J. Chem. Sci. Vol. 124, No. 4, July 2012, pp. 901–905.

Selectfluor^{TM}: A novel and efficient reagent for the rapid α-thiocyanation of ketones

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MS received 1 August 2011; revised 16 October 2011; accepted 2 December 2011

Abstract. The direct α-thiocyanation of ketones with ammonium thiocyanate has been achieved using Selectfluor^{TM} under mild and neutral conditions to produce α-ketothiocyanates, in excellent yields and with high selectivity.

Keywords. Thiocyanation; ketones; ammonium thiocyanate; Selectfluor^{TM}; synthesis

1. Introduction

Molecules with thiocyanate functional group can be readily transformed into the other sulphur-bearing functionalities,[1] providing compounds with pharmaceutical properties.[2] In particular, α-ketothiocyanates are versatile intermediates in the synthesis of sulphur-containing heterocycles.[3] Some of these compounds exhibit herbicidal and other important biological activities.[4] Therefore, it is important to find new methods for the direct α-thiocyanation of ketones. Several methods have been developed for the direct α-thiocyanation of ketones using bromodimethylsulphonium bromide/ammonium thiocyanate,[5] oxone/ammonium thiocyanate,[6] heteropoly acid/ammonium thiocyanate,[7] (dichloroiodo)- benzene/lead(II) thiocyanate,[8] potassium peroxydisulphate/copper(II) complex,[9] I_2/ammonium thiocyanate,[10] $FeCl_3$/ammonium thiocyanate,[11] and NBS/ammonium thiocyanate.[12] However, some of these methods suffer from disadvantages, such as low yields, the use of strongly acidic or oxidizing conditions, the use of special conditions (long reaction time and (or) high temperature), and also the use of toxic reagents. In this research, we have developed a new route for the direct α-thiocyanation of ketones.

Selectfluor^{TM} (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octanebis(tetrafluoro-borate)) (figure 1) is a commercially available, stable, nonvolatile, nonhygroscopic and easy to handle solid and is more widely used for site-selective fluorination of a variety of carbonyl compounds. Besides its fluorinating ability, it is also recognized as a convenient mediator of several 'fluorine free' functionalization of organic compounds.[13] These kinds of reactions are based on the fact that F-TEDA-BF4 has considerable oxidative power. In this article, we report a simple, convenient, and efficient protocol for the α-thiocyanation of ketones using Selectfluor^{TM} in acetonitrile (scheme 1).

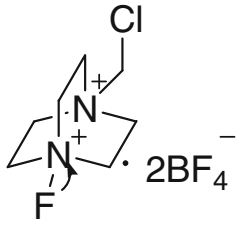
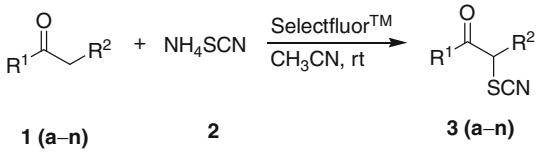


Figure 1. Structure of Selectfluor^{TM}.



Scheme 1. α-Thiocyanation of ketones.

*For correspondence

Table 1. α-Thiocyanation of ketones promoted by Selectfluor™[a].

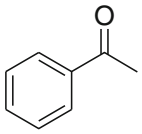
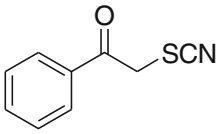
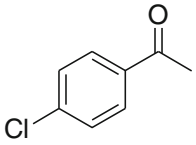
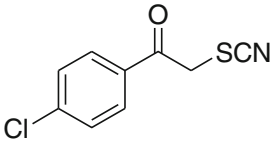
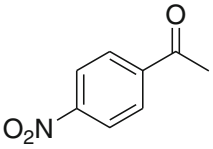
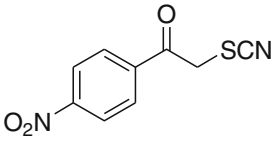
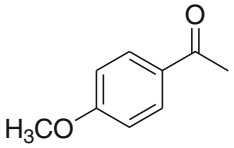
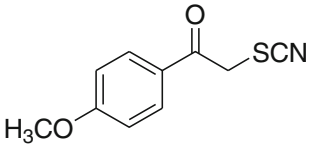
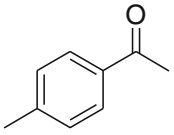
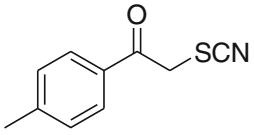
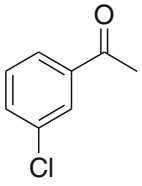
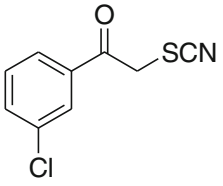
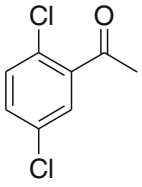
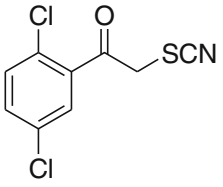
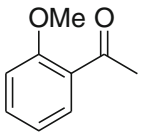
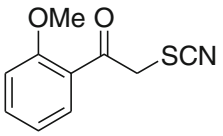
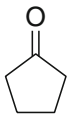
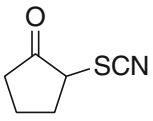
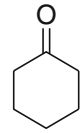
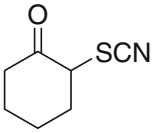
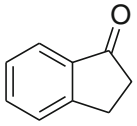
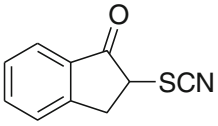
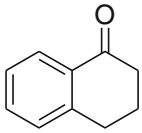
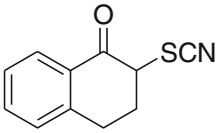
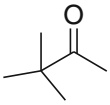
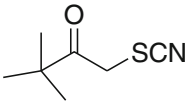
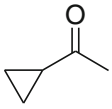
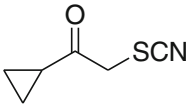
Entry	Ketones (1)[b]	Product (3)[b]	Time/ min	Yield/ %[b]	m.p. (lit.)/ °C
a			40	93	68–70 (67–69)[11]
b			50	89	133–135 (132–134)[5]
c			50	90	118–120 (119–120)[5]
d			40	91	120–122 (121–125)[5]
e			40	86	104–107 (103–106)[5]
f			50	88	65–66 (68–70)[11]
g			60	89	191–193 (190–192)[11]
h			60	86	86–88 (85–87)[11]
i			25	94	Oil (oil)[11]

Table 1. (continued)

Entry	Ketones (1)[b]	Product (3)[b]	Time/ min	Yield/ %[b]	m.p. (lit.)/ °C
j			25	91	Oil (oil)[11]
k			40	92	90–92 (92–93)[14]
l			40	88	Oil (oil)[11]
m			75	84	Oil (oil)[11]
n			60	87	Oil

[a]Reaction conditions: ketones (1.0 mmol); NH_4SCN (2.0 mmol); Selectfluor™ (1 mmol); rt; CH_3CN.
[b]Isolated yield

2. Experimental

2.1 *Materials, methods and instruments*

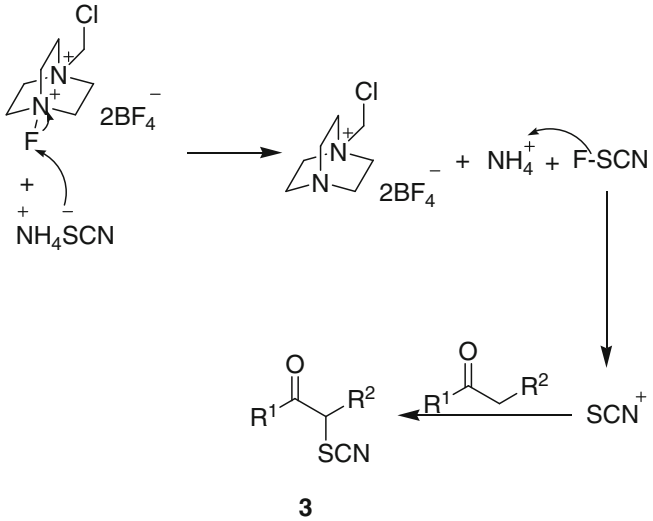
NMR spectra were recorded on a Bruker AV-400 spectrometer at room temperature using TMS as internal standard, coupling constants (J) were measured in Hz. Elemental analysis were performed by a Vario-III elemental analyzer. Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used throughout without further purification unless otherwise stated.

2.2 *General procedure for α-thiocyanation of ketones*

To a solution of ammonium thiocyanate (2 mmol) and ketones (1 mmol) in acetonitrile (10 mL), Selectfluor™ (1 mmol) was added and the resulting mixture was stirred at room temperature for an appropriate time period. After complete conversion as indicated by TLC, the reaction mixture was quenched with water. The reaction mixture was successively extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The resulting product was purified by column chromatography on silica gel (200–300 mesh, ethyl acetate:hexane = 1:20) to afford pure **3**.

2.3 *Spectroscopic data*

2.3a *1-phenyl-2-thiocyanatoethanone (**3a**)*: Solid, mp 68–70°C; IR (KBr): υ 2946, 2150 (-SCN),



3

Scheme 2. A plausible mechanism for this reaction.

Table 2. Selectfluor^{TM}-promoted α-thiocyanation of acetophenone in comparison with other literatures.

Entry	Catalyst and conditions	Solvent	Time/ min	Yield/ %	Ref.
1	$FeCl_3$ (100 mol%); rt	CH_2Cl_2	30	75	[11]
2	Oxone (100 mol%); rt	MeOH	360	86	[6]
3	Heteropoly acid (25 mol%); rt	$ClCH_2CH_2Cl$	20	86	[7]
4	NBS (100 mol%); rt	CH_3CN	240	85	[12]
5	Selectfluor^{TM} (100 mol%); rt	CH_3CN	40	93	The work

1672 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.02–7.80 (m, 2H), 7.66–7.25 (m, 3H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.2, 135.0, 133.6, 128.8, 128.0, 112.1, 43.1; Anal. calcd for C_9H_7NOS: C 60.99, H 3.98, N 7.90, S 18.09; found: C 70.06, H 3.92, N 7.95, S 18.00.

2.3b *2-Thiocyanatocyclohexanone* ***(3j)***: Oil; IR (KBr): υ 2925, 2154 (-SCN), 1702; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.35–4.20 (m, 1H), 2.85–2.38 (m, 3H), 2.20–1.73 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.2, 111.8, 60.2, 39.8, 34.6, 24.9, 23.2; Anal. calcd for C_7H_9NOS: C 54.17, H 5.84, N 9.02, S 20.66; found: C 54.11, H 5.92, N 9.12, S 20.60.

2.3c *1-Cyclopropyl-2-thiocyanatoethanone* ***(3n)***: Oil; IR (KBr): υ 2927, 2152 (-SCN), 1700; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.20 (s, 2H), 2.15–2.00 (m, 1H), 1.35–0.98 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.3, 111.3, 44.7, 120.5, 12.8; Anal. calcd for C_6H_7NOS: C 51.04, H 5.00, N 9.92, S 22.71; found: C 51.12, H 4.94, N 10.01, S 22.65.

3. Results and discussion

When a mixture of ammonium thiocyanate (2 mmol), ketone (1 mmol), and a stoichiometric amount of Selectfluor^{TM} was stirred at room temperature in CH_3CN corresponding α-ketothiocyanates (**3a–n**) were obtained in excellent yield (table 1). The reactions were completed smoothly within 25 to 75 min, and the products were isolated by a simple workup procedure. Various ketones such as acetophenones, cyclic ketones, and aliphatic ketones all gave regioselective products in good to excellent yields. No fluoride products were observed under the reaction conditions. All the products were characterized by ^1H NMR, ^{13}C NMR, IR, element analysis, and by comparison with known samples, IR spectrum showed the characteristic peak of -SCN at 2122–2168 cm^{-1}.

A plausible mechanism for this reaction is proposed in scheme 2, the reaction may proceed *via* the electrophilic substitution of ketones by *in situ* generated thiocyanogen (^+SCN) from Selectfluor and ammonium thiocyanate (scheme 2).

To illustrate the efficiency of the proposed method, table 2 compares some of our results with some of those reported for relevant reagents in the literature, which demonstrates its significant superiority. Compared with some of the reported methods in table 2, the present method has a short reaction time, good yield, and solvent-free conditions.

4. Conclusion

In summary, Selectfluor^{TM} can effectively promote the reaction of ammonium thiocyanate with ketones to afford α-ketothiocyanates. The reactions are conducted under mild conditions and afford regioselective thiocyanated products in good to excellent yields.

Acknowledgement

We acknowledge the financial support from Xinxiang Central Hospital and Xinxiang Medical University.

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