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Short communication

Selectfluor™ F-TEDA-BF_4 mediated thiocyanation or isothiocyanation of alcohols by in situ generation of [$^+$SCN] under heterogeneous and neutral conditions

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ABSTRACT

A convenient approach for thiocyanation of alcohols has been developed using ammonium thiocyanate as thiocyanating agent in the presence of a catalytic amount of Selectfluor™ F-TEDA-BF_4 in aqueous acetonitrile. In this method various alcohols generally afforded the corresponding thiocyanates or isothiocyanates directly in good to high yield under heterogeneous and neutral conditions.

1. Introduction

Thiocyanate is a versatile synthon which has been used extensively in synthetic organic chemistry such as medicinal, biological and heterocyclic chemistry [1]. Alkyl thiocyanates are generally prepared via nucleophilic displacement of leaving groups attached to C by thiocyanateion [2]. Consequently, a variety of systems have been introduced for the preparation of alkyl thiocyanates, for example NH_4SCN/(PEG) [3], KSCN/$CuBr_2$ [4], cyanuric chloride/N,N-dimethylformamide/KSCN [5], Ph_3P/dichlorodicyanoquinone/Bu_4NSCN [6,7], 1-butyl-3-methylimidazolium thiocyanate ([bmim]SCN) [8], phasetransfer agents/thiocyanate ions [9–12], NBS/NH_4SCN [13], (IL-OPPh_2)/Br_2/NH_4SCN [14], $Ph_3P(SCN)_2$ [15], 2-hydroxy-N,N,N-tributylethanammonium thiocyanate [16], Ph_3P/diethylazodicarboxylate/NH_4SCN [17], Selectfluor™/NaSCN [18], 2-Chloro-1-methylpyridinium iodide/NH_4SCN [19], trichloroisocyanuric acid/NH_4SCN [20] and $Ph_3P(Br)_2$/NH_4SCN [21–23].

However, several of the reported methods are associated with drawbacks, including strong oxidizing agents, toxicity of metal thiocyanates, long reaction times, expensive reagents, less availability and incompatibility with other functionalities. Thus, there is still a need for a mild, neutral, catalytically efficient alternative, preferably using a heterogeneous catalyst, the thiocyanateion of alcohols as alkyl thiocyanate compounds. In view of the versatility of thiocyanate group in the field of pharmaceuticals and drugs the development of convenient, simple and highly efficient approaches is desirable.

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate) (Fig. 1), commercially known as Selectfluor™ F-TEDABF_4, is one of the most valuable reagents for electrophilic fluorination and a versatile mediator or catalyst for various other functionalization of organic compounds. Selectfluor™, an exceptionally stable, virtually nonhygroscopic crystalline solid, represents a significant improvement on traditional electrophilic fluorinating agents, which require special handling and tend to be synonymous with danger [24]. Organic molecules bearing a reactive N–F bond are excellent reagents for selective fluorination of organic compounds under mild reaction conditions and Selectfluor™ is one of the most popular members of this family. On the other hand, the N–F reagents possess moderate to strong oxidative power [25–30], but investigations taking advantage of this property are still scarce [31,32]. Furthermore, there have been no examples on the use of Selectfluor™ for the electrophilic thiocyanation or isothiocyanation of alcohols.

2. Results and discussion

In continuation of our studies on using *N*-halo compounds [33–39], we report here the use of readily available NH_4SCN for thiocyanation of various alcohols in the presence of Selectfluor™ under mild and heterogeneous conditions (Fig. 2).

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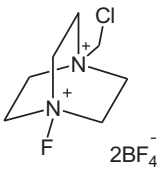


Fig. 1. Selectfluor™.

The data in Table 1 clearly shows that primary and secondary alcohols were successfully converted to the corresponding alkyl thiocyanates in short time and in almost quantitative yields. We observed that tertiary alcohols with sterically hindered structure were not converted under this reaction even after prolonged reaction times (Table 1, Entry 16) but the primary and secondary alcohols with the similar structure were converted to the corresponding alkyl thiocyanates in short time (Table 1, Entries 6 and 7). The reaction of cinnamyl alcohol as an allylic alcohol with NH_4SCN/Selectfluor™ system produced a trace of a mixture of unidentified products after 24 h (Table 1, Entry 15). The rule and influence of electron-releasing substituents at aromatic ring of alcohols is so notable. The comparison between alcohols with the same structures showed that the addition of electron-releasing substituents such as –OMe to each compound increased the reaction rate (Table 1, Entries 5 and 8). As shown in Table 1, a range of various alcohols reacted with ammonium thiocyanate to give the desired products in high yields. The reaction of aliphatic, cyclic (Table 1, Entries 9–11) and some benzylic alcohols (Table 1, Entries 1–3) with NH_4SCN/Selectfluor™ system produced the corresponding alkyl thiocyanates without the formation of any alkyl isothiocyanates. As shown in Table 1 (Entries 4–8 and Entries 12–14), in the media reaction condition the other alcohols produced the corresponding alkyl thiocyanates with minor amount of corresponding alkyl isothiocyanates.

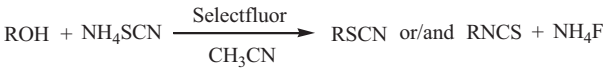


Fig. 2. The reactions of alcohols with ammonium isothiocyanate in presence of acetonitrile.

In all cases, the reactions proceeded rapidly at room temperature. As solvent, acetonitrile appeared to give the best results. Also

Table 1
Thiocyanation or isothiocyanation of alcohols by in situ generation of [$^+$SCN] under heterogeneous and neutral conditions.

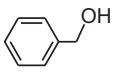
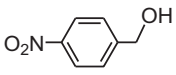
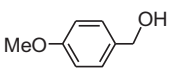
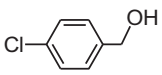
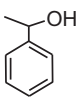
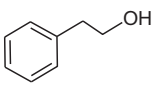
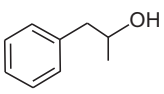
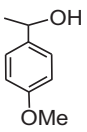
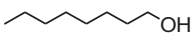
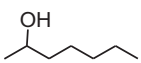
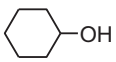
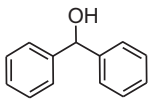
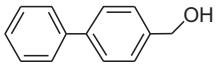
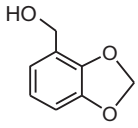
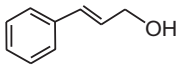
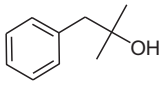
Entry	Alcohol	Time (min)	RSCN/RNCS[a] (%)	Yield[b,d] (%)
1		5	100/0	91
2		60	100/0	78
3		3	100/0	89
4		30	86/14	92[c]
5		30	85/15	88[c]
6		35	83/17	90[c]
7		30	80/20	80[c]
8		3	77/33	84[c]
9		15	100/0	75
10		50	100/0	80
11		75	100/0	77

Table 1 (*Continued*)

Entry	Alcohol	Time (min)	RSCN/RNCS[a] (%)	Yield[b,d] (%)
12		30	70/30	90[c]
13		60	92/8	81[c]
14		10	88/12	80[c]
15		24 h	Trace	–
16		24 h	NR	–

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

between KSCN, NaSCN and NH_4SCN as thiocyanating reagents, NH_4SCN appeared to give the best results. The products were characterized by ^1H NMR, IR, and by comparison with authentic samples.

3. Conclusion

In conclusion, Selectfluor™ has proved to be an effective reagent for the electrophilic thiocyanates or isothiocyanates of alcohols under heterogeneous and neutral conditions.

This present method is featured with relatively mild reaction conditions, simple operation, broad substrate scope, excellent selectivity and also avoids tedious purifications and the use of toxic reagents. This method provides the direct access to a wide range of potentially valuable biologically well-defined thiocyanates.

4. Experimental

4.1. General procedure for thiocyanation or isothiocyanation of alcohols by in situ generation of [$^+$SCN]

The Selectfluor™ (1.5 mmol) and ammonium thiocyanate (3 mmol) were dissolved in acetonitrile (7 mL) at room temperature. The reaction mixture was stirred for 20 min to form a yellow solid. Next, alcohol (1 mmol) was added to the reaction mixture. After completion of the reaction (TLC), mixture was filtered and then diluted with water (10 mL) and then extracted with diethyl ether (3× 10 mL), the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and reaction mixture was passed through a short column of silica gel using n-hexane/ethyl acetate (8/2) as eluent. Then solvent was evaporated to dryness to afford the pure product.

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