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A Greener, Versatile and Convenient Approach for Catalyst Free Conversion of Pyrazole Aldehydes into Carbonitriles

SELVARAJ JAYANTHI, MANICKAM PRAMESH, PERIYASAMY MONISHA, MOORTHY VETRISELVAN and RAGUNATHAN VENKATACHALAM*

PG and Research Department of Chemistry, A.V.V.M. Sri Pushpam College (Affiliated to Bharathidasan University, Tiruchirappalli), Poondi-613503, India

*Corresponding author: E-mail: mprameshchemistry@gmail.com

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A new, efficient and catalyst-free synthetic strategy was developed for ten carbonitriles by the combination of pyrazole aldehydes and hydroxylamine hydrochloride in the presence of green solvent-glycerol. All the synthesized carbonitriles were confirmed from by ^{1}H, ^{13}C NMR and high resolution mass spectroscopies. The proposed synthetic process was simple, effective with high product yields and environmentally benign with mild reaction conditions.

Keywords: Carbonitriles, Hydroxylamine hydrochloride, Glycerol, Pyrazole aldehyde.

INTRODUCTION

Compounds containing substituted carbonitriles are the important building blocks utilized in synthesis of various agrochemicals, natural products, herbicides, dyes and pharmaceuticals [1,2]. The nitrile moieties are highly versatile functional groups in organic synthesis and could be employed as an intermediate for the synthesis of various other functional groups and heterocycles. Nitriles are the important precursors for the synthesis of amines, amidines, amides, carboxylic acids, esters, ketones, *etc.* [3]. The nitrile groups can also be found in biologically active drugs including periciazine (an antipsychotic medicine), letrazole and fadrozole (a breast cancer treatment), HIV protease inhibitors and 5-lipoxygenase inhibitors and citalopram (an antidepressant drug) [4,5].

The nucleophilic displacement of the leaving groups such as halogens, alcohols, nitro or amino groups, esters, ethers and diazonium salts with inorganic cyanide ions are the well-known procedures for the synthesis of nitriles [6]. The other methods for nitrile synthesis [7] includes dehydration of amides and aldoximes [8], from alcohols [9], aldehydes [10-12], carboxylic acids using various reagents [13-18] and direct transformation of amines [19,20]. The conventional methods involve hazardous chemicals, expensive catalysts, difficult reaction conditions and substrates [21-23]. Various methods for the transformation of nitriles into aldehydes such as *o*-phenylhydroxylamine [24], chloramination [25], ammonium carbamate [26], Schmidt reaction [27], TEMPO (2,2,6,6-tetramethylpiperidinyl-l-oxy) as mediator [28], catalyst free method in glycerol as a green solvent using hydroxyl amine hydrochlorides [1] are also reported in the literature. However, these methods are very long, tedious and expensive. So, direct conversion of aldehydes to nitriles using readily available hydroxylamine hydrochloride might help to overcome the economic and environmental difficulties faced by the conventional methods. Thus, in this work, a catalyst free, one-pot synthetic stregedy of the conversion of aldehydes into nitriles, using hydroxylamines without oxime intermediates isolation is reported.

EXPERIMENTAL

The chemicals utilized in the reaction were procured from Sigma-Aldrich (USA). Analytical thin layer chromatography was carried out on aluminium sheets precoated with silica gel [CCM Gel de silice 60 F_{254} with a thickness of 0.2 mm (Merck)]. Column chromatography was carried out using silica gel (230-400 mesh, Merck, India).

Melting points were measured on Galen III hot stage equipment (Cambridge Instruments). FTIR spectrophotometer-Lambda Scientific was used to record FTIR spectra. ^{1}H & ^{13}C NMR spectral data were obtained at 400 and 100 MHz, respectively, using a Bruker spectrometer using deuterated chloroform with tetramethylsilane (TMS) as an internal standard.

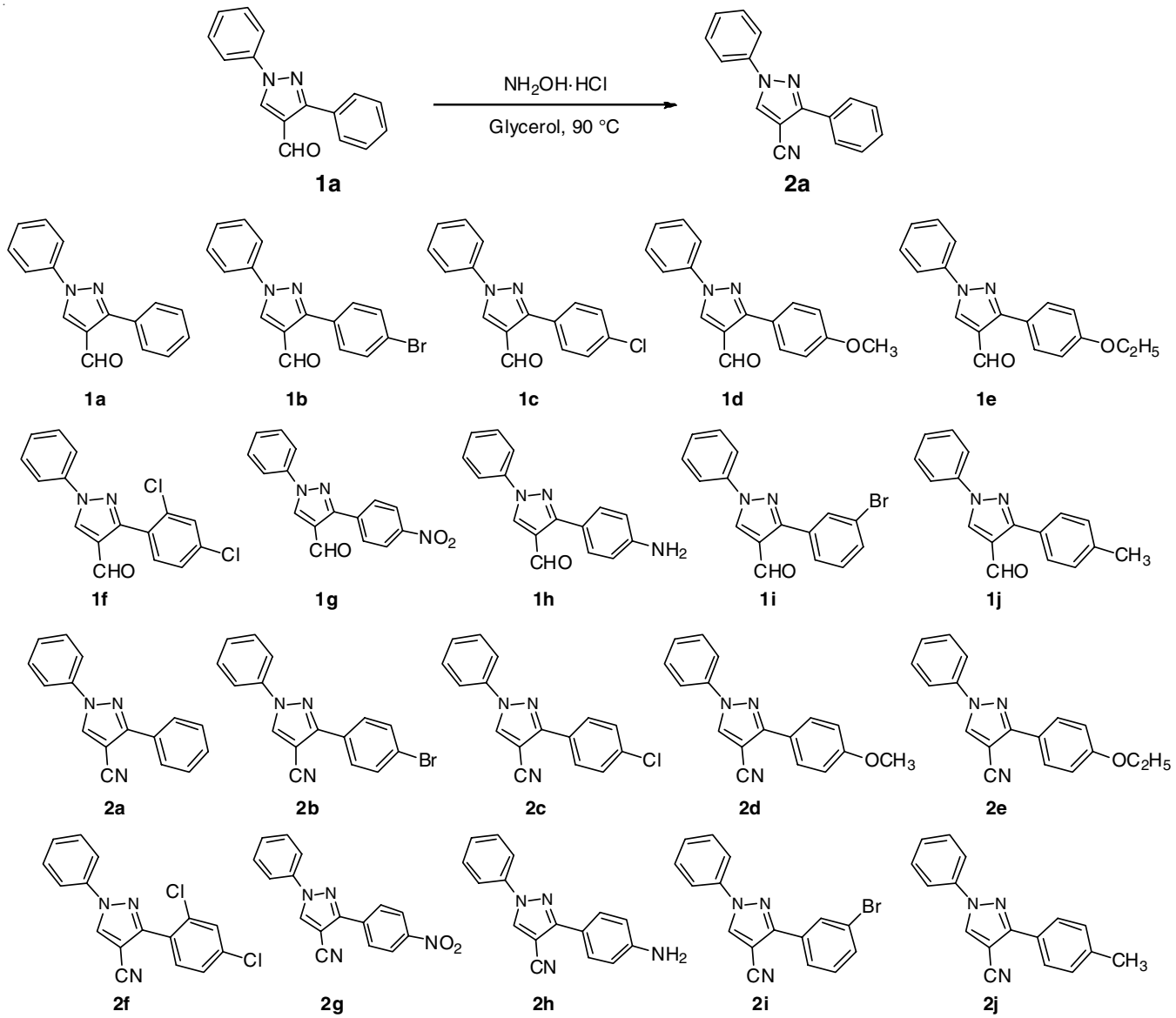
The JEOL GC MATE-II HR Mass (70 eV) E1 spectrometer was used to record mass spectra.

General procedure for the synthesis of carbonitriles (2a-j): In a round bottom flask, pyrazole aldehydes (1.0 mmol) and hydroxylamine hydrochloride (1.0 mmol) were added in glycerol (5 mL). The reaction mixture was stirred at 90 ºC for 20 min. The reaction completion was confirmed using TLC. After the completion of reaction, the reaction mixture was washed with hexane/ethyl acetate mixture (95:5) (3 × 5 mL). The organic phase was separated from the glycerol, dried with $MgSO_4$ and evaporated using rotatory evaporator under reduced pressure (**Scheme-I**). The crude products were purified using column chromatography with hexane/ethyl acetate eluent.

1,3-Diphenyl-1*H*-pyrazole-4-carbonitrile (2a): White solid; yield: 96%; time: 20 min; R_f = 0.35 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.37-7.42 (m, 5H), 7.44-7.74 (m, 5H), 8.91 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 113.87, 119.36, 119.66, 125.96, 127.16, 127.26, 128.54, 128.76, 128.82, 129.08, 129.54, 131.94, 132.08, 139.53, 143.41 and 153.84; HRMS (ESI): *m/z* $[M]^+$ 245; Anal. calcd. (found) % for $C_{16}H_{11}N_3$: C, 78.35 (78.33); H, 4.52 (4.48); N, 17.13 (17.10).

3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2b): White solid; yield: 89%; time: 20 min; R_f = 0.40 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.42-7.68 (m, 5H), 7.55 (dd, 2H), 7.68 (dd, 2H), 8.44 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 93.4,113.5, 118.36, 119.91, 126.21, 128.29, 128.86, 129.01, 129.36, 129.51, 129.73, 129.94, 133.0, 134.34, 139.87, 150.05; HRMS (ESI): *m/z* $[M]^+$ 324; Anal. calcd. (found) % for $C_{16}H_{10}N_3Br$: C, 59.28 (59.25); H, 3.11 (3.06); N, 12.96 (12.93); Br, 24.65 (24.60).

3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2c): White solid; yield: 92%; time: 20 min; R_f = 0.45 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.44-7.78 (m, 5H), 7.91 (dd, 2H), 7.55 (dd, 2H), 8.41 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 93.9, 113.9, 118.96, 119.01, 123.21, 126.21, 128.39, 129.31, 129.56, 130.05, 132.15, 132.57, 133.50, 139.54, 139.87, 150.12; HRMS (ESI): *m/z* $[M]^+$ 279; Anal.



Scheme-I: Synthesis of carbonitriles

calcd. (found) % for $C_{16}H_{10}N_3Cl$: C, 68.70 (68.19); H, 3.60 (3.55); N, 15.02 (14.95); Cl, 12.67 (13.62).

3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2d): White solid; yield: 96%; time: 22 min; R_f = 0.50 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 3.84 (t, 3H), 7.46-7.69 (m, 5H), 7.03 (dd, 2H), 7.55 (dd, 2H), 8.49 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 55.8,93.1,113.9, 114.8, 119.51, 119.73, 123.59, 126.20, 128.56, 128.81, 128.93, 129.36, 129.56, 134.34, 139.73, 133.04, 150.25; HRMS (ESI): *m/z* $[M]^+$ 275; Anal. calcd. (found) % for $C_{17}H_{13}N_3O$: C, 74.17 (74.14); H, 4.76 (4.73); N, 15.26 (15.24); O, 5.81 (5.78).

3-(4-Ethoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2e): White solid; yield: 90%; time: 20 min; R_f = 0.35 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 1.35 (t, 3H), 4.07(d, 2H), 7.45-7.63 (m, 5H), 7.08 (dd, 2H), 7.62 (dd, 2H), 8.39 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 14.8, 64.6, 93.7, 113.9, 114.36, 118.91, 126.26, 127.29, 128.26, 128.91, 129.06, 129.41, 129.63, 129.84, 133.05, 134.54, 147.87 and 150.32; HRMS (ESI): *m/z* $[M]^+$ 289; Anal. calcd. (found) % for $C_{18}H_{15}N_3O$: C, 74.72 (74.65); H, 5.23 (5.19); N, 14.52 (14.47); O, 5.53 (5.50).

3-(2,4-Dichlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2f): White solid; yield: 90%; time: 25 min; R_f = 0.45 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.38-8.03 (m, 8H), 8.36 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 93.6, 113.5, 120.1, 126.4, 127.8, 128.0, 129.7, 131.0, 131.4, 133.6, 134.2, 136.1, 140.3, 150.9; HRMS (ESI): *m/z* $[M]^+$ 314; Anal. calcd. (found) % for $C_{16}H_9N_3Cl_2$: C, 61.17 (61.07); H, 2.89 (2.81); N, 13.38 (13.30); Cl, 22.57 (22.52).

3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2g): white solid; yield: 94%; time: 25 min; R_f = 0.40 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.40-7.78 (m, 5H), 7.97 (dd, 2H), 8.26 (dd, 2H), 8.49 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 93.1,113.46, 118.56, 119.95, 124.21, 124.59, 126.26, 126.31, 126.56, 129.34, 129.79, 133.54, 137.05, 139.34, 147.07, 150.29; HRMS (ESI): *m/z* $[M]^+$ 290; Anal. calcd. (found) % for $C_{16}H_{10}N_4O_2$: C, 66.20 (66.21); H, 3.47 (3.41); O, 11.02 (10.96); N, 19.30 (19.26).

3-(4-Aminophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2h): White solid; yield: 92%; time: 22 min; R_f = 0.50 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 5.24 (t, 2H), 7.38-7.58 (m, 5H), 6.59 (dd, 2H), 7.65 (dd, 2H), 8.90 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 93.0,112.95, 113.39, 115.21, 115.51, 119.19, 119.46, 119.81, 121.02, 126.21, 128.63, 128.94, 129.0, 129.4, 139.8 and 150.16; HRMS (ESI): *m/z* $[M]^+$ 260; Anal. calcd. (found) % for $C_{16}H_{12}N_4$: C, 73.83 (73.79); H, 4.65 (4.62); N, 21.52 (21.49); Br, 24.62 (24.60).

3-(3-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2i): White solid; yield: 90%; time: 20 min; R_f = 0.55 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 7.42-7.83 (m, 9H), 8.42 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, δ ppm): 93.8, 113.4, 120.6, 126.8, 127.3, 128.5, 129.2, 131.3, 131.8, 133.9, 134.7, 136.9, 140.1, 150.5; HRMS (ESI): *m/z* $[M]^+$ 324; Anal. calcd. (found) % for $C_{16}H_{10}N_3Br$: C, 59.28 (59.24); H, 3.11 (3.06); Br, 24.65 (24.60); N, 12.96 (12.91).

1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazole-4-carbonitrile (2j): White solid; yield: 88%; time: 24 min; R_f = 0.45 (15% EA-PE); ^{1}H NMR: (300 MHz, $CDCl_3$, δ ppm): 2.34 (t, 3H), 7.39-7.62 (m, 5H), 7.17 (dd, 2H), 7.58 (dd, 2H), 8.43 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 21.7, 93.2, 113.9, 119.36, 119.95, 125.21, 125.79, 126.26, 128.01, 129.56, 129.91, 129.97, 131.44, 133.0, 139.34, 139.87 and 150.5; HRMS (ESI): *m/z* $[M]^+$ 259; Anal. calcd. (found) % for $C_{17}H_{13}N_3$: C, 78.74 (79.25); H, 3.05 (3.06); N, 16.20 (16.93); Br, 24.63 (24.60).

RESULTS AND DISCUSSION

In the presence of glycerol, hydroxylamine hydrochloride was introduced to pyrazole aldehyde **1a** and stirred for 20 min at 90 ºC. To get good outstanding yields of carbonitriles, the reaction mixture was extracted with ethyl acetate and further purified with column chromatography (15% ethyl acetate-pet. ether mixture). The structures of the synthesized compounds were thoroughly characterized using ^{1}H, ^{13}C NMR and HRMS spectroscopic techniques. Using different solvents *viz*. water, ethanol, ethylene glycol, glycerol and a mixture of water-glycerol were used as screening solvent and it was revealed that while using glycerol, the best results were obtained (Table-1).

TABLE-1
SCREENING OF SOLVENT

Entry	Solvent	Isolated yield (%)
1	Water	Trace
2	Ethanol	Trace
3	Ethylene glycol	Trace
4	Glycerol	92
5	Water-glycerol	30

The ^{1}H NMR spectrum of compound **2a** exhibited ten protons multiplet at δ 7.37-7.74 ppm, which was attributed to aromatic protons. The singlet δ 8.91 ppm was assigned to pyrazole ring proton. In ^{13}C NMR spectra, the peaks ranges between 119.3-143.4 ppm were assigned to aromatic ring carbons. The carbon at position 3, 4 and 5 of pyrazole ring are appeared at 153.84, 113.87 and 132.08 ppm respectively. The peak at 119.36 ppm showed to nitrile carbon. The HRMS spectrum reveals the molecular ion peak $[M]^+$ at *m/z* 245.

Conclusion

In summary, a novel, effective and one-pot catalyst-free method was proposed for the synthesis of carbonitriles from pyrazole aldehydes using hydroxylamine hydrochloride in glycerol as a green solvent. The method was straightforward, efficient with high product yields, has high atom economy and environmentally benign with mild reaction conditions and is environmentally friendly. The synthesized compounds were characterized using ^{1}H, ^{13}C NMR and HRMS.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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