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L-Proline catalyzed one pot synthesis of α-aminonitriles

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Abstract: L-Proline (20 mol %) was found to be an efficient organocatalyst for one pot synthesis of a variety of α-aminonitriles from aldehydes, amines and trimethylsilyl cyanide (TMSCN) in acetonitrile at ambient temperature giving good to excellent yields (72- 95 %).

Keywords: L-proline, aldehydes, amines, trimethylsilyl cyanide, α-aminonitriles.

Bifunctional α-amino nitriles are versatile intermediates in organic synthesis. They also exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications.[1a] The nucleophilic additions to the nitrile group provide access to α-amino aldehydes, α-amino ketones, α-amino alcohols, 1,2-diamines and many nitrogen containing heterocycles.[1b,2] In particular, stereodefined α-amino acid-derived amino nitriles have shown a high potential for molecular diversity generation.[3,4]These are the key precursors for the synthesis of various biologically useful molecules such as proteins, and have several applications as the chiral building blocks in the pharmaceutical industry.[5-8]

Numerous methods describing the preparation of α-amino nitriles have been reported in the literature. Among the reported methods the most important route for the synthesis of α-aminonitriles is the Strecker reaction.[9,10] Several modifications of the Strecker reaction have been

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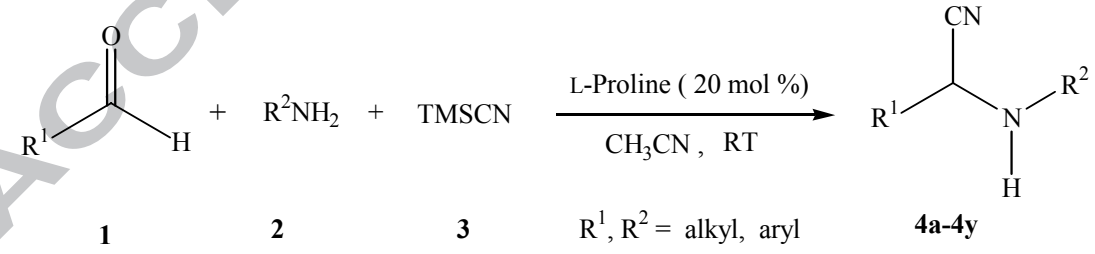
made and a variety of cyanating agents such as α-trimethylsiloxy nitriles and diethyl phosphorocyanidates[11] and trimethylsilyl cyanide[12] were used under various conditions. The classical Strecker experimental procedure is tedious and thus, several modified methods have been reported using a variety of catalysts,[13-35] Ionic liquids like [Hbim$^+$][Cl$^-$],[36] TSIL,[37] xanthansulphuric acid as biosupported solid acid catalyst,[38] β-cyclodextrin[39] and oxalic acid.[40]

Organocatalysis[41] has gained widespread attention as a result of the efficiency and selectivity of many reactions. Novel methods employing organic molecules are advantageous from both a practical and an environmental standpoint. Recently, the commercially available and inexpensive amino acid L-proline has been elegantly used to catalyze many reactions such as the Mannich reaction and the direct asymmetric aldol reaction.[42] The L-proline function has been proposed to act like a 'microaldolase' that facilitates each step of the mechanism including the formation of the intermediate imine and the carbon-carbon bond. L-Proline has been exploited as an efficient organocatalyst in the organic synthetic routes for carbon-carbon, carbon-heteroatom bonds and heterocycles.[43,44]

As a continuation of our recent efforts to develop new organic transformations we would like to report a highly efficient route for the synthesis of α-aminonitriles by one pot three-component coupling of aldehydes, amines catalyzed by commercially available, inexpensive, mild L-proline as organocatalyst and trimethylsilyl cyanide as a cyanide ion source, (Scheme-1) which is a safer and more easily handled reagent compared to alkali cyanides and HCN.[37]



Scheme-1 One pot three-component synthesis of α-aminonitriles

In the present study we extend the scope of the L-proline catalyzed synthesis of α-aminonitriles[45] and the results are presented here. In order to optimize the reaction conditions initially we studied the efficacy of L-proline by taking catalytic amount of 20 mol % and benzaldehyde (1 mmol), aniline (1 mmol) and TMSCN (1.2 mmol), in acetonitrile (5 mL) as model reaction, the reaction gave corresponding 2-(*N*-anilino)-2-phenylacetonitrile with 95% yield in 2 h (Table-1, entry-5). In the absence of L-proline even up to 10 h (Table-1 entry-1) no reaction was observed. Although the amount of catalyst has been optimized to 20 mol % lesser amount (10 mol %) also worked when longer reaction times were employed. (Table-1, entry-3).

Table-1 Screening of catalyst L-proline on model reaction between benzaldehyde (1 mmol), aniline (1 mmol) and TMSCN (1.2 mmol), in acetonitrile (5 mL)

Entry	Catalyst (mol %)	Time (hours)	Yield[b] (%)
1	No catalyst	10	0
2	5	7	40
3	10	6	70
4	15	6	85
5	20	2	95
6	25	2	95

[b] Isolated yields

The model reaction was performed in various solvents using L-proline as the catalyst to identify the best medium for the reaction. A range of solvents such as $CHCl_3$, DCM, THF, DMSO, toluene, H_2O, acetonitrile, were examined and acetonitrile emerged as the solvent of choice in terms of reaction kinetics and product yield. (Table-2, entry-8).

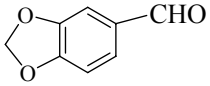
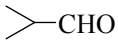
Table-2 Screening of solvents for the synthesis of 2-(*N*-anilino)-2-phenylacetonitrile from benzaldehyde (1 mmol), aniline(1 mmol) and TMSCN (1.2 mmol) in the presence of L-proline (20 mol %)

Entry	Solvent	Time (hours)	Yield(%)
1	$CHCl_3$	2.5	70
2	DCM	2.5	68
3	THF	3	60
4	DMSO	4	30
5	Toluene	4.5	35
6	H_2O	5	NR
7	No Solvent	7	NR
8	CH_3CN	2	95

NR; No Reaction

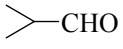
Ketones largely remained inert under these reaction conditions. Longer reaction times and greater amounts of L-proline also failed to make a significant improvement. On the other hand aliphatic and aromatic aldehydes afforded excellent yields. Various kinds of primary and secondary amines are readily coupled to give the desired product in good yields. Furthermore aldehydes such as cinnamaldehyde and furfuraldehyde (Table-3 entry, 14, 15- 4n, 4o) also worked well without any decomposition or polymerization under these reaction conditions. This method is equally effective with aldehydes bearing electron withdrawing substituents in the aromatic ring. No undesired side product such as cyanohydrin trimethylsilylether, an adduct between the aldehyde and trimethylsilyl cyanide was observed because of the rapid formation of iminium intermediate. The scope and generality of the reaction are illustrated with respect to various amines and aldehydes including unsaturated and heterocyclic aldehydes **4a-4y** (Table-3).

Table-3 L-Proline catalyzed synthesis of α-aminonitriles from aldehydes (1) amines (2) TMSCN (3)

Entry	Aldehyde **(1)**	Amine **(2)**	Product **(4a - 4m)**[a]	Time (hours)[c]	Yield **(%)**[b]
1	C_6H_5CHO	$C_6H_5NH_2$	**4a**	2	95
2	3-$CH_3OC_6H_4CHO$	$C_6H_5NH_2$	**4b**	2	90
3	2-$C_2H_5OC_6H_4CHO$	2-$CH_3C_6H_4NH_2$	**4c**	3	83
4		$C_6H_5CH_2CH_2NH_2$	**4d**	4	80
5	3,4,5-$(CH_3O)_3C_6H_2CHO$	4-$FC_6H_4NH_2$	**4e**	4	80
6		4-$FC_6H_4NH_2$	**4f**	5	80
7	4-$CH_3C_6H_4CHO$	$C_6H_5NH_2$	**4g**	3	85
8	4-ClC_6H_4CHO	$C_6H_5NH_2$	**4h**	3	78
9	4-CNC_6H_4CHO	$C_6H_5NH_2$	**4i**	4	75
10	2-ClC_6H_4CHO	$C_6H_5NH_2$	**4j**	3	80
11	3-$CH_3OC_6H_4CHO$	$C_6H_5NH_2$	**4k**	4	80
12	C_6H_5CHO	4-$ClC_6H_4NH_2$	**4l**	4	75
13	C_6H_5CHO	4-$CH_3OC_6H_4NH_2$	**4m**	3	80

[a] all the products are characterized by spectral analysis [b] isolated yields [c] room temperature

Table-3 continued

Entry	Aldehyde(**1**)	Amine**(2)**	Product**(4n-4Y)**[a]	Time(hours)[b]	Yield(%)[c]
14	$C_6H_5CH=CHCHO$	$C_6H_5NH_2$	**4n**	4.5	80
15	C_4H_3OCHO	$C_6H_5NH_2$	**4o**	4.5	75
16	$5\text{-}CH_3C_4H_2OCHO$	$C_6H_5NH_2$	**4p**	4.5	72
17	C_6H_5CHO		**4q**	4	75
18	$3\text{-}CH_3OC_6H_4CHO$	$C_6H_5CH_2NH_2$	**4r**	3.5	85
19	C_4H_9CHO	$C_6H_5CH_2NH_2$	**4s**	4	75
20	C_4H_9CHO	$C_6H_5NH_2$	**4t**	4	78
21	C_6H_5CHO	$C_6H_5CH_2NH_2$	**4u**	3.5	78
22	$4\text{-}CH_3C_6H_4CHO$	$C_6H_5CH_2NH_2$	**4v**	3.5	80
23	$4\text{-}ClC_6H_4CHO$	$C_6H_5CH_2NH_2$	**4w**	3.5	82
24		$C_6H_5CH_2NH_2$	**4x**	4	75
25	C_6H_5CHO	$CH_3(CH_2)_3$	**4y**	4.5	75

[a] all the products are characterized by spectral analysis [b] isolated yields [c] room temperature

In conclusion we have developed a clean and environmentally friendly alternative protocol for the one pot synthesis of α-aminonitriles in good to excellent yields by using commercially available inexpensive L-proline as an organocatalyst. The present protocol has several advantages: mild reaction conditions, operational and experimental simplicity. We believe that this L-proline promoted methodology will be a valuable addition for the synthesis of α-aminonitriles which are important synthetic intermediates for the synthesis of biologically active compounds and industrial materials.

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45. **Representative procedure is as follows:** To a mixture of aldehyde **1** (1 mmol), amine **2** (1 mmol), and trimethylsilyl cyanide **3** (TMSCN) (1.2 mmol) in acetonitrile (5 mL) L-proline (20 mol %) was added and the reaction mixture was stirred for the time specified in Table-3. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ followed by brine solution and then extracted with ethylacetate, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate 2:1) (Merck 100-200 mesh) to afford the corresponding pure α-aminonitriles **4a-4y** (Table-3). All the products are well characterized by spectral analysis (IR, ^{1}H NMR,^{13}C NMR, MS) elemental analysis and were found to be identical with those reported in the literature.[24, 35- 40]

Spectral data for selected compounds: 2-(*N*-Anilino)-2-phenyl acetonitrile (4a): White crystalline solid, m.p. 82-84^{o}C. IR(KBr): 3369, 3025, 2955, 2229, 1604, 1517, 1480, 1317, 1148, 985, 769 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): d= 3.84 (d, 1H,J = 8.0 Hz) 5.22 (d, 1H, J= 8.4 Hz), 6.62 (d, 2H, J= 8.0 Hz), 6.76 (t,1H, J= 8.0 Hz), 7.06-7.15 (m, 2H), 7.27-7.35 (m, 3H), 7.43-7.46 (m, 2H) ppm; ^{13}CNMR(125 MHz, DMSO-d_6) d= 50.1, 114.6, 118.3, 120.8, 127.4, 129.5, 129.3, 133.9, MS (EI): m/z (%) 208 (M^+); Anal. Calcd. for $C_{14}H_{12}N_2$: C,80.77; H, 5.77; N, 13.46 %; Found: C, 80.73; H, 5.70; N, 13.42 %.

2-(*N*-Anilino)-2-(4-cyano phenyl) acetonitrile (4i): Pale yellow solid, m.p.116-119^{o}C. IR(KBr): 3386, 2879, 2236, 1594, 1496, 1449, 1276, 1124, 1006, 789 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): d= 4.17 (bs, 1H), 5.59 (s,1H), 6.82 (d, 2H, J= 7.8 Hz), 6.98 (t, 1H, J= 7.4

Hz), 7.34 (t, 2H, J =7.6 Hz), 7.82 (s, 4H) ppm; ^{13}CNMR (125MHz, DMSO-d_6): d= 49.7, 114.3, 118.2, 120.9, 127.2, 129.6, 133.1, 144.2 ppm;MS(EI): m/z (%) 233 (M^+); Anal.Calcd. for $C_{15}H_{11}N_3$: C,77.25; H, 4.72; N, 18.03 %; Found: C, 77.37; H,4.68; N, 18.05 %.

2-(*N*-Anilino)-2-(2-chloro phenyl) acetonitrile (4j): White solid, m.p. 66-69 ^oC. IR(KBr): 3401, 2903, 2239, 1603, 1507, 1459, 1294, 1146, 1007, 786 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): d= 3.84 (d, 1H, J = 7.5 Hz), 5.56 (d, 1H, J= 8.1 Hz), 6.62 (d, 2H, J= 8.1 Hz), 6.74 (t, 1H,J= 7.7 Hz), 7.07 (t, 2H, J = 8.2 Hz), 7.20–7.24 (m, 2H), 7.28-7.30 (m, 1H), 7.54-7.57 (m, 1H) ppm; ^{13}CNMR (125 MHz, DMSO-d_6): d= 50.3, 55.7, 114.5, 118.3, 119.2, 120.4, 129.7, 130.2, 135.144.9 ppm; MS (EI): m/z (%) 243 (M^+); Anal.Calcd. for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.55; N, 11.57 %; Found: C, 69.22; H, 4.45; N, 11.46 %.

2-(*N*-4-Chloroanilino)-2-phenyl acetonitrile (4l): White solid, m.p. 109-110 ^oC. IR (KBr): 3377, 2898, 2228, 1611, 1509, 1450, 1299, 1122, 1018, 781 cm^{-1}; ^{1}HNMR(500 MHz, DMSO-d_6): d= 3.83 (bs, 1H), 5.22 (d, 1H, J= 6.0 Hz), 6.58 (d, 2H, J= 7.77 Hz), 6.77 (t, 1H, J= 7.2 Hz), 7.05 (t, 2H, J= 8.0 Hz), 7.29 (d, 2H, J= 8.77 Hz), 7.44 (d, 2H, J= 8.4 Hz) ppm; ^{13}CNMR(125 MHz, DMSO-d_6): d= 50.2, 115.5, 117.7, 124.6, 127.2, 129.3, 129.5, 130.2, 133.6, 143.4 ppm; MS (EI): m/z(%) 243 (M^+); Anal.Calcd. for $C_{14}H_{11}N_2Cl$: C, 69.25; H, 4.54; N, 11.53 %; Found: C, 69.29; H, 4.52; N, 11.55%.

2-(*N*-4-Methoxyanilino)-2-phenyl acetonitrile (4m): White solid, m.p. 94-97 ^oC. IR (KBr): 3369, 3035, 2928, 2249, 1597, 1505, 1445, 1306, 1105, 993, 779 cm^{-1}; ^{1}HNMR(500 MHz, DMSO-d_6): d= 3.61(s, 3H), 3.73 (bs, 1H), 5.13 (d, 1H, J= 6.4 Hz), 6.52 (d, 2H, J= 8.0 Hz), 6.60 - 6.73 (m, 3H), 7.07 (d, 2H, J= 8.0 Hz), 7.45 (d, 2H, J = 8.1 Hz) ppm; ^{13}CNMR(125 MHz, DMSO-d_6): d= 48.5, 114.7, 117.9, 120.4, 121.6, 127.3, 128.7, 129.9, 132.6, 135.7, 144.4 ppm; MS (EI): m/z (%) 238 (M^+); Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.77 %; Found: C, 75.64; H, 5.92; N, 11.78 %.

2-(*N*-Anilino)-2-cinnamyl acetonitrile (4n): Pale yellow solid, m.p. 110-112 ^oC. IR (KBr): 3349, 2934, 2222, 1609, 1505, 1463, 1278, 1035, 978, 894, 778 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): d= 3.94 (d, 1H,J= 9.7 Hz), 5.06 -5.10 (m, 1H), 6.34 (dd, 1H, J= 4.7, 15.9 Hz), 6.83(d, 1H, J= 8.2 Hz), 6.96 (t, 1H, J= 8.5 Hz), 7.09 (d, 1H, J= 16.4 Hz), 7.35-7.47 (m, 8H) ppm; ^{13}CNMR (125 MHz, DMSO-d6): d= 47.5, 114.7, 117.4, 120.7, 121.4, 126.6, 128.9, 128.7, 129.9, 134.7, 135.2, 144.8 ppm; MS(EI): m/z (%) 234 (M^+) ; Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.96%; Found: C, 82.11; H, 5.97; N, 12.01%.

2-(*N*-Anilino)-2-furfuryl acetonitrile (4o): Dark brown solid, m.p. 68-70 ^{o}C. IR (KBr): 3359, 2985, 2247, 1648, 1565, 1503, 1445, 1296, 1254, 1148, 1015, 889, 754 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): d= 4.21 (bs, 1H), 5.59 (d, 1H, J= 6.9 Hz), 6.49 (t, 1H, J= 2.7 Hz), 6.68 (d, 1H, J= 3.6 Hz), 6.89 (d, 2H, J= 7.9 Hz), 6.99 (t, 1H, J= 7.6 Hz), 7.37 (t, 2H, J= 7.8 Hz), 7.56 (d, 1H, J= 1.0 Hz) ppm; ^{13}CNMR (125 MHz, DMSO-d_6): d= 48.3, 111.4, 111.6, 116. 5, 122.7, 129.8, 134.5, 137.4, 146.7 ppm; MS (EI): m/z (%) 198(M^+); Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.73; H, 5.05; N, 14.14 %; Found: C, 72.74; H,5.04; N,14.13 %.

2-(*N*-Benzylamino)-2-phenyl acetonitrile (4u): Colorless oil; IR (neat): 3408, 2925, 2235, 1649, 1518, 1409 cm^{-1}; ^{1}H NMR (300. MHz, $CDCl_3$): d= 1.80 (brs, 1H), 3.96 (q, J= 13.5 Hz, 2H), 4.71 (s, 1H), 6.77 (d, J= 8.0 Hz, 1H), 7.14 (t, J= 7.8 Hz, 1H), 7.25-7.44 (m, 6H), 7.48-7.53 (m, 2H) ppm; ^{13}CNMR(125 MHz, DMSO-d_6): d= 51.6, 53.7, 119.2, 128.6, 128.9, 129.3, 129.4, 130.6, 135.3, 138.5, 143.9 ppm; MS (EI): m/z (%) 222 (M^+), Anal.Calcd for $C_{15}H_{14}N_2$: C,81.05; H, 6.35; N,12.60 %; found: C, 80.05, H, 6.25, N, 12.36 %.

2-(*N*-Benzylamino)-2-isopropyl acetonitrile (4x): Colorless oil; IR (neat): 3365, 3020, 2945, 2862, 2234, 1506, 1465,1315cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): d= 1.05 (d,J= 6.6 Hz, 3H), 1.08 (d, J= 6.6 Hz, 3H), 1.55 (brs, 1H), 1.95-2.00 (m, 1H), 3.26 (d, J= 6.0 Hz, 1H), 3.84 (d, J= 13.0 Hz, 1H), 4.08 (d, J= 13.0 Hz, 1H), 7.21-7.46 (m, 5H) ppm; ^{13}CNMR (125MHz, DMSO-d_6): d = 17.9, 18.1, 29.3, 51.9, 53.3, 118.3, 127.5, 128.4, 128.7, 137.4 ppm; MS (EI): m/z (%) = 188 (M^+) Anal.Calcd for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88 % Found C, 76.46; H, 8.58; N, 14.76 %.

Graphical Abstract

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L -Proline catalyzed one pot synthesis of α-aminonitriles

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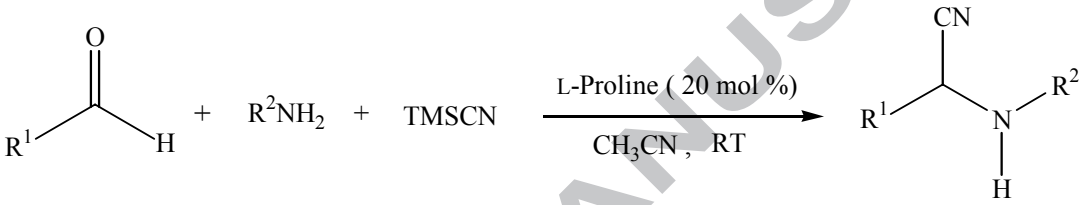
Aayesha Nasreen



1 **2** **3** R^1, R^2 = alkyl, aryl **4a-4y**

L - Proline (20 mol %) was found to be an efficient organocatalyst for one pot synthesis of a variety of α-aminonitriles from aldehydes (1), amines (2) and trimethylsilyl cyanide (TMSCN, 3) in acetonitrile at ambient temperature giving good to excellent yields (72-95 %).