Chemistry of Heterocyclic Compounds, Vol. 46, No. 3, 2010

SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY OF 4,5-DIARYLIMIDAZOLE-2-THIONES (REVIEW)

K. M. Dawood[1] and B. F. Abdel-Wahab[2]*

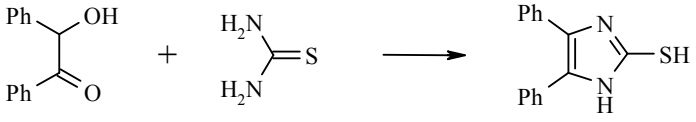
The data on the methods of synthesis, chemical properties, and biological activities of 4,5-diaryl-imidazole-2-thiones published over the last years till the middle of 2008 are reviewed.

Keywords: 4,5-diarylimidazole-2-thiones, imidazole-2-thiones, alkylation, oxidation.

4,5-Diarylimidazole-2-thiones are ambident compounds containing a thioureide moiety. The chemistry of imidazole-2-thiones is of constant interest owing to the occurrence of this ring system in various biologically important compounds. Some 4,5-diarylimidazole-2-thiones are known as antimicrobials [1, 2], anti-inflammatory [3, 4], antiarthritic [5], antihypercholesteremics [6, 7], and as cholesterol acyltransferase and blood platelet aggregation inhibitors [8]. The preparation of imidazole-2-thiones and their nucleophilic addition reactions were reviewed in 1991 [9]. This article covers the methods for preparing 4,5-diarylimidazole-2-thiones; it also includes their reactions in the past years, some of which have been applied to the synthesis of biologically important compounds.

1. Synthesis of 4,5-diarylimidazole-2-thiones

Generally, the synthesis of 4,5-diarylimidazole-2-thiones is based on the condensation of α-hydroxy ketones with ammonium thiocyanate, thiourea, and its derivatives. Thus, 4,5-diphenylimidazole-2-thione (**1**) (Ar = Ph) was prepared by treating thiourea with benzoin; in the same sense, 4,5-diarylimidazole-2-thiones (Ar = 2-pyridyl, 2-furyl, etc.) have been prepared similarly [10-14].



1

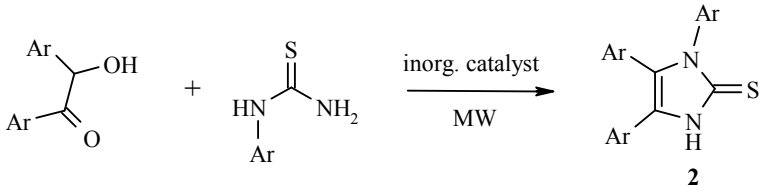
* To whom correspondence should be addressed, e-mail: bakrfatehy@yahoo.com.

[1]Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt.

[2]Applied Organic Chemistry Department, National Research Centre, Dokki, Giza, Egypt.

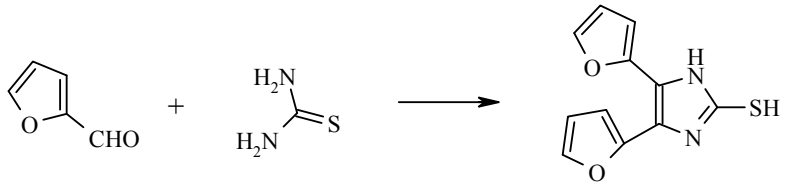
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 328-357, March, 2010. Original article received November 11, 2008.

An eco-friendly synthesis of some 1,4,5-triarylimidazole-2-thiones **2** and 1,3,4,5-tetraarylimidazole-2-thiones involves benzoin condensation with various N-substituted thioureas and N,N'-disubstituted thioureas over recyclable inorganic solid catalyst using microwave irradiation [15].



2

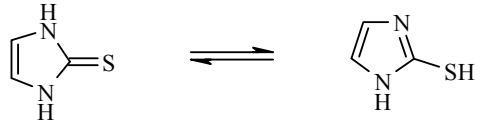
The condensation reactions of furfural with thiourea led to 4,5-di(furan-2-yl)-1H-imidazole-2-thiol (**3**), which was used as an accelerator of rubber vulcanization [16, 17].



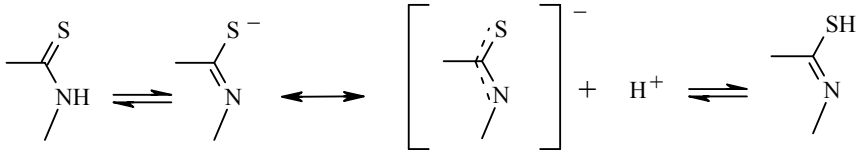
3

2. Chemical Properties

Imidazole-2-thiones can exist in two tautomeric forms, a thione and a thiol.



Imidazole-2-thiones belong to the so-called "ambifunctional nucleophilic compounds" and are readily involved in reactions with electrophilic agents. The ambident anion of compounds with a thioamide group, generated by proton abstraction, represents a triatomic moiety **II**, the negative charge being unevenly distributed between the two end points [18].

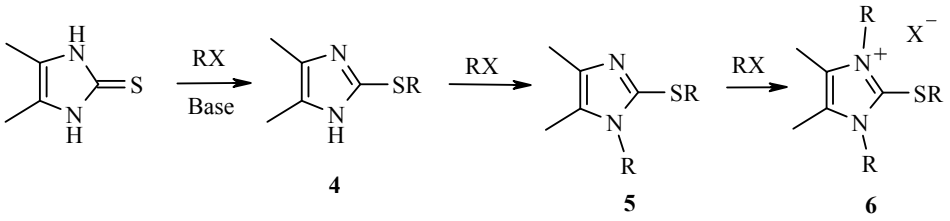


I **II** **III**

The interaction of imidazole-2-thione with electrophilic reagents normally involves the readily polarized and highly nucleophilic sulfur atom. In the case of polar electrophiles, however, the new bond is formed with the more electronegative nitrogen atom.

2.1. Alkylation and Arylation

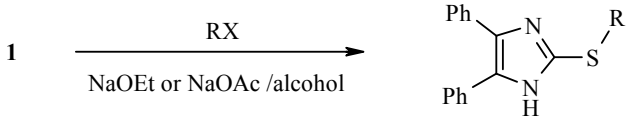
The alkylation of 4,5-diarylimidazole-2-thiones is carried out mostly using alkyl halides, epoxides, or alcohols. The alkylation is usually preformed in an alcoholic, aqueous alcoholic, or aqueous medium in the presence of alkali metal hydroxides or carbonates for the removal of the hydrogen halide formed. The more nucleophilic sulfur atom is the first to be alkylated, which leads to the formation of 2-(alkylthio)imidazoles **4**. Treatment of the latter with excess alkyl halide gives the dialkyl-substituted derivatives **5** and quaternary salts **6** [9].



4 **5** **6**

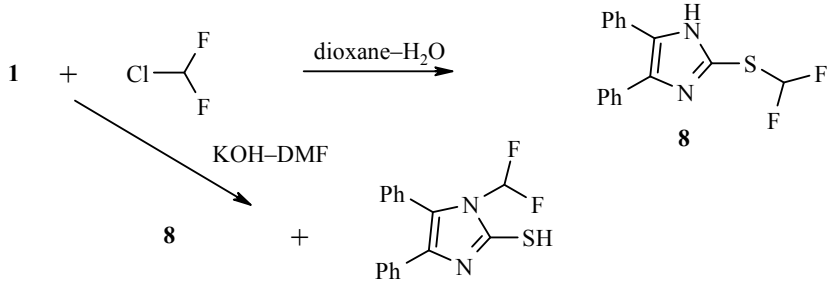
2.1.1. Haloalkanes

Under both the conventional method (CM) and microwave irradiation (MW) conditions, alkylation of 4,5-diphenylimidazole-2-thione **1** with halo alkanols in the presence of sodium ethoxide or sodium acetate in alcohol afforded regioselectively the corresponding S-alkylated derivatives **7** (R = $(CH_2)_2OH$, $(CH_2)_3OH$, $CH_2CH(OH)CH_2OH$) in high yields [5, 19].



7

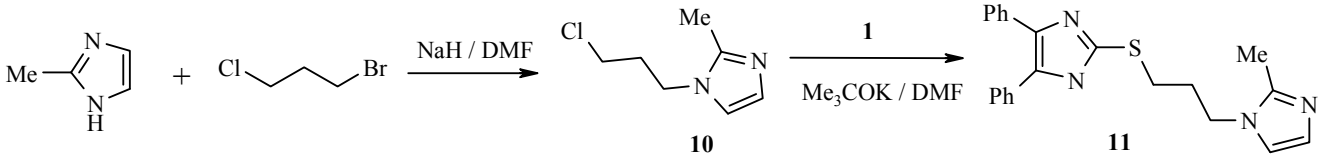
Reactions of imidazolethione **1** with chlorodifluoromethane under basic conditions were investigated. S-difluoromethylated product **8** was obtained in dioxane–water solution. Both N- and S-difluoromethylated products **8** and **9** were obtained in a solid KOH–DMF system [20].



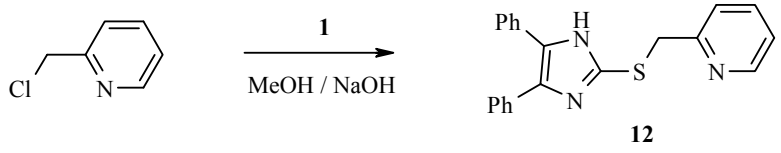
8 **8** **9**

2.1.2. Aralkyl (hetaralkyl) Halogenides

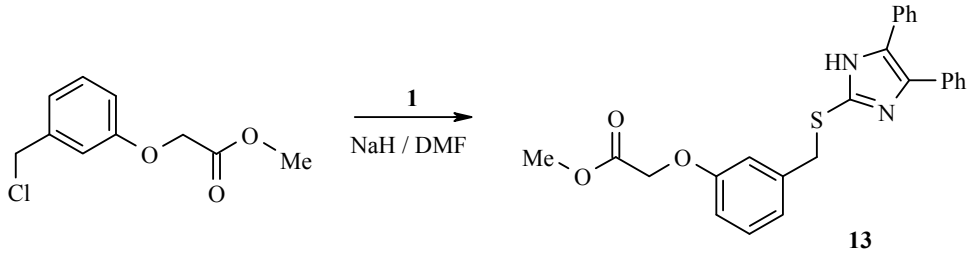
2-Methylimidazole was condensed with 1-bromo-3-chloropropane in DMF using NaH; the resulting chloropropyl derivative **10** was condensed with imidazolethione **1** in DMF using potassium *t*-butoxide to give 2-[3-(2-methyl-1H-imidazol-1-yl)propylthio]-4,5-diphenyl-1H-imidazole (**11**), which at 0.03 wt% in feed gave 26–74% inhibition of diet-induced elevation of plasma cholesterol in rats [21].



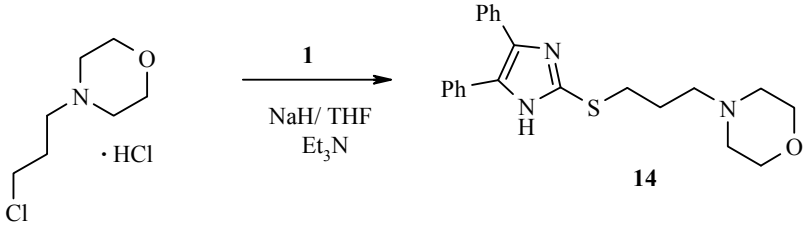
Imidazolethione **1** and 2-(chloromethyl)pyridine hydrochloride were refluxed in aqueous methanol containing sodium hydroxide to give 2-((4,5-diphenyl-1H-imidazol-2-ylthio)methyl)pyridine (**12**), which showed excellent antiulcer and anti-inflammatory activities and platelet aggregation inhibitor properties [3, 8].



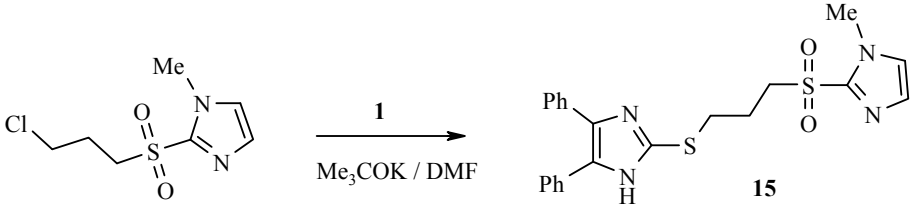
Imidazolethione **1** and methyl (3-chloromethylphenoxy)acetate were heated with NaH in DMF to give 58% methyl 2-(3-((4,5-diphenyl-1H-imidazol-2-yl-thio)methyl)phenoxy)acetate (**13**), which inhibited aggregation of human platelets [22].



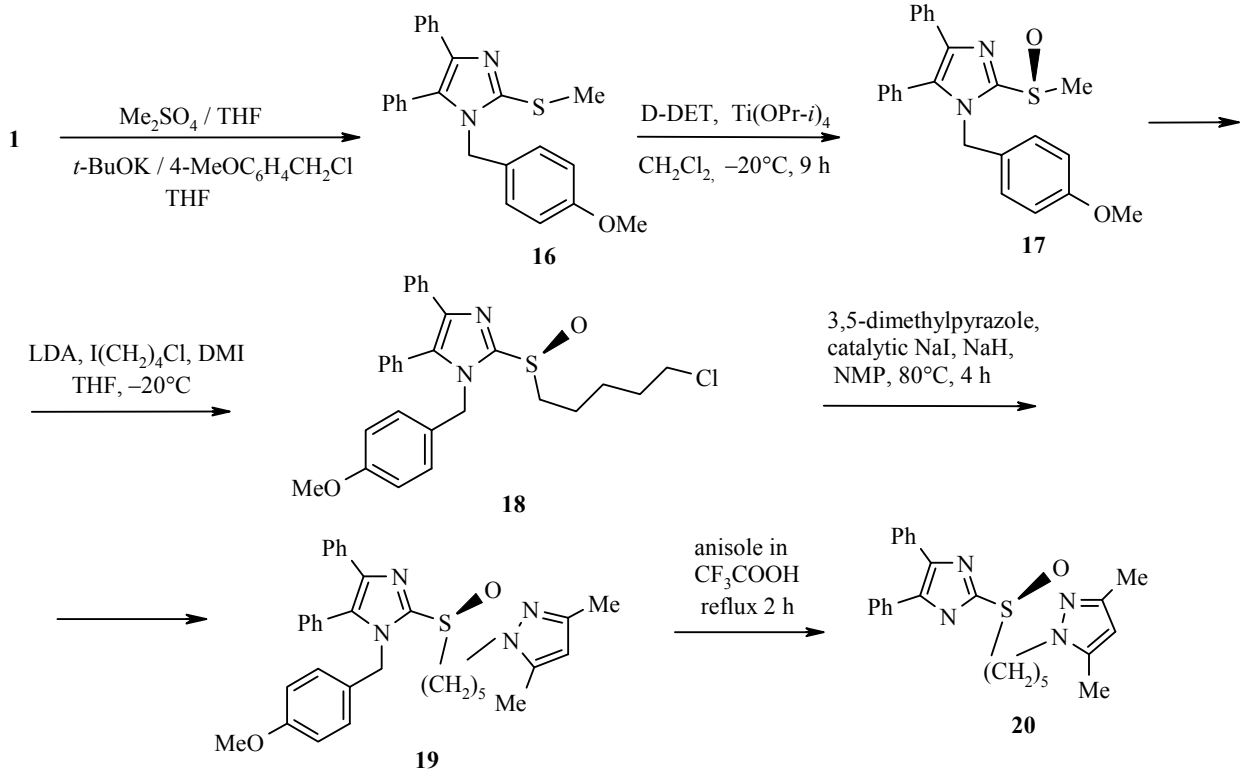
Sodium hydride was added to a stirred suspension of imidazolethione **1** in THF at ambient temperature and after 0.5 h stirring, N-(3-chloropropyl)morpholine hydrochloride followed by triethylamine were added. The mixture was refluxed for 48 h to give 4-(3-(4,5-diphenyl-1H-imidazol-2-ylthio)propyl)morpholine (**14**), which in vitro at 10 μg/ml inhibited acyl-CoA: cholesterol-O-acyltransferase (ACAT) in 91% [23].



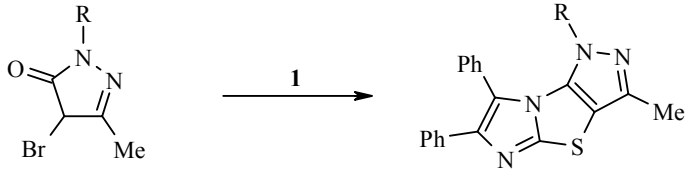
Imidazolethione **1**, potassium *t*-butoxide, and 2-(3-chloropropylsulfonyl)-1-methylimidazole were reacted overnight in DMF at ambient temperature to give 2-(3-(4,5-diphenyl-1H-imidazol-2-ylthio)propyl-sulfonyl)-1-methyl-1H-imidazole (**15**), which gave the maximum inhibition of increase in plasma cholesterol induced by a cholesterol-supplemented diet [24].



The asymmetric oxidation of sulfide **16** optimized using 0.5 mol equivalent of Ti(OPr-*i*)$_4$ and 1 equiv. of D-diethyl tartrate (D-DET) in anhydrous conditions afforded compound **17**. Alkylation of compound **17** by 4-chloro-1-iodobutane using lithium diisopropylamide (LDA) as a base required the presence of a polar aprotic co-solvent such as HMPA or 1,3-dimethyl-2-imidazolidinone (DMI) and gave compound **18** as a viscous oil in quantitative crude yield. After the reaction of compound **18** with dimethylpyrazole, deprotection of compound **19** was realized without racemization in refluxing trifluroacetic acid in the presence of anisole to afford compound **20** [25-27].

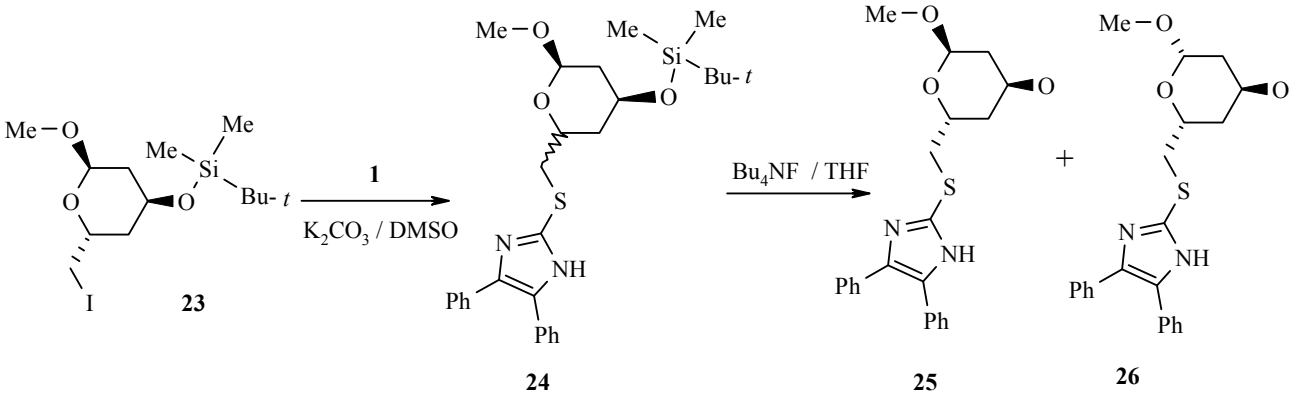


Bromomethylpyrazolones **21** (R = H, Ph) underwent cyclocondensation with cyclic thioureas, e.g., compound **1** gave pyrazoloimidazolothiazole **22** [28].

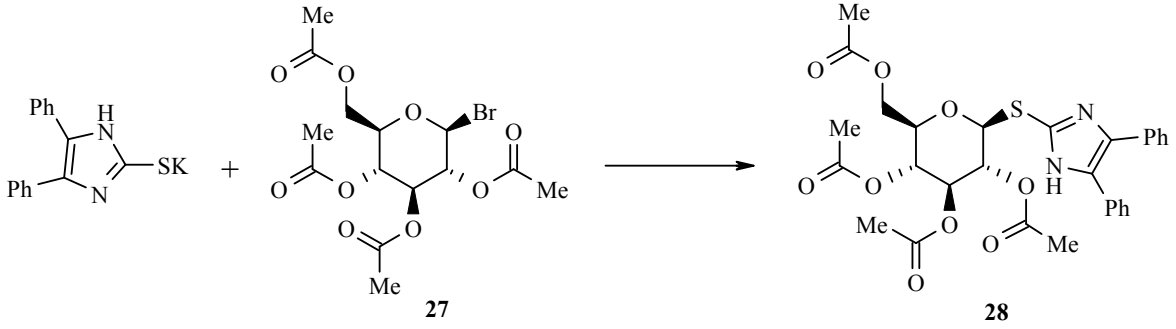


2.1.3. Halo Alcohols and Ethers

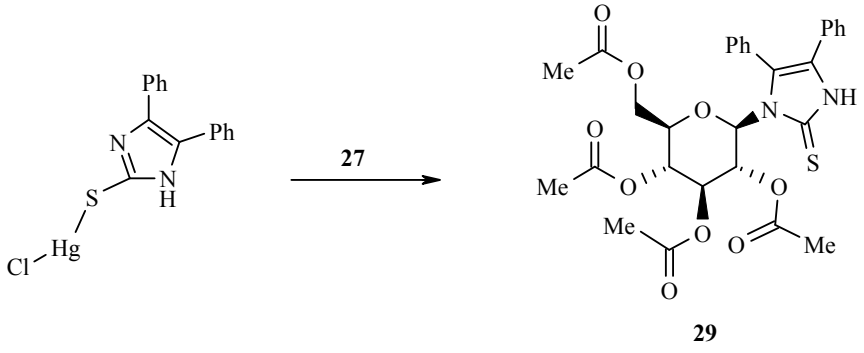
A mixture of imidazolethione **1**, (2S,4R,6S)-4-*tert*-butyldimethylsiloxy-6-iodomethyl-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (**23**), and potassium carbonate was stirred for 4.5 h in Me_2SO at 60°C to give a mixture of (2S,4R,6S)- and (2R,4R,6S)-4-*tert*-butyldimethylsiloxy-6-(4,5-diphenylimidazol-2-yl)thiomethyl]-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (**24**). The mixture was treated with Bu_4NF in THF followed by chromatographic separation to give compounds **25** and **26**. Compound **25** inhibited ACAT [29].



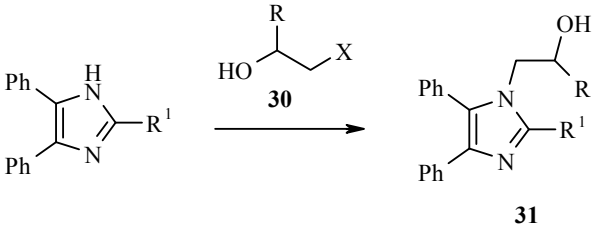
Tetra-O-acetyl-β-D-glucopyranosyl bromide (**27**) reacted with potassium 4,5-diphenylimidazole-2-thiolate to give 4,5-diphenyl-2-(tetra-O-acetyl-β-D-glucopyranosylthio)imidazole (**28**) [30].



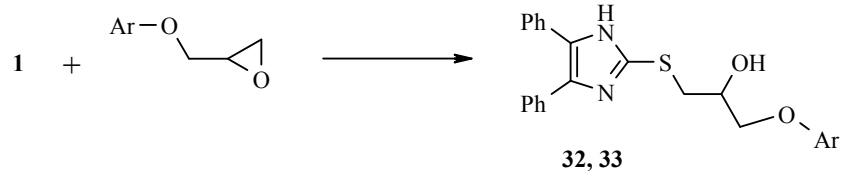
When the bromide **27** was treated with chloromercury 4,5-diphenylimidazole-2-thiolate, 4,5-diphenyl-1-(tetra-O-acetyl-β-D-glucopyranosyl)-4-imidazoline-2-thione (**29**) was formed [30].



Imidazolylethanols **31** (R = H, Me, Ph, *p*-$O_2NC_6H_4$, R^1 = MeS, $PhCH_2S$) were prepared in 62-97% yields by treatment of the corresponding diphenylimidazoles with β-halo alcohol **30** (X = Cl, Br). Compounds **31** are useful as fungicides, bactericides, and antihypertensives [31].



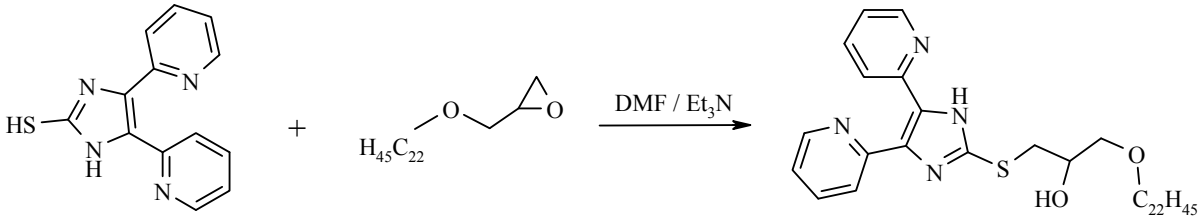
4,5-Diphenylimidazoles **32** and **33** were prepared as cholesterol acyltransferase inhibitors by the reaction of thione **1** with *p*-(2,3-epoxypropoxy)benzoic acid or its isobutyl ester, respectively, in ethanol [32, 33].



32, 33

32 Ar = $C_6H_4CO_2H$, **33** Ar = $C_6H_4CO_2Bu$-*i*

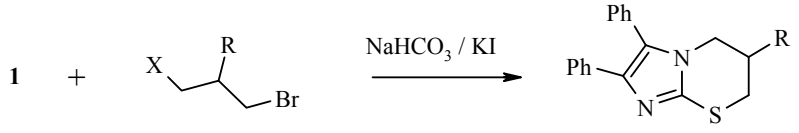
4,5-Di(2-pyridyl)-2-imidazolethiol **34** reacted with docosyl glycidyl ether in the presence of triethylamine in DMF at 80°C for 4 h to give 1-[4,5-di(2-pyridyl)-2-imidazolylthio]-3-docosyloxy-2-propanol (**35**) in 42% yield, which showed inhibitory activity on human cytosolic phospholipase A2 [34].



34 **35**

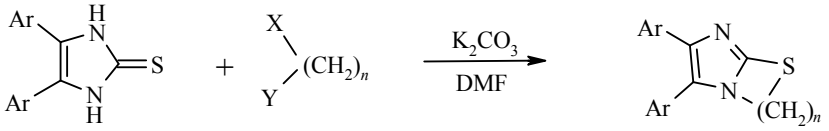
2.1.4. Dihaloalkanes

Imidazo[2,1-*b*][1,3]thiazines **36** (R = H, Me, OH) were prepared by the reaction of 4,5-diphenyl-imidazole-2-thione **1** with 1,3-dibromopropane (X = Br; R = H), 1-bromo-3-chloro-2-methylpropane (X = Cl; R = Me), and 1-bromo-3-chloropropan-2-ol (X = Cl; R = OH) in 2-propanol containing sodium bicarbonate and potassium iodide [35].



36

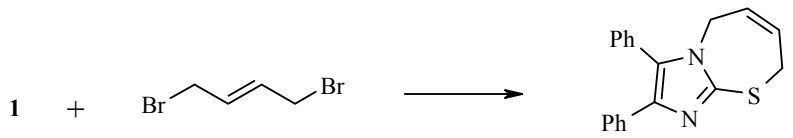
Cyclization of 4,5-diarylimidazole-2-thiones (Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$) by dihaloalkanes (*n* = 2, 3; X = Cl; Y = Br) in DMF in the presence of K_2CO_3 afforded imidazo[2,1-*b*][1,3]thiazoles **37a** (*n* =2) and thiazines **37b** (*n* = 3) [19, 36-38].



37a,b

2.1.5. Dihaloalkenes

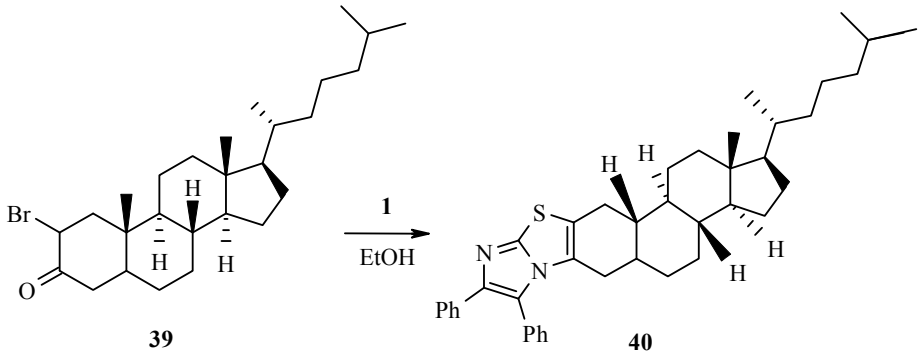
The reaction of imidazole-2-thione **1** with 1,4-dibromo-2-butene gave 7,8-disubstituted imidazo-2H,5H[2,1-*b*][1,3]thiazepine **38** [39].



38

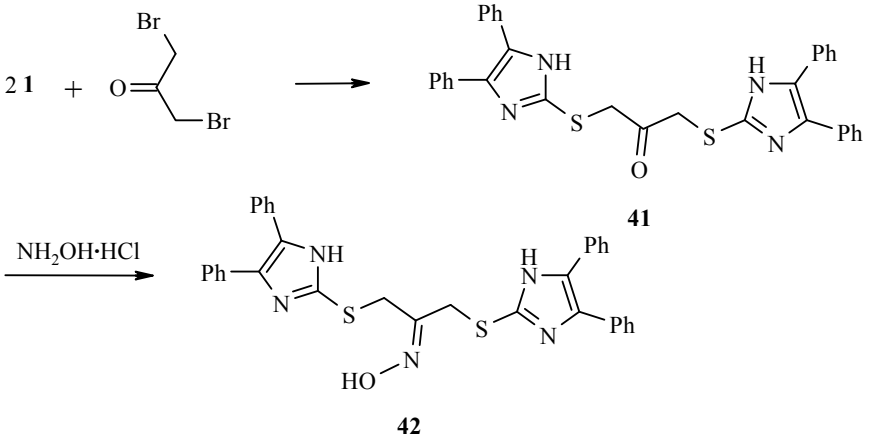
2.1.6. Halo Ketones

Condensation reaction of bromocholestanone **39** with thione **1** in refluxing ethanol gave imidazothiazole **40** [40].



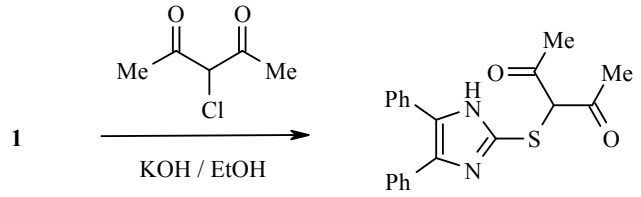
39 **40**

4,5-Diphenylimidazole derivatives **42** used as ACAT inhibitors were prepared by the reaction of 4,5-diphenylimidazole-2-thione **1** with 1,3-dibromoacetone to afford 1,3-bis(4,5-diphenylimidazol-2-ylthio)-2-oxopropane (**41**), which was stirred with hydroxylamine hydrochloride in isobutanol to give 64% 1,3-bis-(4,5-diphenylimidazol-2-ylthio)-2-hydroxyiminopropane (**42**) [41].



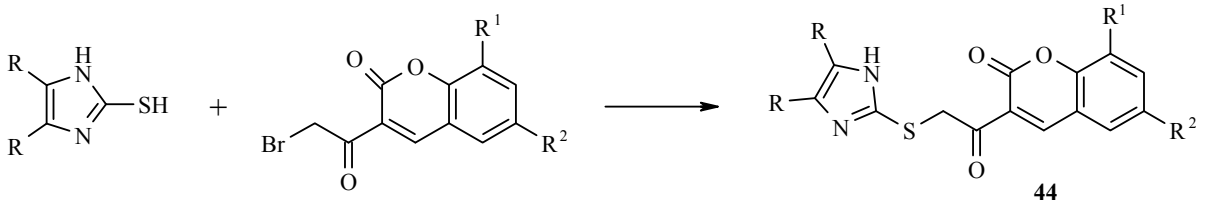
42

The potassium salt of imidazolethione **1** reacted with 3-chloro-2,4-pentanedione to give the S-alkyl derivative **43** [42].



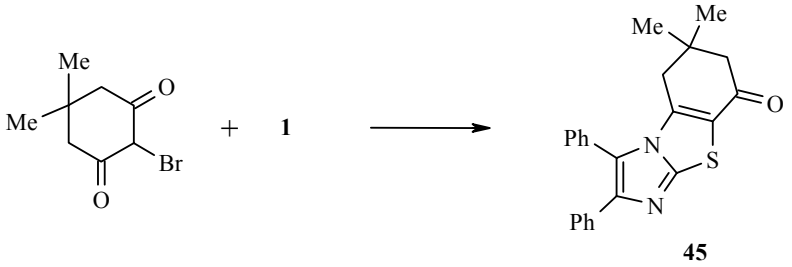
43

The reaction of 4,5-disubstituted 2-mercaptoimidazoles (R = Ph, 4-$MeOC_6H_4$) with 3-(ω-bromoacetyl)coumarins gave the intermediate ketones **44** (R^1 = H, R^2 = H, Br; R^1 = OMe, R^2 = H; R^1 = R^2 = Br) [43].



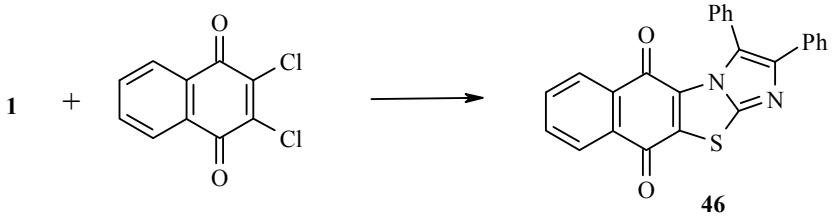
44

Thione **1** when condensed with 2-bromo-5,5-dimethylcyclohexane-1,3-dione afforded 6,6-dimethyl-2,3-diphenyl-5,6-dihydroimidazo[2,1-*b*]benzothiazol-8(7H)-one (**45**) [44].



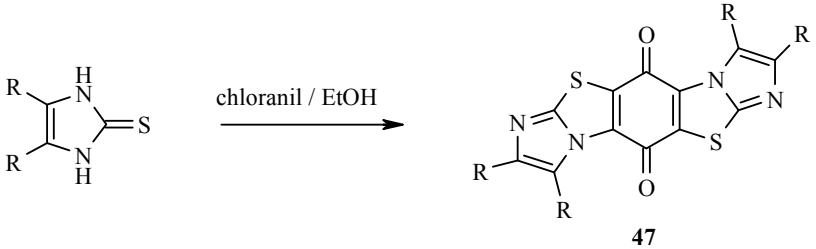
45

Reaction of thione **1** with 2,3-dichloro-1,4-naphthoquinone gave imidazo[2,1-*b*]thiazole **46** in 67% yield [45].



46

The reaction of chloranyl with cyclic ureas gave fused pentacyclic compound **47**, which showed herbicidal and fungicidal activities [46].

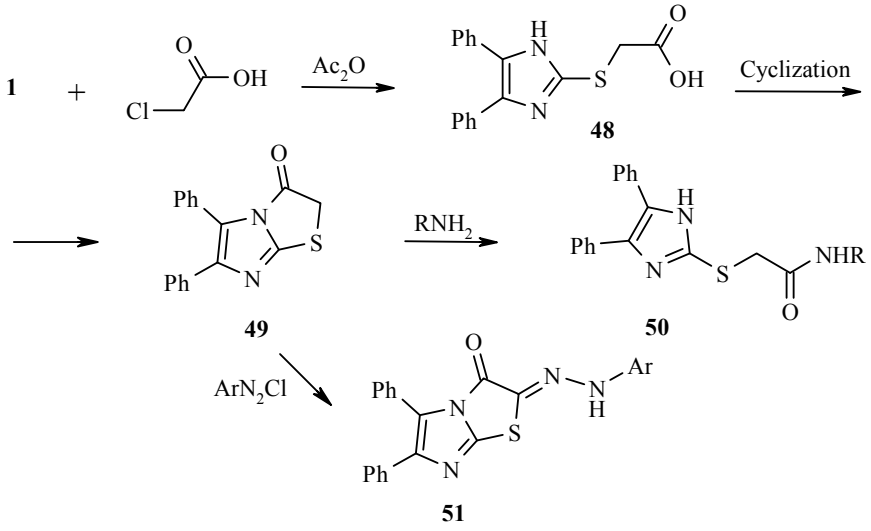


47

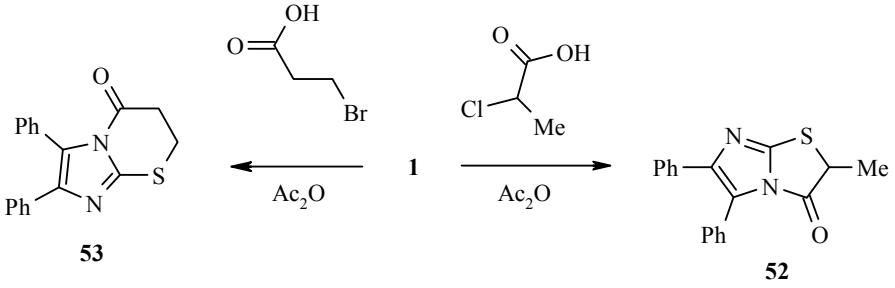
R = H, Me, Ph

2.1.7. Halo Acids (Esters)

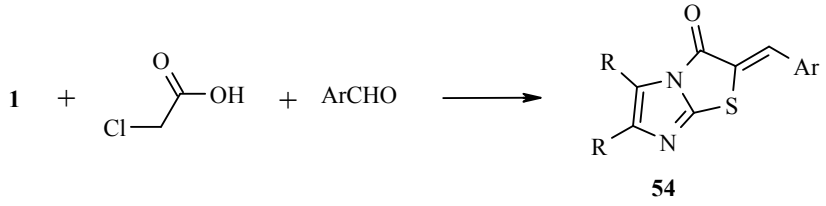
The reaction of thione **1** with chloroacetic acid gave 2-(carboxymethylthio) derivatives **48** (R = Ph or *p*-$MeOC_6H_4$), which on cyclization gave imidazothiazolones **49**. Ring cleavage of compound **49** with amines gave (2-imidazolylthio)acetamides **50** (R = H, $PhCH_2$, PhNH, Ph, or *p*-MeC_6H_4) in 72–81% yields. The reaction of compound **49** with diazotized amines gave 2-(arylhydrazono) compounds **51** (81-98%, Ar = Ph and substituted phenyls) [47].



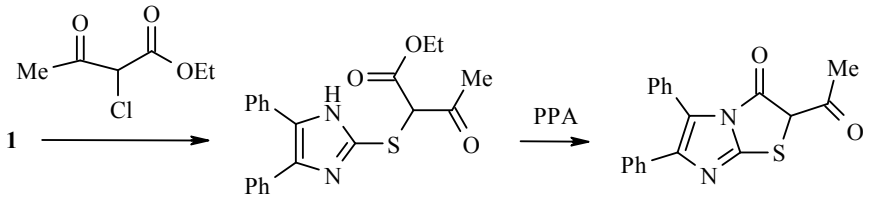
2-Methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-3(2H)-one (**52**) and 6,7-diphenyl-2,3-dihydro-4H-imidazo-[2,1-*b*][1,3]thiazinone (**53**) were prepared by cyclodehydration with acetic anhydride of the corresponding acid obtained by condensing thione **1** with α-chloropropionic acid or β-bromopropionic acid, respectively [38, 48, 49].



The synthesis of substituted 2-arylidene-5,6-diphenylimidazo[2,1-*b*][1,3]thiazol-3-(2H)-ones **54** was performed in one-pot reaction by condensation of thione **1** with chloroacetic acid and aldehydes in the presence of acetic anhydride, anhydrous sodium acetate, and glacial acetic acid [47, 50].



The treatment of compound **1** with ethyl 2-chloroacetoacetate gave compound **55**, which when heated with polyphosphoric acid gave cyclized product **56** [2].

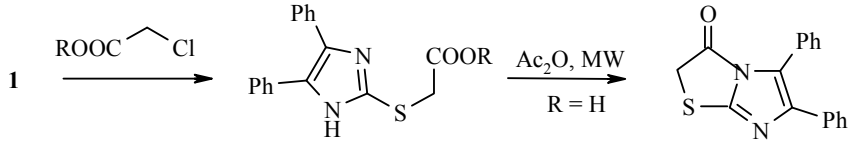


55 **56**

A mixture of imidazolethione **1**, ethyl bromoacetate, and potassium carbonate was stirred overnight in DMF to give ethyl 2-(4,5-diphenyl-1H-imidazol-2-ylthio)acetate (**57**), which inhibited by 90% the increase in plasma cholesterol in rats fed a cholesterol-supplemented diet [7].

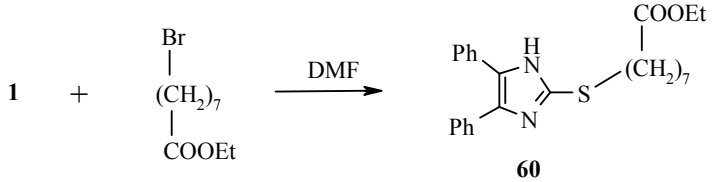
57

The reaction of compound **1** with chloroacetic acid and ethyl chloroacetate afforded the respective acid **58** (R = H) and its ester (R = Et). Dehydrative cyclization of acid **58** (R = H) gave 5,6-diphenyl-2,3-dihydroimidazo[2,1-*b*]thiazol-3-one (**59**) by the action of acetic anhydride under MW irradition [51].



58 **59**

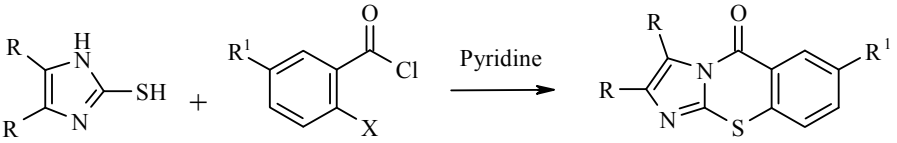
Ethyl 8-bromooctanoate was added dropwise to a solution of thione **1** in DMF and the mixture was refluxed overnight to give 4,5-diphenyl-2-substituted thioimidazole **60**, which inhibited ACAT [6].



60

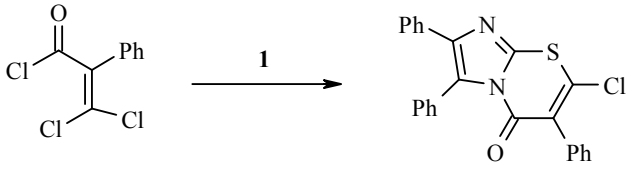
2.1.8. Acyl Halogenides

Imidazo[2,1-*b*][1,3]benzothiazin-4-ones **61** (R = Me, Ph; R^1 = H, NO_2) were prepared by reacting 4,5-disubstituted 2-mercaptoimidazoles with *o*-halobenzoic acid (X = F, Cl) in the presence of pyridine at 80-115°C [52].



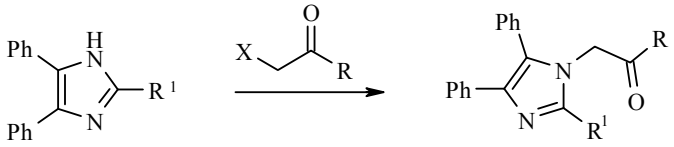
61

3,3-Dichloro-2-phenylacryloyl chloride was directly transformed into imidazo[2,1-*b*][1,3]thiazin-5-one **62** by condensation with thione **1** [53].



62

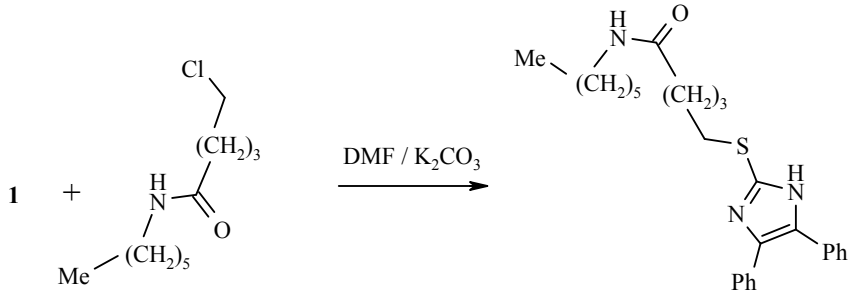
Treatment of diphenylimidazoles with phenacylbromides gave 42–83% of compounds **63** (R = Ph, *p*-BrC_6H_4, R^1 = MeS, $MeSO_2$). Compounds **65** are useful as fungicides, bactericides, and antihypertensives [31].



63

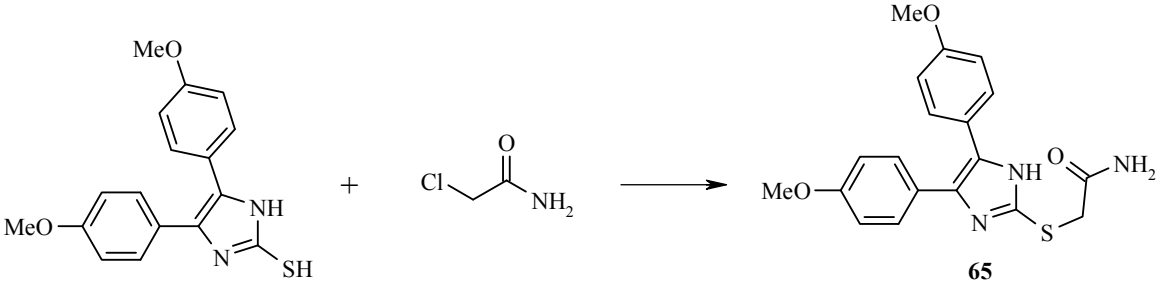
2.1.9. Amides

Treatment of N-heptyl-5-chloropentanamide with 4,5-diphenyl-1H-imidazole-2-thiol **1** in DMF in the presence of K_2CO_3 at 50-55°C gave 73% of ω-substituted alkanamide **64** [54].



64

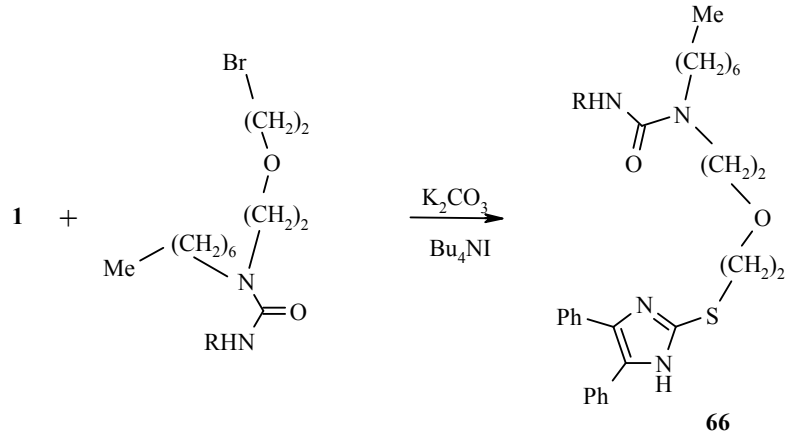
Imidazole **65** was prepared by S-alkylation of thiol with 2-chloroacetamide. It may be used as a cyclooxygenase inhibitor for the treatment of diseases that are associated with a disturbed immune system [55].



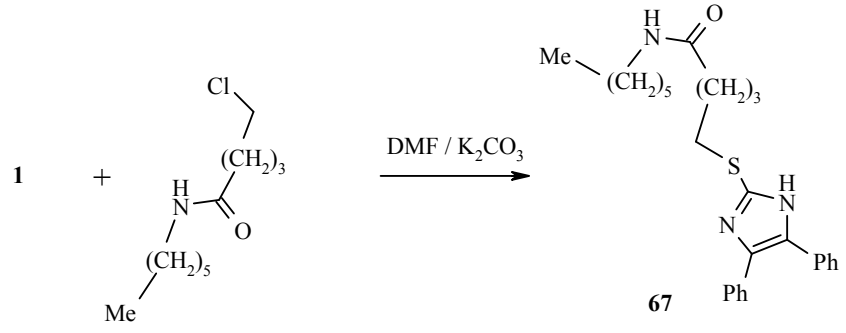
65

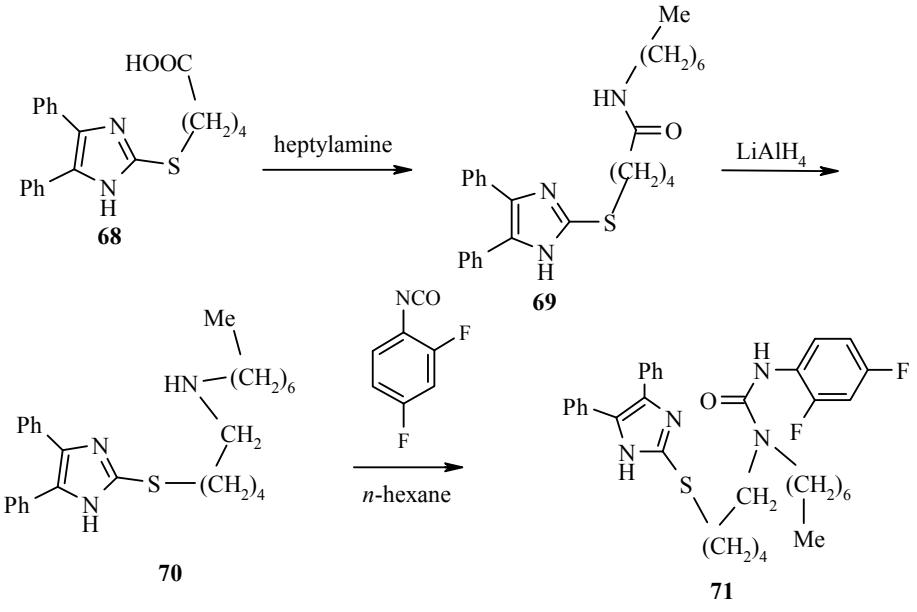
2.1.10. Ureas

Preparation of compounds with an ether linkage in the "inner" chain (connecting the imidazole sulfide and the urea groups), such as compounds **66**, which are potent ACAT inhibitors, occurred by S-alkylation of imidazole-2-thione **1** [11, 56-59].



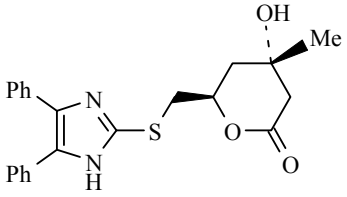
The treatment of N-heptyl-5-chloropentanamide with imidazolethione **1** in DMF in the presence of K_2CO_3 at 50-55°C gave 73% of ω-substituted alkanamide **67** [54].



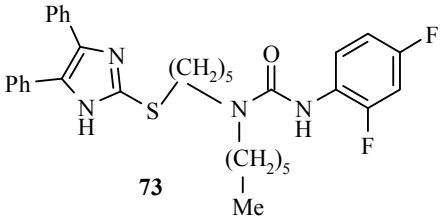


Amidation of pentanoic acid derivative **68** with heptylamine gave amide **69**, which was reduced with $LiAlH_4$ to give amine **70**, isolated as the HCl salt. A solution of 2,4-difluoro-1-isocyanatobenzene in hexane was added to a solution of compound **70** in hexane with stirring at room temperature to give urea **71**, which *in vitro* inhibited cholesterol acyltransferase [60].

2-(Alkylthio)-4,5-diphenyl-1H-imidazoles such as **72** and **73** are potent, bioavailable ACAT inhibitors. They have beneficial effects in the treatment of atherosclerosis by (i) reducing the absorption of dietary cholesterol, (ii) reducing the secretion of very low density lipoproteins into plasma from the liver, and (iii) preventing the transformation of arterial macrophages into foam cells [61, 62].



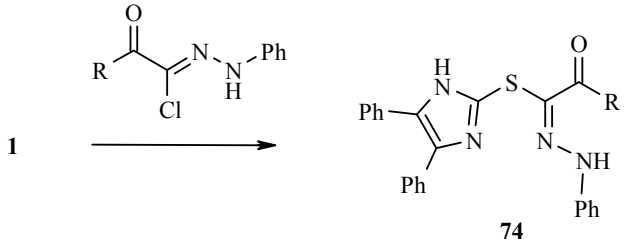
72



73

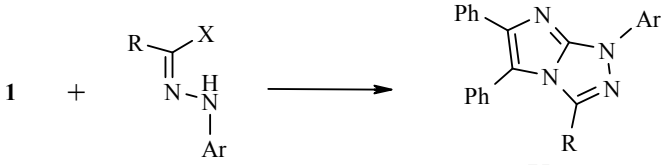
2.1.11. Halo Hydrazones

Imidazolethione **1** was treated with hydrazonoyl halides (R = Me, Ph, NHPh, OEt; X = Cl, Br) to give S-alkyl derivatives **74** [2].



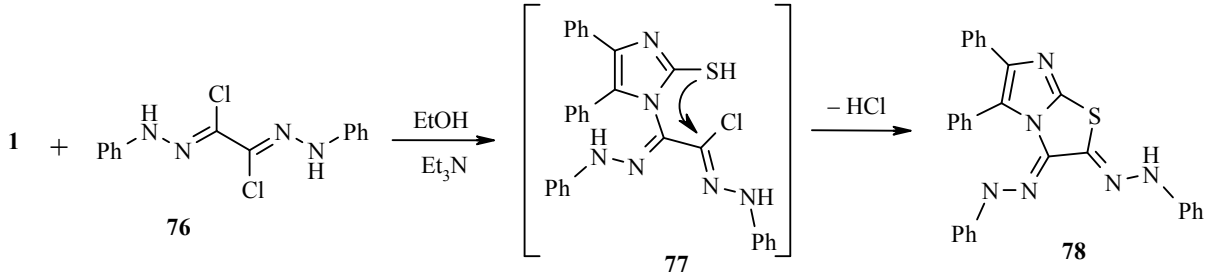
74

Imidazolinethione **1** reacted with hydrazonoyl halides (R = Ph, 2-thienyl, 2-furyl, Ar = Ph, 4-$O_2NC_6H_4$, X = Cl, Br) to give 5,6-diphenylimidazo[2,1-*c*][1,2,4]triazoles **75** [9].



75

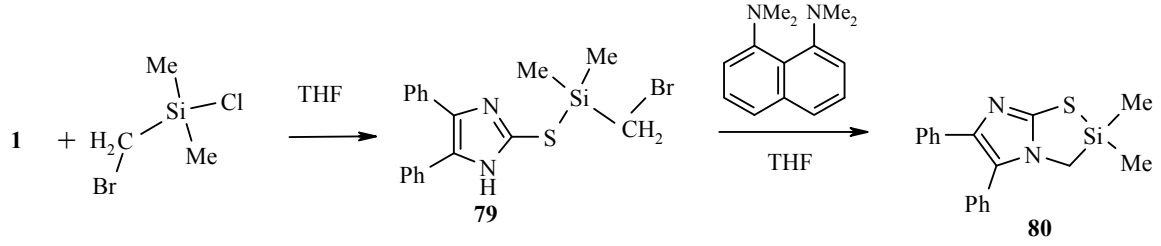
When compound **1** was allowed to react with bis-hydrazonoyl chloride **76**, 2,3-bisphenylhydrazono-2,3-dihydroimidazo[2,1-*b*]thiazole (**78**) was formed through the nonisolable intermediate **77** [63].



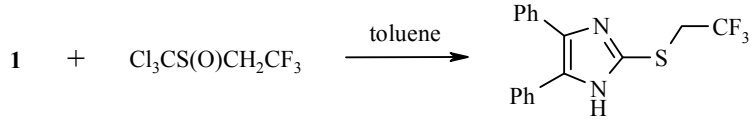
76 **77** **78**

2.1.12. Miscellaneous Alkylations

Imidazolethione **1** reacted with bromomethyldimethylchlorosilane in anhydrous tetrahydrofuran to give bromomethyldimethylsilylthioimidazole (**79**). Cyclodehydrohalogenation of compound **79** by 1,8-bis(dimethylamino)naphthalene afforded 2,2-dimethyl-5,6-diphenyl-2,3-dihydroimidazo[1,2-*d*][1,4,2]thiazasilole (**80**) [64].

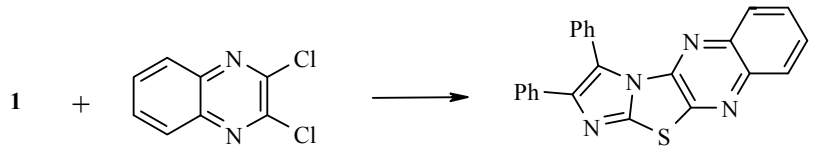


Imidazolethione **1** was heated with 1,1,1-trifluoro-2-(trichloromethylsulfinyl)ethane and triethylamine in toluene to give anti-inflammatory 4,5-diphenyl-2-(2,2,2-trifluoroethylthio)imidazole (**81**) [4, 65].



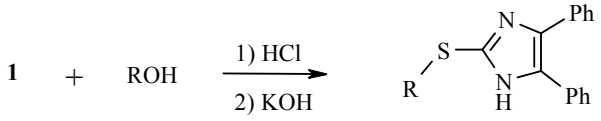
81

Condensation of thione **1** with 2,3-dichloroquinoxaline gave similarly 2,3-diphenylimidazo-[2',1':2,3]thiazolo[4,5-*b*]quinoxaline (**82**) [38].



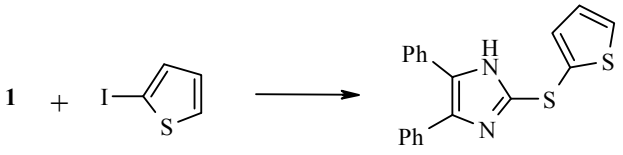
82

Alkylation of imidazole-2-thione **1** with alcohols (R = Me, Et, Pr, Bu) containing HCl gave intermediate alkylthio hydrochlorides, which were neutralized by KOH to afford the corresponding alkylthio derivatives **83** in 80-95% yields [66, 67].



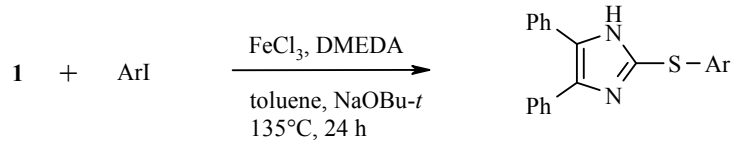
83

Imidazole **84** was prepared by the reaction of thione **1** with 2-iodothiophene, it had an oral ED_{40} of 20 mg/kg in the adjuvant arthritis test in rats [68].



84

S-Arylation of thione **1** with aryl iodide (Ar = Ph, 2-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$) was carried out using an inexpensive catalyst system formed by combining ferric chloride and N,N'-dimethylethylenediamine (DMEDA) at 135°C to afford the corresponding sulfide **85** [69].

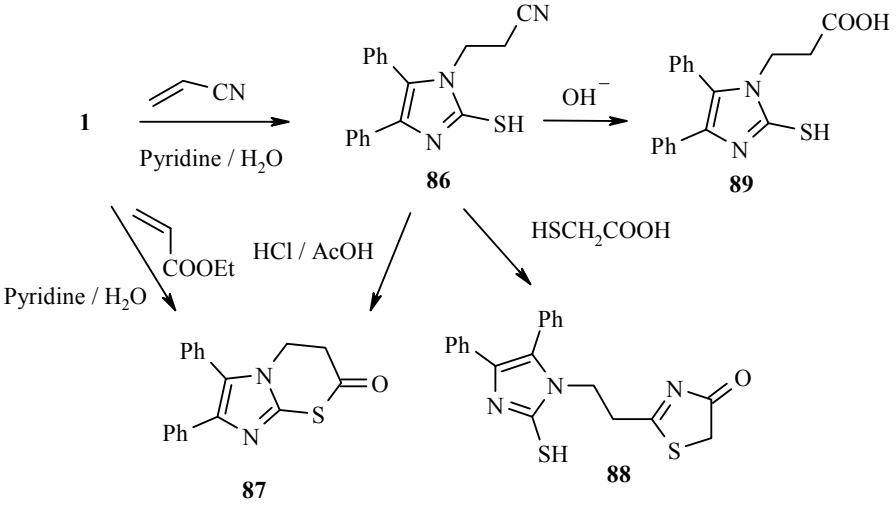


85

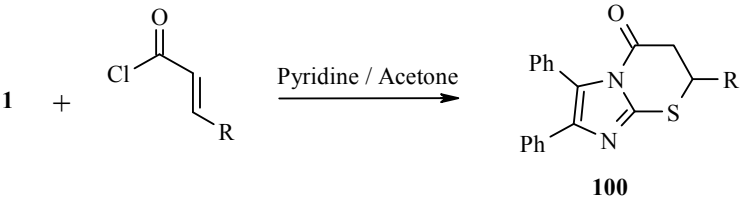
2.2. Addition to Activated Double Bonds

Cyanoethylation of imidazolethione **1** in pyridine and water gave 3-(2-cyanoethyl)-2-mercaptoimidazole (**86**). Cyclization of the latter with AcOH/HCl gave imidazo[2,1-*b*]thiazine **87**. The reaction of compound **86** with thioglycolic acid gave thiazole derivative **88**, while compound **87** can also be prepared in one-pot reaction by reacting thione with ethyl acrylate [70-72].

Hydrolysis of nitrile **86** by alkali gave the carboxyethyl derivative **89**, while in acidic medium imidazo-[2,1-*b*][1,3]thiazine derivative **87** was obtained [73].

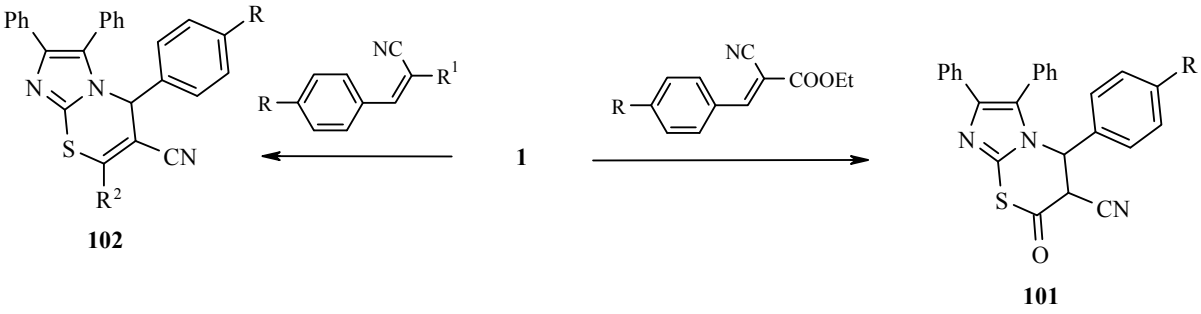


The reactions of 4,5-diphenylimidazole-2-thione (**1**) with acryloyl chloride (R = H), crotonyl chloride (R = Me), and 3-aryl-2-propenoyl chlorides in pyridine and acetone afforded 7-substituted 6,7-dihydro-5H-imidazo[2,1-*b*][1,3]thiazin-5-ones **100** [74].



100

Several imidazo[2,1-*b*][1,3]thiazine derivatives **101** (R = H, MeO, Cl) and **102** were synthesized *via* the reaction of thione **1** with α,β-unsaturated nitriles (R^1 = CN, COPh, R^2 = NH_2, Ph) [75].

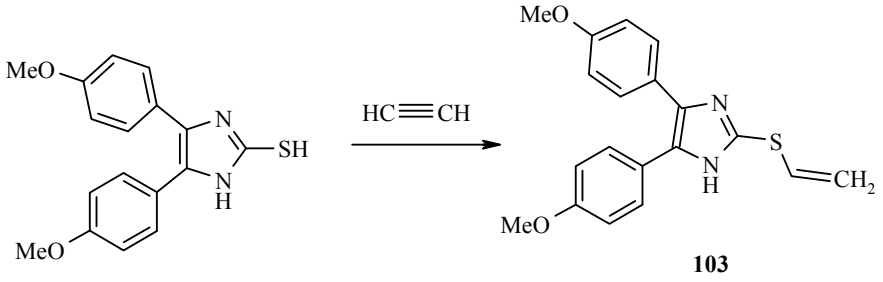


102 **101**

2.3. Reaction with Alkynes

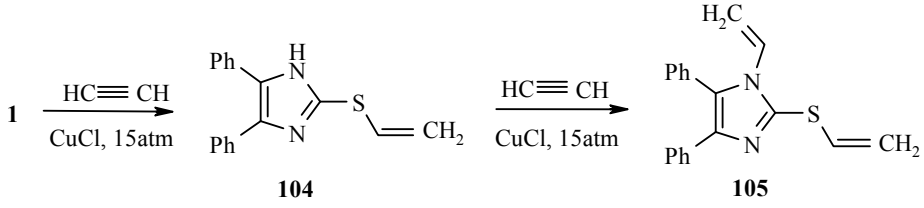
2-Mercaptoimidazole, which has a thioamide fragment in its five-membered ring and is capable of tautomeric transformations, adds acetylene not only at the sulfur atom, but also simultaneously at both heteroatoms [76].

Vinyl sulfide **103** was prepared by the cuprous chloride-catalyzed addition of 2-mercapto-4,5-bis-(4-methoxyphenyl)imidazole to acetylene [5].



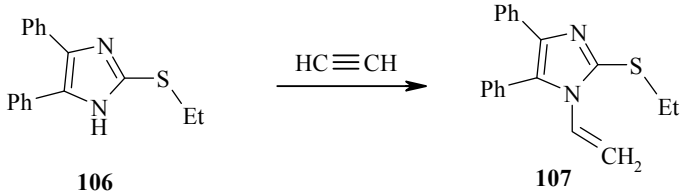
103

Vinylation of thione **1** by acetylene gave a high yield of vinyl sulfide **104**, which on continued treatment gave the N,S-divinyl derivative **105** in 85% yield [77-80].



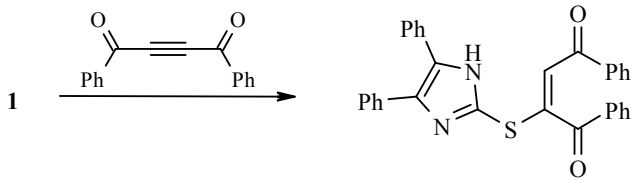
104 **105**

Treatment of 2-(ethylthio)-4,5-diphenyl-1H-imidazole (**106**) with acetylene gave 2-(ethylthio)-4,5-diphenyl-1-vinyl-1H-imidazole (**107**) in 65% yield [79].



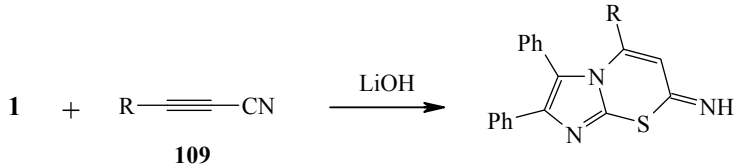
106 **107**

2-(1,2-Dibenzoylvinyl)thio-4,5-diphenylimidazole (**108**) can be prepared by condensation of imidazole-2-thione **1** with dibenzoylacetylene [72].



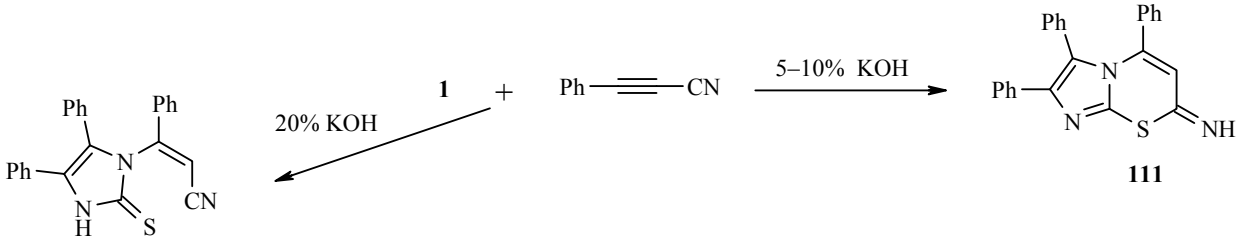
108

Substituted 1,3-thiazinoazoles **110** [R = Me_2COH, EtMeCOH, BuMeCOH, 1-hydroxycyclohexyl and -cyclopentyl, $Me_2COCH(OBu)Me$] were prepared in 54-98% yields by the reaction of thione **1** with cyanoacetylenes **109** in the presence of lithium hydroxide [81, 82].



109 **110**

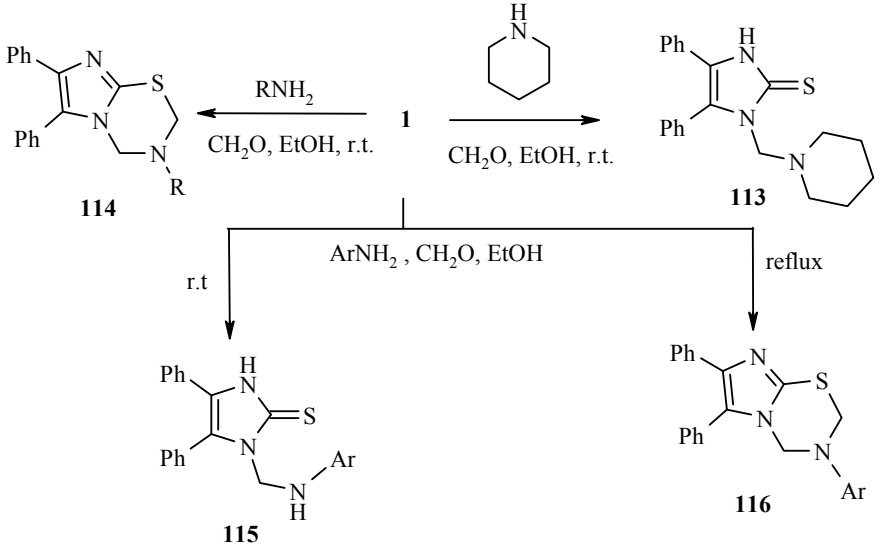
The reaction of imidazolethione **1** with phenylcyanoacetylene in the presence of 5-10% KOH gave the cyclization product **111**, while using 20% KOH cleaved the thiazine ring to give an uncyclized addition product **112** [83].



112 **111**

2.4. Mannich Reaction

Condensation of imidazole-2-thione **1** with formaldehyde and secondary amine in ethanol at room temperature gave the corresponding N-substituted aminomethyl derivatives **113**. The reaction of thione **1** with

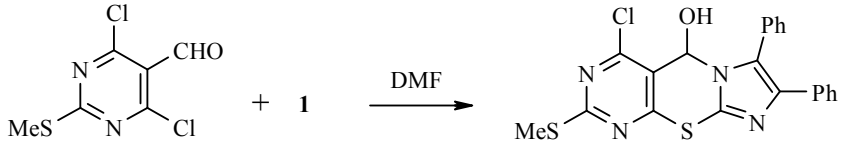


114 **113** **115** **116**

primary aliphatic amines under Mannich reaction conditions at room temperature led to the formation of bicyclic products **114**. Similarly, compound **1** was condensed with primary aromatic amines at room temperature to yield uncyclized products **115**, while in boiling ethanol the corresponding cyclized products **116** were obtained [84].

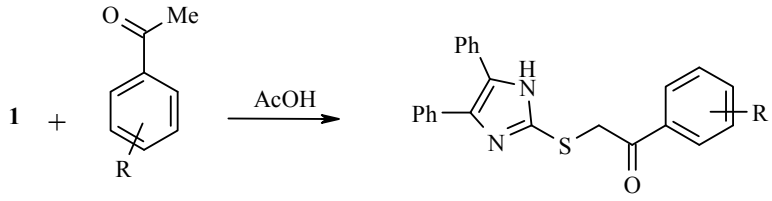
2.5. Reaction with Carbonyl Compounds

Cyclocondensation of 4,6-dichloro-2-methylthiopyrimidine-5-carbaldehyde and thione **1** in DMF gave tricyclic heterocycles containing a pyrimido[5,4-*e*][1,3]thiazine fragment **117** [85].



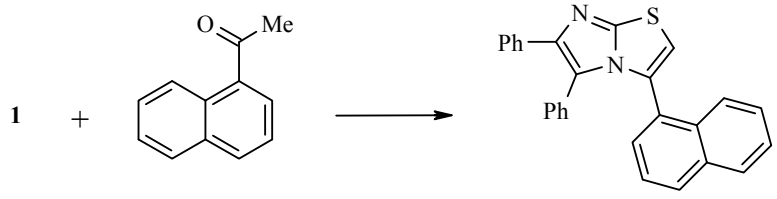
117

The reaction of thione **1** with aromatic ketones using acetic acid afforded (4,5-diphenyl-2-imidazolylthio)acetophenones **118** in good yields [86].



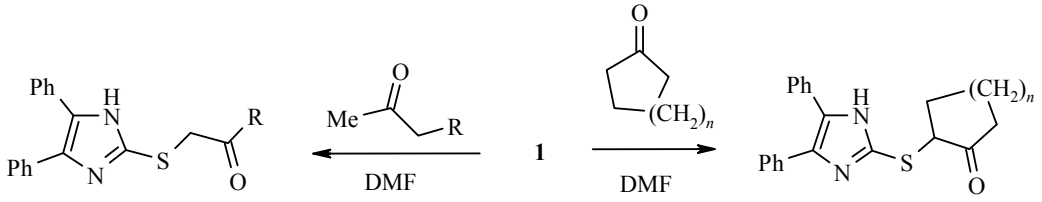
118

At the same time, the reaction with α-acetylnaphthalene gave directly cyclized product **119** [86].



119

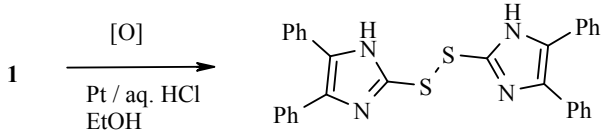
In the same manner, the reaction of thione **1** with aliphatic and/or alicyclic ketones (*n* =1-3) gave 3-(4,5-diphenyl-2-imidazolylthio)acetones **120** and 2-(4,5-diphenylimidazolylthio)cycloalkanones **121** [86].



120 **121**

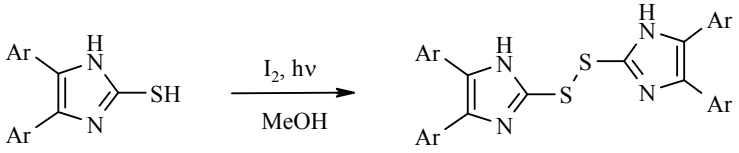
2.6. Oxidation

Oxidation of thione **1** on a Pt electrode in aqueous HCl solution containing ethanol gave the corresponding bis(4,5-diphenyl-2-imidazolyl) disulfide **122** in 90% yield [87, 88].



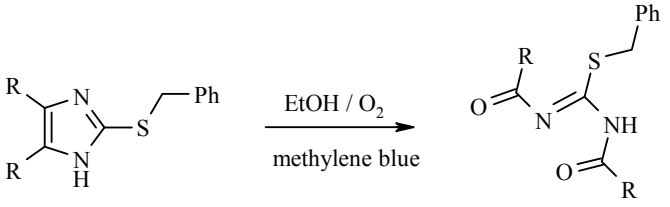
122

4,5-Diaryl-2-imidazolinethiones (Ar = Ph, 4-Me and 4-ClC_6H_4) were converted to bis(4,5-diaryl-2-imidazolyl) sulfides **123** by photolysis in methanol containing iodine [89].



123

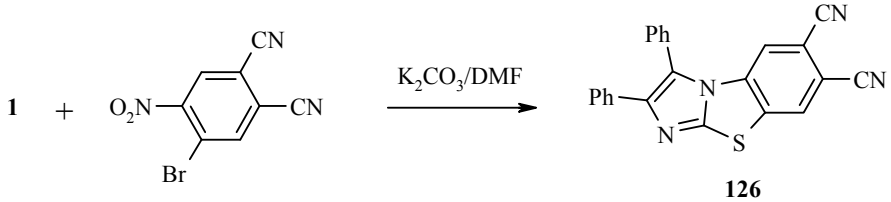
Photochemical singlet oxygenation of 4,5-diaryl-2-(benzylthio)imidazoles **124** in ethanol in the presence of methylene blue and oxygen led to the formation of N,N'-diaroyl-S-benzylisothioureas **125** in 35-62% yields [90].



124 **125**

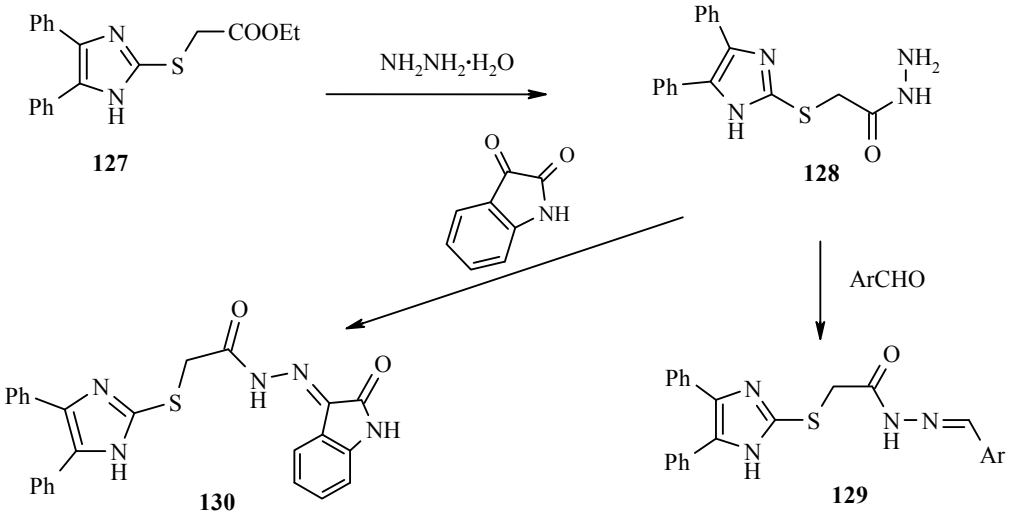
2.7. Other Reactions

Heterocyclic *o*-dinitrile **126** was prepared in high yield and selectivity by the cyclocondensation reaction of 4-bromo-5-nitrophthalonitrile in DMF and in the presence of potassium carbonate with thione **1** [91].



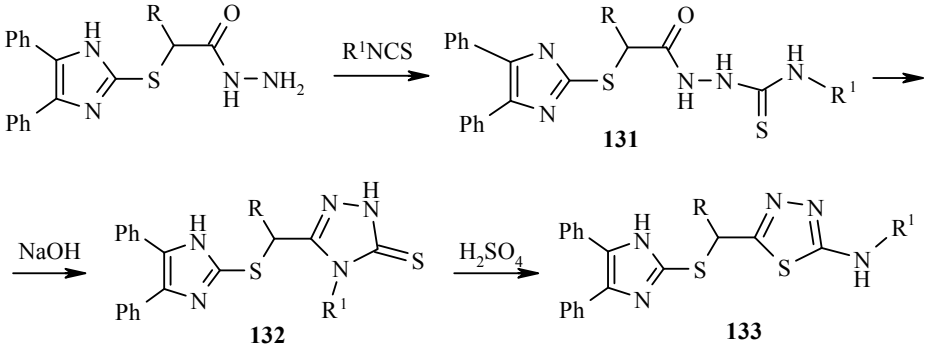
126

Hydrazinolysis of compound **127** gave the hydrazide **128**, whose condensation with aromatic aldehydes and isatin gave the corresponding hydrazones **129** and **130** [51].



The reaction of [(4,5-diphenyl-1H-imidazol-2-yl)thio]acetic acid hydrazide with isothiocyanates gave the corresponding thiosemicarbazides **131**.

Cyclization of **131** (R = H, *i*-Pr, R^1 = Et, Pr, Ph) in the presence of sodium hydroxide afforded triazoline-5-thiones **132** or cyclized into 1,3,4-thiadiazoles **133** in the presence of sulfuric acid [91].



REFERENCES

1 A. Gursoy, S. Demirayak, Z. Cesur, J. Reisch, and G. Otuk, *Pharmazie*, **45**, 246 (1990).

2, A. A.-A. Mahfouz, and F. M. Elhabashy, *Arch. Pharm. Res.*, **13**, 9 (1990).

3. M. Tsuji, T. Inoue, K. Ikesue, N. Fujimoto, and K. Noda, Jpn. Kokai Tokkyo Koho JP 01040467 (1989); *Chem. Abstr.*, **111**, 97243 (1990).

4. S. C. Cherkofsky and T. R. Sharpe, US Pat. 4190666; *Chem. Abstr.*, **93**, 8178 (1981).

5. T. R. Sharpe, S. C. Cherkofsky, W. E. Hewes, D. H. Smith, W. A. Gregory, S. B. Haber, M. R. Leadbetter, and J. G. Whitney, *J. Med. Chem.*, **28**, 1188 (1985).

6. J. T. Billheimer, P. J. Gillies, and W. W. Wilkerson, US Pat. 4900744; *Chem. Abstr.*, **113**, 23915 (1991).

7. A. W. Bridge, E. C. J. Coffee, N. V. Harris, D. J. Lythgoe, and C. Smith, PCT Int. Appl. WO 9113876 (1991); *Chem. Abstr.*, **116**, 6561 (1993).

8. M. Hayashi, S. Yokomori, K. Hatayama, and K. Soda, Jpn. Kokai Tokkyo Koho JP 62187469; *Chem. Abstr.*, **108**, 21896 (1989).

9. B. V. Trzhtsinskaya and N. D. Abramova, *J. Sulfur Chem.*, **10**, 389 (1991).
10. F. Friedrich, R. Pohloudek-Fabini, and K. Kottke, *Pharmazie*, **24**, 429 (1969).
11. T. P. Maduskuie, R. G. Wilde, J. T. Billheimer, D. A. Cromley, S. Germain, P. J. Gillies, C. A. Higley, A. L. Johnson, and P. Pennev, *J. Med. Chem.*, **38**, 1067 (1995).
12. P. M. Kochergin, *Zh. Obshch. Khim.*, **31**, 1093 (1961); *Chem. Abstr.*, **55**, 124804 (1962).
13. Z. Yoshida, H. Masuda, and R. Oda, *Nippon Kagaku Kaishi*, **54**, 685 (1951); *Chem. Abstr.*, **48**, 14716 (1951).
14. M. V. Bhatt, B. H. Iyer, and P. C. Guha, *Curr. Sci.*, **17**, 184 (1948).
15. M. Kidwai, S. Kukreja, S. Rastogi, and K. Singhal, *Indian J. Chem.*, **46B**, 1549 (2007).
16. K. O. Utaev, Kh. I. Kadirov, and D. Yusupov, *O'zbekiston Kimyo J.*, **5–6**, 42 (1999); *Chem. Abstr.*, **132**, 334400 (2000).
17. A. C. Sircar and S. C. Guha, *J. Indian Chem. Soc.*, **13**, 704 (1936).
18. R. Gompper, *Angew. Chem.*, **76**, 412 (1964).
19. E. S. H. El Ashry, N. Rashed, L. F. Awad, E. Ramadan, S. M. Abdel-Maggeed, and N. Rezki, *Nucleosides*, *Nucleotides Nucleic Acids*, **26**, 423 (2007).
20. I. K. Petko, *Ukr. Khim. Zh.*, **68**, 115 (2002); *Chem. Abstr.*, **139**, 101073 (2003).
21. A. W. Bridge, N. V. Harris, D. J. Lythgoe, and C. Smith, PCT Int. Appl. WO 9110662; *Chem. Abstr.*, **115**, 207994 (1992).
22. N. Meanwell, Eur. Pat. Appl. EP 442448; *Chem. Abstr.*, **116**, 59369 (1993).
23. A. W. Bridge, N. V. Harris, D. J. Lythgoe, and C. Smith, PCT Int. Appl. WO 9109030; *Chem. Abstr.*, **115**, 183331 (1992).
24. A. W. Bridge, N. V. Harris, D. J. Lythgoe, and C. Smith, PCT Int. Appl. WO 9109021; *Chem. Abstr.*, **115**, 232240 (1992).
25. P. Pitchen, C. J. France, I. M. McFarlane, C. G. Newton, and D. M. Thompson, *Tetrahedron Lett.*, **35**, 485 (1994).
26. M. J. Ashton, A. W. Bridge, R. C. Bush, D. I. Dron, N. V. Harris, G. D. Jones, D. J. Lythgoe, D. Riddell, and C. Smith, *Bioorg. Med. Chem. Lett.*, **2**, 375 (1992).
27. P. Pitchen, Eur. Pat. Appl. EP 523941 (1993); *Chem. Abstr.*, **118**, 213297 (1994).
28. V. K. Chadha and G. R. Sharma, *J. Indian Chem. Soc.*, **67**, 610 (1990).
29. E. C. Coffee, Eur. Pat. Appl. EP 391796 (1990); *Chem. Abstr.*, **114**, 101991 (1992).
30. P. Nuhn and G. Wagner, *J. Prakt. Chem.*, **312**, 90 (1970).
31. M. V. Povstyanoi, B. A. Priimenko, and P. M. Kochergin, *Khim.-Farm. Zh.*, **12**, 59 (1978); *Chem. Abstr.*, **89**, 109238 (1979).
32. M. Bani, R. Bormetti, W. Ceccarelli, R. Fiocchi, M. Gobetti, M. Lombroso, S. Magnetti, V. Olgiati, and M. Palladino, *Eur. J. Med. Chem.*, **30**, 39 (1995).
33. M. Palladino, E. Vanotti, M. Villa, M. Bani, R. Bormetti, and V. Olgiati, Ger. Offen. DE4428025 (1995); *Chem. Abstr.*, **122**, 265372 (1996).
34. A. Makita, Y. Isobe, H. Tomizawa, S. Chiba, and M. Sasaki, Jpn. Kokai Tokkyo Koho JP 2000038380; *Chem. Abstr.*, **132**, 137387 (2000).
35. A. K. Bagrii, G. F. Galenko, and P. M. Kochergin, *Dopov. Akad. Nauk Ukr. RSR*, *Ser. B: Geol.*, *Geofiz.*, *Khim. Biol.*, **9**, 801 (1975); *Chem. Abstr.*, **84**, 43959 (1977).
36. A. Meric, Z. Incesu, and I. Hatipoglu, *Med. Chem. Res.*, **17**, 30 (2008).
37. H. J. M. Dou, M. Ludwikow, P. Hassanaly, J. Kister, and J. Metzger, *J. Heterocycl. Chem.*, **17**, 393 (1980).
38. J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem.*, **11**, 747 (1973).
39. S. Malhotra, V. Manher, and V. K. Chadha, *Indian J. Heterocycl. Chem.*, **12**, 13 (2002).
40. J. S. Bajwa and P. J. Sykes, *J. Chem. Soc. Perkin Trans. 1*, **10**, 2146 (1980).

41. M. Gobetti, M. Palladino, E. Vanotti, M. Villa, M. Bani, R. Bormetti, and V. Olgiati, PCT Int. Appl. WO 9514673; *Chem. Abstr.*, **123**, 286028 (1996).
42. A. M. Abdel-Fattah, H. A. Daboun, and S. M. Hussain, *Egypt. J. Chem.*, **26**, 409 (1983); *Chem. Abstr.*, **101**, 230419 (1985).
43. U. Veerabhadraiah, V. R. Rao, and T. V. P. Rao, *Sulfur Lett*., **9**, 167 (1989).
44. V. K. Chadha, S. Joshi, and A. Bhargava, *J. Indian Chem. Soc.*, **69**, 884 (1992).
45. A. M. Simonov and V. N. Komissarov, *Khim. Geterotsikl. Soed.*, 783 (1976); *Chem. Abstr.*, **85**, 123818 (1977).
46. R. P. Soni and J. P. Saxena, *J. Indian Chem. Soc.*, **58**, 922 (1981).
47. A. Mustafa, M. I. Ali, M. A. Abou-State, and A.-E. G. Hammam, *J. Prakt. Chem.*, **314**, 785 (1972).
48. M. I. Ali, M. A. Abou-State, and A. F. Ibrahim, *J. Prakt. Chem.*, **316**, 147 (1974).
49. A. K. Bagryi, G. F. Galenko, and P. M. Kochergin, *Farm. Zh.*, No. 3, 17 (1975); *Chem. Abstr.*, **87**, 201399 (1978).
50. V. H. Bhaskar, K. Puli, B. Sangameswaran, and B. Jayakar, *Indian J. Heterocycl. Chem.*, **15**, 299 (2006).
51. E. S. H. El Ashry, N. Rashed, L. F. Awad, E. Ramadan, S. M. Abdel-Maggeed, and N. Rezki, *ARKIVOC*, vii, 30 (2007).
52. Yu. M. Volovenko, F. S. Babichev, S. V. Litvinenko, and A. V. Turov, USSR SU 1414849; *Chem. Abstr.*, **110**, 8224 (1990).
53. C. Lamberth and F. Querniard, *Tetrahedron Lett.*, **49**, 2286 (2008).
54. P. R. Buckland, PCT Int. Appl. WO 9215562; *Chem. Abstr.*, **118**, 22238 (1994).
55. G. Dannhardt and L. Hahn, PCT Int. Appl. WO 2002076951; *Chem. Abstr.*, **137**, 279188 (2002).
56. R. G. Wilde, US Pat. 5358946; *Chem. Abstr.*, **122**, 265370 (1996).
57. C. A. Higley, R. G. Wilde, T. P. Maduskuie, A. L. Johnson, P. Pennev, J. T. Billheimer, C. S. Robinson, P. J. Gillies, and R. R. Wexler, *J. Med. Chem.*, **37**, 3511 (1994).
58. R. G. Wilde, C. A. Higley, J. T. Billheimer, and R. R. Wexler, PCT Int. Appl. WO 9323381; *Chem. Abstr.*, **120**, 217676 (1995).
59. T. P. Maduskuie, US Pat. 5179117; *Chem. Abstr.*, **118**, 254933 (1994).
60. J. T. Billheimer, P. J. Gillies, R. R. Wexler, C. A. Higley, and T. P. Maduskuie, Eur. Pat. Appl. EP 372445; *Chem. Abstr.*, **114**, 6503 (1992).
61. N. V. Harris, A. W. Bridge, R. C. Bush, E. C. J. Coffee, D. I. Dron, M. F. Harper, M. J. Ashton, D. J. Lythgoe, and C. Smith, *J. Med. Chem.*, **35**, 4384 (1992).
62. J. T. Billheimer, P. J. Gillies, C. A. Higley, T. P.Maduskuie, and R. R. Wexler, PCT Int. Appl. WO 9118885; *Chem. Abstr.*, **116**, 151761 (1993).
63. K. M. Dawood and N. M. Elwan, *J. Chem. Res.*, **4**, 264 (2004).
64. H. Alper and M. S. Wolin, *J. Org. Chem*., **40**, 437 (1975).
65. S. C. Cherkofsky and T. R. Sharpe, Ger. Offen. DE 2635876; *Chem. Abstr.*, **87**, 5974 (1978).
66. N. D. Abramova, G. G. Skvortsova, and B. V. Trzhtsinskaya, *Zh. Org. Khim.*, **20**, 2031 (1984); *Chem. Abstr.*, **102**, 45836 (1986).
67. N. D. Abramova, G. G. Skvortsova, and B. V. Trzhtsinskaya, USSR SU 1085977; *Chem. Abstr.*, **101**, 130694 (1985).
68. U. Niedballa and I. Boettcher, Eur. Pat. Appl. EP 43788; *Chem. Abstr.*, **96**, 181284 (1983).
69. A. Correa, M. Carril, and C. Bolm, *Angew. Chem.*, *Int. Ed.*, **47**, 2880 (2008).
70. A. A. Magd-Eldin, *Egypt. J. Pharm. Sci.*, **35**, 181 (1994); *Chem. Abstr*., **123**, 198654 (1996).
71. A. K. Bagrii and T. E. Vasilenko, *Farm. Zh.,* No. 4, 33 (1978); *Chem. Abstr.*, **90**, 72111 (1980).
72. B. V. Trzhtsinskaya, A. E. Aleksandrova, N. D. Abramova, L. V. Andriyankova, T. I. Vinogradova, and R. A. Shchegoleva, *Khim.-Farm. Zh.*, **26**, 57(1992); *Chem. Abstr.*, **118**, 147507 (1994).

73. H. A. Hammouda, S. O. Abd-Allah, and H. H. Zoorob, *Acta Chim. Hung.*, **119**, 49 (1985); *Chem. Abstr.*, **104**, 109537 (1987).
74. V. M. Britsun, A. M. Esipenko, V. M. Bodnar, and M. O. Lozinskii, *Ukr. Khim. Zh.*, **68**, No. 11–12, 52 (2002); *Chem. Abstr.*, **139**, 101084 (2003).
75. A. A. Magd-El-Din, H. M. Abou-Youssef, and T. M. Ibrahim, *Phosphorus, Sulfur*, *Silicon*, *Relat. Elem.*, **68**, 297 (1992).
76. G. G. Skvortsova, N. D. Abramova, and B. V. Trzhtsinskaya, *Khim. Geterotsikl. Soed.*, 1390 (1974). [*Chem. Heterocycl. Comp*., **10**, 1217 (1974)].
77. G. G. Skvortsova, B. V. Trzhtsinskaya, N. D. Abramova, and L. F. Teterina, *Tezisy Dokl. Vses. Konf. Khim. Atsetilena*, 5th, 319 (1975); *Chem. Abstr*., **89**, 6285 (1979).
78. G. G. Skvortsova, T. Yu. Il'yuchenok, N. D. Abramova, L. M. Frigidova, K. S. Shadurskii, L. F. Teterina, and B. V. Trzhtsinskaya, *Khim.-Farm. Zh.*, **12**, 82 (1978); *Chem. Abstr.*, **88**, 170037 (1979).
79. B. V. Trzhtsinskaya, L. F. Teterina, V. K. Voronov, and G. G. Skvortsova, *Khim. Geterotsikl. Soed.*, 516 (1976); *Chem. Abstr.*, **85**, 94277 (1977). [*Chem. Heterocycl. Comp*., **12**, 433 (1976)].
80. G. G. Skvortsova and B. V. Trzhtsinskaya, USSR 487073; *Chem. Abstr.*, **84**, 59472 (1977).
81. N. D. Abramova, L. V. Andriyankova, Yu. M. Skvortsov, A. G. Mal'kina, E. I. Kositsyna, A. I. Albanov, and G. G. Skvortsova, *Khim. Geterotsikl. Soed.*, 1412 (1986); *Chem. Abstr*., **107**, 39705 (1988). [*Chem. Heterocycl. Comp*., **22**, 1145 (1986)].
82. L. V. Andriyankov, G. G. Skvortsova, N. D. Abramova, A. G. Malkina, and Yu. M. Skvortsov, USSR SU 1121265; *Chem. Abstr*., **102**, 203978 (1986).
83. G. G. Skvortsova, N. D. Abramova, A. G. Mal'kina, Yu. M. Skvortsov, B. V. Trzhtsinskaya, and A. I. Albanov, *Khim. Geterotsikl. Soed.* 963 (1982); *Chem. Abstr.*, **97**, 162892 (1983). [*Chem. Heterocycl. Comp*., **18**, 736 (1982)].
84. Z. A. Hozien, *J. Chem. Res. (S)*, **99**, 401 (2000).
85. A. Brukshtus and S. Tumkevicius, *Khim. Geterotsikl. Soed.*, 854 (2000). [*Chem. Heterocycl. Comp.*, **36**, 751 (2000)].
86. Z. A. Hozien, A. A. O. Sarhan, H. A. H. El-Sherief, and Ab. M. Mahmoud, *J. Heterocycl. Chem.*, **37**, 943 (2000).
87. A. A. O. Sarhan, *Heteroatom Chem.*, **11**, 399 (2000).
88. F. Freeman, M. C. Keindl, H. N. Po, E. Brinkman, and J. A. Masse, *Synthesis*, **9**, 714 (1989).
89. E. Purushothaman and V. N. R. Pillai, *Indian J. Chem.*, **29B**, 18 (1990).
90. J. Mathew, and E. Purushothaman, *J. Indian Chem. Soc.*, **68**, 670 (1991).
91. S. A. Ivanovskii, I. G. Abramov, M. B. Abramova, A. V. Smirnov, V. V. Plakhtinskii, S. V. Shamshin, and M. S. Belysheva, Russ. Pat. RU 2165929 (2001); *Chem. Abstr.*, **137**, 279201 (2002).