yield along with the sulfide in 65% yield.



SCHEME 29

5.10 *Polymerization*

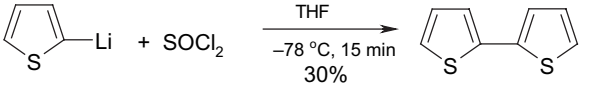
Polyarylene sulfides have wide applications [140], and several methods for their synthesis are based on high-pressure processes [141, 142]. A new method for the synthesis of poly-(*p*-phenylene sulfide) by oxidation of thiophenol (benzenethiol) with thionyl chloride in the presence of $AlCl_3$ in benzene has been described (Scheme 30) [143].



SCHEME 30

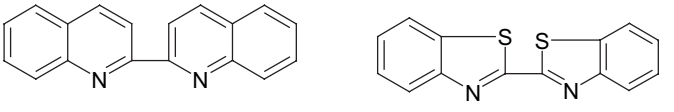
5.11 *Formation of heterocyclic biaryls*

When 2-thienyllithium was treated with thionyl chloride, the reaction product was shown to be 2,2′-bithienyl [equation (99)] [144].



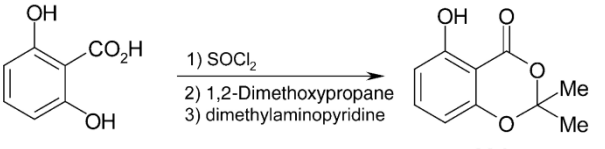
(99)

2,2′-Biquinolyl and 2,2′-bibenzothiazyl [145] can be prepared in the same manner.



5.12 *Preparation of 1,3-dioxines*

Modification of a known procedure [146], involving the interaction of thionyl chloride, acetone, and 2,6-dihydroxybenzoic acid, was found to provide 5-hydroxy-2,2-dimethyl-4-oxobenzo-1,3-dioxine **334** [equation (100)] [147].

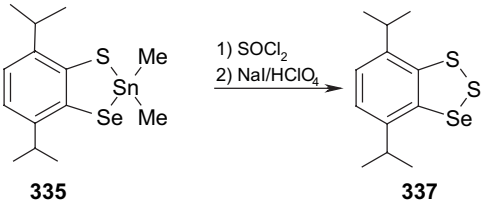


334 (66%)

(100)

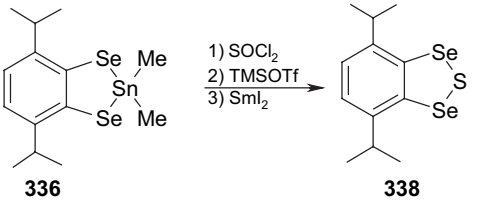
5.13 *Formation of benzotrichalcogenoles*

Stable 4,7-disubstituted benzotrichalcogenoles, *e.g.* **337** and **338**, containing both sulfur and selenium in the five-membered ring, have been prepared by reaction of the corresponding benzodichalcogenastannoles **335** and **336**, synthetic equivalents of benzenedichalcogenoles, with thionyl chloride [equations (101) and (102)] [148].



335 **337**

(101)



336 **338**

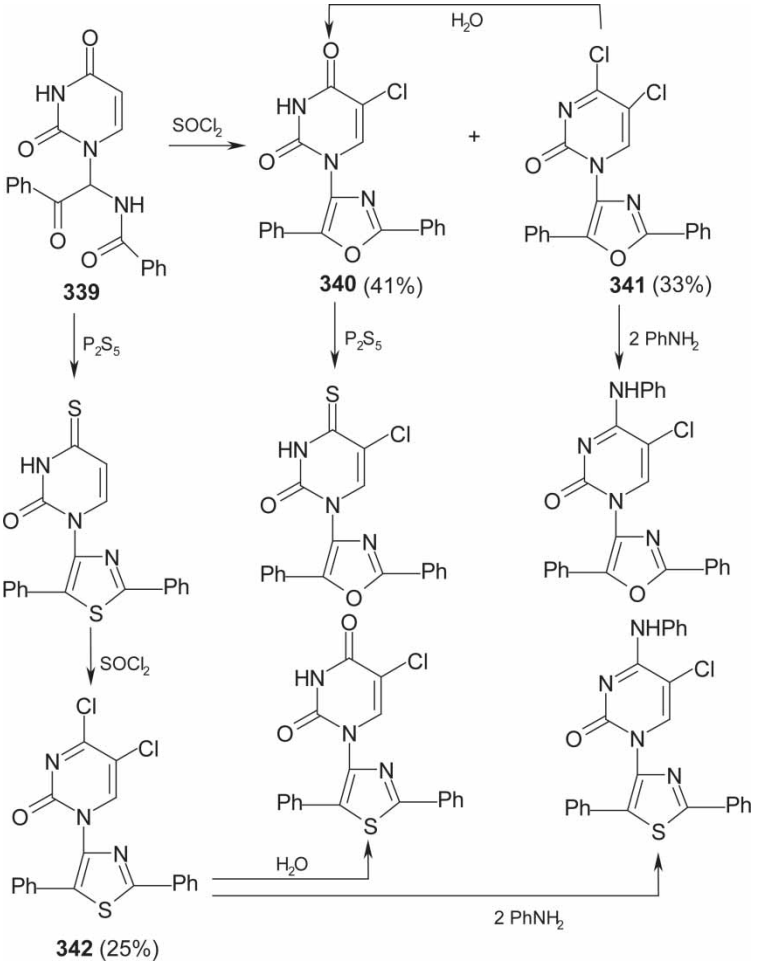
(102)

TMSOTf = trimethylsilyl trifluoromethanesulfonate

The characterization of these new trichalcogenole frameworks was performed by ^{77}Se NMR, and the cyclic voltammograms of the trichalcogenoles showed a reversible electrochemical oxidation with low oxidation potential [148].

5.14 *Heterocyclization*

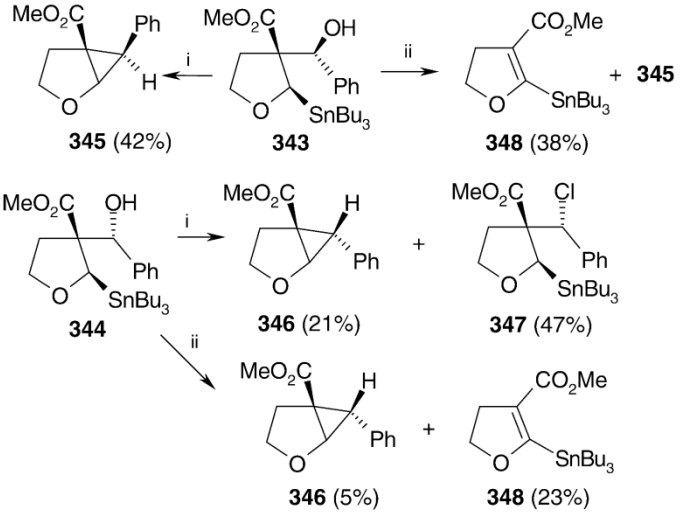
On treatment of 1-[benzoyl(benzamido)methyl]uracil **339** with thionyl chloride, or with phosphorus pentasulfide then thionyl chloride, along with other reactions, the substituent attached to the uracil nitrogen was shown to undergo cyclization that led to 1-(oxazol-4-yl)uracils **340** and **341** and 1-(thiazol-4-yl)-4-thiouracil **342** (Scheme 31) [149].



SCHEME 31

The diastereoisomerically pure alcohols **343** and **344** were subjected to cyclization using Johnson's conditions [150] (thionyl chloride, 3 molar equivalents; pyridine, 4 molar equivalents; THF; 0 °C; 90 min). In the case of the *syn*-aldol **343** examination of the high-field (300 MHz) ^{1}H NMR spectrum of the crude reaction mixture indicated that a clean 1,3-elimination had taken place, affording the 6-*exo*-substituted cyclopropane **345** as a single diastereoisomer

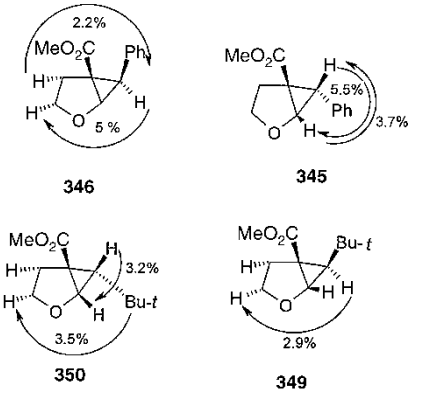
(Scheme 32). Column chromatography afforded the cyclopropane **345** in 42% yield. In the case of the *anti*-diastereoisomer **344**, cyclization under the same conditions afforded the 6-*endo*-cyclopropane **346** in a lower yield (21%) together with the diastereoisomerically pure **347** in 47% isolated yield.



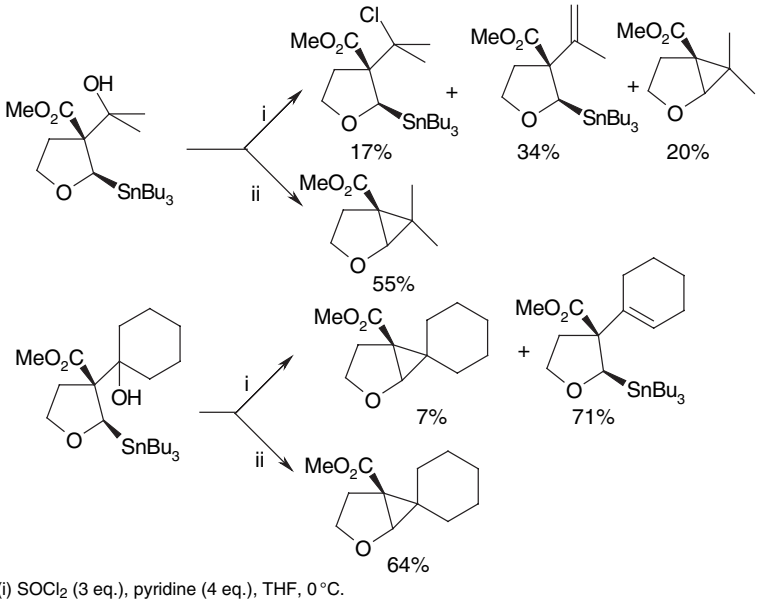
(i) $SOCl_2$ (3 eq.), pyridine, (4 eq.), CH_2Cl_2, 0 °C, 90 min.
(ii) $BF_3 \cdot 2AcOH$, (1.1 eq.), CH_2Cl_2, 0 °C, 30 min.

SCHEME 32

Further investigations showed that 1,3-elimination proceeds best with secondary or benzylic alcohols, with thionyl chloride/pyridine as promoter, whereas optimum yields for the cyclization involving tertiary alcohols require the use of the Lewis acid system developed by Fleming [151] (*i.e.*, $BF_3 \cdot 2AcOH$). Of note is the observation that high yields of cyclopropanes can be realized when sterically demanding substituents are directly attached to the reacting centres (*e.g.*, in the cyclopropanes **349** and **350**, even in the case of the 6-*endo*-substituted cyclopropanes). The stereochemical correlations in this series of compounds are based upon extensive ^1H NMR studies. These correlations were further substantiated by a single-crystal X-ray structure determination of the 6-*exo*-substituted cyclopropane **349** [152].



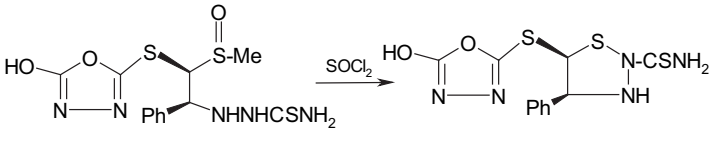
Cyclopropanes possessing two contiguous quaternary centres may also be prepared using this methodology, as exemplified in Scheme 33. This clearly demonstrates the effect of cyclization conditions upon the product distribution.



(i) $SOCl_2$ (3 eq.), pyridine (4 eq.), THF, 0 °C.
(ii) $BF_2 \cdot 2AcOH$, CH_2Cl_2, 0 °C.

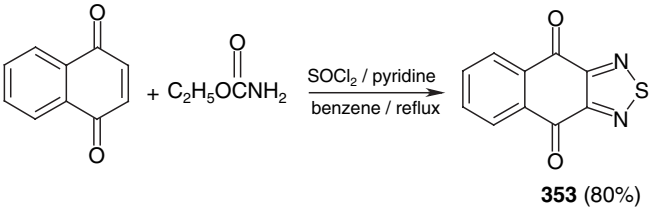
SCHEME 33

Adducts, *e.g.* **351**, obtained by nucleophilic addition of sulfenylated DMSO derivatives to thiosemicarbazone, undergo cyclization involving deoxygenative demethylation to yield 5-sulfenylated-4-aryl-2-thiocarbamoyl-1,2,3-thiadiazolidines, *e.g.* **352**, on treatment with thionyl chloride [equation (103)] [153].



351 **352** (68%) (103)

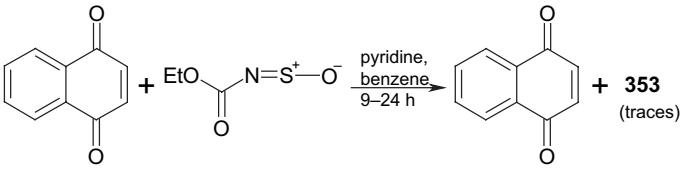
Naphtho[2,3-*c*][1,2,5]thiadiazole-4,9-dione **353** has been made by refluxing 1,4-naphthoquinone, ethyl carbamate (the methyl and benzyl esters work as well), thionyl chloride, and pyridine in benzene for a few hours [equation (104)] [154].



353 (80%) (104)

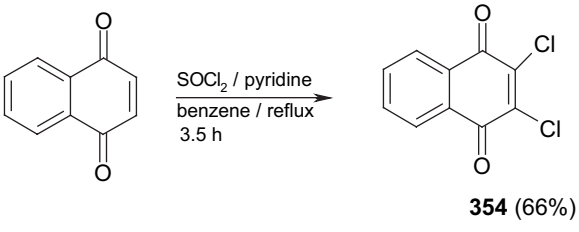
This result suggests that it is the alkyl *N*-sulfinylcarbamate (ROCONSO), formed under the reaction conditions [37, 155] that adds to the quinone. However, when ethyl

N-sulfinylcarbamate is mixed with naphthoquinone and pyridine in benzene, no significant amounts of **353** are formed [equation (105)].



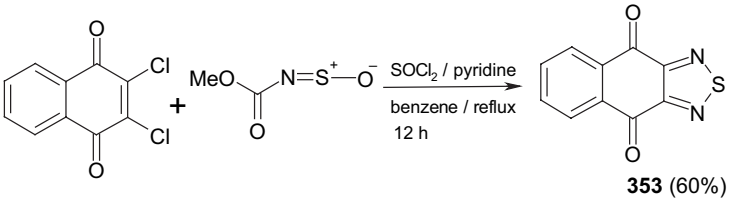
(105)

The implication is that thionyl chloride transforms 1,4-naphthoquinone into a reactive species. Accordingly, naphthoquinone was treated with thionyl chloride and pyridine in benzene and was shown to give 2,3-dichloro-1,4-naphthoquinone **354** in good yield [equation (106)].



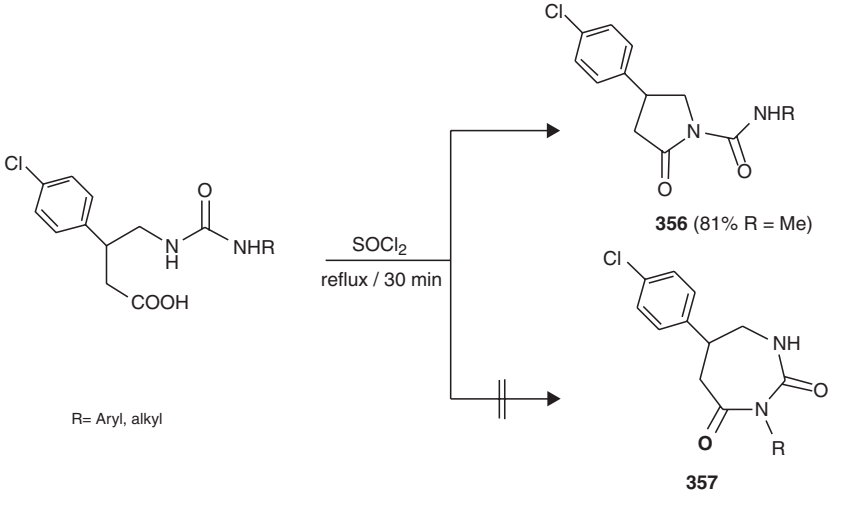
(106)

Moreover, **354** reacts with methyl *N*-sulfinylcarbamate and pyridine in refluxing benzene to give the thiadiazole **353** [equation (107)].



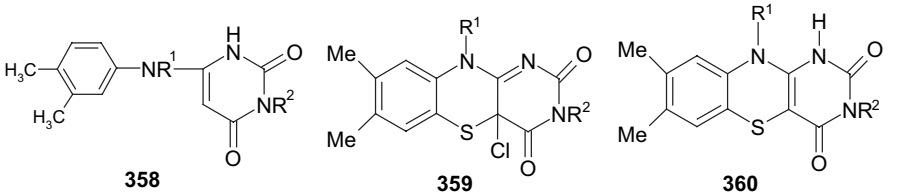
(107)

The structures of the previously reported [156] aryl-perhydro-1,3-diazepine-2,4-diones **357** prepared by cyclization of 4-ureidobutyric acids **355** with thionyl chloride, were shown to be pyrrolidine carboxamide derivatives **356** by NMR spectroscopy (108) [157].



(108)

Uracils **358** reacted with thionyl chloride to give 53–61% yields of **359**. Dechlorination of **359** with N_2H_4 gave **360** (the ribityl group being aminolyzed during the process), while compounds **359** (R^1 = Me; R^2 = H, Me) were converted into their sulfoxides [158].

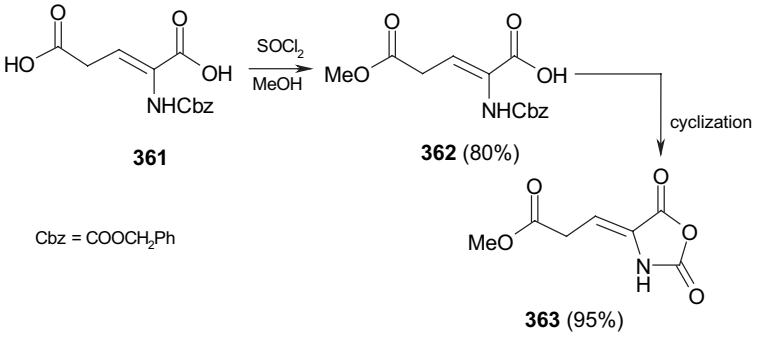


358 **359** **360**

R^1 = tetracetylribityl, Me; R^2 = H
$R^1 = R^2$ = Me

R^1 = H, Me; R^2 = H
$R^1 = R^2$ = Me

Esterification of dehydroglutamic acid **361** with MeOH in diethyl ether in the presence of thionyl chloride gave the γ-ester Cbz-ΔGlu(Me)-OH **362**. Subsequent cyclization between the α-carboxy and α-Cbz groups of **362** with an excess of thionyl chloride in acetyl chloride gave the expected ΔGlu(Me)-NCA **363** [equation (109)] [159].

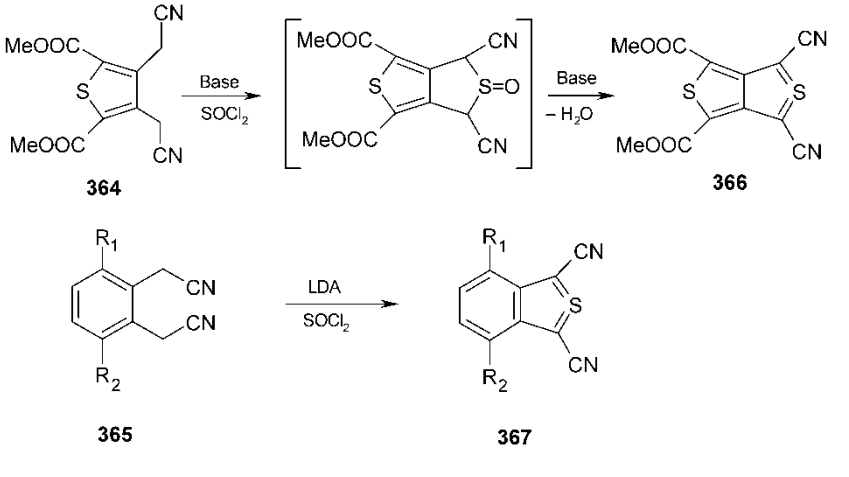


361 **362** (80%) **363** (95%)

Cbz = $COOCH_2Ph$

(109)

Thionyl chloride serves as an S-transfer reagent upon reactions with carbanions in the presence of a base. Thus 3,4-cyanomethyl-substituted thiophene **364** and 1,2-phenylenediacetonitriles **365** gave dicyano-substituted $2\lambda^4$-thieno[3,4-*c*]thiophenes **366** and dicyano-substituted $2\lambda^4$-benzo[*c*]thiophenes **367**, respectively [equation (110)] [160].



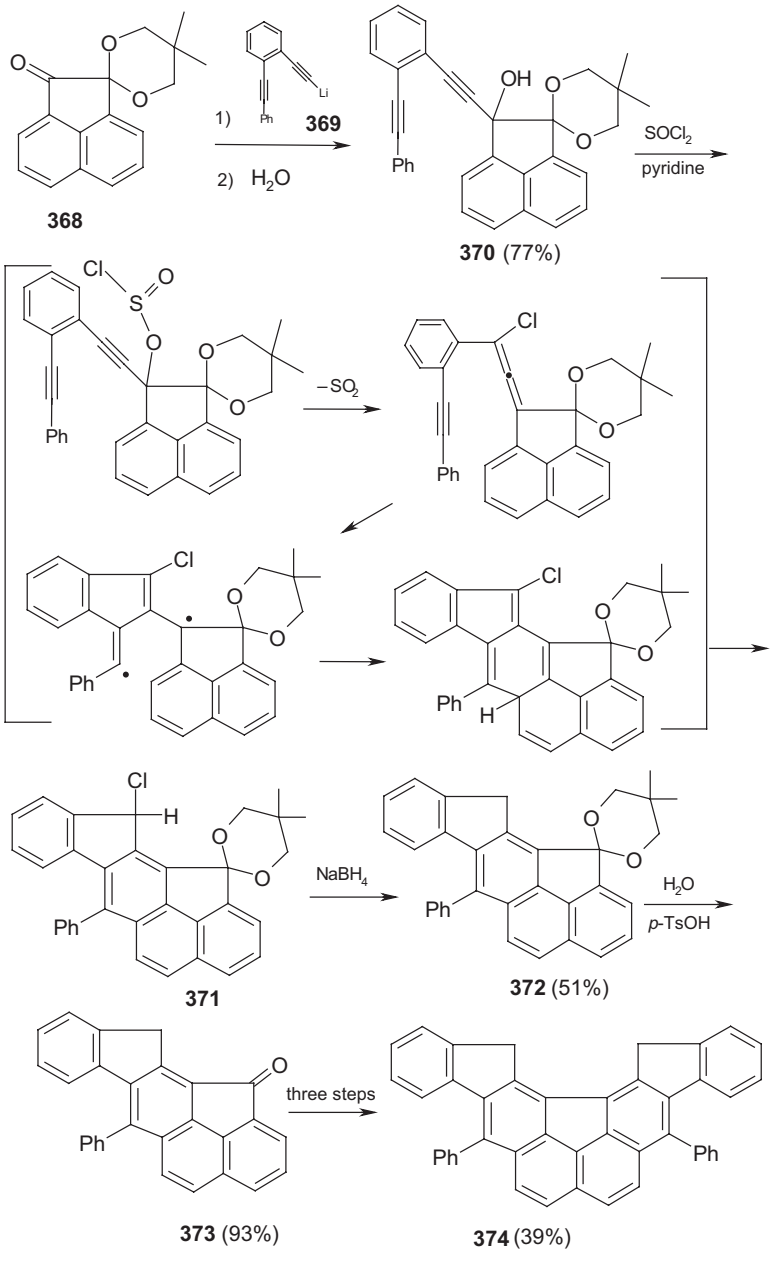
364 **366**

365 **367**

$R_1 = R_2$ = H
R_1 = Cl, R_2 = Br

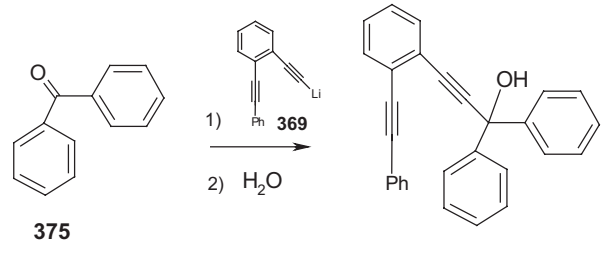
(110)

Thionyl chloride reacted with the monoprotected diacetylenic alcohol **370** to give the chloride **371**, which was reduced to **372**. Deprotection of ketal **372** then afforded **373**, having a carbonyl group to allow a repeat of the condensation and the Schmidt cyclization sequence to give polycycle **374** [161]. The alcohol **370** was obtained from monoprotected acenaphthenequinone **368** and the lithium acetylide **369** (Scheme 34) [162].

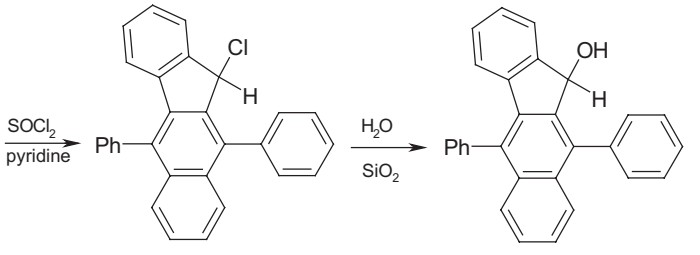


SCHEME 34

To prove the scope and limitations of thionyl chloride-induced cascade transformations, several representative aryl ketones (*e.g.*, **375**, **376**, and **377**) were selected for condensation with **369** and further reaction with thionyl chloride. A new synthetic route to the benzoenyne-allenes without a chloro substituent was also developed to allow a direct transformation to the corresponding polycyclic aromatic hydrocarbons [equations (111–113)] [162].

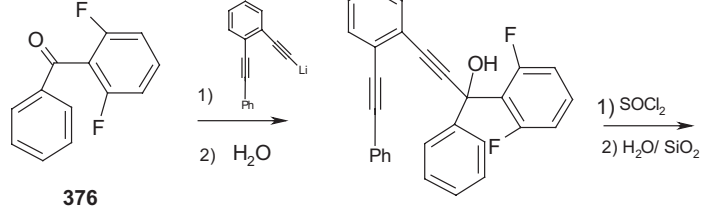


375

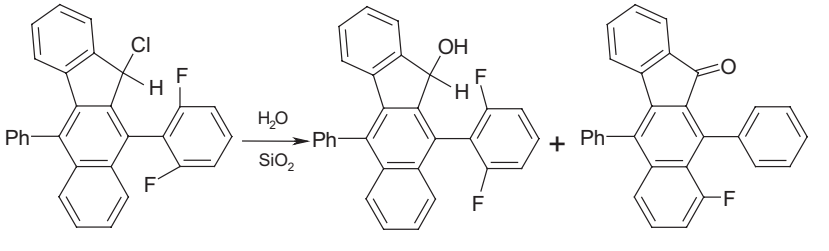


378

(111)

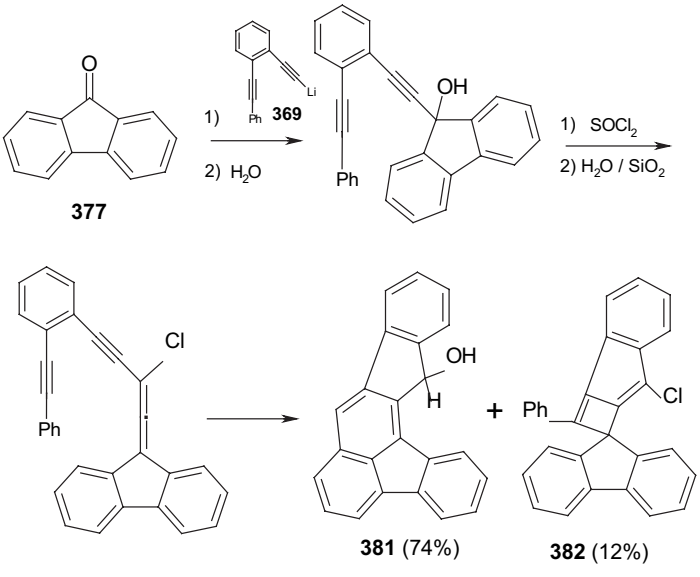


376



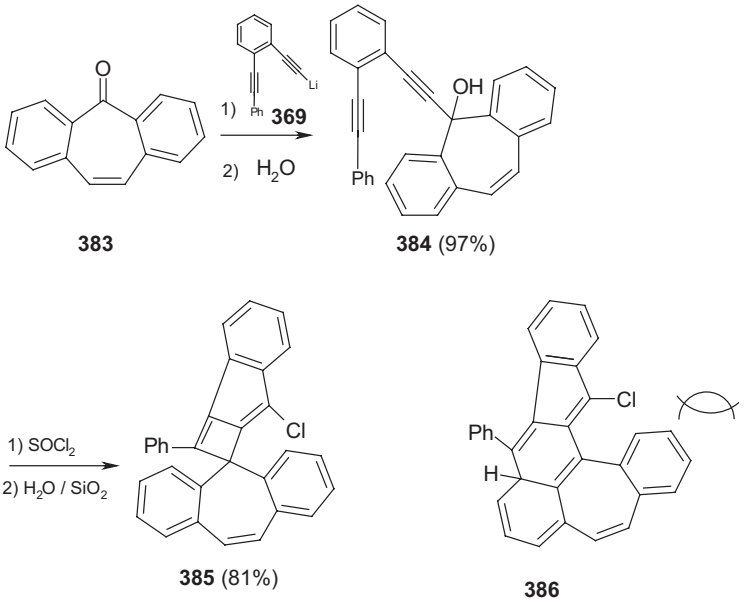
379 (52%) **380** (37%)

(112)



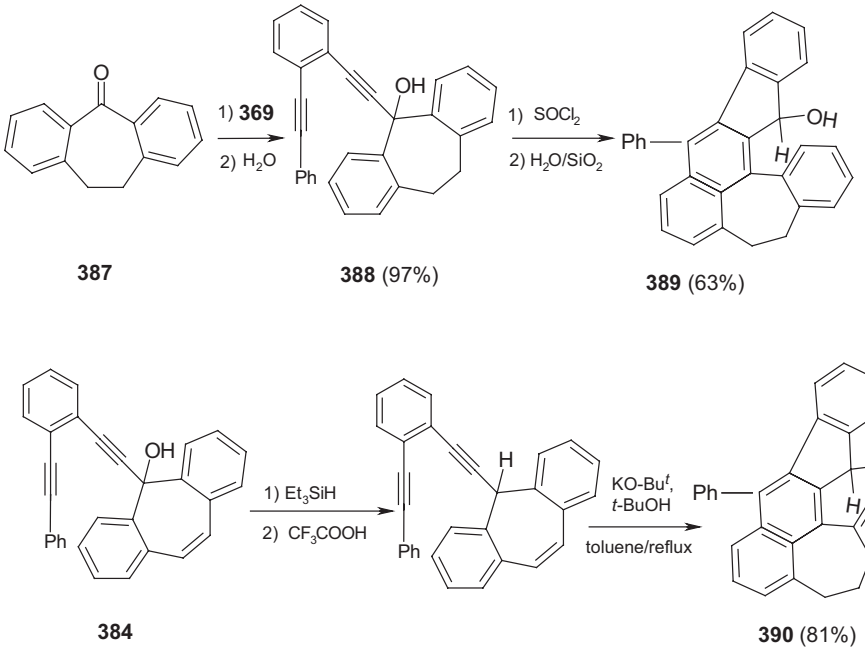
(113)

Interestingly, in the case of diacetylenic alcohol **384** obtained from the dibenzosuberenone **383**, an intramolecular [2 + 2] cycloaddition of the chlorinated benzoenyne-allene intermediate occurred, furnishing the ^{1}H-cyclobut[*a*]indene **385** exclusively. This dramatic change is the reaction pathway could be attributed to the emergence of steric strain due to the nonbonded interactions with the chloro substituent along the pathway toward the formal Diel–Alder adduct **386** [equation (114)] [162].



(114)

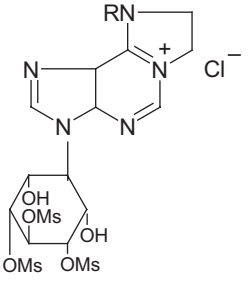
On the other hand, with **388**, derived from dibenzosuberone **387** and **369**, the formal [4 + 2] cycloaddition reaction of the chlorinated benzoenyneallene was again the preferred pathway, leading to formation of the alcohol **389**. Exclusive formation of the [4 + 2] cycloaddition adduct **390** was also observed, starting from **384** [equation (115)] [162].



(115)

5.15 *Preparation of nucleosides*

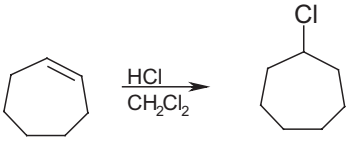
The reaction of mono- and di-ethanolamine with a 6-chloropurinyl-inositol gave 6-ethanolaminopurinyl-inositol derivatives, which by reaction with thionyl chloride generated, through quaternization of N-1 of the purine, condensed imidazo-purinyl carbocyclic nucleoside analogues **391** (R = H, CH_2CH_2Cl). Proliferation of primary cultures of murine breast adenocarcinoma by the diverse metastatic capacity of **391** has been reported [163].



391
R = H, CH_2CH_2Cl

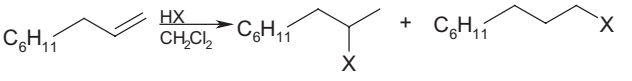
5.16 *Use as an HCl precursor*

The use of silica gel and alumina facilitates the electrophilic addition of hydrogen halides to alkenes and alkynes. This procedure is rendered even more convenient by using HX precursors in conjunction with the adsorbent; *e.g.*, adding thionyl chloride as an HCl precursor to a solution of an alkene **392** or **394** or an alkyne **397** containing a suspension of silica gel or alumina gave the chlorides **393**, **395**, or **399** (X = Cl) rapidly and in high yields [equations (116–118) [164].



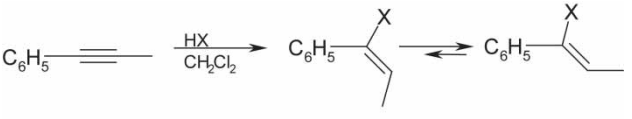
392	**393**
97% HCl	0%
3% HCl, SO_2	62%
3% $SOCl_2$, SiO_2	81%

(116)



394 **395** **396**

(117)

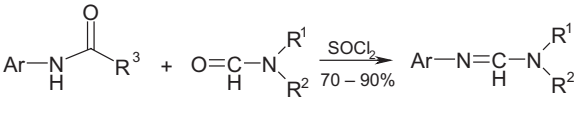


397 *(E)*-**398** *(Z)*-**399**

(118)

5.17 *As a condensing agent*

Acetanilides **400** react with dialkylformamides **401** in the presence of thionyl chloride as a condensing agent to give the formamidines **402**, which are used as acaricides and/or insecticides [equation (119)] [165].



400 **401** **402**

(119)

a; Ar = 2,4-Me(Cl)C_6H_3, Ph; R^1 = R^2 = Me
b; Ar = 2,4$Cl_2C_6H_3$; R^1 = CH_2SMe, R^2 = Me
c; Ar = 2-MeC_6H_4; R^1 = Et; R^2 = H, R^3 = Me, CH_2Cl

The mechanism of the reaction may be similar to that described by Pedersen [166].

5.18 *Co-ordinating power and reactivity of thionyl chloride*

The enthalpies of mixing of thionyl and sulfuryl chlorides with organic solvents were determined by calorimetry. Thionyl and sulfuryl chlorides exhibit electron-acceptor properties in mixtures with organic solvents, and the enthalpies of mixing increase with increasing basicity

of the solvents. In the case of strong electron donors, the electron-acceptor power of sulfuryl chloride is higher than that of thionyl chloride. The enthalpies of reaction of cellulose with the complexes of thionyl chloride with DMF and of sulfuryl chloride with *tert*-butyl hydroperoxide in Et_2O were evaluated [167].

6. Conclusions

The reactions of thionyl chloride, submitted in this review, can be summarized as follows. Thionyl chloride reacts with amines, sulfonamides, imines, carbamates, or enols to form sulfinyl chlorides. In the case of primary amines and methylene compounds, the first-formed sulfinyl chlorides are dehydrochlorinated to give sulfines [107]. In the case of active methyl or active methylene compounds, sulfenyl chlorides are formed through Pummerer-type rearrangement [168].

Thionyl chloride reacts with carbonyl compounds through electrophilic addition to the C=O group. It reacts with compounds containing C−C multiple bonds through electrophilic addition or substitution. The first-formed above intermediates are transformed to other useful compounds either by intramolecular transformations, including cyclization, by rearrangements, or by reactions with dienes. Thionyl chloride can be used in oxidation and partial dehydrogenation of organic compounds. It can also be used as a chlorinating agent through its oxidation in atmospheric oxygen to give sulfuryl chloride, which is a well known chlorinating agent. Thionyl chloride can be used as an HCl precursor for attacking multiple bonds. It can be also used as a condensing agent.

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