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An efficient base-mediated intramolecular condensation of 2-(disubstituted amino)-benzonitriles to 3-aminoindoles

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ABSTRACT

A concise and versatile method for the preparation of 3-aminoindoles from 2-(disubstituted amino)-benzonitriles is described, and in situ functionalizations were illustrated.

The indole nucleus is one of the most ubiquitous scaffolds found in natural products, pharmaceuticals, functional materials, and agrochemicals.[1] The structural diversity and biological importance of indoles have made them attractive targets for synthesis over years.[2] 3-Substituted indoles, in particular, are important building blocks for the synthesis of various biologically active molecules. Consequently, there is a continuing interest in the development of improved methods for the synthesis of these molecules.[3] The synthesis of the indoles from nonindolic starting materials has received considerable attention, and numerous approaches were developed. The most versatile and widely applied reaction is the Fischer indole synthesis starting from phenylhydrazine with ketones or aldehydes.[4]

3-Aminoindoles are unique intermediates in the substituted indole synthesis, and have been produced by hydrolysis of the corresponding isocyanates,[5] by reduction of the salts of isonitrosoindoles obtained from indoles,[6] or by the Fischer cyclization of the phenylhydrazines of ω-(*N*-acylamino)acetophenones.[7] The 3-aminoindole formation by cyclization under basic conditions also remains challenging.[8] In connection with these studies, we envisioned that the reaction between acidic CH_2 of *N*-benzylic group in *ortho*-position and nitrile would lead to the formation of 3-aminoindoles in a single step (Scheme 1). In this Letter, we wish to report a new facile and efficient method for the synthesis of 3-amino-2-phenylindoles by direct cyclization of 2-(disubstituted amino)-benzonitriles in the presence of either sodium hydride or potassium *t*-butoxide as a base.

The 2-(disubstituted amino)-benzonitriles (**3a–d**) were readily prepared by reductive amination of 1-aminobenzonitrile **1** with benzaldehyde using $NaBH_4$, followed by alkylation with the appropriate bromides (or iodides) in the presence of NaH. 2-(Benzyl-phenyl-amino)-benzonitrile **3e** was readily prepared from the corresponding benzoic acid via the benzamide by a literature procedure.[9,10]

First we investigated the optimal combination between the base and the solvent for the cyclization of 2-(disubstituted amino)-benzonitriles 3 (Table 1). We were delighted to find that the treatment of precursors **3d** with NaH as a base in DMF at 80 °C produces 3-amino-2-phenylindoles **4d** (entry 5). We also found that *t*-BuOK serves as an attractive alternative to NaH (entry 7) when the reaction was carried out in benzene under reflux. The disubstituted amino-benzonitrile **3d** was converted cleanly within 1 h to **5d** after subsequent treatment of Ac_2O. In contrast, neither K_2CO_3 nor Cs_2CO_3 was effective in any solvent we used (DMF, THF, and benzene). NaH was only effective in aprotic polar solvent such as DMF. Presumably, the solubility of a base in the solvents used plays an important role to mediate the cyclization.

Next, as shown in Table 2, we were conducted the base-mediated intramolecular condensation of various precursors **3** with NaH as a base in DMF at 80 °C produces 3-amino-2-phenyl-indoles **4**. After isolation, the free amino indoles **4** slowly decomposed to unidentified compounds at ambient temperature. Due to lack of stability of the intermediates **4**, they were directly converted to

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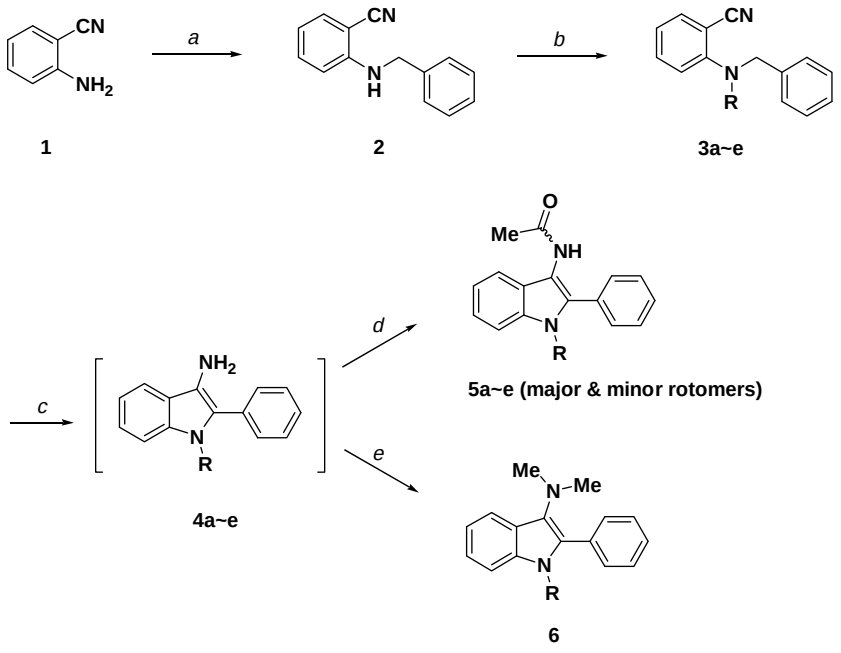


Scheme 1. Reagents and conditions: (a) PhCHO, $NaBH_3CN$/AcOH, 0–25 °C; (b) R-Br or R-I, NaH/DMF, 25 °C; (c) NaH/DMF, 80 °C, 30 min; (d) Ac_2O, 0–25 °C; (e) MeI, NaH/DMF, 25 °C.

the acylated amino indoles **5** (entries 1–5; 85–90%) by addition of Ac_2O. The acylated products **5** were identified as an inseparable mixture of rotamer **5**. The ratio of rotamers **5** was determined by ^1H NMR spectra. Similarly, intermediate 1-benzyl-3-aminoindole **4d** reacts with excess iodomethane in the presence of NaH in DMF at 25 °C afforded 3-dimethylaminoindole **6** as the sole alkylated product in 62% yield.[11]

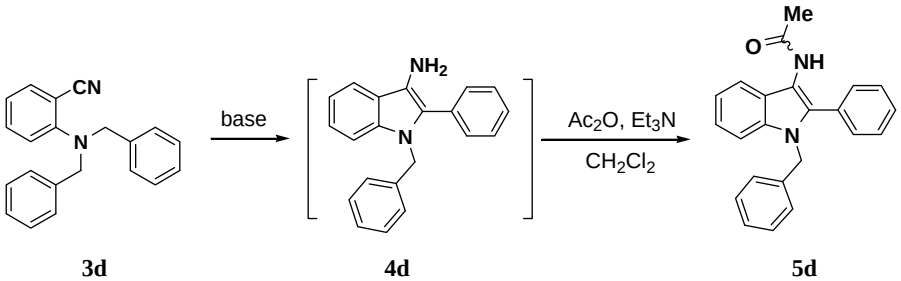
A mechanistic rationalization for this reaction sequence is illustrated in Scheme 2. We envisioned deprotonation of a disubstituted amino-benzonitrile **3** could be facilitated by the base at elevated temperature to generate anionic species A. Facile intramolecular condensation led to intermediate 1,2-dihydro-indol-3-

Table 2
The base-mediated cyclization of disubstituted amino-benzonitriles **3** via Scheme 1[11]

Entry	**R**	Benzonitrile	Product	Yield[a](%)	Ratio[b]
1	Me	**3a**	**5a**	85	1.4
2	Et	**3b**	**5b**	80	1.3
3	*n*-Pro	**3c**	**5c**	86	1.2
4	Bn	**3d**	**5d**	87	1.3
5	Ph	**3e**	**5e**	90	1.5
6	Bn	**3d**	**6**	62	—

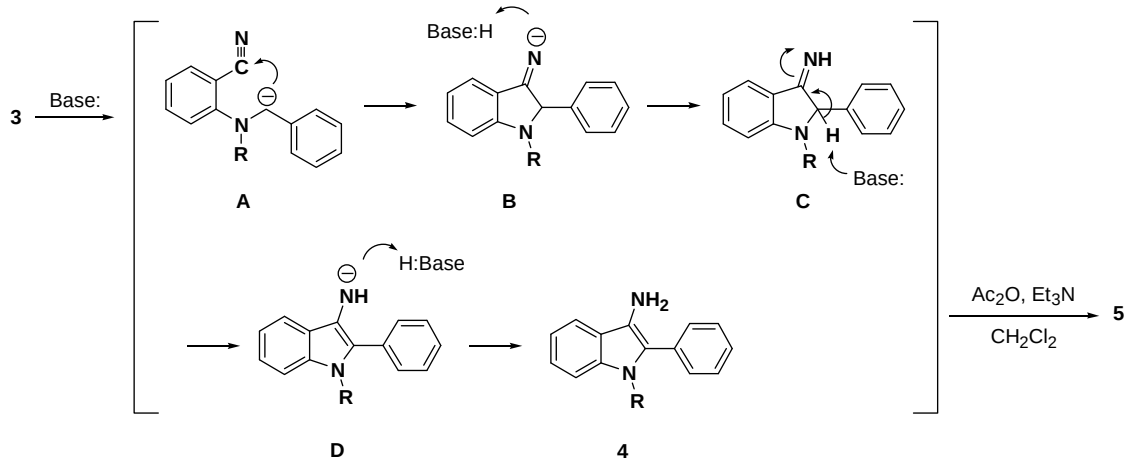
[a] Overall yield from compound **3**.
[b] Major to minor rotamer ratio.

Table 1
The cyclization of **3d** under various reaction conditions



Entry	Reaction conditions	Time	Isolated products	Yield[a] (%)	Ratio[b]
1	K_2CO_3/DMF, 80 °C	2 days	**3d**[c]	—	—
2	NaH/THF, reflux	1 day	3d	—	—
3	NaH/benzene, reflux	1 day	**3d**	—	—
4	NaH/DMF, rt	1 day	**3d**	—	—
5	NaH/DMF, 80 °C	40 min	**5d**	87	1.34
6	*t*-BuOK/DMF, 80 °C	30 min	Unknown P[d]+ **5d**	<5	—
7	*t*-BuOK/benzene, reflux	40 min	**5d**	73	1.32
8	*t*-BuOK/THF, reflux	1 day	**3d**	—	—

[a] Overall yield of **5d** from compound **3d**.
[b] Major to minor rotomer ratio.
[c] Starting material **3d** was recovered.
[d] **5d** was obtained in low yield (<5%), along with several unidentified compounds presumably due to decomposition under reaction conditions.



Scheme 2. A plausible mechanism for the cyclization of a disubstituted amino-benzonitrile **3**.

ylideneamine. Tautomerization of intermediate C to the 1*H*-indol-3-ylamine **4** and subsequent acylation by Ac_2O afforded acetylated amino indoles **5**. The cyclization of the amino-benzonitriles **3** tolerates with a wide variety substituents such as methyl, ethyl, propyl, benzyl, and phenyl, and hence represents a potential general method for the synthesis of 3-(*N*-acylamino)-2-phenylindoles. Moreover, the cyclization featuring mild reaction conditions, short reaction time, easy workup, and good yields would make it attractive for the synthesis of 3-amino indole derivatives.

In summary, the base-mediated intramolecular condensation of 2-(disubstituted amino)-benzonitriles has proved to be a useful and highly efficient process for the synthesis of potentially valuable 3-aminoindoles under mild conditions.

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11. *General procedure for the preparation of 1-substituted-N-(2-phenyl-1H-indol-3-yl)acetamides* **5:** Disubstituted amino-benzonitrile **3** (1.0 mmol) was added to a mixture of 60% NaH (1.3 mmol, 60% (w/w) in mineral oil) in DMF (5.0 mL) at room temperature and was stirred at 80 °C for 40 min. Acetic anhydride (1.2 mmol) was added at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (40 mL), extracted with CH_2Cl_2 (50 mL), dried, concentrated, and purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to give an inseparable mixture of two amide rotamers **5**. Spectral data for selected products:*N-1-Benzyl-2-phenyl-1H-indol-3-yl)acetamide* **(5d)**: bright yellow solid (ratio of two amide rotamers = 1:1.3); 87% yield; mp 170–174 °C; ^{1}H NMR (200 MHz, $CDCl_3$) (major rotamer) δ 2.18 (s, 3H, $COCH_3$), 5.31 (s, 2H, $PhCH_2$), 6.77 (br s, 1H, NH), 6.93–7.04 (m, 2H, ArH), 7.16–7.42 (m, 11H, ArH), 7.55–7.62 (m, 1H, ArH) (minor rotamer) δ 1.83 (s, 3H, $COCH_3$), 5.25 (s, 2H, $PhCH_2$), 6.72 (br s, 1H, NH), 6.93–7.04 (m, 2H, ArH), 7.16–7.42 (m, 11H, ArH), 7.55–7.62 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) (major rotamer) δ 23.3, 47.8, 110.7, 111.1, 119.0, 120.5, 122.7, 124.9, 126.0, 127.2, 128.5, 128.7, 128.8, 129.4, 130.1, 137.3, 137.5, 137.9, 170.5 (minor rotamer) δ 20.3, 47.8, 110.9, 112.1, 117.8, 121.0, 123.1, 125.8, 126.0, 127.5, 128.2, 128.7, 129.0, 129.7, 130.0, 135.4, 135.7, 136.0, 174.4; MS (EI) *m*/*e* (relative intensity): 340 (M^+, 100), 297 (29), 207 (67); HRMS (EI): *m*/*e* $[M]^+$ calcd for $C_{23}H_{20}N_2O_1$: 340.1576; found: 340.1572.*(1-Benzyl-2-phenyl-1H-indol-3-yl)dimethylamine (6)*: Benzonitrile **3d** (300 mg, 1.00 mmol) was added to a mixture of 60% NaH (50 mg, 1.3 mmol) in DMF (5.0 mL) at room temperature and was stirred at 80 °C for 1 h. After the starting benzonitrile **3d** was disappeared, the additional amount of 60% NaH (50 mg, 1.3 mmol) and an iodomethane (140 μL, 2.20 mmol) were added to the reaction mixture. After stirring at room temperature for 2 h, the reaction was quenched by the addition of 0.1 N HCl aqueous solution (50 mL). The resulting mixture was extracted with CH_2Cl_2 (50 mL × 3), washed with water (50 mL × 3), and dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure. Purification of the residues was done by a flash column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:10) to afford a yellow solid **6** (202 mg, 62%): mp 96–98 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (s, 6H, $N(CH_3)_2$), 5.12 (s, 2H, $PhCH_2$), 6.91–7.01 (m, 2H, ArH), 7.11–7.23 (m, 6H, ArH), 7.25–7.35 (m, 5H, ArH), 7.82 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.8, 47.2, 110.4, 119.0, 119.6, 121.8, 124.5, 126.1, 127.0, 128.0, 128.1, 128.4, 128.5, 131.0, 132.2, 133.2, 135.5, 138.4; MS (EI) *m*/*e* (relative intensity): 326 (M^+,71), 235 (100), 219 (57), 91 (15); HRMS (EI): *m*/*e* $[M]^+$ calcd for $C_{23}H_{22}N_2$: 326.1783; found: 326.1774.