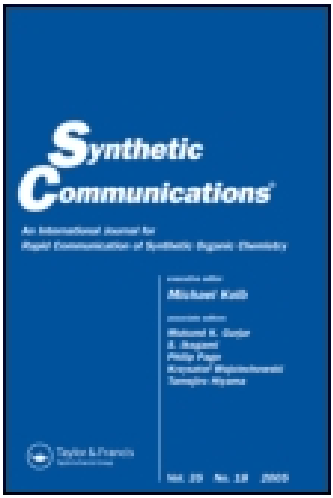

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Vanadyl Triflate as an Efficient and Recyclable Catalyst for the Synthesis of α-Aminonitriles

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Vanadyl Triflate as an Efficient and Recyclable Catalyst for the Synthesis of α-Aminonitriles

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Abstract: Vanadyl triflate to catalyzed Strecker-type reactions were successfully carried out by simply mixing aldehydes, amines, and trimethylsilyl cyanide at room temperature to afford α-aminonitriles in good yields.

Keywords: α-Aminonitriles, aldehydes, amines, recyclability, trimethylsilyl cyanide, vanadyl triflate

INTRODUCTION

In view of the tremendous versatility of α-aminonitriles in synthetic organic chemistry as important intermediates for the synthesis of amino acids[1] and nitrogen-containing heterocycles,[2] a plethora of procedures has been reported for their preparation.[3–10] The classical Strecker reaction is generally carried out with alkaline cyanides in an aqueous solution. Among various cyanide-ion sources, trimethysilyl cyanide is a safer and more easily handled reagent compared with hydrogen cyanide, sodium cyanide, or potassium cyanide. However, many of these methods have some drawbacks, such as low yields of the products, long reaction times, harsh reaction conditions, difficulties in workup, the requirement for an inert atmosphere, and

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the use of stoichiometric and/or relatively expensive reagents. Moreover, many of the catalysts used for these reactions are deactivated or sometimes decomposed by amines and water that exist during imine formation. Therefore, there is reason to search a better catalyst in terms of operational simplicity and reusability.

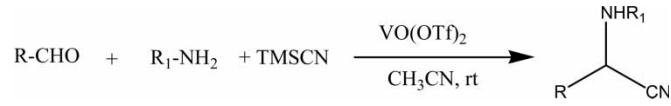
Most recently, vanadyl triflate has been introduced as promising mild and selective reagent in organic synthesis.[11] The catalyst vanadyl triflate is readily prepared using a reported method [11] and can be used for the preparation of α-aminonitriles through a one-pot, three-component coupling of aldehydes, amines, and trimethylsilyl cyanide. Although most conventional Lewis acids are decomposed in the presence of water, $VO(OTf)_2$ is stable in water and does not decompose under aqueous workup conditions. Thus, recyclization is often possible. In continuation of my work to develop new synthetic methodologies,[12] I herein report that vanadyl triflate, which acts as a mild Lewis acid, might be an important and reusable catalyst for the synthesis of α-aminonitrile.

RESULTS AND DISCUSSION

The reaction of benzaldehyde and aniline with trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of $VO(OTf)_2$ afforded the corresponding 2-(N-anilino)-2-phenylacetonitrile in 94% yield (Scheme 1). Thus, various aromatic, aliphatic, and heterocyclic 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 $VO(OTf)_2$ to give the corresponding α-aminonitriles. However, ketones did not give any satisfactory results. On the other hand, all types of primary and secondary amines are readily coupled to give good yields. Moreover, acid-sensitive aldehydes such as furfuraldehyde afforded the desired product in high yield. The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various aldehydes and amines.

CONCLUSION

In conclusion, a very simple, mild, and practical method has been developed for the synthesis of α-aminonitriles through a one-pot, three-component coupling of aldehydes, amines, and trimethylsilyl cyanide using a catalytic



Scheme 1.

Table 1. $VO(OTf)_2$-catalyzed synthesis of α-amino nitriles with trimethylsilyl cyanide

Entry	Aldehyde	Amine	Time (h)	Yield[a] (%)
1	Benzaldehyde	Aniline	12	94
2	4-Chlorobenzaldehyde	Aniline	14	88
3	Isobutyraldehyde	Benzyl amine	12	79
4	Decylaldehyde	Aniline	14	75
5	3-Methoxybenzaldehyde	Benzyl amine	10	92
6	Furfural	Benzyl amine	7	85
7	Thiophene 2-carboxaldehyde	Benzyl amine	8	89
8	Benzaldehyde	Morpholine	11	88
9	Butyraldehyde	Pyrrolidine	9	85
10	Benzaldehyde	Furfurylamine	11	74
11	Benzaldehyde	3-Methoxybenzyl amine	10	89
12	Benzaldehyde	Butylamine	14	91
13	2,4-Dimethoxybenzaldehyde	3,4,5-Trimethoxy-aniline	11	95
14	4-Methylbenzaldehyde	Aniline	10	91

[a]All products were characterized by ^1H NMR and mass spectra.

amount of vanadyl triflate. Further, the catalyst can be readily recovered and reused, thus making the procedure more environmentally acceptable.

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 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 in high-grade quality and used without any purification. All yields refer to isolated products.

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 in the presence of vanadyl triflate (15 mol%) at room temperature. After completion of the reaction (TLC), the reaction mixture

was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel (20% ethyl acetate in hexane) to afford the pure product. The aqueous layer containing the catalyst can be evaporated under reduced pressure (30 mm at 80°C) to give a solid, which was reused for the next reaction. The catalyst can be reused three times without significant loss of activity.

Product Characterization Data

2-(N-Anilino)-2-phenylacetonitrile (entry 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (br s, 1H), 5.40 (s, 1H), 6.74 (d, $J = 7.8$ Hz, 2H), 6.89 (t, $J = 7.8$ Hz, 1H), 7.24 (t, $J = 7.8$ Hz, 2H), 7.41–7.49 (m, 3H): ^{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 calcd. for $C_{14}H_{12}N_2$ 208.1004, found 208.1006.

2-(N-Anilino)-2-(4-chlorophenyl)acetonitrile (entry 2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (br s, 1H), 5.39 (s, 1H), 6.75 (d, $J = 8$ Hz, 2H), 6.91 (t, $J = 7.8$ Hz, 1H), 7.15 (t, $J = 7.9$ Hz, 2H), 7.38 (d, $J = 7.8$ Hz, 2H), 7.61 (d, $J = 8$ Hz, 2H): ^{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.

2-(N-Benzylamino)-2-isopropylacetonitrile (entry 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, $J = 6.5$ Hz, 3H), 1.09 (d, $J = 6.5$ Hz, 3H), 1.56 (br s, 1H), 1.97–2.02 (m, 1H), 3.24 (d, $J = 6$ Hz, 1H), 3.80 (d, $J = 13$ Hz, 1H), 4.07 (d, $J = 13$ Hz, 1H), 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 calcd. for $C_{12}H_{16}N_2$ 188.1313, found 188.1316.

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

2-(N-Benzylamino)-2-(3-methoxyphenylacetonitrile (entry 5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (br s, 1H), 3.76 (s, 3H), 3.95 (AB, q, $J = 13$ Hz, 2H), 4.65 (s, 1H), 6.85 (dd, $J = 2.4$, 9 Hz, 1H), 7.14–7.36 (m, 2H), 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 calcd. for $C_{16}H_{16}N_2O$ 252.1262, found 252.1258.

2-(N-Benzylamino)-2-furfurylacetonitrile (entry 6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (br s, 1H), 3.94 (AB, q, $J = 13$ Hz, 2H), 4.75 (s, 1H),

6.27–6.32 (m, 1H), 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 calcd. for $C_{13}H_{12}N_2O$ 212.0950, found 212.0955.

2-(N-Benzylamino)-2-thiophenylacetonitrile (entry 7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (br s, 1H), 3.96 (AB, q, $J = 13$ Hz, 2H), 4.91 (s, 1H), 6.94–6.98 (m, 1H), 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 calcd. for $C_{13}H_{12}N_2S$ 228.0721, found 228.0725.

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 calcd. for $C_{12}H_{14}N_2O$ 202.1106, found 202.1109.

2-*n*-Propyl-2-(N-pyrrolidino)acetonitrile (entry 9). ^{1}H NMR (300 MHz, $CDCl_3$) 0.98 (t, $J = 7.7$ Hz, 3H), 1.42–1.51 (m, 2H), 1.69–1.89 (m, 6 H), 2.62–2.71 (m, 4 H), 3.75 (t, $J = 7.5$ Hz, 1H): ^{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 calcd. for $C_9H_{16}N_2$ 152.1313, found 152.1311.

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

2-(N-3-Methoxybenzylamino)-2-phenylacetonitrile (entry 11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (br s, 1H), 3.81 (s, 3H), 3.94 (AB, q, $J = 13$ Hz, 2H), 4.71 (s, 1H), 6.81–6.96 (m, 3H), 7.24 (t, $J = 7.8$ Hz, 1H), 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 calcd. for $C_{16}H_{16}N_2O$ 252.1262, found 252.1265.

2-(N-*n*-Butylamino)-2-phenylacetonitrile (entry 12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, $J = 7.2$ Hz, 3H), 1.25–1.47 (m, 4 H), 2.68–2.78 (m, 2H), 4.74 (s. 1H), 7.38–7.38 (m, 3H), 7.65–7.71 (m, 2H): ^{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 calcd. for $C_{12}H_{16}N_2$ 188.2689, found 188.2693.

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

2-(N-Anilino)-2-(4-methylphenyl)acetonitrile (entry 14). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.90 (s, 1H), 5.41 (s, 1H), 6.78 (d, $J = 8$ Hz, 2H), 6.91 (t, $J = 7.8$ Hz, 1H), 7.21–7.31 (m, 4 H), 7.50

(d, $J = 8$ Hz, 2H), 7.51 (d, $J = 8$ Hz, 2H); EIMS m/z 222 (M^+), 176, 103, 77. HRMS calcd. for $C_{15}H_{14}N_2$ 222.1156, found 222.1158.

REFERENCES

1. Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. Synthesis of α-aminonitriles. *Russ. Chem. Rev.* **1989**, *58*, 148.
2. (a) Weinstock, L. M.; Davis, P.; Handelsman, B.; Tull, R. General synthetic system for 1,2,5-thioadiazoles. *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. Antihypertensive agent. Synthesis and biological properties of 2-amino-4-aryl-2-imidazolines. *J. Med. Chem.* **1973**, *16*, 901.
3. Mai, K.; Patil, G. Facile synthesis of aminonitriles. *Tetrahedron Lett.* **1984**, *25*, 4583.
4. Harusawa, S.; Hamada, Y.; Shiori, T. Diethylphosphorocyanidated: A novel reagent for the classical Strecker's synthesis of α-aminonitriles. *Tetrahedron Lett.* **1979**, *20*, 4663.
5. Iyer, M. S.; Gigstad, M.; Namdev, N. D.; Lipton, M. Asymmetric catalysis of the steacker amino acid synthesis by a cyclic dipeptide. *J. Am. Chem. Soc.* **1996**, *118*, 4910.
6. Sigman, M. S.; Jacobsen, E. N. Enantioselective addition of hydrogen cyanide to imines by a chiral salen Al(III) complex. *J. Am. Chem. Soc.* **1998**, *120*, 5315.
7. Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650.
8. Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc. Chem. Commun.* **1998**, 981.
9. Ranu, B. C.; Dey, S. S.; Hajra, A. Indium trichloride catalyzed one-step synthesis of α-amino nitriles by a three-component condensation of carbonyl compounds, amines, and potassium cyanide. *Tetrahedron* **2002**, *58*, 2529.
10. Yadav, J. S.; Reddy, B. V.; Eeshwaraiah, B.; Srinivas, M. Montmorillonite KSF clay–catalyzed one-pot synthesis of α-amino nitriles. *Tetrahedron* **2004**, *60*, 1767.
11. (a) Hirao, T. Vanadium in modern organic synthesis. *Chem. Rev.* **1997**, *97*, 2707 For a general review on V(IV), see; (b) Chen, C. T.; Kuo, J. H.; Li, C. J.; Barhate, N. B.; Hon, S. W.; Li, T. W.; Chao, S. D.; Liu, C. C.; Li, I. H.; Chang, J. S.; Lin, J.; Liu, Y. C. Catalytic nucleophilic acyl substitution of anhydrides by amphoteric vanadyl triflate. *Org. Lett.* **2001**, *3*, 3729. For catalyst preparation see, Also available from Bestgen Bio Tech, Taiwan.
12. (a) De, S. K. $SiBr_4$/wet silica gel as an efficient heterogeneous system for cleavage of C = N. *Tetrahedron Lett.* **2003**, *44*, 9055; (b) De, S. K. Cobalt(II) chloride–catalyzed chemoselective thioacetalization of aldehydes. *Tetrahedron Lett.* **2004**, *45*, 1035; (c) De, S. K. Yttrium triflate as an efficient and useful catalyst for chemoselective protection of carbonyl compounds. *Tetrahedron Lett.* **2004**, *45*, 2339; (d) De, S. K. Ruthenium(III) chloride–catalyzed acylation of alcohols, phenols, thiols, and amines. *Tetrahedron Lett.* **2004**, *45*, 2919; (e) De, S. K. Scandium chloride–catalyzed chemoselective thioacetalization of aldehydes. *Synthesis* **2004**, 828; (f) De, S. K. $RuCl_3$-catalyzed facile conversion of aromatic ketoximes to amides. *Synth. Commun.* **2004**, *34*, 3431; (g) De, S. K. A mild and efficient method for cleavage of C=N using imidazolium dichromate. *Synth. Commun.* **2004**, *34*, 2751.