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Trimethylsilyl isothiocyanate (TMSNCS): an efficient reagent for the one-pot synthesis of mercapto-1,2,4-triazoles

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ABSTRACT

A mild, convenient, and efficient one-pot synthesis of mercapto-1,2,4-triazoles is described. Various hydrazides efficiently reacted with trimethylsilyl isothiocyanate (TMSNCS) under basic condition to give mercapto-1,2,4-triazoles in high yields.

During the last 40 years there has been a tremendous growth in the chemistry of organosilicon compounds due to the metalloid nature of silicon. Organosilicon species can generate electrophilic and nucleophilic agents from organic derivatives under relatively mild conditions, which lead to develop many new types of reactions in organic synthesis.[1,2] Functional groups containing silicon species play important roles in organic synthesis.[1,2] For example, silyl cyanides and silyl azides have shown to be highly versatile reagents, which converted carbonyl compounds into α-siloxy cyanides,[1] α-siloxy azides,[3] and gem-diazides.[4,5] Among all silicon reagents, silylated nucleophile, trimethylsilyl isothiocyanate (TMSNCS) is a versatile reagent in organic chemistry, since it easily undergoes many important reactions (Fig. 1), such as thiocyanations or isothiocyanations of (a) alkyl halides,[6] (b) acetals and aldehydes,[7] (c) unsaturated compounds,[8,9] (d) aziridines and oxiranes,[10] (e) polycyclic aromatic hydrocarbons,[11] and (f) acetylated hexoses.[12] In addition to those, TMSNCS is a useful reagent for (g) the peptide analysis.[13] As a part of our continuing studies on such silicon species, we investigated the synthetic utility of trimethylsilyl isothiocyanate (TMSNCS); to the best of our knowledge, the synthesis of mercapto-1,2,4-tiazoles utilizing TMSNCS as a reagent has not been reported yet.

1,2,4-Triazoles are important class of heterocycles, which are widely used in the field of medicinal chemistry and materials science. Moreover derivatives of 1,2,4-triazole are known to exhibit antimicrobial,[14] antiviral,[15] anti-inflammatory,[16] anti-asthmatic,[17] antiproliferative,[18,19] and hypotonic activities.[20] The most frequently used triazoles are fluconazole and itraconazole that display a broad spectrum of antifungal activity and reduce toxicity compared with imidazole antifungals.[21–23]

Due to broad biological applications of 1,2,4-triazoles, several synthetic protocols have been reported in the literature.[24–27] In addition to these biological applications, mercapto-1,2,4-triazoles are also of great utility in preparative organic chemistry.[28] We report herein highly efficient one-step protocol to prepare mercapto-1,2,4-triazoles from the reaction of commercially available hydrazides and TMSNCS in EtOH under basic condition at 70 °C. The procedure does not require an anhydrous solvent, inert gas atmosphere, and any chromatographic purification.

Initially benzohydrazide **1a** was selected to optimize the reaction conditions. The effects of different solvents and reaction temperatures were investigated. The results were summarized in Table 1. In the conversion of **1a** to **2a**, EtOH was the best solvent among various solvents such as toluene, THF, and MeOH.

In the first instance, we synthesized 3-phenyl-5-mercapto-4H-1,2,4-triazole (**3a**) by step wise protocol. Benzohydrazide (**1a**) and TMSNCS in EtOH were refluxed for about 5 h to give pure benzoyl thiosemicarbazide (**2a**). Compound **2a** in EtOH was refluxed with 4 N NaOH for about 4 h and followed by neutralization to afford a pure white solid 3-phenyl-5-mercapto-4H-1,2,4-triazole (**3a**) (Scheme 1) with 86% yield.

The plausible mechanism for the formation of mercapto-1,2,4-triazoles (**3**) is shown in Scheme 2. The cleavage of weak Si–N bond in TMSNCS takes place in the presence of EtOH and formed highly reactive unstable isothiocyanic acid intermediate. Carboxylic acid hydrazides (**1**) immediately undergo nucleophilic addition to isothiocyanic acid, leading to corresponding stable thiosemicarbazides

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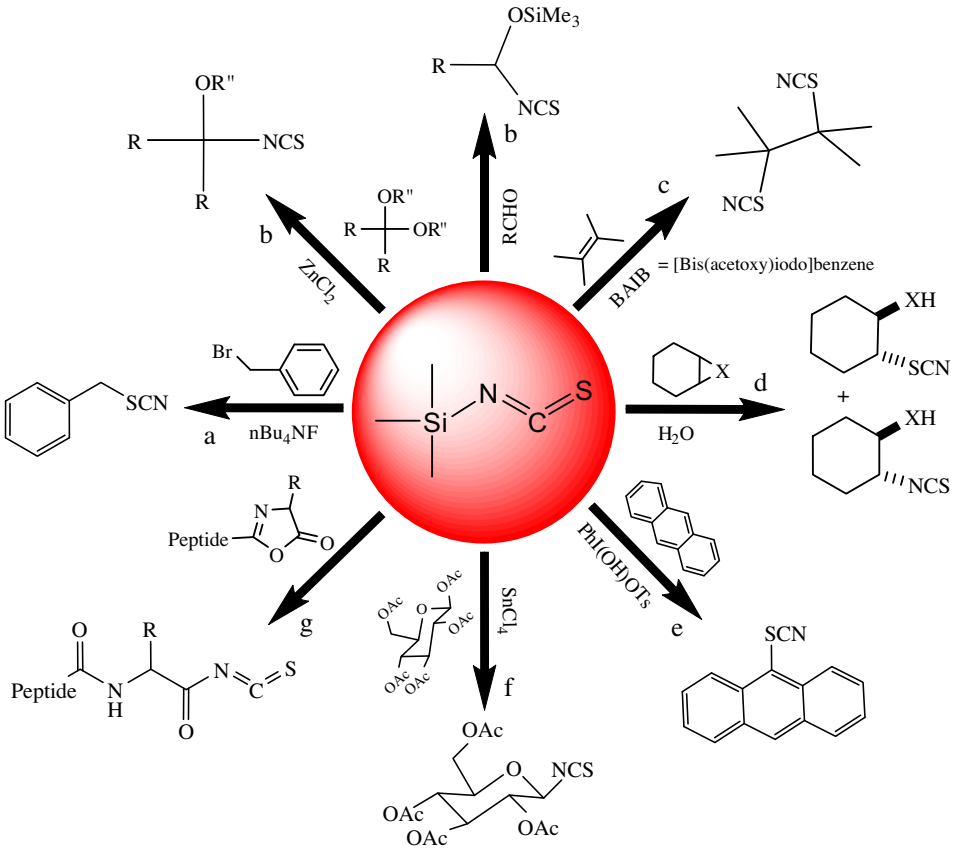
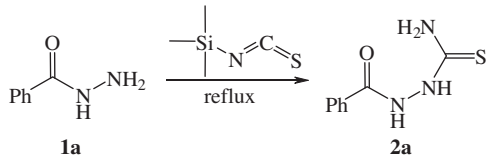


Figure 1. Synthetic utility of TMSNCS reagent.

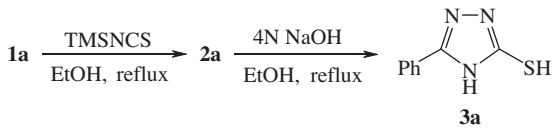
Table 1
Optimization of reaction conditions for the synthesis of benzoyl thiosemicarbazide (**2a**)



1a **2a**

Entry	Solvents	Time[a] (h)	Yield[b] (%)
1	Toluene	14	10
2	THF	11	40
3	MeOH	9	68
4	EtOH	5	89

[a] Monitored by TLC until **1a** was fully consumed.
[b] Isolated yield.



3a

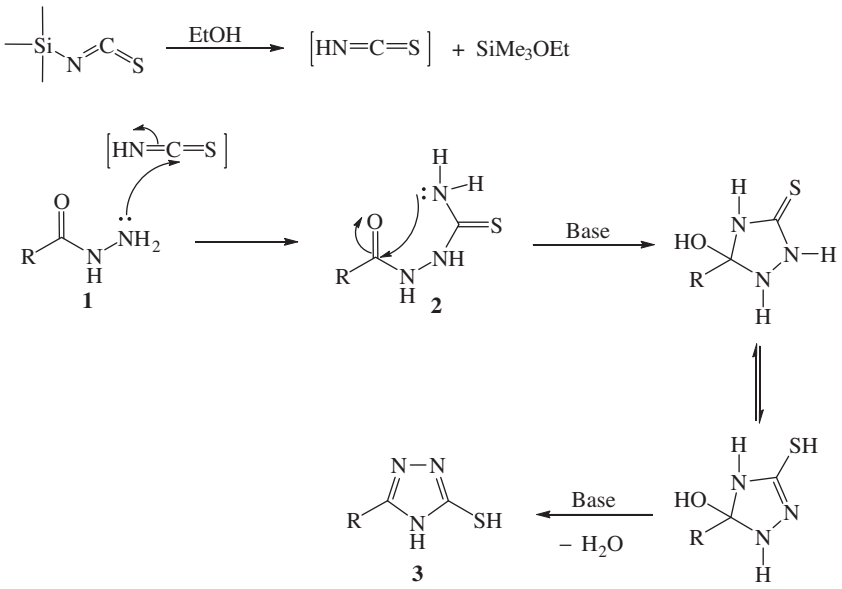
Scheme 1. Step wise synthesis of mercapto-1,2,4-triazole (**3a**).

(**2**), of which base-catalyzed cyclization followed by tautomerization of S=C–N–H unit and dehydration afforded mercapto-1,2,4-triazoles (**3**).

For an additional simplification of the reaction protocol, we studied one pot reaction without the isolation of thiosemicarbazide **2**. After the equimolar mixture of benzohydrazide and TMSNCS was refluxed in the presence of EtOH for 5 h, we added 4 N NaOH to the reaction mixture and the solution was refluxed for 4 h. Cooling and neutralization with acetic acid resulted in pure compound **3a** with 88% yield. The yield is higher than that of two-step reaction. In both two-step and one pot process we obtained pure compounds without any chromatographic purification.

The mild and practical one-pot reactions of various carboxylic acid hydrazides (**1a–l**) were carried out in the presence of TMSNCS to give the mercapto-1,2,4-triazoles (**3a–l**)[29] (Table 2). As shown in Table 2, compound **3a** (entry 1) was obtained in the highest yield comparing to those of electron-rich and electron-poor aryl substituted derivatives **3b–h** (entries 2–8). In particular, 4-substituted derivatives **1b–d** (entries 2–4) reacted more efficiently than the corresponding 2-substituted regioisomers **1e–h** (entries 5–8), possibly because of the steric hindrance of the *ortho* substituent. To demonstrate the generality of our methodology, we extended our investigation to substrates bearing alkyl and hetero-aromatic groups. With heteroaryl acid hydrazides (entries 11 and 12), yields were similar to those with aromatic derivatives, but with alkyl acid hydrazides (entries 9 and 10), yields were lower than those of aromatic and heteroaromatic acid hydrazides.

In summary we have developed a mild and efficient one-pot synthetic methodology to synthesize a variety of 3-aryl-, 3-heteroaryl-, and 3-alkyl-5-mercapto-1,2,4-triazoles from commercially available carboxylic acid hydrazides with TMSNCS. The experimental procedure is operationally simple, does not require anhydrous solvent, inert gas atmosphere, any chromatographic purification, and avoids the use of harsh reagents.



Scheme 2. Plausible mechanism for the formation of mercapto-1,2,4-triazole (**3a**).

Table 2
One-pot synthesis of mercapto-1,2,4-triazoles (**3**)

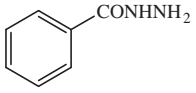
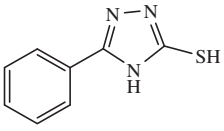
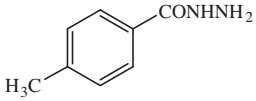
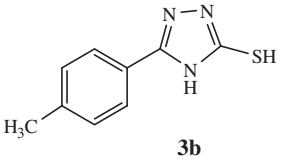
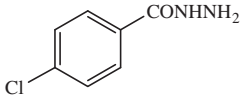
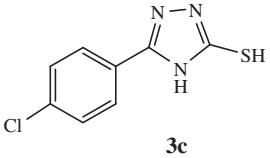
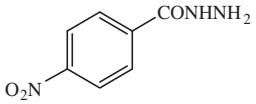
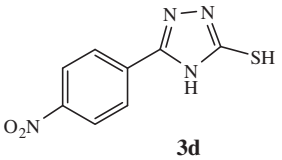
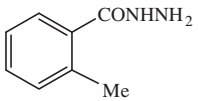
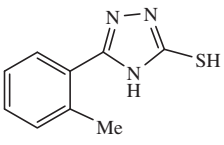
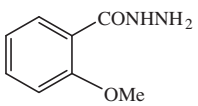
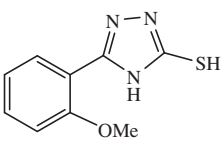
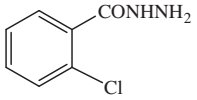
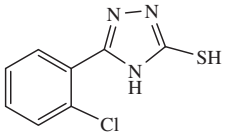
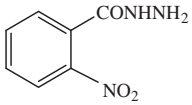
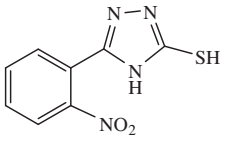
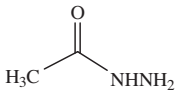
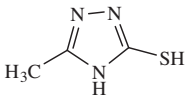
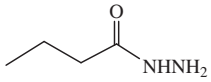
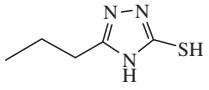
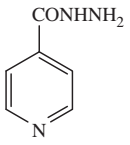
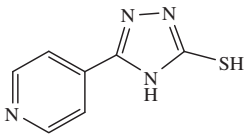
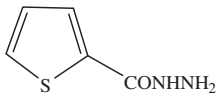
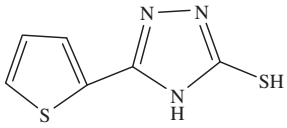
Entry	Hydrazides	Products	Yield (%)
1	 **1a**	 **3a**	88
2	 **1b**	 **3b**	84
3	 **1c**	 **3c**	86
4	 **1d**	 **3d**	48
5	 **1e**	 **3e**	74
6	 **1f**	 **3f**	76

Table 2 (*continued*)

Entry	Hydrazides	Products	Yield (%)
7	 **1g**	 **3g**	79
8	 **1h**	 **3h**	20
9	 **1i**	 **3i**	52
10	 **1j**	 **3j**	64
11	 **1k**	 **3k**	76
12	 **1l**	 **3l**	74

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.054.

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29. *Typical experimental procedure for synthesis of 3-substituted-5-mercapto-4H-1,2,4-triazoles (**3a–l**)*: A mixture of acid hydrazide (1.0 mmol) and trimethylsilyl isothiocyanate (1.0 mmol) and ethanol (10 ml) was refluxed for 3–5 h and then 2 ml of 4 N NaOH was added. The solution was refluxed for additional 4–6 h, cooled and poured into ice-cold water with acetic acid (pH 5–6). A resultant solid was filtered on a Buchner funnel and dried. Recrystallization of the solid from ethanol afforded pure products.