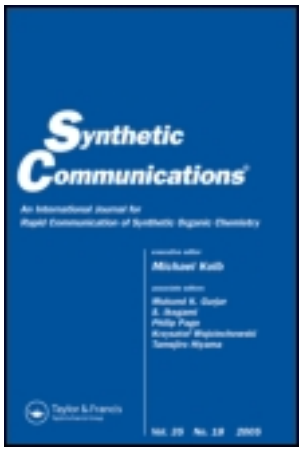

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Lithium Perchlorate Mediated Three-Component Preparation of α-Aminonitriles Under Solvent-Free Conditions

Najmedin Azizi [a] & Mohammad R. Saidi [a]

[a] Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Iran

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Lithium Perchlorate Mediated Three-Component Preparation of α-Aminonitriles Under Solvent-Free Conditions

Najmedin Azizi and Mohammad R. Saidi*

Department of Chemistry, Sharif University of Technology, Tehran, Iran

ABSTRACT

A three-component reaction between aliphatic or aromatic aldehyde, an amine and trimethylsilyl cyanide mediated by solid $LiClO_4$, gave amino nitriles in good to excellent yields. The reaction proceeded smoothly under solvent-free conditions without any side products.

Key Words: Lithium perchlorate; α-Aminonitriles; Solvent-free conditions; Three-component condensation.

*Correspondence: Mohammad R. Saidi, Department of Chemistry, Sharif University of Technology, P.O. Box 11365-9516, Tehran, Iran; Fax: +98-21-601-2983; E-mail: saidi@sharif.edu.

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INTRODUCTION

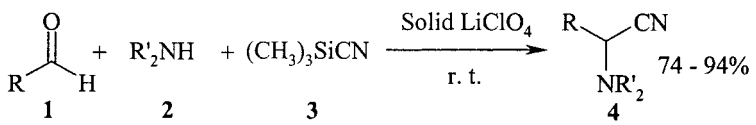
Three-component condensations are interesting and important, not only because three components are reacting together in one pot, but also because this methodology would be useful for the preparation of a broad variety of organic compounds. α-Aminonitriles are important intermediates in the synthesis of amino acids, amides, and diamines.[1,2] Numerous methods describing the preparation of α-aminonitriles are reported in the literature using different kind of catalysts including a variety of Lewis acids.[3] However, it can be difficult to recover the Lewis acid catalyst in the three-component condensation for the synthesis of α-aminonitriles, because of the strong affinity of the Lewis acids for the amino groups or because its reaction with water does not allow regeneration of the Lewis acid. Also, in many cases, in Lewis acid-catalyzed three-component synthesis of amino nitriles, a stoichiometric amount of expensive Lewis acid is needed.[4]

RESULTS AND DISCUSSION

In continuation of our current work on the use of 5 M ethereal lithium perchlorate for three-component Mannich-type organic transformations,[5] and the current challenge for developing solvent-free and environmentally benign synthetic systems,[6] herein, we report a mild, convenient, and rapid method for cyano amination of aldehydes with TMSCN using solid $LiClO_4$ as a promoter under solvent-free conditions.

Treatment of benzaldehyde with a secondary amine such as piperidine, and trimethylsilyl cyanide in the presence of solid $LiClO_4$ afforded the corresponding α-aminonitriles in 90% yield without using any solvent at room temperature. Similarly, several aromatic aldehydes and 2-methylpropanal reacted under the same conditions to give the corresponding α-aminonitriles in good to excellent yields, Sch. 1.

The reaction proceeded smoothly at room temperature and the products were isolated in good yields after a short reaction time. The generality of this reaction is evident from the results summarized in Table 1, which shows that a variety of aldehydes and secondary amines are converted into



Scheme 1.

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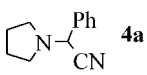
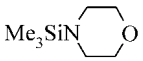
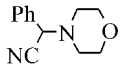
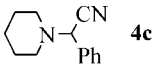
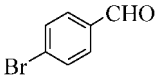
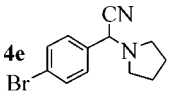
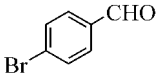
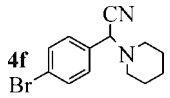
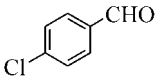
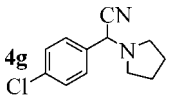
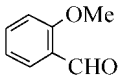
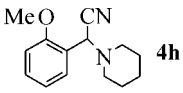
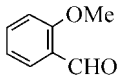
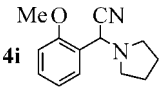
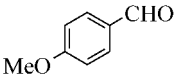
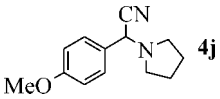
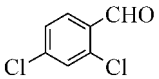
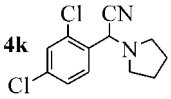
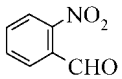
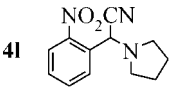
Table 1. Solid $LiClO_4$-catalyzed aminocyanation of aldehydes by TMSCN.

Entry	Aldehyde	Amine	Product	Yields[a] (%)
1	PhCHO		 **4a**	90
2	PhCHO			76[b]
3	PhCHO		 **4c**	90
4	PhCHO		 **4d**	84[c]
5			 **4e**	92
6			 **4f**	93
7			 **4g**	90
8			 **4h**	94
9			 **4i**	90
10			 **4j**	76
11			 **4k**	84
12			 **4l**	92

(*continued*)

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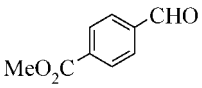
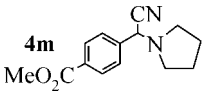
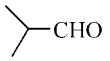
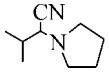
Table 1. Continued.

Entry	Aldehyde	Amine	Product	Yields[a] (%)
13			 **4m**	91
14			 **4n**	74

[a]Isolated yields.
[b]By using morpholine the aminocyanation reaction did not proceed, but with *N*-(trimethylsilyl)morpholine, the corresponding α-amino nitrile was formed.
[c]Me_2NTMS was used, because dimethylamine is gas at r.t.

the corresponding α-aminonitriles. By using morpholine as a secondary amine at the same reaction conditions, no product was formed. By using *N*-(trimethylsilyl)morpholine the corresponding α-aminonitriles was produced in 76% yield (Table 1, Entry 2). Since aqueous solution of dimethylamine could not be used as an amine, instead, *N*-(trimethylsilyl)dimethylamine was used (Table 1, Entry 4). $LiClO_4$ is not an expensive reagent, it can be quantitatively recovered and reused after activation. The recovery procedure and recycling are very simple. After the reaction is complete dichloromethane is added with stirring; $LiClO_4$ precipitates and can be quantitatively separated by filtration. The recovered $LiClO_4$ can be reactivated by heating in vacuum at 160°C and reused. This is another feature of this reaction for developing environmentally benign synthetic methods.

In conclusion, solid lithium perchlorate is found to be an efficient promoter for the cyano amination of aldehydes. The reactions proceed smoothly under solvent-free conditions with a very easy work up procedure.

EXPERIMENTAL

Typical Procedure for the Synthesis of α-Aminonitriles

The aldehydes (1 mmol), $LiClO_4$ (2 mmol) were placed in a 5-mL flask under argon and stirred for 1 min, then an amine (3 mmol) was added via syringe. After 5 min, TMSCN (1.2 mmol) was added and the mixture was stirred at r.t. for about 20 min. After the reaction is complete, the organic materials separated by adding CH_2Cl_2 (10 mL). The precipitated $LiClO_4$ was recovered by filtration. Then the organic layer was washed with aqueous $NaHCO_3$

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(2 × 10 mL), water (2 × 10 mL), and dried over Na_2SO_4. The reaction product was recovered by simple removal of solvent and purified by column chromatography on silica gel eluting with petroleum ether/EtOAc, if necessary. All compounds are known and were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

2-(*N*-Pyrrolidino)-2-phenylacetonitrile (4a).[4] M.p. 84–86°C (Lit.[4] 85°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80–1.81 (m, 4H), 2.66–2.72 (m, 4H), 5.30 (s, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 50.1 (CH), 27.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 124.0 (CH), 125.8 (CH), 130.8 (CH), 135.4 (CH), 140.4 (C); IR: (CH_2Cl_2), 2239 cm^{-1}.

2-(*N*-Morpholino)-2-phenylacetonitrile (4b).[4] M.p. 92–93°C (Lit.[4] 90°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.57–2.58 (m, 4H), 3.70–3.75 (m, 4H), 4.80 (s, 1H), 7.37–7.54 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 50.3 (CH), 62.7 (CH_2), 67.1 (CH_2), 115.6 (CN), 127.5 (CH), 128.4 (CH), 130.3 (CH), 132.1 (C); IR: (CH_2Cl_2), 2230 (CN) cm^{-1}.

2-(*N*-Piperidino)-2-phenylacetonitrile (4c). M.p. 100–102°C (Lit.[4] 101°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.45–1.60 (m, 6H), 2.49 (m, 4H), 4.81 (s, 1H), 7.33–7.38 (m, 3H), 7.52–7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.3 (CH_2), 26.2 (CH_2), 51.3 (CH), 63.2 (CH_2), 115.9 (CN), 128.2 (CH), 128.8 (CH), 129.3 (CH), 135.1 (C); IR: (CH_2Cl_2), 2232 (CN) cm^{-1}.

2-(*N*,*N*-Dimethyl)-2-phenylacetonitrile (4d). Oil.[4] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 2.22 (s, 6H), 7.31–7.37 (m, 3H), 7.51–7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 45.2 (CH_3), 51.3 (CH), 115.9 (CN), 128.2 (CH), 128.8 (CH), 129.3 (CH), 135.1 (C); IR: (CH_2Cl_2), 2232 (CN) cm^{-1}.

2-(*N*-Pyrrolidino)-2-(*p*-bromophenyl)acetonitrile (4e). M.p. 89–90°C (Lit.[1] 91°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.67–1.80 (m, 4H), 2.64–2.71 (m, 4H), 5.31 (s, 1H), 7.25–7.28 (m, 2H), 7.30–7.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 25.2 (CH_2), 50.1 (CH), 64.1 (CH_2), 114.9 (CN), 124.0 (CH), 125.8 (CH), 132.8 (CH), 134.4 (CH), 146.4 (C); IR: (CH_2Cl_2), 2239 cm^{-1}.

2-(*N*-Piperidino)-2-(*p*-bromophenyl)acetonitrile (4f). M.p. 106–107°C (Lit.[1] 108°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.45–1.60 (m, 6H), 2.49 (m, 4H), 4.81 (s, 1H), 7.33–7.40 (m, 2H), 7.52–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.3 (CH_2), 26.2 (CH_2), 51.3 (CH), 63.2 (CH_2), 115.9 (CN), 128.2 (CH), 128.8 (CH), 129.3 (C), 139.1 (C); IR: (CH_2Cl_2), 2232 (CN) cm^{-1}.

2-(*N*-Pyrrolidino)-2-(*p*-chlorophenyl)acetonitrile (4g). M.p. 85–86°C (Lit.[1] 84°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80–1.81 (m, 4H), 2.66–2.72 (m, 4H), 5.30 (s, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 50.1 (CH), 64.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 124.0 (CH), 125.8 (CH), 130.8 (CH), 138.4 (C), 143.4 (C); IR: (CH_2Cl_2), 2239 cm^{-1}.

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2-(*N*-Piperidino)-2-(2-methoxyphenyl)acetonitrile (4h). Oil.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.45–1.60 (m, 6H), 2.49 (m, 4H), 3.84 (s, 3H), 5.15 (s, 1H), 6.91–7.10 (m, 2H), 7.34–7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.2 (CH_2), 26.6 (CH_2), 51.8 (CH), 63.3 (CH_2), 114.5 (CN), 112.4 (CH), 120.3 (CH), 124.1 (C), 129.1 (CH), 131.8 (CH), 157.1 (C); IR: (CH_2Cl_2), 2231 cm^{-1}.

2-(*N*-Pyrrolidino)-2-(2-methoxyphenyl)acetonitrile (4i). Oil.[2] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80–1.81 (m, 4H), 2.66–2.75 (m, 4H), 3.82 (s, 3H), 5.35 (s, 1H), 6.90–6.99 (m, 2H), 7.31–7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 26.4 (CH_2), 51.4 (CH), 54.2 (CH_2), 114.9 (CN), 113.4 (CH), 122.8 (CH), 125.1 (C), 129.1 (CH), 132.4, 158.4 (C); IR: (CH_2Cl_2), 2235 cm^{-1}.

2-(*N*-Pyrrolidino)-2-(4-methoxyphenyl)acetonitrile (4j). Oil.[2b] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.79–1.81 (m, 4H), 2.65–2.77 (m, 4H), 3.81 (s, 3H), 5.30 (s, 1H), 6.70–6.80 (m, 2H), 7.21–7.24 (m, 2H); IR: (CH_2Cl_2), 2236 cm^{-1}.

2-(*N*-Pyrrolidino)-2-(2,4-dichlorophenyl)acetonitrile (4k). M.p. 110–112°C (Lit.[4b] 110°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.83–1.85 (m, 4H), 2.68–2.79 (m, 4H), 5.39 (s, 1H), 7.33–7.41 (m, 2H), 7.66–7.68 (m, 1H); IR: (CH_2Cl_2), 2235 cm^{-1}.

2-(*N*-Pyrrolidino)-2-(*o*-nitrophenyl)acetonitrile (4l). M.p. 116–118°C (Lit.[2d] 116°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.79–1.81 (m, 4H), 2.66–2.69 (m, 4H), 4.95 (s, 1H), 7.62 (m, 1H), 7.92 (m, 1H), 8.22 (m, 1H), 8.38 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 50.1 (CH), 64.9 (CH_2), 67.2 (CH_2), 114.9 (CN), 123.2 (CH), 123.7 (C), 134.6 (CH), 135.4 (CH), 139.8 (CH), 148.4 (C); IR: (CH_2Cl_2), 1347, 1534, 2235 cm^{-1}.

2-(*N*-Pyrrolidino)-2-(methyl 4-carboxylphenyl)acetonitrile (4m). M.p. 120–122°C (Lit.[1a] 120°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80–1.81 (m, 4H), 2.66–2.75 (m, 4H), 3.82 (s, 3H), 5.35 (s, 1H), 6.90–6.99 (m, 2H), 7.38–7.43 (m, 2H); IR: (CH_2Cl_2), 2240, 1730 cm^{-1}.

2-(*N*-Pyrrolidino)-3-methylbutanonitrile (4n). Oil.[3b] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.91 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H), 1.60 (m, 1H), 1.80–1.83 (m, 4H), 2.59–2.69 (m, 4H), 3.29 (d, $J = 10.1$ Hz, 1H); IR: (CH_2Cl_2), 2225 (CN) cm^{-1}.

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