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, thiaazolo[1,2-a]pyridazines, benzimidazoles, dithiolane, spiro-fused oxazolines, triazoles, 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. \(^3\)

![Chemical structure of isothiocyanates](image)

**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 synths 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](image)

**Scheme 1**
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 a slight conjugative donation in the case of acyl isothiocyanates (Figure 2). 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.](image)

![Figure 3. Reactive sites of acyl isothiocyanates.](image)
A thermal 1,3-shift of substituent R in acyl isothiocyanates 1 is reported to proceed via the transition state TS (Figure 4).\textsuperscript{15,16} Goerdeler and coworkers have reported the isomerization of thioacyl isocyanates 1a to acyl isothiocyanates 1, in solution at temperatures around 100 °C.\textsuperscript{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.

\begin{center}
\textbf{Figure 4.} 1,3-Rearrangement of acyl isothiocyanates.
\end{center}

\begin{center}
\textbf{Figure 5.} Selected heterocyclic compounds synthesized from acyl isothiocyanates.
\end{center}
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, benzoazole, and
benzimidazole derivatives (Figure 5) which will be discussed in the succeeding sections.

2.1. Cyclization reactions involving both electrophilic centers

\[
\begin{align*}
\text{Nu} & \quad \text{Nu} \\
\text{NC} & \quad \text{S} \\
\text{R} & \quad \text{Nu} \\
\text{O} & \quad \text{Nu} \quad \text{Nu}
\end{align*}
\]

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).\textsuperscript{19}
Subsequent acylation of the hydroxyl group in products 3 led to the formation of corresponding
\textit{O}-acyl derivatives 4 which exhibited anti-inflammatory activity. In a similar fashion, the reaction
of benzoyl isothiocyanate 1 with \(\beta\)-cyanoethylhydrazine 5 resulted in development of a new and
efficient one-step synthesis of 5-thioxo-1,2,4-triazole derivative 6 (Scheme 4).\textsuperscript{20}
Scheme 3

Scheme 4

Several isatin derivatives have been reported in literature to have different types of biological activity. According to a recent report, treatment of N-acyl isothiocyanate substituted isatin 7 with hydrazine hydrate in boiling dry benzene afforded compound 8. The latter compound, on refluxing in freshly distilled acetic anhydride, yielded 1-[(5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl) methyl]-1H-indole-2,3-dione 9 (Scheme 5). Some aroyl isothiocyanates, 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).

Scheme 5
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-phenylacetyl isothiocyanate 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 \(N, N'-\text{di(phenylacetyl)hydrazine}\). 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
Scheme 8

Benzoyl isothiocyanate reacts with some N-alkyl hydrazones of acetone 19 readily to afford the 1,3,4,6-oxatriazepine-5(2H)-thiones 20 in 29-75% yields (Scheme 9). 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.

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 CO₂ and ethanol, to triazoles 27 via triazolinethione 26 (Scheme 11).
Scheme 10

\[
\begin{align*}
R-C-N=C=S + \text{NH}_2\text{NHCO}_2\text{Et} & \xrightarrow{\text{DMF, 100 °C, 1 h}} \text{Ph-C-NH-C-NH-NH-CO}_2\text{Et} \\
R = \text{Ph} & \\
\end{align*}
\]

Scheme 11

\[
\begin{align*}
R-C-N=C=S + \text{NH}_2\text{NH-C-NHR}^1 & \xrightarrow{\text{MeOH, r.t., 1-2 h}} \text{R-C-NH-C-NH-NH-C-NHR}^1 \\
R = \text{Ph, 4-ClPh} & \quad R^1 = \text{Ph} \\
\end{align*}
\]

Scheme 12
An equimolar reaction of aroyl isothiocyanates 1 and aminoguanidine 28 affords amidinothiosemicarbazides 29 in excellent yields. 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). Aroyl isothiocyanates 1 were reacted with urea in dry acetone to give the good yields of 1-aryloxybiurets 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-thio-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).
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-2H-pyrimido[6,1-a]isoquinoline-1-carbonitrile 46 in 85% yield (Scheme 18).35
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. The latter compounds react with 5-amino-3-methyl-(1H)-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.

Scheme 18

\[
\begin{align*}
&\text{O} \\
&\text{R-C-N=C=S} \\
&\text{1} \\
&\text{R = Ph}
\end{align*}
\]

\[
\begin{align*}
&\text{MeO} \\
&\text{MeO} \\
&\text{45} \\
&\text{R = Ph} \\
&\text{NC}
\end{align*}
\]

\[
\begin{align*}
&\text{MeCN} \\
&50^\circ C, 15 \text{ min} \\
&\text{45} \\
&\text{46}
\end{align*}
\]

Scheme 19

\[
\begin{align*}
&\text{R = Ph (90%), 4-MePh (74%), 4-ClPh (93%), 4-O_2NPh (61\%)}
\end{align*}
\]
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(1H)-thione 53 (Scheme 20).  

\[
\begin{align*}
\text{R-C-N=C=S} & \quad \text{et}_{2}O & \quad \Delta & \quad \text{EtOH} & \quad \Delta \quad \text{THF} & \quad \Delta \\
\text{1} & \quad \text{R = Ph} & \quad \text{51} & \quad \text{52} & \quad \text{53}
\end{align*}
\]

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 H₂ 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-3H-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-3H-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 R² group in the iso thiourea 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.
A solid-supported synthesis of 2-aminobenzothiazoles is reported by employing the resin-bound acyl isothiocyanate 59 and a series of anilines (Scheme 22). 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

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>R^4</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. 4-CNPh</td>
<td>isopropyl</td>
<td>CO_2Et</td>
<td>Me</td>
<td>77</td>
</tr>
<tr>
<td>b. 4-CNPh</td>
<td>cyclopentyl</td>
<td>CO_2Et</td>
<td>Me</td>
<td>62</td>
</tr>
<tr>
<td>c. 4-O_2NPh</td>
<td>isopropyl</td>
<td>CO_2Et</td>
<td>Me</td>
<td>86</td>
</tr>
<tr>
<td>d. 4-MeOPh</td>
<td>isopropyl</td>
<td>CO_2Et</td>
<td>Me</td>
<td>35</td>
</tr>
<tr>
<td>e. 4-O_2NPh</td>
<td>isopentyl</td>
<td>H</td>
<td>Me</td>
<td>81</td>
</tr>
<tr>
<td>f. 4-O_2NPh</td>
<td>isopentyl</td>
<td>CO_2Et</td>
<td>OH</td>
<td>36</td>
</tr>
</tbody>
</table>
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-isoproxy-4-methyloxazole \(^{65}\) led to the synthesis of 5-\(N\)acylimino-2-isoproxy carbonyl-2-methyl-3-thiazolines \(^{66}\). The transformation occurred via formal [3+2]-cycloaddition of the C=S bond of acyl isothiocyanate to the 2\(^{\text{nd}}\) and 4\(^{\text{th}}\) atoms of the oxazole ring.

![Scheme 23](image)

\[ R-N=C=S + \text{Scheme 23} \]

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

\[
\begin{align*}
\text{R-C-N=C=S} + \text{N=C=S} & \quad \xrightarrow{\text{dioxane, } \Delta, 15 \text{ min}} \quad \text{N=C=S} \\
1 & \quad 67 & \quad 68 & \quad 69
\end{align*}
\]

a. \( R = \text{Me} \)

b. \( R = \text{Ph} \)

c. \( R = \text{EtO} \)

a. \( R^1 = \text{Me} \)

b. \( R^1 = \text{Ph} \)

\[70\]

a. \( R = \text{Me}, \ R^1 = \text{Me}, 66\% \)

b. \( R = \text{EtO}, \ R^1 = \text{Me}, 71\% \)

c. \( R = \text{Me}, \ R^1 = \text{Ph}, 90\% \)

d. \( R = \text{Me}, \ R^1 = \text{Ph}, 82\% \)

e. \( R = \text{EtO}, \ R^1 = \text{Me}, 70\% \)

f. \( R = \text{Ph}, \ R^1 = \text{Ph}, 92\% \)

Scheme 25

\[
\begin{align*}
\text{R-C-N=C=S} + \text{P(\text{O})(\text{OEt})2} & \quad \xrightarrow{\text{MeCN, } 80 \degree \text{C, 2 h}} \quad \text{MeCN} \\
1 & \quad 71 & \quad 72
\end{align*}
\]

a. \( R = \text{Me} (92\%), \ b. \ R = \text{Ph} (99\%), \ c. \ R = \text{OEt} (99\%) \)

Scheme 26

Organic azides 76, bearing a nitrile function at the \( \gamma \)- or \( \delta \)-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 dihydrothiazole 77 was
reported by L'abbe and coworkers.\textsuperscript{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.\textsuperscript{53} The heterocycles 77 are expected to be unstable since they would decompose by anchimeric assistance of the carbonyl group. The 1,2,4-oxathiazol-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).

\begin{center}
\begin{tikzpicture}
\path (0,0) node[circle, draw, inner sep=0.5cm] (1) {76} edge[bend left] (77) edge[bend right] (78) edge[bend left] (79);
\end{tikzpicture}
\end{center}

\textbf{Scheme 27}

\begin{center}
\begin{tikzpicture}
\path (0,0) node (1) {CH$_2$Cl$_2$, \(\Delta\), 22 h} edge (A) edge[bend left=50] (2) edge[bend right=50] (3) edge[bend left=50] (A)
\path (2) node {CH$_2$Cl$_2$, 40 \(^\circ\)C, 30 h} edge (b) edge (c)
\path (3) node {CH$_2$Cl$_2$, \(\Delta\), 16 h} edge (d) edge (e)
\path (4) node {CH$_2$Cl$_2$, r.t., 5 d} edge (f) edge (g)
\path (1) node {R = CCl$_3$ (28\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (2) node {R = CCl$_3$ (37\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (3) node {R = Ph (22\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (4) node {R = CCl$_3$ (52\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (5) node {R = Ph (83\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (6) node {R = CCl$_3$ (46\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\path (7) node {R = Ph (41\%)} edge (a) edge (b) edge (c) edge (d) edge (e) edge (f) edge (g)
\end{tikzpicture}
\end{center}

\textbf{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{59} In principle, both the C=\textit{N} and C=S bonds of isothiocyanates are capable of cycloaddition with diazoazoles to form either a 1,2,3,5-thiatetrazine or a 1,2,3,5-tetrazine ring system or a mixture of both. Recently, the reactions of diazoazoles with acyl isothiocyanates is reported to occur readily at C=S to give azolo[5,1-d] [1,2,3,5]thiatriazines as the sole products (Scheme 29). It is noteworthy to mention that this reaction was unsuccessful with methyl-, phenyl- or benzenesulfonylisothiocyanate.\textsuperscript{60} The acyl substituent on the isothiocyanate probably led to a stabilization of the final product 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 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.

![Scheme 29](image)

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>CH</td>
<td>N</td>
<td>OEt</td>
<td>CO\textsubscript{2}Et</td>
<td>79</td>
</tr>
<tr>
<td>b.</td>
<td>CH</td>
<td>N</td>
<td>Ph</td>
<td>CO\textsubscript{2}Et</td>
<td>88</td>
</tr>
<tr>
<td>c.</td>
<td>CH</td>
<td>N</td>
<td>OEt</td>
<td>CONHMe</td>
<td>69</td>
</tr>
<tr>
<td>d.</td>
<td>CH</td>
<td>N</td>
<td>Ph</td>
<td>CONHMe</td>
<td>76</td>
</tr>
<tr>
<td>e.</td>
<td>N</td>
<td>CH</td>
<td>OEt</td>
<td>CO\textsubscript{2}Et</td>
<td>72</td>
</tr>
<tr>
<td>e.</td>
<td>N</td>
<td>CH</td>
<td>Ph</td>
<td>CO\textsubscript{2}Et</td>
<td>84</td>
</tr>
</tbody>
</table>
2.3. Cyclization reactions involving azomethine linkage of isothiocyanates

\[
\begin{align*}
R^1C\overset{\text{N=C=S}}{\longrightarrow} & \quad R^1C\overset{\text{N=C=S}}{\longrightarrow} \\
& \quad R^1N\text{H}_2N
\end{align*}
\]

Tolpygin and co-workers, in order to develop cation and anion sensors,\(^\text{61}\) have carried out the reactions of 4-arylalkyl- and 4-arylthiosemicarbazides \(^\text{82}\) with benzoyl isothiocyanates \(^\text{1}\) to get substituted 1,2-bis(thiocarbamoyl)hydrazines \(^\text{83}\).\(^\text{62}\) These compounds readily cyclized to 1,2,4-triazole-5-thiones \(^\text{84}\) containing N-arylamino group at C-5 (Scheme 30). An alternative cyclization to 1,2,4-triazole-5-thiones \(^\text{85}\) 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.

\[
\begin{align*}
\text{route A} & \quad \text{route B} \\
1 & \quad 1 \text{-BuOH} \quad 4-6 \text{h} \\
82 & \quad \text{amidines} \quad \text{imidazoles} \\
83 & \quad \text{imidazoles} \\
84 & \quad \text{imidazoles}
\end{align*}
\]

**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 isothiocyanates.\(^\text{63}\) Various derivatives of imidazole-2-thione have attracted widespread attention owing to their diverse pharmacological properties and bioactivities. Isothiocyanates \(^\text{86}\) reacted with anilines \(^\text{87}\) providing 1-isomeric methylbenzoyl thioureas \(^\text{88}\). The base-catalyzed condensation of \(^\text{88}\) was achieved in the presence of bromine to get the 1-tolyl-3-aryl-4-methylimidazole-2-thiones \(^\text{89-91}\) in reasonable yields (Scheme 31).
Scheme 31

\[
\text{Me} + \text{NH}_2\text{CO}_2\text{H} \xrightarrow{\Delta, 6 \text{ h}} \text{NCS} \xrightarrow{\text{Ac}_2\text{O}, \Delta, 2 \text{ h}} \text{S} \xrightarrow{\text{Et}_3\text{N}, \text{Br}_2/\text{acetone}/\text{N}_2} \text{R}
\]

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%)

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. 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). 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. 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). Thioureas 99 underwent cyclization on heating in under basic conditions to give the tetrahydrobenzo[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, and by carboxylic acids using carbonyldiimidazole. Chemoselective N-acylation has also been achieved using amine hydrochlorides and anhydrides in the presence of sodium bicarbonate. Nair and Joshua have reported mixed benzoic dithiocarbamic anhydrides as benzoylating reagents. Katritzky and coworkers have suggested N-acyl-benzotriazoles as useful acylating reagents for amines. 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. 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. The use of a base, pyridine in this case, was a necessity for the reaction of isothiocyanates with a phenolic hydroxyl group.

\[
\begin{align*}
R-C-N=C=S + \text{salicylamide} & \quad \xrightarrow{\text{pyridine, } \Delta, \text{4-5 h}} \quad (70-80\%) \\
& \quad \xrightarrow{-\text{HS-CN}} \\
\end{align*}
\]

\[\text{Scheme 34}\]

\[
\begin{align*}
\text{R} & = \text{Ph (86%), 2-MePh (74%), 3-MePh (79%), 4-MePh (83%), 4-MeOPh (80%), 4-Cl(Ph 75%), 4-O2NPh (73%)} \\
\end{align*}
\]

A 2:1 molar reaction of benzoyl isothiocyanates 1 with 1,2-phenylenediamines 104 in benzene afforded the corresponding \(N,N^\prime\)-bis(benzoylthiocarbamoyl)-1,2-phenylene diamines 105. 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. The intermediate product 107 leads to the formation of 2-arylbenzimidazoles 106 by...
dethiocyanation to intermediate product 108 and concomitant cyclodehydration.\textsuperscript{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.\textsuperscript{76}

\[
\text{R}_1\text{C}-\text{N}=\text{C}=\text{S} + \text{PhH, r.t.} \rightarrow \text{R}_2\text{N}=\text{C}=\text{S} + \text{NHCOR}_1 + \text{pyridine} \rightarrow \text{N=CHCOR}_1 + \text{H}_2\text{O}
\]

<table>
<thead>
<tr>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>75%</td>
</tr>
<tr>
<td>4-MeOPh</td>
<td>H</td>
<td>88%</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>H</td>
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</tr>
<tr>
<td>3-MePh</td>
<td>Me</td>
<td>82%</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>85%</td>
</tr>
<tr>
<td>3-MePh</td>
<td>Me</td>
<td>94%</td>
</tr>
<tr>
<td>4-MeOPh</td>
<td>Me</td>
<td>79%</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>Me</td>
<td>87%</td>
</tr>
</tbody>
</table>

Scheme 36

The reactivity of β-cyanoethylhydrazine 109 with aroyl isothiocyanates has been investigated by Elmoghayar and coworkers.\textsuperscript{20} This work has resulted in development of new efficient one-step synthesis of 5-thioxo-1,2,4-triazole derivatives. The reaction of benzoyl isothiocyanate 1 with β-cyanoethyl hydrazine 109 in dioxane at room temperature yielded the 5-thioxo-1,2,4-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).

\[
\text{O} \quad \text{R-C-N=C=S} + \text{H}_2\text{NNHNCH}_2\text{CH}_2\text{CN} \quad \text{dioxane} \quad \Delta, 3 \text{~h} \rightarrow \text{[PhC-NH-C=O]} \rightarrow \text{[PhC-NH-NH-CH}_2\text{CH}_2\text{CN]} \rightarrow \text{PhCONCS} \rightarrow \text{[PhN-C-CH}_2\text{CH}_2\text{CN]} \rightarrow \text{[PhN-C-NH-CH}_2\text{CH}_2\text{CN]} \rightarrow \text{[PhN-C-NH-COPh]} + \text{[PhCONCS]}
\]

Scheme 37
The reaction of acyl isothiocyanates with β-dicarbonyl compounds proceeds as C-thiocarbamoylation of the dicarbonyl component. For example, the formation of C-thiocarbamoylated derivatives of 1,3-cyclohexanedione or dimedone 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).

\[
\begin{align*}
R-C-N=C=S + & \quad \text{KOH, EtOH} \\
\text{(1 equiv.)} & \quad \text{-KSCN} \\
\to & \quad \text{113}
\end{align*}
\]

\[
\begin{align*}
R = \text{Ph, } R^1 = \text{H (76%)}; & \quad \quad \text{R = 4-ClPh, } R^1 = \text{H (61%)}; \\
R = \text{Ph, } R^1 = \text{Me (72%)}; & \quad \quad \text{R = 4-ClPh, } R^1 = \text{Me (63%)}; \\
R = \text{4-BrPh, } R^1 = \text{Me (60%)}; & \quad \quad \text{R = 4-MeOPh, } R^1 = \text{Me (65%)}
\end{align*}
\]

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. 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.

\[
\begin{align*}
R^1-C-N=C=S + & \quad \text{R^2-C-H} \\
\text{N\textsubscript{3}} & \quad \text{MeCN} \\
\text{(1 equiv.)} & \quad \text{r.t., 2 h} \\
\to & \quad \text{115}
\end{align*}
\]

\[
\begin{align*}
R^1 = \text{Ph} & \quad \quad R^2 = \text{Ph (64%), 4-MeOPh (81%), 4-BrPh (77%)}
\end{align*}
\]

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). 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.
3. Multicomponent Reactions of Acyl Isothiocyanates

In recent years, multicomponent reactions have acquired conspicuous popularity in design and synthesis of complex organic molecules. Acyl isothiocyanates have also been employed in multicomponent reactions to synthesize functionalized thiourea and heterocycles. A multicomponent reaction of benzoyl isothiocyanates, alkyl propiolates, secondary amines, and Ph₃P leading to an efficient synthesis of functionalized thioureas has been reported. 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. Initially a 1,3-dipolar intermediate was formed from Ph₃P and the acetylenic ester, which was subsequently protonated by the benzoyl thiourea, formed from addition of amine to aroyl isothiocyanates. A nucleophilic attack of the nitrogen atom of the conjugate base to the vinylphosphonium cation leads to the formation of an ylide, which is converted to products by elimination of Ph₃P.
Yavari and coworkers have described an equimolar reaction of benzoyl isothiocyanate 1, dialkyl acetylenedicarboxylates 134 and Ph₃P to afford the dialkyl 2-(benzoylimino)-5-phenyl-4H-[1,3]dithiol[4,5-b]pyrrole-4,6-dicarboxylates 135, with double insertion of the isothiocyanate, and dialkyl 2-phenyl-4-thioxo-4H-1,3-oxazine-5,6-dicarboxylates 136 in a 3:1 ratio (Scheme 43).87

Scheme 42

R = Ph
134. R¹ = Me, Et, tBu
r.t., 24 h

Scheme 43

R = Ph
134. R¹ = Me, Et, tBu
The plausible mechanistic rationalization suggests that the *zwitterionic* intermediate \( \text{137} \), formed from \( \text{Ph}_3\text{P} \) and dialkylacetylenedicarboxylates, adds onto the benzoyl isothiocyanate to furnish an intermediate \( \text{138} \), which then adds onto another molecule of benzoyl isothiocyanate to form another intermediate \( \text{139} \) (Scheme 44). This intermediate undergoes cyclization to furnish the fused structure \( \text{140} \) by the elimination of triphenylphosphine oxide. The pyrrole derivative \( \text{140} \) rearranges to the final product \( \text{135} \) by a carbon to nitrogen carboxyl transfer via the tricyclic intermediate \( \text{141} \). Formation of oxazinethiones \( \text{136} \) involves addition of the *zwitterionic* intermediate \( \text{137} \) to benzoyl isothiocyanate. The cyclization of intermediate \( \text{142} \) and subsequent elimination of \( \text{Ph}_3\text{P} \) leads to the formation of oxazines \( \text{143} \).

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.\(^8^8\) A three-component reaction of acyl isothiocyanates \( \text{1} \), ethyl bromopyruvate \( \text{144} \) 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 \( \alpha \)-halocarbonyl compounds.\(^{89} \) In this method, thiourea derivatives are formed \textit{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 \textit{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, arylisothiocyanates 1 and α-bromoketones 152 in an ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]Br as a solvent has been reported (Scheme 47). 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 H₂O.

**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 dibenzyloacetylene 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-dicarboxylates 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 C
N
C
S
O
1
NC
R1
2+
+ COR2
COR2
O
N
S
NR1
NR1
COR2
R2OC
R2 = OMe, OEt, OiPr, Ph
R1 = tBu, 1,1,3,3-tetramethylbutyl, 2,6-dimethylphenyl
CH2Cl2
r.t., 24 h

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).
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 H₂S from this heterocycle afforded the final product. The release of H₂S gas during the reaction progress was detected by turning a paper wet with lead acetate solution into black.

\[
\begin{align*}
\text{R-CN(C=S)NH₂CNNH₂} & \quad \text{MeCN} \\
\Delta, 3 \text{ h} & \quad \begin{cases}
\text{R-CN(C=S)NH₂CNNH₂} \\
\text{S-N=CS} \quad \text{R = CH₂Ph}
\end{cases}
\end{align*}
\]

Scheme 51

\[
\begin{align*}
\text{167} & \quad \text{R = Ph} (57\%), 4-\text{MePh} (62\%), 4-\text{MeOPh} (68\%), 4-\text{ClPh} (55\%), 4-\text{MeOCMePh} (54\%), \text{CH₂Ph} (66\%)
\end{align*}
\]

Scheme 52

\(\alpha,\beta\)-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-1-yl)-5,6-dihydro-4H-1,3-thiazin-4-ones 169. A nucleophilic addition of sodium hydrogen sulfide to isothiocyanate 167 affords two products, 6-(propen-1-yl)-2-thioxotetrahydro-4H-1,3-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, 1,2,4-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

The authors are grateful to the Chemistry Department, University of Botswana, Gaborone, Botswana, for providing the necessary facilities. KGB is thankful to the DAAD scholarship through NAPRECA.
7. References

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   http://dx.doi.org/10.1021/cr00001a001
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Kibrom G. Bedane was born in Addis Ababa, Ethiopia. He received his B.Sc. in 2000 from Bahir Dar University, Ethiopia and M.Sc. in Organic Chemistry from Addis Ababa University, Ethiopia in 2006. From 2002 to 2008 he was working as a Lecturer at the Department of Chemistry, Abiyi Addi College of Teacher Education, Ethiopia. Since 2009 he has been lecturing organic chemistry at the Department of Chemistry, Addis Ababa University. In 2011, he stayed for three months at Spiez Laboratory, Switzerland, with OPCW internship program: Internship for organic chemistry skills development. The internship was on synthesis of compounds related to precursors, degradation products and by-products of chemical weapon agents. Currently, he is a Ph.D. student at the Chemistry Department of the University of Botswana with DAAD (the German Academic Exchange Service) scholarship through the Natural Products Research Network for Eastern and Central Africa (NAPRECA). His current research work involves phytochemical investigations of medicinal plants and organic synthesis.