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Trichloroisocyanuric Acid as a Novel and Versatile Reagent for the Rapid α-Thiocyanation of Ketones

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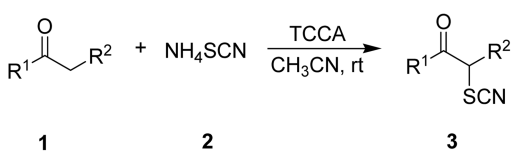
α-Thiocyanation of ketones is one of the most important reactions in organic synthesis. The thiocyano substituted compounds are useful intermediates in the synthesis of sulfur-containing heterocycles, in which the thiocyanate group will be readily transformed into other sulfur-bearing functionalities.[1] They are particularly useful for producing drugs and pharmaceuticals.[2] In view of the versatility of thiocyanate group in heterocyclic construction,[3] it will be of significance to probe the α-thiocyanation of ketones. Consequently, various methods have been developed for the α-thiocyanation of ketones, with a variety of reagents and under diverse reaction conditions.[4] However, these classical methods involve multi-step synthetic sequences and often harsh reaction conditions, and the yields are typically low, because of the poor nucleophilicity of thiocyanate. The use of the bromodimethylsulfonium 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] and I_2/ammonium thiocyanate[10] reagent systems have been reported for the direct thiocyanation of ketones. However, most 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, which in turn limit their practical utility in organic synthesis. 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.

Trichloroisocyanuric acid (TCCA), an inexpensive and easily available reagent with low toxicity and less corrosive property, has been widely used in organic reactions.[11] However, there have been no previous reports on the direct α-thiocyanation of ketones with ammonium thiocyanate in the presence of TCCA. In this article, we report a simple, convenient, and efficient protocol for the α-thiocyanation of ketones using TCCA in acetonitrile (Scheme 1).



1 **2** **3**

Scheme 1

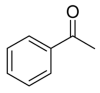
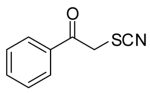
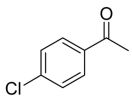
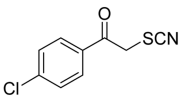
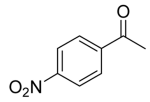
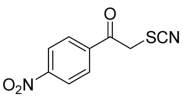
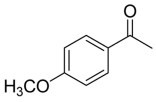
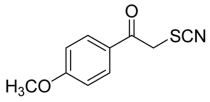
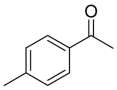
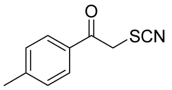
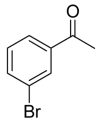
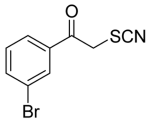
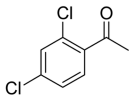
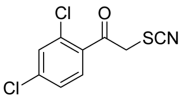
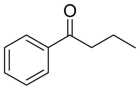
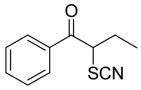
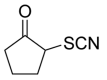
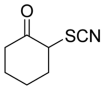
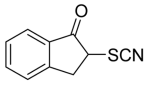
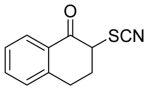
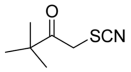
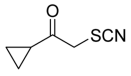
Initially, we attempted the α-thiocyanation of acetophenone (**1a**) with 1 equiv of ammonium thiocyanate (**2**) using a 0.35 eqiuv (see footnote a in Table 1) of TCCA. The reaction went to completion within 3 h at room temperature and the product, 1-phenyl-2-thiocyanatoethanone (**3a**), was obtained in 89% yield (Table 1, entry a).

Encouraged by this result, we turned our attention to various acetophenones. Interestingly, several substituted acetophenone such as 4-chloroacetophenone, 4-nitroacetophenone, 4-metoxylacetophenone, 4-methylacetophenone, 3-bromoacetophenone, 2,4-chloroacetophenone, and 1-phenylbutan-1-one reacted rapidly with ammonium thiocyanate to aord the corresponding 2-thiocyanatoethanone derivatives (Table 1, entry b-h). In addition, various cyclic ketones such as cyclopentanone, cyclohexanone, 1-tetralone, and indanone (Table 1, entries i-l) also participated effectively in this reaction. It is noteworthy to mention that aliphatic ketones also gave the corresponding α-thiocyanated products in 78-84% yield (Table 1, entries m-n). In all cases, the reactions proceeded rapidly at room temperature with high regioselectivity. No chlorination of acetophenone was observed under the reaction conditions. As solvent, acetonitrile appeared to give the best results. The products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and element analysis and also by comparison with authentic samples.

Mechanistically, we assume that TCCA reacts initially with ammonium thiocyanate **2** to generate electrophilic intermediate **4**. Subsequently ketones react rapidly with **4** to give the desired α-thiocyanatoketone **3** (Scheme 2).

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

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

Entry	Ketones	Product	Time/h	Yield/%[b]
a			3	89
b			4	87
c			3	88
d			4.5	86
e			4	85
f			4	80
g			5	82
h			6	79
i			4	88
j			4	90
k			5	91
l			5	89
m			6	78
n			5	84

[a]Reaction conditions: ketones (1.0 mmol); NH_4SCN (2.0 mmol); TCCA (0.35 mmol), rt, CH_3CN. [b]Isolated yields

Experimental Section

To a stirred solution of ammonium thiocyanate (2 mmol) and TCCA (0.35 mmol) in acetonitrile (10 mL) was added ketones (1 mmol) and the resulting mixture was stirred at room temperature for the appropriate time (Table 1). 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 product **3**.

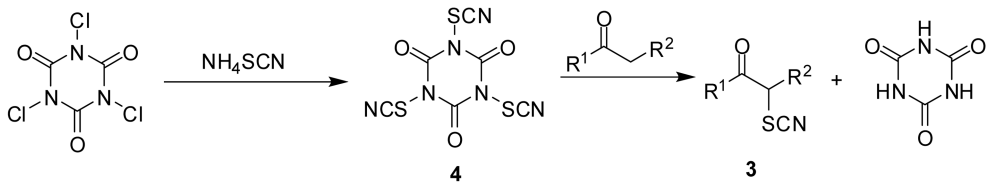
1-Phenyl-2-thiocyanatoethanone (3a). Solid, mp 68-70 °C; IR (KBr): ν 2946, 2150 (-SCN), 1672, 1591, 1420, 996, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02-7.80 (m, 2H), 7.66-7.25 (m, 3H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.2, 135.0, 133.6, 128.8, 128.0, 112.1, 43.1; Anal. calcd for 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.

1-(4-Chlorophenyl)-2-thiocyanatoethanone (3b). Solid, mp 133-135 °C; IR (KBr): ν 2968, 2146 (-SCN), 1666, 1590, 1420, 1223, 996 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 4.70 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.2, 139.0, 132.6, 129.6, 129.2, 111.9, 43.1; Anal. calcd for C_9H_6ClNOS: C 51.07, H 2.86, N 6.62, S 15.15; found: C 51.00, H 2.96, N 6.57, S 15.14.

1-(4-Nitrophenyl)-2-thiocyanatoethanone (3c). Solid, mp 118-120 °C; IR (KBr): ν 2972, 2150 (-SCN), 1672, 1599, 1420, 1200, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, J = 9.2 Hz, 2H), 8.08 (d, J = 9.2 Hz, 2H), 4.71 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.9, 150.4, 139.8, 129.2, 120.5, 111.9, 43.4; Anal. calcd for $C_9H_6N_2O_3S$: C 48.64, H 2.72, N 12.61, S 14.43; found: C 48.72, H 2.77, N 12.54, S 14.28.

1-(4-Methoxyphenyl)-2-thiocyanatoethanone (3d). Solid, mp 120-122 °C; IR (KBr): ν 2933, 2152 (-SCN), 1669, 1596, 1200, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.71 (s, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.9, 162.7, 130.2, 127.1, 114.6, 111.8, 56.2, 43.0; Anal. calcd for $C_{10}H_9NO_2S$: C 57.95, H 4.38, N 6.76, S 15.47; found: C 58.02, H 4.30, N 6.82, S 15.39.

1-(4-Methylphenyl)-2-thiocyanatoethanone (3e). Solid, mp 104-107 °C; IR (KBr): ν 2937, 2142 (-SCN), 1672, 1592, 1204, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.70 (s, 2H),



Scheme 2

2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.5, 145.6, 130.9, 129.2, 126.8, 111.8, 43.0, 21.4; Anal. calcd for $C_{10}H_9NOS$: C 62.80, H 4.74, N 7.32, S 16.77; found: C 62.85, H 4.69, N 7.39, S 16.82.

1-(4-Bromophenyl)-2-thiocyanatoethanone (3f). Solid, mp 138-140 °C; IR (KBr): ν 2930, 2138 (-SCN), 1679, 1590, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 4.70 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.0, 137.9, 134.2, 131.8, 129.8, 128.3, 124.9, 111.4, 43.0; Anal. calcd for $C_9H_6BrNO_2S$: C 42.21, H 2.36, N 5.47, S 12.52; found: C 42.33, H 2.30, N 5.42, S 12.50.

1-(2,4-Dichlorophenyl)-2-thiocyanatoethanone (3g). Solid, mp 87-88 °C; IR (KBr): ν 2966, 2149 (-SCN), 1672, 1595, 998 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00-7.48 (m, 3H), 4.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.8, 139.2, 136.3, 134.8, 130.9, 129.8, 127.1, 111.9, 42.8; Anal. calcd for $C_9H_5Cl_2NOS$: C 43.92, H 2.05, N 5.69, S 13.03; found: C 43.90, H 2.10, N 5.62, S 13.00.

1-Phenyl-2-thiocyanatobutanone (3h). Oil, IR (KBr): ν 2932, 2152 (-SCN), 1674, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, J = 7.6 Hz, 2H), 7.60-7.50 (m, 3H), 5.00 (t, J = 5.2 Hz, 1H), 2.34-2.12 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.2, 135.1, 134.0, 129.2, 128.2, 111.9, 55.7, 30.2, 11.2; Anal. calcd for $C_{11}H_{11}NOS$: C 64.36, H 5.40, N 6.82, S 15.62; found: C 64.22, H 5.45, N 6.88, S 15.60.

2-Thiocyanatocyclopentanone (3i). Oil; IR (KBr): ν 2929, 2154 (-SCN), 1725, 14530, 1134, 533; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.72-3.66 (m, 1H), 2.73-2.65 (m, 1H), 2.42-1.99 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.4, 111.7, 51.2, 39.8, 29.9, 11.2; Anal. calcd for C_6H_7NOS: C 51.04, H 5.00, N 9.92, S 22.71; found: C 51.00, H 4.98, N 9.97, S 22.70.

2-Thiocyanatocyclohexanone (3j). Oil; IR (KBr): ν 2925, 2154 (-SCN), 1702, 1455, 1129, 546; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35-4.20 (m, 1H), 2.85-2.38 (m, 3H), 2.20-1.73 (m, 5H); ^{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.

2,3-Dihydro-2-thiocyanatoinden-1-one (3k). Oil; IR (KBr): ν 2956, 2152 (-SCN), 1712, 1460, 1273, 937; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 7.6 Hz, 1H), 7.73-7.69 (m, 1H), 7.55-7.46 (m, 2H), 4.15-3.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.6, 150.9, 137.2, 131.2, 129.2, 126.8, 125.0, 111.0, 49.2, 34.6; Anal. calcd for $C_{10}H_7NOS$: C 63.47, H 3.73, N 7.40, S 16.94; found: C 63.55, H 3.70, N 7.35, S 16.90.

2-Oxo-1,2,3,4-tetrahydro-2-naphthyl Thiocyanate (3g). Oil; IR (KBr): ν 2933, 2154 (-SCN), 1690, 1223; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05-7.99 (m, 1H), 7.60-7.53 (m, 1H), 7.40-7.27 (m, 2 H), 4.55-4.51 (m, 1H), 3.21-3.17 (m, 2 H), 2.89-2.84 (m, 1H), 2.45-2.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.6, 141.2, 135.3, 133.7, 129.6, 128.6, 126.7, 111.7, 55.8, 31.2, 27.8; Anal. calcd for $C_{11}H_9NOS$: C 65.00, H 4.46, N 6.89 S 15.78; found: C 65.12, H 4.52, N 6.83, S 15.70.

3,3-Dimethyl-2-oxobutyl Thiocyanate (3m). Oil; IR (KBr): ν 2930, 2158 (-SCN), 1700, 1472, 1273; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (s, 2H), 7.60-7.53, 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 209.5, 110.8, 44.2, 24.9; Anal. calcd for $C_7H_{11}NOS$: C 53.47, H 7.05, N 8.91, S 20.39; found: C 53.38, H 7.00, N 8.99, S 20.32.

1-Cyclopropyl-2-thiocyanato-1-ethanone (3n). Oil; IR (KBr): ν 2924, 2152 (-SCN), 1696, 1470, 1265; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (s, 2H), 2.12-1.99 (m, 1H), 1.28-1.04 (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 51.11, H 5.06, N 9.99, S 22.65.

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