# Iron(III) Chloride as Mild and Efficient Reagent for the α-Thiocyanation of Ketones: An Expedient Synthesis of α-Oxo Thiocyanates

Jhillu S. Yadav,* Basi V. Subba Reddy, Ummareddy V. Subba Reddy, Darshanoju N. Chary

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax +91(40)27160512.; E-mail: yadav@iict.res.in

*Received 9 January 2008; revised 22 January 2008*

**Abstract:** A simple and efficient method for the α-thiocyanation of ketones has been developed; anhydrous iron(III) chloride is used under mild conditions to produce α-oxo thiocyanates in good to high yields and with high selectivity. The use of inexpensive and readily available iron(III) chloride makes this procedure simple, convenient, and practical.

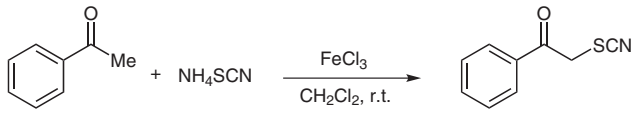
**Key words:** thiocyanation, ketones, iron(III) chloride, catalysis, α-oxo thiocyanates

α-Oxo thiocyanates are versatile intermediates in the synthesis of sulfur-containing heterocycles such as thiazoles and 2-amino-1,3-thiazines.[1,2] Some of these compounds exhibit herbicidal and other important biological activities.[3] Furthermore, the thiocyanato group occurs as an important functionality in several anticancer natural products formed by deglycosylation of glucosinolates derived from cruciferous vegetables.[4] The thiocyanate functionality is useful as a masked thiol group. Thiocyanation is generally carried out by nucleophilic substitution with thiocyanate anions. The low nucleophilicity of the thiocyanate anion requires rather harsh reaction conditions. Metal thiocyanates and organic halides or sulfonates are generally used to introduce the thiocyanate functionality into an organic molecule.[5] However, the thiocyanate group is not stable under heating conditions, and normally undergoes intramolecular rearrangement to form the thermodynamically favored isothiocyanate isomers.[6] Thus, the direct thiocyanation of ketones is of prime importance.

Consequently, various methods have been developed for the α-thiocyanation of ketones, with a variety of reagents and under diverse reaction conditions.[7,8] 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 (dichloroiodo)benzene/lead(II) thiocyanate reagent system has been reported for the direct thiocyanation of ketones, and works well with silyl enol ethers.[9] 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,[10] which 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. In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst, and performs many useful organic transformations under mild reaction conditions.[11] Moreover, iron salts are inexpensive, easy to handle, and environmentally friendly. However, there have been no previous reports on the direct α-thiocyanation of enolizable ketones with ammonium thiocyanate in the presence of iron(III) chloride as a catalyst.

In this article, we report a direct, iron(III) chloride promoted, selective α-thiocyanation of enolizable ketones with ammonium thiocyanate under mild conditions. We first attempted the thiocyanation of acetophenone (**1**) with two equivalents ammonium thiocyanate (**2**) (Scheme 1). The reaction was carried out with a stoichiometric amount of iron(III) chloride in dichloromethane, and went to completion in 25 minutes at room temperature, giving the product, 1-phenyl-2-thiocyanatoethanone (**3a**) in 75% yield (Scheme 1).




**1a** **2** **3a**

**Scheme 1**

This prompted us to study further reactions, with other enolizable ketones. Interestingly, various substituted ketones, such as 3-chloroacetophenone (**1b**), 4-hydroxyacetophenone (**1c**), 2,5-dichloroacetophenone (**1d**), 2-acetylnaphthalene (**1e**), and 2-methoxyacetophenone (**1f**) reacted readily with ammonium thiocyanate to provide the corresponding α-thiocyanato ketones **3b–f** in good yields (Table 1, entries 2–6). Like the acetophenones, cyclic ketones such as 1-tetralone (**1g**) (Scheme 2), 2-phenylchroman-4-one (**1h**), cyclopentanone (**1i**), cyclohexanone (**1j**), 4,4-dimethylcyclohex-2-enone (**1k**), 2-methylcyclohexanone (**1l**), cycloheptanone (**1m**), and cyclododecanone (**1n**) reacted well under similar conditions to give α-oxo thiocyanates **3g–n** (Table 1, entries 7–14).

**SYNTHESIS** 2008, No. 8, pp 1283–1287
Advanced online publication: 18.03.2008
DOI: 10.1055/s-2008-1072517; Art ID: Z00708SS

**Table 1** Thiocyanation of Ketones with Ammonium Thiocyanate Promoted by Iron(III) Chloride

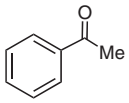
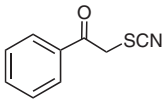
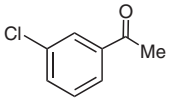
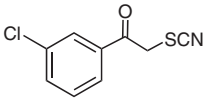
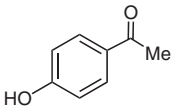
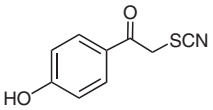
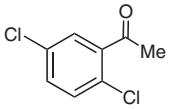
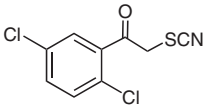
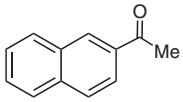
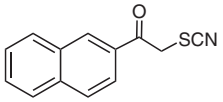
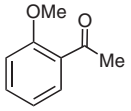
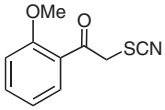
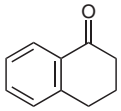
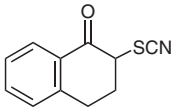
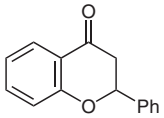
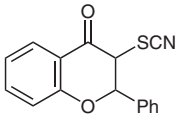
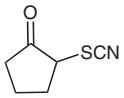
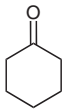
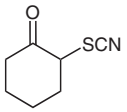
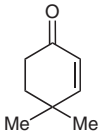
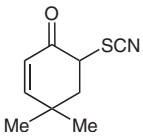
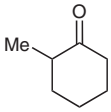
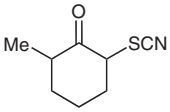
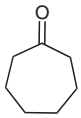
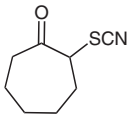
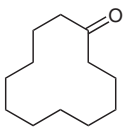
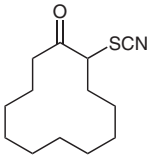
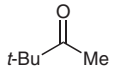
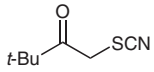
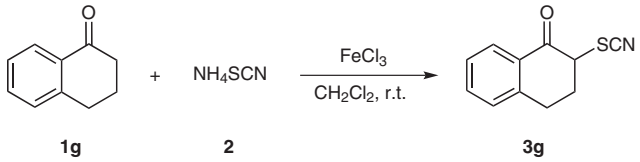
| Entry | Ketone | 1 | Product[a] | 3 | Time (min) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  | **1a** |  | **3a** | 25 | 75 |
| 2 |  | **1b** |  | **3b** | 30 | 72 |
| 3 |  | **1c** |  | **3c** | 23 | 78 |
| 4 |  | **1d** |  | **3d** | 30 | 70 |
| 5 |  | **1e** |  | **3e** | 25 | 75 |
| 6 |  | **1f** |  | **3f** | 25 | 76 |
| 7 |  | **1g** |  | **3g** | 35 | 80 |
| 8 |  | **1h** |  | **3h** | 45 | 82 |
| 9 |  | **1i** |  | **3i** | 40 | 78 |
| 10 |  | **1j** |  | **3j** | 35 | 84 |
| 11 |  | **1k** |  | **3k** | 30 | 80 |
| 12 |  | **1l** |  | **3l** | 30 | 78 |
| 13 |  | **1m** |  | **3m** | 40 | 75 |
| 14 |  | **1n** |  | **3n** | 50 | 68 |

**Table 1** Thiocyanation of Ketones with Ammonium Thiocyanate Promoted by Iron(III) Chloride (continued)

| Entry | Ketone | 1 | Product[a] | 3 | Time (min) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 15 |  | **1o** |  | **3o** | 40 | 80 |

[a] Products were characterized by $^1$H NMR and IR spectroscopy and MS.
[b] Yields are of pure products after chromatography.




**Scheme 2**

Furthermore, the sterically hindered acyclic ketone *tert*-butyl methyl ketone (**1o**) also afforded the corresponding thiocyanate **3o** in good yield (Table 1, entry 15). α-Thiocyanation of bulky substrates such as cyclododecanone (**1n**) gave comparatively low yields (Table 1, entry 14). The best conversions were obtained with cyclohexanone derivatives. It is noteworthy that the reactions were sluggish and the products were obtained in low yields (30–40%) when a catalytic amount of iron(III) chloride (10 mol%) was used in the reaction. Best conversions were obtained with a stoichiometric amount of iron(III) chloride. However, no reaction was observed in the absence of catalyst, even under reflux over a long reaction time (12 h). As solvent, dichloromethane appeared to give the best results. The products were characterized by $^1$H NMR and IR spectroscopy and mass spectrometry and also by comparison with authentic samples.[9,12] This method was clean and free of side products. Among the various oxidants tested, such as (diacetoxyiodo)benzene, manganese(III) acetate, and iron(III) nitrate, anhydrous iron(III) chloride was found to be the most effective in terms of conversion. Various metal triflates such as bismuth(III)-, indium(III)-, samarium(III)-, ytterbium(III)-, and scandium(III) triflate were also found to be ineffective for this conversion. The advantages of this procedure include mild conditions, short reaction times, easy workup, and good yields. The scope and generality of this process is illustrated with respect to various enolizable ketones and ammonium thiocyanate (Table 1).

In summary, anhydrous iron(III) chloride has proved to be a useful and highly efficient catalyst for a facile α-thiocyanation of ketones with ammonium thiocyanate under mild reaction conditions. In addition to its simplicity and efficiency, this method produces α-oxo thiocyanates in good yields in short reaction times. This method provides an access to a wide range of potentially valuable α-oxo thiocyanates.

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 and $^{13}$C NMR spectra, of samples in $CDCl_3$ with TMS as internal standard, were recorded on a Gemini-200 spectrometer (200 MHz). Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed on Merck silica gel (60–120 mesh).

**Thiocyanates 3 by α-Thiocyanation of Ketones 1; General Procedure**

The appropriate ketone **1** (1.0 mmol) was added to a soln of $NH_4SCN$ (**2**; 2 mmol) and $FeCl_3$ (1 mmol) in $CH_2Cl_2$ (10 mL), and the resulting mixture was stirred at r.t. for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with $H_2O$ (15 mL) and extracted with EtOAc (2 × 15 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The resulting product was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:9.5); this afforded the corresponding pure thiocyanate derivative **3**.

**2-Oxo-2-phenylethyl Thiocyanate (3a)**

Pale yellow solid; mp 67–69 °C.

IR (KBr): 3423, 2984, 2934, 2361, 2155, 1676, 1593, 1448, 955, 755 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.5 Hz, 2 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 2 H), 4.75 (s, 2 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 42.9, 111.7, 128.4, 129.1, 133.8, 134.7, 190.7.

MS (EI, 70 eV): *m*/*z* = 200 [M$^+$ + Na], 178 [M$^+$ + H].

HRMS (EI): *m*/*z* calcd for $C_9H_8NOS$: 178.0326; found: 178.0332.

**2-(3-Chlorophenyl)-2-oxoethyl Thiocyanate (3b)**

Pale yellow solid; mp 68–70 °C.

IR (KBr): 3065, 2988, 2929, 2152, 1680, 780, 678 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.92 (s, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.64 (d, *J* = 7.5 Hz, 1 H), 7.48 (m, 1 H), 4.72 (s, 2 H).

MS (EI, 70 eV): *m*/*z* = 211 [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_9H_7NOSCl$: 211.9939; found: 211.9939.

**2-(4-Hydroxyphenyl)-2-oxoethyl Thiocyanate (3c)**

Colorless solid; mp 160–162 °C.

IR (KBr): 3280, 2970, 2924, 2166, 1668, 1599, 1442, 1279, 1203, 833, 561 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 10.14 (s, 1 H), 7.83 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 4.87 (s, 2 H).

$^{13}$C NMR (50 MHz, $CDCl_3$ + DMSO): δ = 42, 111, 114, 124, 129, 162, 188.

MS (EI, 70 eV): *m*/*z* = 216 [M$^+$ + Na], 194 [M$^+$ + 1], 195 [M$^+$ + 2], 137.

**2-(2,5-Dichlorophenyl)-2-oxoethyl Thiocyanate (3d)**
Colorless solid; mp 190–192 °C.

IR (KBr): 3150, 2925, 2853, 2155, 1649, 1575, 1377, 1106, 824, 706 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.74 (m, 1 H), 7.49–7.53 (m, 1 H), 7.39–7.43 (m, 1 H), 4.64 (s, 2 H).

MS (EI, 70 eV): *m*/*z* = 247 [M$^+$ + H].

HRMS (EI): *m*/*z* calcd for $C_9H_6Cl_2NOS$: 247.0452; found: 247.0459.

**2-(2-Naphthyl)-2-oxoethyl Thiocyanate (3e)**
Pale yellow solid; mp 102–104 °C.

IR (KBr): 3051, 2991, 2933, 2153, 1661, 1622, 739, 674 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 7.94 (m, 4 H), 7.64 (m, 2 H), 4.90 (s, 2 H).

MS (EI, 70 eV): *m*/*z* = 228 [M$^+$ + H].

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}NOS$: 228.0483; found: 228.0492.

**2-(2-Methoxyphenyl)-2-oxoethyl Thiocyanate (3f)**
Colorless solid; mp 85–87 °C.

IR (KBr): 2923, 2852, 2157, 1644, 1461, 1014, 756, 623 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 7.90–7.96 (m, 1 H), 7.51–7.60 (m, 1 H), 6.97–7.10 (m, 2 H), 4.80 (s, 2 H), 4.05 (s, 3 H).

MS (EI, 70 eV): *m*/*z* = 230 [M$^+$ + Na].

**2-Oxo-1,2,3,4-tetrahydro-2-naphthyl Thiocyanate (3g)**
Colorless liquid.[12]

IR (neat): 3064, 2924, 2154, 1681, 1598, 1221, 745, 607 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.0–8.03 (m, 1 H), 7.52–7.57 (m, 1 H), 7.25–7.39 (m, 2 H), 4.54 (dd, *J* = 4.5, 5.2 Hz, 1 H), 3.17–3.20 (m, 2 H), 2.84–2.88 (m, 1 H), 2.35–2.44 (m, 1 H).

MS (EI, 70 eV): *m*/*z* = 204 [M$^+$ + H].

**4-Oxo-2-phenyl-3,4-dihydro-2*H*-chromen-3-yl Thiocyanate (3h)**
Colorless liquid.

IR (neat): 3036, 2924, 2854, 2157, 1693, 1606, 1463, 1301, 761, 698, 618 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.96–8.06 (m, 1 H), 7.44–7.62 (m, 6 H), 7.03–7.19 (m, 2 H), 5.49 (d, *J* = 11.3 Hz, 1 H), 4.40 (d, *J* = 11.3 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* = 281 [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_{16}H_{11}NO_2SNa$: 304.0408; found: 304.0418.

**2-Oxocyclopentyl Thiocyanate (3i)**
Colorless liquid.[9]

IR (neat): 2924, 2854, 2155, 1746, 1635, 1453, 1148, 813, 513 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.65–3.74 (m, 1 H), 2.62–2.71 (m, 1 H), 1.95–2.45 (m, 5 H).

MS (EI, 70 eV): *m*/*z* = 142 [M$^+$ + H].

**2-Oxocyclohexyl Thiocyanate (3j)**
Pale yellow liquid.[9]

IR (neat): 2925, 2860, 2154, 1710, 1449, 1125, 536 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.22–4.29 (m, 1 H), 2.77–2.85 (m, 1 H), 2.61–2.68 (m, 1 H), 2.36–2.46 (m, 1 H), 1.70–2.22 (m, 5 H).

MS (EI, 70 eV): *m*/*z* = 178 [M$^+$ + Na], 156 [M$^+$ + H].

HRMS (EI): *m*/*z* calcd for $C_7H_{10}NOS$: 156.0483; found: 156.0482.

**4,4-Dimethyl-6-thiocyanatocyclohex-2-enone (3k)**
Yellow liquid.

IR (neat): 2965, 2928, 2870, 2083, 1718, 1681, 813, 761 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 6.75 (d, *J* = 10.1 Hz, 1 H), 5.93 (d, *J* = 10.1 Hz, 1 H), 4.47 (m, 1 H), 3.75 (m, 2 H), 1.34 (s, 3 H), 1.27 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 25.4, 30.3, 43.9, 51.5, 99.7, 124.8, 160.6, 192.7.

MS (EI, 70 eV): *m*/*z* = 181 [M$^+$].

HRMS (EI): *m*/*z* calcd for $C_9H_{11}NOSNa$: 204.0459; found: 204.0453.

**3-Methyl-2-oxocyclohexyl Thiocyanate (3l)**
Pale yellow liquid.

IR (neat): 2923, 2852, 2154, 1713, 1458, 1380, 760, 565 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.17–4.33 (m, 1 H), 1.24–2.81 (m, 7 H), 1.12 (d, *J* = 1.5 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.7, 21.7, 33.6, 34.9, 43.7, 49.2, 99.9, 207.0.

MS (EI, 70 eV): *m*/*z* = 170 [M$^+$ + H].

**2-Oxocycloheptyl Thiocyanate (3m)**
Liquid.

IR (neat): 2929, 2152, 1700, 1451, 953, 766, cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.42 (m, 1 H), 2.41–2.74 (m, 3 H), 1.62–2.17 (m, 7 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 23.9, 28.1, 29.5, 32.7, 41.7, 61.0, 100.1, 205.0.

MS (EI, 70 eV): *m*/*z* = 170 [M$^+$ + H].

**2-Oxocyclododecyl Thiocyanate (3n)**
Liquid.

IR (neat): 2933, 2858, 2152, 1692, 1464, 1036, 736, 618 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 4.29–4.35 (m, 1 H), 2.92–3.05 (m, 1 H), 1.95–2.42 (m, 4 H), 1.08–1.72 (m, 15 H).

MS (EI, 70 eV): *m*/*z* = 262 [M$^+$ + Na], 240 [M$^+$ + H].

HRMS (EI): *m*/*z* calcd for $C_{13}H_{21}NOSNa$: 262.1205; found: 262.1211.

**3,3-Dimethyl-2-oxobutyl Thiocyanate (3o)**
Liquid.

IR (neat): 2970, 2929, 2157, 1706, 1474, 1292, 1061, 724, 570 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): δ = 4.33 (s, 2 H), 1.23 (s, 9 H).

MS (EI, 70 eV): *m*/*z* = 158 [M$^+$ + H].

## References

(1) Wood, J. L. *Organic Reactions*, Vol. 3; Adams, R., Ed.; John Wiley & Sons: New York, **1946**, Chap. 6.
(2) (a) Metzer, J. B. *Comprehensive Heterocyclic Chemistry*, Vol. 6; Katritzky, A., Ed.; Pergamon: Oxford, **1984**, 235. (b) Yadav, L. D. S.; Patel, R.; Rai, V. K.; Srivastava, V. P. *Tetrahedron Lett.* **2007**, *48*, 7793.

(3) Kawamura, S.; Izumi, K.; Satoh, J.; Sanemitsu, Y.; Hamada, T.; Shibata, H.; Satoh, R. Pat. Appl. EP 446802, **1991**; *Chem. Abstr.* **1992**, *116*, 59360j.
(4) (a) Shahidi, F. *Sulphur Compounds in Foods*; Mussinan, C. J.; Keelan, M. E., Eds.; American Chemical Society: Washington DC, **1984**, Chap. 9, 1067–1286. (b) Mehta, R. G.; Liu, J.; Constantinou, A.; Thomas, C. F.; Hawthorne, M.; You, M.; Gerhaeuser, C.; Pezzuto, J. M.; Moon, R. C.; Moriarty, R. M. *Carcinogenesis* **1995**, *16*, 399.
(5) Guy, R. G. In *The Chemistry of Cyanates and Their Thio Derivatives*, Part 2; Patai, S., Ed.; John Wiley & Sons: New York, **1977**, Chap. 18, 819.
(6) Bacon, R. G. R.; Guy, R. G. *J. Chem. Soc.* **1961**, 2428.
(7) Dittmer, D. C. *Comprehensive Heterocyclic Chemistry*, Vol. 7; Katritzky, A., Ed.; Pergamon: Oxford, **1984**, 178.
(8) Prakash, O.; Saini, N. *Synth. Commun.* **1993**, *23*, 1455.
(9) (a) Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S. P.; Moriarty, R. M. *J. Org. Chem.* **2001**, *66*, 2019. (b) Prakash, O.; Rani, N.; Sharma, V.; Moriarty, R. M. *Synlett* **1997**, 1255.
(10) Atkins, E. F.; Dabbs, S.; Guy, R. G.; Mahomed, A. A.; Mountford, P. *Tetrahedron* **1994**, *50*, 7253.
(11) (a) Bolm, C.; Legros, J.; Paiti, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Ruping, M.; Nactshim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717. (c) Komeyma, K.; Morimoto, T.; Takaki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2938. (d) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19. (e) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457. (f) Iovel, I.; Kristin, M.; Kischel, J.; Zapf, A.; Mathias, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913.
(12) Kumar, A.; Ahamd, P.; Maurya, R. A. *Tetrahedron Lett.* **2007**, *48*, 1399.