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Potassium *tert*-Butoxide-Promoted Synthesis of 1-Aminoisoquinolines from 2-Methylbenzonitriles and Benzonitriles under Catalyst-Free Conditions

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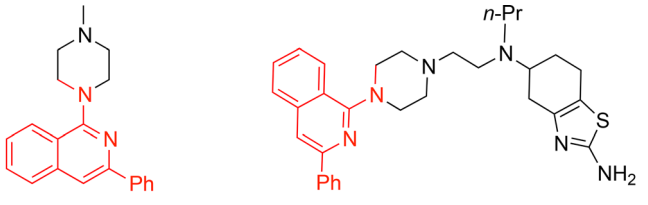
Abstract: Herein a practical and efficient protocol for preparing a range of aminoisoquinolines is reported. Various aminoisoquinolines were prepared in moderate to good yields from the corresponding 2-methylbenzonitriles and benzonitriles upon treatment with potassium *tert*-butoxide.

Keywords: 1-aminoisoquinolines; base-promoted reaction; benzonitriles; cascade reaction; metal-free conditions

The derivatives of amino-substituted isoquinolines are prevalent in natural products and functional materials. Additionally it has been reported that several examples in this family of compounds have been found to have activity in cancer,[1] tumor,[2] malaria[3] and Parkinson's disease cell lines (Scheme 1).[4] The isoquinoline backbone is apparent also in the skeleton of chiral ligands for asymmetric catalysts.[5] Given the important properties outlined, numerous preparation methods have been developed for aminoisoquinolines. A general protocol to obtain 1-aminoisoquinolines is *via* the direct amination of 1-haloisoquinolines.[6] In recent years, some alternative procedures have also been used. These methods include the domino electrophilic cyclization of 2-alkynylbenzamides or 2-alkynylbenzaldoximes[7,8] and the oxidative annulation of benzamidine derivatives with internal alkynes catalyzed by either rhodium, ruthenium or cobalt catalysts.[9] These newly developed procedures have a wider substrate scope as well as the benefit of needing mild reaction conditions. However, the necessity of either transition metal catalysts or preparing prefunctionalized substrates still remains. The involvement of transition metal catalysts not only raises the cost but also brings potential transition metal contamination into the heterocyclic products, which can be an issue with subsequent bioassay studies. In an effort to eliminate the above impediments and based on our continuing interest in developing new transition metal-free synthetic methodologies,[10] we intended to develop a simpler transition metal-free procedure for the preparation of 1-aminoisoquinolines from commercially available substrates. With *t*-BuOK as the only promoter, moderate to good yields of the desired aminoisoquinolines were achieved from the corresponding *o*-toluenenitriles and benzonitriles in a simple one-pot manner.



antitumor agent

potent *in vivo* activity in a Parkinson's disease animal model

Scheme 1. Selected examples of biologically active 1-aminoisoquinolines.

Initially, a variety of solvents was tested with *o*-toluenenitrile and benzonitrile as the model substrates, in the presence of *t*-BuOK at 110 °C for 16 h (Table 1, entries 1–4). Encouragingly, 7% and 42% of the 3-phenylisoquinolin-1-amine were obtained in DMAc and toluene, respectively (Table 1, entries 1 and 4). Further reactions replacing *t*-BuOK with various inorganic bases only resulted in no desired product formation (Table 1, entries 5–10). To our delight the desired product was isolated in 81% yield when 2 equivalents of *t*-BuOK were employed (Table 1, entry 11) however further equivalents of *t*-BuOK were ineffective

Table 1. Optimization of the reaction conditions in the production of **3a**.[a]

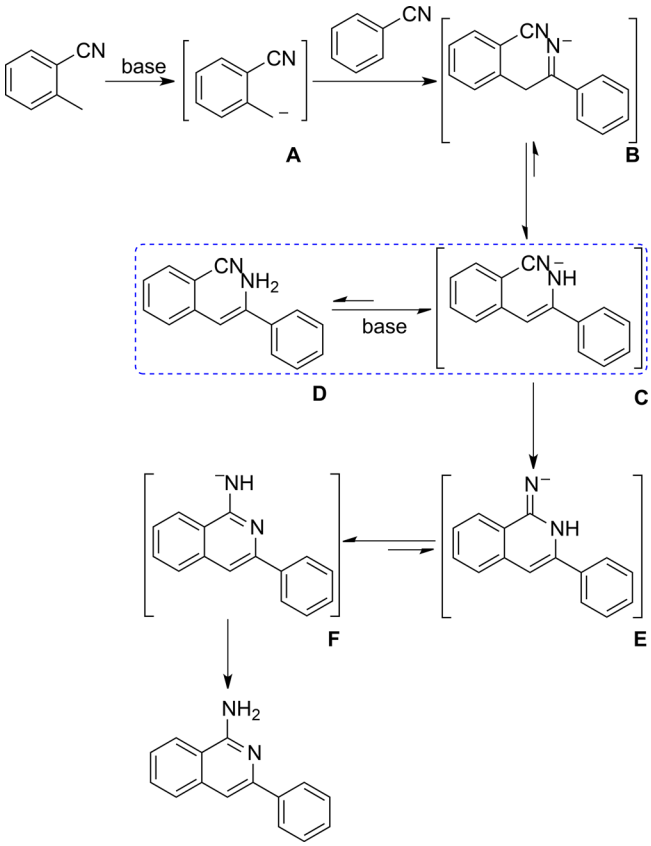
Entry	Base (equiv.)	Solvent	T [°C]	Yield [%]
1	*t*-BuOK (1)	DMAc	110	7
2	*t*-BuOK (1)	DMF	110	10
3	*t*-BuOK (1)	DMSO	110	4
4	*t*-BuOK (1)	toluene	110	42
5	*t*-BuOLi (2)	toluene	110	0
6	*t*-BuONa (2)	toluene	110	0
7	K_2CO_3 (2)	toluene	110	0
8	NaOAc (2)	toluene	110	0
9	NaOMe (2)	toluene	110	0
10	KOH (2)	toluene	110	0
11	*t*-BuOK (2)	toluene	110	81
12	*t*-BuOK (3)	toluene	110	75
13	*t*-BuOK (2)	toluene	90	47
14	*t*-BuOK (2)	toluene	130	73
15	*t*-BuOK (2)	toluene	110	66[b]
16	*t*-BuOK (2)	toluene	110	80[c]

[a] All reactions were performed under air, *o*-toluenenitrile (1 mmol), benzonitrile (1.5 equiv.), base (2 equiv.), solvent (1 mL), 80 °C, 16 h, isolated yield.
[b] Benzonitrile (1.0 equiv.).
[c] Benzonitrile (2.0 equiv.).

(Table 1, entry 12). Modifying either the reaction temperature or the ratio between benzonitrile and *o*-toluenenitrile did not further improve the yield (Table 1, entries 13–16).

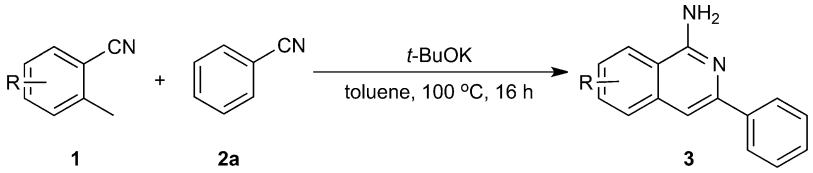
Following optimization of the reaction conditions, an investigation of the substrate scope was conducted (Table 2). When a methyl group was introduced into the 3- or 6-positon of *o*-toluenenitrile (Table 2, entries 2 and 3), a distinct substituent effect was observed where a moderate yield was first obtained for 2,6-dimethylbenzonitrile (Table 2, entry 2). Alternatively when the two methyl groups were adjacent to one another (Table 2, entry 3), the yield dramatically decreased. That may be due to the steric hindrance or the decreased activity of the methyl group. Halogen-derived substrates remained intact in the strong basic conditions and gave the corresponding products in good to moderate yields (Table 1, entries 5–9). Here, the obtained products could be used for a plethora of different reactions, in particular transformations through transition metal-catalyzed coupling reactions. In these cases, the decreased yields can be explained by the reaction of the halogens with *t*-BuOK to give the corresponding *tert*-butoxy ethers. As expected, the reaction between a primary amine and a benzonitrile occurred when both were present in the reaction mixture under our reaction conditions (Table 2, entry 10). For the strong electron-withdrawing groups like nitro and trifluoromethyl, no desired products could be detected (Table 2, entries 11 and 12). 2-Ethylbenzonitrile was investigated, but only trace amounts of the corresponding product were detected. This might due to the decreased reactivity resulting from the increased carbon chain length.

Afterwards, numerous substituted benzonitriles were tested with *o*-toluenenitriles under the standard reaction conditions (Table 3). Chloro-substituted benzonitriles could be used as the reaction partner and in these cases the corresponding products were isolated in moderate yields (Table 3, entries 1–3). However, for the fluoro-substituted starting materials such as 2-fluorobenzonitrile and 4-fluorobenzonitrile, only trace amounts of the target products could be detected by GC-MS. In these cases it was discovered that the corresponding *tert*-butoxy ether and amide were present. The same scenario was observed for Br-, I-, and NO_2-substituted benzonitriles, as these groups are good leaving groups in nucleophilic substitution processes. Benzonitriles with electron-donating groups afforded the corresponding products in moderate to good yields. In the case of methyl-substituted benzonitriles, *o*-methyl-derived compound **3r** gave the product with

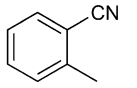
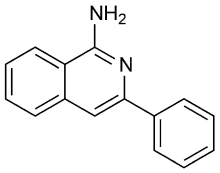
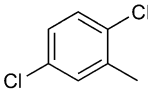
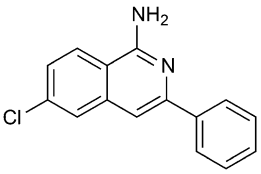
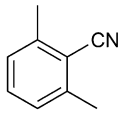
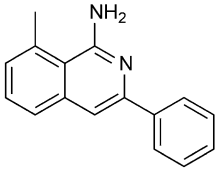
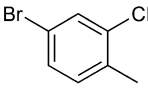
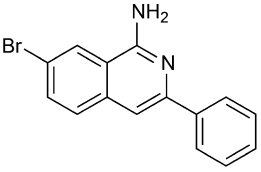
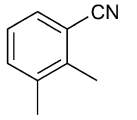
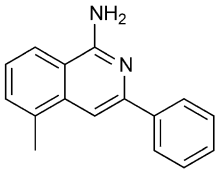
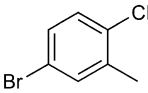
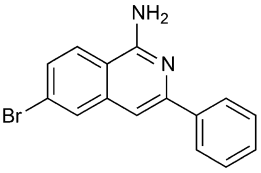
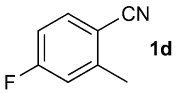
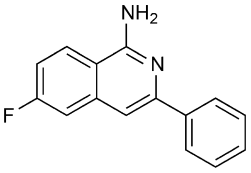
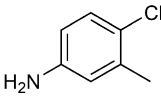
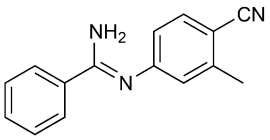
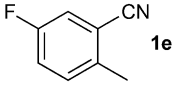
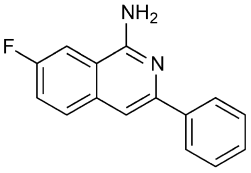
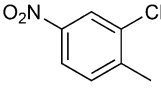
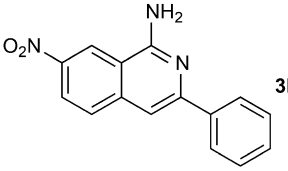
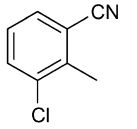
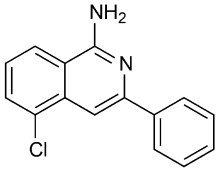
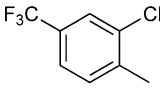
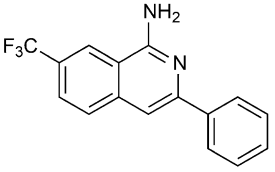


Scheme 2. A proposed mechanism for the synthesis of aminoisoquinolines.

Table 2. Synthesis of aminoisoquinolines from benzonitrile and substituted *o*-toluenenitriles.[a]



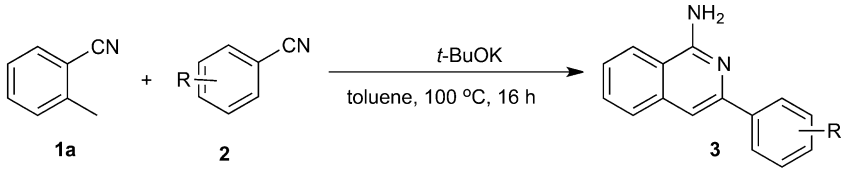
1 2a 3

Entry	Substrate	Product	Yield [%][b]	Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **3a**	81	7	 **1g**	 **3g**	55
2	 **1b**	 **3b**	62	8	 **1h**	 **3h**	36
3	 **1c**	 **3c**	28	9	 **1i**	 **3i**	50
4	 **1d**	 **3d**	35	10	 **1j**	 **3j**	62
5	 **1e**	 **3e**	40	11	 **1k**	 **3k**	0
6	 **1f**	 **3f**	76	12	 **1l**	 **3l**	0

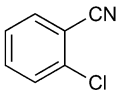
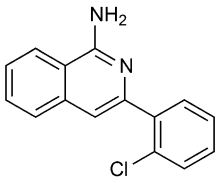
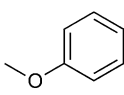
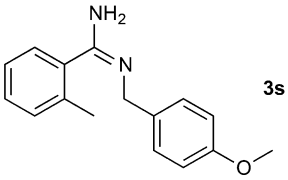
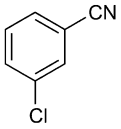
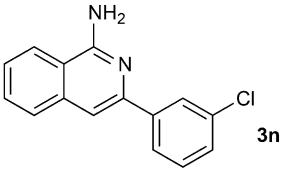
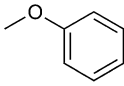
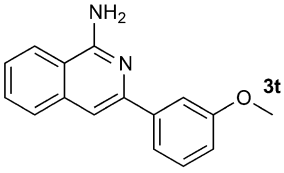
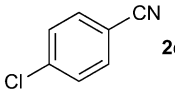
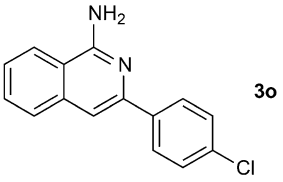
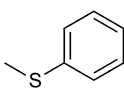
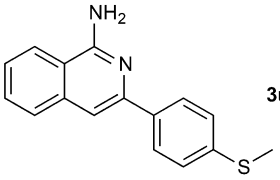
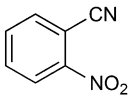
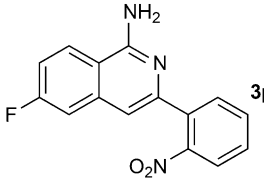
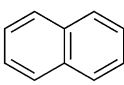
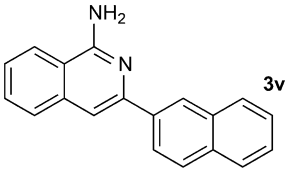
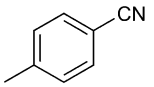
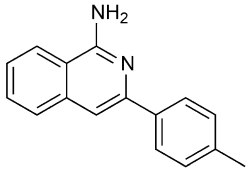
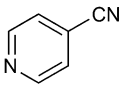
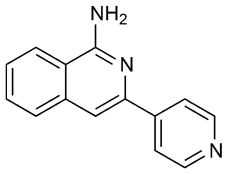
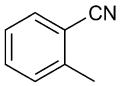
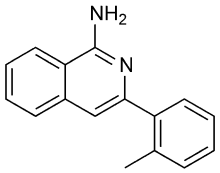
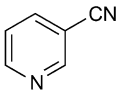
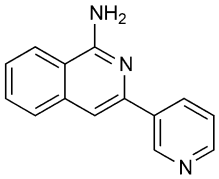
[a] *Reaction conditions:* benzonitrile (1 mmol), *o*-toluenenitriles (1.5 equiv.), *t*-BuOK (2.0 equiv.), 110 °C, 16 h, isolated yield.

higher yield compared with the *p*-methyl-substituted case (Table 3, entries 5 and 6). It also should be mentioned that the undesired homo-coupled product between two molecules of *o*-toluenenitrile could be detected in all cases during the optimization process. However, the amount of homo-coupled product is much less pronounced in the presence of benzonitrile. Thus, using an excess of *o*-toluenenitrile in our protocol is necessary to avoid this undesired product. Through a highly concerted process, benzonitrile can quickly consume this intermediate and inhibit the generation of the undesired homo-coupled product. Good yields of the desired 1-aminoisoquinolines can be achieved from methoxy- or methylthio-substituted

Table 3. Synthesis aminoisoquinolines from *o*-toluenenitrile and benzonitriles.[a]



1a 2 3

Entry	Substrate	Product	Yield [%][b]	Entry	Substrate	Product	Yield [%][b]
1	 **2b**	 **3m**	46	7	 **2k**	 **3s**	80
2	 **2c**	 **3n**	54	8	 **2l**	 **3t**	55
3	 **2d**	 **3o**	51	9	 **2l**	 **3u**	72
4	 **2e**	 **3p**	0	10	 **2m**	 **3v**	47
5	 **2f**	 **3q**	57	11	 **2n**	 **3w**	54
6	 **2g**	 **3r**	81	12	 **2o**	 **3x**	49

[a] *Reaction conditions:* benzonitriles (1 mmol), *o*-toluenenitrile (1.5 equiv.), *t*-BuOK (2.0 equiv.), 110 °C, 16 h, isolated yield.

benzonitriles without any further optimization (Table 3, entries 7–9). Moreover, the protocol can be applied with fused aromatic and heteroaromatic nitriles. The corresponding products **3v–3x** were isolated in moderate yields (Table 3, entries 10–12). Unfortunately, no reaction occurred when aliphatic nitriles, such as acetonitrile, cyclohexanecarbonitrile, isobutyronitrile and 2-phenylacetonitrile were used as starting materials.

A possible reaction pathway has been derived for this new reaction process (Scheme 2). The reaction is proposed to begin with the generation of carbanion

A, generated from *o*-toluenenitrile in the presence of *t*-BuOK which will give intermediate **B** after reacting with benzonitrile. Intermediate **C** was considered as a more stable resonance structure of intermediate **B**. It should be noted that intermediate **C** can be used mechanistically to arrive at the protonated product **D** in the presence of a proton source. This process is reversible in the presence of base. Then nucleophilic addition of the nitrogen ion to the cyano of the *o*-toluenenitrile occurs and generates intermediate **E**, which can give the final product after rearrangement and protonation.

In conclusion, a practical and efficient methodology for the synthesis of 1-aminoisoquinolines has been developed. Moderate to good yields of the desired products can be obtained from the corresponding commercially available *o*-toluenenitriles and benzonitriles. The strong base *t*-BuOK was used as the only reaction promoter and no addition of any transition metal catalyst was required.

Experimental Section

General Procedure

Under an open atmosphere, a 25-mL pressure tube was charged with 1 mmol of *o*-toluenenitrile, 1.5 mmol of benzonitrile, 2 mmol of *t*-BuOK and 1 mL toluene. Then the tube was sealed and the mixture was heated under stirring at 110 °C for 16 h. After this time the mixture was cooled to room temperature and the mixture was concentrated under vacuum. The pure products were obtained after purification by column chromatography (ethyl acetate-pentane = 1:4).

3-Phenylisoquinolin-1-amine (3a): yield: 178 mg (81%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 8.19–7.99 (m, 2H), 7.82–7.71 (m, 2H), 7.61 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.56–7.35 (m, 5H), 5.35 (s, 2H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 155.92, 149.49, 139.83, 138.12, 130.16, 128.51, 128.12, 127.45, 126.78, 125.82, 122.52, 116.87, 108.80; GC-MS (EI, 70 eV): *m*/*z* (%) = 220 (M^+, 100), 221 (17), 219 (30).

8-Methyl-3-phenylisoquinolin-1-amine (3b): yield: 145 mg (62%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.11–8.04 (m, 2H), 7.60–7.53 (m, 1H), 7.52–7.45 (m, 2H), 7.44 (s, 1H), 7.43–7.36 (m, 2H), 7.18 (dt, J = 7.1, 1.1 Hz, 1H), 5.49 (s, 1H), 2.91 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 157.13, 148.69, 140.39, 139.45, 134.24, 129.45, 128.98, 128.44, 128.06, 126.61, 126.08, 117.69, 109.46, 24.45; GC-MS (EI, 70 eV): *m*/*z* (%) = 234 (M^+, 100), 235 (17), 233 (46), 77 (14).

5-Methyl-3-phenylisoquinolin-1-amine (3c): yield: 66 mg (28%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 8.18–8.02 (m, 2H), 7.64 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.56–7.28 (m, 5H), 5.32 (s, 2H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 156.46, 149.52, 140.27, 137.39, 134.31, 130.61, 128.51, 128.08, 126.89, 125.26, 120.46, 116.67, 105.45, 19.30; GC-MS (EI, 70 eV): *m*/*z* (%) = 234 (M^+, 100), 235 (18), 233 (16), 104 (14), 195 (12), 168 (17), 167 (32).

6-Fluoro-3-phenylisoquinolin-1-amine (3d): yield: 83 mg (35%); light yellow solid); ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.10–7.97 (m, 1H), 7.83–7.74 (m, 0H), 7.47 (tt, J = 6.9, 0.9 Hz, 1H), 7.43–7.32 (m, 1H), 7.18 (ddd, J = 9.0, 8.3, 2.6 Hz, 0H), 5.27 (s, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 163.43 (d, J = 250.7 Hz), 155.78, 150.85, 140.09 (d, J = 10.3 Hz), 139.45, 128.58, 128.47, 126.86, 125.49 (d, J = 9.8 Hz), 115.58 (d, J = 25.2 Hz), 113.87, 110.93 (d, J = 20.7 Hz), 108.52 (d, J = 4.4 Hz); GC-MS (EI, 70 eV): *m*/*z* (%) = 238 (M^+, 100), 239 (16), 237 (29), 212 (11), 195 (12), 168 (17), 167 (32).

7-Fluoro-3-phenylisoquinolin-1-amine (3e): yield: 95 mg (40%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.12–7.97 (m, 2H), 7.75 (ddd, J = 9.9, 4.6, 2.0 Hz, 1H), 7.57–7.33 (m, 6H), 5.21 (s, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 160.25 (d, J = 247.1 Hz), 161.84–161.03 (m), 159.43–157.71 (m), 155.40 (d, J = 4.9 Hz), 149.05 (d, J = 2.7 Hz), 139.56, 135.11, 129.89 (d, J = 8.3 Hz), 128.57, 128.22, 126.69, 120.22 (d, J = 24.6 Hz), 117.28 (d, J = 7.7 Hz), 108.43 (d, J = 1.6 Hz), 106.82 (d, J = 21.5 Hz); GC-MS (EI, 70 eV): *m*/*z* (%) = 238 (M^+, 100), 239 (17), 237 (26), 219 (13), 195 (12), 218 (25), 193 (13), 190 (17), 116 (10), 104 (11), 77 (10).

5-Chloro-3-phenylisoquinolin-1-amine (3f): yield: 193 mg (76%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.17–8.04 (m, 2H), 7.85 (d, J = 1.0 Hz, 1H), 7.70 (ddd, J = 8.5, 7.4, 1.0 Hz, 2H), 7.53–7.45 (m, 2H), 7.43–7.38 (m, 1H), 7.35 (dd, J = 8.3, 7.5 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 156.03, 150.85, 139.53, 136.11, 131.99, 130.35, 128.60, 126.99, 125.41, 121.49, 117.86, 105.09; GC-MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 100), 256 (33), 255 (18), 219 (20), 218 (12), 190 (11), 96 (10).

6-Chloro-3-phenylisoquinolin-1-amine (3g): yield: 140 mg (55%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 8.06–7.99 (m, 2H), 7.71–7.68 (m, 1H), 7.65 (dt, J = 8.8, 0.7 Hz, 1H), 7.52–7.44 (m, 2H), 7.43–7.36 (m, 1H), 7.36–7.30 (m, 2H), 5.36 (s, 2H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 155.83, 150.81, 139.35, 139.17, 136.26, 128.56, 128.47, 126.82, 126.41, 126.17, 124.27, 114.96, 107.81; GC-MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 100), 256 (33), 255 (21), 218 (16), 193 (12), 190 (11), 109 (11), 95 (14), 77 (10).

7-Bromo-3-phenylisoquinolin-1-amine (3h): yield: 107 mg (36%); light yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.08–7.97 (m, 2H), 7.90 (d, J = 2.0 Hz, 1H), 7.62 (dt, J = 8.8, 0.7 Hz, 1H), 7.54–7.43 (m, 3H), 7.42–7.38 (m, 1H), 7.36 (d, J = 0.9 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 155.86, 150.85, 139.57, 139.37, 129.56, 129.05, 128.59, 128.51, 126.83, 124.84, 124.29, 115.24, 107.73; GC-MS (EI, 70 eV): *m*/*z* (%) = 300 (M^+, 100), 301 (17), 299 (26), 298 (98), 218 (25), 218 (25), 193 (10).

6-Bromo-3-phenylisoquinolin-1-amine (3i): yield: 149 mg (50%); brown solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.11–7.98 (m, 2H), 7.92 (d, J = 1.9 Hz, 1H), 7.66 (dt, J = 8.8, 0.7 Hz, 1H), 7.53 (dd, J = 8.8, 1.9 Hz,1H), 7.50–7.43 (m, 2H), 7.42–7.35 (m, 2H), 5.27 (s, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 155.82, 150.82, 139.61, 139.31, 129.62, 129.14, 128.62, 128.56, 126.84, 124.92, 124.33, 115.28, 107.78; GC-MS (EI, 70 eV): *m*/*z* (%) = 298 (M^+, 100), 301 (17), 300 (98), 219 (13), 195 (12), 218 (25), 193 (13), 190 (17), 116 (10), 104 (11), 77 (10).

(*Z*)-*N*′-(3-Cyano-4-methylphenyl)benzimidamide (3j): yield: 146 mg (62%); white solid); ^{1}H NMR (300 MHz, chloroform-*d*): δ = 7.88–7.74 (m, 2H), 7.53–7.39 (m, 3H),

7.34–7.24 (m, 1H), 7.19 (d, J=2.2 Hz, 1H), 7.10 (dd, J=8.1, 2.3 Hz, 1H), 4.84 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): δ=136.15, 131.46, 130.92, 128.63, 126.77 (d, J=2.6 Hz), 125.15, 118.13, 113.44, 19.76; GC-MS (EI, 70 eV): m/z (%)=235 (M^+, 100), 236 (16), 234 (80), 219 (35), 132 (52), 131 (29), 116 (15), 105 (13), 104 (92), 103 (16), 89 (36), 77 (53), 76 (11), 63 (11), 51 (21), 32 (11).

3-(2-Chlorophenyl)isoquinolin-1-amine (3m): yield: 117 mg (46%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=7.82 (dd, J=8.3, 1.0 Hz, 1H), 7.78–7.74 (m, 1H), 7.68–7.60 (m, 2H), 7.56–7.45 (m, 2H), 7.41–7.27 (m, 3H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.72, 148.61, 139.63, 137.42, 132.40, 131.49, 130.29, 130.04, 128.91, 127.50, 126.75, 126.32, 122.50, 116.74, 113.15; GC-MS (EI, 70 eV): m/z (%)=254 (M^+, 100), 266 (30), 265 (18), 220 (18), 219 (63), 218 (21), 190 (14).

3-(3-Chlorophenyl)isoquinolin-1-amine (3n): yield: 137 mg (54%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.18–8.04 (m, 1H), 7.93 (dt, J=7.3, 1.7 Hz, 1H), 7.83–7.72 (m, 2H), 7.63 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.54–7.44 (m, 2H), 7.44–7.28 (m, 2H), 5.28 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.90, 147.95, 141.65, 138.04, 134.58, 130.38, 129.72, 128.08, 127.62, 126.95, 126.27, 124.75, 122.55, 117.16, 109.12; GC-MS (EI, 70 eV): m/z (%)=254 (M^+, 100), 256 (34), 255 (21), 253 (10), 218 (18).

3-(4-Chlorophenyl)isoquinolin-1-amine (3o): yield: 130 mg (51%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.06–7.95 (m, 2H), 7.85–7.73 (m, 2H), 7.63 (ddd, J=8.2, 6.9, 1.2 Hz, 1H), 7.55–7.38 (m, 4H), 5.30 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.86, 148.08, 138.09, 134.15, 130.47, 128.69, 128.02, 127.58, 126.20, 122.59, 116.99, 108.79; GC-MS (EI, 70 eV): m/z (%)=254 (M^+, 100), 256 (33), 255 (20), 253 (11), 218 (20).

3-(*p*-Tolyl)isoquinolin-1-amine (3q): yield: 133 mg (57%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.10–7.91 (m, 2H), 7.85–7.69 (m, 2H), 7.60 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.51–7.35 (m, 2H), 7.35–7.20 (m, 2H), 5.28 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.81, 149.56, 138.23, 137.99, 137.01, 130.11, 129.25, 127.41, 126.62, 125.64, 122.53, 116.78, 108.34, 21.24; GC-MS (EI, 70 eV): m/z (%)=234 (M^+, 100), 235 (15).

3-(*o*-Tolyl)isoquinolin-1-amine (3r): yield: 190 mg (81%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=7.89–7.78 (m, 1H), 7.73 (ddt, J=8.3, 1.1, 0.5 Hz, 1H), 7.63 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.58–7.40 (m, 2H), 7.33–7.27 (m, 3H), 7.12 (d, J=0.9 Hz, 1H), 5.38 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.46, 151.86, 140.77, 137.79, 135.96, 130.54, 130.20, 129.57, 127.78, 127.25, 125.88, 125.69, 122.54, 116.36, 112.08, 20.39; GC-MS (EI, 70 eV): m/z (%)=233 (M^+, 100), 234 (53), 216 (20), 116 (18).

3-(4-Methoxyphenyl)isoquinolin-1-amine (3s): yield: 200 mg (80%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.11–7.97 (m, 2H), 7.82–7.68 (m, 2H), 7.59 (ddd, J=8.2, 6.9, 1.2 Hz, 1H), 7.50–7.37 (m, 2H), 7.08–6.87 (m, 2H), 5.25 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): δ=159.81, 155.77, 149.25, 138.31, 132.48, 130.12, 127.97, 127.33, 125.48, 122.54, 116.57, 113.91, 107.76, 55.31; GC-MS (EI, 70 eV): m/z (%)=250 (M^+, 100), 251 (16), 235 (25), 207 (23).

3-(3-Methoxyphenyl)isoquinolin-1-amine (3t): yield: 137 mg (55%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=7.83–7.73 (m, 2H), 7.71–7.56 (m, 3H), 7.48 (dd, J=5.2, 1.0 Hz, 1H), 7.46–7.33 (m, 2H), 6.95 (ddd, J=8.2, 2.6, 1.0 Hz, 1H), 5.34 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, chloroform-d): δ=159.98, 155.96, 149.39, 141.48, 138.22, 130.29, 129.59, 127.61, 126.01, 122.64, 119.31, 117.08, 114.24, 112.14, 109.07, 55.40; GC-MS (EI, 70 eV): m/z (%)=250 (M^+, 100), 251 (18), 249 (77), 221 (13), 220 (36), 219 (27), 205 (11), 204 (12), 190 (11), 220 (36), 219 (27), 205 (11).

3-[4-(Methylthio)phenyl]isoquinolin-1-amine (3u): yield: 192 mg (72%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.08–7.91 (m, 2H), 7.82–7.69 (m, 2H), 7.59 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.49–7.38 (m, 2H), 7.38–7.29 (m, 2H), 5.32 (s, 2H), 2.53 (s, 1H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.86, 148.79, 138.52, 138.15, 136.57, 130.20, 127.41, 127.07, 126.46, 125.77, 122.55, 116.84, 108.24, 15.72.

3-(Naphthalen-2-yl)isoquinolin-1-amine (3v): yield: 127 mg (47%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.60 (d, J=1.7 Hz, 1H), 8.19 (dd, J=8.6, 1.8 Hz, 1H), 8.01–7.76 (m, 5H), 7.70–7.58 (m, 2H), 7.48 (ddd, J=9.7, 6.1, 1.6 Hz, 3H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=155.92, 149.20, 138.26, 136.97, 133.64, 133.36, 130.36, 128.65, 128.13, 127.60, 126.05 (d, J=3.1 Hz), 125.97, 124.68, 122.62, 117.04, 109.28; GC-MS (EI, 70 eV): m/z (%)=270 (M^+, 100), 271 (23), 269 (27).

3-(Pyridin-4-yl)isoquinolin-1-amine (3w): yield: 119 mg (54%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=8.85–8.57 (m, 2H), 8.08–7.89 (m, 2H), 7.90–7.75 (m, 2H), 7.66 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.61–7.42 (m, 2H), 5.41 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=156.20, 149.93, 147.04, 146.35, 137.71, 130.59, 127.83, 126.94, 122.64, 121.00, 117.78, 110.00; GC-MS (EI, 70 eV): m/z (%)=221 (M^+, 100), 222 (16), 220 (30), 193 (10).

3-(Pyridin-3-yl)isoquinolin-1-amine (3x): yield: 108 mg (49%); light yellow solid; ^{1}H NMR (300 MHz, chloroform-d): δ=9.77–8.95 (m, 1H), 8.60 (dd, J=4.8, 1.7 Hz, 1H), 8.36 (dt, J=8.0, 2.0 Hz, 1H), 7.98–7.72 (m, 2H), 7.65 (ddd, J=8.2, 6.9, 1.1 Hz, 1H), 7.55–7.44 (m, 2H), 7.41–7.31 (m, 1H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, chloroform-d): δ=156.22, 149.10, 148.28, 146.74, 138.01, 135.33, 134.19, 130.57, 127.67, 126.51, 123.45, 122.66, 117.25, 109.26; GC-MS (EI, 70 eV): m/z (%)=221 (M^+, 100), 222 (16), 220 (30), 193 (10).

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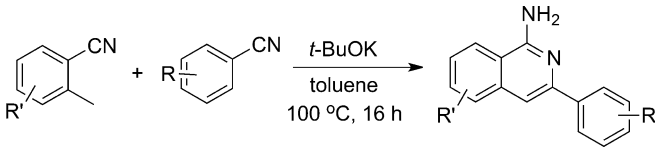
8 Potassium *tert*-Butoxide-Promoted Synthesis of 1-Aminoisoquinolines from 2-Methylbenzonitriles and Benzonitriles under Catalyst-Free Conditions



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