A Novel and Efficient Method for the Synthesis of α-Azidoketones and α-Ketothiocyanates

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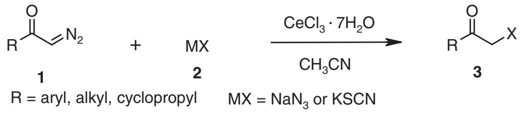
α-Diazoketones underwent insertion smoothly with sodium azide and potassium thiocyanate in the presence of $CeCl_3{\cdot}7H_2O$ under mild reaction conditions to afford the corresponding α-azidoketones and α-ketothiocyanates in excellent yields.

α-Azidoketones are useful intermediates in organic synthesis especially for the synthesis of a variety of heterocyclic compounds such as oxazoles, pyrazines, 2-acylimidazoles, substituted pyrroles, and many others.[1] In particular, α-azidoketones are important intermediates for β-aminoalcohols which are, in turn, useful as chiral ligands in asymmetric synthesis[2] and as β-blockers in pharmaceuticals.[3] The ready availability, relative stability, and facile decomposition of α-diazocarbonyl compounds under acid or thermal or photochemical conditions make them useful intermediates in organic synthesis.[4] Furthermore, α-diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H, X–H (X = O, S, NH) insertion reactions and cyclization reactions.[5] Lanthanide salts are unique Lewis acids that are currently of great research interest.[6] In particular, cerium reagents are relatively non-toxic, readily available at low cost and are fairly stable to air or moisture. Owing to its unique properties, $CeCl_3$ has been extensively used for a variety of organic transformations.[7]

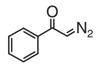
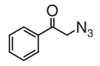
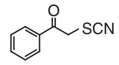
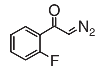
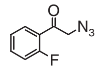
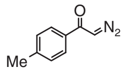
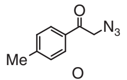
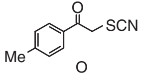
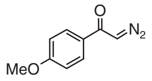
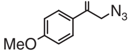
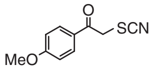
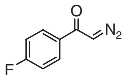
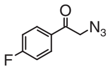
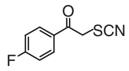
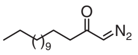
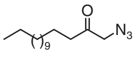
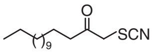
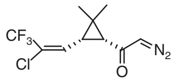
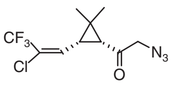
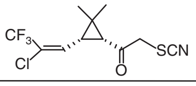
In continuation of our interest on the use of cerium(III) chloride heptahydrate for various transformations,[8] we herein report a novel protocol for the preparation of α-azidoketones and α-ketothiocyanates using $CeCl_3{\cdot}7H_2O$ as an efficient reagent (Scheme 1).



Scheme 1.

Thus treatment of α-diazoacetophenone with sodium azide in the presence of cerium(III) chloride heptahydrate in acetonitrile afforded 2-azido-1-phenyl-1-ethanone in 91% yield. The remarkable catalytic activity of cerium(III) chloride encouraged us for further study of reactions with other α-diazocarbonyl compounds. Interestingly, various α-diazoketones reacted smoothly with sodium azide in the presence of $CeCl_3{\cdot}7H_2O$ at 80 °C to give the corresponding 2-azidoaryl and 2-azidoalkylketones. Both aromatic and aliphatic α-diazoketones afforded the respective α-azidoketones in high yields (Table 1). The diazoketone derived from *cis*-cyhalothric acid also gave similar results. In a similar manner, potassium thiocyanate also reacted efficiently with α-diazoketones to furnish 1-aryl-2-thiocyanato-1-ethanones or 1-alkyl-2-thiocyanato-1-ethanones in high yields. The method is clean and the products are obtained in high yields.[9] However, treatment of sodium bromide and sodium iodide with diazoketones failed to give the corresponding α-haloketones under similar conditions. No side product arising from a Wolff rearrangement was observed under these reaction conditions. Other side products such as α-chloro- and α-hydroxy ketones (the products of chloride or OH insertion) arising from $CeCl_3{\cdot}7H_2O$ were not detected under these reaction conditions. To know the efficiency of this procedure, we have also carried out the reactions with other cerium salts such as cerium(III) triflate and ceric ammonium nitrate. Among these catalysts, cerium(III) chloride was found to be the most effective reagent and giving the best results. The reaction proceeded smoothly by $CeCl_3{\cdot}7H_2O$ in

Table 1. $CeCl_3{\cdot}7H_2O$-Promoted Synthesis of α-Azidoketones and α-Ketothiocyanates

Entry	Diazoketone 1	Nucleophile 2	Product[a] 3	Time/h	Yield /%[b]
a		NaN_3		5.0(6.5)	91(86)
b	"	KSCN		6.0(7.0)	85(79)
c		NaN_3		6.5(7.5)	89(81)
d		NaN_3		4.5(6.0)	87(75)
e	"	KSCN		6.5(7.0)	84(71)
f		NaN_3		5.0(6.0)	89(80)
g	"	KSCN		5.0(6.5)	86(78)
h		NaN_3		6.0(7.0)	88(75)
i	"	KSCN		7.0(8.5)	82(70)
j		NaN_3		6.5(8.0)	90(85)
k	"	KSCN		7.0(9.0)	87(81)
l		NaN_3		5.5(6.5)	85(70)
m	"	KSCN		6.0(7.5)	80(75)

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.
[c] Yield and time shown in parenthesis obtained by $Ce(OTf)_3$.

acetonitrile at 80 °C. Furthermore, we have examined the possibility of $CeCl_3{\cdot}7H_2O$ functioning catalytically or at least, in less than stoichiometric amounts. But best results were obtained with an equimolar ratio of $CeCl_3{\cdot}7H_2O$. There are many advantages in the use of cerium(III) chloride for this transformation, which avoids the use of strongly acidic or basic conditions. The method does not require the use of expensive or corrosive reagents and no precautions need to be taken to exclude moisture from the reaction medium. The scope and generality of this procedure is illustrated with respect to various diazoketones and the results are summerized in the Table 1.

In summary, we disclose a new procedure for the preparation of 2-azidoketones and 2-ketothiocyanates using $CeCl_3{\cdot}7H_2O$ as a novel catalyst under mild conditions. The notable features of this procedure are high conversions, simplicity in operation, cleaner reaction profiles, and ready availability of reagents at low cost which make it a useful and attractive strategy for the synthesis of 2-azidoketones and 2-ketothiocyanates of synthetic importance.

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References and Notes

1 a) V. J. Majo and P. T. Perumal, *J. Org. Chem.*, **63**, 7136 (1998). b) X. Fan and Y. Zhang, *Tetrahedron Lett.*, **43**, 1863 (2002) c) M. V. R. Reddy, R. Kumareswaran, and Y. D. Vankar, *Tetrahedron Lett.*, **36**, 6751 (1995).

2 a) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987). b) J. Takehara, S. Hashiguchi, A. Fujii, S.-I. Inoue, T. Ikariya, and R. Noyori, *Chem. Commun.*, **1996**, 233. c) H. C. Brown, U. S. Racherla, and P. J. Pellechia, *J. Org. Chem.*, **55**, 1868 (1990).

3 a) B. L. Chng and A. Ganesan, *Bioorg. Med. Chem. Lett.*, **7**, 1511 (1997). b) P. Van de Wenge and J. Collin, *Tetrahedron Lett.*, **36**, 1649 (1995).

4 a) A. Padwa and M. D. Weingarten, *Chem. Rev.*, **96**, 223 (1996). b) A. Padwa, *Top. Curr. Chem.*, **189**, 121 (1997). c) M. A. Calter, *Curr. Org. Chem.*, **1**, 37 (1997).

5 a) T. Ye and M. A. McKervey, *Chem. Rev.*, **94**, 1091 (1994). b) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, **91**, 263 (1991). c) M. P. Doyle, *Chem. Rev.*, **86**, 919 (1986).

6 T. Imamoto, "Lanthanides in Organic Synthesis," Academic Press, New York (1994).

7 a) A. Cappa, E. Marcantoni, E. Torregiani, G. Bartoli, M. C. Bellucci, M. Bosco, and L. Sambri, *J. Org. Chem.*, **64**, 5696 (1999). b) E. Marcantoni, F. Nobili, G. Bartoli, M. Bosco, and L. Sambri, *J. Org. Chem.*, **62**, 4183 (1997). c) M. Di Dea, E. Marcantoni, E. Torregiani, G. Bartoli, M. C. Bellucci, M. Bosco, and L. Sambri, *J. Org. Chem.*, **65**, 2830 (2000).

8 a) J. S. Yadav, B. V. S. Reddy, K. B. Reddy, and M. Satyanarayana, *Tetrahedron Lett.*, **43**, 7009 (2002). b) J. S. Yadav, B. V. S. Reddy, M. S. K. Reddy, and G. Sabitha, *Synlett*, **2001**, 1134. c) J. S. Yadav and B. V. S. Reddy, *Synlett*, **2000**, 1275.

9 Experimental procedure: A mixture of α-diazoketone (5 mmol), sodium azide or potassium thiocyanate (6 mmol) $CeCl_3{\cdot}7H_2O$ (5 mmol) in acetonitrile (10 mL) was stirred at 80 °C for a specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 1:9) to afford pure 2-azidoketone or 2-ketothiocyanate. Spectral data for the compounds **3e**: Yellow solid, mp 102–103 °C, IR (KBr): ν 2930, 2854, 2100, 1685, 1606, 1598, 1451, 1389, 1249, 981, 922, 772, 550 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 4.78 (s, 2H), 7.38 (d, 2H, $J = 8.0$ Hz), 7.85 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 21.6, 44.6, 111.8, 126, 129.4, 131.7, 132.5, 133.3, 140.0, 193.0. EI–MS: m/z: 191 M$^+$, 155, 141, 119, 105, 91, 77, 65, 39. **3j**: Colourless solid, mp 41–42 °C, IR (KBr): ν 2923, 2852, 2105, 1734, 1637, 1467, 1190 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (t, 3H, $J = 6.8$ Hz), 1.20–1.35 (m, 20H), 1.45–1.65 (m, 2H), 2.40 (t, 2H, $J = 6.7$ Hz), 3.80 (s, 2H). ^{13}C NMR (Proton decoupled. 75 MHz, $CDCl_3$): δ 14.0, 22.6, 23.5, 24.9, 29.0, 29.1, 29.3, 29.4, 29.6, 31.9, 34.3, 39.6, 48.1, 202. EI–MS: m/z: 267 M$^+$, 257, 212, 127, 102, 97, 88, 63, 43. **3l**: Liquid, IR (KBr): ν 3448, 2924, 2107, 1713, 1650, 1459, 1278, 1141, 951, 770, 671 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3H, $-CH_3$), 1.35 (s, 3H, $-CH_3$), 2.23 (dd, 1H, $J = 8.0$, 8.6 Hz, $-CH{-}CH{=}CClCF_3$), 2.26 (d, 1H, $J = 8.0$ Hz, $-CH{-}CO{-}$), 3.90 (s, 2H, $-CH_2-$), 6.90 (d, 2H, $J = 8.6$ Hz, $-CH{=}CClCF_3$). ^{13}C NMR (Proton decoupled. 75 MHz, $CDCl_3$): δ 28.5, 29.6, 34.4, 37.4, 59.1, 111.2, 118.4, 121.6, 122.0, 122.9, 128.4, 129.0, 200.6. EI–MS: m/z: 281 M$^+$, 224, 197, 184, 161, 141, 97, 71, 58, 41. **3m**: Liquid, IR (KBr): ν 3432, 2926, 2100, 1699, 1653, 1410, 1278, 1140, 953, 771 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3H, $-CH_3$), 1.35 (s, 3H, $-CH_3$), 2.30 (dd, 1H, $J = 8.1$, 8.5 Hz, $-CH{-}CH{=}CClCF_3$), 2.35 (d, 1H, $J = 8.1$ Hz, $-CH{-}CO{-}$), 3.99–4.05 (ABq, 2H, $J = 13.7$ Hz, $-CH_2-$), 6.83 (d, 1H, $J = 8.5$ Hz, $-CH{=}CClCF_3$). ^{13}C NMR (Proton decoupled. 75 MHz, $CDCl_3$): δ 28.3, 33.6, 35.2, 38.9, 45.2, 111.0, 118.3, 121.9, 122.4, 122.9, 128.4, 128.5, 197.4. EI–MS: m/z: 297 M$^+$, 259, 226, 198, 184, 162, 142, 133, 91, 72, 60, 52, 41.