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Praseodymium Trifluoromethylsulfonate as an Efficient and Recyclable Catalyst for the Synthesis of α-Aminonitriles

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Abstract: Praseodymium trifluoromethylsulfonate (triflate) has been found to be an efficient and recyclable catalyst for the synthesis of α-aminonitrile by a one-pot, three-component condensation of aldehydes, amines, and trimethylsilyl cyanide at room temperature.

Keywords: Aldehydes, amines, praseodymium triflate, recyclability, trimethylsilyl cyanide

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 aqueous solution. Among various cyanide-ion sources, trimethylsilyl cyanide is a more reactive reagent than 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

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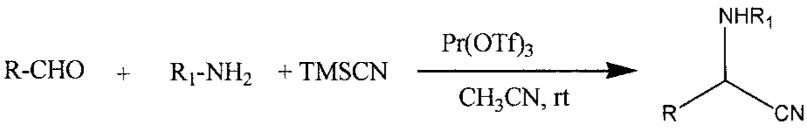
workup, the requirement for an inert atmosphere, and the use of stoichiometric[10] and/or relatively expensive reagents.[8,9] Moreover, many of the catalysts used for these reactions are deactivated or sometimes decomposed by amines and water that are present during imine formation. Therefore, there is need to search for a better catalyst in terms of operational simplicity, reusability, and economic viability.

Most recently, lanthanide triflates have been introduced as promising mild and selective reagents in organic synthesis.[11] The catalyst praseodymium triflate is commercially available, five times less expensive than scandium triflate, and can be used for the preparation of α-aminonitriles through a one-pot, three-component coupling of aldehydes, amines, and trimethylsilyl cyanide. Whereas most conventional Lewis acids are decomposed in the presence of water, $Pr(OTf)_3$ is stable in water and does not decompose under aqueous workup conditions. Thus, recycling is often possible. The reaction of benzaldehyde and aniline with TMSCN in the presence of a catalytic amount of $Pr(OTf)_3$ afforded the corresponding 2-(N-anilino)-2-phenylacetonitrile in 89% yield. 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 $Pr(OTf)_3$ to give the corresponding α-aminonitriles. No undesired side product (such as cyanohydrin trimethyl silyl ether, an adduct between the aldehyde and trimethylsilyl cyanide) was observed because the rapid formation of the imine intermediate. The attempted aminocyanation of ketones did not afford the desired products in satisfactory yield. However, acid-sensitive aldehydes such as furfuraldehyde afforded the desired product in high yield (Scheme 1). The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various aldehydes and amines.

In comparison with other catalysts such as $Sc(OTf)_3$,[8] $InCl_3$,[9] and KSF-clay,[10] which are recently reported in the aminocyanation of benzaldehyde, $Pr(OTf)_3$ employed here shows more catalytic reactivity than $InCl_3$ and KSF-clay in terms of the amount of catalyst and yields of the product (Table 2).

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



Scheme 1.

Table 1. $Pr(OTf)_3$ catalyzed synthesis of α-amino nitriles with trimethylsilyl cyanide

Entry	Aldehyde	Amine	Time (h)	Yield[a] (%)
1	Benzaldehyde	Aniline	10	89/82[b]
2	4-Chlorobenzaldehyde	Aniline	11	81/76[b]
3	Isobutyraldehyde	Benzyl amine	12	77
4	Decylaldehyde	Aniline	10	79
5	3-Methoxybenzaldehyde	Benzyl amine	8	91
6	Furfural	Benzyl amine	8	82
7	Thiophene 2-carboxaldehyde	Benzyl amine	9	86
8	Benzaldehyde	Morpholine	10	78
9	Butyraldehyde	Pyrrolidine	8	81
10	Benzaldehyde	Furfurylamine	10	74
11	Benzaldehyde	3-Methoxybenzyl amine	10	88
12	Benzaldehyde	Butyl amine	10	77
13	2,4-Dimethoxybenzaldehyde	3,4,5-Trimethoxyaniline	9	79
14	4-Methylbenzaldehyde	Aniline	10	81

[a] All products were characterized by comparison of their mp, IR, and ^1H NMR spectra with those of authentic samples (Refs.[9,10]).

[b] Isolated yield with reused catalyst.

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

EXPERIMENTAL

All products are known and were identified by comparing of their spectral data and physical properties with those of authentic samples.[9,10] The progress of

Table 2. Comparison of the effect of catalysts in the synthesis of 2-(N-benzylamino)-2-phenylacetonitrile

Catalyst	Catalyst load (mol%)	Time (h)	Yield (%)
$Sc(OTf)_3$	10	20	88 (Ref.[8])
$InCl_3$	30	5	73 (Ref.[9])
KSF-clay	more than 100	4.5	87 (Ref.[10])
$Pr(OTf)_3$	10	10	89

reaction was monitored by thin-layer chromatography on silica gel. 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 anhydrous commercially available (Aldrich) praseodymium triflate (118 mg, 10 mol%) at room temperature. After completion of reaction (TLC), the reaction mixture was extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with water (20 mL) and satd. brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo.* The residue was chromatographed over silica gel (30% ethyl acetate in hexane) to afford the pure product. The aqueous layer containing the catalyst can be evaporated under reduced pressure (20 mm Hg pressure, 100°C temperature) to give a white solid, which is reused for the next reaction. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich). The catalyst can be recycled and reused three times without any 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, 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 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, 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 calcd. for $C_{14}H_{11}ClN_2$ 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 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, 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 calcd. for $C_{15}H_{14}N_2$ 222.1156, found 222.1158.

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