Review

Galal H. Elgemeie* and Reham A. Mohamed

Recent trends in synthesis of five- and six-membered heterocycles using dimethyl *N*-cyanodithioiminocarbonate

Abstract: New approaches to synthesis of five- and six-membered heterocyclic compounds utilizing dimethyl *N*-cyanodithioiminocarbonate are surveyed. The scope and limitation of the most important approaches are discussed.

Keywords: dimethyl *N*-cyanodithioiminocarbonate; heterocycles; synthesis.

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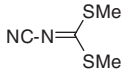
Introduction

Dimethyl *N*-cyanodithioiminocarbonate (**1**) is a highly reactive compound that plays a key role in the synthesis of a wide variety of heterocycles. The cyano and methylthio functions of this compound enable reactions with common bidentate reagents to form heterocyclic compounds. The active double bond of this compound can take part in a variety of addition reactions. Besides its importance as synthetic imtermediates, its derivatives are endowed with biological activity. In particular, diverse biological activities have been reported for many derivatives of **1** and have also drawn an immense interest of biochemists over the past decade. Compound **1** is a precursor to cyanoguanidines, to protein tyrosine kinase inhibitors, particulary compounds that function as inhibitors of c-fms kinase [1], to tricyclic *N*-cyanoimines useful as inhibitors of farnesylprotein transferase [2], and heterocyclic GABA-B modulators [3]. Compound **1** is also a starting material in the synthesis of cannabinoid receptor ligands [4, 5], antiseptics [6], inhibitors of various enzymes [7, 8], antibacterial amidinomethyl- and guanidinomethyl-oxazolidinones [9], cancer metastasis inhibitors [10, 11], a metformin derivative [12], 5-HT_{2B} receptors antagonists [13, 14], agmatine derivatives [15], guanidine derivatives [16], herbicides, crop [17], and plant growth regulators [18–22], potassium channel-activating agents that are useful as cardiovascular drugs, especially as anti-ischemic drugs [23, 24]. Additional syntheses of biologically active compounds from **1** have been described [25–36]. Despite the enormous literature on this compound, to our knowledge, no recent attempt to survey its wide range of chemical reactivity has been made. The present review is intended to fill this gap. It should be, however, stated clearly that it was not our plan to make an encyclopedic scan of the subject. Some reports were not included because they seemed to be a repetition of the established chemistry. Meanwhile, some of the old literature was included to better appreciate the chemistry and importance of this class of compounds.



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Synthesis

The most common method to access dimethyl *N*-cyanodithioiminocarbonate (**1**) involves the reaction of cyanamide with carbon disulfide in the presence of alkali metal hydroxide in aqueous ethanol [37]. The intermediate dialkali metal salt of *N*-cyanodithioiminocarbonic acid (**2**) is then alkylated with methyl iodide [38, 39] or dimethyl sulfate [40] (Scheme 1).

A cyclic cyanodithioiminocarbonate, which is a growth-regulating agent, can be prepared by reacting dipotassium cyanodithioiminocarbonate (**2**) with a dibromoalkane [41]. It has been discovered that the

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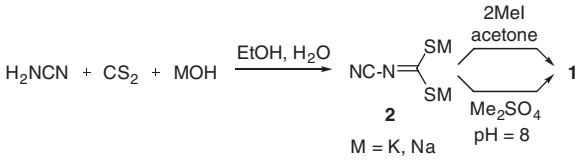
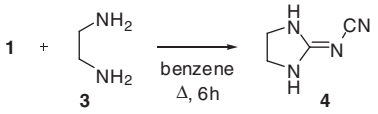


Scheme 1



Scheme 2

water-soluble alkali and alkaline-earth metal salts of cyanodithioiminocarbonic acid are bactericidal and they are useful in preventing the formation of slime in pulp and paper mills and generally in preventing microbiological deterioration of a large variety of organic substances [42]. Such salts are also used to control sulfate-reducing bacteria [43] and find applications as industrial biocides in the manufacture of pulp paper [44] and paperboard products that are used in food packaging [44–46].

Utility in heterocyclic synthesis

Disubstituted *N*-cyanodithioiminocarbonates are used extensively as intermediates in heterocyclic synthesis [35]. They are precursors to pyrimido[6,1-*a*]isoquinolin-4-ones [47], substituted quinolones [48], pyridyl carboximide compounds useful in treating high blood pressure [49], guanidino-substituted benzopyrans [50], [1,2,4]-triazolo[1,5-*a*][1,3,5]triazines [51], bicyclic heterocyclic substituted phenyloxazolidinone antibacterials [52], benzenesulfonamide derivatives [53], imidazolidonones [54], fused heterocyclic compounds useful as kinase modulators [55], substituted methyl benzoate esters [56], imidazo[4,5-*c*]pyrimidines(purines) [57], 7-amino-2-(2-furyl)-5-methylthiopyrazolo[2,3-*a*][1,3,5]triazines [58], pyrazolo[2,3-*a*][1,3,5]triazines [58, 59], 2-furyl-triazolo[1,5-*a*]-[1,3,5]triazines [59], aryl-substituted 6-methylthiol-4-pyrimidones [60], the (*S*)-4-diphenylmethyl-NCT agent [61], substituted benzopyrans and related compounds [62], triazoles [63, 64], oxazoles [64], other azoles [65, 66], 5-*O*-desosaminylerythronolide derivatives [67], *N*-cyano-*N*′-alkyl-*N*″-2-mercaptoethylguanidines [68], dimeric phosphoaramidites [69], and cyanoguanidines [70].

Five-membered heterocycles

Five-membered rings with two heteroatoms

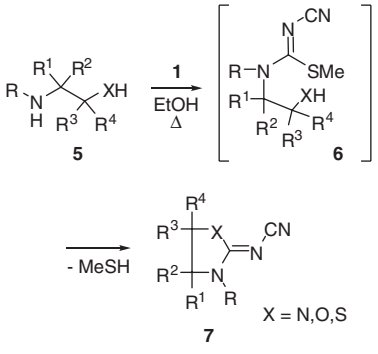
As shown in Scheme 2, compound **1** reacts readily with primary and secondary amines to give *N*-cyanoguanidines. For example, the reaction of 1,2-diaminoethane with **1** proceeds readily in benzene at reflux temperature and affords the imidazolidine **4** [71].

The synthesis of the imidazolidine, oxazolidine, and thiazolidine derivatives **7** is outlined in Scheme 3 by the reaction of **1** with secondary amino compounds **5** in refluxing ethanol solution. Products **7** are obtained by cyclization of the intermediate products **6** [72] (Scheme 3).

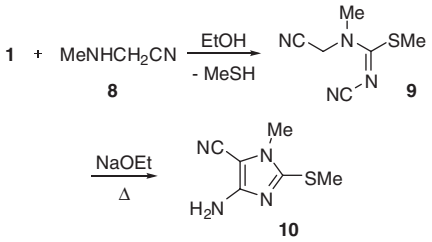
To obtain the imidazole derivative **10**, methylaminoacetonitrile (**8**) was allowed to react with **1.** The intermediate product **9** was isolated and then cyclized to **10** in the presence of sodium ethoxide [73] (Scheme 4).

It has been reported that the reaction of **1** with ethyl aminoacetate derivatives **11** in the presence of a base gives compound **12**, which can be reacted with primary amines to afford the imidazolidinones **13** (Scheme 5) [74].

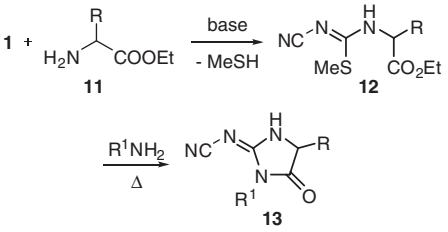
In the synthesis of the thiazole derivatives **17**, compound **1** is allowed to react with secondary amines **14** in refluxing ethanol to afford isothioureas **15**, the subsequent reaction of which with methyl mercaptoacetate is followed by thermolysis of the intermediate product **16** (Scheme 6) [75].



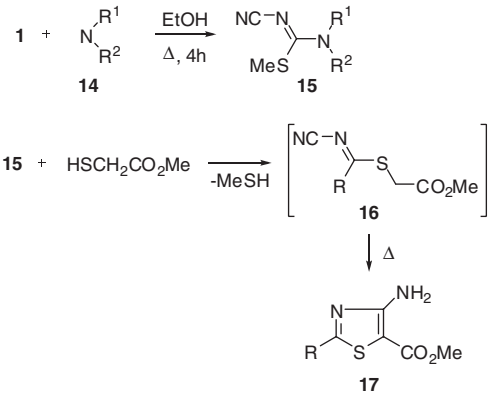
Scheme 3



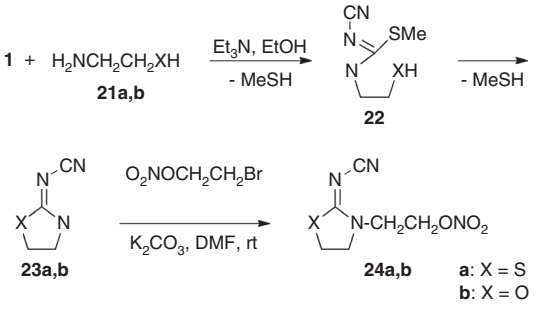
Scheme 4



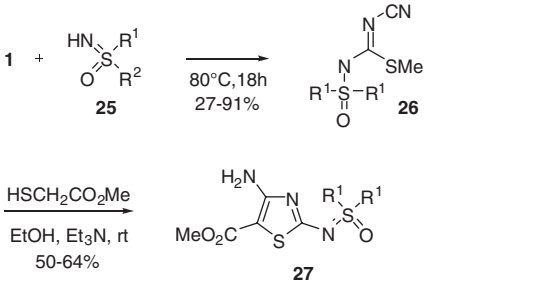
Scheme 5



Scheme 6



Scheme 8

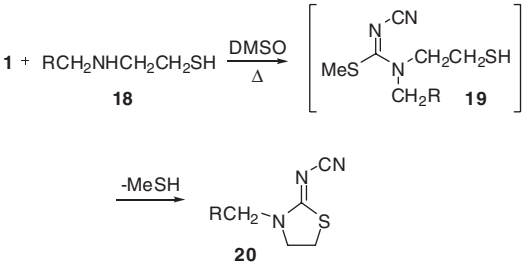


Scheme 9

2-Cyanoiminothiazoldines **20** were prepared by the reaction of **1** with mercaptoamine derivatives **18** in refluxing dimethylsulfoxide (DMSO), *via* cyclization of the intermediate product **19** (Scheme 7) [76].

The reaction of **1** with amino compounds **21** in the presence of a base affords the 2-cyanoiminothiazolidine and 2-cyanoiminooxazolidine, respectively, **23a,b**; compounds **22** are the suggested intermediates. Treatment of compounds **23** with 2-bromoethyl nitrate affords the substituted products **24** (Scheme 8) [77].

Sulfoximides **25** undergo a reaction with **1** to give compounds **26**. Treatment of **26** with methyl mercaptoacetate in triethylamine affords thiazole compounds **27** (Scheme 9) [78–81].

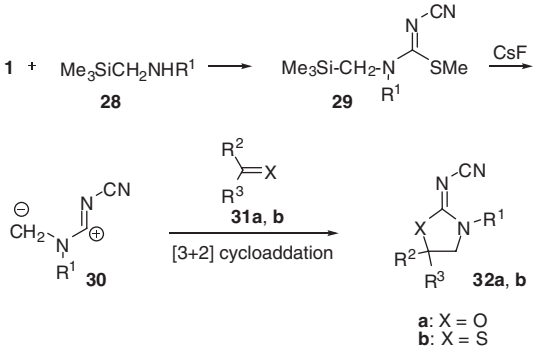


Scheme 7

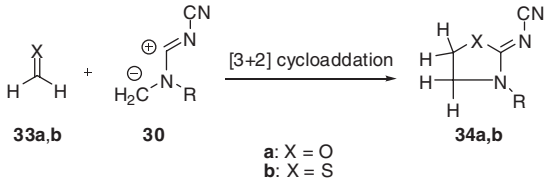
The reaction of **1** with trimethylsilylemethylamine **28** yields the adducts **29.** Treatment of **29** with cesium fluoride generates intermediate products **30,** which in the presence of hetero dipolarophiles such as carbonyl compound **31a** (X=O) and thiocarbonyl compounds **31b** (X=S) undergo a 1,3-dipolar cycloaddition to yield 2-iminooxazolidines and 2-iminothiazolidine **32a,b** (Scheme 10) [82].

Similarly, the 4,5-dihydro-2-iminooxazoles **34a** and 4,5-dihydro-2-iminothiazoles **34b** can be prepared by treatment of compounds **30** with formaldehyde **33a** or thioformaldehyde **33b** as shown in Scheme 11 [83–85].

The reaction of **1** with methyl mercaptoacetate in the presence of ammonium carbonate and potassium



Scheme 10



Scheme 11

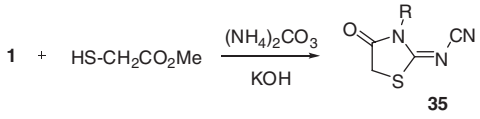
hydroxide affords 2-(*N*-cyanoiminothiazolidin)-4-one derivatives **35** (Scheme 12) [86].

The oxazolidine derivatives **37** are obtained by the reaction of compound **1** with 2*S*-amino-1*S*-*p*-nitrophenyl-1,3-propanediol **36** in refluxing ethanol (Scheme 13) [87].

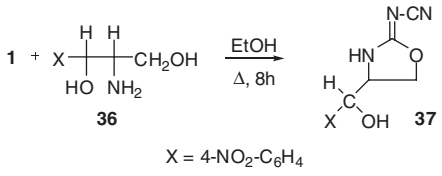
Five-membered rings with three heteroatoms

The reaction of compound **12,** derived from **1** and **11**, with hydrazine hydrate or hydroxylamine hydrochloride affords the triazole **38** or the oxadiazole **39**, respectively (Scheme 14) [74, 88].

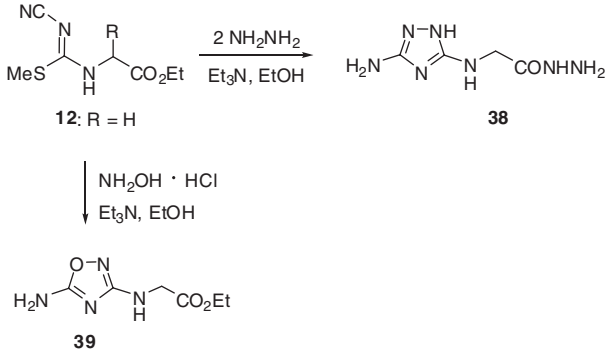
In a similar way, the reaction of **1** with substituted hydrazines in refluxing ethanol for 5 h affords the substituted triazoles **40** (Scheme 15) [89–91].



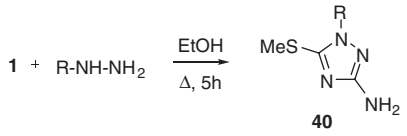
Scheme 12



Scheme 13



Scheme 14

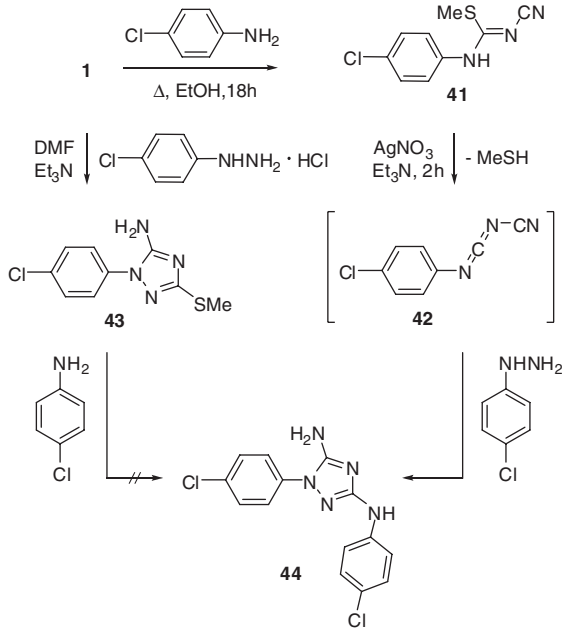


Scheme 15

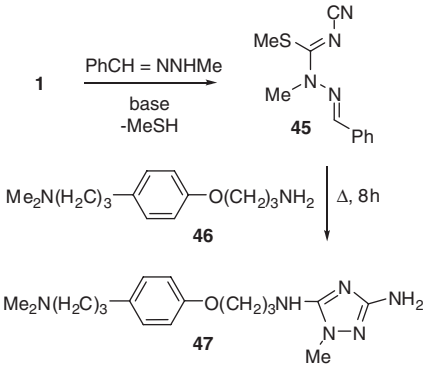
1,2,4-Triazoles-3,5-diamines **44** were obtained as shown in Scheme 16. When the intermediate product **41** was allowed to react with silver nitrate and triethylamine in *N*,*N*-dimethylformamide, *N*-cyanocarbodiimide **42** was generated. Although the intermediate compound **42** could not be isolated, subsequent addition of 4-chlorophenylhydrazine to the solution yielded the 1,2,4-triazole-3,5-diamine **44**. All attempts to prepare **44**, by reaction of **43** with amine or by reaction **41** with aryl hydrazine were unsuccessful (Scheme 16) [92].

Reaction of **1** with benzalmethylhydrazone derivatives in the presence of a base affords compound **45**, the reaction of which with a diamine **46** yields the 1,2,4-triazole compound **47** (Scheme 17) [93].

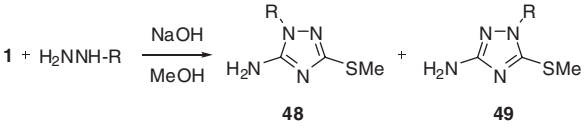
Reaction of **1** with different alkyl, aralkyl, and aryl hydrazines to yield 1-substituted 3-*R*-thio-5-amino-1*H*-1,2,4-triazoles **48** and 2-substituted 3-R-thio-5-amino-2*H*-1,2,4-triazoles **49** was studied. The reaction involves a nucleophilic attack on one of the hydrazino nitrogen atoms against the central and probably the most nucleophilic carbon atom of **1** to form **48** and **49** (Scheme 18) [94–102].



Scheme 16



Scheme 17



Scheme 18

The reaction of methylhydrazine with **1a** and **1c** predominantly resulted in displacement of a methylthio group by the more nucleophilic substituted nitrogen atom and attack of the cyano function by primary amine to afford the 3-aminotriazoles **50** and **53** and the respective minor byproducts **51** and **52**. Meanwhile, the reaction of methylhydrazine with **1b** leads to the isomeric amino triazole **51** instead of the regoisomer **53**. The structure assignment of **52** was confirmed by X-ray crystallographic analysis of the benzene sulfonyl isocyanate adduct **55** derived from **52** and **54** (Scheme 19) [72, 103–108].

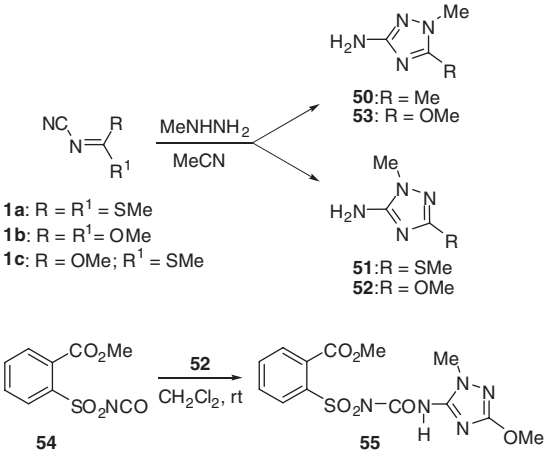
The reaction of 1-(*p*-methylbenzyl)piperazine (**56**) with **1** in refluxing ethanol afforded a disubstituted piperazine **57**, which was cyclocondensed with hydrazine to afford the triazole derivative **58** (Scheme 20) [109, 110].

The cyclocondensation of thiosemicarbazides **59** with **1** under basic conditions afforded the triazole derivatives **60** (Scheme 21) [111, 112].

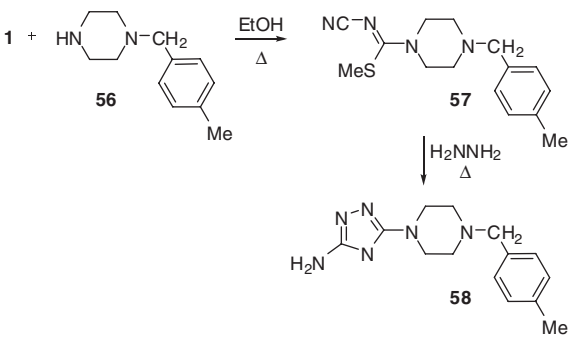
Isothiourea derivatives **62** were prepared by reacting commercially available *S*,*S*-dimethyl-*N*-cyanodithioiminocarbonate **1** with primary or secondary amines **61**; the latter products were transformed into triazoles **63**, **64** in 63–89% yields as shown in Scheme 22 [113].

As shown in Scheme 23, the reaction of the primary amino function of dihydropyridine **65** with **1** affords the *N*-cyano-*S*-methylisothiourea **66** in good yield. Compound **66** was converted into 3,5-diaminotriazole **67**, *N*-methyl-3,5-diaminotriazole **68** and 3,5-diaminooxadiazole **69** by reaction with hydrazine, methylhydrazine, and hydroxylaminehydrochloride, respectively [114–118].

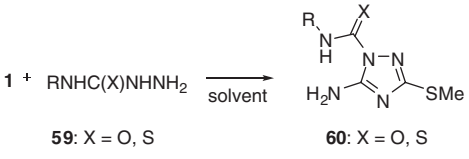
The reaction of **1** with hydroxylamine hydrochloride **70** in the presence of a base afforded the 5-amino-3-methylthio-1,2,4-oxadiazole **71** (Scheme 24) [40].



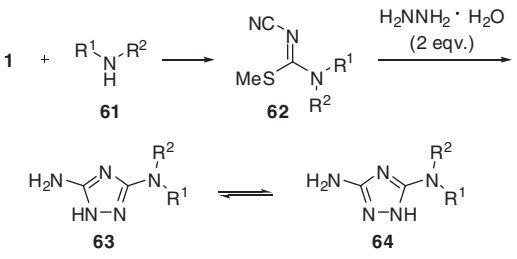
Scheme 19



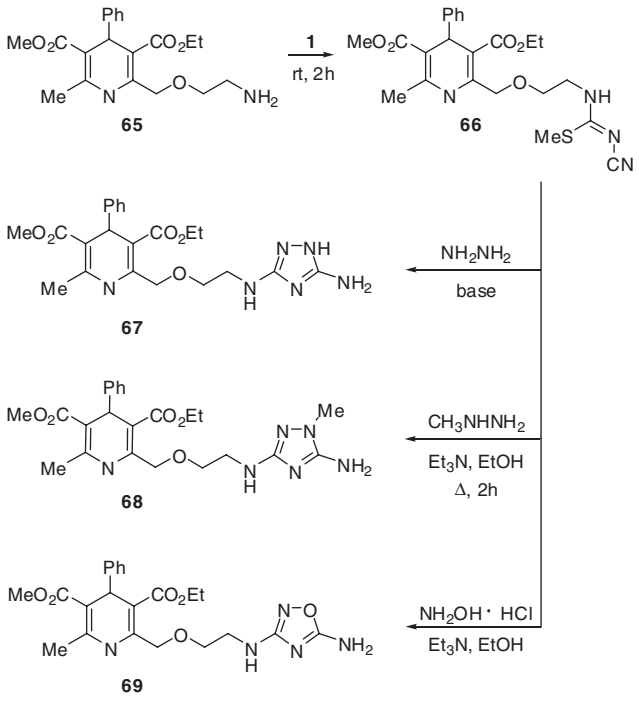
Scheme 20



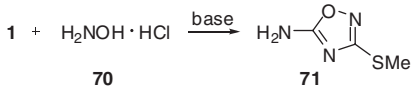
Scheme 21



Scheme 22



Scheme 23



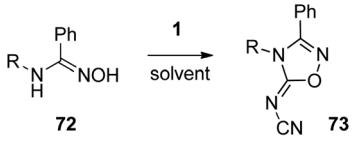
Scheme 24

The reaction of **1** with oximes **72** afforded oxadiazoles **73** (Scheme 25) [119].

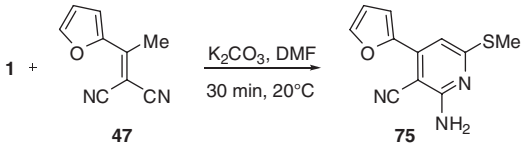
Six-membered heterocycles

Six-membered rings with one heteroatom

The furylpyridine **75** was synthesized by stirring a mixture of [1-(2-furyl)ethylidene]malononitrile **74** and **1** in the presence of potassium carbonate in *N*,*N*-dimethyformamide (Scheme 26) [120, 121].



Scheme 25



Scheme 26

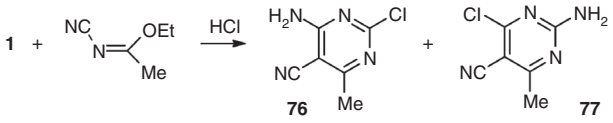
Six-membered rings with two heteroatoms

A mixture of 5-cyanopyrimidine **76** and its isomer **77** was obtained as shown in Scheme 27 [122].

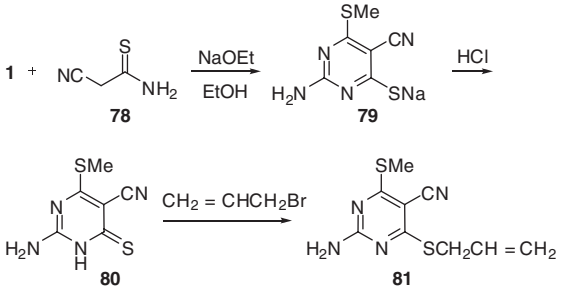
Cycloaddition of **1** with cyanothioacetamide **78** in ethanol afforded pyrimidinium salt **79**, which was acidified with aqueous hydrochloric acid to give 5-cyano-4-methylthiopyrimidine-6-thione **80**. Alkylation of **80** with allyl bromide yielded allylthiopyrimidine derivative **81** (Scheme 28) [123–125].

The synthesis of the substituted pyrimidines **83** was conveniently performed by reacting **1** with the enaminonitrile **82** under basic conditions (Scheme 29) [126].

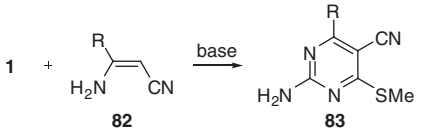
The synthesis of a substituted uracil **87** by the reaction of **1** with alkyl cyanoacetates **84** in the presence of potassium carbonate or potassium hydroxide in DMSO proceeds through the intermediaries of **85** and **86**, as shown in Scheme 30 [32, 127].



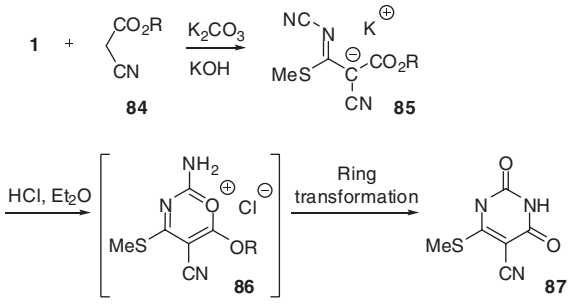
Scheme 27



Scheme 28



Scheme 29



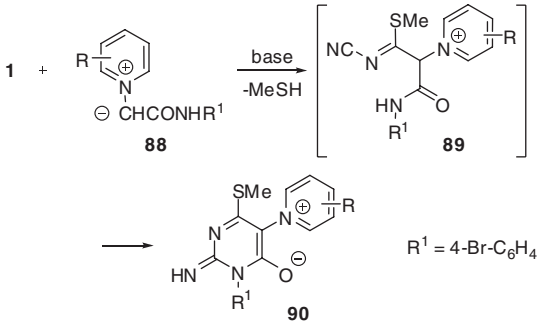
Scheme 30

Synthesis of pyrimidinium inner salts **90** was achieved by the reaction of a pyridinium salt **88** with **1** under basic conditions (Scheme 31) [128]. The presumed intermediate product **89** was not isolated.

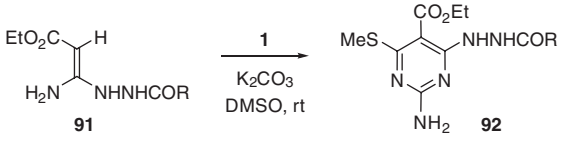
A facile synthesis of polysubstituted pyrimidines **92** involves the reaction of N^1-acetylacetamidrazones **91** with **1** at room temperature in the presence of potassium carbonate. Formation of **92** or its analogues depends on amidrazone and the reaction time (Schemes 32 and 33) [129, 130].

The treatment of **1** with ethyl or methyl cyanoacetate **84** in the presence of sodium ethoxide followed by treatment of the resultant product **85** with hydrochloric acid in ether afforded 2-amino-6*H*-1,3-oxazin-6-one **93** through intermediary of a 1,3-oxazinium salt **86** (Scheme 34) [86, 131, 132].

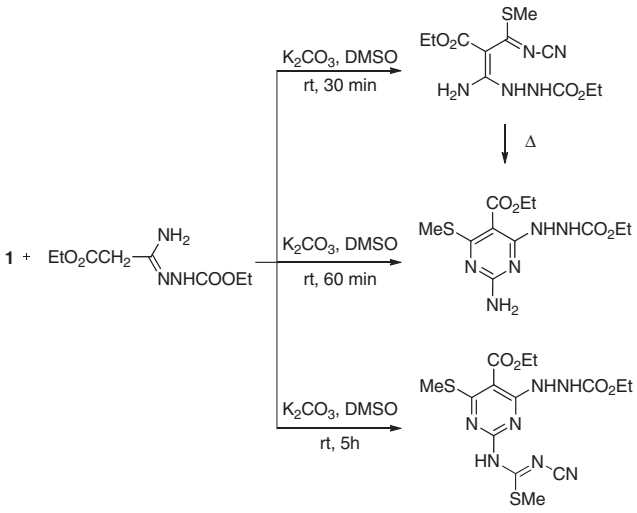
Cyclocondensation of **1** with a reagent **94** under basic conditions afforded 1-methyl-4-azathiabenzene-1-oxide **95**,



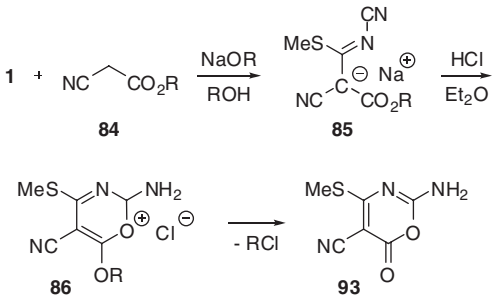
Scheme 31



Scheme 32



Scheme 33



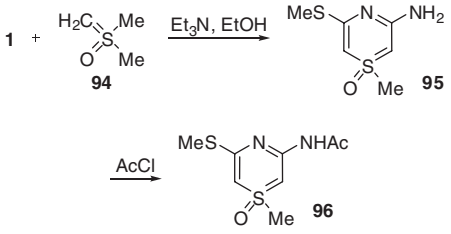
Scheme 34

the acetylation of which yielded product **96** (Scheme 35) [133].

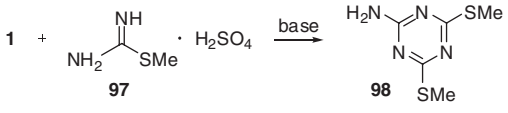
Six-membered rings with three heteroatoms

The reaction of *S*-methylisothiourea **97** with **1** in the presence of a base afforded the 2-amino-4,6-dimethylthio-1,3,5-triazine **98** (Scheme 36) [40].

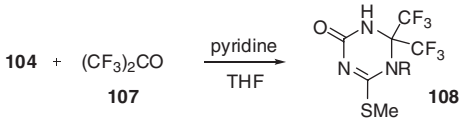
A new metformin derivative **103** was synthesized as shown in Scheme 37. First, the treatment of **1** with *N*,*N*-dimethylguanidine sulfate (**99**) in the presence of potassium carbonate afforded the triazine **100,** which



Scheme 35



Scheme 36

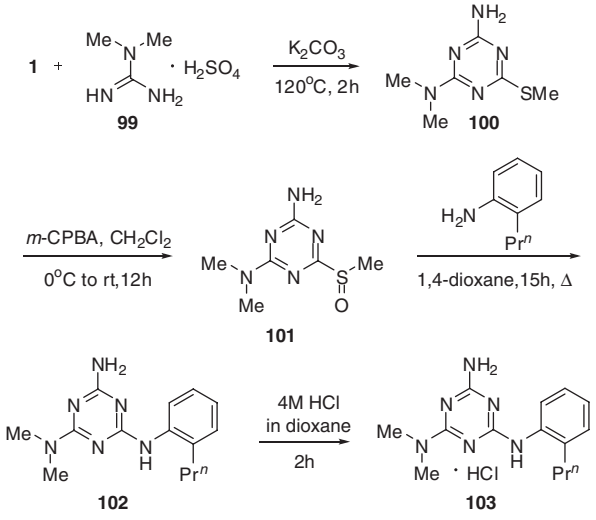


Scheme 39

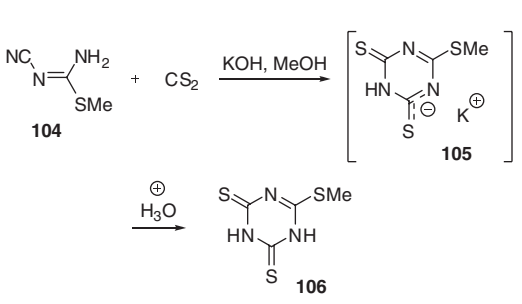
subsequently was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature to give the sulfoxide **101.** Then, treatment of compound **101** with 2-propylaniline in 1,4-dioxane under reflux conditions gave compound **102**, which is a direct precursor to the desired product **103** (Scheme 37) [12].

The *S*-methylisothiourea **104** (Scheme 38) is a derivative of **1.** The reaction of **104** with carbon disulfide in methanolic potassium hydroxide yielded the triazine **106** through the intermediary of a potassium salt **105** [40].

Compound **104** was allowed to react with hexafluoroacetone **107** in the presence of pyridine to afford triazine compound **108** *via* Chapman-type rearrangement (Scheme 39) [134].



Scheme 37



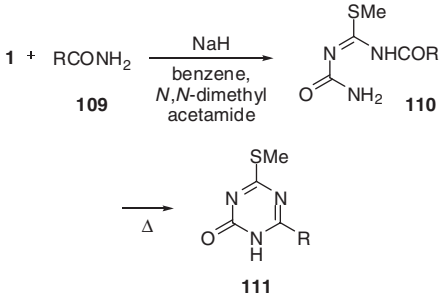
Scheme 38

The reaction of **1** with amides **109** in the presence of sodium hydride in a mixture of benzene and *N*,*N*-dimethylacetamide affords products **110,** which can be cyclized in refluxing methanol to 1,3,5-triazin-2(1*H*)-one derivatives **111** (Scheme 40) [135].

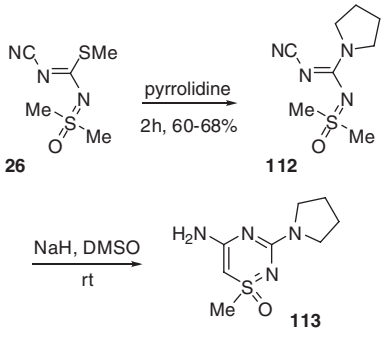
Compound **26**, which was prepared from treatment of **1** with **25**, was allowed to react with pyrrolidine in refluxing ethanol to yield a pyrrolidine derivative **112.** This compound was cyclized to a thiadiazine **113** by treatment with sodium hydride in DMSO at room temperature (Scheme 41) [136, 137].

Six-membered rings with four heteroatoms

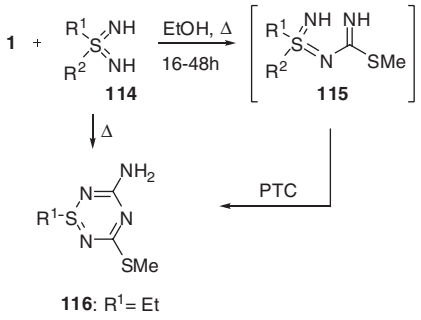
The reaction of *S*,*S*-dialkyl sulfurdiimides **114** with **1** in refluxing ethanol, affords 1,2,4,6-thiatriazines **116**, through cyclization of the intermediate products **115** (Scheme 42) [138–140].



Scheme 40



Scheme 41



Scheme 42

Conclusion

A large series of five- and six-membered heterocycles with diverse biological activities has been synthesized from the highly reactive compound *N*-cyanodithioiminocarbonate **1.**

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