Reactivity and diverse synthetic applications of acyl isothiocyanates

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Abstract
Isothiocyanates constitute a group of heterocumulenes containing –N=C=S functionality that is of immense importance in organic synthesis. The presence of carbonyl group in acyl isothiocyanates imparts unique reactivity to acyl isothiocyanates. The chemistry of acyl isothiocyanates, in particular, is very rich and diverse, and has been employed in synthesis of a number of biologically important heterocycles. This review article discusses the acyl isothiocyanate chemistry leading to the synthesis of biologically important heterocyclic skeletons. These include highly functionalized thiazoles, thiadiazoles, triazoles, benzimidazoles, dithiolane, spiro-fused oxazolines, triazines, and oxazines, etc. The role of acyl isothiocyanates as acylating agent and thiocyanate transfer reagent is also discussed.

Keywords: Acyl isothiocyanates, thiocyanate-transfer reagent, acylating agent, heterocycles, thiazoles, imidazoles

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1. Introduction

Isothiocyanates (ITCs) constitute a group of heterocumulenes containing –N=C=S functionality that is of immense importance in organic synthesis. Some of the edible plants such as Cruciferous vegetables (e.g. broccoli, kale, brussels sprouts, cabbage, mustard, garden cress, and cauliflower) are rich sources of benzyl-ITC (BITC), phenethyl-ITC (PEITC), allyl-ITC (AITC), and sulforaphane (SFN) (Figure 1).[1] Recently, the isothiocyanate sesquiterpenes have been isolated from a sponge of the genus *Axinyssa*.[2] The ITCs are of biological interest as well. They have been observed to exhibit anticancer activity in animals treated with chemical carcinogens due to their inhibition of carcinogen metabolic activation.[3]
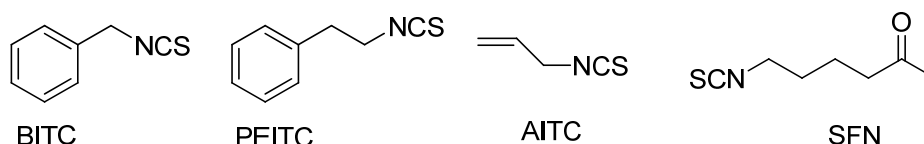

Figure 1. Chemical structure of, benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), allyl-ITC (AITC) and sulforaphane (SFN).

    Isothiocyanates, well-known as a key reagent in the Edman peptide sequencing,[4] are very useful synthons in organic chemistry, especially in the architecture of heterocycles such functionalized thiazoles, thiadiazoles, triazoles, benzimidazoles, dithiolane, spiro-fused oxazolines, triazines, and oxazines, etc.[5-11] The methods of synthesis of isothiocyanates have drawn attention of chemists.[12] Acyl isothiocyanates, in particular, are easily accessible by the reaction of acyl chlorides with thiocyanate salts such as lead thiocyanate, potassium thiocyanate and ammonium thiocyanate (Scheme 1). Recently, a simple, rapid and efficient method for the synthesis of benzoyl isothiocyanate under phase transfer catalysis using microwave irradiation under solvent-free conditions is reported (Scheme 2).[13]
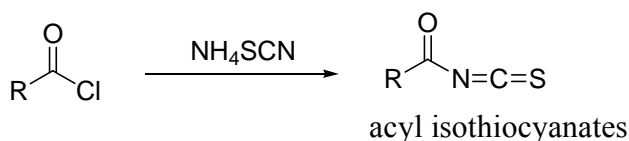

Scheme 1
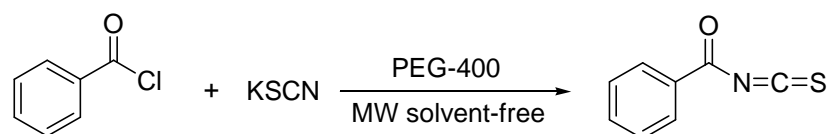
Scheme 2

The chemistry of isothiocyanates is well documented. The presence of carbonyl group in acyl isothiocyanates imparts unique reactivity to acyl isothiocyanates. The chemistry of acyl isothiocyanates, in particular, is very rich and diverse, and has been employed in synthesis of a number of biologically important heterocycles. However, there is no review article in literature focusing on reactivity and application of acyl isothiocyanates in organic synthesis. This article, therefore, discusses acyl isothiocyanate chemistry leading to the synthesis of biologically important heterocyclic skeleton. The role of acyl isothiocyanates as acylating agent and thiocyanate transfer reagent is also discussed.

2. Reactivity and Applications of Acyl Isothiocyanates

Acyl isothiocyanates are bifunctional compounds containing an acyl group and a thiocyanate group. They are more reactive than alkyl isothiocyanates obviously due to the presence of electron-withdrawing acyl group. There are evidences which suggest of a slight conjugative donation in the case of acyl isothiocyanates (Figure 2).[14] The reactivity of acyl isothiocyanates are, thus, determined by three active centres - the nucleophilic nitrogen atom, and the electrophilic carbon atoms of the carbonyl and thiocarbonyl groups (Figure 3), which make them capable of participating in diverse type of addition and cyclization reactions.
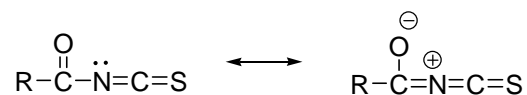
Figure 2. Resonance structures of acyl isothiocyanates.
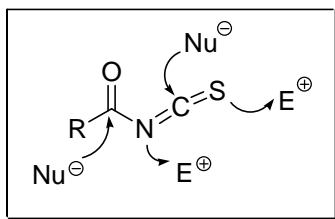
Figure 3. Reactive sites of acyl isothiocyanates.

A thermal 1,3-shift of substituent R in acyl isothiocyanates **1** is reported to proceed via the transition state TS (Figure 4).[15,16] Goerdeler and coworkers have reported the isomerization of thioacyl isocyanates **1a** to acyl isothiocyanates **1**, in solution at temperatures around 100 °C.[17,18] Although the acyl isothiocyanates **1** are more stable an equilibrium between the two may be achieved from either side under favorable conditions. The migratory aptitude of the group R has been observed in the following order: $(Alk)_2N$, $Alk(Ar)N > ArS > AlkS > ArO > AlkO$. If R was aryl, *tert*-butyl, or CCl_3, no rearrangement occurred.
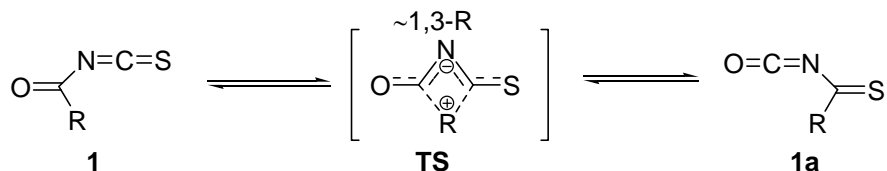

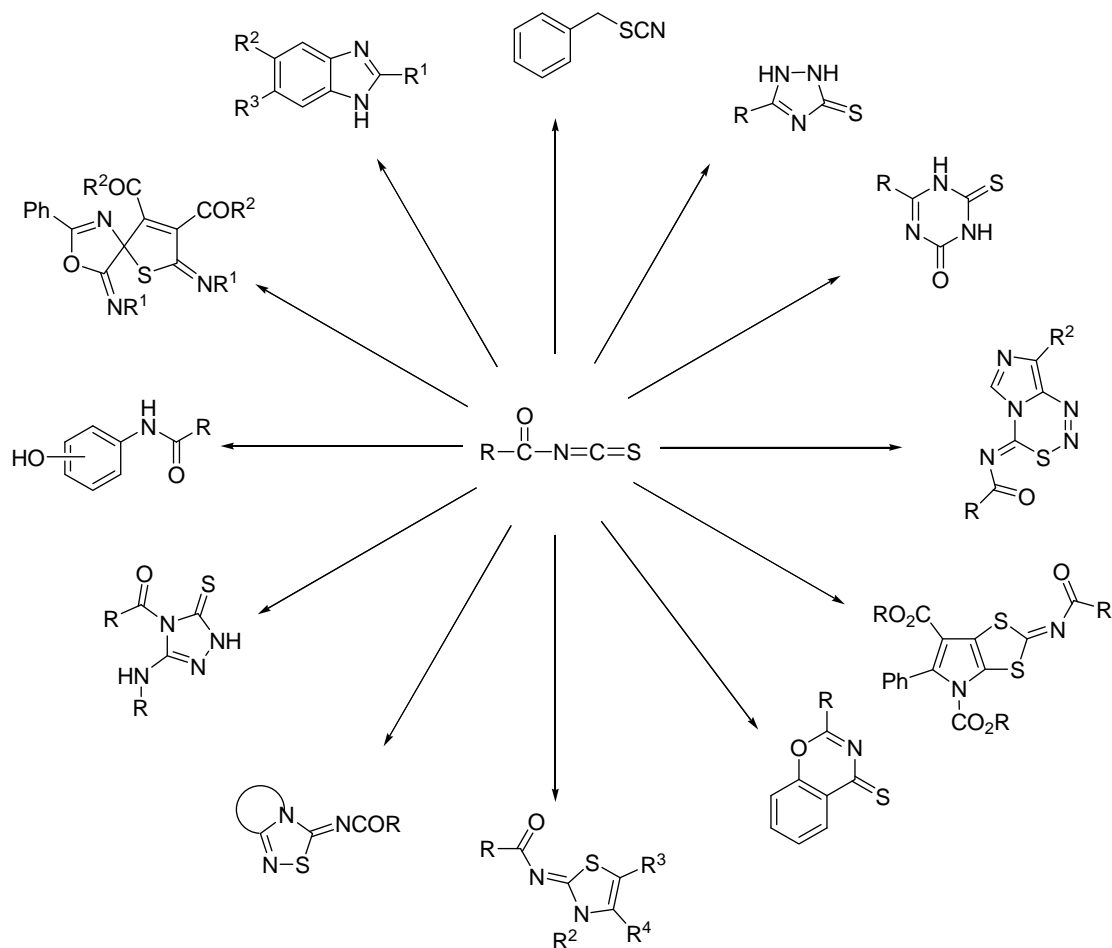**Figure 4.** 1,3-Rearrangement of acyl isothiocyanates.

Figure 5. Selected heterocyclic compounds synthesized from acyl isothiocyanates.

The strong electron-withdrawing nature of an adjacent acyl group enhances the reactivity of the isothiocyanate group and promotes nucleophilic addition at this site. The most common nucleophiles that have been investigated in reactions of acyl isothiocyanates are nitrogen nucleophiles such as amines, hydrazines, hydrazides, amidines, etc. Simultaneous or subsequent cyclization of the resulting adducts offer access to a variety of 5- or 6-membered heterocyclic molecules, including bicyclic condensed ring-systems. The use of reactants incorporating free amino group, such as benzoylhydrazine, thiosemicarbazide, phenylhydrazine, anthranilic acid, 2-aminothiophenol, 2-aminophenol and *o*-phenylenediamine have provided access to diversely substituted 1,2,4-triazoline, thiadiazoline, benzoxazine, benzothiazole, benzoxazole, and benzimidazole derivatives (Figure 5) which will be discussed in the succeeding sections.

2.1. Cyclization reactions involving both electrophilic centers
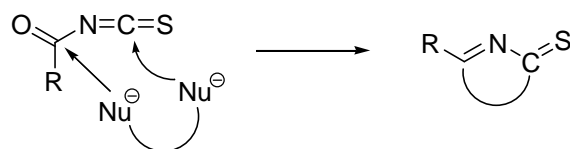
The electrophilic sites in acyl isothiocyanates are located on the two carbon atoms. Due to the presence of these active sites, the reaction of acyl isothiocyanates may lead to the formation of different heterocyclic compounds depending on the starting isothiocyanate, the nature of the nucleophile, and the reaction conditions. Two- and three-component reactions of acyl isothiocyanates have been employed in the synthesis of functionalized thioureas and five- to six-membered heterocycles with one or more heteroatoms.

2.1.1. Formation of five-membered heterocycles. The reaction of acyl isothiocyanates with hydrazine, 1,2-diamines or 1,3-diamines is one of the earliest known heterocyclization reactions. Among five-membered heterocycles, the syntheses of triazolinethiones have been investigated due to their pharmacological properties. The reaction of acyl isothiocyanates **1** with 2-hydrazinylethanol **2**, afforded 1,2,4-triazole-3-thiones **3** in excellent yields (Scheme 3).[19] Subsequent acylation of the hydroxyl group in products **3** led to the formation of corresponding *O*-acyl derivatives **4** which exhibited anti-inflammatory activity. In a similar fashion, the reaction of benzoyl isothiocyanate **1** with β-cyanoethylhydrazine **5** resulted in development of a new and efficient one-step synthesis of 5-thioxo-l,2,4-triazole derivative **6** (Scheme 4).[20]
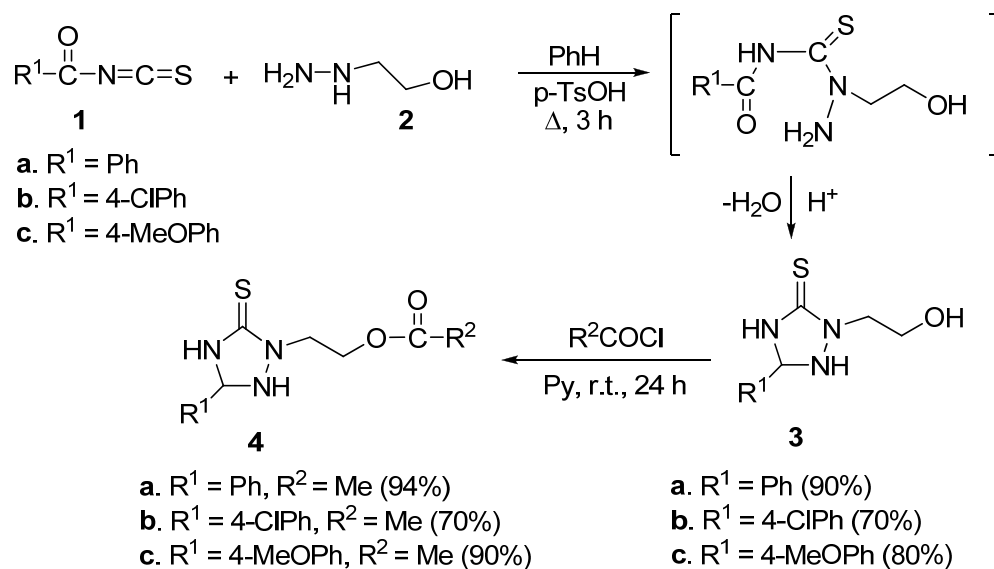
Scheme 3
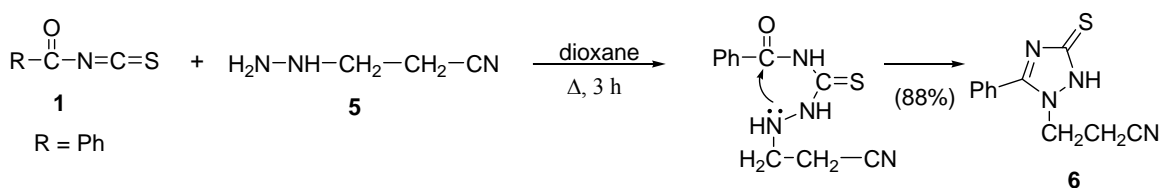
Scheme 4

Several isatin derivatives have been reported in literature to have different types of biological activity.[21-24] According to a recent report, treatment of *N*-acyl isothiocyanate substituted isatin **7** with hydrazine hydrate in boiling dry benzene afforded compound **8**.[25] The latter compound, on refluxing in freshly distilled acetic anhydride, yielded 1-[(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl) methyl]-1*H*-indole-2,3-dione **9** (Scheme 5). Some aroyl isothiocyantaes, however, react with hydrazine hydrate in ethanol at room temperature in just 5 min time to afford the 3-aryl-5-mercapto-1,2,4-triazoles **11**, in low yields, through the intermediate 4-acylthiosemicarbazide **10** which undergoes acid catalyzed cyclization (Scheme 6).[26]

Scheme 5

11. R = Ph (23%), 4-MeOPh (37%), 4-ClPh (36%)
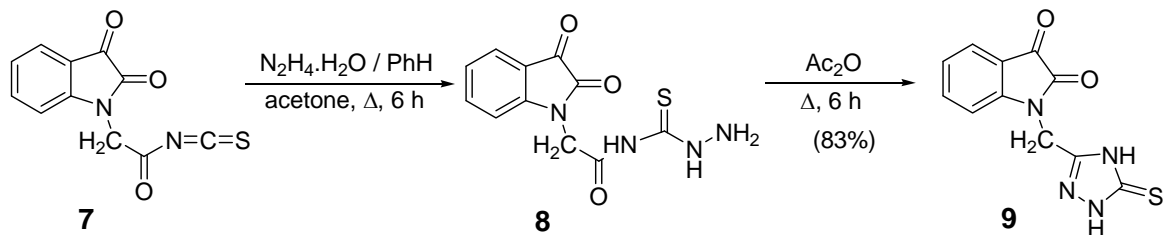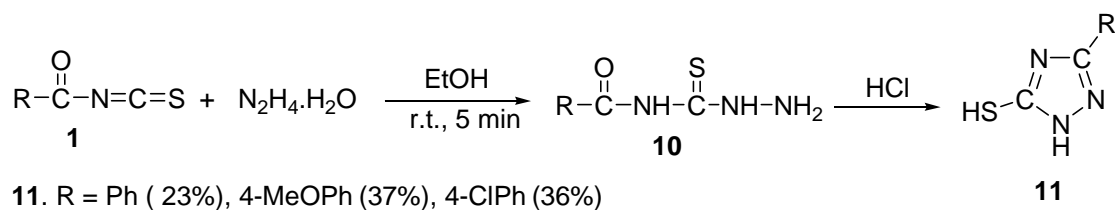
Scheme 6

Hemdan and co-workers have reported the synthesis of 1,2,4-triazoline-3-thione derivatives **13** and **14** *via* addition-cyclization sequence employing 2-phenylacetyl isothiocyanate.[27] The reaction of 2-phenylacetylisothiocyanate **1** with benzoylhydrazine in acetonitrile furnished the corresponding thiosemicarbazide **12**. The latter compound underwent a dehydrative cyclization in polyphosphoric acid to furnish the 1,2,4-triazoline-5-thione derivative **13** or **13'**. Similarly, treatment of isothiocyanate **1** with phenylhydrazine in acetonitrile yielded the 1,2,4-triazoline derivative **14** (Scheme 7). This reaction was sensitive to solvent and substrate. The use of dry acetone instead of acetonitrile in the reaction of phenacyl isothiocyanate with phenylhydrazine afforded a thiadiazolidine derivative **15** in 37% yield together with 1,2,4-triazoline **14**. Hydrazine hydrate failed to cyclize and afforded *N,N'*-di(phenylacetyl)hydrazine. There is scope for further structural elucidation of compound **13** in this report employing 2D NMR spectroscopy and single crystal X-ray. The formation of **15** was explained through the reaction of acetone with phenylhydrazine forming the corresponding hydrazone which underwent cyclocondensation with the isothiocyanate **1**.
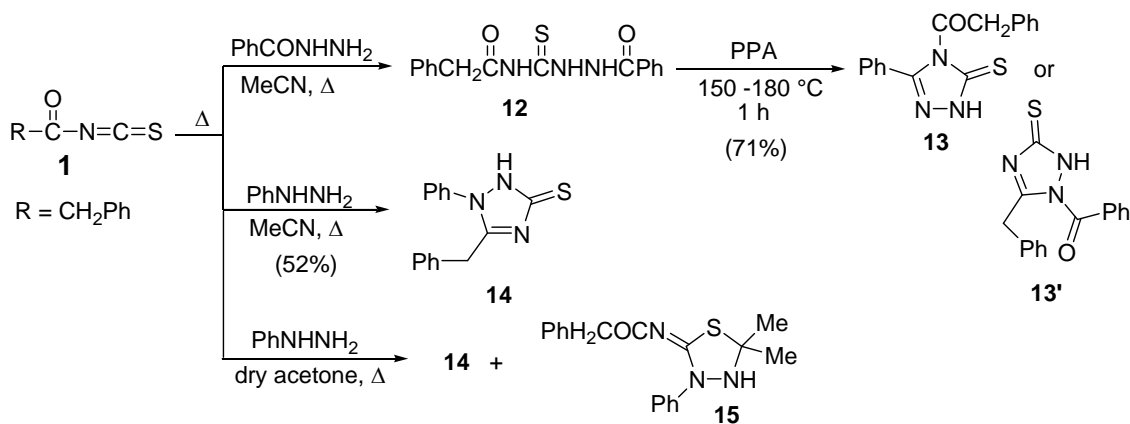
Scheme 7

Benzoyl isothiocyanate **1** reacts with *N*-alkyl- and *N*-aryl-substituted hydrazines **16** to give the corresponding 1,2,4-triazoline-5-thiones **18**, through the thiosemicarbazide **17** (Scheme 8).[28]

R = Ph R^1 = PhCH$_2$CH$_2$ (61%), Me (20%), PhMe (42%)
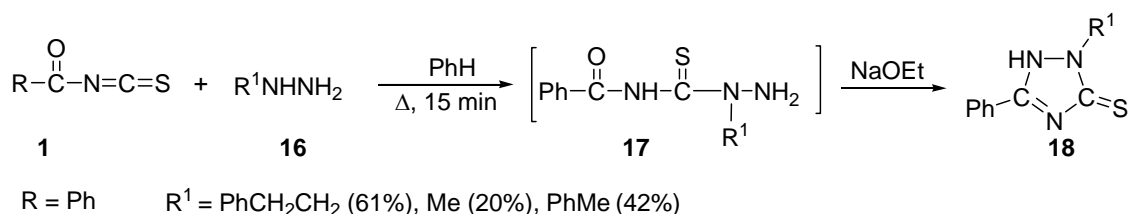
Scheme 8

Benzoyl isothiocyanate reacts with some *N*-alkyl hydrazones of acetone **19** readily to afford the 1,3,4,6-oxatriazepine-5(2*H*)-thiones **20** in 29-75% yields (Scheme 9).[29] The oxatriazepinethiones **20** are highly sensitive to acids, and rapidly break down to yield the triazolinethiones **21** on acidic treatment with concomitant removal of acetone. The rate of acid hydrolysis was much faster than that expected for an acetone thiosemicarbazone derivative. It was, however, in accordance with the presence of the cyclic aminoacetal structure.

R = Ph R^1 = 2,6-Me$_2$C$_6$H$_3$O(CH$_2$)$_2$,
              Me, Ph(CH$_2$)$_2$, PhCH$_2$
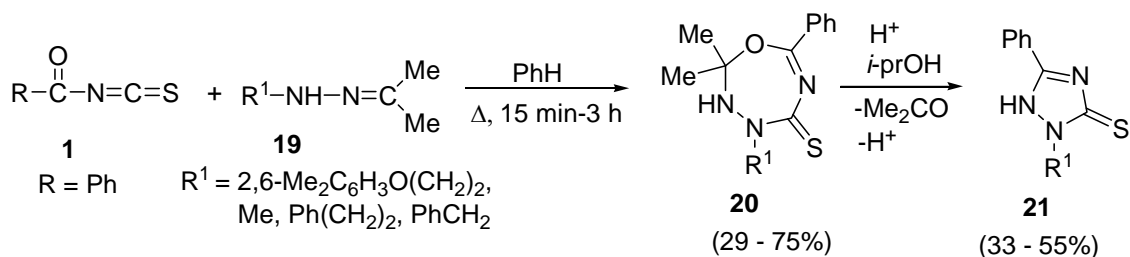
Scheme 9

The formation of oxatriazepinethiones **20** from the hydrazones **19** and benzoyl isothiocyanate **1** was envisaged as taking place by the nucleophilic reaction of hydrazone at thiocarbonyl carbon (Scheme 10). The nucleophilicity of the nitrogen carrying the proton in the hydrazones **19** must be of sufficient magnitude to make an attack at this centre, leading to the formation of product **22**, the initial step in the reaction. The protonation of N-H in oxatriazepinethiones **20** followed by ring cleavage leads to the formation of intermediate **23**. This intermediate affords the final products by nucleophilic attack of the amino group on azomethine carbon and subsequent removal of acetone and deprotonation (Scheme 10).

The reaction of benzoyl isothiocyanate with ethoxycarbonyl hydrazine **24** yields 4-acyl-1-ethoxycarbonyl-3-thiosemicarbazide **25**, which is cyclized in alkaline medium, with loss of CO$_2$ and ethanol, to triazoles **27** via triazolinethione **26** (Scheme11).[30]
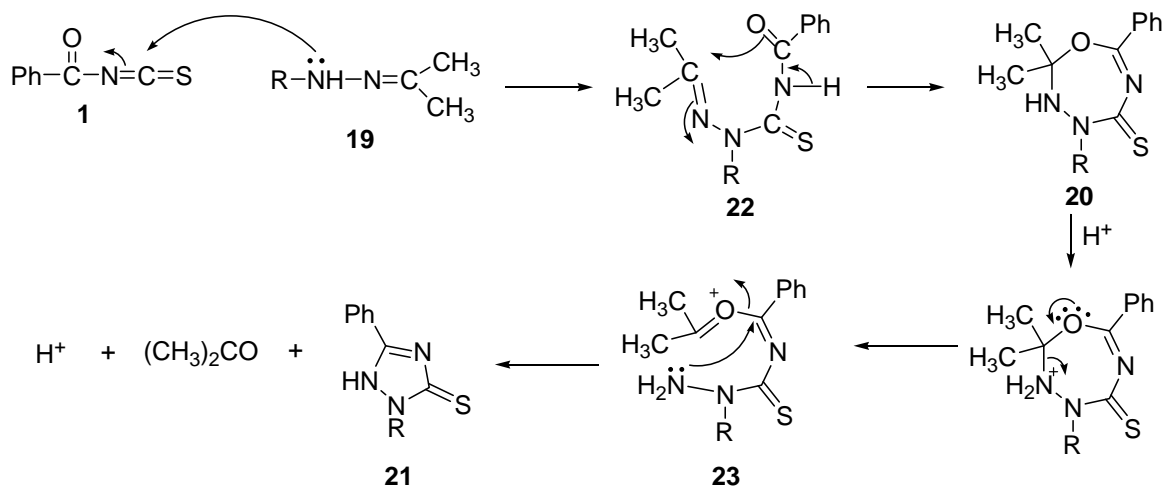
Scheme 10
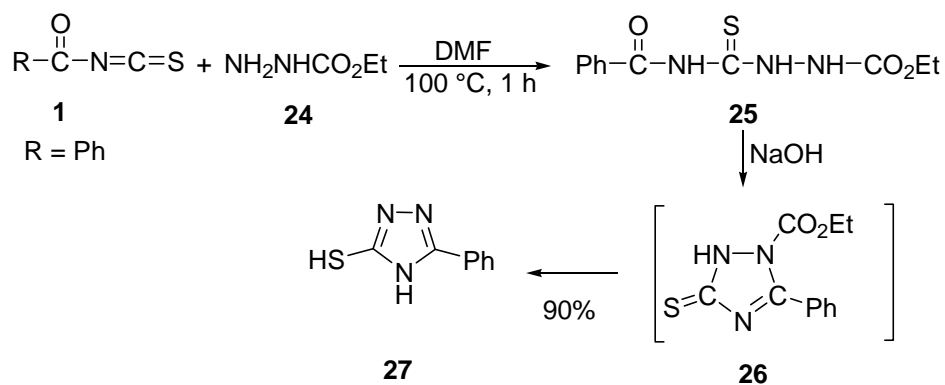
Scheme 11
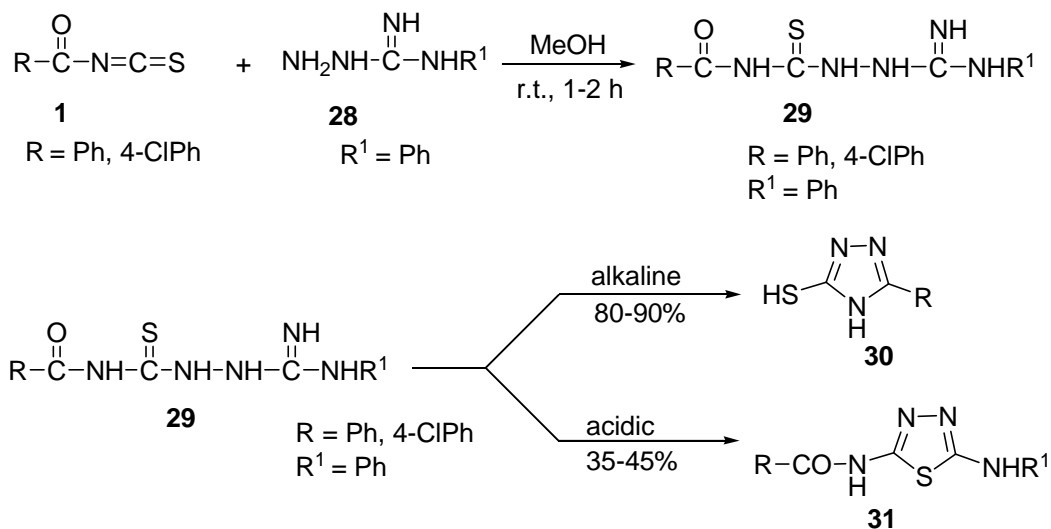
Scheme 12

An equimolar reaction of aroyl isothiocyanates **1** and aminoguanidine **28** affords amidinothiosemicarbazides **29** in excellent yields.[31] The addition occurs at the more reactive hydrazino group. The adducts **29** are cyclized to 1,3,4-triazoles **30** in alkaline medium and to 1,3,4-thiadiazoles **31** in acidic medium (Scheme 12).

2.1.2. Formation of six-membered heterocycles. Amidines, isoureas, isothioureas and guanidines **32** have been added to aroyl isothiocyanates **1** to form the 1,3,5-triazinethione derivatives **33** (Scheme 13).[32] Aroyl isothiocyanates **1** were reacted with urea in dry acetone to give the good yields of 1-aroyl-2-thiobiurets **34** (Scheme 14). The formation of 2-thiobiurets **34** was explained by exclusive attack of guanidines on the C=S function of the isothiocyanates. Treatment of an ethanolic solution of 2-thiobiurets **34** with aqueous NaOH afforded, after acidification, 6-aryl-4-thioxo-1,2,3,4(or 2,3,4,5)-tetrahydro-1,3,5-triazin-2-ones **35** in a good yields (Scheme 14). Similarly, 1-phenylsemicarbazide **36**, a relatively weaker nucleophile, reacted with aroyl isothiocyanates **1** of varying electrophilicity to give 6-aryl/cinnamyl-2-(2-phenylhydrazinyl)-2,3-dihydro-1,3,5-oxadiazine-4-thiones **37** in good yields (Scheme 15).[33]
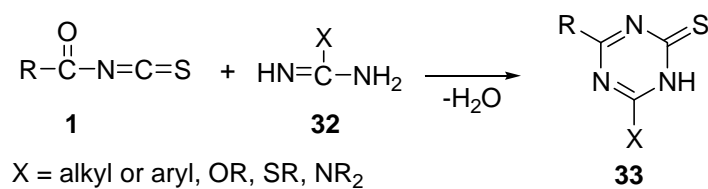
Scheme 13
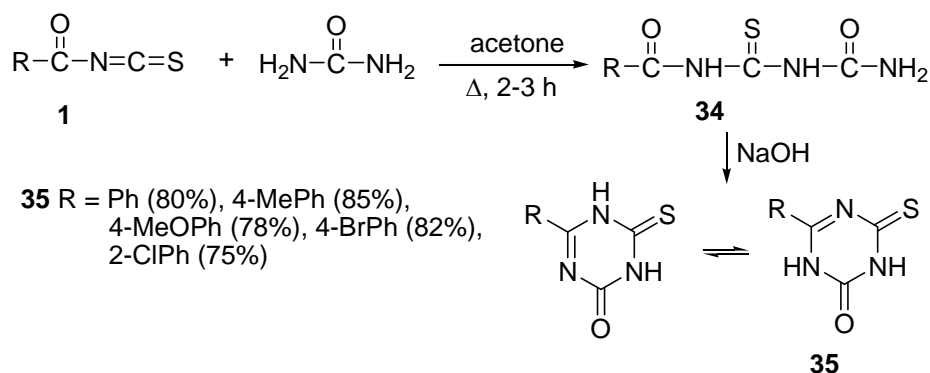
Scheme 14
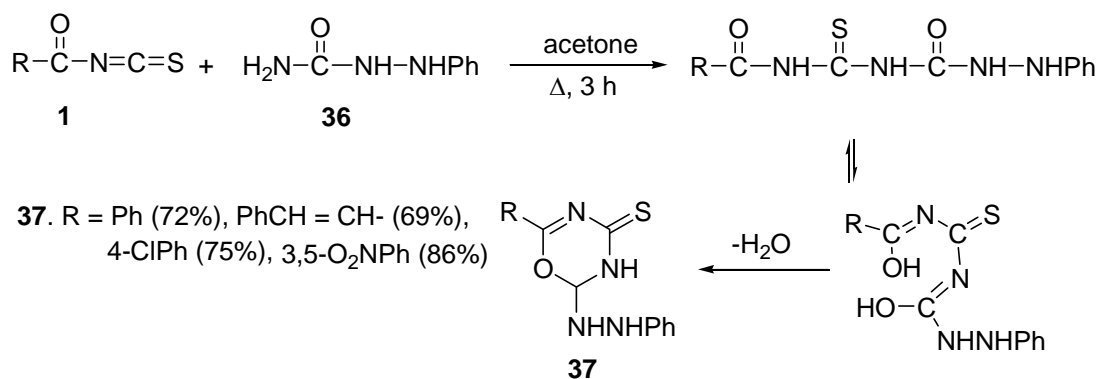
Scheme 15

An excellent example of a solvent-free reaction of acyl isothiocyanates **1** with phenol, and 1- and 2-naphthols **38** in the presence of *N*-methylimidazole (Scheme 16) leading to the formation of benz- and naphthoxazine-4-thiones **39** in very good yields has been reported by Khalilzadeh and coworkers.[34] This procedure has the advantage that the reaction is performed under neutral conditions and the starting material can be used without any activation or modification. 4-Chloro-substituted benzoyl isothiocyanate afforded the lowest yield. It was conceived that the protonation of 1:1 adduct **40** from isothiocyanate and *N*-methylbenzimidazole and the nucleophilic reaction of product naphtholate **42** with protonated intermediate **41** led to the formation of product **43** (Scheme 17). The cyclization of this product followed by elimination of water from the resulting fused heterocycle **44** led to the formation of final product.
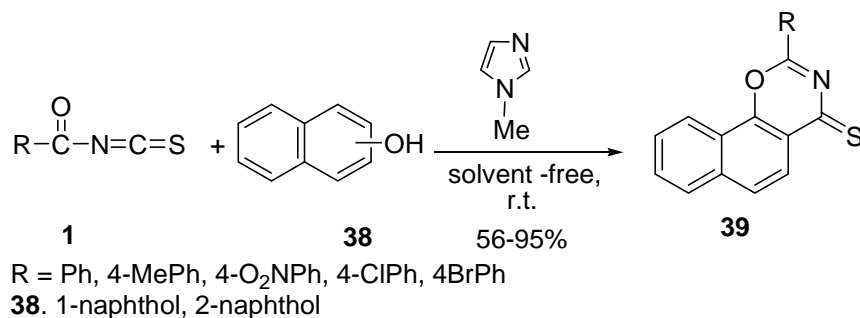
Scheme 16

Benzoyl isothiocyanate **1** is reported to reacts with 6,7-dimethoxy-3,4-dihydroisoquinolin-1-ylacetonitrile **45** in anhydrous acetonitrile leading to the formation of the 9,10-dimethoxy-2-thioxo-4-phenyl-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile **46** in 85% yield (Scheme 18).[35]
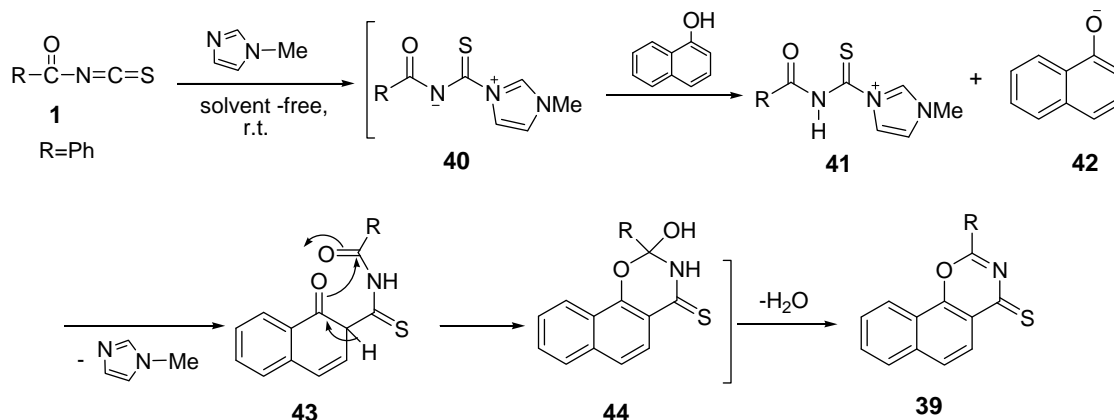
Scheme 17
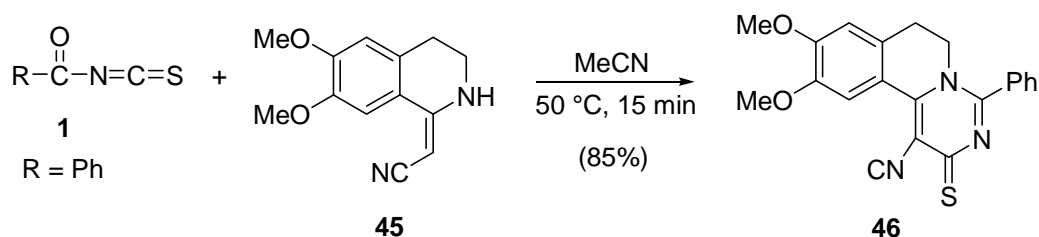
Scheme 18

Insuasty and coworkers have reported a simple synthesis of 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*]-[1,3,5]-triazines **50** employing the chemistry of aroyl isothiocyanates **1**.[36] The latter compounds react with 5-amino-3-methyl-(1*H*)-pyrazole **47** in refluxing acetonitrile to give the corresponding thioureas **48** (Scheme 19). In next step, the thioureas **48** were treated with ethyl bromide in the presence of sodium hydride in DMF at room temperature to render the *S*-alkylated product **49** which afforded the final product on refluxing.

50. R = Ph (90%), 4-MePh (74%), 4-ClPh (93%), 4-O$_2$NPh (61%)
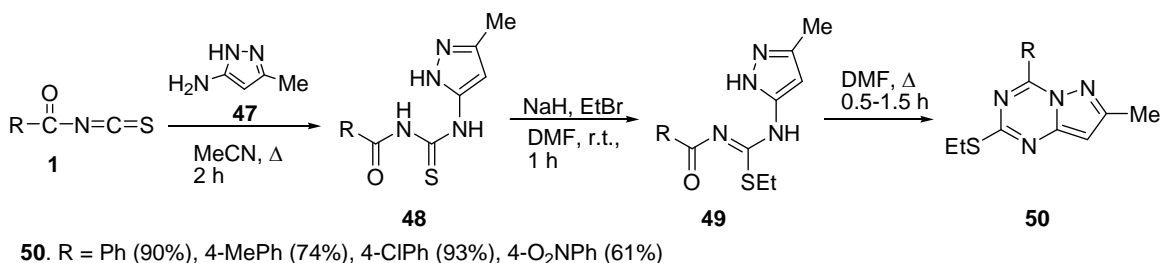
Scheme 19

Benzoylisothiocyanate **1** reacts with enamine 1-(*N*-phenylamino)cyclohexene **51** at its C=C bond to afford an adduct **52**. The adduct cyclizes in refluxing tetrahydrofuran to form the tetrahydroquinazoline-4(1*H*)-thione **53** (Scheme 20).[37]
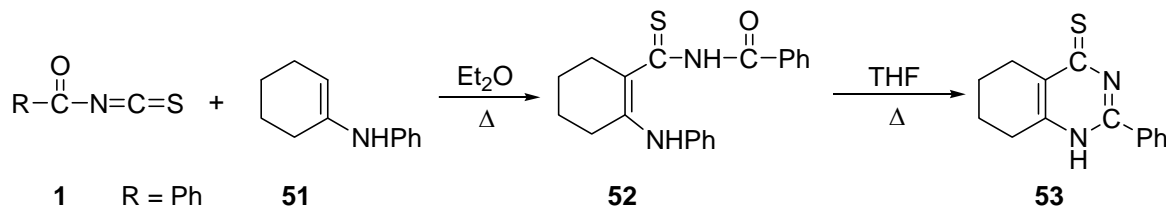
Scheme 20

2.2. Cyclization reactions involving the thiocarbonyl group
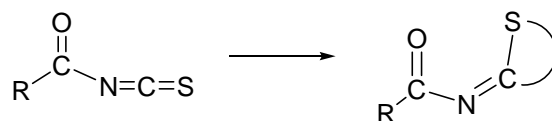
The thiazole scaffold is one of the privileged structures in medicinal chemistry. Various compounds featuring this particular scaffold have been prepared, many exhibiting remarkable biological activities such as anticonvulsant activity against administration of glutamic acid in rat and in the design of active H_2 receptor histamine antagonists.[38,39] A single-pot three-component condensation of aroylisothiocyanates, amines and α-halocarbonyls constitutes an excellent example of synthesizing the 3-alkyl-3*H*-thiazoline ring system.[40] Aroyl isothiocyanates **1** react smoothly with various amines in usual manner to afford acyl thioureas **54** (Scheme 21). The latter compounds have been condensed with α-halocarbonyl derivatives to construct a 3-alkyl-3*H*-thiazolines in a single-pot reaction. The configuration of the acylimino moiety was confirmed as *syn*. The *syn* selectivity in this reaction is explained on the basis of the steric hindrance of the acyl group and the R^2 group in the isothiourea intermediates. Elimination of hydrogen halide from sulfonium intermediate **55** affords the final product through elimination of water from intermediate **56**. An alternative route to thiazolines from sulfonium intermediates **55** via intermediate **58** to give *anti*-**57** is avoided due to intermolecular steric hindrance. Diverse functionalities are accommodated at all four positions of the thiazoline skeleton to obtain β-turn tripeptide mimics.

Scheme 21

57	R^1	R^2	R^3	R^4	Yield (%)
a.	4-CNPh	isopropyl	CO$_2$Et	Me	77
b.	4-CNPh	cyclopentyl	CO$_2$Et	Me	62
c.	4-O$_2$NPh	isopropyl	CO$_2$Et	Me	86
d.	4-MeOPh	isopropyl	CO$_2$Et	Me	35
e.	4-O$_2$NPh	isopentyl	H	Me	81
f.	4-O$_2$NPh	isopentyl	CO$_2$Et	OH	36
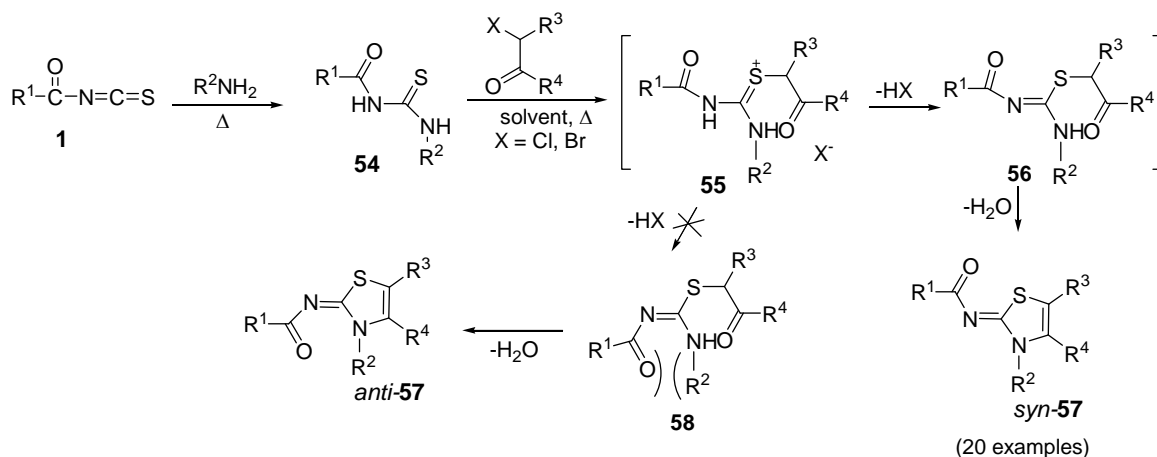
A solid-supported synthesis of 2-aminobenzothiazoles is reported by employing the resin-bound acyl isothiocyanate **59** and a series of anilines (Scheme 22).[41] The resin-bound isothiocyanate **59**, prepared from the carboxy-polystyrene in two steps, got readily transformed to the corresponding thioureas **60** on treatment with anilines at room temperature. The cyclization of **60** to 2-acylaminobenzothiazole **61** was performed by treatment with six equivalents of bromine in acetic acid (Method A when X = H)). Alternatively, benzothiazoles were obtained by treatment of the corresponding *N*-acyl, *N*'-phenylthioureas (X = Cl, Br) with sodium hydride (Methods B) via an S$_N$Ari mechanism. Hydrazinolysis of solid-supported benzothiazoles afforded the 2-aminobenzothiazoles **62**.
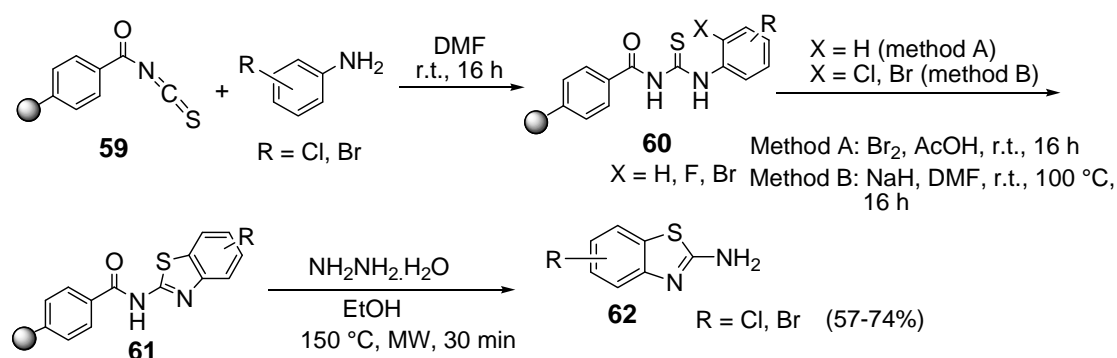
Scheme 22

Recent years have witnessed an extensive investigation on the formal [3+2]-cycloadditions to oxazoles **63** accompanied by opening of the oxazole ring and formation of another heterocyclic framework **64** (Scheme 23). A diverse type of systems with multiple bonds such as C=C, C=N, N=N, C=O, N=O, and C=S of thioaldehydes have been studied.[42-47] Dudin *et. al.* for the first time reported the reaction of oxazoles with acyl isothiocyanate heterocumulenes.[48] The reaction of acyl isothiocyanates **1** with 5-isopropoxy-4-methyloxazole **65** led to the synthesis of 5-*N*-acylimino-2-isopropoxy carbonyl-2-methyl-3-thiazolines **66**. The transformation occurred *via* formal [3+2]-cycloaddition of the C=S bond of acyl isothiocyanate to the 2nd and 4th atoms of the oxazole ring.

a. R = Ph (96%), **b**. R = Me (25%), **c**. R = 4-O$_2$NPh (75%)
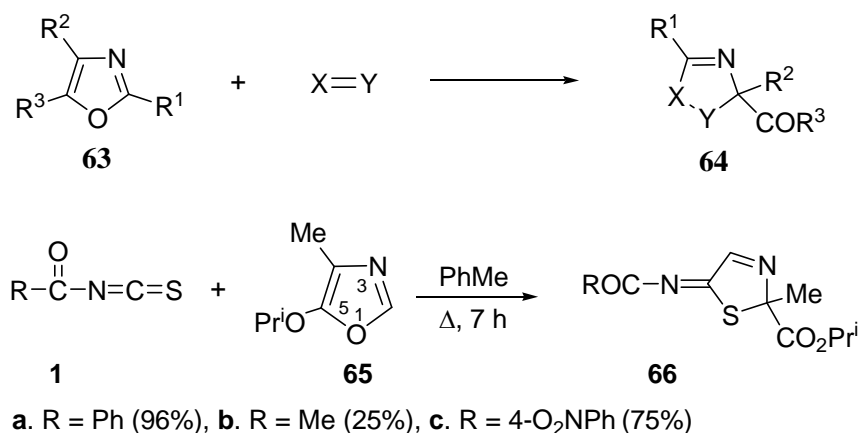
Scheme 23

Drach and coworkers have reported the reaction of hydrazino-1,3-oxazoles with acyl isothiocyanates to furnish 1,3,4-thiadiazole.[49] The 2-methyl/phenyl-4-cyano-5-hydrazino-1,3-oxazoles **67** add onto the acyl isothiocyanates **1** (Scheme 24). The reaction initially generated expected adducts **68** that were capable of prototropism. The prototropic tautomers **69** lacked the aromatic oxazole ring, and, therefore, could undergo recyclization under fairly mild conditions to form the new 1,3,4-thiadiazole derivatives **70**. In a similar fashion, acyl isothiocyanates reacted with diethyl 5-hydrazino-2-(4-methylphenyl)-1,3-oxazol-4-yl-phosphonate **71** to give the phosphorylated derivatives of 1,3,4-thiadiazoles **72** (Scheme 25).[50] In another approach to synthesize the 1,3,4-thiadiazole skeleton, the acyl thiosemicarbazides **74** from nicotinoyl/isonicotinoyl hydrazide **73** have been cyclized with phosgene in the presence of sodium acetate forming 1,3,4-thiadiazol-2(3*H*)-ones **75** in good to excellent yields (Scheme 26).[51] Some of these compounds exhibited significant anti-inflammatory activity.

Scheme 24

70
a. R = Me, R^1 = Me, 66%
b. R = EtO, R^1 = Me, 71%
c. R = Me, R^1 = Ph, 90%
d. R = Me, R^1 = Ph, 82%
e. R = EtO, R^1 = Me, 70%
f. R = Ph, R^1 = Ph, 92%

a. R = Me (92%), b. R = Ph (99%), c. R = OEt (99%)

Scheme 25
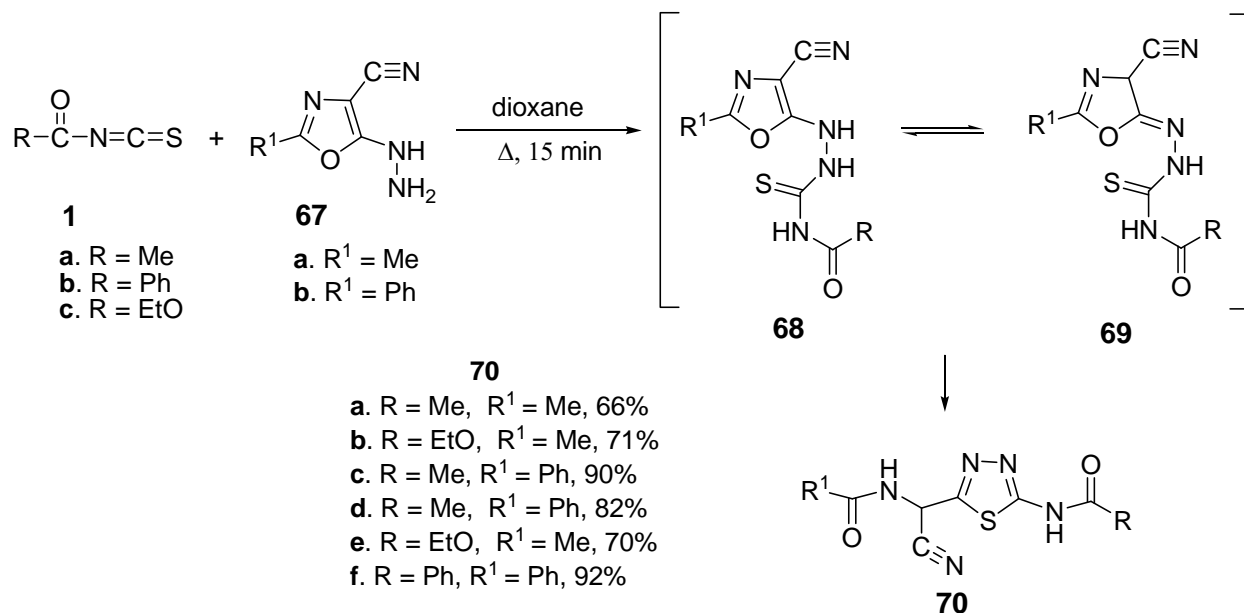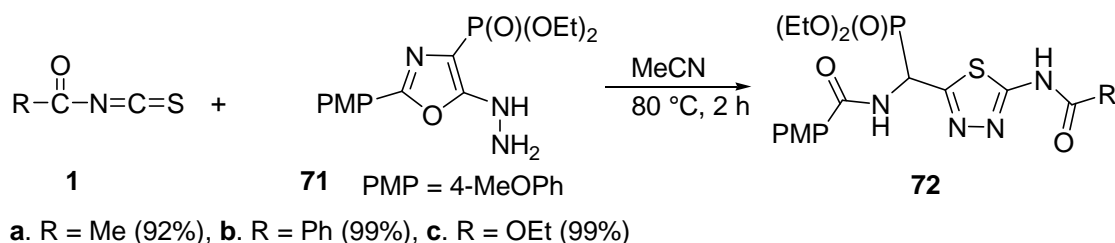
75 pyridin-3-yl: **a**. R = Ph (86%), **b**. 4-MePh (90%), **c**. 4-MeOPh (90%), **d**. 4-ClPh (84%), **e**. 2-furyl (65%)
75 pyridin-4-yl: **a**. R = Ph (90%), **b**. 4-MePh (90%), **c**. 4-MeOPh (55%), **d**. 4-ClPh (91%), **e**. 2-furyl (45%)
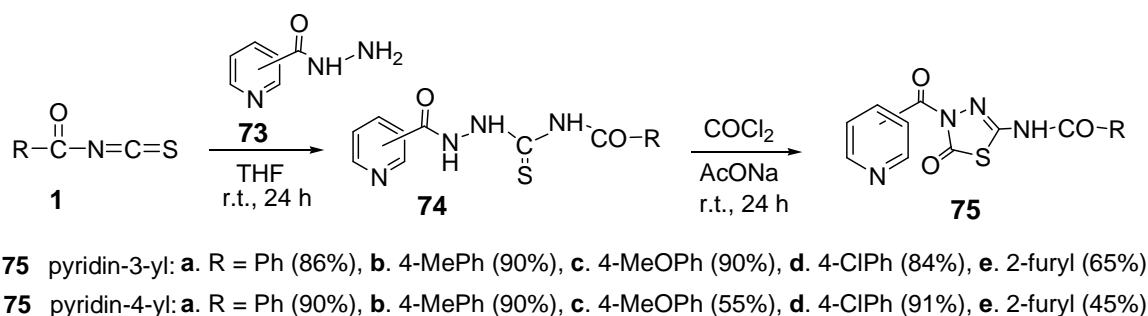
Scheme 26

Organic azides **76**, bearing a nitrile function at the γ- or δ-position undergo tandem reaction with acyl isothiocyanates to give the fused dihydro-1,2,4-thiadiazolimines **79**. The preparation of such heterocycles by tethering the nitrile group at the 4-position of the dihydrothiatriazole **77** was

reported by L'abbe and coworkers.[52] The dihydrothiatriazoles **77** were obtained by cycloaddition of azides across the C=S bond of the acyl isothiocyanates. The cycloaddition of azides across the C=S was not a new phenomenon. It was reported earlier.[53] The heterocycles **77** are expected to be unstable since they would decompose by anchimeric assistance of the carbonyl group. The 1,2,4-oxathiazo1-3-imine **78** formed possess a reactive thioimidate structural unit and should be capable of undergoing intramolecular cycloaddition ring-opening reactions, leading to the fused thiadiazoles **79** (Scheme 27). Using this methodology, a series of azidonitriles have been reacted with benzoyl isothiocyanate, to get 1,2,4-thiadiazoles (Scheme 28).
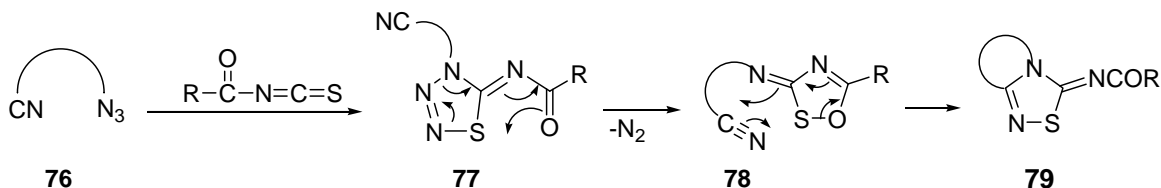
Scheme 27
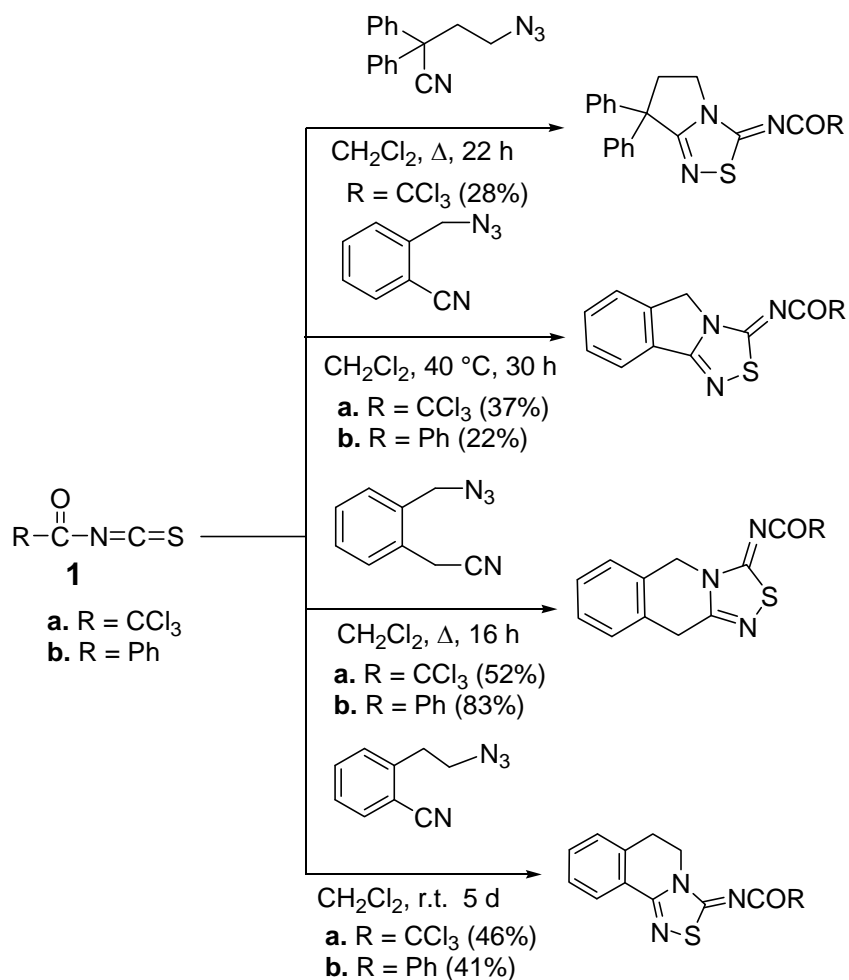
Scheme 28

The reaction of benzoyl isothiocyanate with diazomethane was reported in the mid 1960s by Martin and Mucke to furnish the 5-amino-1,2,3-thiadiazole.[54] The diazo compounds with an α carbon incorporated into the heteroaromatic system are known to react as 1,7-dipoles with electron-rich olefins, acetylenes, and isocyanates leading to six-membered heterocyclic compounds.[55-58] Recently, synthesis of new imidazo- and pyrazolo[5,1-d][1,2,3,5] thiatriazines based on the reaction of diazoazoles with acyl isothiocyanates controlled by S/O interaction has been reported.[59] In principle, both the C=N and C=S bonds of isothiocyanates are capable of cycloaddition with diazoazoles to form either a 1,2,3,5-thiatriazine or a 1,2,3,5-tetrazine ring system or a mixture of both. Recently, the reactions of diazoazoles **80** with acyl isothiocyanates is reported to occur readily at C=S to give azolo[5,1-*d*] [1,2,3,5]thiatriazines **81** as the sole products (Scheme 29). It is noteworthy to mention that this reaction was unsuccessful with methyl-, phenyl- or benzenesulfonylisothiocyanate.[60] The acyl substituent on the isothiocyanate probably led to a stabilization of the final product **81** due to an S/O interaction which could be the main reason of difference in the reactivity of acyl isothiocyanates with alkyl or aryl isothiocyanates in their reaction with diazoazoles. The Gibbs energies for two possible conformations of compound **81** were calculated which confirmed that conformer **A** with hypervalent thiadiazoles sulfur atom was more stable than the conformer **B** where non-bonded S/O through-space interactions were absent.

81	x	y	R^1	R^2	% Yield
a.	CH	N	OEt	CO$_2$Et	79
b.	CH	N	Ph	CO$_2$Et	88
c.	CH	N	OEt	CONHMe	69
d.	CH	N	Ph	CONHMe	76
e.	N	CH	OEt	CO$_2$Et	72
e.	N	CH	Ph	CO$_2$Et	84

Conformation **A**   Conformation **B**
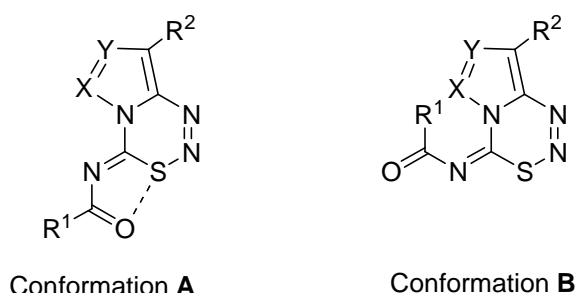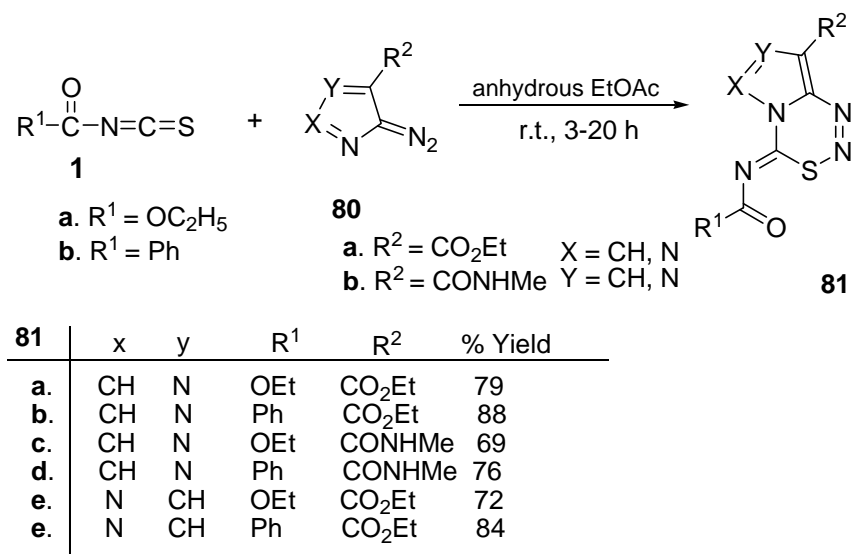
Scheme 29

2.3. Cyclization reactions involving azomethine linkage of isothiocyanates
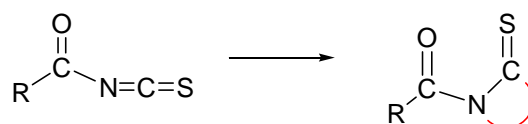
Tolpygin and co-workers, in order to develop cation and anion sensors,[61] have carried out the reactions of 4-arylalkyl- and 4-arylthiosemicarbazides **82** with benzoyl isothiocyanates **1** to get substituted 1,2-bis(thiocarbamoyl)hydrazines **83**.[62] These compounds readily cyclized to 1,2,4-triazole-5-thiones **84** containing *N*-arylamino group at C-5 (Scheme 30). An alternative cyclization to 1,2,4-triazole-5-thiones **85** containing *N*-acylamino group on C-5 was ruled out by spectroscopic studies of the product but no explanation has been advanced for this selectivity.

84 a. R^1 = 4-ClPh, R^2 = 9-anthrylmethyl (67%)
    b. R^1 = 4-FPh, R^2 = CH$_2$Ph (79%)
    c. R^1 = 3-FPh, R^2 = CH$_2$CH$_2$Ph (76%)
    d. R^1 = 4-MePh, R^2 = 2-OMePh (72%)
    e. R^1 = 4-MePh, R^2 = CH$_2$Ph (67%)
    f. R^1 = 2-MePh, R^2 = thien-2-yl (78%)
    g. R^1 = 4-ClPh, R^2 = CH$_2$Ph (81%)
    h. R^1 = 4-ClPh, R^2 = CH$_2$CH$_2$Ph (76%)
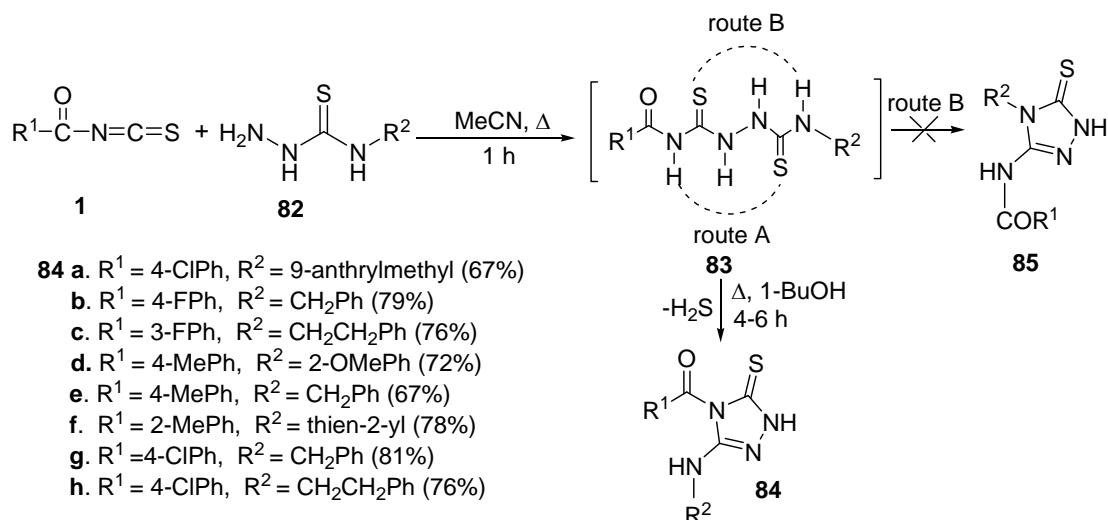
Scheme 30

Saeed and Batool have reported the synthesis of 1-(isomeric methyl) benzoyl-3-aryl-4-methylimidazole-2-thiones by base-catalyzed condensation of acetone with thioureas obtained from benzoyl iosothiocyanates.[63] Various derivatives of imidazole-2-thione have attracted widespread attention owing to their diverse pharmacological properties and bioactivities. Isothiocyanates **86** reacted with anilines **87** providing 1-isomeric methylbenzoyl thioureas **88**. The base-catalyzed condensation of **88** was achieved in the presence of bromine to get the 1-tolyl-3-aryl-4-methylimidazole-2-thiones **89-91** in reasonable yields (Scheme 31).

86: 2-Me, 3-Me, 4-Me
87: R = H, 2-Cl, 3-Cl, 4-Cl, 4-Br,
2-Me, 3-Me, 2-OMe, 3-OMe

89: 2-Me (50-64%)
90: 3-Me (50-66%)
91: 4-Me (57-79%)

89-91
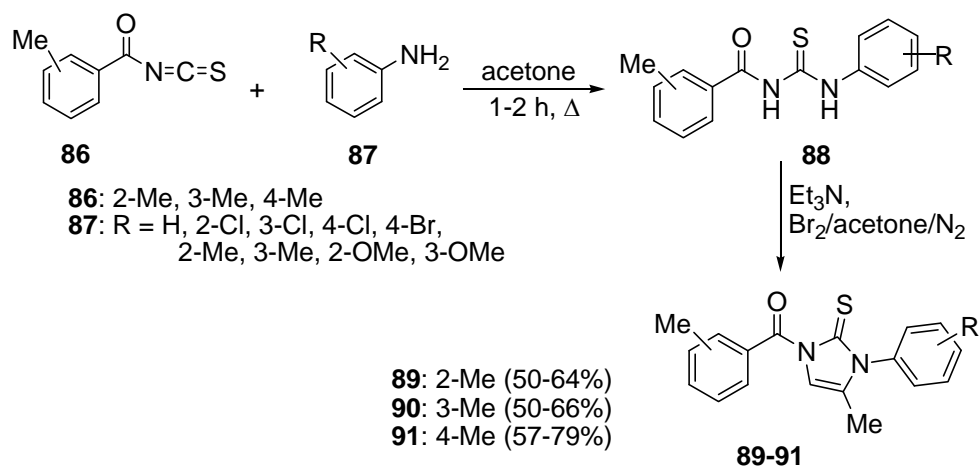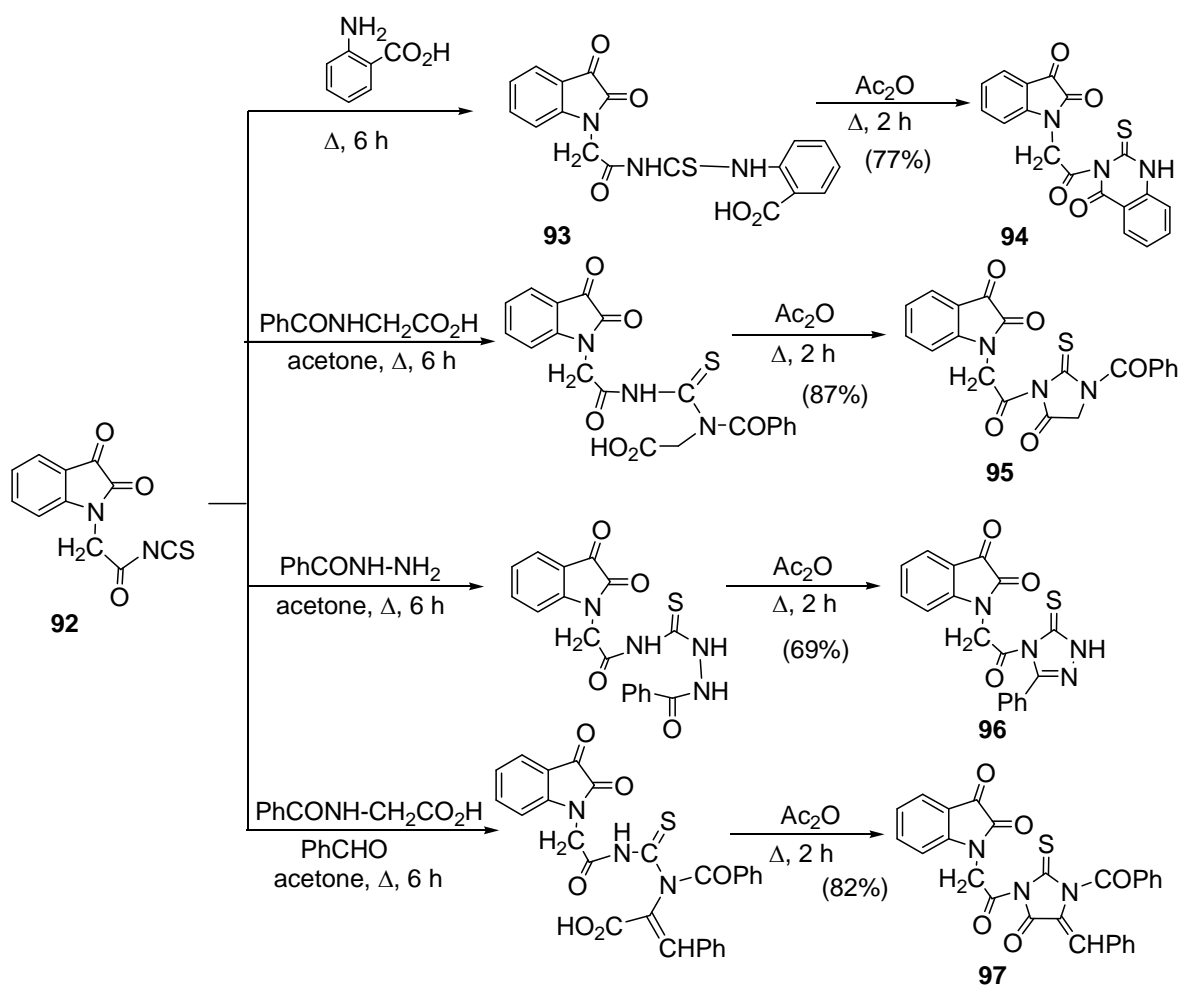
Scheme 31

Scheme 32

Since the isatin ring is present in the structures of many biologically active compounds, methods for synthesis of its derivatives still hold the interest of chemists.[64] In a recent report, 2-(2,3-dioxoindolin-1-yl)acetyl isothiocyanate **92** was used as a substrate to synthesize some new heterocyclic compounds containing isatin ring (Scheme 32).[25] The thiourea derivative **93**, obtained from treatment of the acyl isothiocyanate **92** with anthranilic acid, was cyclized in acetic anhydride to afford the isatin-thioxoquinazolinone derivative **94**. Similar reactions of acyl isothiocyanate **92** with *N*-benzoyl glycine, bezoyl hydrazine, and *N*-benzoyl glycine in the presence of benzaldehyde forming adducts, and their cyclization to heterocycles **95-97** are also described by the authors.

El-Sharkawi and coworkers have recently reported the reaction of benzoylisothiocyanate with 2-aminotetrahydrobenzothiophenes in the synthesis of annulated thiophenes containing tetrahydropyrimidine ring of pharmaceutical interest.[65] The reaction of benzoylisothiocyanate **1** with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives **98** in 1,4-dioxane at room temperature gave the *N*-benzoylthiourea derivatives **99** (Scheme 33). Thioureass **99** underwent cyclization on heating in under basic conditions to give the tetrahydrobezo[*b*]thieno[2,3-*d*]pyrimidine derivatives **100**.
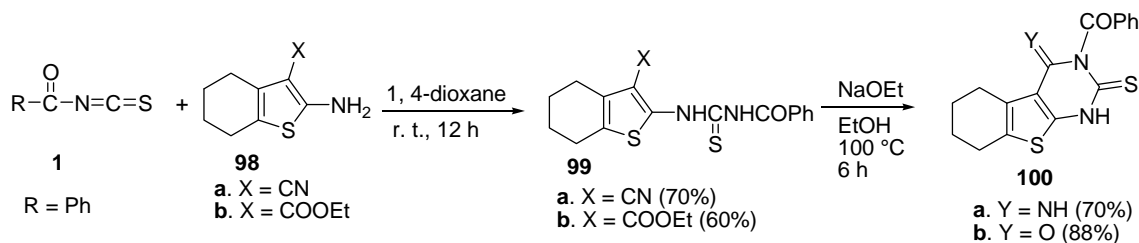
Scheme 33

2.4. Acyl isothiocyanates as acylating agents

There are several reports in the literature on chemoselective acylation of amines using diverse reagents under different conditions. A few examples include the chemoselective acylation and benzoylation of the amino group in preference to the hydroxyl group by carboxylic anhydrides in the presence of sodium dodecyl sulfate as a catalyst,[66] and by carboxylic acids using carbonyldiimidazole.[67] Chemoselective *N*-acylation has also been achieved using amine hydrochlorides and anhydrides in the presence of sodium bicarbonate.[68] Nair and Joshua have reported mixed benzoic dithiocarbamic anhydrides as benzoylating reagents.[69] Katritzky and coworkers have suggested *N*-acyl-benzotriazoles as useful acylating reagents for amines.[70] Acyl isothiocyanates are also used as acylating agents in different reactions. Recently our group has reported a chemoselective *N*-benzoylation of aminophenols using benzoyl isothiocyanates as acylating agents.[71] An equimolar reaction of benzoyl isothiocyanates **1** with aminophenol **101** in refluxing pyridine afforded the corresponding *N*-(hydroxyl-phenyl)benzamides **102** in good yields (Scheme 34). The formation of product has been explained through formation of the

corresponding thioureas followed by elimination of HSCN as shown in Scheme 34. When the reactions of benzoyl isothiocyanates with salicylamide were carried out *O*-benzoyl derivatives **103** were obtained (Scheme 35) by similar method.[72] The use of a base, pyridine in this case, was a necessity for the reaction of isothiocyanates with a phenolic hydroxyl group.[73]

	R	OH		R	OH
a.	Ph	2-OH	**f**.	4-ClPh	2-OH
b.	2-MePh	2-OH	**g**.	4-O$_2$NPh	2-OH
c.	3-MePh	2-OH	**h**.	Ph	4-OH
d.	4-MePh	2-OH	**i**.	3-MePh	4-OH
e.	4-MeOPh	2-OH	**j**.	4-MeOPh	4-OH
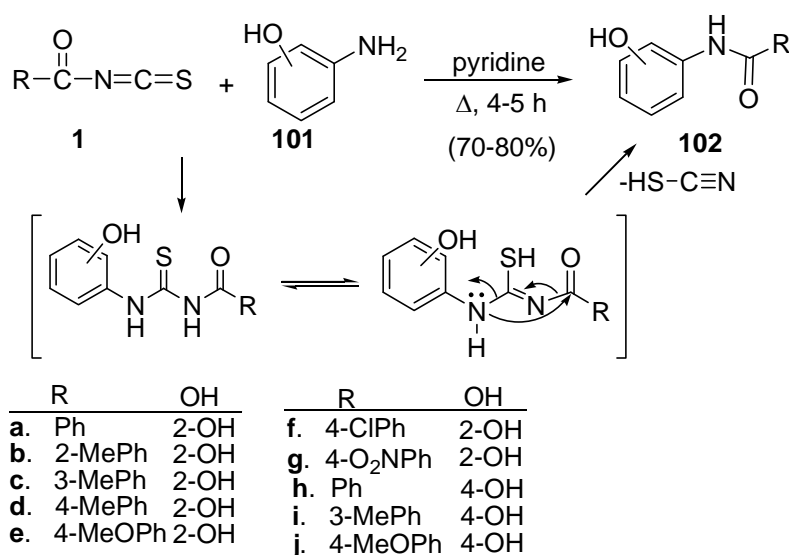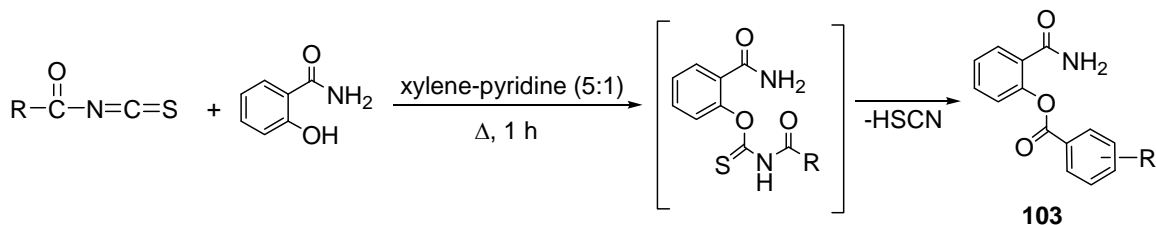
Scheme 34

103. R = Ph (86%), 2-MePh (74%), 3-MePh (79%), 4-MePh (83%), 4-MeOPh (80%), 4-Cl(Ph 75%), 4-O$_2$NPh (73%)

Scheme 35

A 2:1 molar reaction of benzoyl isothiocyanates **1** with 1,2-phenylenediamines **104** in benzene afforded the corresponding *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylene diamines **105**.[74] The products **105**, were cyclized in pyridine to afford 2-aryl benzimidazoles **106**. The formation of products **105** has been explained by usual nucleophilic attack of amines **104** on carbon atom of the isothiocyanate linkage in substrates **1** (Scheme 36). On refluxing in pyridine, the removal of one aroyl isothiocyanate moiety may lead to the formation of *N*-(benzoylthiocarbamoyl)-1,2-phenylenediamines **107**. The formation of **107** from the reaction of amines **104** with isothiocyanates **1** has been reported previously by refluxing in acetonitrile.[75] The intermediate product **107** leads to the formation of 2-arylbenzimidazoles **106** by

dethiocyanation to intermediate product **108** and concomitant cyclodehydration.[75] Nucleophilic addition reactions of α,β-unsaturated acyl isothiocyanates with aromatic and heteroaromatic amines such as 3-amino-1,2,4-triazole and 2-aminothiazole were also reported earlier to yield the acyl amino derivatives through elimination of HSCN.[76]

106	R¹	R²	%
a.	Ph	H	75%
b.	4-MeOPh	H	88%
c.	4-ClPh	H	68%
d.	3-MePh	H	82%
e.	Ph	Me	85%
f.	3-MePh	Me	94%
g.	4-MeOPh	Me	79%
h.	4-ClPh	Me	87%
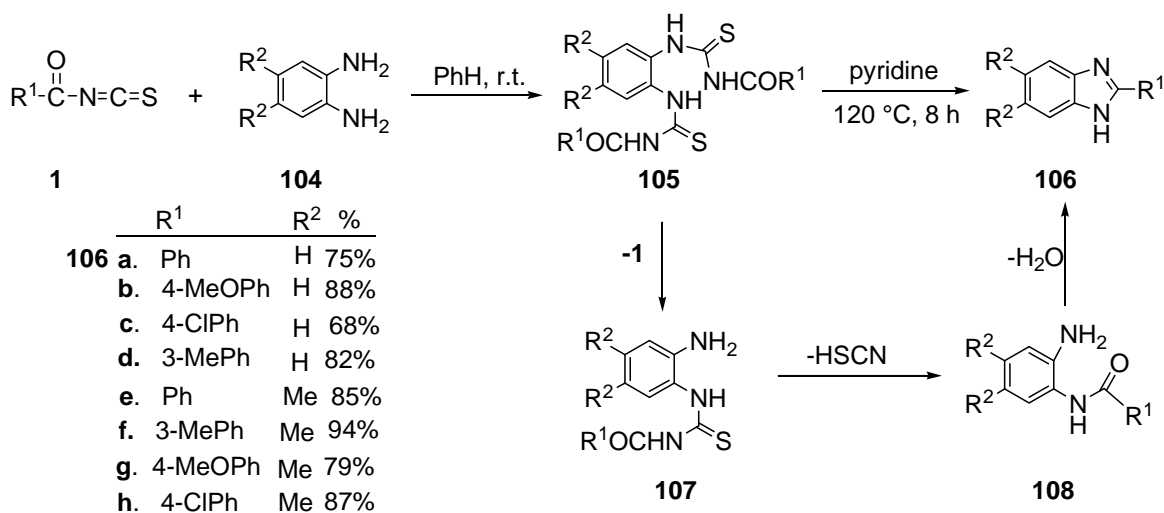
Scheme 36

The reactivity of β-cyanoethylhydrazine **109** with aroyl isothiocyanates has been investigated Elmoghayar and coworkers.[20] This work has resulted in development of new efficient one-step synthesis of 5-thioxo-l,2,4-triazole derivatives. The reaction of benzoyl isothiocyanate **1** with β-cyanoethyl hydrazine **109** in dioxane at room temperature yielded the 5-thioxo-l,2,4-triazole **110**. Treatment of compound **110** with benzoyl isothiocyanate resulted in the formation of imidazole-3-thione derivative **111** via loss of HSCN (Scheme 37).
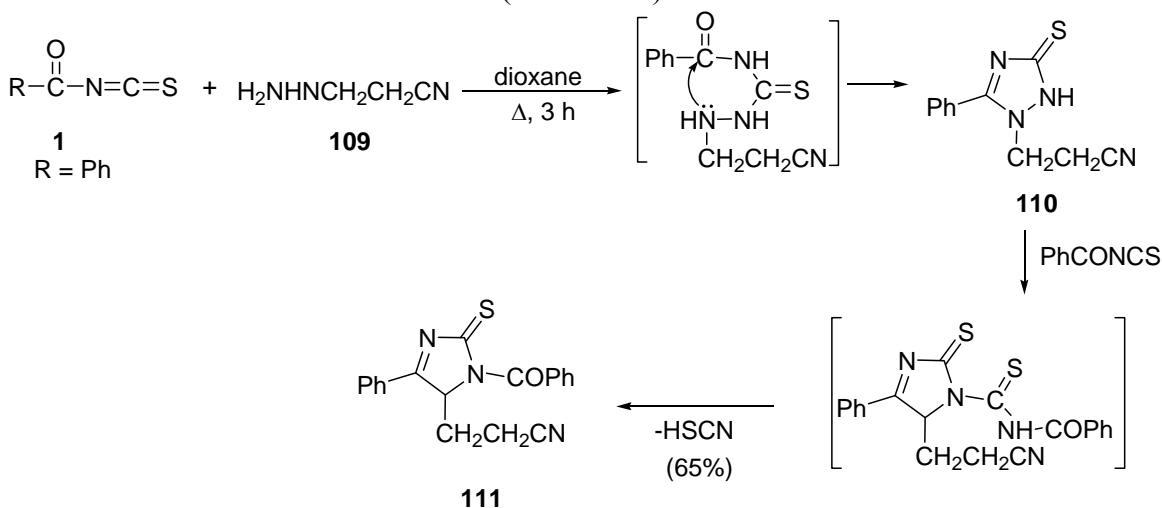
Scheme 37

The reaction of acyl isothiocyanates with β-dicarbony compounds proceeds as *C*–thiocarbamoylation of the dicarbonyl component. For example, the formation of *C*-thiocarbamoylated derivatives of 1,3-cyclohexanedione[77] or dimedone[78,79] in good yields are reported. However, in the reaction of the benzoyl isothiocyanate **1** with cyclic diketone **112** in the presence of an equimolar amount of KOH at room temperature, the former reacted as an acylating agent to furnish *O*-acylation products **113** (Scheme 38).[80]

R = Ph, R^1 = H (76%); R = 4-ClPh, R^1 = H (61%);
R = Ph, R^1 = Me (72%); R = 4-ClPh, R^1 = Me (63%);
R = 4-BrPh, R^1 = Me (60%); R = 4-MeOPh, R^1 = Me (65%)
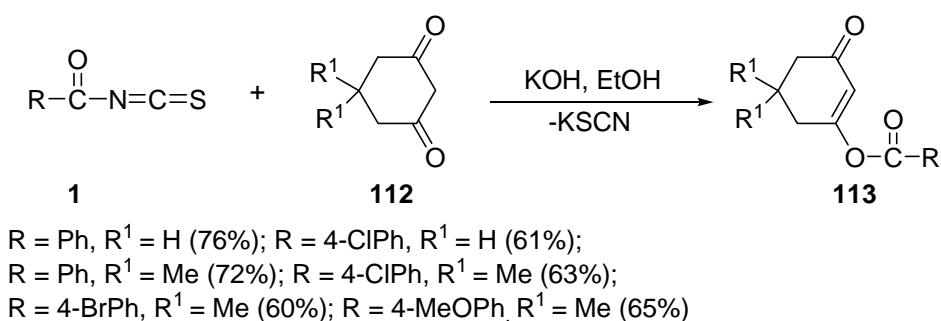
Scheme 38

2.5. Acyl isothiocyanates as thiocyanate transfer reagents

An unprecedented transfer of a thiocyanate (SCN) group from aroyl/acyl isothiocyanate to alkyl or benzylic bromide in the presence of a tertiary amine has been reported by Patel and coworkers.[81] Treatment of benzoyl isothiocyanate **1** with α-bromoacetophenones **114** in the presence of *N*-methylimidazole in acetonitrile afforded the acyl thiocyanates **115** (Scheme 39). Since no reaction was observed in the absence of *N*-methylimidazole, it was definitely involved in the reaction process. The reaction has been further extended to benzyl bromide and *p*-nitrobenzyl bromide. The methodology is also compatible in the presence of amide and ester functionalities.

R^1 = Ph
R^2 = Ph (64%), 4-MeOPh (81%), 4-BrPh (77%)
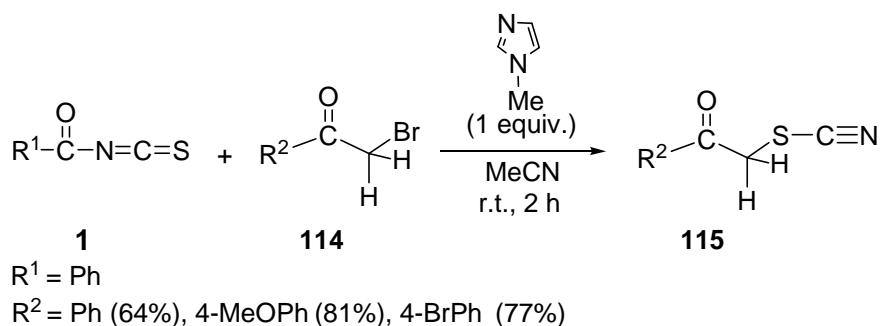
Scheme 39

The authors have proposed two possible mechanisms– (i) through an attack of imidazole nitrogen on carbonyl carbon (path A) and (ii) through an attack of imidazole carbon on

cumulenic carbon of benzoyl isothiocyanate (Scheme 40). In path A, the resulting activated intermediate **116** transfers the NCS group to the α-bromoketone. In path B, the resulting activated thiourea species **117** may react with haloketone giving the *S*-alkylated product **118**, which may undergo nucleophilic attack (*N*-methylimidazole or water from MeCN) giving rise to a tetrahedral intermediate **119**. The collapse of the latter intermediate with concomitant departure of *N*-methylimidazole may give the final product.
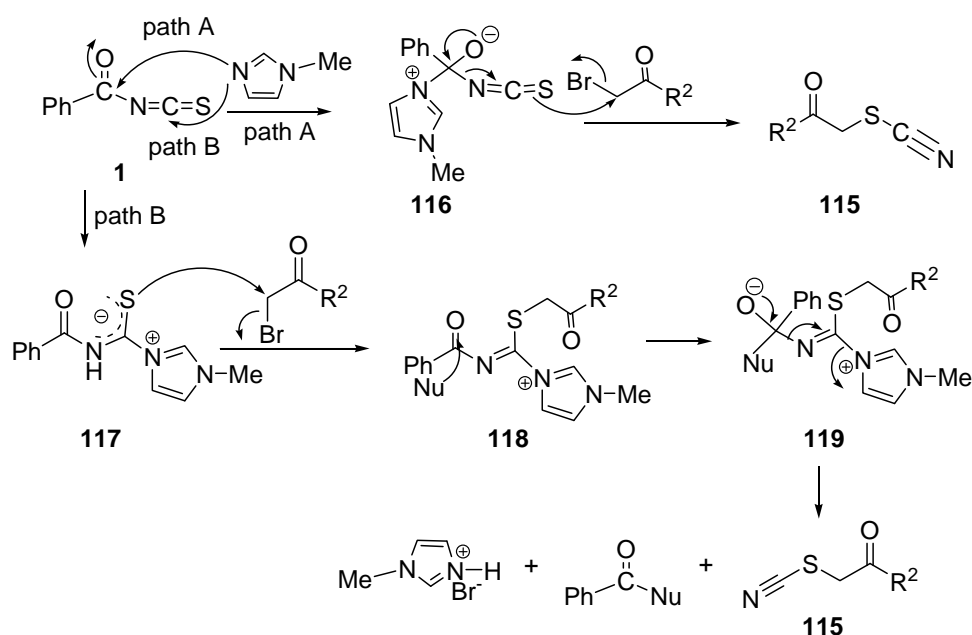
Scheme 40

The reaction of benzoylisothiocyanate with 2-bromoethylacetoacetate **120** under the identical reaction conditions, however, yielded the 1,3-oxathiol-2-ylidine **122** as a major product and thiocyanate transfer product **123** only in 10% yield (Scheme 41).[81] The formation of the 1,3-oxathiol-2-ylidine **122** has been explained by the *S*-alkylation of zwitterionic intermediate **117** with 2-bromoethylacetoacetate **117** followed by an intramolecular enol attack on the imine carbon in intermediate **124** displacing the 2-methylimidazole. The product **123** is obtained by a thiocyanate transfer process from the isomerized 2-bromoethylacetoacetate **120** to 4-bromoethylacetoacetate **121.**
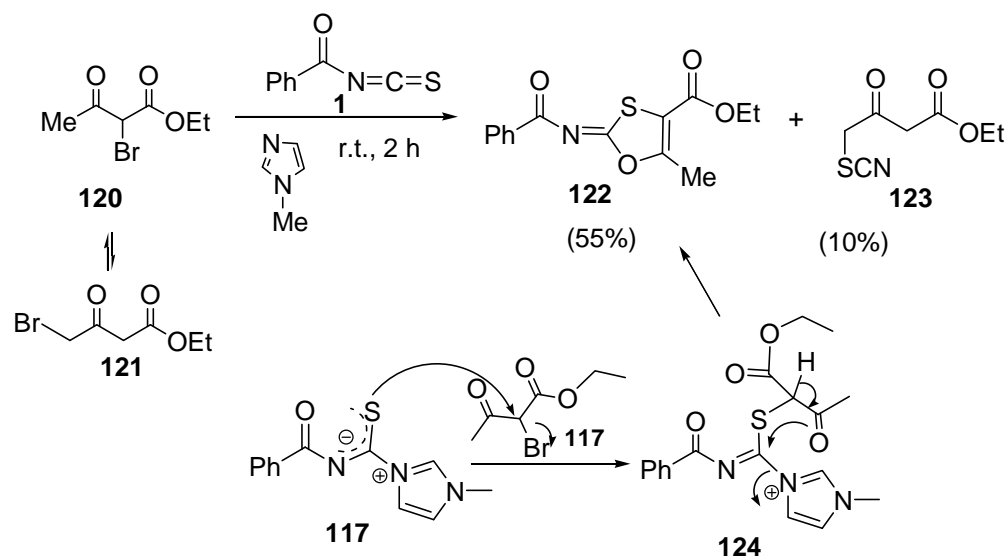
Scheme 41

3. Multicomponent Reactions of Acyl Isothiocyanates

In recent years, multicomponent reactions have acquired conspicuous popularity in design and synthesis of complex organic molecules.[82-84] Acyl isothiocyanates have also been employed in multicomponent reactions to synthesize functionalized thiourea and heterocyles. A multicomponent reaction of benzoyl isothiocyanates **125**, alkyl propiolates **126**, secondary amines **127**, and Ph₃P leading to an efficient synthesis of functionalized thioureas has been reported.[85] Addition of Ph₃P to various activated alkynes like dibenzoylacetylene, dicyanoacetylene, or dimethylacetylenedicarboxylate (DMAD) generating *zwitterionic* intermediate was reported as early as 1961 by Tebby and coworkers.[86] Initially a 1,3-dipolar intermediate **130** was formed from Ph₃P and the acetylenic ester, which was subsequently protonated by the benzoyl thiourea **129**, formed from addition of amine **127** to aroyl isothiocyanates **125**. A nucleophilic attack of the nitrogen atom of the conjugate base **132** to the vinylphosphonium cation **131** leads to the formation of an ylide **133**, which is converted to products **128** by elimination of Ph₃P (Scheme 42).

125. R = H, Br
126. R^1 = Me, Et
127. R^2 = Et, (CH$_2$)$_5$, (CH$_2$)$_4$, (CH$_2$)$_2$O(CH$_2$)$_2$

128	R	R^1	R^2	Yield %	Z/E
a	H	Et	C$_2$H$_5$	85	3
b	H	Me	C$_2$H$_5$	80	2
c	H	Et	(CH$_2$)$_5$	90	3.8
d	H	Me	(CH$_2$)$_5$	87	5.8
e	Br	Et	(CH$_2$)$_5$	75	2
f	H	Et	(CH$_2$)$_4$	80	4
g	H	Me	(CH$_2$)$_2$O(CH$_2$)$_2$	90	3
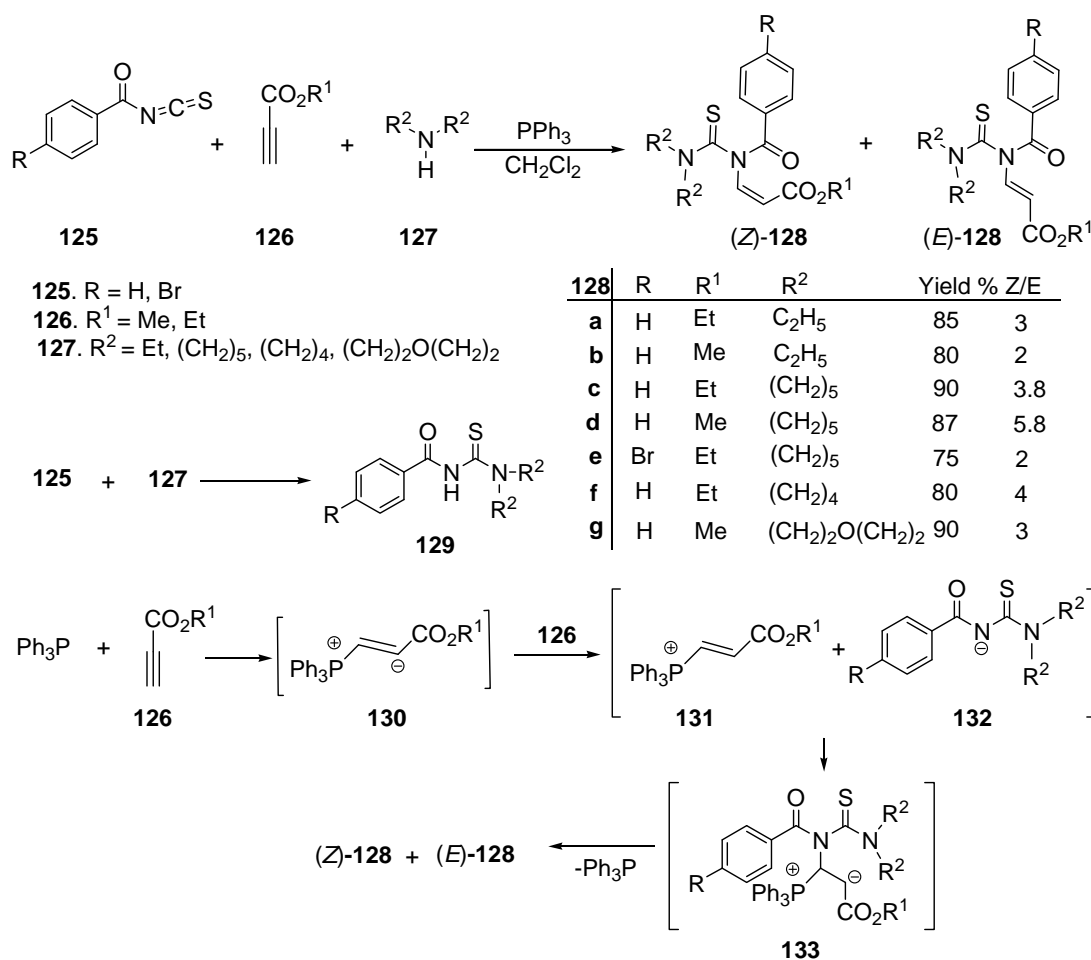
Scheme 42

Yavari and coworkers have described an equimolar reaction of benzoyl isothiocyanate **1**, dialkyl acetylenedicarboxylates **134** and Ph$_3$P to afford the dialkyl 2-(benzoylimino)-5-phenyl-4*H*-[1,3]dithiolo[4,5-*b*]pyrrole-4,6-dicarboxylates **135**, with double insertion of the isothiocyanate, and dialkyl 2-phenyl-4-thioxo-4*H*-1,3-oxazine-5,6-dicarboxylates **136** in a 3:1 ratio (Scheme 43).[87]

	R^1	Yield (%) of **135**	Yield (%) of **136**
a	Me	38	10
b	Et	40	8
c	^{t}Bu	35	10
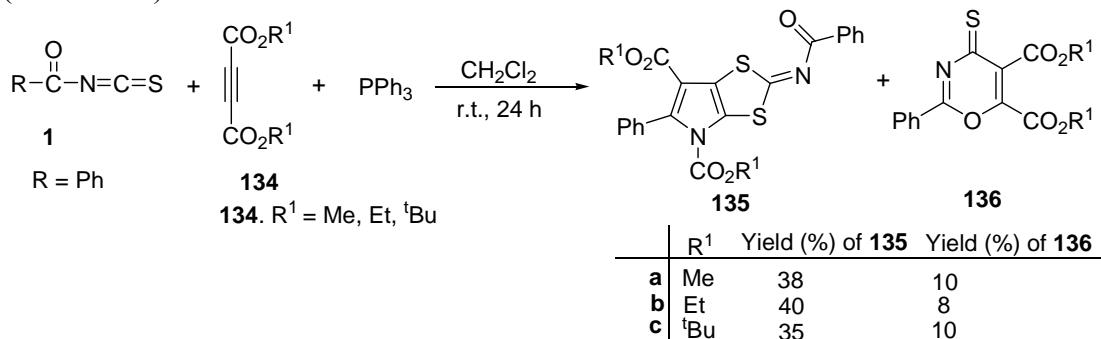
Scheme 43

The plausible mechanistic rationalization suggests that the *zwitterionic* intermediate **137**, formed from Ph₃P and dialkylacetylenedicarboxylates, adds onto the benzoyl isothiocyanate to furnish an intermediate **138**, which then adds onto another molecule of benzoyl isothiocyanate to form another intermediate **139** (Scheme 44). This intermediate undergoes cyclization to furnish the fused structure **140** by the elimination of triphenylphosphine oxide. The pyrrole derivative **140** rearranges to the final product **135** by a carbon to nitrogen carboxyl transfer via the tricyclic intermediate **141**. Formation of oxazinethiones **136** involves addition of the *zwitterionic* intermediate **137** to benzoyl isothiocyanate. The cyclization of intermediate **142** and subsequent elimination of Ph₃P leads to the formation of oxazines **143**.

Scheme 44

Several methods for the synthesis of thiazole derivatives have been developed employing acyl isothiocyanates, the most widely used method being the Hantzsch's synthesis.[88] A three-component reaction of acyl isothiocyanates **1**, ethyl bromopyruvate **144** and secondary amines

145 in acetone at room temperature affords ethyl 2-(4-aryl-2-dialkylamino-1,3-thiazole-5-yl)-2-oxoacetates **146** (Scheme 45). This procedure modified the Hantzsch method for thiazole synthesis via the reaction of thioureas with *α*-halocarbonyl compounds.[89] In this method, thiourea derivatives are formed *in situ* from acyl isothiocyanates **1** and amines **145** which react with bromopyruvate **144** to afford highly functionalized thiazoles **146**.

Scheme 45

The formation of thiazoles **146** from *in situ* generated thioureas **147** has been explained by nucleophilic alkylation of the thioureas with ethyl bromopyruvate forming intermediate **148**, which undergoes HBr elimination and subsequent enolization to generate another intermediate **149**. This intermediate undergoes intramolecular cyclization to form the heterocyclic intermediate **150** which loses water to afford thiazoles **146** (Scheme 46).

Scheme 46

   Recently, the formation of thiazol-2(*3H*)-imines in a three-component reaction of α-amino acids **151**, aroylisothiocyanates **1** and α-bromoketones **152** in an ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]Br as a solvent has been reported (Scheme 47).[90] Functionalized thiazol-2(*3H*)-imines **153** are obtained in excellent yields. The method is also advantageous because the ionic liquid can be recycled by extraction from the aqueous base. Also, the configuration of the amino acid component remained unchanged after the reaction. The reaction presumably starts with the formation of thiourea derivative **154**, followed by its alkylation by **152** to generate intermediate **155** (Scheme 48). This intermediate underwent a cyclization reaction to afford **156**, which is converted to product **153** by elimination of H_2O.

153	R^1	R^2	R^3	Yiled (%)	**153**	R^1	R^2	R^3	Yiled (%)
a.	Ph	H	CO_2Et	76	**g.**	Ph	i-Pr	CO_2Et	92
b.	Ph	H	4-MeOPh	79	**h.**	Ph	i-Pr	4-MeOPh	89
c.	Ph	H	4-BrPh	86	**i.**	Ph	i-Pr	4-BrPh	96
d.	Ph	Me	CO_2Et	96	**j.**	*p*-Tolyl	Me	CO_2Et	80
e.	Ph	Me	4-MeOPh	94	**k.**	*p*-Tolyl	Me	4-MeOPh	85
f.	Ph	Me	4-BrPh	97	**l.**	*p*-Tolyl	Me	4-BrPh	83

Scheme 47

Scheme 48

Yavari and Djahaniani have reported a three-component reaction in which two moles of alkyl(aryl) isocyanides **157** react with one mole each of the benzoyl isothiocyanate **1** and dialkylacetylenedicarboxylates or dibenzoylacetylene **158** to afford the spiro-fused heterocyclic compounds dialkyl 4,7-bis[alkyl(aryl)imino]-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-diene-8,9-dicarboxy-lates **159a-e** or [8-benzyoyl-4,7-bis[(tert-butyl imino)-2-phenyl-3-oxa-6-thia-1-aza-spiro[4.4]nona-1,8-dien-9-yl](phenyl)methanone **159f**, with double insertion of the isocyanide, in reasonable yields (Scheme 49).[91]

	R^2	R^1	Yield %
a.	OMe	^{t}Bu	48
b.	OEt	^{t}Bu	48
c.	O^{i}Pr	^{t}Bu	40
d.	OMe	1,1,3,3-tetramethylbutyl	44
e.	OMe	2,6-dimethylphenyl	40
f.	Ph	^{t}Bu	38

R = Ph
R^1 = ^{t}Bu,1,1,3,3-tetramethylbutyl,
    2,6-dimethylphenyl
R^2 = OMe, OEt, O^{i}Pr, Ph
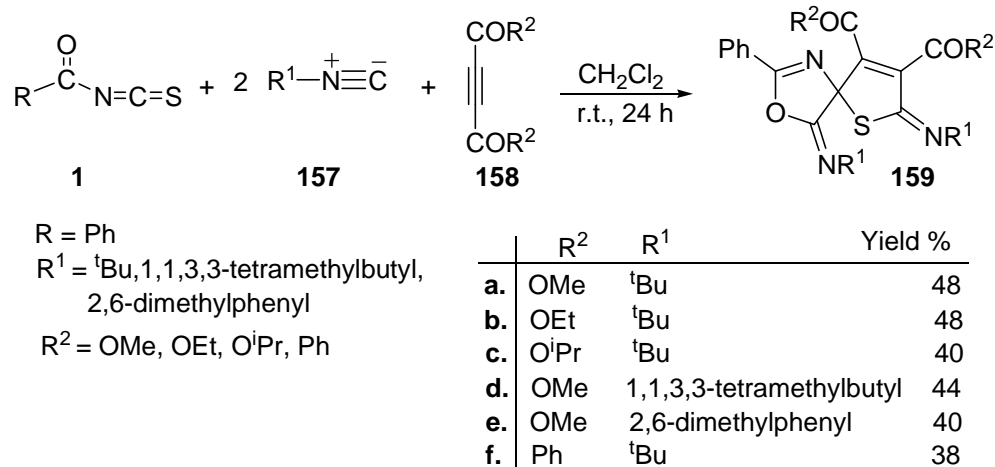
Scheme 49

The reaction may involve the initial formation of a 1:1 *zwitterionic* intermediate **160** between the isocyanide and the acetylenic compound, which can undergo further reaction with **1** to produce **161**. Cyclization of intermediate **161** leads to the formation of **162**, which undergoes [4+1]-cycloaddition with isocyanides **157** to form the final products **159** (Scheme 50).
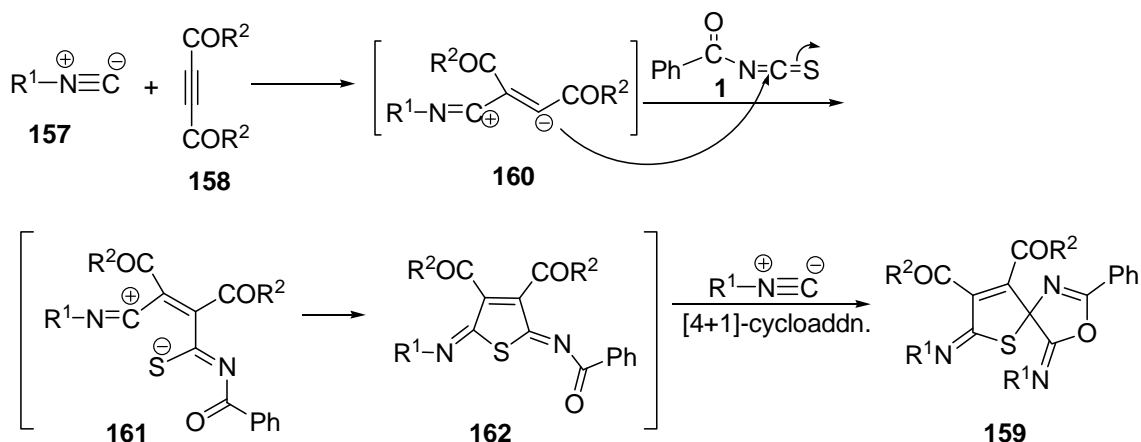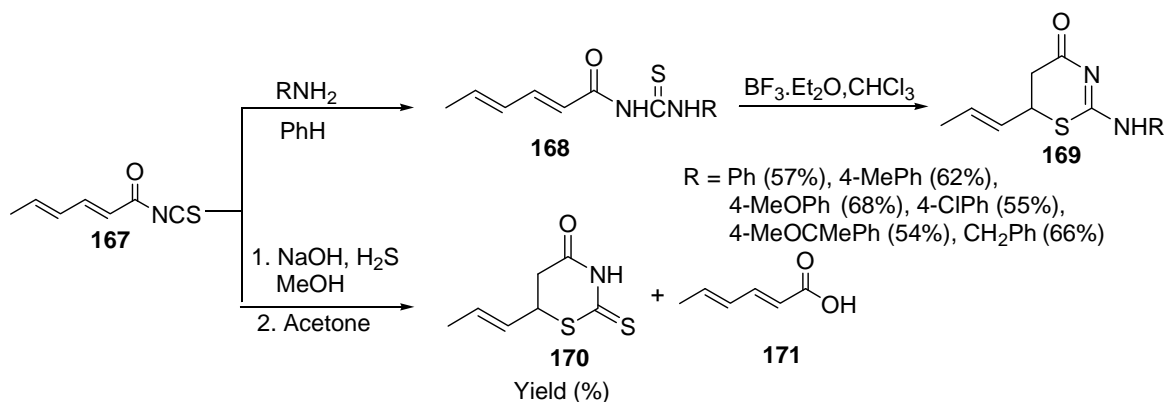

Scheme 50

4. Miscellaneous Reactions

The reaction of isothiocyanate **1** with thiosemicarbazide **163** yielded the 1,2,4-triazoline derivative **166** (Scheme 51).[27] The formation of product **166** was explained through cyclization of the nucleophilic addition product **164** forming the heterocycle **165**. The elimination of H$_2$S from this heterocycle afforded the final product. The release of H$_2$S gas during the reaction progress was detected by turning a paper wet with lead acetate solution into black.
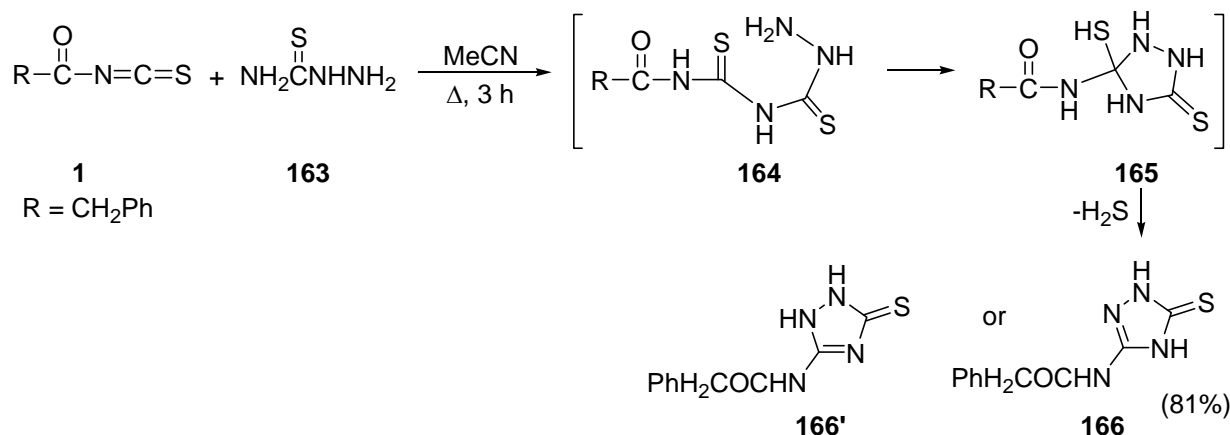
Scheme 51

Scheme 52

α,β-Unsaturated acyl isothioucyanates react with primary and secondary amines in usual manner forming stable thioureas, which are synthons for the synthesis of diverse types of thia- and thiaza-heterocycles such as 1,3-thiazines, thiouracils, thiazolines, and benzothiazoles.[92-94] Treatment of isothiocyanate **167** with amines in benzene or acetone afforded the corresponding *N*-substituted *N'*-(hexa-2,4-dienoyl)thioureas **168** in 79-92 % yields (Scheme 52).[95] Boron

trifluoride-catalyzed cyclization of thioureas **168** in chloroform resulted into the formation of the 2-substituted 6-(propen-l-yl)-5,6- dihydro-4*H*-l,3-thiazin-4-ones **169**. A nucleophilic addition of sodium hydrogen sulfide to isothiocyanate **167** affords two products, 6-(propen-l-yl)-2-thioxotetrahydro-4*H*-l,3-thiazin-4-one **170** and hexa-2,4-dienoic acid **171** in 37% and 31% yields, respectively. The formation of carboxylic acid **171** could be explained by partial hydrolysis of transiently formed sodium *N*-(hexa-2,4-dienoyl)dithiocarbamate.

5. Concluding Remarks

Acyl isothiocyanates are bifunctional reagents capable of participating in a wide range of additions and cyclizations. The reactivity of acyl isothiocyanates is determined by the three active centers. One of them is associated with the nitrogen atom with the unshared pair of electrons, and the others are on the thiocarbonyl and carbonyl groups. The strong electron-withdrawing potential of the acyl group enhances the reactivity of the adjacent isothiocyanate functionality and promotes the nucleophilic addition at this center.

Acyl isothiocyanates are reported to undergo cyclization involving thiocarbonyl and carbonyl carbon with nitrogen nucleophiles forming triazolinethiones, l,2,4-triazoles, 1,2,4-triazoline-5-thiones, 1,3,5-triazinethiones, and oxadiazines.

Cyclization through thiocarbonyl group results into the formation of different thiazoline skeletons and thiadiazoles. Organic azides, bearing a nitrile function at the γ- or δ-position, react with acyl isothiocyanates to furnish the fused dihydro-1,2,4-thiadiazolimines. In the reaction of diazo compounds with acyl isothiocyanates, thiadiazole derivatives are formed, apparently by a 1,3-cycloaddition across the C=S bond. The [3+2]-cycloaddition of oxazoles to the C=S group of acyl isothiocyanates have been employed in the synthesis of thiazolines.

Another commonly investigated reaction of acyl isothiocyanates is as an acylation reagent in different reactions through an elimination of thiocyanic acid from the reaction intermediate products. The reaction of acyl isothiocyanates with β-dicarbonyl compounds furnished *O*-acylation products. A novel transfer of a thiocyanate (SCN) group from acyl isothiocyanate to alkyl or benzylic bromide in the presence of an *N*-methylimidazole is reported recently. The ability of acyl isothiocyanates to form a variety of nitrogen- and sulphur-containing heterocyclic compounds makes it an important building block in organic synthesis. Use of acyl isothiocyanates as acylating agents and thiocyanate-transfer reagent has further diversified its chemistry. We anticipate a lot more interesting chemistry of acyl isothiocyanates to appear in coming days.

6. Acknowledgements

7. References

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