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Novel $Bu4N^{+}Br^{-}$ catalyzed one-pot multi-component synthesis of 2-amino nicotinonitriles in aqueous medium

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Abstract An efficient single-pot strategy for 2-amino nicotinonitrile derivatives **5** has been developed by multi-component reaction of arylaldehydes **1**, methylketones **2**, malononitrile **3**, and ammonium acetate **4** using tetrabutyl ammonium bromide as catalyst in aqueous medium.

Keywords Arylaldehydes · Methylketones · Malononitrile · Nicotinonitrile · Tetrabutyl ammonium bromide · Ammonium acetate

Introduction

Pyridine-based molecules exhibit diverse pharmacological and biological activities useful as HIV-1 inhibitors [1], IKK-B inhibitors [2, 3], and adenosine receptor antagonists [4], and were recently recognized as potential targets for the development of new drugs. Among pyridine derivatives, 2-amino nicotinonitriles have attracted considerable attention because of their promising bio-activity [5–10]. A recent report [11] describes the preparation of 2-amino nicotinonitriles by using ytterbium perfluorooctanoate as catalyst. Most of the existing methods involves multiple steps [12], long reaction times and usage of hazardous solvents [13, 14]. A mild, convenient and high yield procedure for the preparation of 2-amino nicotinonitriles using inexpensive catalyst and eco-friendly solvent would be valuable.

In the recent past, tetrabutyl ammonium bromide (TBAB) has emerged as a mild, water-tolerant, inexpensive, and environmentally compatible homogenous catalyst in various organic transformations [15–17]. Biginelly-type compounds [18] and biscoumarine and 3,4-dihydro pyrano[c]chromone derivatives [19] were prepared

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by using TBAB as catalyst. In continuation of our interest in the development of new synthetic methods [20, 21], we report here a convenient and novel approach for the synthesis of 2-amino nicotinonitriles by multi-component reaction of aryl aldehydes, ketones, malononitrile, and ammonium acetate using $Bu_4N^+Br^-$ (TBAB) as catalyst in aqueous medium.

Experimental

Melting points were recorded on a Casia-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr discs. ^{1}H NMR spectra were recorded on Bruker AV spectrometers at 300 MHz and INOVA 400 MHz in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectra were recorded on a Bruker AV 75 MHz in $CDCl_3$. Electron impact (EI) mass spectra were recorded on a VG 7070 H instrument at 70 eV. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel of 60–120 mesh; spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography. CHN analyses were recorded on a vario EL analyzer.

Synthesis of 2-aminonicotinonitrile derivatives (**5a–5o**)

General procedure

A mixture of aldehyde (1 mmol), ketone (1 mmol), malononitrile (1 mmol), ammonium acetate (1.5 mmol) and tetrabutyl ammonium bromide (TBAB) (10 mol%) was stirred in one-pot in water (5 mL) at refluxing temperature for 2 h. The mixture was allowed to cool to room temperature and was extracted with ethyl acetate twice (2 × 20 ml). Combined extracts were washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by passing through a column packed with silica gel.

*2-Amino-4,6-diphenyl-nicotinonitrile (**5a**) [14], 2-amino-4-(4-chloro-phenyl)-6-phenyl-nicotinonitrile (**5b**) [14], 2-amino-6-phenyl-4-p-tolyl-nicotinonitrile (**5c**) [14], and 2-amino-4-(4-fluoro-phenyl)-6-phenyl-nicotinonitrile (**5d**)*

I.R. (KBr, cm^{-1}): 3,364, 3,313 (–NH2), 2,209 (–CN); ^{1}H NMR (CDCl3, 300 MHz): δ 5.34 (br., s, 2H, NH2), 7.15 (s, 1H, Py–H), 7.18–7.23 (m, 2H, Ar–H), 7.42–7.46 (m, 3H, Ar–H), 7.60–7.65 (m, 2H, Ar–H), 7.95–7.99 (m, 2H, Ar–H); MS (EI, 70 eV); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 87.6, 113.7, 114.5, 116.0, 127.3, 127.6, 129.2, 130.7, 134.6, 139.0, 154.5, 156.2, 159.2, 161.4; MS (EI, 70 eV): *m/z* $M^{+\cdot}$, 289; Anal. Calcd. for $C_{18}H_{12}FN_3$: C 74.73, H 4.18, N 14.52 %. Found: C 74.45, H 4.19, N 14.42 %.

*2-Amino-4-(4-methoxy-phenyl)-6-phenyl-nicotinonitrile (**5e**) [12], 2-amino-6-phenyl-4-(2-trifluoromethyl-phenyl)-nicotinonitrile (**5f**)*

I.R. (KBr, cm^{-1}): 3,492, 3,351 (–NH_2), 2,222 (–CN); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.31 (br., s, 2H, NH_2), 7.11 (s, 1H, Py–H), 7.37–7.46 (m, 4H, Ar–H), 7.58–7.70 (m, 2H, Ar–H), 7.82–7.87 (m, 1H, Ar–H), 7.93–7.98 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 88.9, 112.3, 113.8, 123.9, 125.4, 125.7, 127.5, 127.8, 129.2, 129.4, 129.6, 131.2, 132.5, 139.0, 156.1, 157.6, 161.9; MS (EI, 70 eV): *m/z* $M^{+\cdot}$, 339; Anal. Calcd. for $C_{19}H_{12}F_3N_3$: C 67.25, H 3.56, N 12.38 %. Found: C 67.19, H 3.52, N 12.29 %.

*2-Amino-6-phenyl-4-(2,4,6-trifluoro-phenyl)-nicotinonitrile (**5g**)*

I.R. (KBr, cm^{-1}): 3,473, 3,368 (–NH_2), 2,207 (–CN); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.36 (br., s, 2H, NH_2), 7.11 (s, 1H, Py–H), 7.28–7.35 (m, 1H, Ar–H), 7.42–7.47 (m, 3H, Ar–H), 7.49–7.55 (m, 1H, Ar–H), 7.92–7.99 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 88.2, 104.3, 111.3, 113.7, 115.9, 127.4, 127.7, 129.5, 139.1, 156.2, 156.6, 161.4, 166.1; MS (EI, 70 eV): *m/z* $M^{+\cdot}$, 325; Anal. Calcd. for $C_{18}H_{10}F_3N_3$: C 66.46, H 3.10, F, N 12.92 %. Found: C 66.35, H 3.05, N 12.79 %.

*2-Amino-4-(4-isopropyl-phenyl)-6-phenyl-nicotinonitrile (**5h**)*

I.R. (KBr, cm^{-1}): 3,498, 3,375 (–NH_2), 2,205 (–CN); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32 (d, 6H, $J = 8.01$ Hz, –$(CH_3)_2$), 2.96–3.02 (m, 1H, –CH–), 5.31 (br., s, 2H, NH_2), 7.17 (s, 1H, Py–H), 7.35 (d, 2H, $J = 9.0$ 1 Hz, Ar–H), 7.40–7.46 (m, 3H, Ar–H), 7.56 (d, 2H, $J = 8.01$ Hz, Ar–H), 7.96–8.00 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.8, 33.9, 88.1, 111.2, 117.3, 127.0, 127.3, 128.1, 128.7, 130.1, 134.3, 138.0, 150.8, 155.1, 159.6, 160.2; MS (EI, 70 eV): *m/z* $M^{+\cdot}$, 313; Anal. Calcd. for $C_{21}H_{19}N_3$: C 80.48, H 6.11, N 13.41 %. Found: C 80.50, H 6.01, N 13.45 %.

*2-Amino-4-(furan-2-yl)-6-phenyl-nicotinonitrile (**5i**) [4], 2-amino-6-phenyl-4-(thiophen-2-yl)-nicotinonitrile (**5j**) [4], 2-amino-6-(4-fluoro-phenyl)-4-phenyl-nicotinonitrile (**5k**) [22], 2-amino-6-(4-methoxy-phenyl)-4-phenyl-nicotinonitrile (**5l**) [22], 2-amino-6-(4-bromo-phenyl)-4-phenyl-nicotinonitrile (**5m**) [22], 2-amino-6-(4-hydroxy-phenyl)-4-phenyl-nicotinonitrile (**5n**) [23], and 2-amino-6-(3-methoxy-phenyl)-4-phenyl-nicotinonitrile (**5o**)*

I.R. (KBr, cm^{-1}): 3,478, 3,306 (–NH_2), 2,203 (–CN); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (s, 3H, –OCH_3), 5.36 (br., s, 2H, NH_2), 6.96 (d, 1H, $J = 7.40$ Hz, Ar–H), 7.17 (s, 1H, Py–H), 7.34 (t, 1H, $J = 7.40$ Hz, Ar–H), 7.42–7.45 (m, 1H, Ar–H), 7.48–7.55 (m, 4H, Ar–H), 7.60–7.64 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.9, 87.8, 112.9, 113.7, 114.8, 119.9, 127.4, 127.8, 129.2, 129.6, 130.5, 139.0,

141.2, 154.7, 156.3, 161.2, 161.9; MS (EI, 70 eV): *m/z* $M^{+\cdot}$, 301; Anal. Calcd. for $C_{19}H_{15}N_3O$: C 75.73, H 5.02, N 13.94 %. Found: C 75.65, H 4.98, N 13.89 %.

Results and discussion

In our preliminary studies, we have investigated the multi-component reaction of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1.5 mmol) using various catalysts such as CuF_2, TlF_2, ZnF_2, NiF_2, TiF_4, and $Bu_4N^+Br^-$ in ethanol and obtained the product in 5 h. The $Bu_4N^+Br^-$ (TBAB) was found to be the best catalyst at 10 mol% concentration furnishing 86 % yield of the product with good purity. The details of the catalysts screened are set out in Table 1.

In order to have a choice of solvent, the same reaction was carried out in different solvents using TBAB as catalyst at specific time intervals, with water being found to be the best solvent which gave high yield of 92 % of product **5a**. The details of solvents screened are outlined in Table 2.

After having identified the suitable catalyst and suitable solvent, the reaction was performed with substituted aryl aldehydes, methyl ketones, malononitrile, and ammonium acetate to investigate the role of substituents on the rate of reaction and yield of products and to establish the conditions. In order to further improve the scope of the reaction, the same reaction was repeated with aliphatic aldehyde such as *n*-heptanal and alternatively with methyl isobutyl ketone; however, this could not

Table 1 Screening of various catalysts in ethanol for preparation of 2-amino nicotinonitriles

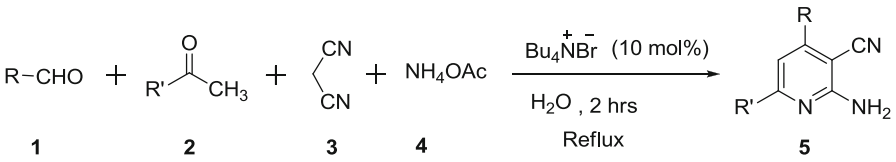
Entry	Catalyst	Amount (mol%)	Time (h)	Yield[a] (%) (**5a**)
1.	None	–	5.0	No reaction
2.	CuF_2	10	5.0	21
3.	TlF_2	10	5.0	39
4.	ZnF_2	10	5.0	46
5.	NiF_2	10	5.0	55
6.	TiF_4	10	5.0	68
7.	$Bu_4N^+Br^-$	10	5.0	86

[a] Isolated yields

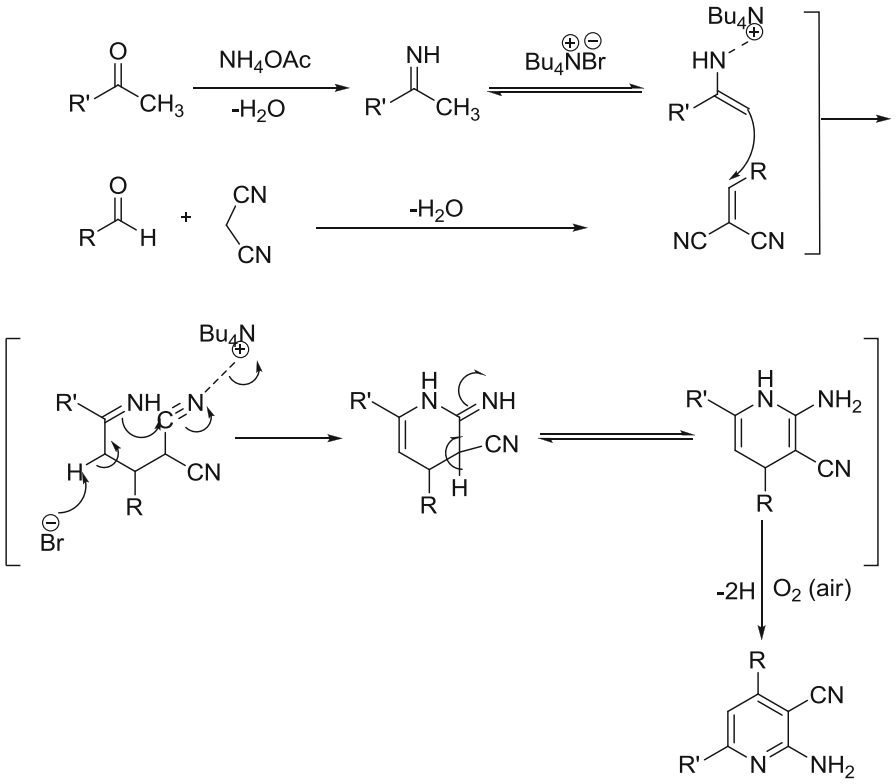
Table 2 Screening of various solvents using TBABr as catalyst for preparation of 2-amino nicotinonitriles

Entry	Solvent	Time (h)	Yield[a] (%) (**5a**)
1.	CH_3CN	5	30
2.	THF	5	43
3.	CH_3OH	5	75
4.	C_2H_5OH	5	86
5.	$(CH_3)_2CHOH$	5	68
6.	$(CH_3)_3COH$	5	79
7.	H_2O	2	92

[a] Isolated yields



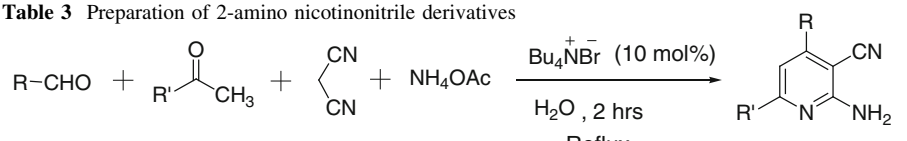
Scheme 1 Preparation of 2-amino nicotinonitrile derivatives



Scheme 2 Reaction pathway for the formation of 2-amino nicotinonitrile derivatives

give the product. This may be attributed to the reduced stability of aliphatic imine and the product from aliphatic aldehyde–malononitrile. The details of the reaction and the possible mechanism are outlined in Schemes 1 and 2, respectively. The sequence of the reaction is mainly the formation of imine by the reaction of methyl ketone with ammonium acetate followed by the activation of imine with the catalyst. The activated imine generated in situ was reacted with arylidene malononitrile, formed from aryl aldehyde and malononitrile, followed by cyclization, isomerization, and by aerial oxidation resulting in product **5**. The yields of the products are shown in Table 3.

Table 3 Preparation of 2-amino nicotinonitrile derivatives



1 **2** **3** **4** **5**

Compound No	R	R	Yield[a] (%)
5a	Ph	Ph	92
5b	4-ClC_6H_4	Ph	88
5c	4-$CH_3C_6H_4$	Ph	76
5d	4-FC_6H_4	Ph	89
5e	4-$OCH_3C_6H_4$	Ph	73
5f	2-$CF_3C_6H_4$	Ph	93
5g	2-F, 4-F, 6-FC_6H_2	Ph	72
5h	4-$(CH_3)_2$-CHC_6H_4	Ph	78
5i		Ph	87
5j		Ph	90
5k	Ph	4-FC_6H_4	84
5l	Ph	4-$OCH_3C_6H_4$	79
5m	Ph	4-BrC_6H_4	81
5n	Ph	4-OHC_6H_4	73
5o	Ph	3-$OCH_3C_6H_4$	75

All products were characterized by ^{1}H NMR, mass, IR, and ^{13}C spectral data

[a] Isolated yields

Conclusion

In conclusion, an efficient and green process has been developed for the synthesis of 2-amino nicotinonitrile derivatives via one-pot condensation of aryl aldehydes, ketones, malononitrile, and ammonium acetate using TBAB as catalyst in aqueous medium, and will be useful for the synthesis of a wide range of compounds.

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