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Bismuth trichloride catalyzed synthesis of α-aminonitriles

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Abstract—A simple and efficient one-pot method has been developed for the synthesis of α-aminonitriles from aldehydes, amines, and trimethylsilyl cyanide in the presence of a catalytic amount of bismuth trichloride.

The addition of cyanide to imines (the Strecker reaction)[1] provides one of the most efficient methods for the synthesis of α-aminonitriles. α-Aminonitriles are important intermediates for the synthesis of amino acids[2] and various nitrogen containing heterocycles such as thiadiazoles and imidazoles.[3] The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. Among various cyanide ion sources,[4] trimethylsilyl cyanide is a safer and easily handled reagent compared to hydrogen cyanide, sodium cyanide, or potassium cyanide.

Recently, there has been considerable interest growing in the use of bismuth(III) halides as potential Lewis acids in various organic reactions[5] because they are inexpensive, relatively non-toxic, fairly insensitive to small amounts of water, and environmentally benign reagents. In this communication, we wish to report a simple and efficient method for the synthesis of α-aminonitriles in the presence of a catalytic amount of bismuth(III) chloride in acetonitrile at room temperature.

The reaction of benzaldehyde and benzyl amine with TMSCN in the presence of a catalytic amount of $BiCl_3$ afforded the corresponding 2-(N-benzylamino)-2-phenylacetonitrile in 85% yield.[6,7] The reaction is successful using both primary and secondary amines with a variety of aldehydes but not ketones. Moreover, acid sensitive aldehyde such as furfuraldehyde afforded with high yield. The reaction conditions are mild enough to perform the reactions in the presence of acid sensitive substrates. This method does not require any additives to promote the reaction. The results have been summarized in Table 1, which clearly indicates the scope and generality of this method with respect to various amines and aldehydes including aromatic, aliphatic, and heterocyclic (Scheme 1).

In conclusion, we 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 bismuth(III) chloride. The major advantage of this method is that it is truly a one-pot

Table 1. $BiCl_3$ catalyzed synthesis of α-amino nitriles with trimethylsilyl cyanide

Entry	Aldehyde	Amine	Time (h)	Yield[a] (%)
1	Benzaldehyde	Aniline	10	84
2	4-Chloro-benzaldehyde	Benzyl amine	8	91
3	Hexanal	Benzyl amine	9	83
4	Pentanal	Aniline	8	81
5	4-Methoxy-benzaldehyde	Benzyl amine	6	90
6	Furfural	Benzyl amine	6	82
7	Thiophene 2-carboxaldehyde	Benzyl amine	6	84
8	Benzaldehyde	Morpholine	7	89
9	4-Methoxy-benzaldehyde	Pyrrolidine	6	86
10	Benzaldehyde	Furfurylamine	5	89
11	Benzaldehyde	3-Methoxybenzyl amine	5	90

[a] Yields refer to pure isolated products, characterized by ^1H NMR and MS.

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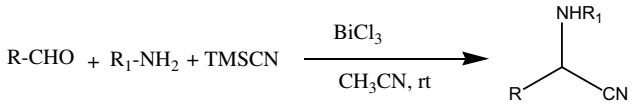

Scheme 1.

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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References and notes

1. Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
2. Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148.
3. (a) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. *J. Org. Chem.* **1967**, *32*, 2823; (b) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901.
4. (a) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *125*, 4583; (b) Harusawa, S.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* **1979**, *20*, 4663; (c) Iyer, M. S.; Gigstad, M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910; (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315; (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650; (f) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 981.
5. Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373.
6. Typical procedure: a mixture of benzaldehyde (106 mg, 1 mmol), benzyl amine (110 mg, 1 mmol), and trimethylsilyl cyanide (148 mg, 1.5 mmol) in acetonitrile (2 mL) in the presence of $BiCl_3$ (32 mg, 0.1 mmol) was stirred at room temperature. After completion of the reaction (TLC), the reaction mixture was partitioned between 100 mL of ether and 50 mL of water. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel (15% ethyl acetate in hexane) to give a pure product.
7. Selected spectral data: 2-(N-benzylamino)-2-phenylacetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (br s, NH), 3.96 (AB, q, J = 13.5 Hz, 2H), 4.72 (s, 1H), 6.77 (d, J = 8 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.22–7.43 (m, 6H), 7.48–7.52 (m, 2H); MS m/z 223 $(M + H)^+$; 2-(N-morpholino)-2-phenylacetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56–2.64 (m, 4H), 4.75–4.83 (m, 4H), 7.35–7.56 (m, 5H); 2-(N-benzylamino)-2-furfurylacetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94 (br s, NH), 3.94 (AB, q, J = 13.1 Hz, 2H), 4.73 (s, 1H), 6.31 (m, 1H), 7.17–7.49 (m, 7H), MS m/z 213 $(M + H)^+$.