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Convenient and simple synthesis of 2-aminothiazoles by the reaction of α-halo ketone carbonyls with ammonium thiocyanate in the presence of *N*-methylimidazole

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ABSTRACT

Substituted 2-aminothiazole derivatives were obtained as a result of *N*-methylimidazole catalyzed cyclization of α-halo ketone carbonyls with ammonium thiocyanate in water–alcoholic media. The generality of the method has been demonstrated by screening a series of aromatic/heteroaromatic/aliphatic α-halo ketones, α-halo β-diketones, and α-halo β-ketoesters. The developed method is simple, mild, and general route for the preparation of diversely functionalized 2-aminothiazoles in good to moderate yields from readily available starting materials.

Natural and synthetic molecules containing thiazole structural motifs are very well known for their broad spectrum of biological activities.[1–5] Particularly, 2-aminothiazoles have been reported to possess antitumor,[6] antiviral,[7] antibacterial,[8] antiprion,[9] and psychotropic activities.[10] Beside this, 2-aminothiazole scaffolds were successfully employed as an adenosine receptor antagonist,[11] as well as heterocyclic bioisosteres of the phenol moiety on dopamine agonists and anti-Parkinsonian agent, pramipexole.[12] Recently, 2-aminothiazole analogue MB06322 is identified as a prodrug for the treatment of type 2 diabetes[13] and 2-aminothiazole-4-carboxylate derivatives as active compounds against *Mycobacterium* tuberculosis H37Rv and the β–ketoacyl–ACP synthase mtFabH[14] (Fig. 1). In addition, the conjugated polyaminothiazole films have been reported to display electrochemical properties with high thermal stability.[15] Along with this, the sulfur-containing aromatics are also attractive candidates for organic semiconductors[16] and can act as unique co-ordination compounds for electronic, magnetic, and optical materials.[17,18]

Due to such a prevalence and prominence of 2-aminothiazoles moiety, many synthetic protocols have been reported which includes Hantzsch's cyclocondensation of thiourea with α-haloketones/α-tosylketone[19] and the reactions of α-thiocyanate carbonyl compounds with aromatic or aliphatic amine hydrochlorides.[20] They are also synthesized by one-pot reaction of enolizable ketones with a mixture of *N*-bromosuccinimide, thiourea, and benzoyl peroxide.[21]

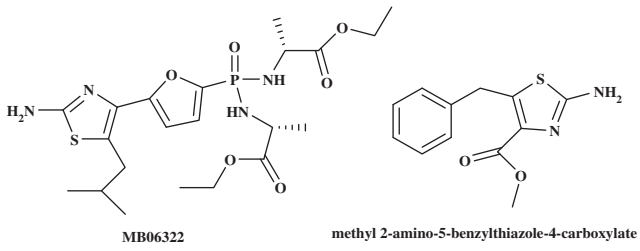

Figure 1. Representative examples of biologically active 2-aminothiazole derivative.

In continuation of our efforts in the development of novel and eco-friendly protocols to synthesize biologically active molecules,[22] we have discovered a new method for the synthesis of highly substituted 2-aminothiazoles by the reaction of α-halo ketone carbonyls with ammonium thiocyanate. Despite some excellent methods have been published which are mild and high yielding[19f,g], our method holds a tag of novel route which first time utilizes the ammonium thiocyanate as both source of ammonia and thiocyanate ion in a one pot reaction sequence. To the best of our knowledge, there is no report concerning single step synthesis of 2-aminothiazole by the reaction of ammonium thiocyanate with α-halo ketone carbonyls. In this Letter, we wish to describe our preli-

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minary result about *N*-methylimidazole catalyzed direct synthesize of highly substituted 2-aminothiazoles in water-alcoholic media. The current observation demonstrates the extended utility of ammonium thiocyanate salt in the exploratory synthesis of highly functionalized 2-aminothiazole-4-carboxylate derivatives.

The initial purpose of this research was to develop a method to synthesize the phenacyl thiocyanates by the reaction of phenacyl bromide with ammonium thiocyanate in the presence of imidazole. Our study started with the reaction between phenacyl bromide (1 mmol) and ammonium thiocyanate (1 mmol) in the presence of imidazole (0.1 mmol) in 5 ml methanol at rt and the selected results are summarized in Table 1. The progress of the reaction was monitored by TLC. After 15 min of stirring we have observed the complete consumption of phenacyl bromide and appearance of only one slightly polar compound on TLC (R_f = 0.64, 20% EtOAc/hexanes in 3 time run). The reaction mixture was subjected to column chromatography and pure isolated compound was taken for spectral analysis. ^{1}H NMR spectrum of compound exhibited characteristic singlet at δ 4.75 ppm corresponds to the two hydrogens attached to carbon between carbonyl and SCN group, ^{13}C NMR shows peak at δ 111.8 ppm for carbon of SCN group. FT-IR spectrum exhibits sharp absorption at 2155 cm^{-1} while mass spectrum exhibited [M+H] peak at m/z = 178. On the basis of spectral data, the structure of isolated compound was assigned as phenacyl thiocyanate.

Unexpectedly, the next reaction between phenacyl bromide and ammonium thiocyanate in the presence of imidazole in methanol was performed for a longer time (2 h). TLC showed the complete consumption of phenacyl bromide and exhibited the formation of two new compounds on TLC approximately in 1:1 area ratios. In comparison with the polarity of phenacyl bromide on TLC (R_f = 0.85, 20% EtOAc/hexanes in a 3 time run), one compound was slightly polar (R_f = 0.64, 20% EtOAc/hexanes in a 3 time run) and another was much polar (R_f = 0.35, 20% EtOAc/hexanes in a 3 time run). From the available authentic sample of previous reaction, slightly polar compound was confirmed as phenacyl thiocyanate. The more polar compound was isolated by column chromatography and taken for spectral characterization. According to the literature,[20] 2-aminothiazole ring can be obtained by the reaction of α-thiocyanate carbonyl compounds with amines. Hence we guessed the isolated polar compound as 4-phenyl-2-aminothiazole which might have formed by the reaction between in situ generated ammonia and phenacyl thiocyanate under the influence of imidazole.

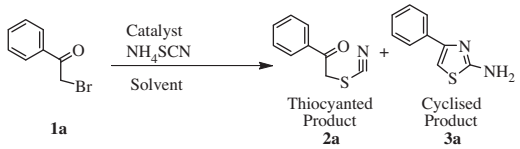
The FT-IR spectra of the isolated polar compound showed the broad peak at 3432 cm^{-1} which corresponds to the primary amino group and does not show any absorption in the range of carbonyl and thiocyanate functionality. The ^{1}H NMR spectrum exhibited a sharp singlet at δ 6.65 ppm and broad singlet at δ 5.21 ppm corresponding to the one hydrogen of thiazole ring at C-5 and two hydrogens of amino group attached to C-2, respectively. Whereas in the ^{13}C NMR spectrum, the signals, respectively at δ 101.8 and 167.6 ppm correspond to C-5 and C-2 of thiazole ring was visible. The mass spectrum exhibited a molecular ion peak [M$^+$] at m/z = 176 for $C_9H_8N_2S$. Based on the analysis of the spectral data, the structure of compound was assigned as 4-phenyl-2-aminothiazole. The assigned structure was also confirmed by comparison with the spectral data obtained for an authentic sample prepared by available literature procedure.[19a]

The above observations reveal that the 4-phenyl-2-aminothiazole can be obtained by the reaction of phenacyl bromide with ammonium thiocyanate in the presence of imidazole in methanol

Table 1
Optimization of reaction condition for the synthesis of 4-phenyl-2-aminothiazole

Entry	Solvent	Catalyst (mol%)	Time	Conversion[a] of phenacyl bromide **1a** (%)	Yield[a] of thiocyanated product **2a** (%)	Yield[a] of cyclized product **3a** (%)
1	MeOH	Imidazole (10)	15 min	100	100	0[b]
2	MeOH	Imidazole (10)	2 h	100	48	52[b]
3	MeOH	Imidazole (10)	2 h	100	37	63
4	EtOH	Imidazole (10)	2 h	100	3	65
5	^{i}PrOH	Imidazole (10)	2 h	100	30	70
6	CH_3CN	Imidazole (10)	2 h	100	33	67
7	H_2O	Imidazole (10)	2 h	92	29	71
8	MeOH:H_2O	Imidazole (10)	2 h	100	28	72
9	EtOH:H_2O	Imidazole (10)	2 h	100	26	74
10	^{i}PrOH:H_2O	Imidazole (10)	2 h	100	22	78
11	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	14	86
12	^{i}PrOH:H_2O	Imidazole (10)	1.2 h	100	31	69
13	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	14	86
14	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	15	85
15	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	28	72
16	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	15	85[c]
17	^{i}PrOH:H_2O	*N*-Methylimidazole (10)	1.2 h	100	13	87[d]
18	^{i}PrOH:H_2O	DMAP (10)	1.2 h	91	81	19
19	^{i}PrOH:H_2O	DABCO (10)	1.2 h	97	91	09
20	^{i}PrOH:H_2O	TEA (10)	1.2 h	99	87	13
21	^{i}PrOH:H_2O	DIPEA (10)	1.2 h	97	89	11
22	^{i}PrOH:H_2O	DBU (10)	1.2 h	94	68	32
23	^{i}PrOH:H_2O	DBN (10)	1.2 h	88	66	34
24	^{i}PrOH:H_2O	—	2 h	98	93	07

[a] By ^{1}H NMR analysis.
[b] Except this all reactions were carried out in closed condition.
[c] With 2 equiv of ammonium thiocyanate.
[d] At 100 °C.



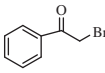
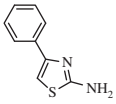
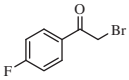
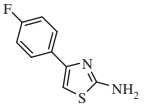
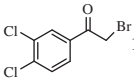
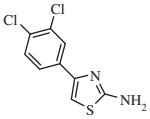
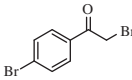
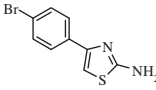
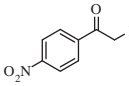
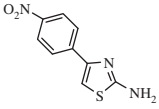
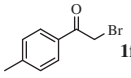
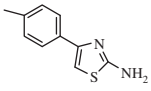
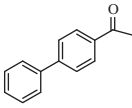
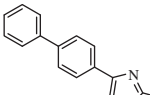
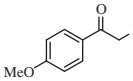
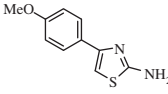
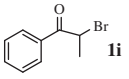
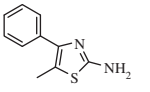
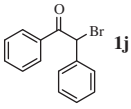
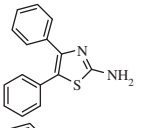
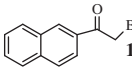
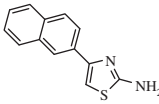
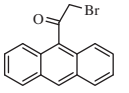
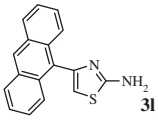
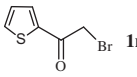
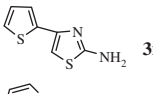
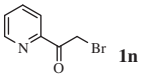
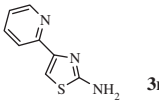
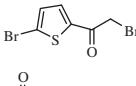
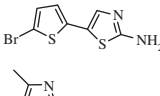
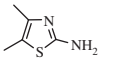
Scheme 1. Optimization of reaction condition for the synthesis of 4-phenyl-2-aminothiazole.

at rt. Previous literature shows the formation of only thiocyanated product[23] **2a** by the reaction of phenacyl bromide with ammonium thiocyanate. The literature does not show any report regarding the sequential use of ammonium thiocyanate as source of both SCN and NH_3 for the synthesis of 2-aminothiazole in one pot reaction. Encouraged by our observations, next we planned to study the reaction in detail to establish the optimized reaction condition to get maximum yield of 4-phenyl-2-aminothiazole **3a** (Scheme 1).

To avoid possible loss of ammonia from the reaction media, we have carried out the reaction in a closed vessel and observed an increase in yield of the desired product. To choose an appropriate solvent for a particular reaction is not a simple issue.[24] Keeping in mind the solubility of ammonium thiocyanate salt, different polar solvents were screened and the results are included in Table 1. Water is an attractive option from an environmental point of view[25] and its ability to enhance the rates and affect the selectivity in various organic transformations due to high hydrogen bonding ability.[26] Hence we also attempted water as solvent for the model reaction. Result shows overall decrease in the yield of reaction but showed some increase in the selectivity of the desired product (Table 1, entry 7). As the use of an aqueous mixture of solvents was found to be advantageous in some organic processess,[27] we tried some 1:1 mixture of solvents and results were encouraging. We observed a noticeable increase in the selectivity of the desired product with the mixture of solvents. After examining various solvent systems, the best result was obtained with 1:1 mixture of ^{i}PrOH:H_2O (Table 1, entry 10). When imidazole was replaced with *N*-methylimidazole, the enhancement in selectivity and rate of reaction was observed (Table 1, entry 11). Other similar bases like 4-dimethylaminopyridine (DMAP), 4-diazabicyclo[2.2.2]octane (DABCO), triethylamine (TEA), diisopropylethylamine (DIPEA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) showed adverse effect on the selectivity of desired product and hence eliminated from further study. Further we screened *N*-methylimidazole with different mol% and delighted to find that the 10 mol % catalyst is sufficient to catalyze the present reaction effectively. There was not much improvement observed in the yield of desired product, even if we doubled the amount of ammonium thiocyanate (Table 1, entry 16). Further to improve the selectivity of the cyclized product, the model reaction was also tested at a higher temperature (100 °C), but significant increase in selectivity was not observed (Table 1, entry 17). It was also found that, the conversion in model reaction was not complete. The exact reason for this is not well understood. But, we assume that, this might be due to the less availability of free NH_3 required for cyclization because of the possible formation of ammonium bromide during the reaction.[29] Control reaction without *N*-methylimidazole in ^{i}PrOH:H_2O (1:1) was also performed which gave very trace amount of the desired cyclized product (Table 1, entry 24). On the basis of the above study, we have chosen ^{i}PrOH:H_2O (1:1) as solvent system and *N*-methylimidazole (10 mol %) as catalyst as the set of optimized condition for the synthesis of 4-phenyl, 2-aminothiazole at rt (Table 1, entry 11).

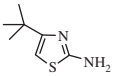
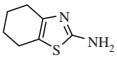
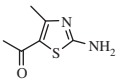
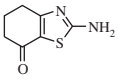
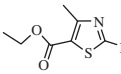
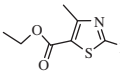
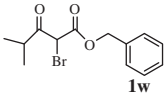
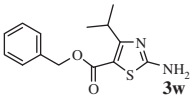
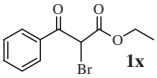
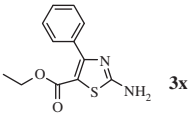
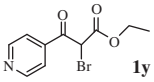
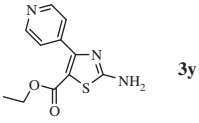
For the general validity of the reaction, the optimized reaction was tested on several structurally varied α-halo ketone carbonyl components and results are summarized in Table 2 (Scheme 2).

Table 2
Synthesis of highly substituted 2-aminothiazoles by using optimized reaction condition[a]

Entry	Reactant	Time (h)	Product	Yield[b] (%)
1	 **1a**	1.2	 **3a**	84
2	 **1b**	1.2	 **3b**	79
3	 **1c**	1.5	 **3c**	84
4	 **1d**	1.5	 **3d**	82
5	 **1e**	1	 **3e**	88
6	 **1f**	1.2	 **3f**	74
7	 **1g**	1.2	 **3g**	81
8	 **1h**	1.5	 **3h**	78
9	 **1i**	1.5	 **3i**	78
10	 **1j**	1.5	 **3j**	78
11	 **1k**	1.2	 **3k**	86
12	 **1l**	1.2	 **3l**	82
13	 **1m**	1.5	 **3m**	73
14	 **1n**	2	 **3n**	68
15	 **1o**	1.5	 **3o**	71
16	 **1p**	2	 **3p**	74

(*continued on next page*)

Table 2 (*continued*)

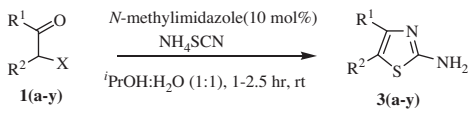
Entry	Reactant	Time (h)	Product	Yield[b] (%)
17	 **1q**	2.2	 **3q**	73
18	 **1r**	2.5	 **3r**	69
19	 **1s**	1.2	 **3s**	78
20	 **1t**	2	 **3t**	57
21	 **1u**	1.2	 **3u**	69
22	 **1v**	1.2	 **3v**	67
23	 **1w**	1.8	 **3w**	67
24	 **1x**	2	 **3x**	79
25	 **1y**	2	 **3y**	73

[a] Reaction condition: all the reactions were carried out with α-halo ketone carbonyls (1 mmol), ammonium thiocyanate (1 mmol) in the presence of *N*-methylimidazole (0.1 mmol) in ^{i}PrOH:H_2O (1:1).

[b] Isolated yields.

Variety of substituted aryl α-halo ketone carbonyls **1**(**a–l**) underwent smooth cyclization under optimized condition to give the desired product in good yield (Table 2, entries 1–12). Fused ring α-halo ketone carbonyls like, 2-bromo-1-(naphthalen-6-yl)ethanone (**1k**) and 1-(anthracen-10-yl)-2-bromoethanone (**1l**) also gave their respective cyclized product in high yield and within short time (Table 2, entry 11, 12). It is noteworthy that different heteroaryl α-bromo ketones **1**(**m–o**) also gave desired product in moderate yields under optimized condition (Table 2, entry 13–15). Desired 2-aminothiazole product can also be obtained for different α-substituted, α-bromo ketones like **1i** and **1j**. Generality of the procedure is further strengthened by examining the aliphatic α-bromo ketones which gave their respective product in good to moderate yields (Table 2, entry 16–18).

As a logical extension, we investigated the scope and limitations of this method for the cyclization of α-halo β-dicarbonyl compounds. Different structurally varied α-bromo/chloro β-dicarbonyls **1**(**s–y**) reacted smoothly with ammonium thiocyanate in the presence of catalytic amount of *N*-methylimidazole to furnish highly substituted 2-aminothiazoles in good to moderate yield. It is worth to mention that, fused 2-aminothiazole like **3r** and **3t** can also be obtained in moderate yield with our method. Similarly, aromatic and heteroaromatic α-bromo β-ketoesters also underwent cyclization to give desired product in good yield (Table 2, entry 24, 25).



R^1 = -Aromatic, -Heteroaromatic, -Aliphatic, X = -Br, -Cl
R^2 = -H, -CH_3, -Ph, -$COCH_3$, -COOEt, -$COOCH_2$Ph

Scheme 2. Synthesis of highly substituted 2-aminothiazoles by using optimized reaction condition.

In conclusion, the reactions of α-halo ketone carbonyls with ammonium thiocyanate in the presence of catalytic *N*-methylimidazole result in one-pot synthesis of 2-aminothiazole derivatives via α-thiocyanate carbonyl compounds. The discovery and development of this method[30] led to a general route for the preparation of diversely functionalized 2-aminothiazoles in good to moderate yields from readily available starting materials. The described method first time utilizes ammonium thiocyanate as both source of ammonia and thiocyanate ion for the synthesis of 2-aminothiazoles in one pot reaction sequence in water-alcoholic media. In addition to its simplicity, mild reaction condition and a wide scope of substrates are the distinct features of this protocol. Further studies on the scope and limitations of this reaction are in progress.

Acknowledgments

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30. *Typical procedure for the synthesis of 2- aminothiazoles*: To a stirred solution of α-halo carbonyl (1.0 mmol) and *N*-methylimidazole (0.1 mmol) in 5 ml ^{i}PrOH:H_20 (1:1) was added ammonium thiocyanate (1 mmol). The reaction flask was closed and the reaction mixture was vigorously stirred at room temperature for the stipulated time (Table 2). After the desired product formation indicated by TLC, the reaction mixture was poured on 10 mL ice cold water and extracted with dichloromethane (3 × 5 mL), washed with brine (10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. Na_2SO_4 was filtered off and solvent was evaporated in rotary vacuum evaporator to obtain the crude products. Crude products were further purified by silica gel column chromatography (100–200 mesh) using ethyl acetate:hexane (1:3 to 1:4) as eluent to obtain the corresponding pure products. All the compounds were characterized by spectral analysis techniques. 2-Aminothiazole derivatives are well documented in the literature with their characterization data. The obtained data for all synthesized compounds were in good agreement with the documented data in the literature. The characterization data for new compound *4-(anthracen-9-yl)-thiazol-2-amine (3l,* Table 2, Entry 12**)** are given. The title compound was prepared according to the typical procedure given above with 82% yield in 1.2 h. R_f(20% EtOAc/hexanes in 3 times run) 0.34; Yellow solid. mp 223–225 °C; ^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 8.44 (s, 1H), 7.99–7.93 (m, 4H), 7.45–7.35(m, 4H), 6.62 (br s, 2H), 6.49 (s, 1H) ppm. ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 169.8, 149.2, 138.19, 130.46, 128.59, 127.81, 126.82, 125.80, 125.44, 123.99, 100.98 ppm. IR(KBr): = 3432, 3111, 2923, 2856, 1654, 1596, 1522, 1483, 1335, 1030, 712 cm^{-1}. MS (ESI): m/z = 299 $[M+Na]^+$.