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REVIEW ARTICLE

Thiocarbamoyl derivatives as synthons in heterocyclic synthesis

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The synthetic utility of thiocarbamoyl derivatives is reported in a formal way. The title compounds are used as precursors for the synthesis of many heterocyclic rings. The reactions of the title compounds are subdivided into groups that cover reactions yielding monocyclic heterocycles *e.g.*, pyrroles, thiophenes, pyrazoles, imidazoles, thiazoles, pyridines, pyrimidines, oxazines, and even fused heterocycles, *e.g.*, thiazolopyrimidines and thiazolotriazines.

Keywords: Isothiocyanates; Thiocarbamoyls; Thiophenes; Thiazoles; Pyrazoles; Pyridines; Pyrimidines; Thiazolopyrimidines

1. Introduction

Thiocarbamoyl derivatives are important intermediates in the synthesis a variety of heterocyclic compounds. In the presence of diverse reagents, they undergo special types of reactions to yield different heterocycles, *e.g.*, thiophenes, pyrimidines, pyridines, *etc.* [1–5]. The chemistry of thiocarbamoy1 derivatives has been published in the older literature by many authors [6–8]. There is only scattered information available in literature about the synthetic utility of thiocarbamoyl derivatives and thus an attempt was made to bring accessible information together in this review.

The highly functional thiocarbamoyl derivatives of the general formulas **1** and **2** have recently received considerable attention due to their synthetic importance for the construction of a variety of heterocyclic compounds. The method for preparation of these thiocarbamoyl derivatives **1** [9–13] and **2** [14–16] involves the basic catalyzed addition of isothiocyanates to active methylene reagents and to primary amine compounds, respectively.

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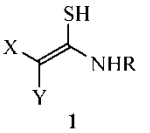
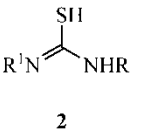


1

X = CN, COOEt, COMe, heteroaryl;
Y = CN, COOEt, COMe



2

R^1 = alkyl, heteroaryl

2. Thiocarbamoyl derivatives in heterocyclic synthesis

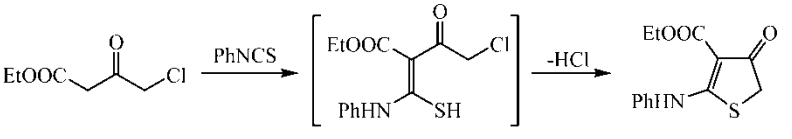
2.1 *Thiophenes*

The thiocarbamoyl derivative **3**, derived from the base catalyzed addition reaction of ethyl 4-chloroacetoacetate with phenyl isothiocyanate, underwent intramolecular cyclization to afford the corresponding thiophen-4-one **4** (scheme 1) [17].

2-Anilinothiophene derivative **6** [18] was prepared by treatment of phenacyl cyanide with PhNCS/NaH and chloroacetonitrile through the non-isolable intermediate **5** (scheme 2).

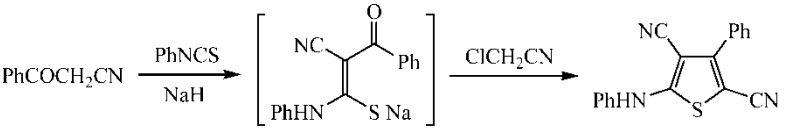
Thiophenes of the general formula **8** (R = alkyl or aryl; R^1 = acyl, ester, NO_2, CN) were prepared by reacting phenyl acetaldehyde with isothiocyanates in an aprotic solvent in the presence of a base followed by *in situ* cyclization of the intermediate thiocarbamoyl salt **7** with R^1-CH_2-X (scheme 3) [19].

In a comparable manner, thiophenes of the general formula **10** (R = Ph, MeCO, PhCO, NO_2) [20] were prepared by the reaction of ω-nitroacetophenone with phenyl isothiocyanate in the presence of sodium hydride followed by *in situ* cyclization of the thiocarbamoyl salt **9** with R-CH_2-Br (scheme 4).



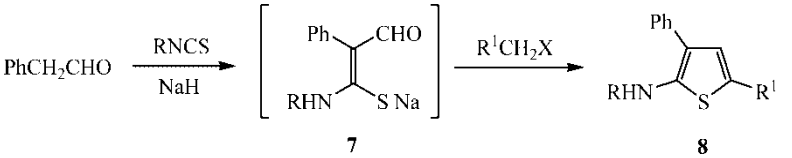
3 **4**

SCHEME 1



5 **6**

SCHEME 2



7 **8**

SCHEME 3

Thiocarbamoyl salts of the type **11** were reacted with bromonitromethane to afford the corresponding nitrothiophenes **12** (R = Me, Ph; $R^1 = CO_2Et$, CN) (scheme 5) [21].

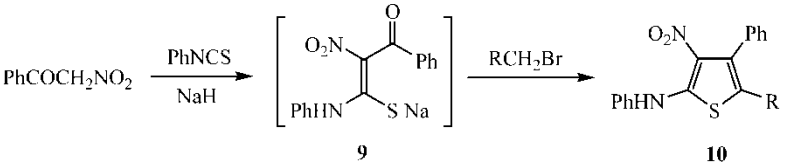
Thiazolines of the formula **13** (R = Ph, CH=CH-CH_3, $R^1 = CO_2Et$; R = Ph, R^1 = CN) were prepared by treating $RNHCSCHR^1CN$ with chloroacetonitrile and gave thiophenes **14** on treatment with sodium ethoxide (scheme 6) [22].

The reaction of malononitrile with isothiocyanates and chloromethylcarbonyl compounds gave the diaminoacylcyanothiophenes **15** ($R^1 = CH_2$=CH-CH_2, Ph; R^1 = Me, MeO, EtO) (scheme 7) [23].

Phenyl isothiocyanate reacted with active methylene components *e.g.* malononitrile followed by cyclization with bromomalononitrile to give thiocarbamoyl derivative **16** and thiophene dicarbonitrile **17** (scheme 8) [24].

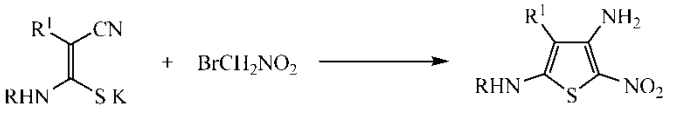
Treatment of the thiocarbamoyl derivative **18** with 2-(2-bromo-1-phenylethylidene)malononitrile in the presence of sodium ethoxide afforded thiophene of the type **19** (scheme 9) [25].

Thioacetanilide derivatives prepared from phenyl isothiocyanate and R^1-CH_2-R^2 (where R^1 = CN; R^2 = CN, COOEt, $R^1 = R^2 = CO_2Et$) reacted with RCH_2COCH_2COOEt



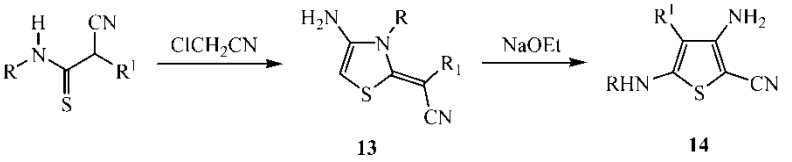
9 **10**

SCHEME 4



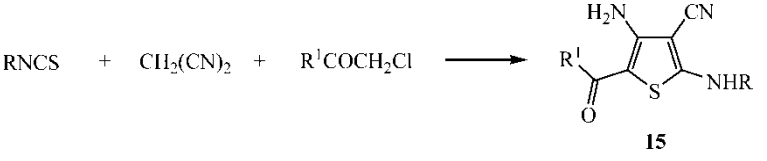
11 **12**

SCHEME 5



13 **14**

SCHEME 6



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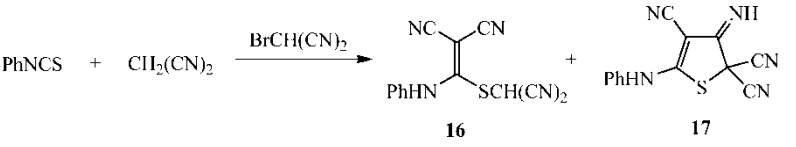
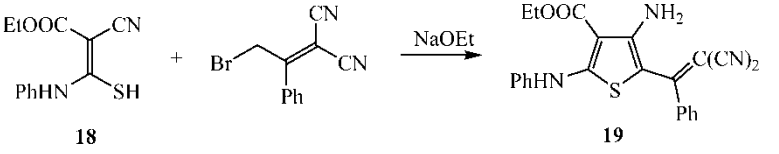
SCHEME 7



SCHEME 8



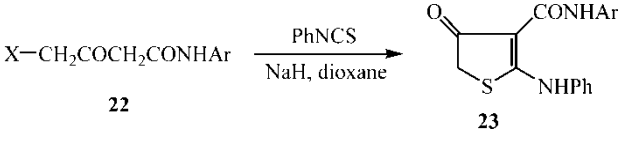
SCHEME 9

(R = Cl; Br) to give the hydroxythiazolidine acetates **20** and the thiophene **21** [26].

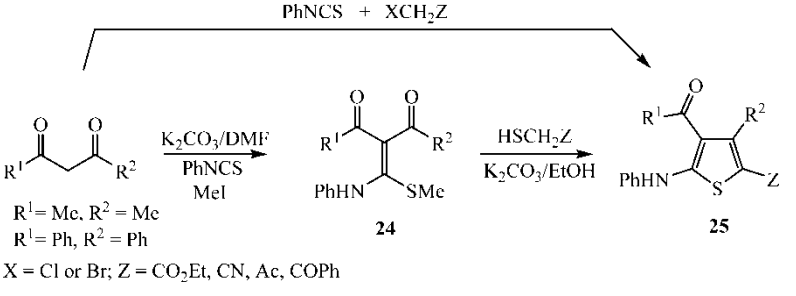
Active methylene compounds **22** reacted with phenyl and aroyl isothiocyanates affording thiophene derivative **23** *via* cyclodehydrohalogenation of the adduct (scheme 10) [27].

Phenyl isothiocyanate condensed with 1,3-dicarbonyl compounds (or its equivalents) in basic media to afford thiocarbamoyl derivatives **24**, which when treated with an activated methylene compounds afforded the corresponding 5-phenylaminothiophenes **25** (scheme 11) [28, 29].

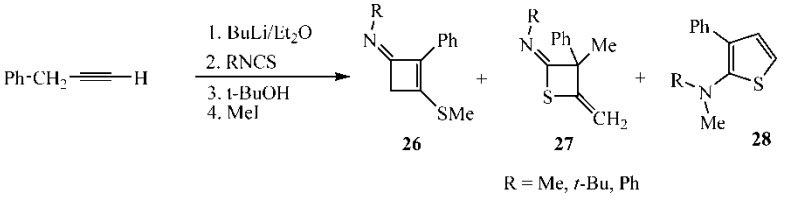
Benzylacetylene undergoes dilithiation to give the dilithiobenzylacetylene as a reactive intermediate, reaction of the dilithiobenzylacetylene with one equivalent of isothiocyanates followed by successive addition of *t*-BuOH, *t*-BuOK in DMSO, and methyl iodide gives unusual cyclobutene **26** (R = Me, Me_3C) and thietane products **27** (R = Me, Ph) in addition



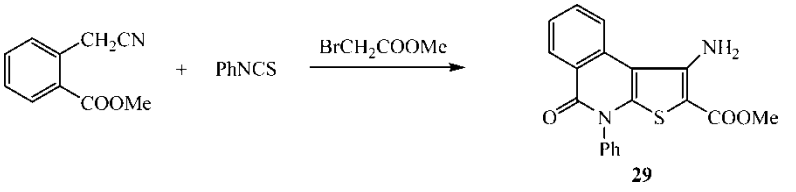
SCHEME 10



SCHEME 11



SCHEME 12



SCHEME 13

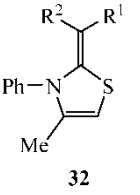
to the desired thiophene derivative **28** (scheme 12, R = Me). The chemoselectivity of the cyclization depends on the structure of the isothiocyanate; when methyl isothiocyanate is used, a mixture of **26** (R = Me, 65% yield), **27** (15% yield) and **28** (15% yield) is isolated, while *t*-butyl isothiocyanate gives a 65% yield of **26** (R = Me_3C) as the sole product, and phenyl isothiocyanate gives **27** (R = Ph) as the only product in 77% yield [30].

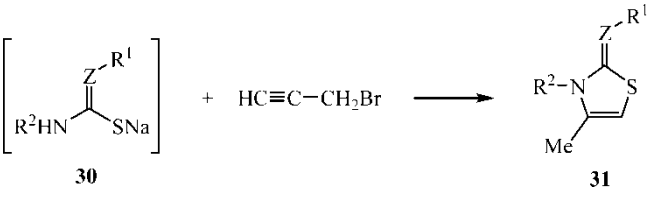
Thienoisoquinoline of formula **29** was prepared by treating 2-$(NCCH_2)C_6H_4$-CO_2CH_3 with phenyl isothiocyanate in THF/NaH followed by cyclization with bromomethyl acetate (scheme 13) [31].

2.2 *Thiazoles*

4-Methyl-4-thiazolines of the general formula **31** (scheme 14, R^1 = aroyl, heteroaroyl, Ph-CH=CH-CO, arylsulfonyl, cyano; R^2 = alkyl, aryl; Z = N, C(CN)) were obtained from the sodium salt of the thiocarbamoyl adduct **30** and HC≡C-CH_2-Br [32].

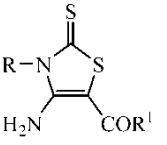
Thiazoles of the type **32** (R^1 = Bz, *p*-MeC_6H_4CO, *p*-$MeOC_6H_4CO$, *p*-ClC_6H_4CO; R^2 = H; R^1 = Ph, R^2 = CN; R^1 = Ac) were prepared by the cyclization of $R^1CH_2R^2$ with PhNCS in the presence of chloroacetone through the thiocarbamoyl intermediate [33].





SCHEME 14

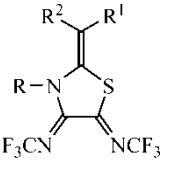
Aminothiazoles **33** (R = Et, benzyl, allyl, Ph, tolyl; $R^1 = NH_2$, NHMe, piperidyl, morpholinyl, PhNHNH) were prepared by the reaction of isothiocyanates with NC-CH_2-$CONHR^1$. The products were screened for their antimicrobial and pharmacological activities. The maximum anti-inflammatory activity was gained when R = o-tolyl and R^1 = morpholinyl [34].



33

Hydrazonoyl halides reacted with cyano-(1-methylbenzimidazol-2-yl) thioacetanilide **34** in DMF in the presence of potassium hydroxide to give 5-arylazo-2,3-dihydrothiazoles **35** (scheme 15, R^1 = Ph, R^2 = H; R^1 = 2-thienyl, 2-furyl, $R^2 = NO_2$; R^1 = Ph, R^2 = H, R^3 = Me, Ph, 2-thienyl, 2-naphthyl) [35].

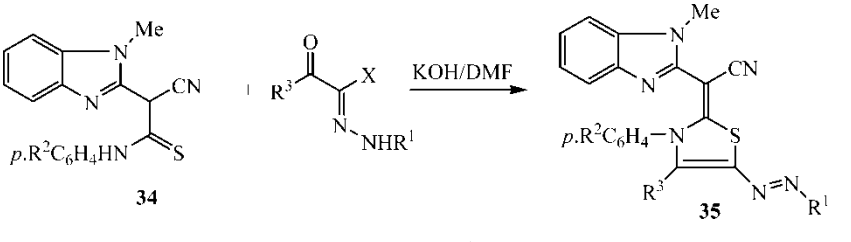
The fungicidal compounds **36** (R = cycloalkyl, aryl, aralkyl, NH_2 or N-heterocyclyl; R^1 = H, CN, alkoxycarbonyl, acyl; R^2 = CN, alkoxylcarbonyl, acyl, alkyl or arylsulfonyl, $CONH_2$, $CSNH_2$) were prepared by the reaction of the thiocarbamoyl derivative $R^1R^2CHCSNHR$ with (F_3CN=CF-CF=NCF_3) in the presence of a fluoride acceptor [36].



36

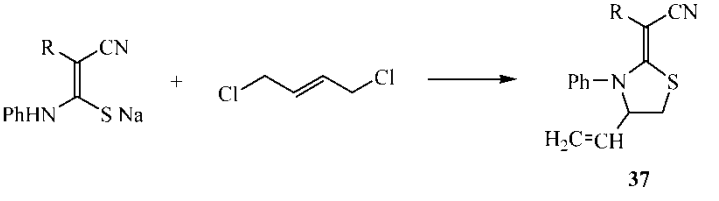
4-Vinylthiazolidines **37** (R = PhCO, 2-furoyl, tosyl, CO_2Et, CN) were prepared by treating R-CH_2-CN with PhNCS and NaH in DMF followed by the addition of Z-1,4-dichloro-2-butene (scheme 16) [37].

Thiazolines of the general formula **38** (R = alkyl; R^1 = Ph, heteroaralkyl, aralkyl) were prepared by treating 2-bromoacetylfuran with ammonium salt of ketene *N*,*S*-acetals, $RO_2C(NC)C{=}C(NHR^1)S\ NH_3R^1$ (scheme 17) [38].



34 **35**

SCHEME 15



37

SCHEME 16

Cyclocondensation of **18** with 3,4,5,6,7-penta-*O*-acetyl-1-bromo-1-deoxy-D-galacto-heptulose gave thiazolidines **39** (scheme 18) [39].

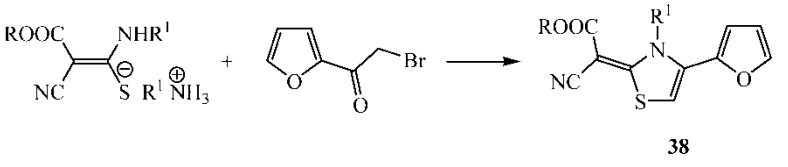
Cycloaddition of arylhydrazo 1,3-dichloroacetone **40** (scheme 19, R = H, Me) with thioamide **18** gave the thiazolines **41** while cyclization of **40** with arylhydrazo of 2-(thioamide)ethyl acetate **42** gave the thiazoles **43** (scheme 20, R^1 = 2-Me, R^2 = 4-NO_2, 4-Cl) [40].

1,3-Thiazolidine **45** was prepared from ring opening of the aroylazridine **44** when treated with phenyl isothiocyanate (scheme 21) [41].

Active methylene components RCH_2R^1 reacted with phenyl isothiocyanate and sulfur in refluxing DMF containing a catalytic amount of triethyl amine to give the thiazoles **46** (scheme 22, R = CN, COMe, CO_2Et; R^1 = CN, CO_2Et, $CONH_2$, COMe; R^2 = NH_2, CH_3, OH) [42].

The active methylene components CH_2RR^1 react with phenyl isothiocyanate followed by cyclization with bromoacetyl coumarin to afford the thiazole derivatives **47** (scheme 23, R = CN, R^1 = CO_2Et; R = COMe, R^1 = COMe, CO_2Et, CONHPh) [43].

Anticholesteremic 2-thiazolones **48** (R = Ph, 4-$MeOC_6H_4$; R^1 = $(Me)_2CHCH_2$; R^2 = H, Me or MeO) were prepared by the reaction of 4-$R^2C_6H_4CH(Cl)COR_1$ with isothiocyanates



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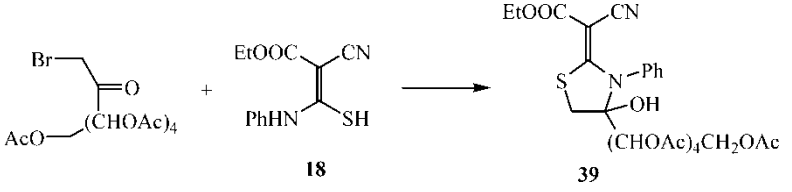
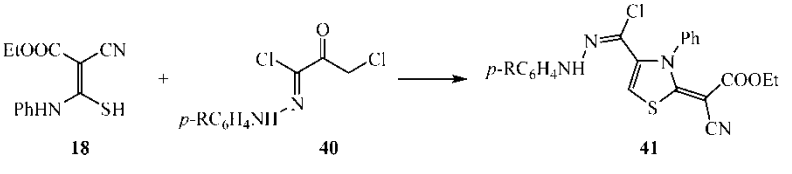
SCHEME 17



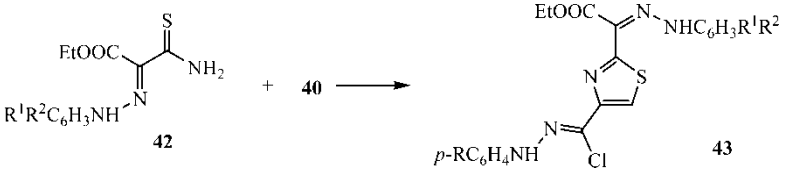
18 **39**

SCHEME 18



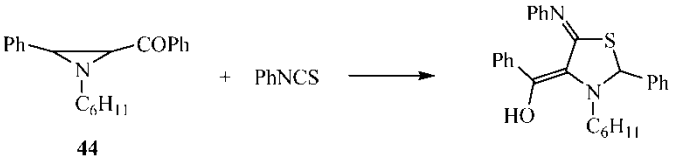
18 **40** **41**

SCHEME 19



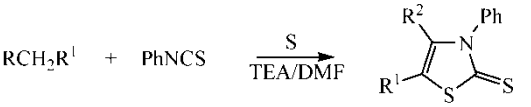
42 **43**

SCHEME 20



44 **45**

SCHEME 21



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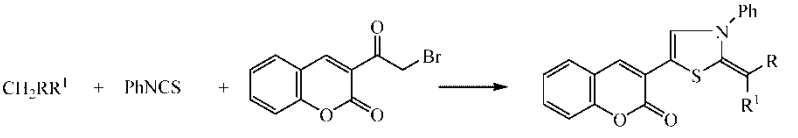
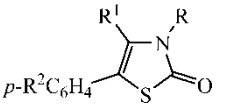
SCHEME 22



47

SCHEME 23

through the intermediate thiocarbamoyl derivatives [44].



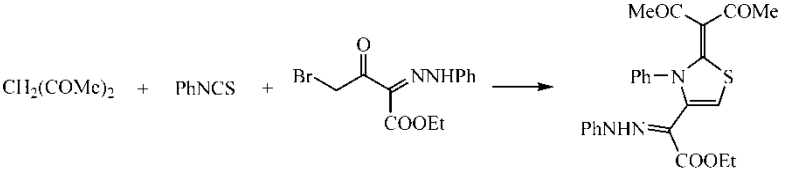
48

The thiocarbamoyl derivative from acetyl acetone undergoes cyclization with ethyl α-bromo phenylhydrazono acetoacetate to afford the thiazole **49** (scheme 24) [45].

The thiadiazolines **52** and thiazolones **53** (scheme 25, R = Ph, p-MeC_6H_4; R^1 = H, Cl; R^2 = Ph, CO_2Et, MeCO, COCl) were prepared by cyclization of β-oxo-thioacid anilides **50** with acylchloride arylhydrazones **51** [46].

The reaction of non-isolable potassium salt adduct **54** with α-halogenated compounds proved to be an easy and facile route for the synthesis of several new highly functionalized thiophene, Δ^4-thiazoline and thiazolidinone derivatives **55**–**59** (scheme 26) [47].

The potassium salt of the adduct **60** reacted with α-halogenated compounds, *e.g.*, chloroacetone, phenacyl bromide, bromoacetyl bromide and chloroacetonitrile to give the corresponding



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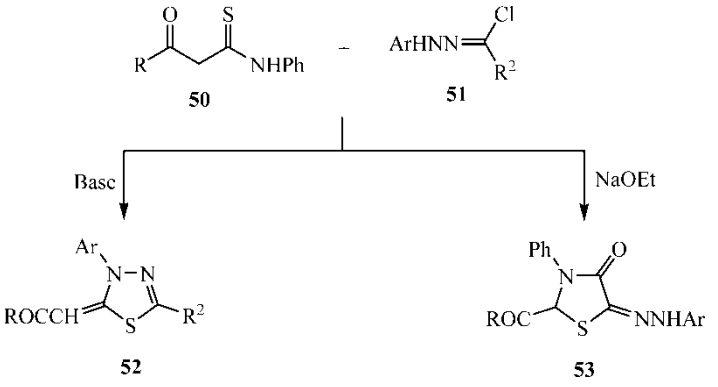
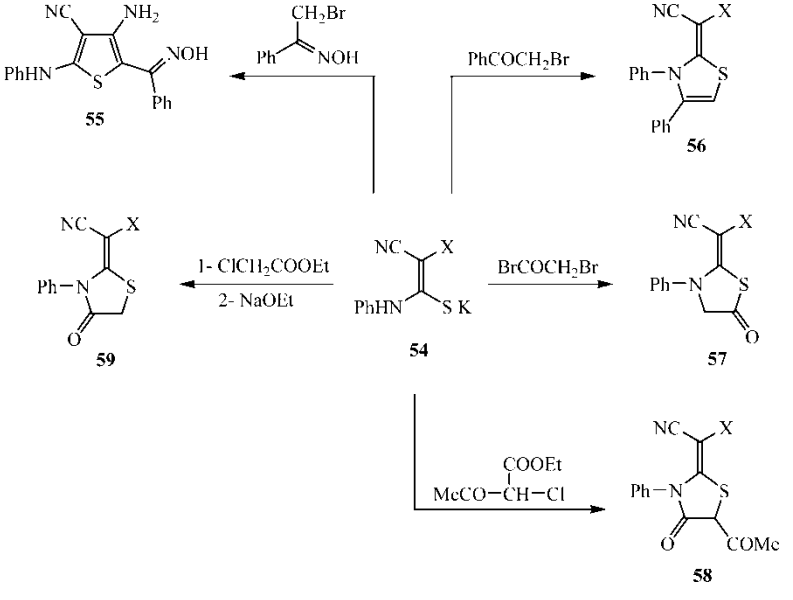
SCHEME 24



SCHEME 25



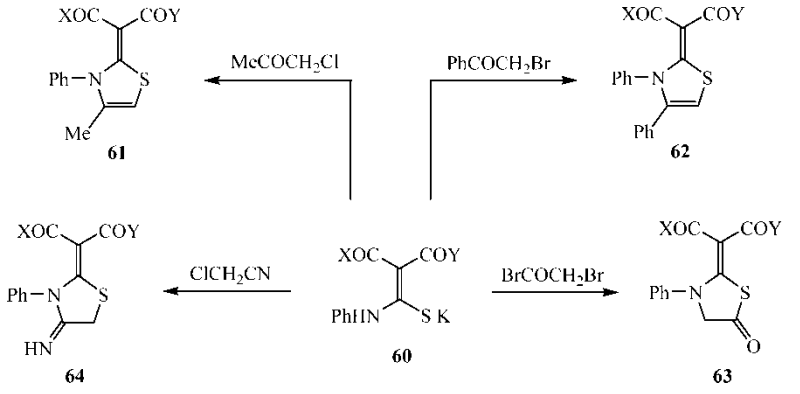
SCHEME 26

polyfunctionally substituted 2,3-dihydrothiazoles **61** and **62**, thiazolidinones **63** and **64** (scheme 27) [48].

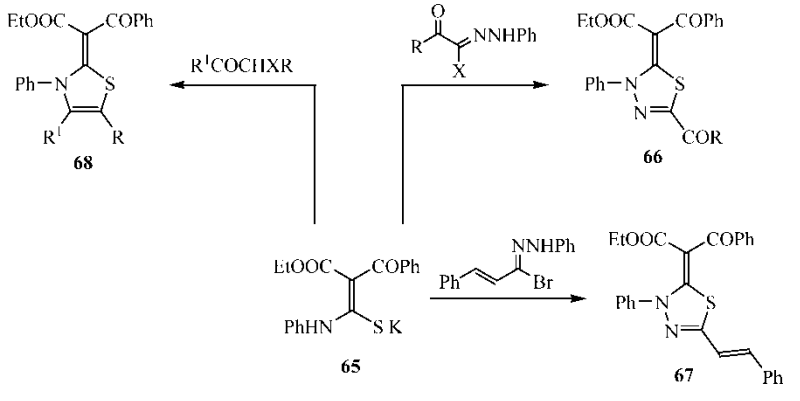
The non-isolable thiocarbamoyl adduct of the type **65** reacted with hydrazonoyl halides to give thiadiazole derivatives **66** and **67**. The adduct **65** reacted with R^1-CO-CH(X)R to give the corresponding 2,3-dihydrothiazoles **68** (scheme 28) [49].

The potassium salt of the thiocarbamoyl adduct **69** (scheme 29, R = CN, MeCO, CO_2Et; R^1 = CO_2Et, CN, COPh, COMe) was alkylated with ethyl cyanobromoacetate to **70** followed by cyclization to compounds **71**–**73** [50].

Various 3-substituted-2-thiono-4-thiazolidinones **74** can be conveniently prepared by the reaction of substituted isothiocyanates with α-mercapto acetic acid or its ester followed by acid cyclization of the resulting (thiocarbamoyl) mercapto acetic acids and acetates (scheme 30) [51].



SCHEME 27



SCHEME 28

N-Methylglycine amide reacts with carbon disulfide in the presence of methanol and gives *N*-methyl-*N*-(carbamoylmethyl) ammonium *N*-methyl-*N*-(carbamoylmethyl) dithiocarbamate. This dithiocarbamate on acidification with concentrated hydro-chloric acid or phosphorus trichloride gives 2-thio-3-methyl-5-thiazolodinone **75** (scheme 31) [52, 53].

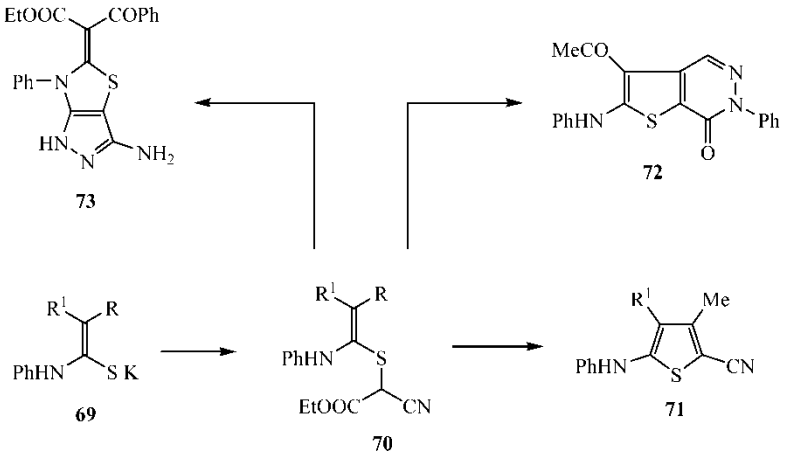
Chloroacetyl isothiocyanate **76** reacted with diphenylamine to afford the corresponding thiourea **77** which cyclized to 2-thiazolin-4-one derivative **78** (scheme 32) [54].

Oxidative cyclization of 4-phenylthiocarbamoyl-3-methyl-1-phenyl-2-pyrazolin-5-one **79** with bromine in ethyl acetate afforded the corresponding 4-benzothiazolylpyrazoline derivative **80** (scheme 33) [55, 56].

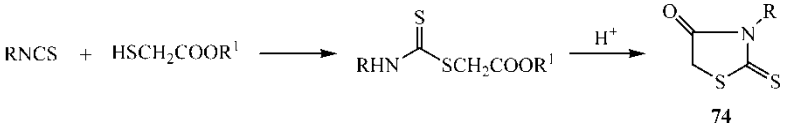
The reaction of benzotriazole with (*E*,*E*)-1-phenyl-*N*,*N*′-bis(phenylmethylene)-methanediamine **81** gave (*E*)-1-phenyl-*N*-(phenylmethylene)-1*H*-benzotriazol-1-methanamine **82**. Condensation of **82** with phenyl isothiocyanate in the presence of BuLi afforded 5-anilino-2,4-diphenylthiazole **83** (scheme 34) [57].

The reaction of 1-tetralone with phenyl isothiocyanate in the presence of sodium hydride in DMF furnished 2-(benzo[*d*]thiazol-2-yl)naphthalen-1-ol **84** (scheme 35) [58].

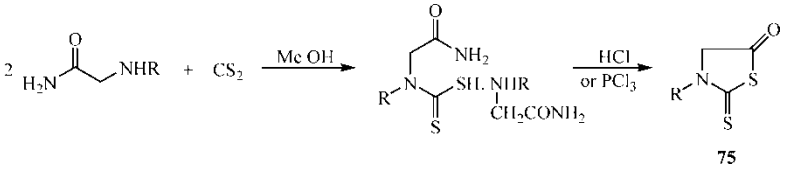
Photocondensation of the unstable azirene **85** with phenyl isothiocyanate leads to 2,4-diarylthiazoles **86** (scheme 36) [59].



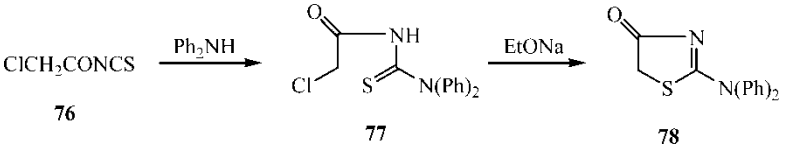
SCHEME 29



SCHEME 30



SCHEME 31



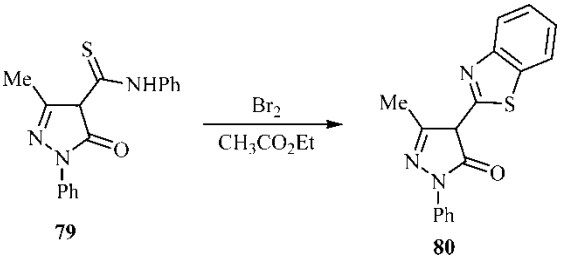
SCHEME 32

2.3 *Pyrazoles*

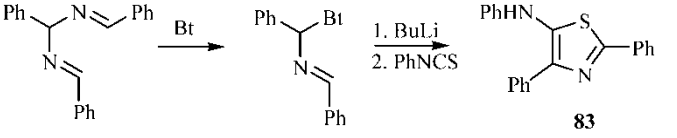
Pyrazoles of the general formula **88** were prepared by heating *p*-RC_6H_4-$NH.CS_2CH_3$ with diethyl malonate followed by cyclization with hydrazine [60] or by condensation of α-carbethoxythioamide **87** with hydrazine (scheme 37) [10].

Grabenko *et al.* studied the reaction of thiocarbamoyl **18** with hydrazine hydrate to yield pyrazole of the general formula **89** (scheme 38) [61].

Pyrazoles of the general formula **91** were prepared by cyclization of **90** with R^2NHNH_2, (scheme 39, R = Me, Et; R^1 = H, OMe, Me; R^2 = H, $PhCH_2CO$, 4-$MeOC_6H_4CO$, Bz) [62].

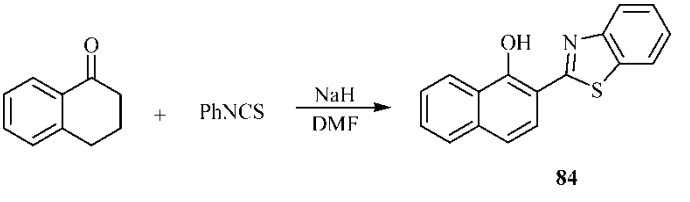


SCHEME 33

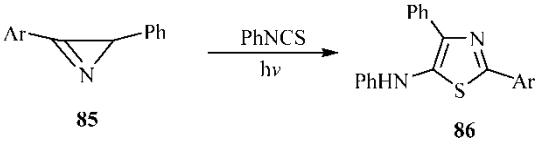


Bt = Benzotriazole

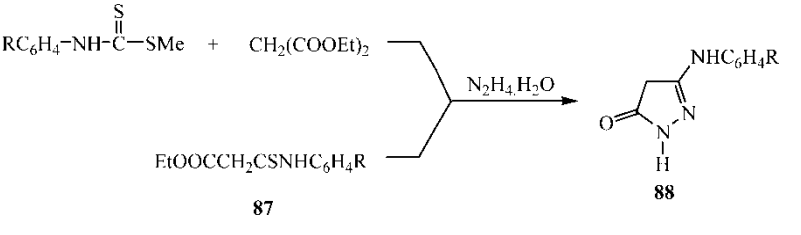
SCHEME 34



SCHEME 35



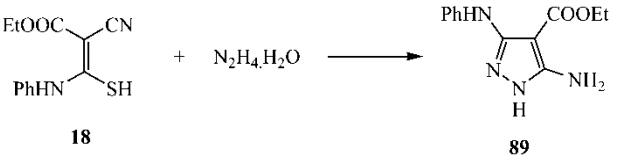
SCHEME 36



SCHEME 37

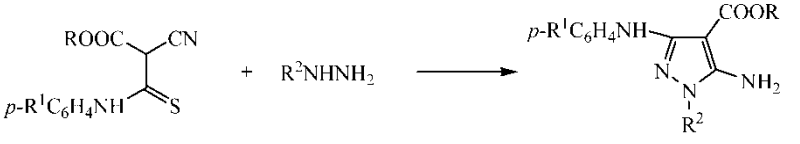
Aminopyrazolo[3,4-*d*]pyrimidine derivatives of the general formula **93** (R, R^1 = alkyl; R^2 = alkyl, acyl) which have diuretic, hypotensive, analgesic and anti-inflammatory activities were prepared by the reaction of pyrimidine derivative **92** with isothiocyanates (scheme 40) [63].

Treatment of ethyl α-phenylthiocarbamoylacetoacetate **94** with aromatic diazonium salts lead to Japp Klingemann acetyl cleavage with the formation of ethyl α-phenyl-thiocarbamoyl



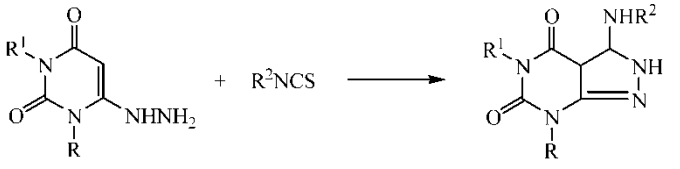
18 **89**

SCHEME 38



90 **91**

SCHEME 39

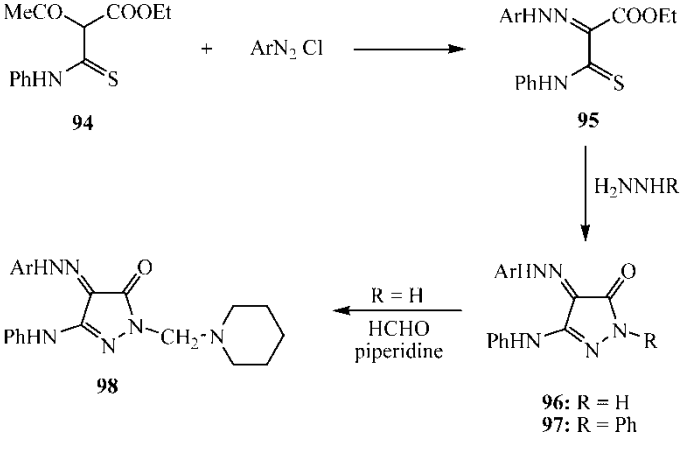


92 **93**

SCHEME 40

glyoxalate arylhydrazones derivatives **95** which afford the anilino-pyrazolones **96** and **97** on treatment with hydrazine and phenyl hydrazine, respectively. The pyrazolones **96** undergo aminoalkylation with formaldehyde and piperidine to give the *N*-Mannich bases **98** (scheme 41) [64].

Junjappa and co-workers have reported an efficient and regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-methylsulfanylpyrazoles **100** and 1-aryl-3-methylsulfanyl-4,5-substituted/annulated pyrazoles **102** *via* cyclocondensation of arylhydrazine with either α-oxoketenedithioacetals **99** or β-oxodithioesters **101** (scheme 42) [65].



94 **95**

96: R = H
97: R = Ph

98

SCHEME 41

2.4 *Imidazoles*

1,2-Disubstituted-4-arylmethylene-2-imidazoline-5-ones **103** (scheme 43, R = Me, Ph; R^1 = Me, Bu, Ph; R^2 = Ph, 3-$O_2NC_6H_4$, 2-HOC_6H_4, 4-$O_2NC_6H_4$, 4-$(Me)_2NC_6H_4$, 3,4-MeO(OH)C_6H_3, Ph-CH=CH) were prepared by heating *N*-acylamino acids with isothiocyanates and suitable aromatic aldehyde in pyridine [66, 67].

$\alpha-$Amino acids or their esters reacted with isothiocyanates to give 2-thiohydntoin **104** carrying different substituents, where the reaction of glycine with phenyl isothiocyanate in the presence of aromatic aldehydes afforded (5-aryl-methylene)-2-thiohydantoin **105** (scheme 44) [68–70].

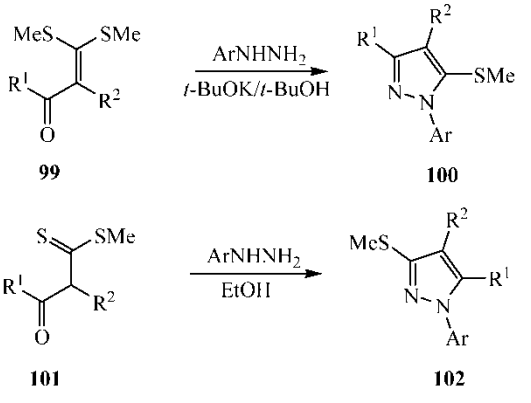
1,3-Disubstituted 4-amino-4-imidazoline-2-thiones **106** (where R = Me, Ph, Ph-CH_2, Bu; R^1 = Me, Et, Pr, Bu, Ph, $PhCH_2$) which were prepared by the reaction of α-alkylaminoacetonitrile with isothiocyanates, are autoxidized in methanol affording 1,3-disubstituted-5-imino-2-thiohydantiones **107** (scheme 45) [71].

o-Phenylene diisothiocyanate reacted with acyl-acetone to give thiocarbamoyl benzimidazolinethiones **108** and with R^1-CH_2CN to give the benzimidazolethiazines **109** (R = Me, Ph; R^1 = CN, CO_2Et) (scheme 46) [72].

The reaction of α-naphthoxyacetyl isothiocyanate with glycine afforded 2-thiohydntoin derivative **110** (scheme 47) [73].

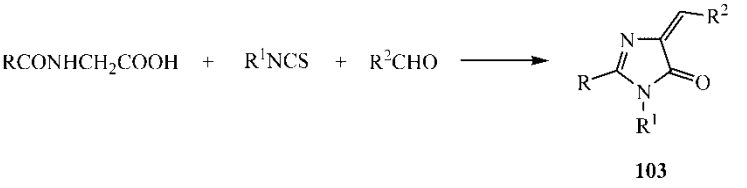
Aryl or alkyl isothiocyanates reacted with aminoketone hydrochloride **111** in the presence of pyridine to afford 2-mercapto-imidazoles **112** (scheme 48) [74].

N-Alkylaminoacetate **113** reacted with ethoxycarbonyl isothiocyanate **114** to give-4-hydoxy-2-mercaptoimidazole derivatives **115** (scheme 49) [75].



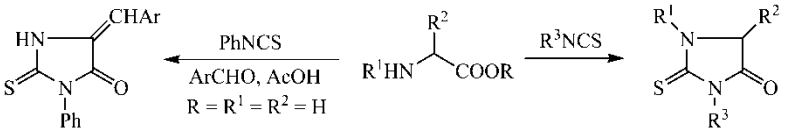
R^1 = C_6H_5, 4-Cl-C_6H_4, 4-MeO-C_6H_4, 3-Pyridyl, Me, i-Pr
R^2 = H, C_6H_5

SCHEME 42



103

SCHEME 43



105 **104**

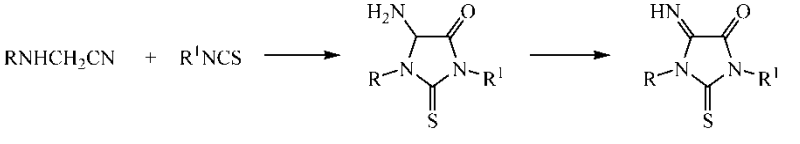
a) $R^1 = R^2 = H$, $R^3 = MeCOCH_2CH_2$

b) $R^1 = NH_2$, $R^2 = H$, R^3 = alkyl, aryl

c) $R^1 = Me_2N$, $R^2 = CH_2COOMe$, R^3 = alkyl, aryl

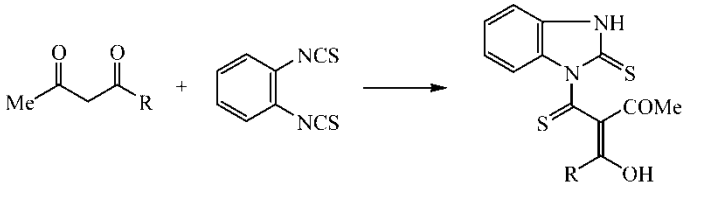
d) $R^1 = CH_2P(OH)_2O$, $R^2 = H$, R^3 = H, alkyl, aryl

SCHEME 44

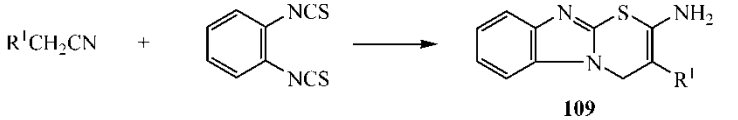


106 **107**

SCHEME 45

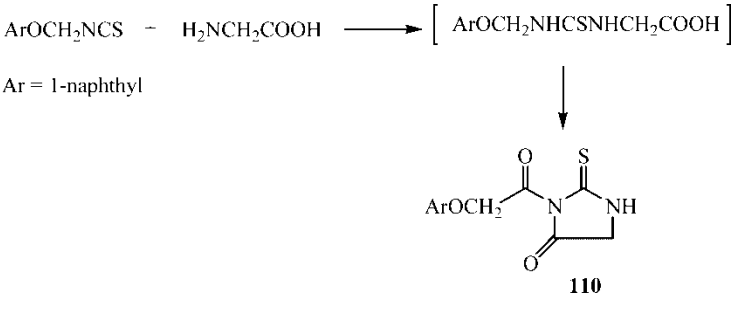


108



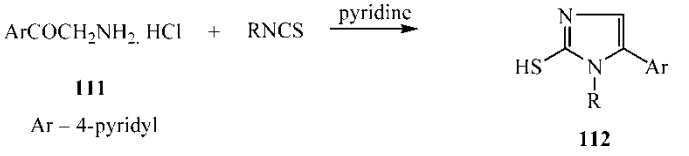
109

SCHEME 46

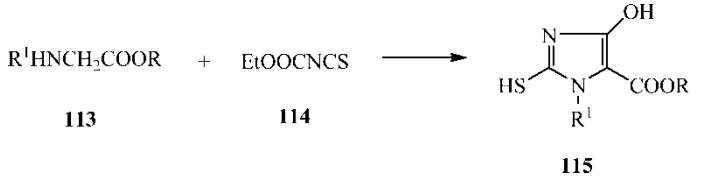


110

SCHEME 47



SCHEME 48

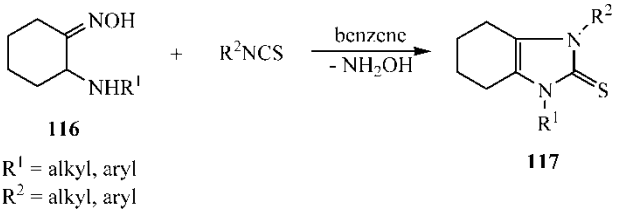


SCHEME 49

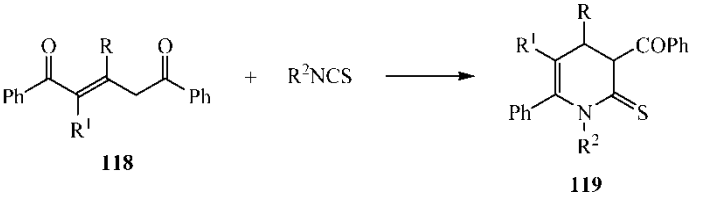
Aminocyclohexanoneoximes **116** reacted with isothiocyanates to afford fused thioimidazolones **117** as the result of extrusion of hydroxylamine moiety during cyclization (scheme 50) [76].

2.5 *Pyridines*

Pyridinethiones of the general formula **118** (R = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^1 = Me, CH_2-Ph; R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4) were prepared by the reaction of **119** with isothiocyanates (scheme 51) [77].

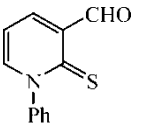


SCHEME 50



SCHEME 51

1-Substituted-3-formyl-2-(1*H*)pyridinethione of the formula **120** was prepared by the reaction of glutacondialdehyde anion with phenyl isothiocyanate [78].



120

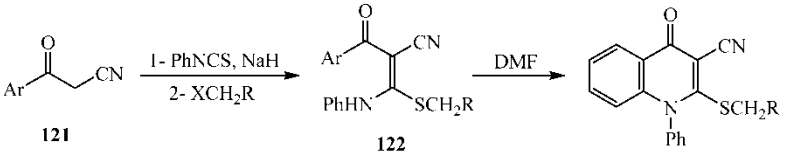
Quinolin-4-ones of the general formula **123** (scheme 52, R = H, Me, Ph, COMe) were prepared by cyclization of the alkylated thiocarbamoyl derivative **122** which results from thiocarbamoylation of **121** with phenyl isothiocyanate [79].

The reaction between 3-cyano-4-methylcoumarin **124** and phenyl isothiocyanate afforded pyrido[3,4-*c*]coumarin derivative **125** (scheme 53) [80].

Condensation of aryl isothiocyanates with anions of diketone **126** afforded pyridinethiones **127** (scheme 54) [81].

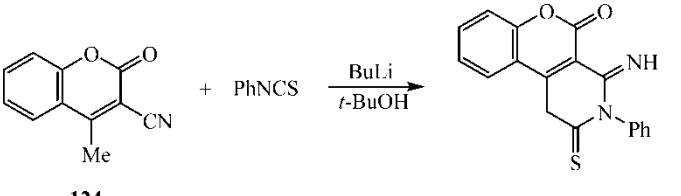
Phenyl isothiocyanate in dry dimethylformamide condensed with active methylene compound **128** at room temperature to afford the potassium sulfide salt **129** (scheme 55) [82].

Thermal cyclization of 5-(phenylamino(methylsulfanyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **130**, which prepared from the reaction of Meldrum's acid with phenyl isothiocyanate and methyl iodide, afforded 2-methylsulfanyl-4(*H*)-quinolin-4-one **131** (scheme 56) [83].



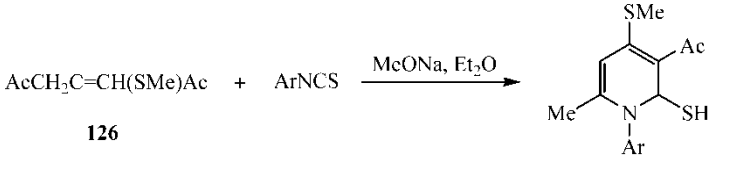
121 **122** **123**

SCHEME 52



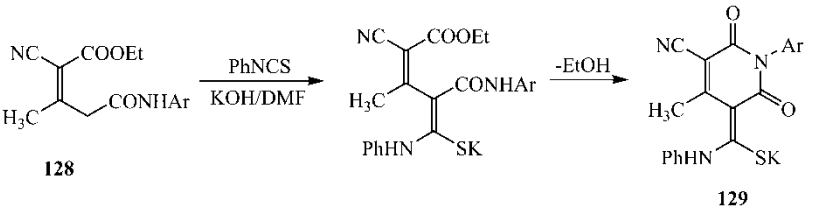
124 **125**

SCHEME 53



126 **127**

SCHEME 54



128 **129**

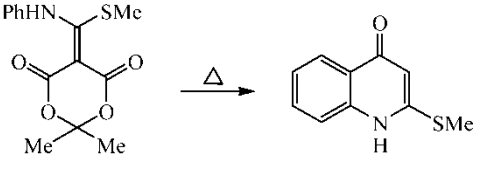
Ar = C_6H_5, p-MeC_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4

SCHEME 55

Nedolya *et al.* reported that unusual thermal rearrangements of *N*-cyclohexylidene-4-methyl-1-(methylsulfanyl)penta-1,3-dien-1-amine **132** to 4,4-dimethyl-2-(methylsulfanyl)-3,3*a*,4,4*a*,5,6,7,8-octahydrobenzo[4,1]cyclobuta[1,2-*b*]pyrrole **133** and 1-cyclohexyl-5-methylpyridine-2(1*H*)-thione **134** (scheme 57) [84].

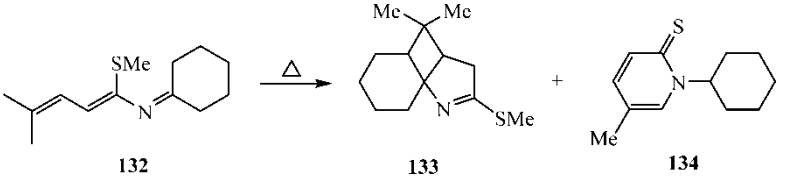
Reaction of lithiated methoxyallene with methoxymethyl isothiocyanate gave iminoformate **135**, which underwent electrocyclization to give dihydropyridine **136** in 100% yield. Treatment of **136** with acid gave pyridine derivative **137** in 72% yield (scheme 58) [85].

Cyclohexylidenemalononitrile **138** was allowed to react with phenyl isothiocyanate under phase-transfer catalysis to give 2-(dicyanomethylene)-*N*-phenylcyclohexane carbothioamide **139**. Cyclization of **139** gave the following bicyclic fused compounds: 3-amino-4-cyano-1-phenylimino-5,6,7,8-tetrahydroisothiachromene **140**, 3-amino-4-cyano-2- phenyl-1-thioxo-5,6,7,8-tetrahy-droisoquinoline **141** and 3-amino-4-cyano-2-phenyl-5,6,7,8-tetrahydroisoquinolin-1-one **142** (scheme 59) [86].



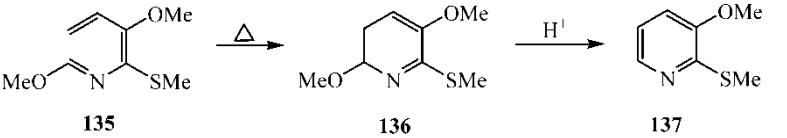
130 **131**

SCHEME 56



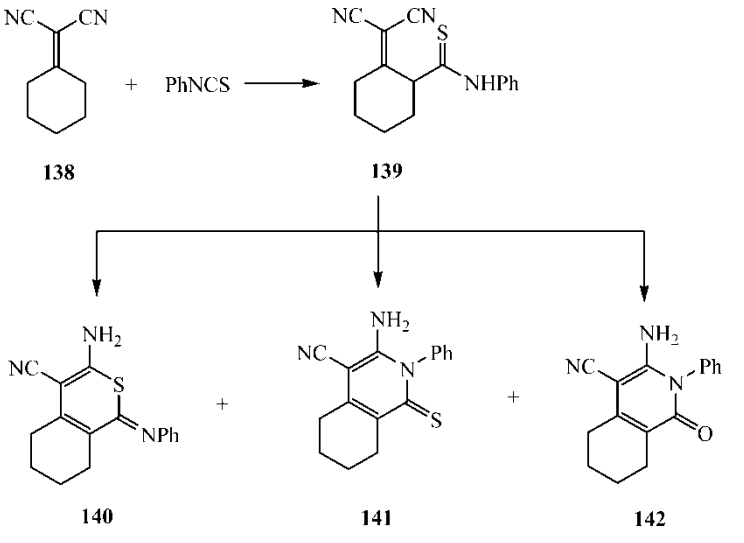
132 **133** **134**

SCHEME 57



135 **136** **137**

SCHEME 58



SCHEME 59

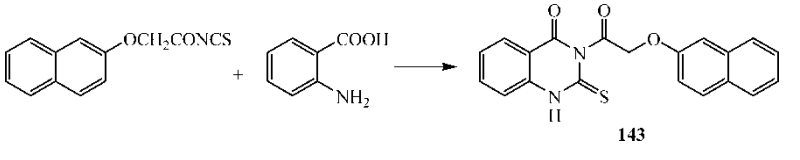
2.6 *Pyrimidines*

Condensation of anthranilic acid with α-naphthoxy acetyl isothiocyanate afforded 2-thioxo-4-quinazolone derivative **143** (scheme 60) [87].

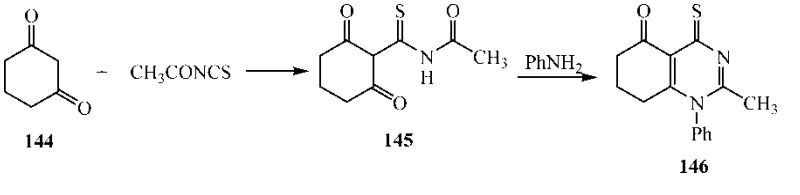
Acetyl isothiocyanate reacted with 1,3-cyclohexanedione **144** in refluxing dioxane affording thioamide **145** which reacted with aniline to produce quinazoline derivative **146** (scheme 61) [88].

The reaction of cyano-cyclohexylidene-acetyl isothiocyanate **147** with aryl amines afforded 1-aryl-4-oxo-2-thioxo-1,3-diazaspiro[5.5]undecane-5-carbonitrile derivatives **148**. This conversion involved nucleophilic addition to heteroallene and subsequent intermolecular Michael reaction. Diphenylamine reacted with **147** to give 2-diphenylamino-4-oxo-1-thia-3-azaspiro[5.5]undec-2-ene-5-carbonitrile **149** (scheme 62) [89].

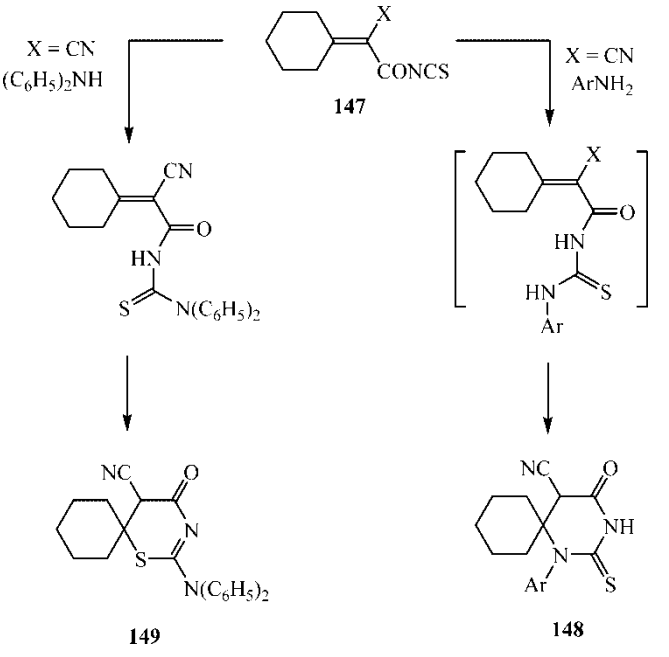
2-Cyano-3-phenylpropenoyl isothiocyanate **150** reacted with aniline to give thiourea derivative. Cyclization of thiourea derivative in NaOH as a base yielded a mixture of *cis* and *trans* isomers of 2-thiouracils **151** (scheme 63) [90].



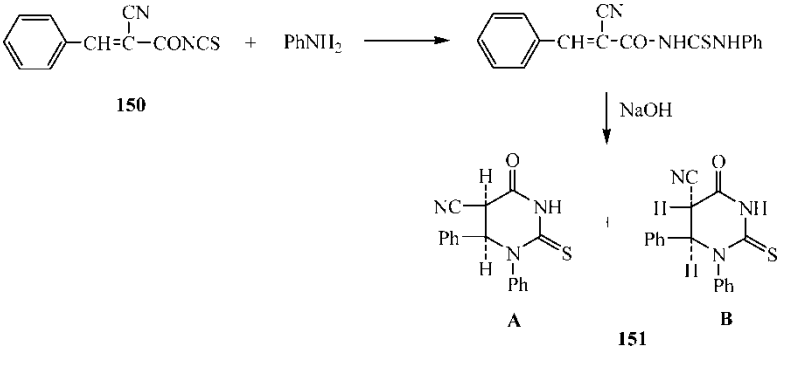
SCHEME 60



SCHEME 61



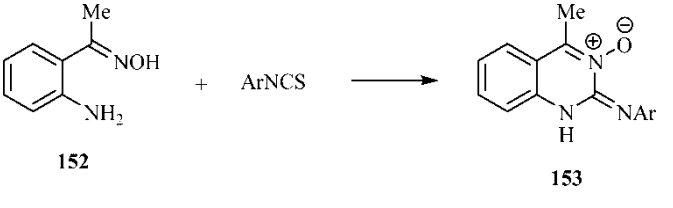
SCHEME 62



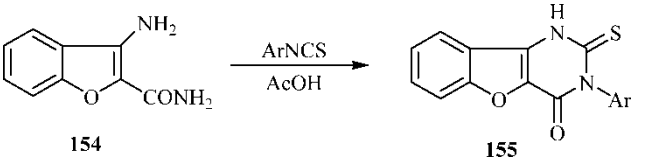
SCHEME 63

The interaction of *o*-aminoacetophenoxime **152** with aryl isothiocyanate afforded quinanzoline-3-oxide derivative **153** (scheme 64) [91].

The reaction of isothiocyanate with heterocycles carrying amino functional group with vicinal carbonyl group was used for the construction of fused pyrimidine rings.

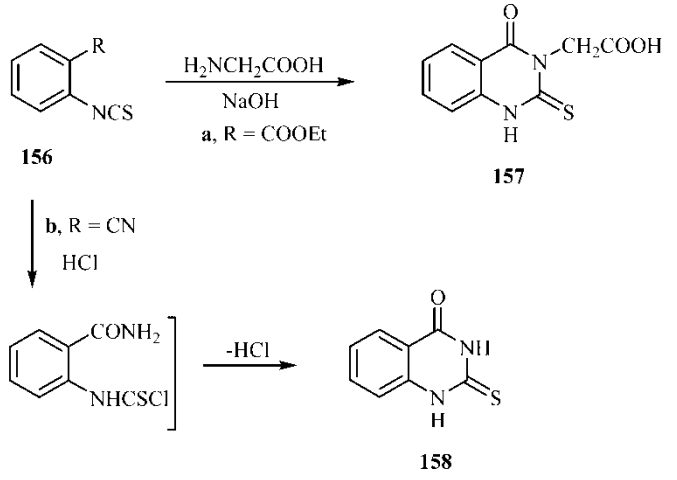


SCHEME 64



154 155

SCHEME 65



156 157 158

SCHEME 66

Thus, 3-amino-benzofuran-2-carboxamide **154** was converted into 2,3-dihydro-3-aryl-2-thioxobenzofuro[3,2-*d*]pyrimidin-4(1*H*)-one **155** (scheme 65) [92].

2-Ethoxycarbonyl phenyl isothiocyanate **156a** (R = CO_2Et) reacted with glycine in the presence of NaOH to give quinazoline-2-thione **157** whereas treatment of 2-cyano phenyl isothiocyanate **156b** (R = CN) with HCl furnished quinazoline-2-thione **158** (scheme 66) [93, 94].

Endo- and *exo*-norbornenes **159** reacted with alkyl and aryl isothiocyanates to from condensed pyrimidines **160** which undergo a retro Diels–Alder reaction by heating to give thiouracils **161** (scheme 67) [95].

Methyl anthranilate **162** reacted with phenyl isothiocyanate to produce thiourea derivative **163** that cyclized with hydrazine to give 2-anilino-3-aminoquinazolin-4-one **164** (scheme 68) [96, 97].

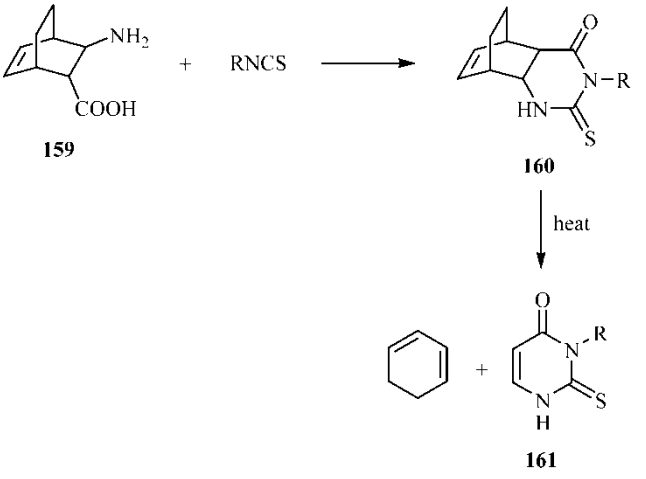
5-Acetyl-4-alkylsulfanyl-6-methyl-2(1*H*)-pyrimidinethiones **165** were prepared from the reaction of diacetylketene *N*,*S*-acetals **166** with isothiocyanates (scheme 69) [98].

The reaction of ketene *N*,*N*-acetals **167** and phenyl isothiocyanate at room temperature in acetonitrile afforded a thioamide intermediate **168**. The thioamide **168** was converted into 6-thioxopyrimidine **169** upon treatment with excess DMF–DMA in toluene (scheme 70) [99].

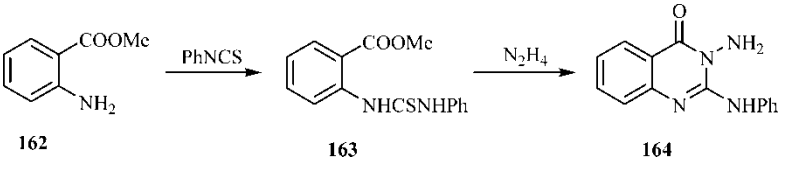
2.7 *Dithiazoles*

Chlorophenylmethyl(methylimino)thiadiazolidine **170** reacted with RNCS (R = Ph, PhCO, CO_2Et) to give diiminodi-thiazolidines of the general formula **171** (scheme 71) [100].

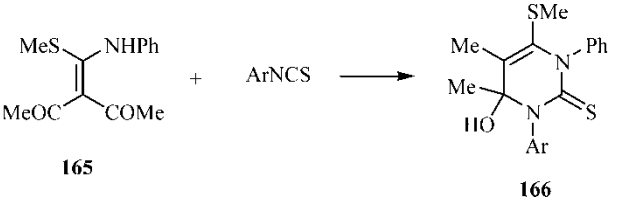
Treatment of 1-thioacetoacetanilide **172** with $SOCl_2$ or SO_2Cl_2 produced 3,5-diacetonylidene-4-phenyl-1,2,4-dithiazolidine **173** (scheme 72) [101].



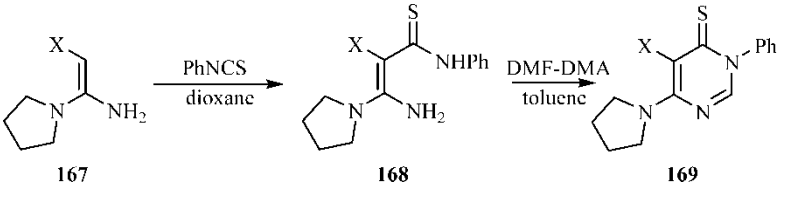
SCHEME 67



SCHEME 68



SCHEME 69

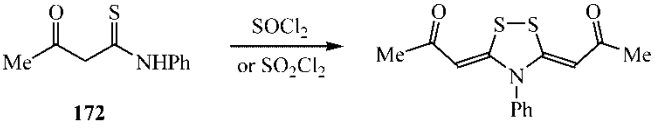


SCHEME 70

Oxidative cyclization of substituted-1-thioacetoacetanilides with bromine gave 3,5-*bis*(acetonylidene)-4-aryl-1,2,4-dithiazolidine derivatives **174** (scheme 73, R = 4-Me, 4-MeO, 2-MeO, 4-EtO, 4-Br) [102].

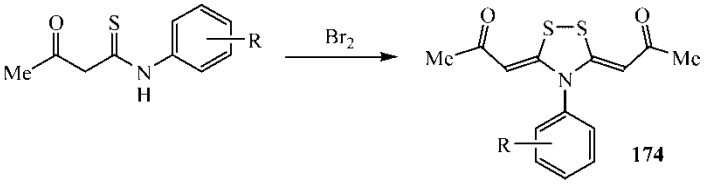
170 **171**

SCHEME 71



172 **173**

SCHEME 72



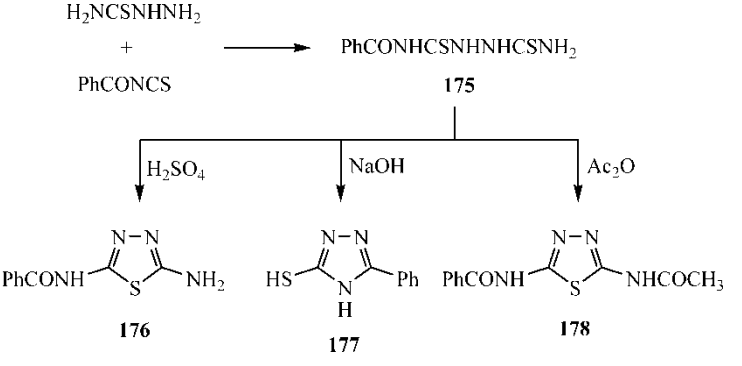
174

SCHEME 73

2.8 *Thiadiazoles*

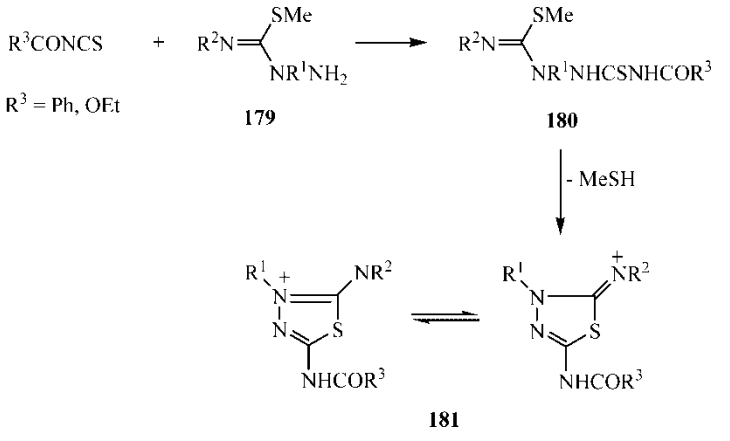
The reaction of benzoyl isothiocyanate with thiosemicarbazide afforded product **175**. Cyclization of **175** afforded different products depending on the cyclizing agents. Thus, base-induced cyclization of **175** afforded 3-phenyl-5-mercapto-1,2,4-triazole **177**. Keeping **175** on concentrated sulfuric acid afforded 2-amino-5-benzamido-1,2,4-thiadiazole **176**, while upon treatment **175** with acetic anhydride produced a mixture of **176** and 1,3,4-thiadiazole **178** (scheme 74) [103].

The reaction of benzoyl isothiocyanate as well as ethoxycarbonyl isothiocyanate with isothiosemicarbazide **179** in toluene resulted in the formation of 1,3,4-thiadiazoline-2-imine **181** through the intermediate **180** (scheme 75) [104].

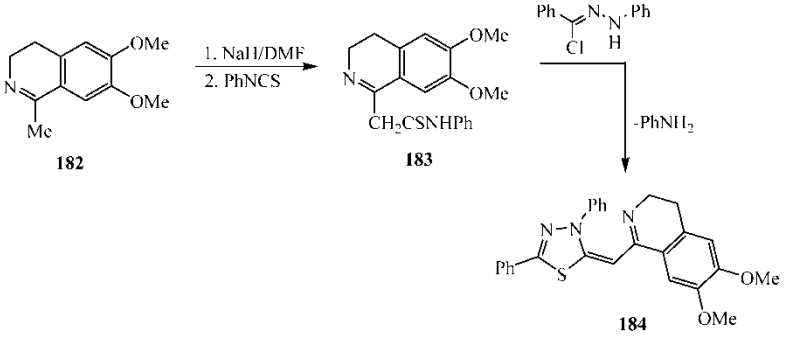


176 **177** **178**

SCHEME 74



SCHEME 75



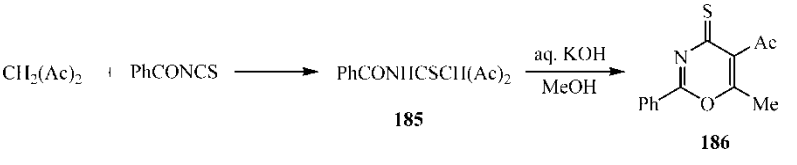
SCHEME 76

3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline **182** was reacted with phenyl isothiocyanate to give 3,4-dihydro-6,7-dimethoxy-*N*-phenyl-1-isoquinoline-ethanethioamide **183**. Treatment of thioanilide **183** with *N*-phenylbenzene-carbohydrazonoyl chloride leads to the formation of 3,4-dihydro-6,7-dimethoxy-[1-(1,3,4-thiadiazol-2-ylidene)methyl]isoquinoline **184** (scheme 76) [105].

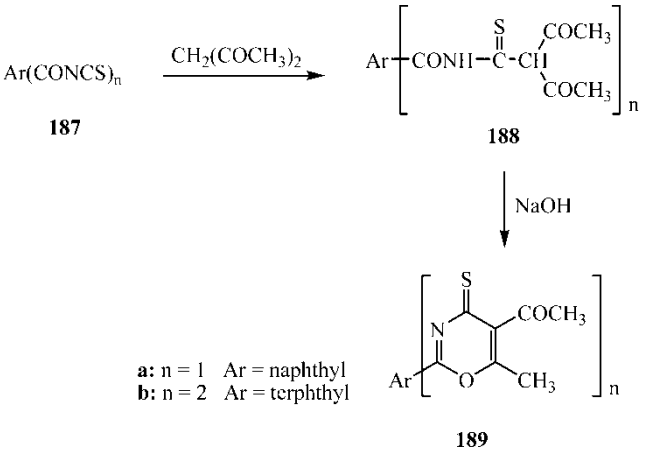
2.9 *Oxazines*

The reaction between benzoyl isothiocyanate and acetylacetone underwent cyclization to afford oxazinethione **186** through the thiocarbamoyl intermediate **185** (scheme 77) [106].

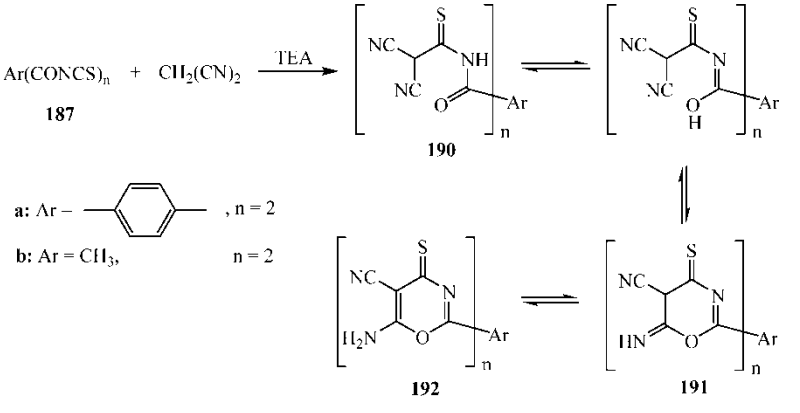
Naphthoyl isothiocyanate or terephthaloyl isothiocyanate **187** reacted with acetylacetone to produce thioamide derivatives **188**, which underwent cyclization to oxazinethiones **189** in a basic medium (scheme 78) [107–109].



SCHEME 77



SCHEME 78



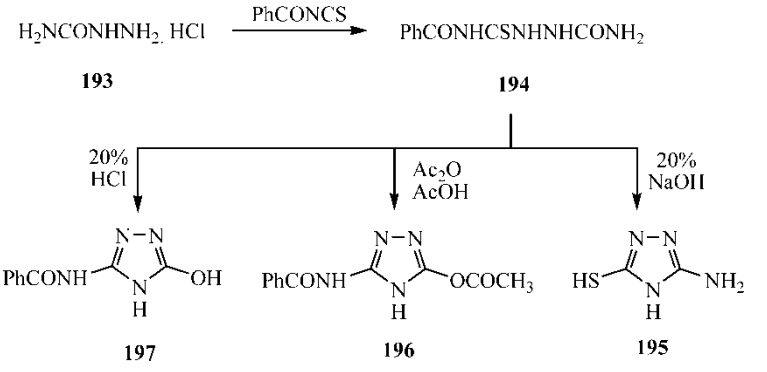
SCHEME 79

Cycloaddition of malononitrile to terephthaloyl isothiocyanate and/or acetyl isothiocyanate **187** in the presence of triethyl amine as a basic catalyst yielded 1,3-oxazine derivative **193** presumbly *via* the initial formation of non-isolable thioamides **191**/**192** (scheme 79) [108, 109].

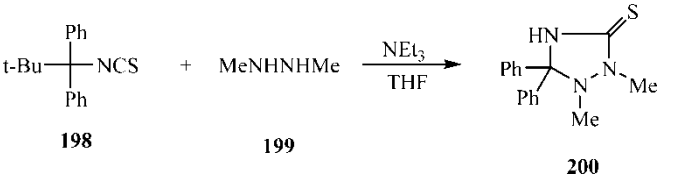
2.10 *Triazoles*

Semicarbazide hydrochloride **193** was reacted with benzoyl isothiocyanate to give the open chain adduct **194**. Compound **194** undergoes heterocyclization depending on the reaction conditions. Thus, treatment of **194** with 20% aqueous sodium hydroxide gave **195** where upon treatment with hydrochloric acid or concentrated sulfuric acid yielded a mixture of **196** and 3-benzamido-1,2,4-triazol-5-ol **197**. The reaction of **194** with acetic anhydride and acetic acid produced 3-benzamido-5-methyl-1,2,4-triazole **196** (scheme 80) [103].

The condensation of hydrazines with isothiocyanates leads to different products depending upon the nature of reactants and the conditions of reaction. The interaction of isothiocyanate **198** and *N*,*N*′-dimethylhydrazine **199** afforded triazolidine derivative **200** (scheme 81) [110].



SCHEME 80



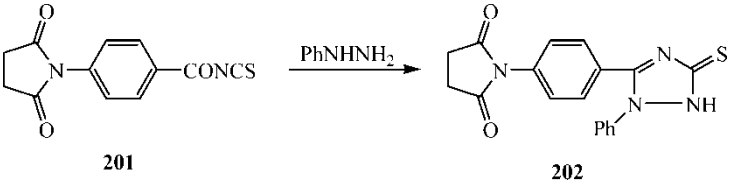
SCHEME 81

p-(*N*-Succinimidobenzoyl) isothiocyanate **201** reacted with phenylhydrazine to afford triazoline derivative **202** (scheme 82) [108].

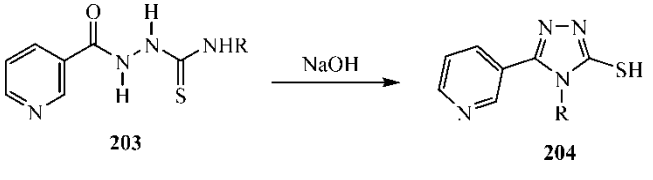
5-Mercapto-3-(3-pyridyl)-1,2,4-triazoles **204** have certain biological activity (antifungal and antibacterial activity) were prepared by the cyclization of **203** in a basic medium (scheme 83) [111].

2.11 *Pyrroles*

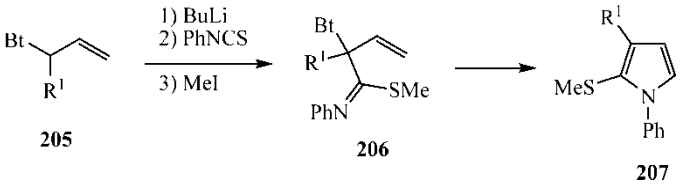
1-Allylbenzotriazole **205** was functionalized by the sequential addition of *n*-BuLi and quenching of the resulting anion with phenyl isothiocyanate followed by an S-methylation. Cyclization



SCHEME 82

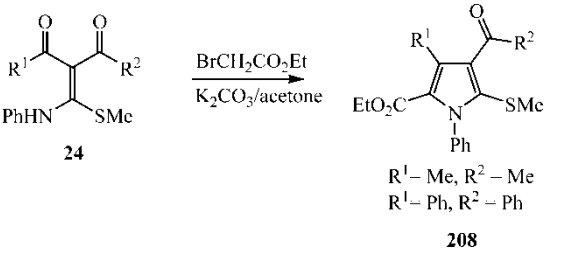


SCHEME 83



205 **206** **207**

SCHEME 84



24 **208**

SCHEME 85

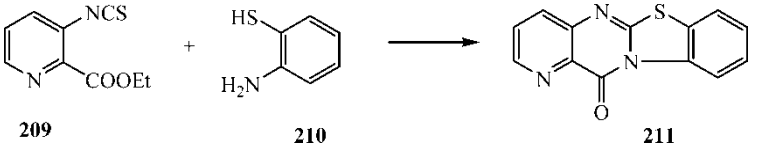
of **206** readily occurred with a Lewis acid in dry methylene chloride to give the corresponding 2-methylsulfanylpyrrole **207** (scheme 84) [112].

Kirsch and co-worker have reported the reaction of ketene *N*,*S*-acetals **24** with ethyl bromoacetate in refluxing acetone and in the presence of anhydrous potassium carbonate as a basic catalyst furnished pyrrole derivatives **208** (scheme 85) [28].

2.12 *Thiazolopyrimidines and Thiazolotriazines*

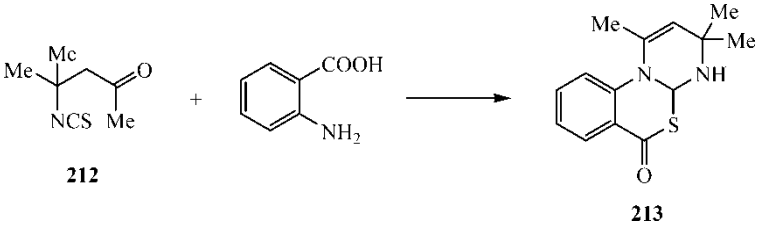
The reaction of ethyl-3-isothiocyanatopyridine-2-carboxylate **209** and *o*-aminothiophenol **210** produced 3-substituted pyrido[3,2-*d*]pyrimidine derivative **211** (scheme 86) [113].

The reaction of anthranilic acid with 4-methyl-4-isothiocyanate-2-pentanone **212** gives 3*H*, 6*H*-pyrimido[1,2-*a*][3,1]benzothiazin-6-one **213** (scheme 87) [114].



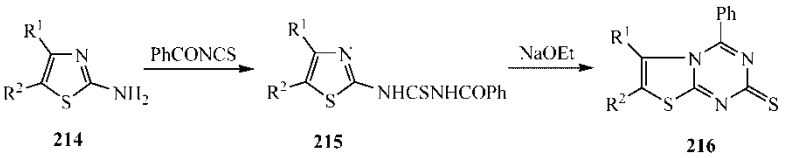
209 **210** **211**

SCHEME 86



212 **213**

SCHEME 87



214 **215** **216**

SCHEME 88

The reaction of 2-aminothiazole derivatives **214** ($R^1 = R^2 = H$; $R^1R^2 = C_6H_4$) with benzoyl isothiocyanate afforded the corresponding *N*-benzoyl-*N*-[thiazol-2-yl] thiourea **215** which underwent cyclization by NaOEt to furnish the thiazolotriazine derivatives **216** (scheme 88) [115–117].

2.13 *Miscellaneous reactions*

Oxadiazolidinethiones of the general formula **218** ($R = C(Me)_3$, 1-admantyl; $R^1 = Ph$, $C(Me)_3$, 2,4-$(MeO)_2C_6H_3$ and $R^2 = Ph$, 4-$O_2NC_6H_4$, Ph-CH_2, 4-ClC_6H_4, Et, allyl) were prepared by cyclization of the *N*-oxide **217** with isothiocyanates (scheme 89) [118].

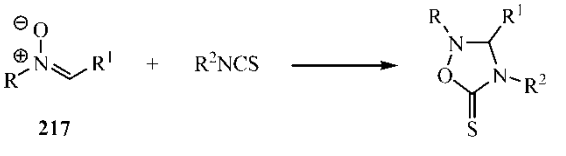
Generally, isothiocyanate **219** added to secondary amines: morpholine, *N*-methylaniline, to provide only 1,3-thiazine system **220** (scheme 90) [110].

Metwally and co-workers reported that the interaction of ethyl α-phenylthiocarbamoylglyoxalate **94** with 3-amino-1,2,4-triazole, 2-amino-5-ethyl-1,3,4-thiadiazole and 2-aminobenzimidazole resulted in the formation of the bridgehead nitrogen compounds **221–223** (scheme 91) [119].

Reaction of 2-chloro-5-nitrobenzoyl isothiocyanate **224** with primary amines afforded thiourea derivatives **225** which cyclized by heating with lithium to give benzothiazine-4-ones **226** (scheme 92) [120].

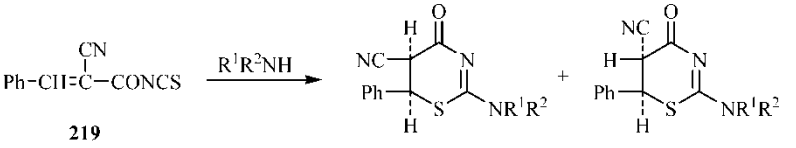
Cyclization of 1-thioacetoacetanilide **172** with carbonyl dichloride gave 1,3-thiazetidin-2-one of the formula **227**. In contrast, condensation of 2-acetyl-1-thio-acetoacetanilides **228** with carbonyl dichloride gave oxazinone **229** (scheme 93) [121].

Imidazole derivative **230** reacted with phenyl isothiocyanate to give **231** (scheme 94) [122].



217 **218**

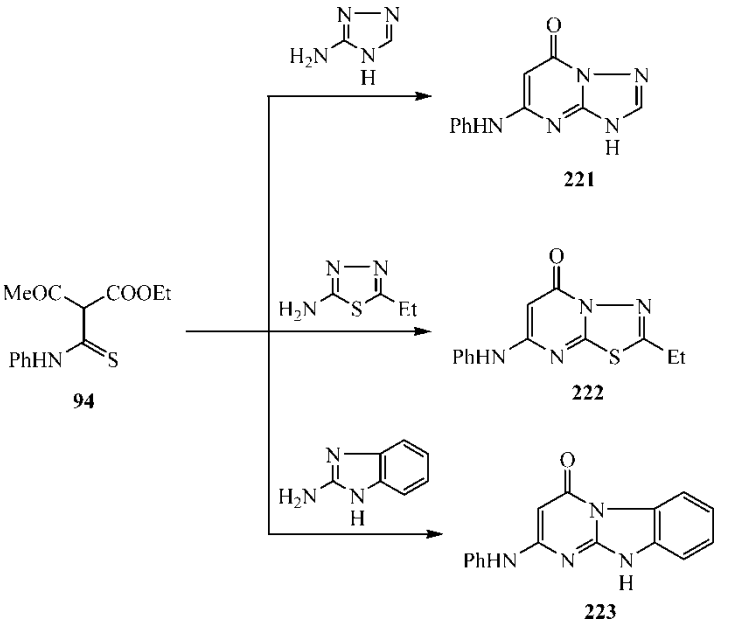
SCHEME 89



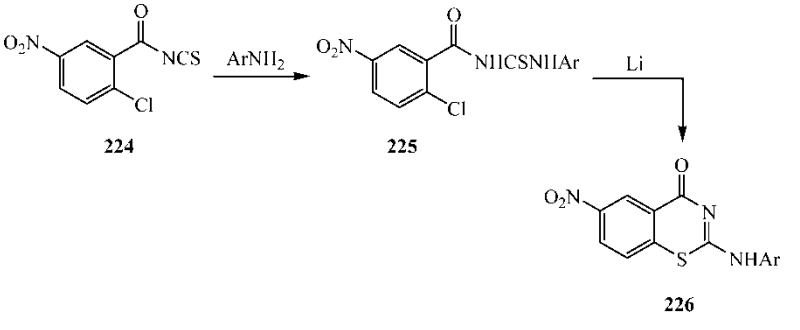
219 **220**

a) $R^1 = R^2 = Ph$
b) $R^1 = Ph$, $R^2 = Me$

SCHEME 90



SCHEME 91



SCHEME 92

1,2,4-Dithioazepines of the general formula **232** (scheme 95, R = Me, Ph; R^1 = Ph, *p*-MeC_6H_4, *o*-$MeOC_6H_4$, *p*-ClC_6H_4) were prepared by heating β-oxothioacid anilides with molar amount of bromine in an organic solvent [123].

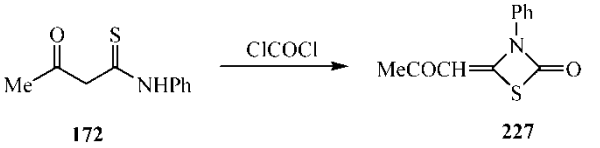
1-Thioacetoacetanilide **172** reacted with an excess of triethyl orthoformate in acetic acid to give thiopyranone **233** in small yield in addition to **234** (scheme 96) [124].

Naphthothiopyrans of the general formula **236** (scheme 97, R = PhNHCS, *p*-ClC_6H_4NHCS, *p*-BrC_6H_4NHCS; R^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4) were prepared by cyclization of enamines **235** with malononitrile [107].

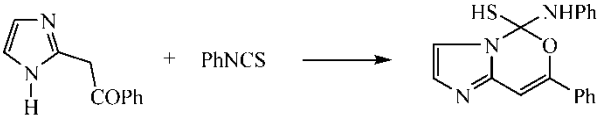
Addition of aryl isothiocyanates to $R^1(CN)C{=}C(Me)CH_2COOEt$ leads to the formation of pyrido[2,3-*d*]pyrimidine derivative **237** (scheme 98, R = Ph, 4-ClC_6H_4; R^1 = CN) [106].

Spiroketone of the general formula **238**, was prepared by condensation of 1-thioacetoacetamide **172** with 2-bromotetralone (scheme 99) [125].

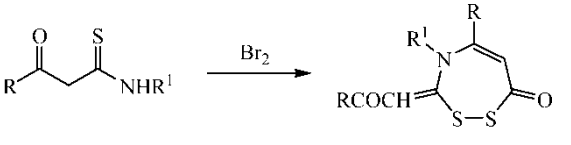
2,3,4,5-Tetrahydro-1,2,4-triazine-6-carbonitriles **239**; (where R = Ph, substituted Ph, 1-naphthyl, 3-pyridyl; R^1 = Me, Ph) were prepared by cyclization of $R^1NHCSN(R)N{=}C(CN)_2$ with NEt_3-EtOH (scheme 100) [126].



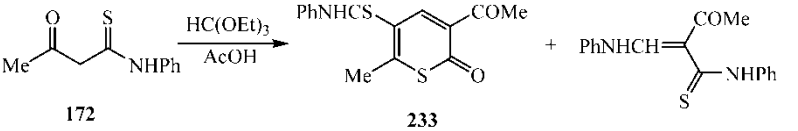
SCHEME 93



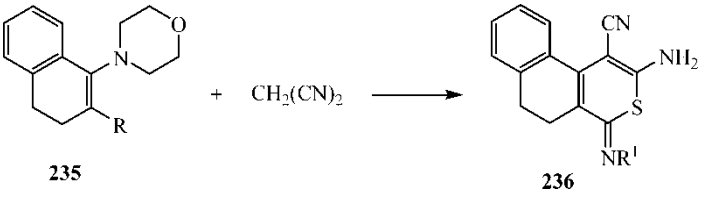
SCHEME 94



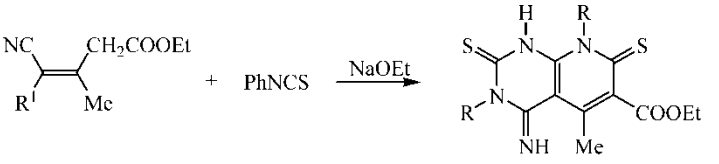
SCHEME 95



SCHEME 96

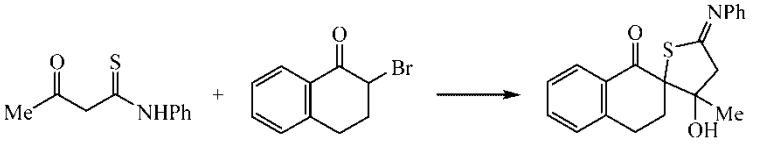


SCHEME 97



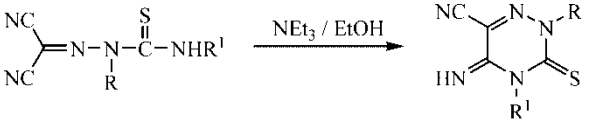
237

SCHEME 98



172 **238**

SCHEME 99



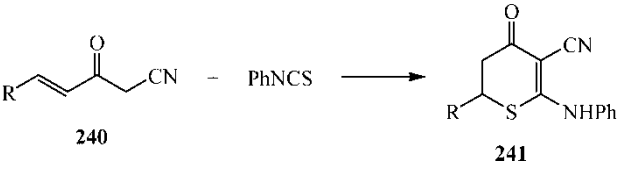
239

SCHEME 100

The thione derivatives **241** [127] (R = Ph, 2-furyl) were prepared by the reaction of unsaturated β-ketonitriles **240** with phenyl isothiocyanate (scheme 101).

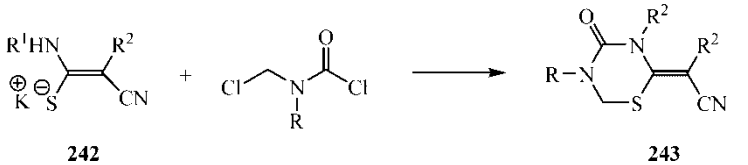
Thiadiazinones **243**, which showed herbicidal activity, were prepared through cyclization of the thiocarbamoyl salt **242** with Cl-CH_2-NR-COCl (scheme 102) [128].

2-Cyano-2-[(phenylamino)thioxomethyl]acetic acid ethyl ester was condensed with pentamethylene oxaziridine to give thiadiazolidine derivative **244** (scheme 103) [129].



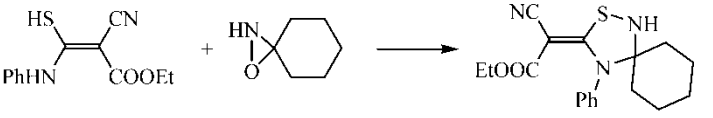
240 **241**

SCHEME 101



242 **243**

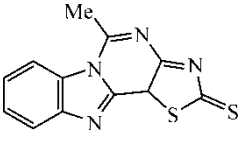
SCHEME 102



244

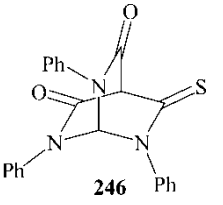
SCHEME 103

Benzimidazolylthiazole **245** was synthesized by condensing 1*H*-benzimidazole-2-acetonitrile with sulfur and phenyl isothiocyanates [130].



245

The bicyclooctanedione **246** was prepared by [4 + 2] dipolar cycloaddition reaction of the pyrimidindione internal salt with phenyl isothiocyanate [131].

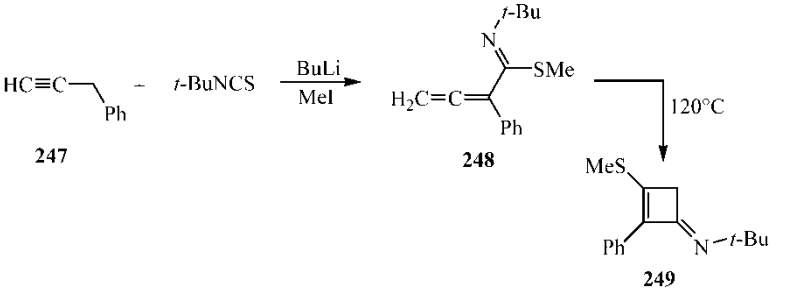


246

Allenic imidothioate **248** has been obtained in good yield by reaction of 1,3-dilithiated 1-(2-propynyl)benzene **247** with *tert*-butyl isothiocyanate and successive addition of methyl iodide. Heating the imidothioate at about 120 °C gave an iminocyclobutene **249** as the only isolated product (scheme 104) [132].

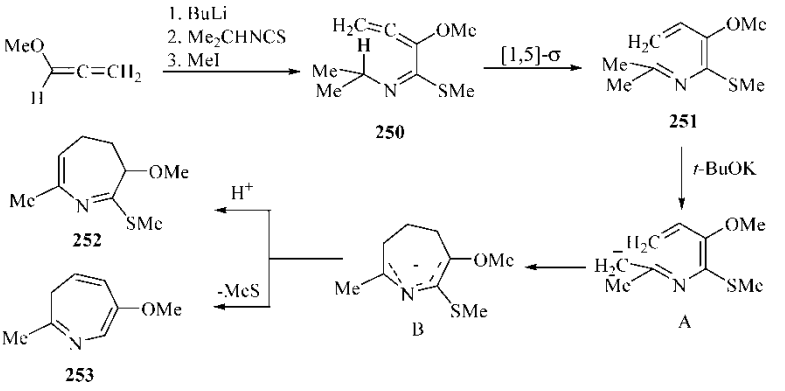
Nedolya and co-workers have first reported that 2-aza-1,3,5-triene **251**, which is readily available *via* [1,5]-sigmatropic rearrangement of 1-aza-1,3,4-triene **250** (*S*-alkylated adduct of 1-lithio-1-methoxyallene and isopropyl isothiocyanate), is converted in quantitative yield to 3-methoxy-7-methyl-2-methylsulfanyl-4,5-dihydro-3H-azepine **252** and 6-methoxy-2-methyl-3H-azepine **253** in ratio (3:1) by the action of potassium *tert*-butoxide (scheme 105) [133].

A new five-components condensation of 3-methylphenyl isothiocyanate, sulfur, 2-(cyanomethyl)benzimidazole, triethylamine and carbon disulfide furnished triethylammonium 3-aryl-[1,3]thiazolo[4′,5′:4,5]pyrimido[1,6-*a*]benzimidazole-2(3H)-thioxo-5-thiolates,



247 248 249

SCHEME 104

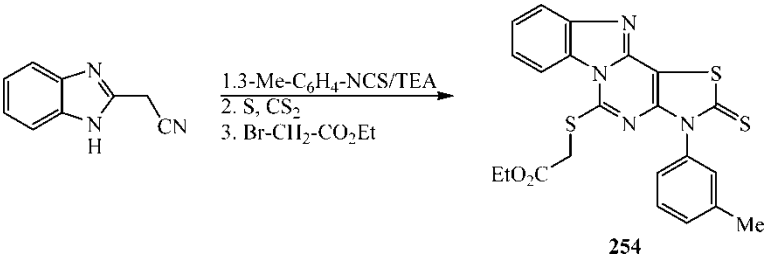


SCHEME 105

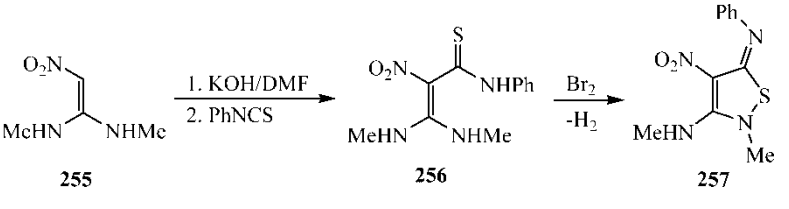
the alkylation of which with ethyl bromoacetate gives 3-aryl-[1,3]thiazolo[4′,5′:4,5]pyrimido [1,6-*a*]benzimidazole-2(3*H*)-thiones **254** (scheme 106) [134].

Acyclic ketene aminal **255** reacted with phenyl isothiocyanate to give the corresponding *β*-carbon adducts **256** in high yield which underwent oxidative cyclization with bromine to afford isothiazole derivative **257** (scheme 107) [135].

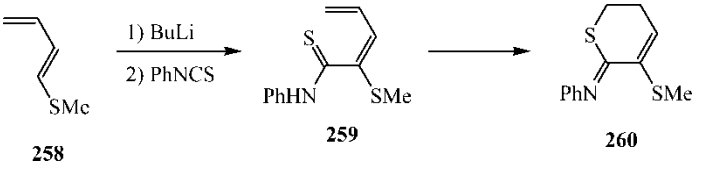
1-Methylsulfanyl-1,3-butadiene **258** is metallated by combination of *n*-BuLi and *t*-BuOK in THF followed by the addition of phenyl isothiocyanate to give an intermediate thioamide



SCHEME 106



SCHEME 107



SCHEME 108

259. The latter undergoes electrocyclization to provide [5-(methylsulfanyl)-2H-thiopyran-6-yl]phenylamine **260** (scheme 108) [136, 137].

3. Conclusion

The aim of this review has been to demonstrate the wide synthetic and preparative applications of a particularly versatile class of compounds *i.e.* the thiocarbamoyl derivatives. It is hoped that a greater understanding of their potential in the synthesis of novel heterocycles, and biologically active compounds. Finally, it is hoped that this review will fill what was an obvious gap by providing an overview of the subject.

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