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Note

Rhodium chloride catalyzed facile synthesis of α-aminonitriles

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The facile synthesis of a series of α-aminonitriles by a one-pot three-component condensation of carbonyl compounds, amines and TMSCN in MeCN in presence of a catalytic amount of rhodium chloride at ambient temperature in high yields is described.

Keywords: α-Aminonitriles, one-pot three-component condensation, carbonyl compounds, amines, rhodium chloride

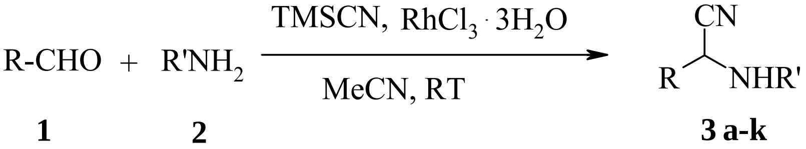
α-Aminonitriles are important building blocks for the synthesis of a variety of organic compounds such as amino acids[1], thiadiazoles and imidazoles[2]. α-Aminonitriles have been used to synthesize 4-amino-2,3-dihydroisothiazole-1,1-dioxides[3] and reports indicate the versatility of these compounds as intermediates in the preparation of highly substituted amines and the use of α-aminonitriles as precursor of new azaspironucleoside analogues of TSAO[4]. They have been synthesised by the nucleophilic addition of cyanide anion to imines, the classical Strecker synthesis provides one of the most important methods which is generally carried out with alkaline cyanides in aqueous solution which has some limitations. Consequently, several modifications of the Strecker synthesis have been reported using a variety of cyanating agents such as α-trimethylsiloxynitriles and diethyl phosphorocyanides under various reaction conditions. Trimethylsilylcyanide (TMSCN) is a cyanide anion source and provides promising and safer routes to this class of reactions.

On the other hand, three-component condensations are interesting and important, because of the usefulness in the preparation of a broad variety of organic compounds. Recently, one-pot procedures for the synthesis of α-aminonitriles from carbonyl compounds have also been developed in the presence of a variety of catalysts such as $InCl_3$ (Ref 5), $BiCl_3$ (Ref 6), $NiCl_2$ (Ref 7), $CoCl_2$ (Ref 8), $Sc(OTf)_3$ (Ref 9), Cd(II)-salt (Ref 10), Pt-salt (Ref 11), I_2 (Ref 12), and montmorillonite KSF clay[13]. Some of these systems still have a few drawbacks including low yields of products, long reaction times, harsh reaction conditions, the requirement of an inert atmosphere, use of highly toxic reagents like HCN or KCN and also require tedious work-up leading to the generation of a large amount of toxic waste. Therefore, there is a need for clean procedures for the synthesis of α-aminonitriles.

In the past 20 years, there has been dramatic growth in the use of transition metal catalysts in synthetically important organic transformations. Rhodium has been proved to be extremely useful due to its ability to catalyze an array of synthetic transformations, with quite often unique selectivity. Hydrogenation[14], C-H activation[15], allylic substitution[16] and numerous other reactions are catalyzed by this metal, which presumably accounts for the dramatic increase in the number of articles that have recently emerged on the topic.

Results and Discussion

In view of the importance of α-aminonitriles as described above, herein is reported a clean procedure for the synthesis of a variety of α-aminonitriles under mild conditions. The reaction is efficient and proceeds with high yield at RT either by the addition of a primary amine to a mixture of aldehyde/trimethylsilyl cyanide (TMSCN) or by the addition of an aldehyde to a mixture of amine/TMSCN in acetonitrile in presence of a catalytic amount of rhodium chloride as shown in **Scheme I**. The combination of benzaldehyde, aniline and TMSCN was chosen for a representative reaction performed in the presence of catalytic amount of $RhCl_3$ in various organic solvents *viz* methanol, dichloromethane, dichloroethane, tetrahydrofuran, ethanol and acetonitrile. The reaction occurred smoothly at ambient temperature giving the corresponding α-aminonitrile in high yield (86%). A range of solvents were examined and acetonitrile emerged as the superior medium.



Scheme I

The condensation of different aldehydes and amines was performed under the above conditions and reaction was completed within 1 to 1.5 hr. The course of reaction was monitored by thin layer chromatography. All the products obtained (listed in **Table I**) by this system were characterized by comparison of their melting points/physical state, TLC, IR and ^{1}H NMR spectra with authentic samples.

Experimental Section

All the reagents including rhodium chloride were purchased from Merck and BDH. The solvents were of analytical grade or were purified according to standard procedures. TLC were run on silica gel plates obtained from Whatman Inc. All reactions were performed under ambient atmosphere. Melting points were obtained with Büchi B-540 apparatus and are uncorrected. IR and ^{1}H NMR spectra were recorded on Nicolet 400D FT-IR and Bruker AMX (200 MHz) spectrometers, respectively. GC analyses were performed on a Shimadzu GC-MS QP 5050A instrument. Yields refer to the isolated products after purification by column chromatography using 60-120 mesh silica gel with 15 : 85 :: ethyl acetate : hexane (v/v) as the eluent.

General procedure for the synthesis of 3a

A mixture of benzaldehyde (212 mg, 2 mmoles), aniline (186 mg, 2 mmoles) and trimethylsilyl cyanide (3 mmoles) in acetonitrile (10 mL) was stirred at RT in the presence of $RhCl_3$ (15 mg, 35 mol %). After completion of reaction (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 (20 mL) respectively, then dried using anhyd. $MgSO_4$ and concentrated. The residue was chromatographed over silica gel (ethyl acetate: hexane ::1.5: 8.5) to afford the pure product **3a**.

Spectral data of products

3a: White crystalline solid, m.p. 73-74°C (Lit. 73-74°C[13]); IR (KBr): 3369, 3021, 2954, 2236, 1603, 1505, 1464, 1313, 1142, 995, 751cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.0 (d, 1H, *J*=8.1 Hz), 5.40 (d, 1H, *J*=8.1 Hz), 6.75 (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.

3b: Colorless oil[13], IR (KBr): 3408, 2925, 2233, 1650, 1515, 1401, 1108, 1028, 920, 825, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.80 (brs, 1H, NH), 3.95 (dd, 2H, *J*=13.5 Hz), 4.70 (s, 1H), 6.78 (d, 1H, *J*=8.0 Hz), 7.15 (t, 1H, *J*=7.8 Hz), 7.25–7.40 (m, 6H), 7.49–7.51(m, 2H); MS: *m/z* 222 M$^+$, 195, 141, 131, 116, 106, 91, 77, 51.

3c: Pale yellow solid, m.p. 73-74°C (Lit. 72-73°C[13]); IR (KBr): 3368, 2935, 2856, 2238, 1605, 1515, 1462, 1275, 1035, 791 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3 H), 3.38 (broad, 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.

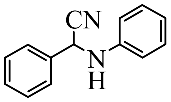
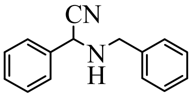
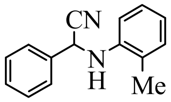
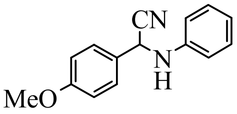
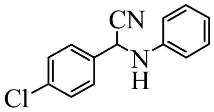
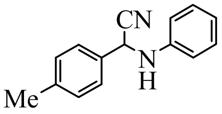
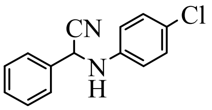
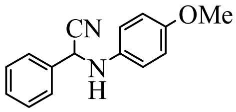
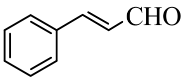
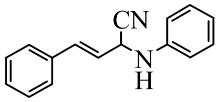
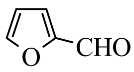
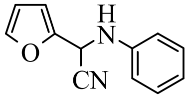
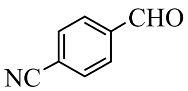
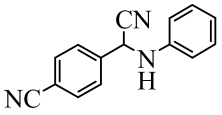
3d: White solid, m.p. 94-95°C (Lit. 94-95°C[13]); IR (KBr): 3381, 3055, 2933, 2246, 1604, 1501, 1455, 1297, 1115, 1040, 922, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.90(d, 1H, *J*=8.1 Hz), 5.30 (d, 1H, *J*=8.1 Hz), 6.75 (d, 2H, *J*=8.0 Hz), 6.80 (t, 1H, *J*=7.9 Hz), 6.90 (d, 2H, *J*=8.0 Hz), 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.

3e: White solid, m.p. 110-112°C (Lit. 109-112°C[13]); IR (KBr): 3405, 2925, 2239, 1601, 1515, 1458, 1275, 1161, 1098, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.0 (d, 1H, *J*=8.1 Hz), 5.39 (d, 1H, *J*=8.1 Hz), 6.75 (d, 2H, *J*=8.0 Hz), 6.90 (t, 1H, *J*=7.9 Hz), 7.15 (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.

3f: Yellow solid, m.p. 77-79°C (Lit. 76-78°C[13]); IR (KBr): 3306, 2924, 2853, 2225, 1691, 1575, 1462, 1215, 1141, 1015, 940, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 6.78 (d, 2H, *J*=8.0 Hz), 6.90 (t, 1H, *J*=7.8 Hz), 7.20–7.30 (m, 4H), 7.50 (d, 2H, *J*=8.0 Hz); MS: *m/z* 222 M$^+$, 194, 176, 131, 103, 91, 77, 41.

3g: Pale yellow solid, m.p. 107-110°C (Lit. 108-110°C[17]); IR (KBr): 3408, 2930, 2228, 1610, 1519, 1460, 1270, 1051, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.07 (d, 4H, *J*=8.0 Hz), 5.29 (d, 1H, *J*=8.0 Hz), 6.61

Table I — Rhodium chloride catalyzed one-pot synthesis of α-aminonitriles **3a-k**

Entry	Aldehyde	Amine	Product	Reaction time	Yield[a]
	(**1**)	(**2**)	(**3a-k**)	(hr)	(%)
a	C_6H_5CHO	$C_6H_5NH_2$		1	86
b	C_6H_5CHO	$C_6H_5CH_2NH_2$		1.25	82
c	C_6H_5CHO	$2\text{-MeC}_6H_4NH_2$		1	85
d	4-OMeC_6H_4CHO	$C_6H_5NH_2$		1.25	88
e	4-ClC_6H_4CHO	$C_6H_5NH_2$		1.25	80
f	4-MeC_6H_4CHO	$C_6H_5NH_2$		1	87
g	C_6H_5CHO	$4\text{-ClC}_6H_4NH_2$		1	86
h	C_6H_5CHO	$4\text{-OMeC}_6H_4NH_2$		1.25	85
i		$C_6H_5NH_2$		1.25	81
j		$C_6H_5NH_2$		1	83
k		$C_6H_5NH_2$		1.25	87

[a] Isolated yield.

(d, 2H, *J*=8.0 Hz), 7.51 (d, 2H, *J*=8.0 Hz), 7.47–7.34 (m, 3H), 7.60–7.48 (m, 2H); MS: *m/z* 242 M$^+$, 215, 178, 126.

3h: Pale yellow solid, m.p. 95-96°C (Lit. 94-96°C[17]); IR (KBr): 3391, 2934, 2850, 2240, 1615, 1519, 1465, 1285, 1045, 790 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.72 (s, 3H). 3.84 (d, 1H, *J*=8.0 Hz), 5.29 (d, 1H, *J*=8.0 Hz), 6.67 (d, 2H, *J*=8.0 Hz), 6.78 (d, 2H, *J*=8.0 Hz), 7.47–7.36 (m, 3H), 7.62–7.51 (m 2H); MS: *m/z* 238 M$^+$, 211, 210, 146.

3i: Pale yellow solid, m.p. 118-120°C (Lit. 117-119°C[13]; IR (KBr): 3350, 2928, 2232, 1604, 1505, 1464, 1275, 1030, 975, 893, 749 cm^{-1}; ^{1}H 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), 7.25–7.45 (m, 8H); MS: *m/z* 234 M$^+$, 206, 128, 115, 77, 51.

3j: Dark brown solid, m.p. 68-69°C (Lit. 68-70°C[13]); IR (KBr): 3354, 2927, 2233, 1695, 1603, 1504, 1442, 1290, 1251, 1147, 1015, 879, 751 cm^{-1}; ^{1}H 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.

3k: Pale yellow solid, m.p. 112-114°C; IR (KBr): 3416, 3359, 3064, 2247, 1610, 1507, 1440, 1300, 1259, 1147, 1093, 845, 757 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 5.57 (s, 1H), 6.79-6.81(d, 2H, *J*=8.0 Hz), 6.97-7.01 (t, 1H, *J*=8.0 Hz), 7.26-7.33 (m, 2H), 7.73 (m, 4H); MS (LCMS): *m/z* 234 M$^+$, 207, 146.

Conclusion

In conclusion, a facile and efficient route for one-pot three-component condensation of carbonyl compounds, amines and TMSCN in acetonitrile in presence of a catalytic amount of rhodium chloride without the need of inert atmosphere has been demonstrated. Most of the reactions were completed in less than 1.5 hr at ambient temperature and the products were found to be analytically pure. Furthermore, the RhCl$_3$/MeCN system is more effective than the earlier methods. This procedure will therefore be of general use and interest to the synthetic chemistry community.

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