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In situ-generated *N*-thiocyanatosuccinimide (NTS) as a highly efficient reagent for the one-pot thiocyanation or isothiocyanation of alcohols

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ABSTRACT

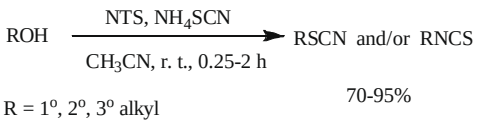
The first application of in situ-generated *N*-thiocyanatosuccinimide (NTS) for the thiocyanation of alcohols is described. This method can be easily applied for the facile conversion of primary, secondary and tertiary alcohols into the corresponding alkyl thiocyanates or alkyl isothiocyanates in good to excellent yields.

N-Thiocyanatosuccinimide (NTS) is a reactive electrophilic sulfur species[1] which has been employed in diverse organic transformations such as thiocyanation of electron-rich aromatic compounds,[2] ring-expansion–thiocyanation of 1,3-dithiolanes and 1,3-dithianes,[3] and α-thiocyanation of *N*-acyl carboximides.[4] This reagent can be easily prepared by the reaction of *N*-bromosuccinimide with thiocyanate.

Organic thiocyanates are important sulfur-containing compounds which have wide application in synthetic and medicinal chemistry.[5] There are two general methods for the preparation of alkyl thiocyanates. In the first approach, alkyl thiocyanates are prepared by reaction of thiocyanate anions with alkyl halides or alkyl tosylates. Based on this general approach, a number of procedures have been reported which include the use of KSCN/$CuBr_2$,[6] solid-supported potassium thiocyanate,[7] metallic salts of thiocyanate ions,[8] thiocyanate ions in the presence of phase-transfer agents,[9–12] NH_4SCN in polyethylene glycol (PEG),[13] and task-specific ionic liquids such as 1-butyl-3-methylimidazolium thiocyanate ([bmim]SCN)[14] and 2-hydroxy-*N*,*N*,*N*-tributylethanammonium thiocyanate.[15] In the second approach, alkyl thiocyanates are prepared directly from alcohols. Phosphine-based reagents have been used for the activation of the hydroxy group of alcohols. These reagents include $Ph_3P(SCN)_2$,[16] $Ph_3P(Br)_2/NH_4SCN$,[17] Ph_3P/dichlorodicyanoquinone/Bu_4NSCN,[18] Ph_3P/diethyl azodicarboxylate/NH_4SCN,[19] diphenylphosphinite ionic liquid (IL-$OPPh_2$)/Br_2/NH_4SCN,[20] and cyanuric chloride/*N*,*N*-dimethylformamide/KSCN.[21] However, these methods have certain limitations arising from the use of expensive and explosive reagents, long reaction times, and tedious work-ups. In continuation of our ongoing program to develop new reagents and synthetic procedures for the thiocyanation of alcohols,[18,20,21] we report here, a new, mild, and efficient procedure for the one-pot conversion of primary, secondary, and tertiary alcohols into their corresponding alkyl thiocyanates or alkyl isothiocyanates using in situ-generated NTS and NH_4SCN in acetonitrile at room temperature (Scheme 1).

Addition of ammonium thiocyanate to an acetonitrile solution of NBS gave *N*-thiocyanatosuccinimide in 15 min. Reaction of alcohols with this reagent in the presence of NH_4SCN gave the corresponding alkyl thiocyanates or isothiocyanates. The reaction of benzyl alcohol with in situ-generated NTS in the presence of NH_4SCN was selected as a model reaction and the effects of various parameters such as reactant/reagent ratio, temperature, and solvent were studied. To optimize the reactant/reagent ratio, reactions were carried out using different molar ratios and amounts of benzyl alcohol, NTS and NH_4SCN.

The maximum yield of benzyl thiocyanate was obtained when the reactions were carried out using a 1:1.5:1.5 molar ratio of benzyl alcohol, NTS, and NH_4SCN.[22] Among several solvents including acetonitrile, dichloromethane, methanol, and acetic acid,



Scheme 1. Conversion of alcohols into alkyl thiocyanates or isothiocyanates.

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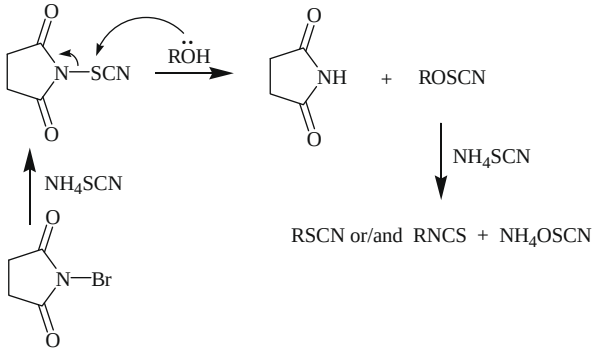
Table 1
Conversion of alcohols into alkyl thiocyanates or isothiocyanates with NTS and NH_4SCN in acetonitrile at room temperature

Entry	Alcohol (ROH)	Time (h)	RSCN/RNCS[a] (%)	Yield[b] (%)	Ref.[c]
1	Benzyl alcohol	0.5	100/0	95	17a
2	4-Methoxybenzyl alcohol	0.25	67/33	90[d]	17b
3	4-Nitrobenzyl alcohol	1	100/0	75	18b
4	4-Chlorobenzyl alcohol	1	100/0	78	17b
5	2-Nitrobenzyl alcohol	1	100/0	70	21
6	2-Chlorobenzyl alcohol	1	100/0	70	21
7	2-Phenylethanol	0.75	100/0	91	13
8	1-Octanol	1.5	100/0	89	13
9	2-Octanol	2	100/0	90	19
10	Cyclohexanol	2	100/0	92	17c
11	1-Phenylethanol	0.75	98/2	95[d]	18a
12	Diphenylmethanol	1.5	88/12	90[d]	17a
13	α,α-Dimethyl-[1,1′-biphenyl]-4-methanol	1.5	97/3	90[d]	19
14	Trityl alcohol	1.5	0/100	95	23

[a] The ratio of RSCN/RNCS was determined by ^1H NMR spectroscopy.
[b] Isolated pure product.
[c] All the products are known compounds and were identified by comparison of their physical and spectral data with those of authentic samples.
[d] A mixture of thiocyanate and isothiocyanate was obtained.



Scheme 2. Suggested mechanism for the formation of alkyl thiocyanates and isothiocyanates.

acetonitrile proved to be the best. Conversion of benzyl alcohol into benzyl thiocyanate was easily achieved at room temperature. These optimized conditions were then applied for the conversion of various alcohols into their corresponding alkyl thiocyanates or alkyl isothiocyanates. The results are summarized in Table 1.

As is clear from Table 1, reaction of primary alcohols (entries 1 and 3–8 but not 4-methoxybenzyl alcohol, entry 2) and non-benzylic secondary alcohols (entries 9 and 10) with NTS produced the corresponding alkyl thiocyanates without the formation of any isothiocyanates. With secondary and benzylic alcohols (entries 11 and 12), 4-methoxybenzyl alcohol (entry 2) and α,α-dimethyl-[1,1′-biphenyl]-4-methanol (entry 13), the formation of alkyl isothiocyanates as minor products was observed. Furthermore, the reaction of trityl alcohol (entry 14) with NTS gave only triphenyl methyl isothiocyanates which can be attributed to the high stability of its carbocation.

Based on our observations and a previous report,[1] a mechanism can be proposed for this reaction (Scheme 2). Nucleophilic attack of the alcohol on the sulfur of NTS produces alkyloxygenyl thiocyanate (ROSCN), which in the presence of NH_4SCN can produce the desired alkyl thiocyanate or alkyl isothiocyanate by nucleophilic substitution.

In conclusion, the procedure described here is very simple and allows a rapid and high-yielding conversion of primary, secondary, and tertiary alcohols into the corresponding alkyl thiocyanates or alkyl isothiocyanates under very mild conditions. This phosphine-free method seems to be more convenient with respect to other reports and avoids tedious purifications and the use of toxic reagents.

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22. *Typical procedure for the conversion of benzyl alcohol into benzyl thiocyanate*: To a flask containing NBS (0.266 g, 1.5 mmol) was added CH_3CN (5–7 mL) followed by NH_4SCN (0.228 g, 3 mmol) at room temperature. The reaction mixture was left to stir for 15 min to form a white solid. Next, benzyl alcohol (0.1 mL, 1 mmol) was added to the reaction mixture. TLC of the reaction mixture showed the completion of the reaction after 30 min. Following evaporation of acetonitrile, water was added to the flask and benzyl thiocyanate was extracted with diethyl ether (3 × 5 mL). Evaporation of the solvent and chromatography on a short silica gel column using *n*-hexane/ethyl acetate (5/1) as eluent gave benzyl thiocyanate as pale yellow crystals in 95% yield (mp 40 °C, lit.[17a] mp 39–40 °C). IR (CCl_4) ν 2150 (SCN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (2H, s), 7.33–7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.22, 133.60, 129.70, 129.45, 111.35, 38.70.
23. Data for triphenylmethyl isothiocyanate (Table 1, entry 14): IR (CCl_4) ν 1950–2100 (NCS) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.38 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.04, 127.30, 128.36, 134.07, 143.12, 146.87.