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Iodine/MeOH as a novel and versatile reagent system for the synthesis of α-ketothiocyanates

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Abstract—Ketones possessing α-hydrogens undergo smooth thiocyanation with ammonium thiocyanate in the presence of molecular iodine in refluxing methanol to produce the corresponding α-ketothiocyanates in excellent yields with high selectivity. The use of iodine makes this procedure simple, convenient and cost effective.

The direct α-thiocyanation of ketones is an important carbon–heteroatom bond forming reaction in organic synthesis.[1] α-Ketothiocyanates are useful intermediates in the synthesis of sulfur-containing heterocycles such as thiazoles.[2] Some of these heterocycles exhibit herbicidal and other important biological activities.[3] In addition to this, the thiocyanato group is found in several anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[4] Thus, the direct thiocyanation of ketones is of prime importance. Consequently, various methods have been developed for the α-thiocyanation of ketones using a variety of reagents under diverse reaction conditions.[5,6] However, these classical methods involve multi-step synthetic sequences and often harsh reaction conditions and also the yields are typically low because of the poor nucleophilicity of thiocyanate. Direct thiocyanation of ketones has been reported using the dichloroiodobenzene/lead(II) thiocyanate reagent system, which works well with silyl enol ethers.[7] Furthermore, many of these reported methods involve the use of a large excess of strong oxidizing agents and toxic metal thiocyanates resulting in low conversions due to the formation of complex mixtures of products.[8] Since organosulfur compounds have become increasingly useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient, and efficient approaches for their synthesis are desirable. Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available reagent for various organic transformations, affording the corresponding products with high selectivity in excellent yields. The mild Lewis acidity associated with iodine has led to its use in organic synthesis in catalytic to stoichiometric amounts.[9]

In continuation of our interest on the use of molecular iodine for various transformations,[10] we herein report the first direct and metal catalyst-free synthesis of α-ketothiocyanates by α-thiocyanation of enolizable ketones with ammonium thiocyanate under neutral conditions. Initially, we studied the α-thiocyanation of acetophenone **1** as a model substrate with 2 equiv of ammonium thiocyanate using 1 equiv of molecular iodine in refluxing methanol. The reaction went to completion in 6 h and the product, 1-phenyl-2-thiocyanatoethanone **2a**, was obtained in 85% yield (Table 1, entry a; Scheme 1).

The excellent catalytic activity of iodine in the thiocyanation of acetophenone prompted us to investigate its use in reactions with other enolizable ketones. Interestingly, various substituted ketones, such as 3-chloroacetophenone, 2-trifluoromethylacetophenone, and 2-acetylnaphthalene, reacted efficiently with ammonium thiocyanate to afford the corresponding α-thiocyanatoketones in high yields (Table 1, entries b–d). Like acetophenones, cyclic ketones such as 1-tetralone, 2-phenylchroman-4-one, cyclopentanone, 2-methylcyclohexanone, 4,4-dimethylcyclohex-2-enone, cycloheptanone, and cyclododecanone reacted well under similar

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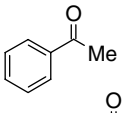
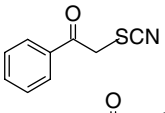
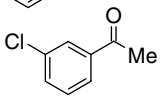
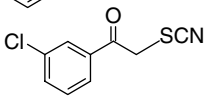
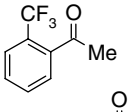
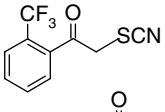
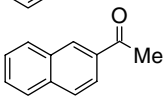
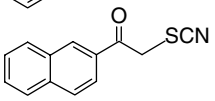
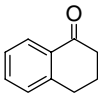
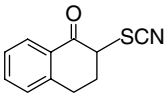
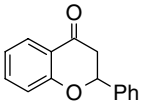
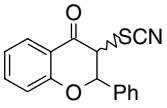
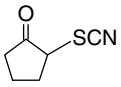
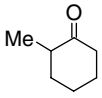
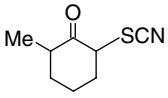
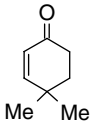
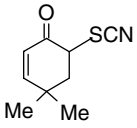
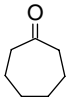
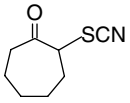
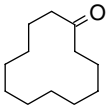
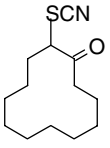
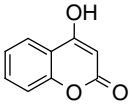
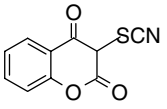
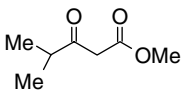
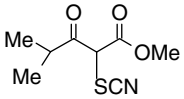
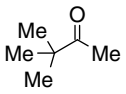
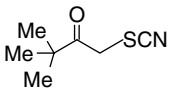
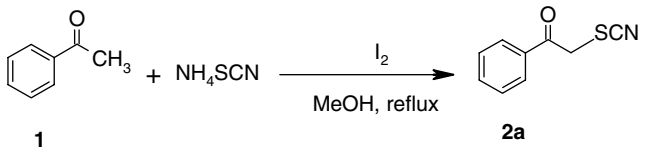
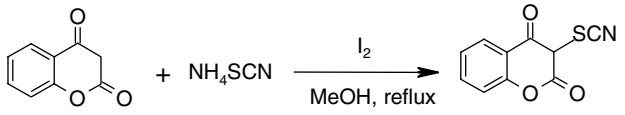
Table 1. Iodine-promoted thiocyanation of ketones with NH_4SCN in methanol

Entry	Ketone	Product[a]	Time (h)	Yield[b] (%)
a			6.0	85
b			6.5	80
c			6.5	82
d			6.0	79
e			5.5	84
f			6.0	85
g			5.5	83
h			5.0	86
i			5.0	81
j			6.5	75
k			7.0	82
l			5.0	84
m			6.5	73
n			6.0	70

[a] Al products were characterized by IR, ^1H NMR and high resolution mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 1.

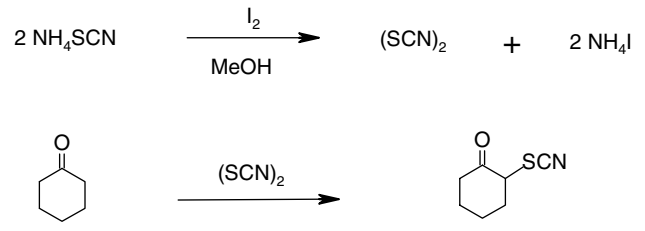


Scheme 2.

conditions to give α-ketothiocyanates (Table 1, entries e–k). Similarly, the β-keto ester, chroman-2,4-dione also afforded the corresponding 3-thiocyanato-chroman-2,4-dione in good yield (Table 1, entry l; Scheme 2).

Furthermore, sterically hindered substrates such as methyl 4-methyl-3-oxopentanoate and *t*-butyl methyl ketone also reacted efficiently under these reaction conditions (Table 1, entries m and n). α-Thiocyanation of cyclic ketones gave higher yields compared to acyclic ketones. The best results were obtained with cyclohexane derivatives in refluxing methanol. Although, the reactions proceeded smoothly at room temperature, the products were obtained in low yields (40–50%) after long reaction times (16 h). However, no reaction was observed in the absence of catalyst, even in refluxing methanol over a long reaction time (12 h). As solvent, methanol appeared to give the best results. The products were characterized by ^{1}H NMR, IR, and mass spectroscopic data and also by comparison with authentic samples.[7] This method is very clean and free from side products. Amongst the various oxidants such as $Mn(OAc)_3{\cdot}2H_2O$, $Bi(NO_3)_3{\cdot}5H_2O$ and IBX tested, molecular iodine was found to be the most effective in terms of conversion and reaction rates. The scope and generality of this process is illustrated with respect to various enolizable ketones and ammonium thiocyanate and the results are presented in Table 1.[11]

The reaction most likely proceeds via the formation of active thiocyanogen, $(SCN)_2$ from molecular iodine and ammonium thiocyanate as reported previously.[12] Thiocyanogen reacts rapidly with the enolizable ketone to produce α-ketothiocyanate (Scheme 3).



Scheme 3.

In summary, molecular iodine has proved to be a useful and novel reagent for selective thiocyanation of ketones to produce α-ketothiocyanates in high yields. The experimental procedure is simple, convenient, and the reaction conditions are amenable to scale up.

Acknowledgements

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11. *General procedure*: To a stirred solution of ammonium thiocyanate (2 mmol), and iodine (1 mmol) in methanol (10 mL), the ketone (1.0 mmol) was added and the mixture was stirred at reflux for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2 × 15 mL). The combined extracts were washed with a 15% solution of aqueous sodium thiosulfate, dried over anhydrous Na_2SO_4 and

concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5:9.5) to afford the pure thiocyanato derivative.

Spectral data for selected products: Compound **2b**: 2-(3-Chlorophenyl)-2-oxo-ethyl thiocyanate (Table 1, entry b): Pale yellow solid, mp 68–70 °C, IR (KBr): ν 3065, 2988, 2929, 2152, 1680, 780, 678 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.72 (s, 2H), 7.48 (m, 1H), 7.64 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.92 (s, 1H). EIMS: m/z (%): 210 M^+ (100), 125 (70), 91 (80), 76 (20). HRMS Calcd for C_9H_7NOSCl: 211.9936. Found: 211.9936 ($M+H^+$).

Compound **2d**: 2-(2-Naphthyl)-2-oxo-ethyl thiocyanate (Table 1, entry d): Light yellow solid, mp 102–104 °C IR (KBr): ν 3051, 2991, 2933, 2153, 1661, 1622, 739, 674 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.90 (s, 2H), 7.64 (m, 2H), 7.94 (m, 4H), 8.44 (s, 1H). EIMS: m/z (%): 227 M^+ (100), 99 (40), 66 (35). HRMS Calcd for $C_{13}H_{10}NOS$: 228.0483. Found: 228.0492 ($M+H^+$).

Compound **2i**: 4,4-Dimethyl-6-thiocyanato-cyclohex-2-enone (Table 1, entry i): Yellow liquid, IR (KBr): ν 2965, 2928,2870, 2083, 1718, 1681, 813, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.34 (s, 3H), 3.75 (m, 2H), 4.47 (m, 1H), 5.93 (d, $J = 10.1$ Hz, 1H), 6.75 (d, $J = 10.1$ Hz, 1H). EIMS: m/z (%): 181 M^+ (100), 178 (15), 149 (20), 122 (40) 107 (65), 47 (60). HRMS Calcd for $C_9H_{11}NOSNa$: 204.0459. Found: 204.0453 ($M+Na^+$).

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