A One-Pot Umpolung Method for Preparation of α-Aryl Nitriles from α-Chloro Aldoximes via Organocuprate Additions to Transient Nitrosoalkenes

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Received: 18.06.2012; Accepted after revision: 05.07.2012

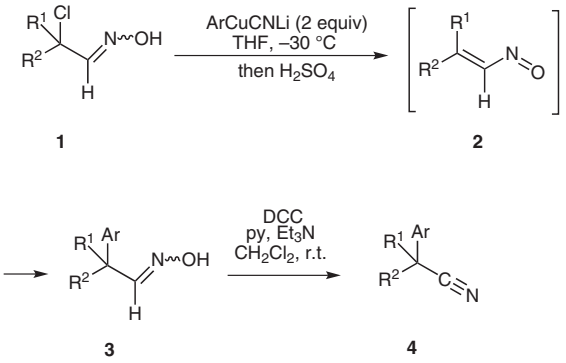
Abstract: Conjugate addition of a variety of aryl lithiocyanocuprates to nitrosoalkenes generated from α-chloro aldoximes, followed by in situ dehydration of the crude α-aryl aldoxime product with *N*,*N*′-dicyclohexylcarbodiimide, affords α-aryl nitriles in good overall yields via a one-pot protocol.

Key words: cuprates, nucleophilic addition, nitriles, aldehydes, arylation

α-Aryl nitriles have found considerable use as intermediates in organic synthesis.[1] In addition, α-aryl nitrile moieties are components of clinically important drugs such as Ariflo[2] and verapamil.[3] A number of traditional methods for accessing such compounds exist,[4] but recently the Hartwig[5] and Verkade[6] groups have investigated the direct palladium-catalyzed α-arylation of nitrile anions with aryl halides. A number of variations of this chemistry have been developed using different catalyst/ligand systems, nitrile anion precursors and additives. These arylations generally work well, although the methodology does have some limitations including the control of mono- versus diarylation of the anion in some cases, as well as problems in the use of certain types of nitrile substrates.

Recently, we have been engaged in exploring the use of highly reactive, transient nitrosoalkenes as enolonium ion equivalents, and in particular have investigated the conjugate addition of a variety of carbon nucleophiles to such species.[7,8] Our observation that aryl cuprates can be added to nitrosoalkenes derived from α-chloro ketoximes[7e] suggested the possibility of accessing α-aryl nitriles via a similar strategy. Our plan was to utilize an α-chloro aldoxime **1** which upon base-promoted dehydrochlorination would generate a nitrosoalkene **2** in situ (Scheme 1). Conjugate addition of an aryl nucleophile to this reactive intermediate, followed by acidification, would lead to the α-aryl aldoxime **3**. Finally, dehydration of this oxime would afford the desired α-aryl nitrile **4**. It should be noted that nitrosoalkenes like **2** derived from aldehydes are known, but have not found wide use in synthesis to date.[7b,c,9] This approach would constitute a two-step umpolung version of the Hartwig/Verkade nitrile anion arylation methodology.

To investigate this process, a series of known[10] α-chloro aldehydes was converted into the corresponding α-chloro aldoximes **1** (Table 1) in good yields using a modification of the oximation procedure of Denmark and Dappen (KOAc and $NH_2OH·HCl$ in glacial AcOH, see experimental procedure).[11] Significantly, if these oximation reactions are conducted for more than about two hours at room temperature, a significant amount of the α-acetoxy aldoxime begins to form, presumably via the nitrosoalkene **2**. Oximes **1** were also found to be unstable to silica gel chromatography, but are sufficiently pure for use in the next step.



Scheme 1 Conversion of α-chloro aldoximes **1** into α-aryl nitriles **4**

After some experimentation, it was found that the best way to arylate the α-chloro aldoximes **1** was with an aryl lithiocyanocuprate[12] prepared from the corresponding aryllithium reagent[13] and cuprous cyanide.[14] Thus, treatment of oximes **1** with two equivalents of the cuprate in tetrahydrofuran at –30 °C led to the α-aryl aldoximes **3**. We believe one equivalent of the organometallic reagent acts as a base for the dehydrochlorination of **1** to the nitrosoalkene **2**, followed by conjugate addition of the second equivalent of the cuprate. Other potential arylating reagents such as phenylmagnesium bromide, phenyllithium and triphenylaluminum did not produce any of the desired products **3** but rather led to decomposition. Lithium diphenylcuprate gave some of the conjugate addition product but only in poor yield. Although oximes **3** could be isolated, we decided that the procedure would be much more efficient if we could dehydrate these intermediates directly to the nitriles.

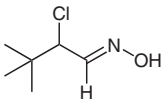
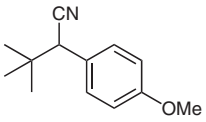
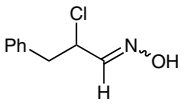
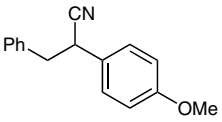
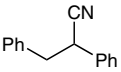
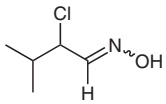
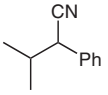
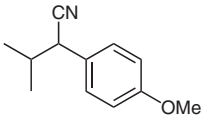
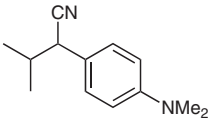
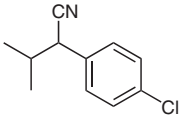
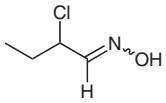
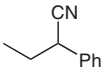
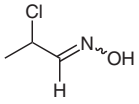
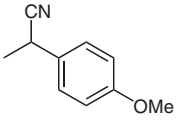
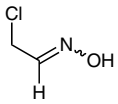
Vowinkel and Bartel have reported an oxime dehydration method using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and triethylamine in the presence of copper(II) salts.[15] We reasoned that since there is already copper in the arylation reaction mixture, we might be able to effect the dehydration

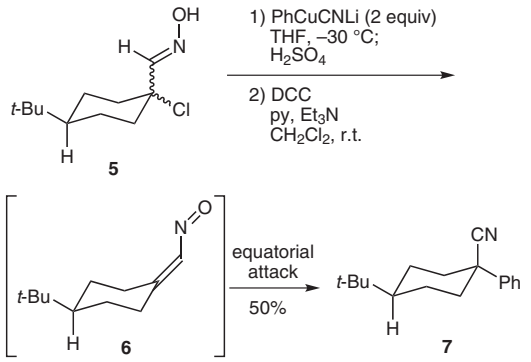
SYNTHESIS 2012, 44, 2933–2937
Advanced online publication: 08.08.2012
DOI: 10.1055/s-0032-1316984; Art ID: SS-2012-M0529-OP

step in situ without any workup. Thus, it was found that initial addition of sulfuric acid to the crude arylation mixture at –30 °C, followed by the addition of DCC, triethylamine and pyridine, after warming the mixture to room temperature led to the desired α-aryl nitrile **4**. This protocol has been applied to a number of α-chloro aldoxime substrates and aryl cuprates, as listed in Table 1.[16] In general, the overall isolated yields of the arylated nitrile products are good for this two-step, one-pot sequence.

We have also examined a stereochemical aspect of the arylation protocol. Thus, α-chloro aldoxime **5** (1.5:1-mixture of diastereomers) was subjected to the arylation/dehydration sequence to afford the known[16f] α-phenyl nitrile **7** as a single diastereomer (Scheme 2). This product would result from conjugate addition of the phenyl cuprate to nitrosoalkene **6** via stereoselective equatorial attack. The result here is in good accord with conjugate additions of organometallic reagents to alkylidenecyclohexanes related to intermediate **6** which have been shown to be equatorial selective.[17]

Table 1 Conversion of α-Chloro Aldoximes **1** into α-Aryl Nitriles **4**

Entry	α-Chloro aldoxime **1**		Aryl cuprate	α-Aryl nitrile **4**		Yield (%)
1	**1a**		4-$MeOC_6H_4CuCNLi$	**4a**		51
2	**1b**		4-$MeOC_6H_4CuCNLi$	**4b**		83
3	**1b**		PhCuCNLi	**4c**		76
4	**1c**		PhCuCNLi	**4d**		87
5	**1c**		4-$MeOC_6H_4CuCNLi$	**4e**		98
6	**1c**		4-$Me_2NC_6H_4CuCNLi$	**4f**		73
7	**1c**		4-$ClC_6H_4CuCNLi$	**4g**		70
8	**1d**		PhCuCNLi	**4h**		85
9	**1e**		PhCuCNLi	**4i**		85
10	**1e**		4-$MeOC_6H_4CuCNLi$	**4j**		70
11	**1f**		PhCuCNLi	**4k**		62



Scheme 2 Stereoselective arylation of a nitrosoalkene

In conclusion, we have developed a simple and convenient method which allows the conversion of readily available α-chloro aldoximes into a variety of α-aryl nitriles using aryl lithiocyanocuprate reagents. This transformation relies on an inital formation of a transient, reactive nitrosoalkene which undergoes a conjugate addition with the organocuprate to form an α-aryl aldoxime. Without any workup or isolation, this intermediate can then be dehydrated with DCC to produce the product α-aryl nitrile in good overall isolated yield. This sequence provides a potentially useful umpolung alternative to the palladium-catalyzed arylation of nitrile anions.

All non-aqueous reactions were carried out under an inert argon atmosphere in flame-dried glassware. Liquid reagents sensitive to air were added via a dry syringe. All solvents and reagents were obtained from commercial sources and used without further purification. EM Science silica gel 60 (230–400 mesh) was used for flash column chromatography, and silica gel 60 PF254 plates were used for analytical thin-layer chromatography. IR spectra were measured on a Perkin-Elmer 1600 Series FTIR. ^{1}H and ^{13}C NMR experiments were performed on Bruker DPX 300, CDPX 300 or DRX 400 MHz spectrometers. Chemical shifts were determined relative to the solvent peak. High-resolution electrospray ionization (ESI) mass spectral data were obtained using a Waters LCT Premier time of flight mass spectrometer (Waters Corporation, Micromass Ltd., Manchester, UK). High-resolution electron ionization (EI) mass spectral data were obtained using a Waters/Micromass GCT coupled to an Agilent 6890N GC instrument.

α-Chloro Aldoximes; General Procedure
To the α-chloro aldehyde (16.67 mmol) was added glacial AcOH (33 mL) at r.t., followed by $NH_2OH{\cdot}HCl$ (1.74 g, 25.05 mmol) and KOAc (2.47 g, 25.17 mmol). The mixture was stirred at r.t. for 2 h, then poured into H_2O (100 mL) and extracted with Et_2O (15 mL). The organic layer was washed with H_2O (3 × 100 mL) and dried over anhyd $MgSO_4$. The solution was concentrated under reduced pressure giving the α-chloro aldoxime, usually as an inseparable mixture of oxime *E*/*Z*-isomers, which was sufficiently pure for use in the next step. These compounds are unstable to silica gel chromatography and also to analysis by mass spectrometry.

2-Chloro-3,3-dimethylbutanal Oxime (1a)
Yellow oil (single oxime isomer); yield: 2.00 g (80%).

IR (thin film): 3265, 2964, 1650, 1470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 9.1 Hz, 1 H), 4.22 (d, *J* = 9.1 Hz, 1 H), 1.04 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8 (CH), 67.8 (CH), 36.1 (C), 26.8 (CH_3).

2-Chloro-3-phenylpropanal Oxime (1b)
Yellow oil (2.7:1-mixture of oxime *E*/*Z*-isomers); yield: 2.72 g (89%).

IR (thin film, *E*/*Z*-mixture): 3254, 3088, 3030, 2911, 1603, 1493, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 8.72 (br s, 1 H, *E* and *Z*), 7.47 (d, *J* = 7.7 Hz, 1 H, *E*), 7.39–7.22 (m, 5 H, *E* and *Z*), 6.86 (d, *J* = 7.3 Hz, 1 H, *Z*), 5.38 (dt, *J* = 13.4, 7.5 Hz, 1 H, *Z*), 4.71 (dt, *J* = 14.4, 7.7 Hz, 1 H, *E*), 3.33–3.11 (m, 2 H, *E* and *Z*).

^{13}C NMR (75 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 150.6 (CH, *E* and *Z*), 136.3 (C, *E* and *Z*), 129.9 (CH, *E* and *Z*), 129.0 (CH, *E*), 128.9 (CH, *Z*), 127.7 (CH, *E* and *Z*), 57.9 (CH, *E*), 53.9 (CH, *Z*), 42.9 (CH_2, *E*), 41.9 (CH_2, *Z*).

2-Chloro-3-methylbutanal Oxime (1c)
Yellow oil (2.7:1-mixture of oxime *E*/*Z*-isomers); yield: 1.97 g (87%).

IR (thin film, *E*/*Z*-mixture): 3264, 2968, 1719, 1463 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 7.62 (br s, 1 H, *E* and *Z*), 7.42 (d, *J* = 8.5 Hz, 1 H, *E*), 6.82 (d, *J* = 7.8 Hz, 1 H, *Z*), 5.02 (dd, *J* = 7.7, 6.3 Hz, 1 H, *Z*), 4.27 (dd, *J* = 8.4, 6.3 Hz, 1 H, *E*), 2.14–2.05 (m, 1 H, *E* and *Z*), 1.08–1.03 (m, 6 H, *E* and *Z*).

^{13}C NMR (100 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 150.6 (CH, *E* and *Z*), 63.9 (CH, *E*), 52.6 (CH, *Z*), 34.3 (CH, *E*), 33.5 (CH, *Z*), 19.5 (CH_3, *E*), 19.4 (CH_3, *Z*), 19.0 (CH_3, *E*), 18.7 (CH_3, *Z*).

2-Chlorobutanal Oxime (1d)
Yellow oil (2.4:1-mixture of oxime *E*/*Z*-isomers); yield: 1.58 g (78%).

IR (thin film, *E*/*Z*-mixture): 3261, 2973, 2937, 2881, 1719, 1457 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 9.41 (br s, 1 H, *E* and *Z*), 7.34 (d, *J* = 8.0 Hz, 1 H, *E*), 6.72 (d, *J* = 7.4 Hz, 1 H, *Z*), 5.03 (q, *J* = 7.1 Hz, 1 H, *Z*), 4.36 (q, *J* = 7.3 Hz, 1 H, *E*), 1.90–1.81 (m, 2 H, *E* and *Z*), 1.02–0.96 (m, 3 H, *E* and *Z*).

^{13}C NMR (75 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 150.8 (CH, *Z*), 150.7 (CH, *E*), 59.4 (CH, *E*), 52.6 (CH, *Z*), 30.2 (CH_2, *E*), 29.4 (CH_2, *Z*), 11.0 (CH_3, *E*), 10.8 (CH_3, *Z*).

2-Chloropropanal Oxime (1e)
Yellow oil (3.0:1-mixture of oxime *E*/*Z*-isomers); yield: 1.43 g (80%).

IR (thin film, *E*/*Z*-mixture): 3312, 2984, 2929, 1709, 1441 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 8.51 (br s, 1 H, *Z*), 8.29 (br s, 1 H, *E*), 7.45 (d, *J* = 7.0 Hz, 1 H, *E*), 6.83 (d, *J* = 6.8 Hz, 1 H, *Z*), 5.26–5.19 (m, 1 H, *Z*), 4.64–4.57 (m, 1 H, *E*), 1.66 (d, *J* = 6.8 Hz, 3 H, *E*), 1.62 (d, *J* = 6.8 Hz, 3 H, *Z*).

^{13}C NMR (100 MHz, $CDCl_3$, *E*-isomer): δ = 151.8 (CH), 52.9 (CH), 23.0 (CH_3).

2-Chloroacetaldehyde Oxime (1f)
This oxime is known[18] and is commercially available but spectra have not been reported.

Yellow oil (1.7:1-mixture of oxime *E*/*Z*-isomers); yield: 1.17 g (75%).

IR (thin film, *E*/*Z*-mixture): 3252, 2916, 1427 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 8.80 (br s, 1 H, *Z*), 8.35 (br s, 1 H, *E*), 7.49 (t, *J* = 6.3 Hz, 1 H, *E*), 6.91 (t, *J* = 4.9 Hz, 1 H, *Z*), 4.29 (d, *J* = 4.9 Hz, 2 H, *Z*), 4.12 (d, *J* = 6.3 Hz, 2 H, *E*).

^{13}C NMR (75 MHz, $CDCl_3$, *E*/*Z*-mixture): δ = 147.9 (CH, *Z*), 147.0 (CH, *E*), 40.0 (CH_2, *E*), 34.7 (CH_2, *Z*).

4-*tert*-Butyl-1-chlorocyclohexanecarbaldehyde Oxime (5)
Yellow oil (~1.5:1-mixture of diastereomers); yield: 3.12 g (86%).

IR (thin film): 3266, 2958, 1703, 1461 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.80 (br s, 1 H), 7.56 (s, 0.6 H), 7.36 (s, 0.4 H), 2.48–2.43 (m, 1 H), 2.15–0.95 (m, 8 H), 0.87 (s, 5.4 H), 0.80 (s, 3.6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0 (CH), 152.7 (CH), 70.6 (C), 68.8 (C), 47.5 (CH), 47.3 (CH), 40.0 (CH_2), 37.6 (CH_2), 32.8 (C), 32.7 (C), 27.9 (CH_3), 27.8 (CH_3), 25.9 (CH_2), 22.5 (CH_2).

α-Aryl Nitriles; General Procedure

To a 25-mL round-bottomed flask flushed with argon was added powdered CuCN (30 mg, 0.33 mmol). The flask was sealed with a rubber septum and a needle connected to an argon line was introduced through the septum. The flask was charged with anhyd THF (1.5 mL) and the mixture was cooled to –10 °C. A hexane–Et_2O soln (~1:2–2:1, ~0.5–1.0 M) of the freshly prepared aryllithium (0.37 mmol)[13] was added slowly by a syringe to the mixture at –10 °C. Upon the addition of the organolithium reagent, the contents of the flask changed from a gray suspension to a colorless solution or to one with a greenish tinge. The solution was cooled to –30 °C and stirred for 5 min at this temperature. The α-chloro aldoxime (0.15 mmol) in THF (1.5 mL) was added dropwise to the mixture at –30 °C; as the α-chloro aldoxime was added, the clear solution slowly became turbid and the color slowly changed to bright yellow. After the addition was complete, the solution was stirred for 20 min at this temperature. Concd H_2SO_4 (0.04 mL, 0.72 mmol) was added to the mixture at –30 °C, followed by CH_2Cl_2 (1.5 mL).

The reaction mixture was warmed to r.t. and anhyd pyridine (0.15 mL, 1.86 mmol) was added followed by anhyd Et_3N (0.2 mL, 1.43 mmol). Solid DCC (250 mg, 1.2 mmol) was added and the resulting mixture was stirred at r.t. After 12 h, the reaction mixture was poured into a separatory funnel containing ethylenediamine (2 mL) dissolved in H_2O (100 mL), and the mixture was extracted with Et_2O (25 mL). The organic layer was washed with H_2O (100 mL), followed by a formic acid soln [100 mL; 96% HCOOH (2 mL) in H_2O (100 mL)]. The organic layer was washed with brine (100 mL) and dried over anhyd $MgSO_4$. The organic solution was concentrated under reduced pressure and the product was purified by flash column chromatography on silica gel [CH_2Cl_2–hexanes, 1:9; followed by EtOAc–hexanes gradient (7–15% EtOAc in hexanes)].

α-Aryl nitriles **4a**, **4b**, **4c**, **4h**, **4i**, **4j**, **4k** and **7** are commercially available or have previously been reported.[16]

3-Methyl-2-phenylbutanenitrile (4d)

Tan oil; yield: 21 mg (87%); R_f = 0.55 (hexanes–EtOAc, 7:1).

IR (thin film): 2960, 2932, 2867, 2239, 2035, 1731, 1599, 1489, 1459, 1374 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 3.67 (d, J = 6.2 Hz, 1 H), 2.19–2.08 (m, 1 H), 1.05 (t, J = 7.4 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0 (C), 128.9 (CH), 128.1 (CH), 128.0 (CH), 120.0 (C), 45.2 (CH), 33.9 (CH), 20.9 (CH_3), 18.9 (CH_3).

HRMS (EI): m/z [M^+] calcd for $C_{11}H_{13}N$: 159.1048; found: 159.1045.

2-(4-Methoxyphenyl)-3-methylbutanenitrile (4e)

Tan oil; yield: 28 mg (98%); R_f = 0.45 (hexanes–EtOAc, 7:1).

IR (thin film): 2964, 2238, 1611, 1511, 1462 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 3.81 (s, 3 H), 3.59 (d, J = 6.3 Hz, 1 H), 2.09–2.05 (m, 1 H), 1.02 (t, J = 5.1 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7 (C), 129.4 (CH), 127.3 (C), 120.6 (C), 114.6 (CH), 55.8 (CH_3), 44.8 (CH), 34.2 (CH), 21.1 (CH_3), 19.3 (CH_3).

HRMS (EI): m/z [M^+] calcd for $C_{12}H_{15}NO$: 189.1154; found: 189.1156.

2-[4-(Dimethylamino)phenyl]-3-methylbutanenitrile (4f)

Tan solid; yield: 22 mg (73%); R_f = 0.43 (hexanes–EtOAc, 7:1).

IR (thin film): 2928, 2802, 2361, 2336, 1612, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 8.6 Hz, 2 H), 6.70 (d, J = 8.4 Hz, 2 H), 3.55 (d, J = 6.4 Hz, 1 H), 2.95 (s, 6 H), 2.09–2.04 (m, 1 H), 1.03 (d, J = 2.3 Hz, 3 H), 1.02 (d, J = 2.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5 (C), 129.0 (CH), 122.7 (C), 120.9 (C), 112.8 (CH), 44.6 (CH), 40.9 (CH_3), 34.2 (CH), 21.1 (CH_3), 19.4 (CH_3).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{19}N_2$: 203.1548; found: 203.1543.

2-(4-Chlorophenyl)-3-methylbutanenitrile (4g)

Tan oil; yield: 20 mg (70%); R_f = 0.55 (hexanes–EtOAc, 7:1).

IR (thin film): 2966, 2932, 2240, 1727, 1597, 1490 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.3 Hz, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 3.64 (d, J = 6.2 Hz, 1 H), 2.13–2.04 (m, 1 H), 1.06–1.01 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.8 (C), 129.6 (CH), 129.5 (CH), 128.6 (C), 119.8 (C), 45.0 (CH), 34.2 (CH), 21.1 (CH_3), 19.1 (CH_3).

HRMS (EI): m/z [M^+] calcd for $C_{11}H_{12}ClN$: 193.0658; found: 193.0670.

Acknowledgment

We are grateful to the National Science Foundation (CHE-1105653) for financial support of this research.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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