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Eco-friendly Synthesis of α -Aminonitriles Catalysed by Epzg

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ABSTRACT

A simple, proficient and ecofriendly procedure has been developed for the three component coupling of aromatic aldehyde, substituted amines and trimethylsilyl cyanide produce α-amino nitriles. The α-amino nitriles are synthesized in high yields (90-91%) in a few minutes (18-45 min) under solvent-free conditions using EPZG catalyst at room temperature.

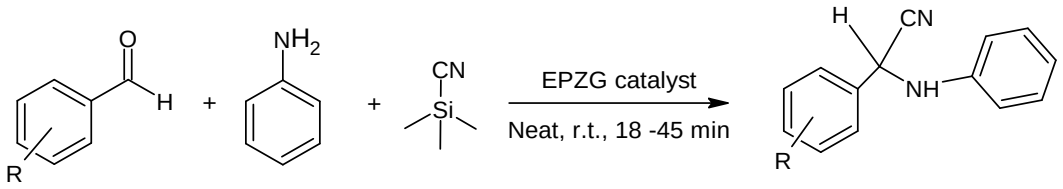
Keywords: α-amino nitriles; EPZG; Ecofriendly; Room temperature

INTRODUCTION

Nitriles are the building blocks of most biologically active substances and natural products. However, amides and carboxylic acids [1-2] have synthesized from nitriles, due to this α-aminonitriles have occupied great position in synthetic organic chemistry, this growing demand of nitriles, satisfied by Strecker reaction [3]. Strecker in 1850 reported the synthesis of α-aminonitriles by multicomponent condensation of aldehyde, amine and hydrogen cyanide [3] hydrocyanation of emines is thus basic C-C bond formation reaction [4] involves conversion of nitriles to carbonyl group [5-6]. Modified Strecker reaction i.e. synthesis of optically active α-amino acid by the hydration of cyanide [7], α-aminonitriles is acts a precursor fragment for the synthesis of α-amino acid [8], imidazole and several biologically active compounds [9] containing nitrogen atom. Bifunctionality of α-aminonitriles acts as a building blocks of pharmaceutical industries [11], such as serine protease inhibitors [12], (-, +)phtalascidine 650 [13] and also in the synthesis of boron containing retinoids [14]. Synthesis of heterocyclic moiety such as 1,2,3-diazaphospholidines, imidazole, oxazoles, and isothiozoles [15] derived from 2-amino-2-alkyl(aryl) propanenitriles as a starting material. Synthesis of 5-amino-4H-imidazoles was achieved by reacting α-aminonitriles with imidoester which is a key material of many biological compounds. Different ptotocols have been eported for the synthesis of α–aminonitriles such as Formic acid [16], ammonium chloride [17], PPh_3/DEAD[18], Bicyclic Guanidine [19], polyethylene glycol (PEG-OSO_3H) [20], MgI_2 [21], sulphated polyborate [22], PEG -400 [23], Zn(CN) [24], cinchona-based thiourea alkaloid [25], 5mol % to 20mol % L –prolineamide derived N,N'-dioxide [26], $Ga(OTF)_3$[27], Nafion –H and NafionSAC-13 [28], SBA-15 supported sulphonic acid [29], indium (III) iodide [30], mesoporous MCM-41 catalyst [31], ionic liquid [bmim]BF_4 or $MgBr_2.OEt_2$ [32], Bismuth Nitrate [33], Fe_3O_4@SiO_2@Me&Et-$PhSO_3H$ [34], Task- Specific ionic liquid [35], chiral ammonium trifluoroacetate, potassium hexacyanoferrate (II) [36], Silica based Scandium (III) [37], Pd(II) [38], magnetically separable nanoparticles [39,40]. We have reported here environmentally green EPZG as catalyst for the synthesis of α–aminonitriles. EPZG is a $FeCl_3$ supported on clay.

Present work

It was clear from the literature review that α–aminonitriles has greater utility in medicinal chemistry as well as in agricultural fields. we have report herein Lewis acid $EPZG^R$ [41-51] catalyzed solvent free synthesis of α–aminonitriles at room temperature (Scheme 1) (Table 1-4).



Scheme 1: Multicomponent synthesis of α –aminonitriles

Table 1: Screen of catalyst for the synthesis of α –aminonitrile

Sr. No	catalyst	Amount mg	Time in minute	Yield %
1	EPZG^R	10	40	60
2	EPZG^R	15	34	88
3	EPZG^R	**20**	**30**	**91**
4	EPZG^R	25	30	91
5	EPZG^R	30	30	91
Reaction condition: Benzaldehyde (1mmol); aniline (1mmol); trimethylsilyl cyanide (1mmol); EPZG^R catalyst 20mg; at room temperature.				

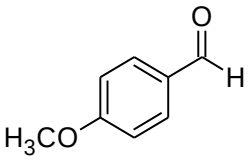
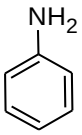
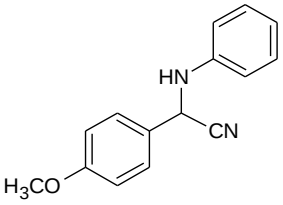
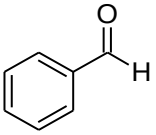
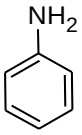
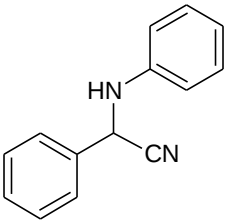
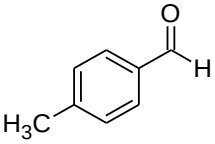
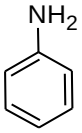
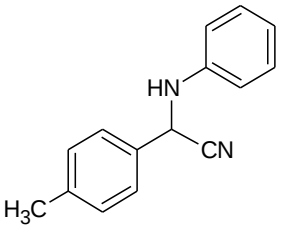
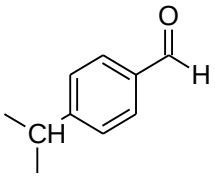
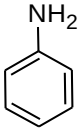
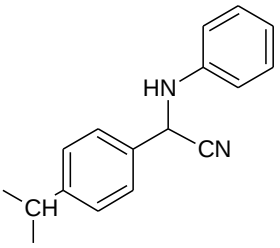
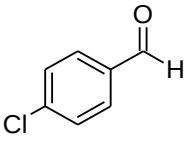
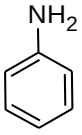
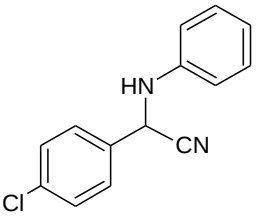
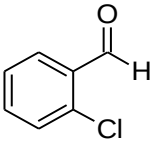
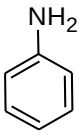
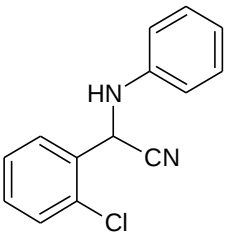
Table 2: Screening of solvents for the synthesis of α –aminonitrile

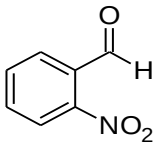
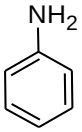
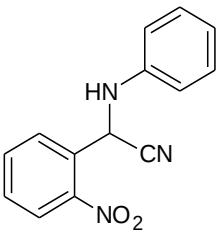
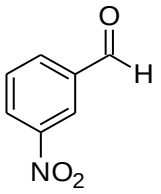
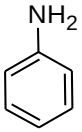
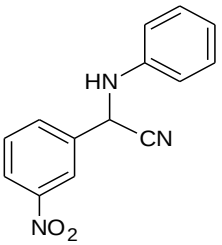
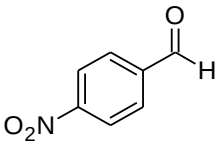
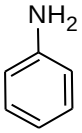
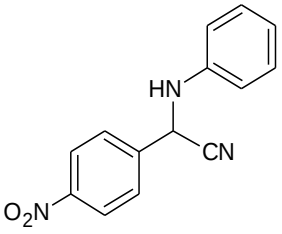
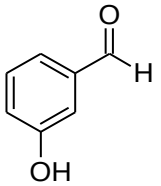
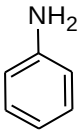
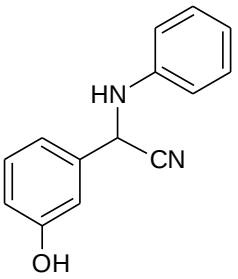
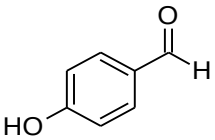
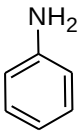
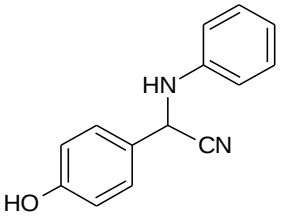
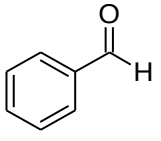
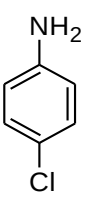
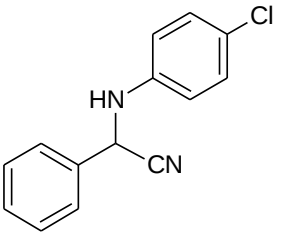
Entry	Solvent	Time (Min.)	Yield%
1	Water	60	69
2	Alcohol	52	58
3	Solvent free	30	91
4	Chloroform	64	69
5	Dichloromethane	70	54
6	Dimethylsulphoxide	90	53
Reaction condition: -Benzaldehyde (1mmol); aniline (1mmol); trimethylsilyl cyanide(1mmol); EPZG^R catalyst 20mg; at room temperature.			

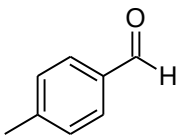
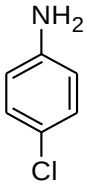
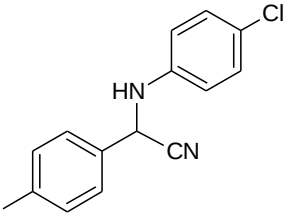
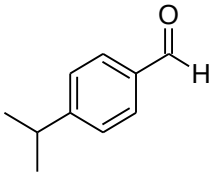
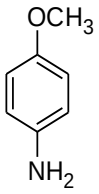
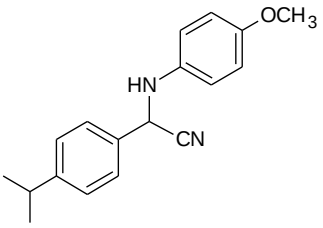
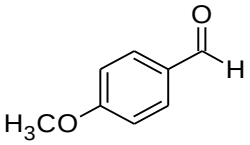
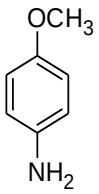
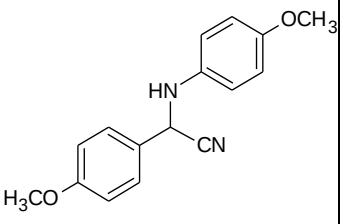
Table 3: Reusability of catalyst for the synthesis of α –aminonitrile

Sr. No.	Catalyst	Amount mg	Time in minute	Yield%
1	EPZG^R	20	30	91
2	EPZG^R	20	30	91
3	EPZG^R	20	31	90
4	EPZG^R	20	32	89
5	EPZG^R	20	32	88
Reaction condition: Benzaldehyde (1mmol); aniline (1mmol); trimethylsilyl cyanide (1mmol); EPZG^R catalyst 20mg; at room temperature.				

Table 4: Multicomponent synthesis of α-aminonitriles

Entry	Aldehyde	Amine	Product	Time min.	Yield %
a				30	94
b				**30**	**91**
c				18	93
d				29	91
e				21	93
f				45	87

g				22	89
h				27	90
i				20	92
j				42	83
k				25	87
l				27	90

m				32	91
n				31	89
o				30	88
Reaction condition: Benzaldehyde (1mmol); aniline (1mmol); trimethylsilyl cyanide (1mmol); EPZG^R catalyst 20mg; at room temperature.					

EXPERIMENTAL SECTION

General

Various substituted aldehyde (Sigma-Aldrich), aniline (Himedia), Trimethylsilyl cyanide (Himedia) were used as received without purification. Melting point measures by melting point apparatus made by Equiptronics model No – EQ- 730A. IR spectra were recorded on FT-IR -7600 Lambda Scientific Spectrometer. NMR Spectra were recorded on a Bruker AC400 MHz spectrometer in $CDCl_3$ using tetramethyl silane as an internal standard material.

General Experimental Procedure

In a 25ml round bottom flask mixture of aldehyde (1mmol), aniline (1mmol) and Trimethylsilyl cyanide (1mmol) was stirred with EPZG^R catalyst 20 mg at room temperature for desired time mentioned in **Table 2; Entry b** completion of reaction was monitored by TLC. Upon completion of reaction crystallization of the product was carried out in ethanol. All the products were purified by same technique and found to be correct. Further structures of the product were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS and IR.

CONCLUSION

We have developed simple process of synthesis of α-aminonitriles by reacting aldehyde, amine and Trimethylsilyl cyanide. New process which was easily applicable, easy separation of product and catalyst, short reaction time at room temperature. Recyclability of the catalyst was found to be efficient for successive five times without loss of its activity.

Spectral data of synthesized α-aminonitriles.

Table 4, Entry a : 2-(4-methoxyphenyl)-2-(phenylamino)acetonitrile, **Color:** White; **M. P.:** 94-96ºC; **IR (KBr):** 3386, 3029, 2249, 1892, 1594, 1498, 1428, 1262, 1192, 1105, 834, 746, 675cm^{-1};**^{1}H NMR (400MHz, $CDCl_3$):**δ (ppm):3.86(s, 3H, -OCH_3), 4.00-4.02(d, 1H, -NH,*J* = 8Hz), 5.38-5.40(d, 1H, -CH, *J* = 8Hz), 6.78-7.54(m, Ar-H);**^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm):49.68, 55.45,114.10, 114.65, 118.44, 120.20,125.95, 128.65, 129.58,114.75, 160.45; **HRMS:**238.16**;Calculated mass:** 238.28.

Table 4, Entry b : 2-(phenyl)-2-(phenylamino)acetonitrile, **Color:** White; **M. P.:** 80-82ºC; **IR (KBr):**3317, 3036, 2242, 1918, 1994, 1489, 1393, 1271, 1096, 999, 746cm^{-1};**^{1}H NMR(400MHz, $CDCl_3$):**δ (ppm): 4.04-4.06 (d, 1H, -NH, *J* = 8Hz),5.44-5.46 (d, 1H, -CH, *J* = 8Hz),6.78-7.63 (m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$):**δ (ppm): 50.19,114.12,118.21, 120.29, 127.29, 129.37, 129.58, 129.60, 133.89, 144.65;

Table 3, Entry d : 2-(4-isopropylphenyl)-2-(phenylamino)acetonitrile, **Color:**White, **M. P**.:78-80 ºC.**IR (KBr):** 3395, 2949, 2897, 2242, 1918, 1603, 1515, 1441, 1296, 1105, 912, 825, 746, 684cm^{-1};**^{1}H NMR(400MHz, $CDCl_3$):**δ (ppm): 1.27-1.29 (d, 6H, -CH_3, *J* = 8Hz), 2.93-3.00 (m, 1H, -CH, *J* = 8Hz),4.00-4.02 (d, 1H, -NH, *J* = 8Hz), 5.39-5.41 (d, 1H, -CH, *J* = 8Hz),6.78-7.54 (m, Ar-H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ (ppm):

23.91, 33.92, 49.94, 114.01, 118.37, 120.16, 127.34,127.43,129.58,131.25,144.75,150.57;

Table 4, Entry f : 2-(2-chlorophenyl)-2-(phenylamino)acetonitrile, **Color:** White; **M. P.:** 62-64ºC;**IR (KBr):**3335, 3020, 2249, 1927, 1594, 1498, 1296, 1236, 1061, 947, 755, 675cm^{-1}; **^{1}H NMR(400MHz, CDCl$_3$):** δ (ppm): 4.03-4.0 (d, 1H, -NH, *J* = 8Hz), 5.73-5.75 (d, 1H, -CH, *J* = 8Hz), 6.79-7.77 (m, Ar-H);**^{13}C NMR (100 MHz, CDCl$_3$):**δ (ppm):48.03, 114.24,117.76,120.48,127.82,129.07, 29.60,130.49,131.07,131.7, 133.55,142.52;

Table 4, Entry h : 2-(3-nitrophenyl)-2-(phenylamino)acetonitrile, **Color:** Yellow; **M. P.:** 86-88ºC; **IR (KBr):**3323, 3107, 3062, 2243, 1920, 1613, 1541, 1543, 1226, 1082, 893, 758, 975cm^{-1}; **^{1}H NMR (400MHz, CDCl$_3$):**δ (ppm): 4.20-4.22 (d, 1H, -NH, *J* = 8Hz), 5.58-5.60 (d, 1H, -CH, *J* = 8Hz), 6.78-8.51 (m, Ar-H);**^{13}C NMR (100 MHz, CDCl$_3$):** δ(ppm): 49.62, 114.58, 117.19,121.09,122.38, 124.53, 129.72,130.50,133.05, 136.09, 143.89, 148.75;

Table 4,Entry j : 2-(3-hydroxyphenyl)-2-(phenylamino)acetonitrile, **Color :** White; M.P.:86-88ºC **IR (KBr):** 3402, 3072, 2249, 2010, 1615, 1504, 1348, 1275, 1063, 854, 794, 676cm^{-1}; **^{1}H NMR (400MHz, CDCl$_3$):** δ (ppm): 3.98-4.00 (d, 1H, -NH, *J* = 8Hz), 5.43-5.45 (d, 1H, -CH, *J* = 8Hz), 6.66-7.74 (m, Ar-H), 9.38 (bs, HO-Ar); **^{13}C NMR (100 MHz, CDCl$_3$):** δ(ppm): 49.20,113.96,114.31, 116.30, 117.95, 118.88, 129.08, 129.22, 130.10, 131.08, 132.04, 132.06, 132.09, 133.11, 133.17, 145.77, 158.03; 130.23, 133.34, 133.50, 133.86, 133.94, 133.99, 135.52, 136.99, 150.55, 152.38, 162.95, 165.38, 168.45;

Table 4, Entry l : 2-(phenyl)-2-(4-chlorophenylamino)acetonitrile, **Color:** White; **M. P.:**80-82 ºC;**IR (KBr):** 3317, 3045, 2242, 1603, 1489, 1262, 1069, 834, 693 cm^{-1}; **^{1}H NMR(400MHz, CDCl$_3$):** δ (ppm): 4.09-4.11(d, 1H, -NH, *J* = Hz), 5.38-5.40(d, 1H, -CH, *J* = 8Hz), 6.69-7.60 (m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ(ppm):50.28, 115.38, 117.89, 122.22, 125.14, 127.23, 128.85,128.89,129.25,129.43, 129.48, 129.71,133.48,143.20,160.80;

Table 4, Entry n : 2-(4-isopropylphenyl)-2-(4-methoxyphenylamino)acetonitrile, **Color:** White;**M. P**.:78-80 ºC;**IR (KBr):** 3395, 2958, 2224, 1603, 1498, 1236, 1025, 834, 755, 650cm^{-1};**^{1}H NMR(400MHz, CDCl$_3$):**δ (ppm): 1.27-1.29 (d, 6H, 2CH3 ofisopropyl gr.*J* = 8Hz), 2.93-3.00(m, 1H, -CH of isopropyl gr. *J* = 8Hz), 3.78 (s, OCH_3),5.31-5.33(d, 1H, -CH, *J*8Hz),6.76-7.54(m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 24.02, 34.15,51.28,55.66,114.99,116.14,118.64,127.30,127.34, δ = 131.51,138.43, 154.02;

Table 3, Entry o : 2-(4-methoxyphenyl)-2-(4-methoxyphenylamino)acetonitrile, **Color:** White; **M. P.:**134-134 ºC**; IR (KBr):** 3530, 2942, 2248, 1630, 1460, 1251, 989, 874, 649cm^{-1}; **^{1}H NMR(400MHz, CDCl$_3$):**δ (ppm): 3.49 (s, -OCH_3),4.04 (s, -OCH_3),5.30-5.32 (d, 1H, -CH, *J* = 8Hz),6.29-8.14 (m, Ar-H);**^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 54.17,55.12, 115.22, 117.33, 119.43, 126.19, 127.56,130.49,139.12,156.62;

Table 4, Entry p : 2-(phenyl)-2-(4-nitrophenylamino)acetonitrile, **Color:** White; **M. P.:**94-96 ºC **;IR (KBr):** 3381,2949, 2246, 1612, 1479, 1269, 1015,843, 664cm^{-1}; **^{1}H NMR(400MHz, CDCl$_3$) :**δ (ppm): 4.96-4.98 (d, 1H, -CH, *J* = 8Hz),5.56-5.58(d, 1H, -CH, *J* = 8Hz),6.60-8.43 (m, Ar-H);**^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 49.14, 114.52, 118.11, 123.02, 124.11, 128.05,128.95,130.14,131.44,132.64, 145.59, 161.12;

Table 4, Entry q : 2-(2-chlorophenyl)-2-(4-nitrophenylamino)acetonitrile, **Color:** White; **M. P.:**104-106 ºC ; **IR (KBr):** 3340, 3012, 2246, 1970, 1592, 1498, 1293, 1242, 1063, 945, 789, 674 cm^{-1}; **^{1}H NMR(400MHz, CDCl$_3$):** δ (ppm): 4.40-4.42 (d, 1H, -CH, *J* = 8Hz),5.80-5.82 (d, 1H, -CH, *J* = 8Hz),6.60-8.30 (m, Ar-H); **^{13}C NMR (100 MHz, CDCl$_3$):** δ (ppm): 48.72, 115.88, 117.72, 124.19, 129.55, 129.91, 129.98,130.12,130.33,131.27, 132.46, 158.17;

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