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Direct α-thiocyanation of carbonyl and β-dicarbonyl compounds using potassium peroxydisulfate–copper(II)☆

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Abstract—A convenient approach for the direct α-thiocyanation of carbonyl and β-dicarbonyl compounds has been developed using ammonium thiocyanate as the thiocyanating agent and potassium peroxydisulfate as the oxidant in the presence of a catalytic amount of copper(II) sulfate in aqueous acetonitrile. The catalyst and oxidizing agent used in the reaction are inexpensive and provide good to excellent yields.

Organic thiocyanates include not only biologically important natural products such as anticancer natural products[1] formed by deglycosylation of glucosinolates derived from cruciferous vegetables, but are also versatile intermediates for the synthesis of various heterocyclic compounds.[2] Some of these heterocycles possess herbicidal and other important biological activities.[3] The traditional method for generating organic thiocyanates involves nucleophilic displacement using thiocyanate. Thus, the α-thiocyanation of carbonyl compounds involves one additional step, functionalization at the desired position before thiocyanation. Functionalization has been carried out by bromination, tosylation[4] and with thiocyanate anions[5,6] via S_N2 displacement. All these methods require drastic conditions due to the poor nucleophilicity of the thiocyanate anion. Thiocyanates can be synthesized via electrophilic or radical reactions using thiocyanogen and thiocyanogen halides. Also, Friedel Crafts catalysis[7] involving heterolytic and homolytic conditions[8] are reported to generate thiocyanate derivatives using different thiocyanogens such as dithiocyano compounds, lead(II) thiocyanate and thiocyanogen chloride. Rearrangement reactions[9] including fragmentation and reaction with diazonium salts[10] have also been reported. Recently, there was a report on the direct thiocyanation of carbonyls using dichloroiodobenzene lead(II) thiocyanates.[11] All the reported methods for thiocyanation of various chemical entities give complex mixtures of products and require high temperatures, toxic chemicals, long reaction times, afford low yields and are costly. Potassium peroxydisulfate has been explored by Bhatt and Perumal for the conversion of electron rich benzylic hydrocarbons to carbonyls.[12] Several other investigations citing the oxidizing properties of potassium peroxydisulfate (PPDS) due to its strong redox potential viz.; Elbs and Baeyer–Villiger oxidation are reported.[13]

The peroxydisulfate ion is a versatile oxidizing agent in aqueous solution[14] and is used in many organic reactions in the presence of metals acetates[15] such as cobalt(III), copper and iron.[16] The reactions involving these ions are generally slow at room temperature and the rate of peroxydisulfate decomposition increases greatly at a higher temperature.[15] The standard oxidation–reduction potential of PPDS in oxidation reactions is estimated to be −2.01 V.[14]

We report here an efficient, selective and direct α-thiocyanation of carbonyl and β-dicarbonyl compounds with ammonium or potassium thiocyanates using potassium peroxydisulfate (PPDS) and copper(II) sulfate as the oxidizing agent in aqueous acetonitrile (MeCN–H_2O, 7:3) (Scheme 1).

In the absence of metal ions the thiocyanation of carbonyl and β-dicarbonyls was less effective. Therefore,

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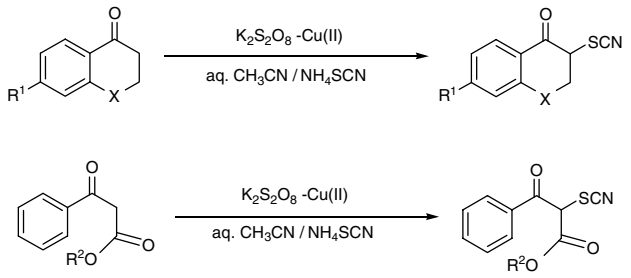


Scheme 1.

we used potassium peroxydisulfate–copper(II) sulfate for the reaction which increased the rate of the reaction in comparison to peroxydisulfate alone. The presence of copper(II) might increase the rate of decomposition of peroxydisulfate into radical anions.

The influence of various solvents on the yield of the reaction was investigated using the carbonyl compound from entry 1, Table 2 as an example. The results obtained showed that aqueous acetonitrile was the best choice. This may be due to the enhanced solubilizing power of this solvent for the oxidant as well as the substrate (Table 1). Potassium peroxydisulfate (PPDS) mediated thiocyanation of cyclic ketones occurred rapidly to afford α-thiocyanoketones in good yields (Table 2). Thiocyanation of β-dicarbonyl compounds occurred in moderate yields (Table 3). The thiocyanation of cyclic ketones gave better yields in comparison with acyclic ketones. The best results were obtained with six-membered rings. The presence of the heteroatom in the six-membered ring did not affect α-thiocyanation.

Typical experimental procedure: Potassium peroxydisulfate (20 mmol) and copper sulfate (2.5 mmol) in water were added to a solution of ammonium thiocyanate (15 mmol) in acetonitrile–water (7:3). The reaction mixture was stirred at room temperature for 10 min followed by the addition of a solution of carbonyl compound (10 mmol) in acetonitrile (15 ml). The reaction mixture was stirred at 60–70 °C for 1–5 h. The reaction was diluted with water and extracted with ethyl acetate. The concentrated residue was purified by column chromatography (elution with EtOAc–hexane 1:9) to afford the thiocyanoketone in a good yield (Tables 2 and 3). The analytical data was in a good agreement with the product structures.[17]

In conclusion, this report offers a simple, efficient and direct α-thiocyanation of carbonyl and β-dicarbonyl compounds. The oxidant, potassium peroxydisulfate–copper(II) [PPDS–Cu(II)] is cost effective and provides good yields.

Table 1. Effect of solvent on the reaction yield of **1** with peroxydisulfate and peroxydisulfate–Cu(II)

Entry	Solvent	Peroxydisulfate[a] yield[b] (%)	Peroxydisulfate–Cu(II)[a] yield[b] (%)
1	$CHCl_3$	15	30
2	CH_2Cl_2	22	37
3	THF	31	44
4	MeOH	38	50
5	CH_3CN	42	68
6	Aq MeOH	44	57
7	Aq CH_3CN	51	86

[a] Reaction conditions: carbonyl compound **1** (10 mmol), peroxydisulfate (20 mmol), Cu(II) (2.5 mmol), ammonium thiocyanate (15 mmol), 70 °C, 1 h.

[b] The yield reported is after isolation by column chromatography on silica gel.

Table 2. α-Thiocyanation of carbonyl compounds

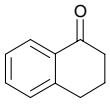
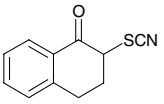
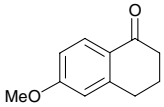
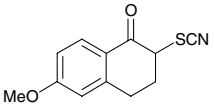
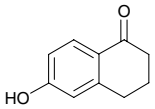
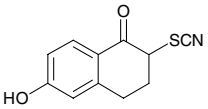
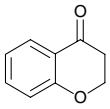
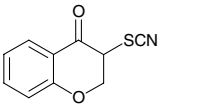
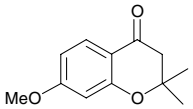
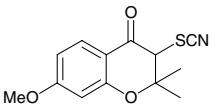
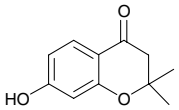
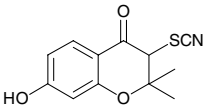
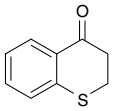
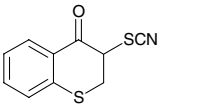
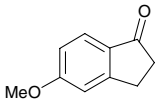
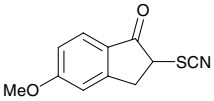
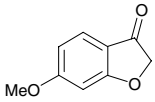
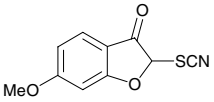
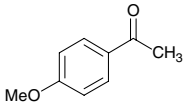
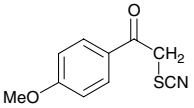
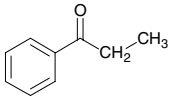
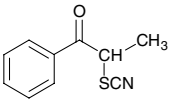
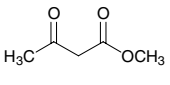
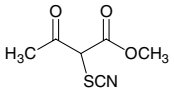
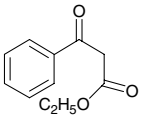
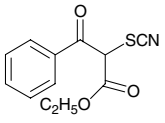
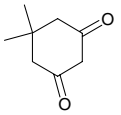
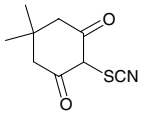
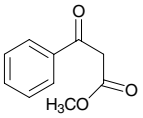
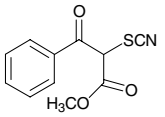
Entry	Carbonyl compound	Thiocyanoketone	Yield (%)	Time (h)
1			86	1
2			82	1
3			68	3
4			84	1.5
5			78	2
6			70	3
7			57	4
8			72	3
9			70	5
10			65	5
11			67	5

Table 3. α-Thiocyanation of β-dicarbonyl compounds

Entry	β-Dicarbonyl	Thiocyanoketone	Yield (%)	Time (h)
1			65	5
2			70	5
3			63	5
4			60	5

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17. *Spectral data of α-thiocyanation of carbonyl (Table 2)*. Compound **1**: ^{1}H NMR ($CDCl_3$, 200 MHz): 1.92–2.07 (m, 2H), 2.51–2.65 (m, 2H), 4.35 (dd, $J = 6.3$, 5.6 Hz, 1H), 6.89–6.98 (m, 2H), 7.38–7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.6, 138.4, 137.3, 132.8, 128.4, 128.2, 124.3, 111.7, 57.1, 31.7, 28.9. MS (FAB): $m/z = 203$. Compound **2**: IR (KBr, cm^{-1}) 2937, 2150, 1660. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.07–2.18 (m, 2H), 2.57–2.66 (m, 2H), 3.80 (s, 3H), 4.50 (dd, $J = 6.4$, 5.6 Hz, 1H), 6.35 (d, $J = 2.2$ Hz, 1H), 6.50 (dd, $J = 2.2$, 8.8 Hz, 1H), 7.76 (d, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.0, 165.2, 146.4, 130.3, 124.2, 114.4, 113.2, 112.0, 56.0, 55.0, 31.2, 29.0; UV (284, 226 and 205 nm); MS(FAB): $m/z = 233$. Compound **4**: IR (KBr, cm^{-1}): 2928, 2156, 1650, 1600. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.20 (m, 2H), 4.41 (dd, $J = 6.2$, 5.4 Hz, 1H), 6.90 (d, $J = 9.6$ Hz, 1H), 7.20–7.32 (m, 2H, ArH), 7.49–7.58 (m, 1H). MS(FAB): $m/z = 205$. Compound **5**: IR (KBr, cm^{-1}): 2155, 1668, 1604. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 6H), 3.85 (s, 3H), 4.11 (s, 1H), 6.37 (d, $J = 2.3$ Hz, 1H), 6.51 (dd, $J = 2.3$ Hz, 8.8 Hz, 1H), 7.78 (d, $J = 8.8$ Hz). MS (FAB): $m/z = 263$. Compound **7**: IR (KBr, cm^{-1}): 2161, 1677, 1600. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.40 (m, 2H), 4.41 (m, 1H), 7.00–7.08 (m, 1H), 7.23–7.38 (m, 2H), 7.46 (d, $J = 10$ Hz, 1H). MS (FAB): $m/z = 221$. Compound **8**: IR (KBr, cm^{-1}): 2158, 1713, 1600. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.80–3.00 (m, 2H), 3.80 (s, 3H), 4.17 (m, 1H), 6.37 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 2.4$ Hz, 8.8 Hz, 1H), 7.78 (d, $J = 8.8$ Hz). MS (FAB): $m/z = 219$. Compound **9**: IR (KBr, cm^{-1}): 2158, 1704, 1600. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.81 (s, 3H), 4.13 (s, 1H), 6.37 (d, $J = 2.3$ Hz, 1H), 6.51 (dd, $J = 2.3$ Hz, 8.8 Hz, 1H), 7.78 (d, $J = 8.8$ Hz, 1H). MS (FAB): $m/z =$ 221. Compound **10**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.70 (s, 3H), 4.34 (s, 2H), 6.89–6.92 (m, 2H), 7.57–7.62 (m, 2H). Compound **11**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (d, $J = 6.2$ Hz, 3H), 4.74 (q, $J = 6.2$ Hz, 1H), 7.31–7.46 (m, 3H) 7.75–7.88 (m, 2H). *Spectral data for the α-thiocyanation of β-dicarbonyl compounds (Table 3)*. Compound **12**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.57 (s, 3H), 3.42 (s, 3H), 5.43 (s, 1H). Compound **13**: IR (KBr, cm^{-1}): 2953, 2157, 1666, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34 (t, $J = 7.2$ Hz, 3H), 4.12 (q, $J = 7.2$ Hz, 2H), 5.47 (s, 1H), 7.24–7.49 (m, 3H), 7.74–7.81 (m, 2H). Compound **14**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 6H), 2.34 (s, 4H), 5.41 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 205.2, 203.1, 112.4, 73.8, 53.4, 53.7, 23.6, 17.6. Compound **15**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.67 (s, 3H), 5.49 (s, 1H), 7.20–7.42 (m, 3H), 7.74–7.81 (m, 2H).