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Oxone as a Mild, Inexpensive, and Environmentally Benign Oxidant for the α-Thiocyanation of Ketones

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Abstract: An efficient and direct approach for the α-thiocyanation of ketones with α-hydrogens has been developed using ammonium thiocyanate as a thiocyanating agent and oxone as an oxidant in methanol.

Keywords: Ammonium thiocyanate; Carbonyl compounds; Oxone; Thiocyanation

INTRODUCTION

α-Thiocyanation of ketones is a one of the most important methods for the formation of carbon–sulfur bonds in organic synthesis.[1,2] Thiocyanates are found in many biologically important natural products such as anticancer agents formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[3] These thiocyanates are versatile intermediates in the synthesis of various sulfur- bearing heterocyclic compounds and many of these heterocycles possess herbicidal and other important biological activities.[4] In view of the versatility of the thiocyanato group in heterocycle formation, it would be significant to probe the thiocyanation of various ketones. The traditional methods for generating organic thiocyanates involve multistep synthetic sequences and drastic reaction conditions because of the poor nucleophilicity of the thiocyanate anion.[5–8] Recently, there have been some reports on the

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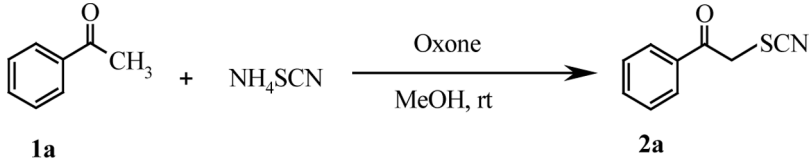
direct α-thiocyanation of ketones using dichloroiodobenzene/lead(II) thiocyanates, potassium peroxydisulphate/copper(II) complex, and iodine/methanol.[9–11] However, some of these reported methodologies for thiocyanation require large amounts of strong oxidizing agents, toxic metal thiocyanates, long reaction times, and high temperature; result in low yields for some compounds; and also involve the formation of a complex mixture of products. Hence, there is a need to develop an alternative method for α-thiocyanation of ketones. Oxone is a cheap, nontoxic, and readily accessible oxidizing reagent. It is a versatile oxidizing agent for a wide range of functional group transformations such as oxidation of alcohols, alkenes, sulfides, and *tert*-amines.[12–15] In addition to this, it is a stable, nonhygroscopic reagent and is easy to handle, which makes it an environmentally friendly oxidant. The reactions with oxone generally occur at room temperature. However, there have been no reports on the use of oxone for the thiocyanation of ketones.

RESULTS AND DISCUSSION

We herein report a simple, efficient, and selective approach for the direct α-thiocyanation of ketones using oxone as a safe and environmentally friendly oxidant. Accordingly, treatment of acetophenone (**1a**) with 2 eq. of ammonium thiocyanate in the presence of 1.2 eq. of oxone in methanol at room temperature gave the α-thiocyanated product (**2a**) in 86% yield (Scheme 1).

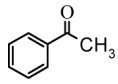
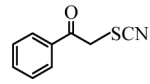
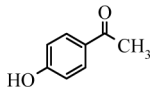
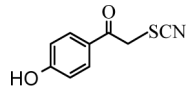
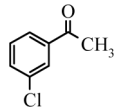
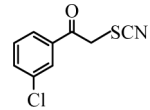
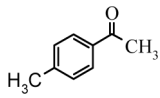
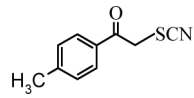
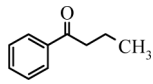
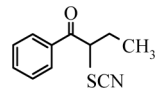
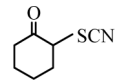
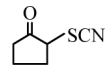
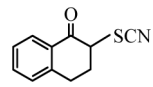
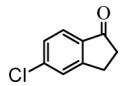
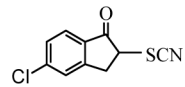
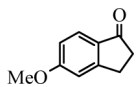
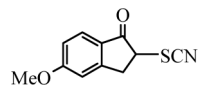
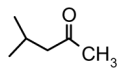
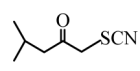
This method was successfully applied to a number of other acetophenone derivatives (entries **b–e**, Table 1) such as 4-hydroxyacetophenone, 4-methylacetophenone, 3-chloroacetophenone, and butyrophenone. The presence of electron-donating groups on acetophenone increases the yields of products (entries **b** and **d**, Table 1). Similarly, various cyclic ketones such as cyclohexanone, cyclopentanone, 1-tetralone, and substituted indanones (entries **f–j**, Table 1) also reacted readily with ammonium thiocyanate to give the corresponding α-thiocyanated products in good yields. When compared to acetophenone derivatives, aliphatic ketones reacted rapidly to give α-thiocyanated products (entries



1a **2a**

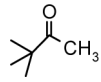
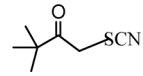
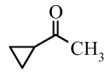
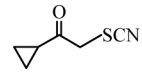
Scheme 1.

Table 1. Thiocyanation of ketones with oxone in methanol at room temperature

Entry	Substrate	Product	Time (h)[a]	Yield (%)[b]
a			6.0	86
b			5.5	90
c			6.0	82
d			6.5	89
e			7.0	88
f			5.5	86
g			5.0	88
h			6.0	86
i			6.5	85
j			6.0	87
k			5.0	86

(*Continued*)

Table 1. Continued

Entry	Substrate	Product	Time (h)[a]	Yield (%)[b]
l			5.0	88
m			5.0	89

[a]The reaction time.
[b]Isolated yields of products after column chromatography.

k–m, Table 1). The main advantage of this method is that a variety of ketones having α-hydrogens readily underwent thiocyanation at room temperature. All the products were characterized by ^{1}H NMR, IR, and mass spectroscopy and by comparison with known samples.[9–11] IR spectrum showed the characteristic peak of -SCN at 2158 cm^{-1}. The scope of this methodology is demonstrated with respect to various ketones, and results are presented in Table 1. The effect of various solvents on the thiocyanation of ketones was primarily observed by taking acetophenone as an example. Both the yields and reaction times are listed in Table 2. In methanol, the reaction took place at room temperature with high conversion. However, low yields were obtained in solvents such as acetonitrile, *tert*-butanol, and carbon tetrachloride. Therefore, methanol is the solvent of choice for the thiocyanation of ketones.

In conclusion, we have described a simple, convenient, and efficient protocol for the thiocyanation of ketones using oxone as an inexpensive and readily available oxidant. This method offers advantages such as mild reaction conditions, operational simplicity and the use of economically

Table 2. Effect of solvent on the thiocyanation of **1a**

Solvent	Time (h)[a]	Yield (%)[b]
Methanol	6	86
Acetonitrile	20	30
tert-Butanol	20	40
Carbon tetrachloride	24	35

[a]Reaction time.
[b]Isolated and optimized yields.

viable reagents, which make it a useful and attractive process for the thiocyanation of ketones.

EXPERIMENTAL

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Varian Unity 200 and Bruker 300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Typical Experimental Procedure

A solution of carbonyl compound (1.0 mmol) and ammonium thiocyanate (2.0 mmol) in 10 mL of methanol was treated with oxone (1.2 mmol), and the resulting mixture was stirred at room temperature until completion of the reaction as monitored by thin-layer chromatography (TLC). After completion of reaction, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The resulting product was purified by column chromatography on silica gel (100–200 mesh, ethyl acetate/hexane) to afford pure α-ketothiocyanate. The products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.

Spectral Data for Selected Compounds

1-(4-Hydroxyphenyl)-2-thiocyanato-1-ethanone (Entry 2**b**)

White solid, mp 160–162°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.14 (s, 1H), 7.83 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.82 (s, 2H);^{13} C NMR ($CDCl_3$, 75 MHz): δ188.9, 162.7, 129.9, 123.8, 114.5, 111.2, 41.5; IR (KBr): 3280, 2924, 2166, 1668 cm^{-1}; LCMS: m/z 216 ($M^+ + Na$).

1-Phenyl-2-thiocyanato-1-butanone (Entry 2**e**)

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, $J = 7.3$ Hz, 2H), 7.64 (t, $J = 7.3$ Hz, 1H), 7.51 (t, $J = 7.3$ Hz, 2H), 5.03 (t, $J = 5.8$, 1H), 2.36–2.10 (m, 2H), 1.05 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.4, 134.3, 133.8, 129.0, 128.5, 111.3, 55.6, 29.5, 10.0; IR (KBr): 2925, 2159, 1672 cm^{-1}; LCMS: m/z 228 ($M^+ + Na$).

5-Chloro-2-thiocyanato-1-indanone (Entry 2**i**)

Light brown solid, mp 116–118°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (d, $J = 7.5$ Hz, 1H), 7.50 (s, 1H), 7.45 (d, $J = 8.3$ Hz, 1H), 4.12 (dd, $J_{1-2} = 4.5$, $J_{1-3} = 8.3$ Hz, 1H), 3.81 (dd, $J_{1-2} = 8.3$, $J_{1-3} = 18.1$ Hz, 1H), 3.38 (dd, $J_{1-2} = 4.5$, $J_{1-3} = 18.1$ Hz, 1H); IR (KBr): 3020, 2158, 1721, 1215 cm^{-1}. LCMS: m/z 224 ($M^+ + 1$).

4-Methyl-1-thiocyanato-2-pentanone (Entry 2**k**)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.00 (s, 2H), 2.44 (d, $J = 6.7$ Hz, 2H), 2.25–2.12 (m, 1H), 0.97 (d, $J = 6.7$ Hz, 6H); IR (KBr): 3020, 2929, 2159, 1718 cm^{-1}; LCMS: m/z 158.2 ($M^+ + 1$).

1-Cyclopropyl-2-thiocyanato-1-ethanone (Entry 2**m**)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.17 (s, 2H), 2.10–1.98 (m, 1H), 1.31–1.00 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 201.1, 111.4, 44.2, 19.7, 12.4; IR (KBr): 2924, 2157, 1696 cm^{-1}; LCMS: m/z 164 ($M^+ + Na$).

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