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Metal-Free One-Pot Chemoselective Thiocyanation of Imidazothiazoles and 2-Aminothiazoles with in situ Generated *N*-Thiocyanatosuccinimide

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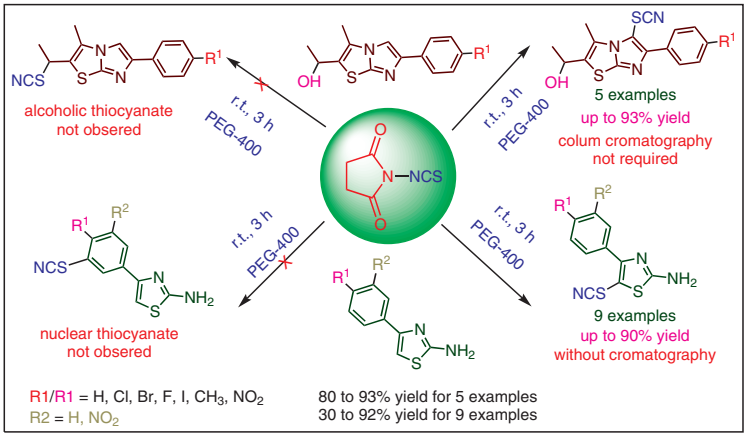

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Abstract A chemoselective thiocyanation of imidazothiazoles and 2-aminothiazoles with use of in situ generated *N*-thiocyanatosuccinimide (NTS) at room temperature is described. The protocol offers mild reaction conditions and high chemoselectivity for electrophilic substitution in imidazothiazoles over nucleophilic substitution. This method provides metal-free and easy conversion of imidazothiazoles and 2-aminothiazoles into their corresponding C-3 and C-5 thiocyanates, respectively, in good to excellent yield. The present protocol also offers the effective thiocyanation of bifunctional imidazothiazoles containing aliphatic –OH and C(sp^2)–H bond functionalities.

Keywords *N*-thiocyanatosuccinimide, thiocyanation, imidazothiazoles, 2-aminothiazoles, PEG-400

Thiocyanates are considered as one of the most versatile synthons in the field of organic chemistry. They have proved their potency as crucial synthetic intermediates in the synthesis of various sulfur-containing heterocycles such as sulfides,[1] thiocarbamates,[2] sulfanyl pyridines,[3] and thiotetrazoles.[4] The intriguing properties of thiocyanate have been utilized for the synthetic transformation of useful functionalities such as aryl nitriles,[5] sulfonyl cyanides,[6] thiazoles,[7] thioesters,[8] imidazoles,[9] and so on. The thiocyanation reaction is one of the most significant protocols for direct C–S bond formation.[10] Consequently, enormous efforts have been made in order to achieve thiocyanation of various heterocyclic compounds.[11] In the midst of various proceedings for thiocyanation of aryl and heteroaryl compounds, incorporating thiocyanate (SCN) particularly into C–H functionalities has always been a center of interest because of its own advantages.[12] For accomplishing this goal several approaches have been encountered (i.e. use of iodinated reagents,[13] oxidants,[14] and brominating agents[15]) in combination with readily available, low-cost thiocyanate salts as thiocyanating agents. But these strategies are mainly focused on imidazopyridines and indoles.[16] Furthermore, the selectivity of direct electrophilic thiocyanation of C(sp^2)–H bonds over nucleophilic substitution by alcoholic –OH, when both groups are present in same compound, by using *N*-thiocyanatosuccinimide (NTS) as a reagent, has not been studied previously.

Imidazothiazoles are considered a significant class of heterocyclic compounds. For example, levamisol and tetramisole, known for their antihelminthic and immunomodulatory properties, respectively, display an imidazothiazole core (Figure 1). The majority of imidazothiazoles exhibit a wide range of biological activities.[17] Thiazoles are structurally very close to imidazoles, with the only difference of sulfur replaced by nitrogen. Vitamin B (thiamin) (Figure 1) is an important naturally occurring vitamin which contains the thiazole ring as an active center involved in various biological processes. Thiazoles are considered to be one of the most compelling heterocyclic compounds because of their broad spectrum of biological activities.[18] Considering these consequential advantages, immense efforts have been made for the synthesis of imidazothiazoles and thiazoles.[19] Introduction of new functional groups into these moieties may modify their biological profile or may imbed new biological activities. For this purpose, direct C-3 and C-5 functionalization of imidazothiazoles and thiazoles, respectively, provides an acceptable strategy.

Conversion of alcohols to their corresponding alkyl thiocyanates or alkyl isothiocyanates has been extensively studied.[20] Recently, Mokhtari et al. reported one-pot thio-

cyanation or isothiocyanation of alcohols by using in situ generated NTS. Thus, existing methods were focused on either thiocyanation of C(sp^2)–H bonds or thiocyanation of alcohols to alkyl thiocyanates or alkyl isothiocyanates. However, chemoselectivity for C-3 electrophilic thiocyanation over nucleophilic substitution at the alcoholic –OH group in imidazothiazoles, when both the possibilities are present in one motif, would be an important synthetic route for medicinal chemistry research. Encouraged by our previous work on the thiocyanation of 2-aminothiazoles,[21] we herein report an efficient, practical, and metal-free approach for the one-pot conversion of functionalized imidazothiazoles and 2-aminothiazoles into their corresponding C-3 and C-5 thiocyanates, respectively. Use of easily accessible NH_4SCN, in situ generated NTS as the reagent, and PEG-400 as the solvent makes the protocol more accessible and efficient (Scheme 1).

We initiated our study on the synthesis of the target compounds by taking 1-(6-(4-chlorophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanol **1a** (Table 1) as the model substrate. In order to investigate the ideal reaction conditions (Table 1), initially, NBS (1.0 mmol) and NH_4SCN (2.0 mmol) were stirred at room temperature (r.t.) in CH_3CN (3 mL) for 15 minutes to induce in situ generation of NTS. Deliberate addition of reactant **1a** (1 mmol) to this reagent led to formation of product **2a** in 80% yield after three hours (Table 1, entry 1). Remarkably, thiocyanation or isothiocyanation of the alcoholic –OH group was not obtained for any derivative **X**, **Z** (Scheme 1) by the nucleophilic substitution route. Enthused by these results, the effect of other solvents such as DMSO, DMF, H_2O, CH_2Cl_2, THF, CH_3OH, and $CHCl_3$ was tested (Table 1, entries 3–9). In search of a "green" solvent for the reaction[22] we preferred to test PEG-400 as a solvent. Interestingly, the best results (93%) were obtained in PEG-400 (Table 1, entry 2). When NCS was employed for the in situ generation of NTS, the formation of the product resulted in a slight decrease in yield with increasing reaction time (Table 1, entry 3). This observation may be related with the fact that Br is a better leaving group than Cl. Thus, formation of NTS may take place faster with NBS rather than with NCS. Other reagent and solvents, such as HIO_3 in methanol and HIO_3 in PEG-400 as solvent were also examined (Table 1, entries 17 and 18); both of these combinations resulted in poor yields. Product formation of was not observed without the use of reagent (Table 1, entry 11). When NBS was used as a reagent for bromination at the C-3 position of imidazothiazole followed by thiocyanation with NH_4SCN, this approach was shown to take more time (24

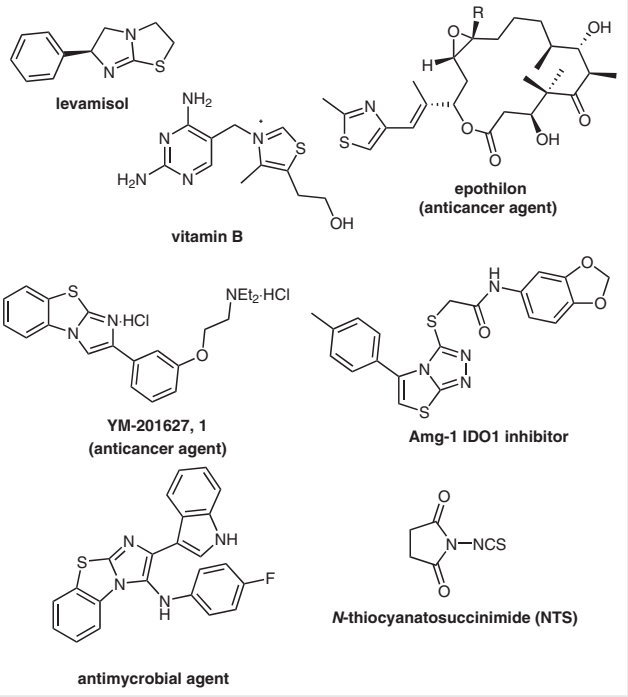
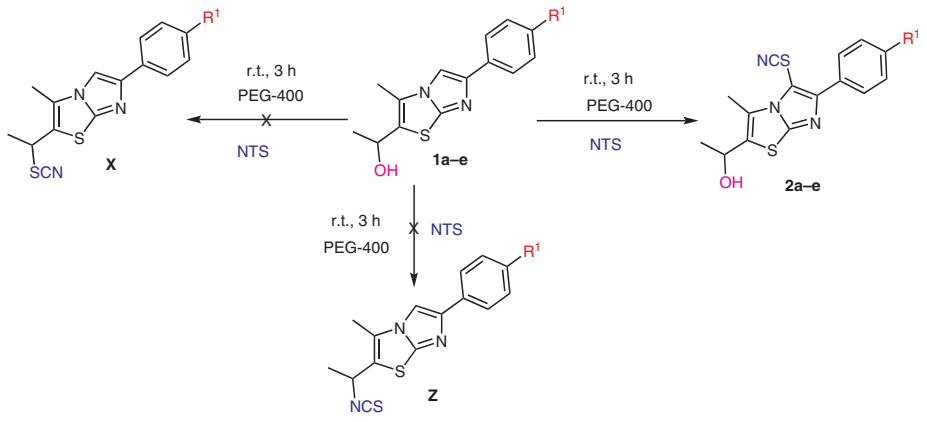


Figure 1 Some important compounds containing imidazothiazole and thiazole as a core structure

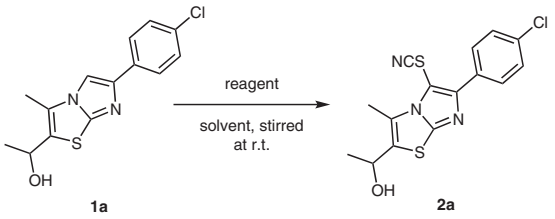


Scheme 1 Thiocyanation of imidazothiazole

hours) with decreased yield of product (75%) (see below Scheme 5, c and Table 1, entry 12). Furthermore, the yield of the reaction decreased when (4.0 mmol) of NH_4SCN was used (Table 1, entry 13). The decrease in the quantity of NH_4SCN also decreased the yield of the product (Table 1, entry 14). We also tested $K_2S_2O_8$ for the same reaction with PEG-400 as the solvent; the reaction took a longer time of 20 hours and resulted in a nonseparable trace amount of product (Table 1, entry 19). The formation of product also decreased when NH_4SCN was replaced by KSCN or NaSCN (Table 1, entries 15 and 16). Finally, the optimized reaction conditions were achieved when NBS (1.0 mmol) and NH_4SCN (2.0 mmol) were stirred at room temperature in PEG-400 (3 mL) for 15 minutes to initiate the in situ generation of *N*-thiocyanatosuccinimide. Following slow addition of **1a** (1.0 mmol) (Table 1, entry 2) led to formation of the product in optimal yield of (93%) by stirring at room temperature for three hours. The product could be obtained in analytically pure form upon washing with cold aqueous ethanol, thus avoiding the use of tedious purification by column chromatography. A gram-scale reaction was also performed by using NBS (0.01 mol), NH_4SCN (0.02 mol), and reactant **1a** (0.01 mol). In this case, the product yield observed was 75%. Having the optimized reaction conditions in our hand, we further investigated the scope of substrates (Scheme 2). The method was compatible with the tested substrates, and most of the substrates afforded the product in good yields. It is clear from Scheme 2 that halogen substituents at R^1 lead to good yields. Compound **2a** (Scheme 2) with a chloro substituent was obtained in excellent (93%) yield, the highest amongst all derivatives. Product **2d** (Scheme 2) with an electron-donating group at R^1 was isolated in moderate yield.

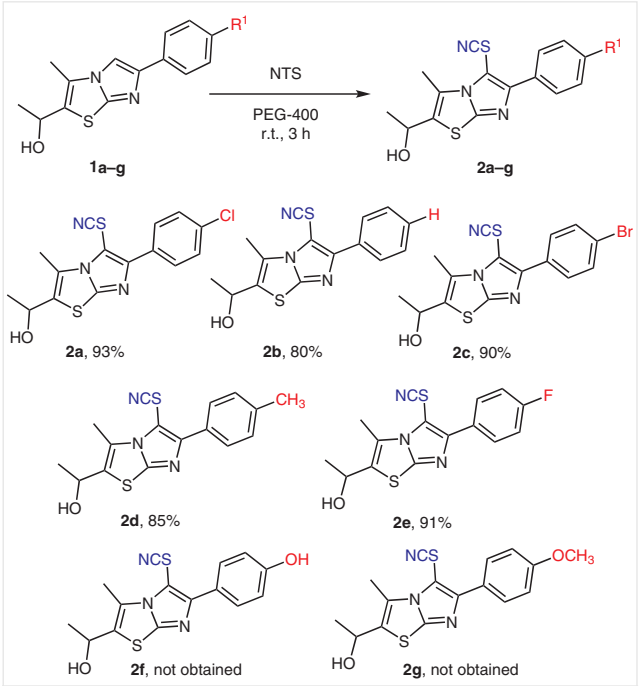
It is notable that no derivative gave alkyl thiocyanate or alkyl isothiocyanate by nucleophilic attack of the alcohol on in situ generated NTS[20a] (Scheme 1). Furthermore, derivatives with hydroxy and methoxy substituents at R^1 were not able to provide the desired product. The probable reason for the deleterious behavior of these derivatives may be positive mesomeric effect of the electron-donating substituents, due to which they were unable to furnish the product.

Table 1 Optimization of the Reaction Conditions[a]

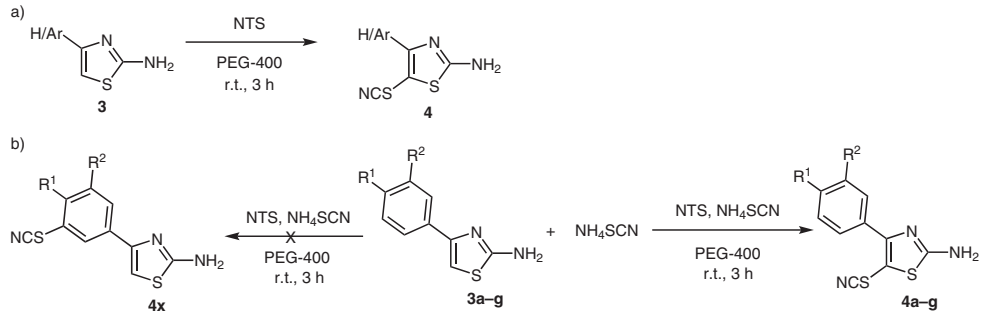


Entry	Reagent	Solvent	Yield (%)
1	NTS	CH_3CN	80
2	NTS	PEG-400	93
3[b]	NTS	PEG-400	80
4	NTS	DMSO	78
5	NTS	DMF	50
6	NTS	H_2O	trace
7	NTS	CH_2Cl_2	75
8	NTS	THF	50
9	NTS	MeOH	70
10	NTS	$CHCl_3$	80
11	–	CH_3CN	n.r.
12	NBS	PEG-400	75
13[c]	NTS	PEG-400	70
14[d]	NTS	PEG-400	69
15[e]	NTS	PEG-400	60
16[f]	NTS	PEG-400	60
17	HIO_3	MeOH	50
18	HIO_3	PEG-400	40
19	$K_2S_2O_8$	PEG-400	trace

[a] *Reaction conditions* (unless otherwise specified): **1a** (1.0 mmol), NH_4SCN (2.0 mmol), solvent (3mL), 3 h, r.t.; n.r. = no reaction.
[b] NCS was employed for in situ generation of NTS.
[c] NH_4SCN (4.0 mmol) was used.
[d] NH_4SCN (1.0 mmol) was used
[e] KSCN (2.0 mmol) was used.
[f] NaSCN (2.0 mmol) was used.



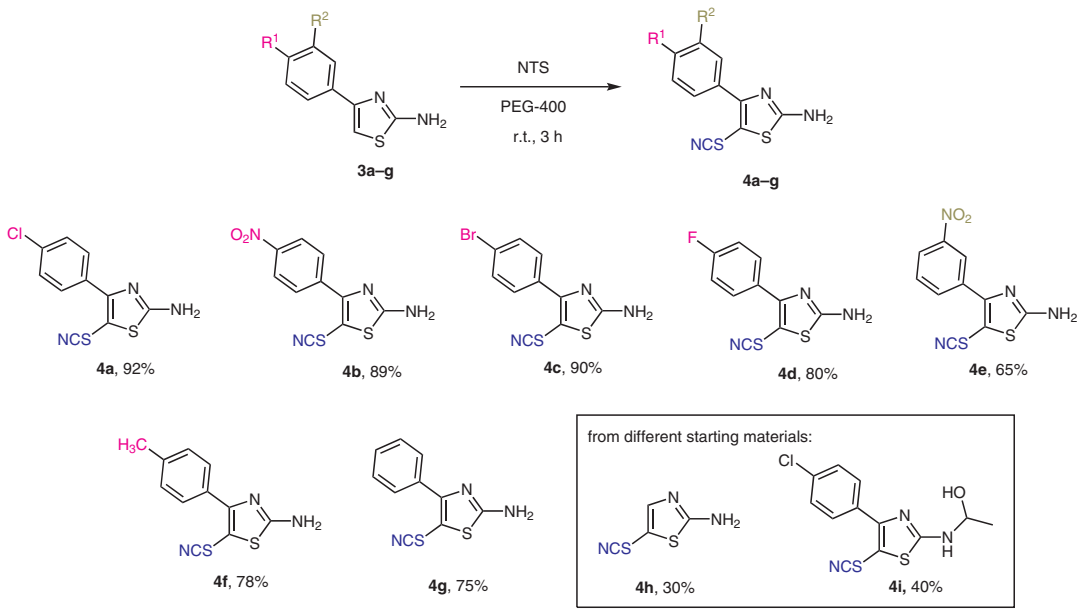
Scheme 2 Scope of substrates: Variation of substituents on imidazothiazole. *Reaction conditions*: NBS (1.0 mmol) NH_4SCN (2.0 mmol), substituted imidazothiazole **1a–g** (1 mmol), PEG-400 (3 mL), 3 h. Isolated yields are given.



Scheme 3 Thiocyanation of 2-aminothiazoles

A similar type of thiocyanation reaction was also tried on 2-aminothiazole and, in accordance to other methods reported in literature (Scheme 3),[24] the obtained product yield was poor (30%) (Scheme 4, compound **4h**). When we tried the present protocol with aryl-substituted thiazoles, the yield of the corresponding products was satisfactory. This indicates that the aryl group present on the 2-aminothiazole ring is activating the substrate for the electrophilic substitution. To prove the generality of the present methodology, we tried C-5 thiocyanation of 2-aminothiazoles (Scheme 3). Electron-withdrawing substituents such as halogens, proved to facilitate the reaction leading to formation of the products in good yield, amongst which compound **4a** (Scheme 4) was obtained with a maximum yield of 92%. Derivatives with electron-donating groups (Scheme 4) furnished the products (such as **4f**) with moderate yield. Furthermore, methyl substitution at R^1 (product **4f**) (Scheme 4) did not lead to nuclear thiocyanation in *ortho* position to the donating group (**4x**) (Scheme 3)[21]. Substitution at *meta* position, R^2, (Scheme 4) delivered the product in poor yield (product **4e**). Reactions for substrates with hydroxy and methoxy substituents were unable to provide the products; this behavior may be justified by the presence of a strong positive mesomeric effect, which may result in inability to form product. The method was further explored for its generality on a new substrate containing an alcoholic group, which led to moderate yield (product **4i**) (Scheme 4).

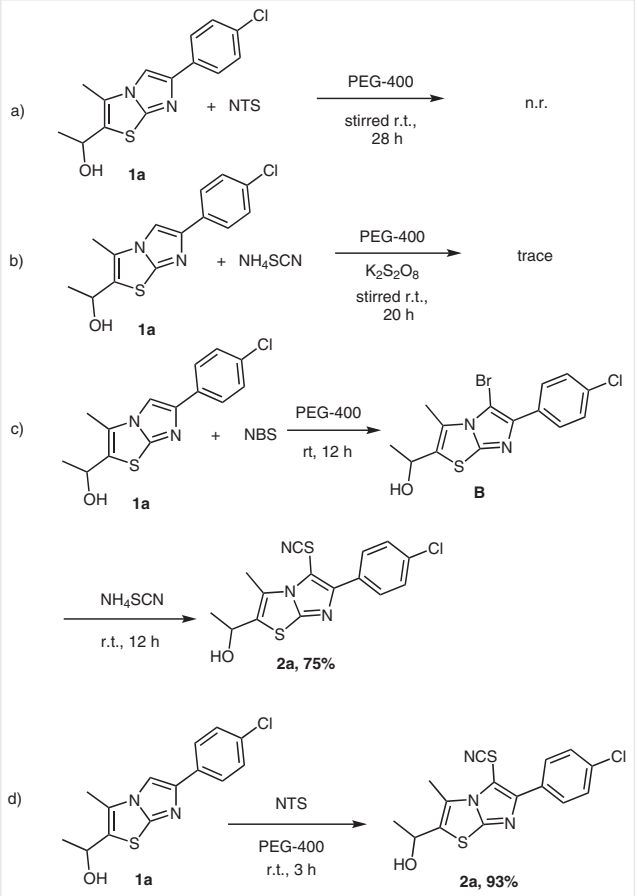
A probable mechanistic path was further studied by taking few other methods into account for control experiments by using the reactions depicted in Scheme 5. It comes to our notice that the reaction did not proceed in the absence of any reagent even after 28 hours (Scheme 5, a). We also tried to use $K_2S_2O_8$ for thiocyanation of these sub-



Scheme 4 Scope of substrates for 2-aminothiazoles. *Reaction conditions*: NBS (1.0 mmol) NH_4SCN (2.0 mmol), substituted 2-aminothiazole **3a–i** (1 mmol), PEG-400 (3 mL), 3 h. Isolated yields are given.

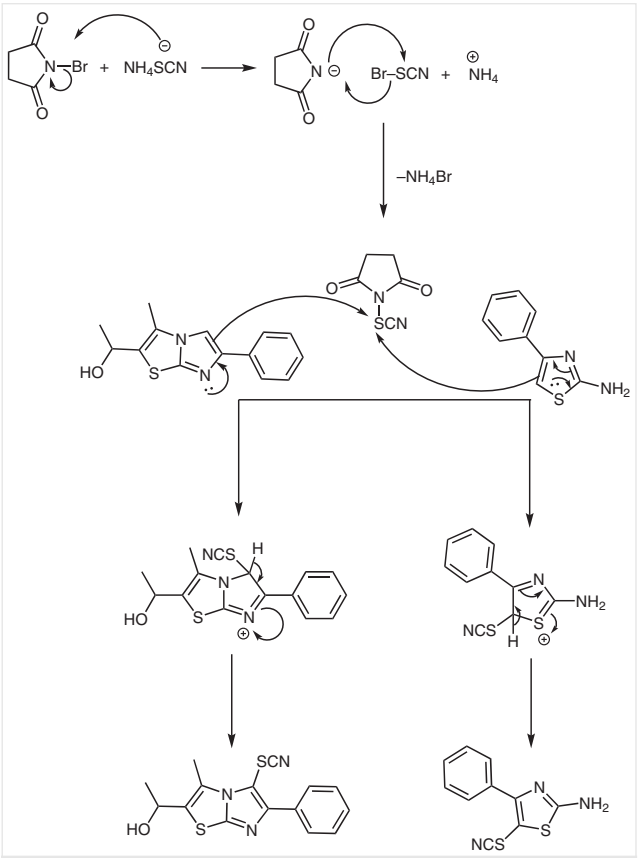
strates using PEG-400 as the solvent; however, only a non-separable trace amount of product was formed after a prolonged period of 20 hours (Scheme 5, b). When the reaction was performed with use of NBS as a reagent it required a prolonged period of 24 hours for the formation of product in 75% of yield indicating that bromination was followed by the thiocyanation approach (Scheme 5, c). It was also observed that some amount of reactant was converted into the corresponding ketone as NBS was supposed to act as an oxidant. The time for completion of the reaction was dramatically reduced to three hours when the present approach with in situ generated (NTS) was employed, and the product was obtained in higher yield of 93% (Scheme 5, d). When NTS was employed as a reagent in the reaction we tested (Scheme 5, d) the progress of reaction by mixing it with the radical quencher butylated hydroxytoluene (BHT) in 1:1 molar ratio of reactant which revealed that the reaction progress was not altered. This indicates that the mechanism does not follow a free-radical pathway.

On the basis of these observations made in control experiments and the previous literature,[14,20a,23] it may be possible that the reaction for C-3 thiocyanation of imidazothiazole proceeds through the mechanism shown in Scheme 6.



Scheme 5 Control experiments

First, ammonium thiocyanate reacts with NBS to initiate the formation of electrophilic NTS. Afterwards, substituted imidazothiazole reacts with NTS at the C-3 position. The formed intermediate finally releases the proton for aromatization to furnish the final product (Scheme 6). This protocol ruled out the possibility of nucleophilic attack of alcoholic –OH on the sulfur atom of NTS to produce alkyloxygenyl thiocyanate (ROSCN), which can further react with NH_4SCN to furnish alkyl thiocyanate **X** (Scheme 1) or isothiocyanate **Z** (Scheme 1). In spite of all these possibilities, the reaction has been observed to promote C-3 thiocyanation in imidazothiazole compounds **2a–e** (Scheme 1).



Scheme 6 Plausible reaction mechanism for imidazothiazole and 2-aminothiazole

The reaction for C-5 thiocyanation of 2-aminothiazole may proceed through the plausible mechanism shown in Scheme 6. Ammonium thiocyanate reacts with NBS to produce electrophilic *N*-thiocyanatosuccinimide, followed by reaction at C-5 position of 2-aminothiazole. Finally, the formed intermediate releases the proton for aromatization, which results in the final product.

In summary, we have developed a one-pot chemoselective synthetic route for C-3 and C-5 thiocyanation of imidazothiazole and 2-aminothiazole at room temperature.[25] The present protocol provides useful information regarding

the reactivity of in situ generated NTS for thiocyanation of imidazothiazoles comprising an alcoholic hydroxy group. The method provides easy and metal-free chemoselective access for thiocyanation at C-3 position in imidazothiazole through electrophilic substitution, ruling out the possibility of forming alkyl thiocyanate or alkyl isothiocyanate through nucleophilic substitution by alcoholic –OH in the same substrate. This method provides high yields of C-3 and C-5 thiocyanates of imidazothiozole and 2-aminothiazole, respectively, under very mild conditions. The transformation provides a new opportunity for the synthesis of bioactive imidazothiazoles and 2-aminothiazoles, which may gain much attention in the field of synthetic and medicinal chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609553.

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(25) **Procedure for the Synthesis of 1-(6-(4-Chlorophenyl)-3-methyl-5-thiocyanatoimidazo[2,1-b]thiazol-2-yl)ethanol (2a) (Table 1)**

A dried 50 mL round-bottomed flask was charged with NBS (177.98 mg, 1 mmol), NH_4SCN (152.24 mg, 2.0 mmol) in PEG-400 (3 mL) and the reaction mixture was stirred at r.t. for 15 min. The reaction mixture turned milky indicating generation of NTS (shown by TLC). Next, reactant **1a** (292.78 mg, 1 mmol) was added slowly, and the reaction mixture was further stirred for 3 h. After completion of the reaction as indicated by TLC, cold water (20 mL) was added to separate the solid product. The white solid was filtered, dried, and washed with cold aqueous ethanol (0.93 mmol, 93% yield).

Compound **2a**: Mp 111–113 °C. FT-IR: 3195, 2966, 2154, 1893, 1644 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.94 (d, 2 H, *J* = 8.0 Hz), 7.62 (s, 2 H), 5.96 (s, 1 H), 5.17 (s, 1 H), 2.73 (s, 3 H), 1.41 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHZ, DMSO-d_6): δ = 152.62, 152.11, 134.68, 134.20, 131.36, 129.84, 128.87, 124.27, 111.02, 97.97, 62.25, 25.24, 12.39 ppm. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{12}ClN_3OS_2$: 349.0110; found: 350.0174.

Procedure for the Synthesis of 5-thiocyanato-4-(*p*-tolyl)thiazol-2-amine (4f) (Scheme 4)

A dried round-bottomed flask was charged with NBS (177.98 mg, 1.0 mmol) and NH_4SCN (152.24 mg, 2.0 mmol). PEG-400 (3 mL) was added and reaction mixture was stirred at r.t. for 15 min. Formation of a milky color indicated the generation of NTS (shown by TLC). Then, 4-(*p*-tolyl)thiazol-2-amine (190.26 mg, 1 mmol) was added slowly, and the reaction mixture was further stirred for 3 h. When completion of the reaction was indicated by TLC, the product was separated by addition of cold water (20 mL). The white solid product was filtered, dried, and washed with cold aqueous ethanol (0.78 mmol, 78% yield).

Compound **4f**: Mp 134–136 °C. FT-IR: 3372, 3269, 3045, 2100, 1612 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.88 (s, 2 H), 7.69–7.31 (m, 4 H), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (100 MHZ, DMSO-d_6): δ = 171.25, 259.25, 139.14, 130.64, 129.39, 129.18, 129.01, 112.57, 21.39 ppm. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{11}H_9N_3S_2$: 247.0238; found: 248.0305.