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EFFICIENT SYNTHESIS OF 2-MONO and 2,3-DISUBSTITUTED INDOLES *VIA* PALLADIUM-CATALYZED OXIDATION OF AMINOALCOHOLS

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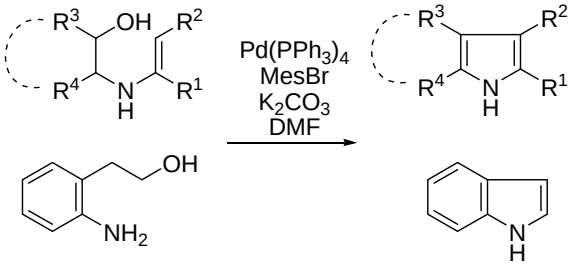
Abstract – Efficient synthesis of 2-mono- and 2,3-disubstituted indoles has been accomplished *via* palladium-catalyzed oxidation of aminoalcohols.

Indole substructure is present in a wide range of biologically active natural products, and the construction of this important heterocyclic unit has been a topic of interest for many years.[1] Of those indoles, many have their own established synthetic routes. As regards the synthesis of 2,3-disubstituted indoles, however, only very few practical methods have been available.[2] In our previous paper,[3] we reported that by the palladium-catalyzed oxidation described by Yoshida and Tamaru *et al*,[4] hydroxy-enamines and commercially available 2-amino-phenylethanol gave the corresponding pyrroles and indole, respectively in moderate to good yields (Scheme 1). In the present study, we report an efficient synthesis of 2-mono and 2,3-disubstituted indoles (**9** and **10**) from aminoalcohols (**3**, **4**, **5**, **6**, and **11**) (Scheme 2). The starting aminoalcohols were prepared easily from commercially available simple *o*-ethylaniline and toluidine *via o*-lithiation. The first step of synthesis was the coupling reaction of aldehydes with toluidines (**1a-c**) or *o*-ethylanilines (**2a-b**) having an *N*-pivaloyl (Piv), an *N*-^{t}butoxycarbonyl (^{t}Boc), or an *N*-trimethylsilyl (TMS) group, to give **3a-f**, **4b-d**, **4f**, **5b-d**, **6d**, and **7f**. The reaction was studied under different reaction conditions, and the results are summarized in Table 1. In the coupling reactions with *N*-^{t}Boc- or *N*-Piv-

Scheme 1



Scheme 2

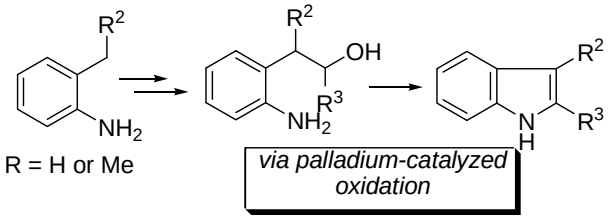
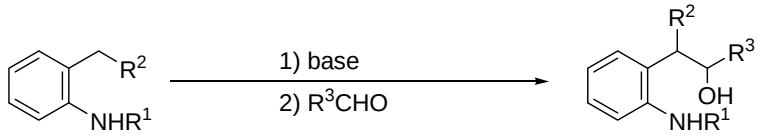


Table 1 Preparation of Aminoalcohol Derivatives *via o*-Lithiation of Aniline Derivatives



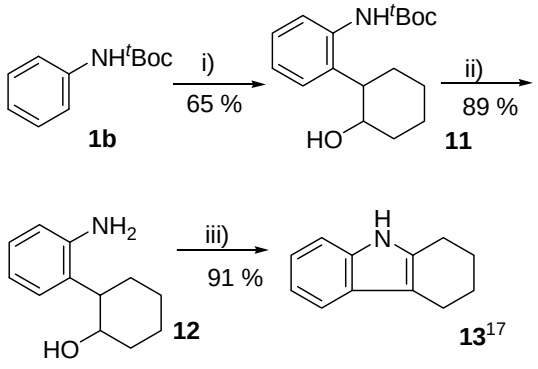
1a-**c**, **2a**-**b** **3a**-**f**, **4b**-**d, f**, **5b**-**d**, **6d** and **7f**

Entry	R^1	R^2	Anilines	Reaction Conditions[a]	R^3	Coupling Products	Yields (%)[b]
1	Piv	H	**1a**	A	Et	**3a**	61
2	Piv	H	**1a**	A	^{n}Pr	**3b**	78
3	Piv	H	**1a**	A	^{i}Pr	**3c**	56
4	Piv	H	**1a**	A	cyclohexyl	**3d**	66
5	Piv	H	**1a**	A	phenyethyl	**3e**	67
6	Piv	H	**1a**	A	Ph	**3f**	28
7	^{t}Boc	H	**1b**	B	^{n}Pr	**4b**	79
8	^{t}Boc	H	**1b**	B	^{i}Pr	**4c**	74
9	^{t}Boc	H	**1b**	B	cyclohexyl	**4d**	74
10	^{t}Boc	H	**1b**	B	Ph	**4f**	60
11	TMS	H	**1c**	C	Ph	**7f**[c, 6]	55
12	Piv	Me	**2a**	D	^{n}Pr	**5b**	84
13	Piv	Me	**2a**	D	^{i}Pr	**5c**	76
14	Piv	Me	**2a**	D	cyclohexyl	**5d**[7]	71
15	^{t}Boc	Me	**2b**	B	cyclohexyl	**6d**	68

[a] Reaction conditions: A) ^{t}BuLi (2.5 eq.) / THF / 0 °C / 1.5 h then R^3CHO (3.0 eq.) / -78 °C → 0 °C; B) ^{t}BuLi (2.2 eq.) / THF / -78 °C → -20 °C / 2 h then R^3CHO (1.5 eq.) / -78 °C → -20 °C; C) ^{n}BuLi (2.2 eq.) / Hexane / 0 °C → reflux / 1.5 h then R^3CHO (1.2 eq.) / -78 °C → 0 °C; D) ^{s}BuLi (2.5 eq.) / TBME / -25 °C / 2 h then R^3CHO (3.0 eq.) / -78 °C. [b] Isolated Yields. [c] During usual work-up, deprotection proceeded to give the deprotected compound **7f** was obtained in 55 % yield.

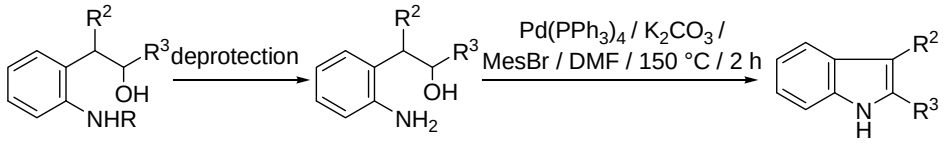
toluidines, the yields of the coupling products were generally moderate to good, though the yield of **3f** was rather low (entry 6 in Table 1). When *N*-TMS-toluidine **1c** was employed as the substrate, deprotection also occurred during the work-up of the reaction to give compound **7f** in 55 %. In the coupling reaction with *N*-protected *o*-ethylanilines, all the reactions proceeded to give satisfactory results (entries 12-15 in Table 1). For the removal of *N*-Piv protecting group, acidic treatment and subsequent sodium hydroxide treatments were necessary (entries 1-6 and 11-12 in Table 2). *N*-^{t}Boc group of anilines was cleaved by the treatment with trifluoroacetic acid to give the corresponding aminoalcohols in good yields (entries 7-10 and 14 in Table 2). Then, for the preparation of indoles, intramolecular cyclization *via* palladium-catalyzed oxidation of the hydroxyl groups was studied, the results of which being shown in Table 2. The aminoalcohols (**7a**-**f**, **8b**-**d**) were treated with an oxidant (mesityl bromide), a base (potassium carbonate), and a catalyst ($Pd(PPh_3)_4$) in DMF, under an argon atmosphere at 150 ℃ for 2 h.[5] In most of the reactions, the desired 2-mono or 2,3-disubstituted indoles were obtained in good to excellent yields (Table 2). Then, the construction of tricyclic indole or 1,2,3,4-tetrahydrocabazole system by an analogous procedure was studied (Scheme 3). *N*-^{t}Boc-aniline was lithiated by using a ^{t}BuLi /TMEDA system followed by the treatment with cyclohexene oxide to give compound **11** in 65 % yield. The removal of *N*-^{t}Boc

Scheme 3



i) ^{t}BuLi (2.2 eq.) / Et_2O / -78 °C → -20 °C / 3 h then TMEDA (2.5 eq.) / -78 °C / cyclohexene oxide (1.5 eq.) / -78 °C → -20 °C / 15 h ii) TFA–CH_2Cl_2 (1 : 1) / 0 °C → rt. / 15 min iii) $Pd(PPh_3)_4$ / MesBr / DMF / 150 °C / 2 h

Table 2 Deprotection of Nitrogen Protecting Groups and Preparation of Indoles



3a-f, **4b-f**, **5b-d**, **6d** **7a-f**, **8b-d** **9a-f, 10b-d**

Entry	Coupling Products	Deprotection Conditions[a]	Aminoalcoholes (Yield %)	Indoles (Yield %)[b]
1	**3a**	A	**7a**[8] (88)	**9a**[10] (97)
2	**3b**	A	**7b** (89)	**9b**[11] (96)
3	**3c**	A	**7c**[9] (58)	**9c**[12] (95)
4	**3d**	A	**7d** (81)	**9d**[11] (92)
5	**3e**	A	**7e** (78)	**9e**[13] (98)
6	**3f**	A	**7f** (---)[d]	---- ----
7	**4b**	B	**7b** (93)	**9b**[11] (93)
8	**4c**	B	**7c** (90)	**9c**[12] (90)
9	**4d**	B	**7d** (90)	**9d**[11] (90)
10	**4f**	B	**7f** (84)[d]	**9f**[14] (84)
11	**5b**	C	**8b** (60)	**10b**[15](85)
12	**5c**	C	**8c** (62)	**10c**[6] (62)
13	**5d**	C	**8d** (---)[c,d]	
14	**6d**	B	**8d** (68)[d]	**10d**[16](77)

[a] Reaction conditions: A) *c*.HCl-EtOH (1 : 1) / reflux / 6h then NaOH aq.–EtOH (1 : 1) / 50 °C / 15 h; B) TFA–CH_2Cl_2 (1 : 1) / 0 °C→rt. / 0.25 h; C) *c*.HCl–EtOH (1 : 1) / reflux / 6h then NaOH aq.–EtOH (1 : 1) / 50 °C / 6 days. [b] Isolated yields. [c] The *N*→*O* migration of the *N*-Piv group of compound **5d** was occurred in 70 % yield. [d] Though aminoalcohols **7f** and **8d** were not obtained from **3f** and **5d** *via* deprotection of *N*-Piv group, these aminoalcohols **7f** and **8d** were prepared by using ^{t}Boc group protected starting compound (entries 6 *vs*. 10 and 13 *vs*. 14).

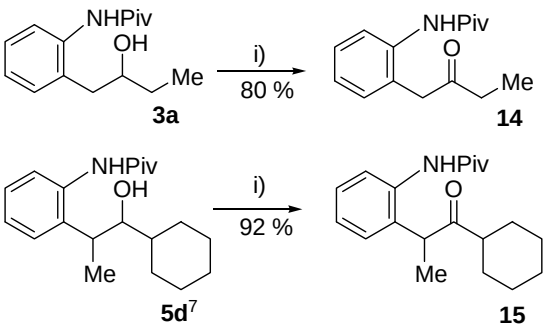
group with TFA gave the corresponding aminoalcohol **12** in 89 % yield. Subsequent palladium-catalyzed oxidation of the **12** gave 1,2,3,4-tetrahydrocarbazole (**13**)[17] in 91 % yield.

To demonstrate that the palladium-catalyzed oxidation of aminoalcohols proceeds *via* a carbonyl intermediate, aminoalco- hols (**3a** and **5d**) bearing an *N*-Piv group were subjected to palladium- catalyzed oxidation. The corresponding ketones **14** and **15** were obtained in good yields (Scheme 4).

Possible reaction involved in the present procedure is summarized in Scheme 5. Thus, palladium-catalyzed oxidation of **A** gives ketone **C** *via* **B**, which by intramolecular cyclization produces a cyclized compound **D**, which *via* subsequent dehydration, gives **E**, then *via* tautomerization, indole **F**.

The present study established an efficient and facile synthetic method of 2-mono- and 2,3-disubstituted indoles from commercially available aniline and toluidine, respectively. This procedure is of value, because the starting substrates, aminoalcohols, are easily available, and because that the method consists of only four steps, each giving moderate to good yields.

Scheme 4



i) $Pd(PPh_3)_4$ / K_2CO_3 / mesityl bromide / DMF / 150°C / 2h

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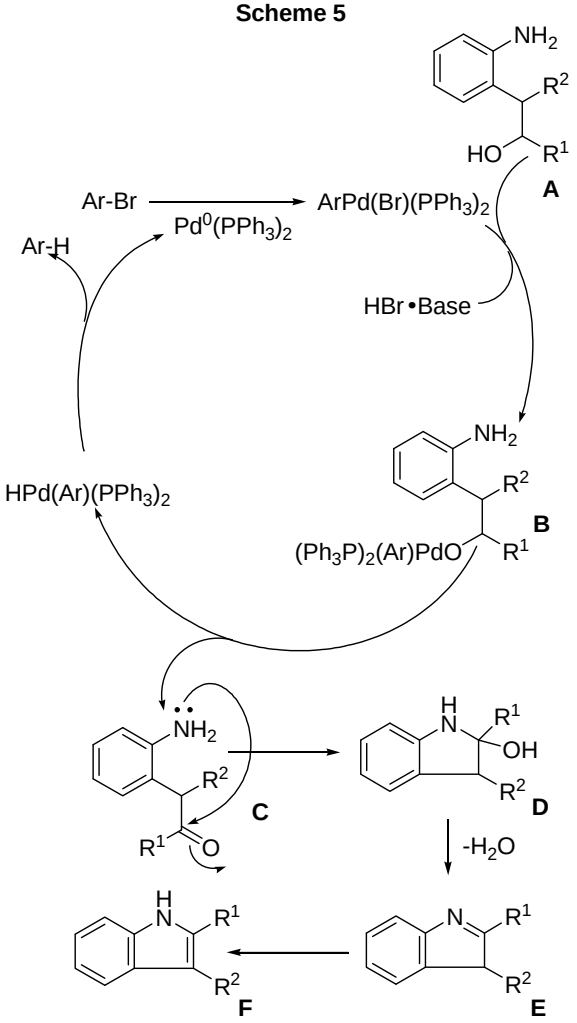
Scheme 5



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5. To a solution of aminoalcohols (**7** and **8**) (1.0 mmol), $Pd(PPh_3)_4$ (38 mg, 3 mol%), and K_2CO_3 (276 mg, 2.0 mmol) in dry DMF (4 mL), mesityl bromide (0.2 mL, 1.2 mmol) was added under an Ar atmosphere. After heating at 150 ℃ for 2 h, the reaction mixture was poured into ice-cooled water (20 mL), extracted with Et_2O (20 mL x 3), and the extracts was dried over Na_2SO_4. After Na_2SO_4 and the solvents were removed, the oily residue was purified with medium pressure liquid chromatography to give indoles (**9** and **10**).
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