Ruthenium and Tin-Catalyzed Synthesis of Indoles from Anilines and Ethylene Glycol

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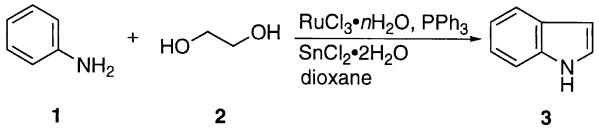
The formation of indoles has been continuously studied since several naturally occurring indoles exert a broad spectrum of physiological activities.[1] Recent advance toward synthesis of indoles has been accelerated by the assistance of homogeneous transition metal catalysts.[2] Watanabe *et al.* reported that anilines reacted with ethylene glycols as C_2-fragment in the presence of a ruthenium catalyst to afford indoles.[3] However, ethylene glycol with primary aromatic amines did not effectively work as cyclization counterpart to give the corresponding indoles, instead, 1,4-diphenylpiperazines being formed. As our series of studies on transition metal catalyzed synthesis of heterocyclic compounds,[4,5] we also have recently developed and reported a ruthenium-catalyzed synthesis of *N*-alkylindoles using *N*-alkylanilines and trialkanolamines as C_2-fragment.[6] However, primary aromatic amines did not work as cyclization counterpart toward the corresponding indoles. Thus, under similar ruthenium-catalyzed system, it was disclosed and reported that the addition of tin(II) chloride dihydrate to the system resulted in the formation of indoles from primary aromatic amines and trialkanolamines.[7] We here report that a ruthenium-tin catalytic system works as an effective catalyst for the formation of indoles from primary aromatic amines and ethylene glycol.

We investigated the cyclization between aniline (**1**) and ethylene glycol (**2**) under various reaction conditions for the effective formation of indole (**3**) (eq 1). Several representative results were summarized in Table 1. The yield of indole (**3**) was considerably affected by the molar ratio of **1** to **2** as has been observed in our recent reports,[6,7] the highest yield of **3** being obtained at the molar ratio of 10. Under the ruthenium-catalyzed system, the reaction did not proceed at all in the absence of tin(II) chloride dihydrate. However, the increase of the amount of tin(II) chloride dihydrate revealed the similar yield of **3**.

We then examined the reactivity of substituted primary



1 **2** **3** (1)

aromatic amines under the optimized reaction conditions described above. Several representative results were summarized in Table 2. The product yield was dependent on the electronic nature of the substituent on anilines. In the case of *m*-toluidine, the product was obtained as a regioisomeric mixture as has been observed in the similar ruthenium-catalyzed cyclization of *m*-toluidine with triethanolamine.[7] Isomeric molar ratio between 4-methylindole and 6-methylindole was determined from the peak areas of the methyl protons in ^{1}H NMR spectrum. In the cases of two methyl substituted anilines such as 2,3-, 2,5- and 3,5-dimethylaniline, the yield of the corresponding indoles was higher than that when mono-substituted primary aromatic amines were used.

Although the clear understanding of the present cyclization and the exact role of tin(II) chloride dihydrate are still obscure, the reaction seems to proceed as has already been proposed in ruthenium-catalyzed synthesis of indoles from anilines and ethylene glycols.[3]

Experimental Section

Table 1. Ruthenium-catalyzed synthesis of **3** from **1** and **2** under various conditions[a]

1/**2**	$RuCl_3 \cdot nH_2O$ (mmol)	$SnCl_2 \cdot 2H_2O$ (mmol)	Time (h)	Yield[b] (%)
4	0.05	1	20	24
6	0.05	1	20	25
8	0.05	1	20	36
10	0.05	1	20	46
10	0.05	-	20	trace
10	0.1	1	20	50
10	0.1	2	24	51

[a]All reactions were carried out with **2** (1 mmol), in dioxane (10 mL) at 180 ℃. [b]Determined by GLC based on **2**.

Table 2. Ruthenium-catalyzed synthesis of indoles from anilines and **2**[a]

Anilines	Indoles	Isolated yield (%)[b]
aniline	indole	40
o-toluidine	7-methylindole	32
m-toluidine	4- and 6-methylindole	33[c]
p-toluidine	5-methylindole	40
p-anisidine	5-methoyindole	17
p-chloroaniline	5-chloroindole	18
2,3-dimethylaniline	6,7-dimethylindole	60
2,5-dimethylaniline	4,7-dimethylindole	56
3,5-dimethylaniline	4,6-dimethylindole	61

[a]All reactions were carried out with anilines (10 mmol), 2 (1 mmol), $RuCl_3 \cdot nH_2O$ (0.1 mmol), PPh_3 (0.3 mmol) and $SnCl_2 \cdot 2H_2O$ (1 mmol) in dioxane (10 mL) at 180 °C for 20 h. [b]Based on **2**. [c]Isomeric molar ratio was determined by ^{1}H NMR (300 MHz), 4-methylindole/6-methylindole=1/1.

Typical procedure for ruthenium-catalyzed synthesis of indoles. A mixture of aniline (0.931 g, 10 mmol), ethylene glycol (0.062 g, 1 mmol), $RuCl_3 \cdot nH_2O$ (0.021 g, 0.1 mmol), $SnCl_2 \cdot 2H_2O$ (0.226 g, 1 mmol) and PPh_3 (0.079 g, 0.3 mmol) in dioxane (10 mL) was placed in a pressure vessel. After the system was flushed with argon, the mixture was stirred at 180 °C for 20 h. The reaction mixture was filtered through a short column (silica gel, dichloromethane) and evaporated under reduced pressure. To the residual oily material was added 30 mL of dichloromethane and washed two times with 30 mL of aqueous 5% HCl solution to remove excess aniline. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure left an oil which was separated by column chromatography (ethyl acetate/hexane=1/20) to give indole (0.047 g, 40% yield).

7-Methylindole. 32% yield; white solid; mp 80-82 °C; IR (KBr) 3398, 2935, 1340, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.53-6.54 (m, 1H), 6.97-7.10 (m, 3H), 7.50 (d, *J*=7.5 Hz, 1H), 7.89 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0, 103.3, 118.8, 120.4, 120.7, 122.8, 124.4, 127.7, 135.7; MS *m/z* (relative intensity) 131 (M^+, 95), 130 (100), 103 (8), 77 (10).

4- and 6-Methylindole. 33% yield; the molar ratio was determined from the peak areas of the methyl protons in ^1H NMR spectrum; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 6-CH_3), 2.56 (s, 4-CH_3), 7.90 (br s, NH), 8.04 (br s, NH); MS *m/z* (relative intensity) 131 (M^+, 74), 130 (100), 103 (9), 77 (14).

5-Methylindole. 40% yield; white solid; mp 59-60 °C; IR (KBr) 3389, 2919, 1476, 796 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.45 (d, *J*=3.6 Hz, 1H), 7.01 (d, *J*=8.4 Hz, 1H), 7.09-7.11 (m, 1H), 7.24 (d, *J*=8.4 Hz, 1H), 7.42 (s, 1H), 7.99 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 101.9, 110.6, 120.2, 123.5, 124.2, 128.0, 128.9, 134.0; MS *m/z* (relative intensity) 131 (M^+, 100), 130 (93), 103 (10), 77 (15).

5-Methoxylindole. 17% yield; white solid; mp 53-54 °C; IR (KBr) 3403, 2938, 1482, 1226, 1153, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.47 (d, *J*=2.7 Hz, 1H), 6.87 (dd, *J*=8.4 and 2.7 Hz, 1H), 7.10-7.14 (m, 2H), 7.24 (d, *J*=8.4 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.9, 102.2, 102.4, 117.1, 112.2, 124.9, 128.2, 131.0, 154.1; MS *m/z* (relative intensity) 147 (M^+, 100), 132 (68), 104 (54), 77 (15).

5-Chloroindole. 18% yield; white solid; mp 65-67 °C; IR (KBr) 3388, 1447, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (d, *J*=2.7 Hz, 1H), 7.14 (dd, *J*=8.4 and 2.6 Hz, 1H), 7.20- 7.22 (m, 1H), 7.29 (d, *J*=8.4 Hz, 1H), 7.61 (d, *J*=1.8 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) d 102.3, 112.0, 120.0, 122.2, 125.4, 125.5, 128.9, 134.1; MS *m/z* (relative intensity) 153 (M^++2, 30), 151 (M^+, 100), 116 (17), 89 (22), 76 (10).

4,6-Dimethylindole. 61% yield; colorless oil; IR (neat) 3406, 2918, 1351, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.48 (s, 3H), 6.44 (d, *J*=3.3 Hz, 1H), 6.74 (s, 1H), 6.78 (s, 1H), 6.85-6.88 (m, 1H), 7.47 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.6, 21.5, 100.4, 108.6, 121.7, 122.9, 125.4, 129.6, 131.6, 135.8; MS *m/z* (relative intensity) 145 (M^+, 69), 144 (100), 130 (56), 129 (48), 115 (13), 102 (4), 91 (5).

6,7-Dimethylindole. 60% yield; white solid; mp 66-67 °C; IR (KBr) 3417, 2913, 1332, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.35 (s, 3H), 6.42-6.44 (m, 1H), 6.85- 6.87 (m, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 7.36 (d, *J*=8.3 Hz, 1H), 7.53 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.8, 19.2, 102.6, 117.6, 117.9, 122.5, 123.5, 125.6, 129.0, 135.9; MS *m/z* (relative intensity) 145 (M^+, 68), 144 (100), 130 (58), 115 (12), 102 (5), 91 (4).

4,7-Dimethylindole. 56% yield; white solid; mp 94-96 °C; IR (KBr) 3381, 2911, 1434, 796 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.53 (s, 3H), 6.55-6.57 (m, 1H), 6.83 (d, *J*=7.8 Hz, 1H), 6.90 (d, *J*=7.8 Hz, 1H), 7.11-7.13 (m, 1H), 7.94 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.3, 18.5, 101.4, 117.6, 119.9, 122.4, 123.3, 127.2, 127.7, 134.9; MS *m/z* (relative intensity) 145 (M^+, 63), 144 (100), 130 (51), 115 (11), 102 (3), 91 (4).

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