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I_2O_5 as a mild, inexpensive, and environmentally benign oxidant for the α-thiocyanation of ketones

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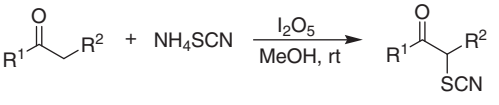
α-Thiocyanation of various ketones has been achieved using ammonium thiocyanate as a thiocyanation reagent and I_2O_5 as an oxidant in methanol solution at room temperature.



Keywords: thiocyanation; ketones; ammonium thiocyanate; I_2O_5; synthesis

1. Introduction

Thiocyanate is a versatile synthon (*1*), which can be readily transferred to other functional groups such as sulfide (*2*), aryl nitrile (*3*), thiocarbamate (*4*), and thionitrile (*5*). The development of new synthetic methods for introducing thiocyanate functionality is always demanded. α-Thiocyanato carbonyl compounds are valuable precursors for the synthesis of heterocyclic ring systems such as 2-amino-1,3-thiazines, thiazoles, and their derivatives (*1*), some of which are associated with herbicidal and other biological activities (*6*). Thiocyanato group plays an important role in certain anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables (*7*).

Several methods have been developed for the thiocyanation of ketones using bromodimethylsulfonium bromide/ammonium thiocyanate (*8*), oxone/ammonium thiocyanate (*9*), heteropolyacid/ammonium thiocyanate (*10*), (dichloroiodo)benzene/lead (II) thiocyanate (*11*), potassium peroxydisulfate/copper(II) complex (*12*), and I_2/ammonium thiocyanate (*13*). However, many of these methodologies are associated with one or more disadvantages such as (*i*) harsh reaction conditions, *e.g.* treatment with 1.2 equiv. (dichloroiodo)benzene/lead (II) thiocyanate at 0 °C in CH_2Cl_2 for 2–4 h (*11*) and heating at 70 °C in aq. CH_3CN in the presence of 2.0 equiv. potassium peroxydisulfate/copper (II) complex for 1–5 h (*12*), (*ii*) prolonged reaction time

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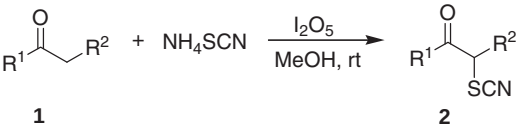
(*9, 11–13*), and (*iii*) requirement of hazardous and carcinogenic organic solvents such as CH_3CN (*12*) and CH_2Cl_2 (*8, 10, 11*). Thus, the development of environmentally benign, high yielding, and clean approaches for the α-thiocyanation of ketones is in demand.

Recently, the use of hypervalent iodine reagents as oxidants in organic synthesis has attracted increasing interest due to their mild, selective, and environmentally benign oxidizing properties (*14*). I_2O_5 is one of the most versatile oxidizing agents due its safe, benign, economic, commercially available, and environmentally friendly nature (*15*). It has been extensively used in industry and organic synthesis (*15, 16*). In this article, we report a direct and metal-free approach to the α-thiocyanation of ketones using I_2O_5 in methanol solution (Scheme 1).



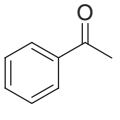
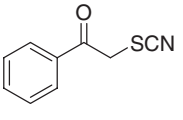
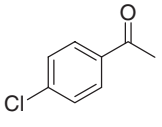
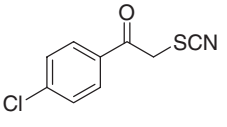
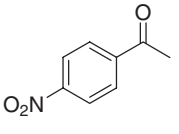
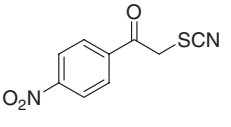
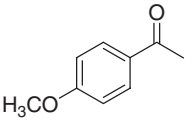
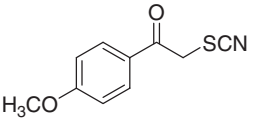
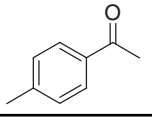
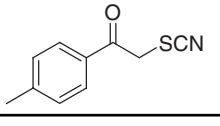
1 **2**

Scheme 1. α-thiocyanation of ketones using I_2O_5.

2. Results and discussion

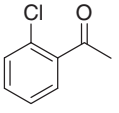
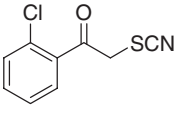
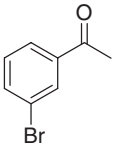
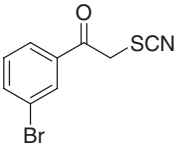
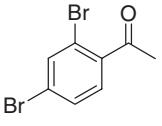
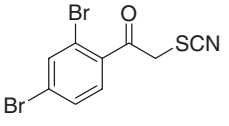
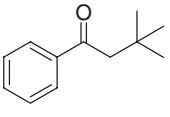
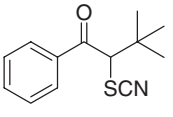
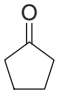
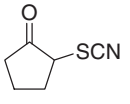
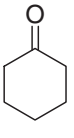
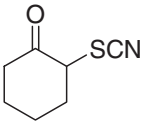
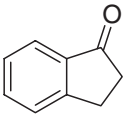
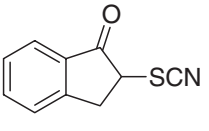
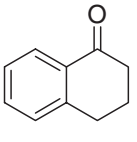
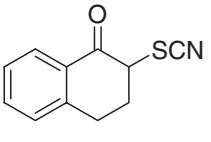
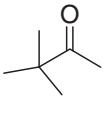
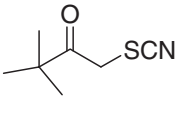
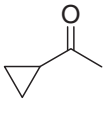
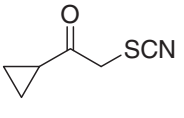
First, we attempted α-thiocyanation of acetophenone (**1a**) with ammonium thiocyanate using a stoichiometric amount of I_2O_5. The reaction went to completion within 20 min at room temperature, and the desired product, 1-phenyl-2-thiocyanatoethanone (**2a**), was obtained in 88% yield (Table 1, Entry **a**).

Table 1. α-Thiocyanation of ketones promoted by I_2O_5.[a]

Entry	Ketones	Product	Time (min)	Yield (%)[b]	Reference
a			20	88	(*8*)
b			25	85	(*8*)
c			30	83	(*8*)
d			20	89	(*8*)
e			15	92	(*8*)

(*Continued*)

Table 1. Continued

Entry	Ketones	Product	Time (min)	Yield (%)[b]	Reference
f			30	81	(*10*)
g			35	79	(*10*)
h			35	80	The work
i			30	78	The work
j			40	85	(*8*)
k			45	88	(*8*)
l			50	86	(*10*)
m			50	84	(*10*)
n			45	79	(*9*)
o			40	82	(*9*)

Notes: [a]Reaction conditions: ketones (1.0 mmol); NH_4SCN (2.0 mmol); I_2O_5 (1.0 mmol); rt; MeOH. [b]Isolated yield.

This result provided an incentive to study further reactions with various acetophenone derivatives (Entries **b**–**i**, Table 1) such as 4-chloroacetophenone, 4-nitroacetophenone, 4-methoxylacetophenone, 4-methylacetophenone, 2-chloroacetophenone, 3-bromoacetophenone, 2,4-dibromoacetophenone, and 3,3-dimethyl-1-phenylbutan-1-one. The presence of electron-donating groups on acetophenone increases the yields of products (Entries **d** and **e**, Table 1). Similarly, various cyclic ketones such as cyclohexanone, cyclopentanone, 1-tetralone, and indanone (Entries **j**–**m**, Table 1) also reacted readily with ammonium thiocyanate to give the corresponding α-thiocyanated products in good yields. When compared with acetophenone derivatives, aliphatic ketones reacted rapidly to give α-thiocyanated products (Entries **n**–**o**, 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 IR, ^{1}H NMR, and element analysis and by comparison with known samples. IR spectra showed the characteristic peaks of $-$SCN group between 2120 and 2160 cm^{-1} and the C$-$S stretching between 650 and 760 cm^{-1}. The scope of this methodology is demonstrated with respect to various ketones, and the results are presented in Table 1.

The solvent effect on product yields was investigated using **1a** as a substrate. Both the yields and reaction times listed in Table 2 suggest that methanol appears to be very favorable for thiocyanations. Therefore, methanol is the solvent of choice for the thiocyanation of ketones.

Mechanistically, the reaction may proceed via the electrophilic substitution of acetophenone by thiocyanogen ($^+$SCN) formed *in situ* from I_2O_5 and ammonium thiocyanate (Scheme 2).

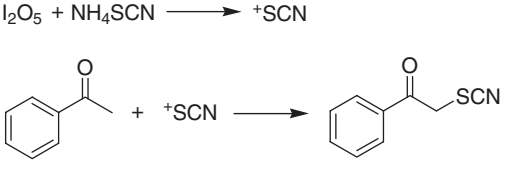
To emphasize the effect of the oxidant, a model reaction between acetophenone and ammonium thiocyanate is described, and different hypervalent iodine oxidants were subjected to the reaction. All the reactions were run under the same conditions and similar amounts of oxidant (1 equiv.) were used. As can be seen in Table 3, satisfactory results were obtained only with I_2O_5 (Entry 4).

To illustrate the efficiency of the proposed method, Table 4 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 4, the present method has a short reaction time, good yield, and solvent-free conditions.

Table 2. Solvent effect on the reaction of acetophenone and ammonium thiocyanate.

Entry	Solvent	Time (min)	Yield (%)[a]
1	CH_3CN	60	46
2	CH_2Cl_2	45	53
3	$CHCl_3$	45	59
4	CCl_4	60	40
5	EtOH	25	75
6	MeOH	20	86
7	THF	35	71

Note: [a]Isolated yield.



Scheme 2. The plausible mechanism of the reaction.

Table 3. Effect of hypervalent iodine oxidant on the reaction of acetophenone and ammonium thiocyanate.[a]

Entry	Hypervalent iodine oxidant	Time (min)	Solvent	Yield (%)[b]
1	Dess–Martin periodinane	35	CH_3CN	52
2	*o*-Iodoxylbenzoic acid	25	CH_3CN	70
3	HIO_3	20	$CHCl_3$	72
4	I_2O_5	20	MeOH	86
5	HIO_4	20	$CHCl_3$	53
6	$PhI(OAc)_2$	30	CH_3CN	68

Notes: [a]Reaction conditions: acetophenone (1 mmol); NH_4SCN (2 mmol); hypervalent iodine oxidant (1 mmol); rt. [b]Isolated yield.

Table 4. α-Thiocyanation of acetophenone in comparison with other literatures.

Entry	Catalyst and conditions	Solvent	Time (h)	Yield (%)	Reference
1	Oxone (1.2 equiv.)/NH_4SCN thiocyanate(2.0 equiv.); r.t.	MeOH	6	86	(*9*)
2	I_2 (1. equiv.)/NH_4SCN (2.0 equiv.); reflux	MeOH	6	85	(*13*)
3	Bromide (1.1 equiv.)/NH_4SCN (2.0 equiv.); r.t.	CH_2Cl_2	0.33	95	(*8*)
4	I_2O_5 (1.0 equiv.)/NH_4SCN (2.0 equiv.); r.t.	MeOH	0.33	86	The work

3. Conclusion

In conclusion, I_2O_5 has proved to be an effective reagent for the α-thiocyanation of various ketones under extremely mild and neutral conditions. In addition to its simplicity and efficiency, this method affords the desired thiocyanates in excellent yields in short reaction times.

4. Experimental

4.1. *General*

IR spectra were determined on an FTS-40 infrared spectrometer; NMR spectra were recorded on a Bruker AV-400 spectrometer at room temperature using TMS as an internal standard, and coupling constants (J) were measured in hertz. Elemental analyses were performed using 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.

4.2. *General procedure for the preparation of 2*

To a stirred solution of ammonium thiocyanate (2 mmol) and ketones (1 mmol) in MeOH (10 mL), I_2O_5 (1 mmol) was added. The resulting mixture was allowed to stir at room temperature for an appropriate time (Table 1). After completion of the reaction (TLC), the reaction mixture was quenched with water. The reaction mixture was successively extracted with ethyl acetate, washed with $Na_2S_2O_3$, 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 **2**. All products were identified by ^1H NMR, IR, and elemental analyses.

4.3. *Spectral data for new compounds*

4.3.1. *1-(2,4-Dibromophenyl)-2-thiocyanatoethanone (**2h**)*

IR (KBr): υ 3152, 2985, 2152 (−SCN), 1674, 1594, 1200, 996 813, 709 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.06–7.55 (m, 3H), 4.82 (s, 2H); Anal. Calcd for $C_9H_5Br_2NOS$: C 32.27, H 1.50, N 4.18, S 9.57; found: C 32.20, H 1.56, N 4.10, S 9.49.

4.3.2. *3,3-Dimethyl-1-phenyl-2-thiocyanatobutan-1-one (**2i**)*

IR (KBr): υ 3058, 2947, 2149 (−SCN), 1676, 1590, 982 745 (C−S) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.98 (d, 2H, $J = 7.6$ Hz), 7.68 (t, 1H, $J = 7.6$ Hz), 7.49 (t, 2H, $J = 7.6$ Hz), 4.92 (s, 1H), 1.01 (s, 9H); Anal. Calcd for $C_{13}H_{15}NOS$: C 66.92, H 6.48, N 6.00, S 13.74; found: C C 67.01, H 6.39, N 6.10, S 13.69.

Acknowledgement

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