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Nickel(II) chloride catalyzed one-pot synthesis of α-aminonitriles

Surya Kanta De*

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy, Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, USA

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Abstract

A simple and efficient method has been developed for the synthesis of α-aminonitriles by simply mixing aldehydes, amines, and trimethylsilyl cyanides in the presence of a catalytic amount of $NiCl_2$ at room temperature.

Keywords: Aldehydes; Amines; Trimethylsilyl cyanide; α-Aminonitriles; Nickel(II) chloride

1. Introduction

The Strecker reaction [1] provides one of the most important methods for the synthesis of α-aminonitriles, which are useful intermediates for the synthesis of amino acids and nitrogen-containing heterocycles such as thiadiazoles, imidazoles etc. [2]. They are generally prepared by the nucleophilic addition of cyanide anion to imines. Among various cyanide ion sources [3–11], trimethylsilyl cyanide is a safer and more easily handled reagent compared to hydrogen cyanide, sodium cyanide or potassium cyanide. However, many of these reported methods have some drawbacks such as low yields of the products, long reaction times, tedious work-up procedure, the requirement for an inert atmosphere, and the use of stoichiometric [10] (KSF clay) or relatively expensive reagents ($Sc(OTf)_3$, $InCl_3$) [8,9]. Therefore, there is further scope to explore a mild and efficient method for the synthesis of α-aminonitriles.

In continuation of my work to develop new synthetic methodologies [12], I, herein, report that nickel(II) chloride, which acts as a mild Lewis acid might be a useful and inexpensive catalyst for the synthesis α-aminonitrile.

2. Results and discussion

The reaction of benzaldehyde and benzyl amine with TMSCN in the presence of a catalytic amount of $NiCl_2$ afforded the corresponding 2-(*N*-benzylamino)-1-phenylacetonitrile in 92% yield. Similarly, a variety of aldehydes were coupled with a wide range of amines and trimethylsilyl cyanide in a one-pot operation in the presence of a catalytic amount of nickel(II) chloride at room temperature to give the corresponding α-aminonitriles in good to excellent yields (Scheme 1). Both aromatic and aliphatic aldehydes afforded excellent yields whereas ketones did not give any satisfactory results. On the other hand, all types of primary and secondary amines are readily coupled to give in good yields. Moreover, acid-sensitive aldehyde such as furfuraldehyde gave with high yield. This method does not require any additives to promote the reaction. The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various aldehydes and amines.

3. Experimental

NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low-resolution mass spectra (CI, EI) were recorded on a Finnigan 4000 mass spectrometer. High-resolution mass spectra (HRMS, EI, CI, ESI) were recorded

* Tel.: +1 76 5743 9702; fax: +1 76 5494 1414.
E-mail address: skd125@pharmacy.purdue.edu.

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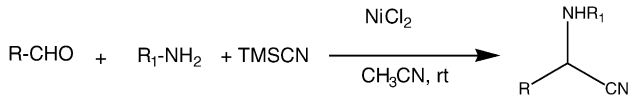

Scheme 1.

on Finnigan MAT XL95 mass spectrometer. The reactions were monitored by TLC, and visualized with UV light followed by development using 15% phosphomolybdic acid in ethanol. All solvents and reagents were purchased from Aldrich with high grade of quality and used without any purification. All yields refer to isolated products.

3.1. A typical procedure

A mixture of benzaldehyde (212 mg, 2 mmol), benzyl amine (214 mg, 2 mmol), and trimethylsilyl cyanide (300 mg, 3 mmol) in dry acetonitrile (2 mL) was stirred at room temperature in the presence of nickel(II) chloride (14 mg, 5 mol%) After completion of reaction (TLC), the reaction mixture was extracted with ethyl acetate (2 mL × 20 mL). The organic layer was washed with water (20 mL), and brine (20 mL), dried (with $MgSO_4$), and concentrated. The residue was chromatographed over silica gel, eluted 20% ethyl acetate in hexane to afford a pure product.

3.1.1. Product characterization data

3.1.1.1. 2-(N-Anilino)-2-phenylacetonitrile (entry 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (br s, 1 H), 5.40 (s, 1 H), 6.74 (d, J = 7.8 Hz, 2 H), 6.89 (t, J = 7.8 Hz, 1 H), 7.24 (t, J = 7.8 Hz, 2 H), 7.41–7.49 (m, 3 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.6, 114.8, 118.8, 120.6, 127.7, 129.7, 130.1, 130.2, 134.5, 145.6; EIMS *m/z* 208 (M^+), 180, 116, 91, 77, 55; HRMS calculated for $C_{14}H_{12}N_2$208.1004, found 208.1006.

Table 1
$NiCl_2$ catalyzed synthesis of α-amino nitriles with trimethylsilyl cyanide

Entry	Aldehyde	Amine	Time (h)	Yield[a] (%)
1	Benzaldehyde	Aniline	12	92
2	4-Chlorobenzaldehyde	Aniline	14	88
3	Isobutyraldehyde	Benzyl amine	15	79
4	Decylaldehyde	Aniline	14	77
5	3-Methoxybenzaldehyde	Benzyl amine	11	90
6	Furfural	Benzylamine	6	76
7	Thiophene 2-carboxaldehyde	Benzyl amine	8	81
8	Benzaldehyde	Morpholine	12	74
9	Butyraldehyde	Pyrrolidine	8	85
10	Benzaldehyde	Furfurylamine	11	73
11	Benzaldehyde	3-Methoxybenzyl amine	15	89
12	Benzaldehyde	Butylamine	18	80
13	2,4-Dimethoxybenzaldehyde	3,4,5-Trimethoxyaniline	12	91
14	4-Methylbenzaldehyde	Aniline	11	88

[a] All products were characterized by NMR and mass spectra and also by comparing their physical properties with those authentic samples.

3.1.1.2. 2-(N-Anilino)-2-(4-chlorophenyl)acetonitrile (entry 2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (br s, 1 H), 5.39 (s, 1 H), 6.75 (d, J = 8 Hz, 2 H), 6.91 (t, J = 7.8 Hz, 1 H), 7.15 (t, J = 7.9 Hz, 2 H), 7.38 (d, J = 7.8 Hz, 2 H), 7.61 (d, J = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 114.2, 117.7, 120.8, 128.5, 129.4, 129.6, 132.3, 135.5, 144.4; EIMS *m/z* 242 and 244 (M^+), 149, 114, 91, 77, 59; HRMS $C_{14}H_{11}ClN_2$242.0610, found 242.0608.

3.1.1.3. 2-(N-Benzylamino)-2-isopropylacetonitrile (entry 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6.5 Hz, 3 H), 1.09 (d, J = 6.5 Hz, 3 H), 1.56 (br s, 1 H), 1.97–2.02 (m, 1 H), 3.24 (d, J = 6 Hz, 1 H), 3.80 (d, J = 13 Hz, 1 H), 4.07 (d, J = 13 Hz, 1 H), 7.24–7.43 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 19.3, 31.3, 51.8, 56.3, 119.3, 127.5, 128.4, 128.7, 138.4; EIMS *m/z* 188 (M^+); HRMS calculated for $C_{12}H_{16}N_2$188.1313, found 188.1316.

3.1.1.4. 2-(N-Anilino)-2-decylacetonitrile (entry 4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 6.7 Hz, 3 H), 1.18–1.38 (m 12 H), 1.50–1.64 (m. 2 H), 1.81–1.91 (m, 2 H), 3.81 (br s, NH), 4.02–4.15 (m, 1 H), 6.61 (d, J = 8 Hz, 2 H), 6.81 (t, J = 7.8 Hz, 1 H), 7.21 (t, J = 7.8 Hz, 2 H); EIMS *m/z* 258 (M^+), 185, 155, 121, 77, 55. HRMS calculated for $C_{17}H_{26}N_2$258.2095, found 258.2092.

3.1.1.5. 2-(N-Benzylamino)-2-(3-methoxyphenylacetonitrile (entry 5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (br s, 1 H), 3.76 (s, 3 H), 3.95 (AB, q, J = 13 Hz, 2 H), 4.65 (s, 1 H), 6.85 (dd, J = 2.4, 9 Hz, 1 H), 7.14–7.36 (m, 2 H), 7.28–7.43 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 53.9, 55.7, 113.4, 114.8, 119.2, 119.8, 128.5, 129.7, 128.8, 130.4, 136.7, 138.6, 160.4; EIMS *m/z* 252 (M^+), 122, 91, 77; HRMS calculated for $C_{16}H_{16}N_2O$ 252.1262, found 252.1264.

3.1.1.6. 2-(N-Benzylamino)-2-furfurylacetonitrile (entry 6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (br s, 1 H), 3.94 (AB, q, J = 13 Hz, 2 H), 4.75 (s, 1 H), 6.27–6.32 (m, 1 H), 7.16–7.52 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.9, 51.4, 109.2, 111.5, 127.5, 127.8, 128.5, 128.9, 138.2, 143.8, 147.9; EIMS *m/z* 212 (M^+); HRMS calculated for $C_{13}H_{12}N_2O$ 212.0950, found 212.0955.

3.1.1.7. 2-(N-Benzylamino)-2-thiophenylacetonitrile (entry 7). ^{13}H NMR (300 MHz, $CDCl_3$) δ 2.02 (br s, 1 H), 3.96 (AB, q, J = 13 Hz, 2 H), 4.91 (s, 1 H), 6.94–6.98 (m, 1 H), 7.21–7.45 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.7, 51.4, 118.4, 126.7, 127.3, 128.3, 128.7, 128.9, 129.2, 138.4, 138.9; EIMS *m/z* 228 (M^+); HRMS calculated for $C_{13}H_{12}N_2S$ 228.0721, found 228.0725.

3.1.1.8. 2-(N-Morpholino)-2-phenylacetontrile (entry 8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51–2.63 (m, 4 H), 4.68–4.79 (m, 5 H), 7.35–7.56 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 62.1, 62.8, 115.7, 128.5, 129.4, 129.8, 133.1; EIMS

m/z 202 (M+); HRMS calculated for $C_{12}H_{14}N_2O$ 202.1106, found 202.1109.

3.1.1.9. 2-n-Propyl-2-(N-pyrrolidino)acetonitrile (entry 9). ^{1}H NMR (300 MHz, $CDCl_3$) 0.98 (t, J = 7.7 Hz, 3 H), 1.42–1.51 (m, 2 H), 1.69–1.89 (m, 6 H), 2.62–2.71 (m, 4 H), 3.75 (t, J = 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 17.4, 21.4, 32.9, 47.9, 53.2, 94.4; EIMS *m/z* 152 (M^+); HRMS calculated for $C_9H_{16}N_2$152.1313, found 152.1311.

3.1.1.10. 2-(N-furfurylamino)-2-phenylacetonitrile (entry 10). ^{1}H NMR (300 MHz, $CDCl_3$) 1.82 (br s, 1 H), 4.01 (s, 2 H), 4.79 (s, 1 H), 6.21–6.41 (m, 2 H), 7.31–7.56 (m, 6 H); EIMS *m/z* 212 (M^+), 186, 81, 77; HRMS calculated for $C_{13}H_{12}N_2O$ 212.0949, found 212.0951.

3.1.1.11. 2-(N-3-Methoxybenzylamino)-2-phenylacetonitrile (entry 11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (br s, 1 H), 3.81 (s, 3 H), 3.94 (AB, q, J = 13 Hz, 2 H), 4.71 (s, 1 H), 6.81–6.96 (m, 3 H), 7.24 (t, J = 7.8 Hz, 1 H), 7.30–7.58 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) 51.4, 53.7, 55.6, 96.6, 113.4, 114.2, 119.1, 120.9, 127.6, 129.4, 130.1, 135.4, 140.1, 160.2; EIMS *m/z* 252 (M^+), 122, 91, 77; HRMS calculated for $C_{16}H_{16}N_2O$ 252.1262, found 252.1265.

3.1.1.12. 2-(N-n-Butylamino)-2-phenylacetonitrile (entry 12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.25–1.47 (m, 4 H), 2.68–2.78 (m, 2 H), 4.74 (s. 1 H), 7.38–7.38 (m 3 H), 7.65–7.71 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.6, 32.3, 47.5, 54.8, 119.4, 127.7, 129.3, 135.5; EIMS m/z 188 (M^+); HRMS calculated $C_{12}H_{16}N_2$188.2689, found 188.2693.

3.1.1.13. 2-(N-3,4,5-Trimethoxyanilino)-2-(2,4-dimethoxyphenyl)acetonitrile (entry 13). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 6 H), 3.86 (s, 3 H), 4.18 (br s, 1 H), 5.44 (s, 1 H), 6.01 (s, 2 H), 6.46–6.53 (m, 2 H), 7.39 (d, J = 9 Hz, 1 H); EIMS *m/z* 358 (M^+); HRMS calculated for $C_{19}H_{22}N_2O_5$358.1529, found 358.1531.

3.1.1.14. 2-(N-Anilino)-2-(4-methylphenyl)acetonitrile (entry 14). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 3.90 (s, 1 H), 5.41 (s, 1 H), 6.78 (d, J = 8 Hz, 2 H), 6.91 (t, J = 7.8 Hz, 1 H), 7.21–7.31 (m, 4 H), 7.50 (d, J = 8 Hz, 2 H), 7.51 (d, J = 8 Hz, 2 H); EIMS *m/z* 222 (M^+), 176, 103, 77; HRMS calculated for $C_{15}H_{14}N_2$222.1156, found 222.1158.

4. Conclusion

In conclusion, I have demonstrated a very simple, efficient, and practical method for the synthesis of α-aminonitriles through a one-pot three component coupling of aldehydes, amines, and trimethylsilyl cyanide using a catalytic amount of nickel(II) chloride. The major advantage of this method is that it is truly a one-pot procedure that does not require a separate step to prepare an imine for subsequent use. The significant features of this method include (a) operational simplicity, (b) inexpensive reagents, (c) no need for any additive to promote the reaction, (d) high yields of products, and (e) the use of relatively non-toxic reagents and solvents.

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