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Note

$ZrCl_4$ promoted efficient one-pot synthesis of α-amino nitriles

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A convenient and efficient one-pot method for the synthesis of a variety of α-amino nitriles from aldehydes, amines and trimethylsilyl cyanide in the presence of a catalytic amount of $ZrCl_4$ at room temperature is described. A simple work-up procedure, inexpensive and non-toxic catalyst, shorter reaction times along with excellent product yields are the significant features of this practical method.

Keywords: $ZrCl_4$, one-pot method, α-amino nitriles

α-Amino nitriles are important intermediates for the synthesis of α-amino acids[1], various nitrogen-containing heterocycles such as imidazoles and thiadiazoles[2], 4-amino-2,3-dihydroisothiazole-1,1-dioxides[3] and azaspironucleoside analogous of TSAO (ref. 4). The classical Strecker reaction for the synthesis of α-amino nitriles involves the treatment of carbonyl compounds with alkaline cyanides and salts of amines in aqueous medium[5]. The experimental procedure is tedious and thus, several modified methods have been reported using a variety of cyanide reagents such as α-trimethylsilyloxy nitrile, diethyl phosphorocyanidate and tri-*n*-butyltin cyanide[6], as well as catalysts such as $Sc(OTf)_3$ (ref. 7), $InCl_3$ (ref. 8), Pt-complex[9], Cd-salt[10], $BiCl_3$ (ref. 11), montmorillonite KSF clay[12], $Pr(OTf)_3$ (ref. 13), $NiCl_2$ (ref. 14), $RuCl_3$ (ref. 15), $CoCl_2$ (ref. 16), I_2 (ref. 17), (bromodimethyl)sulfonium bromide[18], $RhCl_3$ (ref. 19) and cyanuric acid[20] under various reaction conditions. However, many of these methods involve the use of expensive reagents such as metal triflates, extended reaction times, harsh reaction conditions and also require tedious work-up procedure leading to the generation of a large amount of toxic waste with unsatisfactory yields of products. Furthermore, many of these catalysts are deactivated or decomposed by amines and water produced during imine formation. Thus, there is a need to develop a facile one-pot synthesis of α-amino nitriles using an inexpensive reagent.

Recently $ZrCl_4$ has been introduced as promising, mild and selective reagent in organic synthesis[21]. The catalyst $ZrCl_4$ is commercially available, less expensive, non-toxic (LD_{50}, oral rat = 1688 mg Kg^{-1}, ref. 22), additionally Zr^{4+} with a high charge-to-size ratio (22.22 e^2 m^{-10}, ref. 23) enables reactions with high to excellent yields due to strong coordination ability of Zr^{4+}. The ease of handling and high catalytic activity make $ZrCl_4$ a potent green catalyst in the synthetic organic chemistry[21]. Therefore, the application of $ZrCl_4$ in organic synthesis is of renewed interest. Moreover, to the best of our knowledge no report has been made so far about the use of $ZrCl_4$ as catalyst in the synthesis of α-amino nitriles. Based on our past experience with $ZrCl_4$ as an efficient catalyst[24], we, therefore, were interested in exploiting the catalytic activity of $ZrCl_4$ in the synthesis of α-amino nitriles.

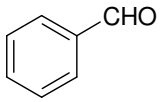
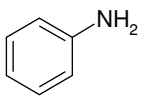
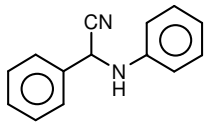
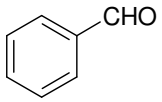
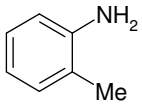
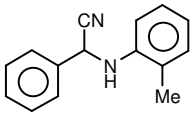
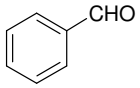
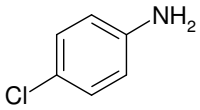
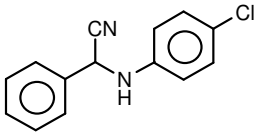
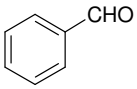
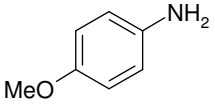
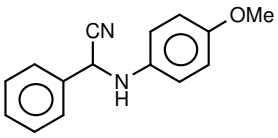
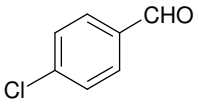
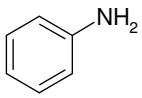
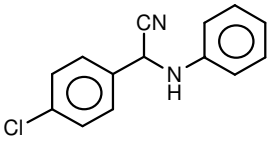
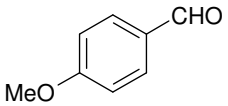
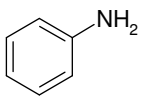
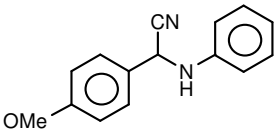
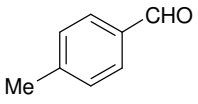
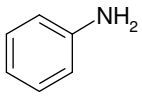
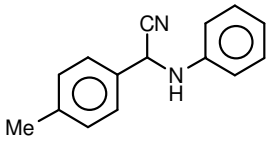
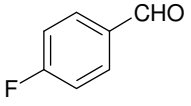
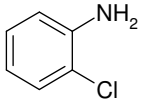
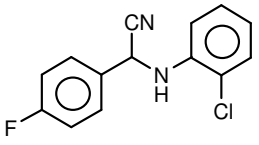
Results and Discussion

Herein is described a convenient and efficient protocol for the three-component coupling reactions of aldehydes, amines and trimethylsilyl cyanide (TMSCN) to prepare α-amino nitriles using $ZrCl_4$ catalyst in ethanol at RT (**Scheme I**).

The treatment of benzaldehyde and aniline with TMSCN in the presence of a catalytic amount of $ZrCl_4$ in ethanol afforded 2-(N-anilino)-2-phenylacetonitrile **4a** in 91% yield. The catalyst was recovered and reused. The yields obtained were 87 and 82% in the second and third run respectively. Encouraged by these results, a variety of aldehydes were coupled with a range of anilines and TMSCN in one-pot operation in the presence of a catalytic amount of $ZrCl_4$ at RT, which resulted in the formation of the corresponding α-amino nitriles in good to excellent yields (**Table I**). A range of solvents such as methanol, dichloromethane, dichloroethane, tetrahydrofuran, ethanol and acetonitrile were examined and ethanol emerged as the solvent of choice in terms of reaction kinetics and

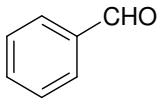
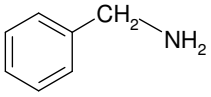
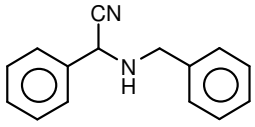
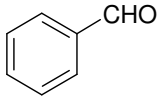
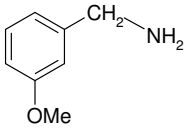
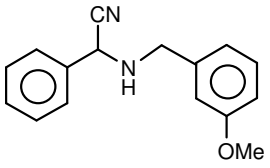
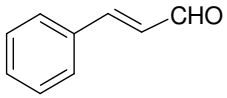
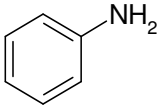
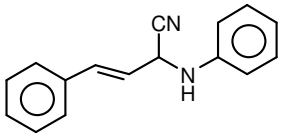
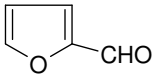
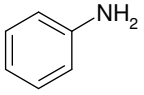
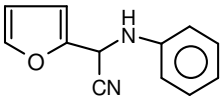
Scheme I

Table I — $ZrCl_4$ promoted one-pot synthesis of α-amino nitriles.

Entry	Aldehyde **(1)**	Amine **(2)**	Time (min)	Product **(4)**	Yield (%)[a]
1			60	 **4a**	91
2			60	 **4b**	93
3			60	 **4c**	86
4			90	 **4d**	84
5			90	 **4e**	82
6			75	 **4f**	89
7			60	 **4g**	88
8			90	 **4h**	85

—-Contd

Table 1 — $ZrCl_4$ promoted one-pot synthesis of α-amino nitriles.—*Contd*

Entry	Aldehyde (1)	Amine (2)	Time (min)	Product (4)	Yield (%)[a]
9			75	 **4i**	87
10			75	 **4j**	90
11			75	 **4k**	86
12			60	 **4l**	89

[a] The yields refer to isolated products

product yields. TMSCN has been used as a safer and more effective cyanide anion source compared to other cyanide reagents used in the Strecker process[25,26].

These three-component coupling reactions proceed efficiently at ambient temperature with high selectivity. No undesired side product such as cyanohydrin trimethylsilyl ether, an adduct between the aldehyde and TMSCN, could be detected because of the rapid formation of the imine intermediate. The reactions are clean and highly selective affording exclusively α-amino nitriles in high yields. This method is equally effective with aldehydes bearing electron-donating and electron-withdrawing substituents in the aromatic ring. Furthermore, acid-sensitive aldehydes such as furfuraldehyde and cinnamaldehyde worked well without any decomposition or polymerization under these reaction conditions. This method does not require any other additives to promote the reaction or any stringent reaction conditions to proceed. The reaction conditions are mild enough to perform these reactions in the presence of either acid or base sensitive substrates.

The scope and generality of this process is illustrated with respect to various amines and aldehydes including aromatic α,β-unsaturated and heterocyclic aldehydes (**Table I**). The progress of the reaction was monitored by TLC on silica gel. All yields refer to isolated products. The products are known molecules and were identified by comparing their spectral data and physical properties with those of authentic samples.

In comparison with other catalysts such as $Sc(OTf)_3$, $InCl_3$, $BiCl_3$, (bromodimethyl) sulfonium bromide, KSF-clay, $Pr(OTf)_3$, $RuCl_3$ and $RhCl_3$ employed for the aminocynation of benzaldehyde, $ZrCl_4$ shows more catalytic reactivity than the others in terms of the amount of catalyst required, reaction time and yield of the product (**Table II**).

Table II — Comparision of the effect of catalysts in the synthesis of 2-(N-anilino)-2-phenylaceto nitrile[a]

Entry	Catalyst	Amount of catalyst (mole %)	Reaction time (min)	Yield (%)[b]
1	$Sc(OTf)_3$ (ref. 7)	10	1200	88
2	$InCl_3$ (ref. 8)	30	300	74
3	$BiCl_3$ (ref. 11)	10	600	84
4	KSF-clay (ref. 12)	more than 100	210	90
5	$Pr(OTf)_3$ (ref. 13)	10	600	89
6	$RuCl_3$ (ref. 15)	20	1200	74
7	(Bromodimethyl)sulfonium bromide[18]	10	60	89
8	$RhCl_3$ (ref. 19)	35	60	86
9	$ZrCl_4$ (present study)	10	60	91

[a] All the reactions were carried out at RT; [b] Isolated yields after purification

Experimental Section

All the reagents were commercially obtained and purified prior to use. Melting points were determined in an open capillary tube on a Cintex melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a VG micromass 7070H (70 eV) instrument. IR spectra were recorded on a Perkin-Elmer spectrum BX series FT-IR 5000 spectrometer using KBr pellet. Column chromatography was carried out with silica gel 100-200 mesh and TLC with silica gel GF_{254}.

General procedure for the preparation of α-amino nitriles 4a-l

To a mixture of an aldehyde **1**(1 mmole), an amine **2** (1 mmole) and trimethylsilyl cyanide **3** (1.2 mmole) in ethanol (10 mL), $ZrCl_4$ (10 mole%) was added and the reaction mixture was stirred at RT. After completion of the reaction (monitored by TLC), the solvent was removed *in vacuo*, quenched with water (10 mL) and the crude product extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water (20 mL) and brine solution (20 mL) respectively, then dried using anhyd. $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography over silica gel (ethyl acetate:hexane, 1:9) as eluent to afford pure α-amino nitrile. The filtrate was concentrated, diluted with ethylacetate, washed with water and the aqueous layer containing the catalyst was evaporated under reduced pressure to give a white solid (catalyst), which was reused.

Product characterization data

4a: White crystalline solid, m.p. 73-74°C (Lit.73-74°C, ref. 13); IR (KBr): 3370, 3020, 2955, 2236, 1600, 1505, 1465, 1310, 1140, 995, 751 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 4.0 (d, 1H, *J* = 8.1 Hz), 5.40 (d, 1H, *J* = 8.1 Hz), 6.74 (d, 2H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.8 Hz), 7.25 (t, 2H, *J* = 7.8 Hz), 7.40-7.50 (m, 3H), 7.60-7.70 (m, 2H); MS: *m/z* 208 (M^+), 180, 116, 91, 77, 55.

4b: Pale yellow solid, m.p. 73-74°C (Lit. 72-73°C, ref. 12); IR (KBr): 3365, 2935, 2855, 2238, 1605, 1515, 1460, 1275, 1035, 790 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 2.20 (s, 3H), 3.38, (brd, 1H, NH, *J* = 8.1 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 6.80 (t, 2H, *J* = 7.9 Hz), 7.10 (d, 1H, *J* = 8.0 Hz), 7.20 (d, 1H, *J* = 7.9 Hz), 7.40-7.50 (m, 3H), 7.50 (d, 2H, *J* = 8.0 Hz); MS: *m/z* 222 (M^+), 194, 155, 141, 116, 106, 91, 73, 65, 45.

4c: Pale yellow solid, m.p. 107-10°C (Lit.108-10°C, ref. 18); IR (KBr): 3410, 2930, 2230, 1610, 1520, 1460, 1270, 1050, 790 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 4.05 (d, 1H, *J* = 8.0 Hz), 5.30 (d, 1H, *J* = 8.0 Hz), 6.62 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 7.34-7.45 (m, 3H) 7.49-7.60 (m, 2H); MS: *m/z* 242 (M^+), 215, 178, 126.

4d: Pale yellow solid, m.p. 95-96°C (Lit.94-96°C, ref. 18); IR (KBr): 3390, 2935, 2850, 2240, 1615, 1520, 1465, 1285, 1045, 790 cm^{-1}; ^{1}H NMR($CDCl_3$): δ 3.70 (s, 3H), 3.85 (d, 1H, *J* = 8.0 Hz), 5.30 (d, 1H, *J* = 8.0 Hz), 6.67 (d, 2H, *J* = 8.0 Hz), 6.79 (d, 2H, *J* = 8.0 Hz), 7.35-7.46 (m, 3H), 7.53-7.61 (m, 2H); MS: *m/z* 238 (M^+), 211, 210, 146.

4e: White solid, m.p. 110-12°C (Lit.109-12°C, ref. 12); IR (KBr): 3405, 2925, 2240, 1600, 1515, 1455, 1270, 1160, 1100, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.0 (d,1H, *J* = 8.1 Hz), 5.40 (d, 1H, *J* = 8.1 Hz), 6.74 (d, 2H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.9 Hz), 7.16 (t, 2H, *J* = 7.9 Hz), 7.40 (d, 2H, *J* = 8.0 Hz), 7.60 (d, 2H, *J* = 8.0 Hz); MS: *m/z* 242 (M^+), 213, 149, 114, 91, 73, 59.

4f: White solid, m.p. 93-95°C (Lit.94-95°C, ref. 12); IR (KBr): 3382, 3050, 2932, 2245, 1600, 1500, 1454, 1300, 1118, 1040, 925, 765 cm^{-1}; ^1H NMR($CDCl_3$): δ 3.80 (s, 3H), 3.90 (d, 1H, *J* = 8.1 Hz), 5.30 (d, 1H, *J* = 8.1 Hz), 6.75 (d, 2H, *J* = 8.0 Hz), 6.80 (t, 1H, *J* = 7.9 Hz), 6.90 (d, 2H, *J* = 8.0 Hz), 7.25 (t, 2H, *J* = 7.9 Hz), 7.50 (d, 2H, *J* = 8.0 Hz); MS: *m/z* 238 (M^+), 211, 181, 167, 141, 104, 77, 51, 40.

4g: Yellow solid, m.p. 77-79°C (Lit.76-78°C, ref. 12); IR (KBr): 3305, 2925, 2850, 2225, 1690, 1575, 1460, 1215, 1140, 1015, 940, 765 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H), 6.79 (d, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.8 Hz), 7.22-7.30 (m, 4H), 7.50 (d, 2H, *J* = 8.0 Hz); MS: *m/z* 222 (M^+), 194, 176, 131, 103, 91, 77, 41.

4h: White crystalline solid**,** m.p. 96-98°C (Lit.95-97°C, ref. 12); IR (KBr): 3410, 2930, 2230, 1610, 1520, 1460, 1270, 1050, 790 cm^{-1}; ^1H NMR($CDCl_3$): δ 4.66 (d, 1H, *J* = 8.1 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 6.90-6.95 (m, 2H), 7.15-7.35 (m, 4H), 7.59-7.65 (m, 2H); MS: *m/z* 260 (M^+), 234, 135, 100, 75.

4i: Colourless oil[12], IR (KBr): 3410, 2925, 2235, 1648, 1515, 1400, 1108, 1029, 920, 825, 751 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.80 (brs, 1H, NH), 3.94 (AB q, 2H, *J* = 13.5 Hz), 4.70 (s,1H), 6.76 (d, 1H, *J* = 8.0 Hz), 7.15 (t, 1H, *J* = 7.8 Hz), 7.25-7.39 (m, 6H), 7.48-7.50 (m, 2H); MS: *m/z* 222 (M^+),195, 141, 131, 116, 106, 91, 77, 51.

4j: Yellow liquid[12], IR (KBr): 3400, 2940, 2890, 2241, 1615, 1528, 1470, 1282, 1160, 1045, 790 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.85 (brs, 1H, NH), 3.80 (s, 3H), 3.95 (AB q, 2H, *J* = 13.0 Hz), 4.70 (d, 1H, *J* = 13.0 Hz), 6.80-6.93 (m, 3H), 7.24 (t, 1H, *J* = 7.9 Hz), 7.30-7.55 (m, 5H); MS: *m/z* 252 (M^+), 225, 122, 91, 77.

4k: Pale yellow solid, m.p. 118-20°C (Lit.117-119°C, ref. 12) IR (KBr): 3350, 2930, 2233, 1605, 1505, 1460, 1275, 1030, 975, 897, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.80 (d, 1H, *J* = 8.1 Hz), 5.05 (m, 1H), 6.30 (dd, 1H, *J* = 6.9, 17.3 Hz), 6.78 (d, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.9 Hz), 7.08 (dd, 1H, *J* = 1.7, 17.3 Hz), 7.25-7.50 (m, 8H); MS: *m/z* 234 (M^+), 206, 128, 115, 77, 51.

4l: Dark brown solid, m.p. 69-71°C (Lit.68-70°C, ref. 12) IR (KBr): 3355, 2925, 2235, 1695, 1605, 1505, 1440, 1290, 1250, 1149, 1015, 880, 750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.05 (d, 1H, *J* = 8.1 Hz), 5.40 (d, 1H, *J* = 8.1 Hz), 6.40 (m, 1H), 6.55 (m,1H), 6.80 (d, 2H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 7.9 Hz), 7.25 (t, 2H, *J* = 7.9 Hz), 7.40 (m, 1H); MS: *m/z* 198 (M^+), 169, 155, 141, 115, 106, 92, 77, 51.

Conclusion

A convenient and efficient one-pot method for the synthesis of α-amino nitriles by a three-component condensation of aldehydes, amines and trimethylsilyl cyanide in the presence of $ZrCl_4$ catalyst has been demonstrated. $ZrCl_4$ acts as a mild Lewis acid, will be a useful and inexpensive catalyst for the synthesis of α-amino nitriles in excellent yields. The simple experimental procedure, mild reaction conditions, inexpensive catalyst, shorter reaction times and high yields of products are the advantages of the present method.

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