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Intramolecular aromatic amination by a hydrazino group for the synthesis of indolo[1,2-*b*]indazole derivatives

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Abstract—A versatile method for the preparation of indolo[1,2-*b*]indazole derivatives was developed by the aid of palladium-catalyzed aromatic amination reaction starting from indoline derivatives.

We have been involved in the chemistry of pyrazolo[1,5-*a*]indole **1**[1] (Fig. 1) and in the course of this study we reported that the derivative **2** had strong antiproliferative activity against cancer cells.[2] The derivatives represented by **2** were proven to be potent inhibitors to both DNA topoisomerases I and II, and also to have a novel inhibition mechanism different from the stabilization of a cleavable complex.[3] A combination of the roles of the D and E ring of **2** is quite important for expression of the activity.[2] Considering the role of the D ring, we figured out the structure **3**, indolo[1,2-*b*]indazole, in which the flexible D ring of **2** is fixed as a benzo[*b*] derivative, and the distance between the D ring and the E ring is changed. The inhibition mechanism of the derivatives of **3** is also of prime interest.[4] There is a quite limited number of reports concerning the synthesis of indolo[1.2-*b*]indazole derivatives,[5] but the yields were poor and the methods are not suitable for obtaining a series of compound **3**. In this paper we provide the first general method for the synthesis of indolo[1,2-*b*]indazole derivatives. In order to construct the skeleton of indolo[1,2-*b*]indazole we intended to use an aromatic amination reaction, which has proven to be a valuable synthetic method with wide applications in organic synthesis.[6] Song and Yee have recently reported versatile methods for the preparation of 1- or 2-arylindazole derivatives by intramolecular amination by hydrazine derivatives.[7] Considering this background, we decided to use 1-aminoindoline derivatives as the starting material. Our synthetic pathway is depicted in Scheme 1.

The starting material **4** was prepared by the standard method: (1) reduction of 2-(2-bromophenyl)indole derivatives[8] with $NaBH_3CN$ in HOAc–TFA;[9] (2) *N*-nitroso formation with $NaNO_2$–HCl; (3) reduction of the *N*-nitroso group with Zn powder in HOAc–ether.[10] Reaction conditions for the cyclization were investigated using **4a** ($R_1=R_2=H$), which was derived from 2-(2-bromophenyl)indole.[11] The result is summarized in Table 1. Although indazole formation from hydrazine derivatives was carried out successfully,[7] we were afraid that there would be some difficulty in the formation of

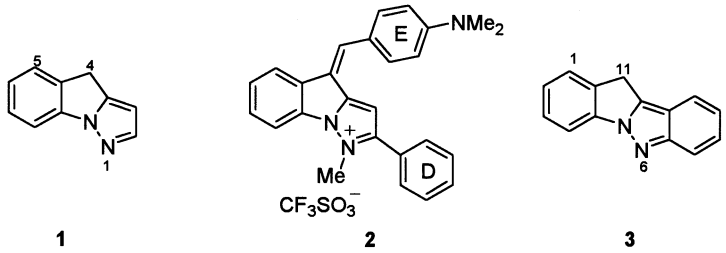

Figure 1.

Keywords: aromatic amination; indolo[1,2-*b*]indazole; cyclization; 1-aminoindoline; air oxidation.

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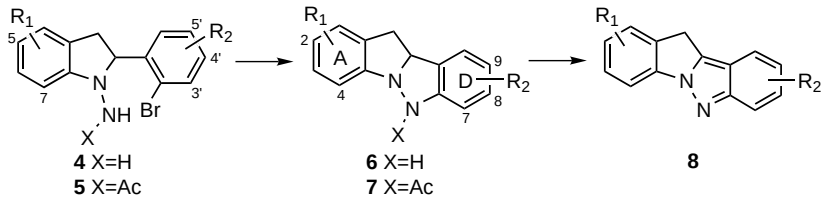


Scheme 1.

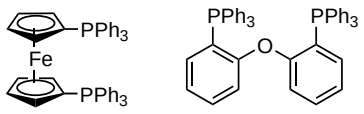
Table 1. Optimization of reaction conditions in palladium-catalyzed intramolecular amination of **4a** ($R_1=R_2=H$) and **5a** ($R_1=R_2=H$)[a]

Entry	Substrate	Pd	Ligand[c]	Base	Product	Yield (%)[b]
1	**4a**	$Pd(OAc)_2$	DPPF	*t*-BuONa	**8a**	40
2	**4a**	$Pd(OAc)_2$	P(*o*-Tol)$_3$	*t*-BuONa	**8a**	10
3	**4a**	$Pd(OAc)_2$	DPEphos	Cs_2CO_3	**8a**	42
4	**5a**	$Pd(OAc)_2$	DPEphos	Cs_2CO_3	**7a**	97
5	**5a**	$Pd(dba)_3$	P(2-Furyl)$_3$	Cs_2CO_3	**7a**	18
6	**5a**	$Pd(dba)_3$	P(*o*-Tol)$_3$	Cs_2CO_3	**7a**	5
7	**5a**	$Pd(OAc)_2$	–	Cs_2CO_3	–	0

[a] Reaction was carried out in a pressure tube. A solution of **4a**, palladium catalyst, ligand and base in anhydrous toluene was heated at 100–110°C until the starting material was totally consumed. In the case of **4a**, the reaction mixture was left stirring at ambient temperature for 3 days before work-up.

[b] Isolated yield by chromatography.

[c]



a five-membered ring because of ring strain involved in the structure of indolo[1,2-*b*]indazole. When the reaction conditions used in the formation of indazole from a hydrazine derivative[7a] were applied to the cyclization of **4a**, no desired product **8a** ($R_1=R_2=H$) was detected on TLC during the reaction. However, exposure of the reaction mixture at ambient temperature to air allowed gradual appearance of **8a**, and, after 3 days, **8a** was obtained in 40% yield (entry 1). Similar cyclization and subsequent oxidation were observed in the formation of the indazole ring by aromatic amination reaction.[7a] Replacement of the chelate ligand with a monochelate ligand resulted in a sharp drop of the yield (entry 2). Employment of DPEphos as a chelate ligand in combination with a weaker base Cs_2CO_3, which is quite an effective ligand for the formation of the indoline ring,[12,13] gave no notable improvement in the yield. Since the amines **4a** and **6a** ($R_1=R_2=H$) were found to be unstable under the reaction conditions, we decided to use amide **5a** ($R_1=R_2=H$) which is readily prepared by the acetylation of **4a**. Amide **5a** showed complicated NMR spectra due to the presence of geometrical isomers. Thus, in the general method the detailed analysis of amide **5** was set aside, and amide **5** was used for the following reaction as received.[11] In aromatic amination with amide, it is general practice to use a weaker base such as Cs_2CO_3, since amide NH is more acidic than amine NH. A strong base such as *t*BuONa is sometimes the cause of side reactions. When a combination of DPEphos and Cs_2CO_3 with palladium in toluene was used in amination of **5a**, cyclization product **7a** ($R_1=R_2=H$) was obtained in 97% yield (entry 4). Product **7a** was the dihydro derivative of **8a** since 10b-H was observed at δ 5.29 ppm as the X part of ABX-type couplings ($J_{AB}=15.5$ Hz, $J_{AC}=8.2$ Hz, $J_{BC}=0$ Hz). Use of monochelate ligands, such as P(Furyl)$_3$ and P(*o*-Tol)$_3$, with $Pd(dba)_3$ for an extended period[12] was found to be again unsuitable (entries 5 and 6). The presence of a proper ligand is requisite for the cyclization reaction (entry 7). Hydrolysis of **7a** was effected with sodium hydroxide in aqueous methanol at 70°C under a nitrogen atmosphere. Work-up of the reaction mixture with ice and extraction with dichloromethane gave NH product **6a** in good yield. The NH product was susceptible to air-oxidation as mentioned above, and its ^{1}H NMR spectrum indicated contamination of oxidation product **8a**.[11] Oxidation of **6a** to **8a** in air was slow, and stirring of a dichloromethane solution of **6a** for 3 days was required to obtain **8a** in moderate yield. A proper oxidant for this transformation was investigated, and basic aluminum oxide was found to be the

choice of oxidant. These steps can be carried out consecutively in the general method, i.e. hydrolysis of **7** and subsequent oxidation of the product **6** without isolation. Thus, the general method for the synthesis of indolo[1,2-*b*]indazole derivatives starting from indoline derivatives was established,† and the result is summarized in Table 2. A few cyclization reactions required a prolonged reaction period without notable effect on the yields (entries 3, 4, and 7). The method is equally effective for the synthesis of indolo[1,2-*b*]indoles **8** having an electron-donating group (entries 2, 3, 6, and 7) and an electron-attracting group (entries 4, 5, and 8) on either the A ring or the D ring.

In summary, we have developed a new method for the synthesis of indolo[1,2-*b*]indazoles **8** in high yields starting from *N*-acetamino-2-(2-bromo)arylindolines **5**, which is available from 2-(2-bromo)indoles by standard method. Intramolecular C–N bond formation catalyzed by palladium acetate was used to transfer **5** to **7** as a key reaction. Hydrolysis of **7** and air oxidation of **6** catalyzed by basic aluminum oxide allowed the preparation of **8** in good yield. To our best knowledge, this is the first general method for the construction of an indolo[1,2-*b*]indazole ring system. Using this method we have undertaken the preparation of compounds with potential bioactivity, and the progress along this line of research will be reported in due course.

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4. The derivative of **3**, 11-(4-dimethylaminobenzylidene)-6-methyl-11*H*-indolo[1,2-*b*]indazolium trifluoromethane sulfonate corresponding to **2**, showed high activity against proliferation of cancer cell lines, MG-MID log GI_{50} −6.36, Log TGI −5.58, in a preliminary test at NCI, although a mixture of isomers was employed. Also, high selectivity to melanoma cancer cells was observed.
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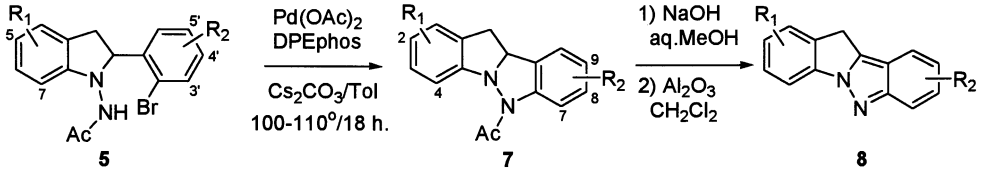
Table 2. Synthesis of indolo[1,2-*b*]indazole derivatives by palladium-catalyzed intramolecular aromatic amination reaction[a]



Entry	**5**: $R_1=$, $R_2=$	**7**: $R_1=$, $R_2=$	Yield (%)[b]	**8**: $R_1=$, $R_2=$	Yield (%)[b]
1	H, H (**5a**)	H, H (**7a**)	97	H, H (**8a**)	95
2	5-Me, H	2-Me, H	86	2-Me, H	91
3	7-Me, H	4-Me, H	82[c]	4-Me, H	94
4	5-Cl, H	2-Cl, H	81[c]	2-Cl, H	84
5	5-F, H	2-F, H	93	2-F, H	96
6	H, 4′-OMe	H, 8-OMe	88	H, 8-OMe	94
7	H, 3′-Me	H, 7-Me	88[c]	H, 7-Me	93
8	H, 5′-F	H, 9-F	99	H, 9-F	92

[a] For general procedure see footnote †. All new compounds were characterized by IR, ^1H, ^{13}C NMR, HRMS or elemental analysis.
[b] Isolated yield by chromatography.
[c] Reaction time 40 h.

† General procedure for the preparation of **8** from **5**. A solution of **5** (2 mmol), $Pd(OAc)_2$ (15 mg, 0.07 mmol), DPEphos (55 mg, 0.1 mmol), Cs_2CO_3 (914 mg, 2.8 mmol) and anhydrous toluene (8 ml) in a pressure tube filled with argon was heated at 100–110°C for 18 h. Filtration via Celite pad, evaporation of the filtrate, and flash chromatography (silica gel, hexane–ethyl acetate) gave the cyclization product **7**. The product **7** (0.6 mmol) was dissolved in a mixture of methanol (6 ml) and an aqueous sodium hydroxide solution (5N, 1.5 ml) and warmed at 70°C for 30 min under a nitrogen atmosphere. The solution was poured into ice-water (20 g) and extracted with dichloromethane (40+20 ml). The extract, after washed (water, 30 ml), was stirred with sodium sulfate (10 g) and active basic aluminum oxide (3 g) overnight. Filtration, evaporation of the filtrate and flash chromatography of the product (silica gel, hexane–dichloromethane) yielded the product **8**.[11]

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11. Data for selected compounds: **1-Amino-2-(2-bromophenyl)indoline 4a**: Amorphous solid, mp 73.0–75.0°C, IR cm^{-1}: 3340, 2845, 1605, 1476, 1459, 1338, 1231, 1020, 842. ^1H NMR: 2.67 (dd, $J=15.4$, 11.4 Hz, 1H), 3.48 (s, 2H), 3.60 (dd, $J=15.4$, 8.6 Hz, 1H), 4.72 (dd, $J=11.4$, 8.6 Hz, 1H), 6.86 (td, $J=7.4$, 1.1 Hz, 1H), 6.94 (d, $J=7.8$ Hz, 1H), 7.10 (d, $J=7.2$ Hz, 1H), 7.15–7.23 (m, 2H), 7.37 (td, $J=7.3$, 1.2 Hz, 1H), 7.59 (dd, $J=7.9$, 1.2 Hz, 1H), 7.75 (dd, $J=7.8$, 1.8 Hz, 1H). ^{13}C NMR δ: 36.4, 76.0, 110.2, 120.6, 124.0, 124.4, 126.4, 127.8, 128.0, 128.06, 128.9, 133.0, 140.7, 153.8.
1-Acetylamino-2-(2-bromophenyl)indoline 5a: Mp 189.0–190°C, IR cm^{-1}: 3188, 1665, 1547, 1477, 1462, 1252, 1022, 753. ^1H NMR (DMSO-d_6) δ: (major isomer) 1.81 (s, 3H), 2.58 (dd, $J=15.6$, 11.5 Hz, 1H), 3.62 (dd, $J=15.6$, 8.9 Hz, 1H), 5.25 (s, 1H), 6.56 (d, $J=8.1$ Hz, 1H), 6.81 (t, $J=7.3$ Hz, 1H), 7.11 (t, $J=6.2$ Hz, 2H), 7.25 (td, $J=7.6$, 1.5 Hz, 1H), 7.42 (t, $J=7.6$, 1H), 7.63 (d, $J=7.9$ Hz, 1H), 7.89 (d, $J=7.7$ Hz, 1H), 9.73 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 20.8, 35.6, 69.6, 109.2, 120.4, 122.6, 124.4, 125.3, 127.3, 128.1, 128.4, 129.2, 132.51, 140.6, 151.2, 168.4.
6-Acetyl-10b,11-dihydro-6*H*-indolo[1,2-*b*]indazole 7a: Mp 130.0–131.0°C, IR cm^{-1}: 1685, 1594, 1476, 1459, 1376, 1318, 1252, 754. ^1H NMR δ: 2.58 (s, 3H), 3.47 (d, $J=15.5$ Hz, 1H), 3.57 (dd, $J=15.5$, 8.2 Hz, 1H), 5.28 (d, $J=8.2$ Hz, 1H), 7.00–7.27 (m, 7H), 7.76 (d, $J=8.1$ Hz, 1H). ^{13}C NMR: 22.7, 33.4, 67.6, 114.4, 117.9, 122.1, 124.5, 125.1×2, 127.9, 128.2, 128.6, 133.6, 139.2, 151.2, 171.3.
10b,11-Dihydro-6*H*-indolo[1,2-*b*]indazole 6a: ^1H NMR δ: 3.45 (dd, $J=15.6$, 2.1 Hz, 1H), 3.54 (dd, $J=16.4$, 8.8 Hz, 1H), 5.35 (dd, $J=8.8$, 2.1 Hz, 1H), 6.19 (s, 1H), 6.90–7.23 (m, 8H).
11*H*-indolo[1,2-*b*]indazole 8a: Mp 170.0–171.0°C, IR cm^{-1}: 3055, 2905, 1621, 1520, 1478, 1450, 1369, 1298, 756, 740. ^1H NMR: 4.17 (s, 2H), 7.13 (t, $J=7.9$ Hz, 1H), 7.31–7.37 (m, 2H), 7.51 (t, $J=7.7$ Hz, 1H), 7.59 (d, $J=7.6$ Hz, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.82 (d, $J=8.9$ Hz, 1H), 7.92 (d, $J=7.8$ Hz, 1H). ^{13}C NMR δ: 28.7, 112.2, 117.1, 118.4, 119.6, 121.6, 126.1×2, 126.4, 128.4, 134.6, 137.3, 140.7, 153.3. IR spectra were measured by KBr pellet, and NMR spectra in $CDCl_3$ unless specified. Molecular weight and formula were determined by MS, HRMS, and elemental analyses.
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