# Notes

## New $C_2$-Fragment for Ruthenium-Catalyzed Synthesis of Indoles

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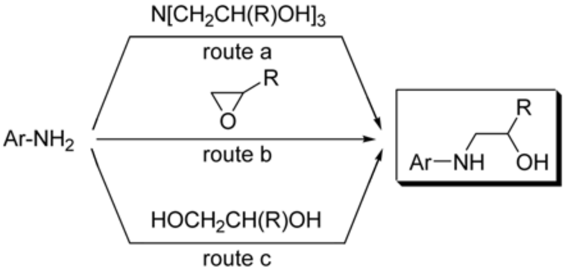
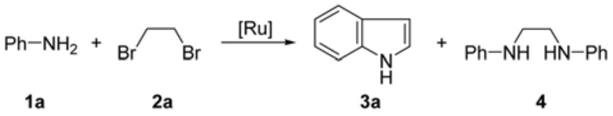
It is well known that indole moiety plays an important role as an intermediate for the synthesis of many pharmacologically and biologically active compounds. Thus, besides conventional popular routes, homogeneous transition metal-catalyzed synthetic methods have also been developed for the construction of indole framework because of the wide availability of substrates.[1] In connection with this report, as the part of our ongoing studies on homogeneous ruthenium catalysis, we recently developed on the synthesis of indoles *via* a ruthenium-catalyzed alkanol group transfer from alkanolamines to N-atom of anilines (amine exchange reaction[2]) (Scheme 1, route a)[3] and ring-opening of epoxides by anilines (Scheme 1, route b).[4,5] Watanabe *et al.* have also reported a ruthenium-catalyzed intermolecular cyclization of anilines with ethylene glycols as $C_2$-fragment leading to indoles (Scheme 1, route c).[6] In these regards, it was suggested that theses reactions proceed *via* a sequence involving an initial formation of 2-anilinoalkanols shown in Scheme 1 and *N*-alkylation of anilines by 2-anilinoalkanols to form 1,2-dianilinoalkanes.[7] These circumstances led us to seek a new $C_2$-fragment for such an intrinsic formation of 1,2-dianilinoalkanes.[8] Herein we report on a ruthenium-catalyzed synthesis of indoles from anilines and 1,2-dibromoethane as $C_2$-fragment.

The results of several attempted cyclization between aniline (**1a**) and 1,2-dibromoethane (**2a**) are listed in Table 1. When **1a** was generally treated with **2a** at 180 °C in dioxane in the presence of a catalytic amount of a ruthenium catalyst, indole (**3a**) was produced with concomitant formation of 1,2-dianilinoethane (**4**). As has been observed in our recent report on ruthenium-catalyzed synthesis of indoles from **1a** and trialkanolamines,[3] the yield of **3a** was considerably affected by the molar ratio of **1a** to **2a**. Table 1 shows that the yield of **3a** increased as the molar ratio [**1a**]/[**2a**] increased, while that of **4** remained nearly constant (entries 1, 2 and 5-7). It was reported by us that the addition of tin(II) chloride or a hydrogen acceptor was necessary for the effective formation of indoles or quinolines *via* ruthenium-catalyzed amine exchange reaction.[3,5] However, the present reaction showed no significant change by the addition of either tin(II) chloride or 1-hexene as hydrogen acceptor (entries 3 and 4). Performing the reaction for a longer reaction time (40 h) under $RuCl_2(PPh_3)_3$ or $RuCl_3\cdot nH_2O/3PPh_3$ did not affect the yield of **3a**, whereas the use of a smaller amount of a ruthenium catalyst affected product distribution, resulting in a relatively increased yield of **4**



**Scheme 1**

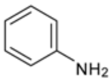
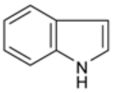
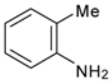
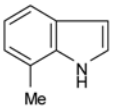
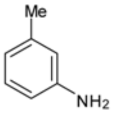
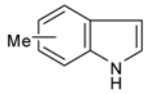
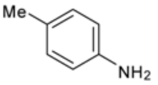
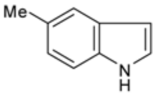
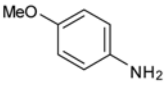
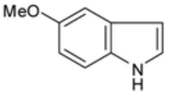
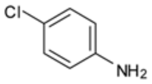
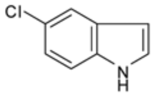
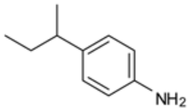
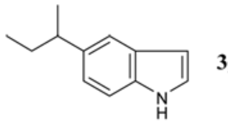
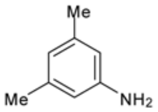
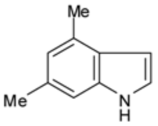
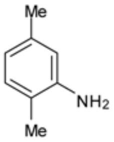
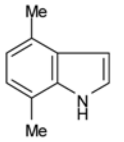
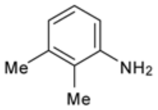
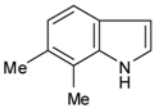
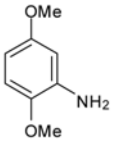
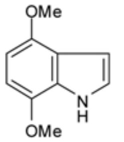
**Table 1**. Ruthenium-catalyzed reaction of **1a** with **2a** under several conditions[a]



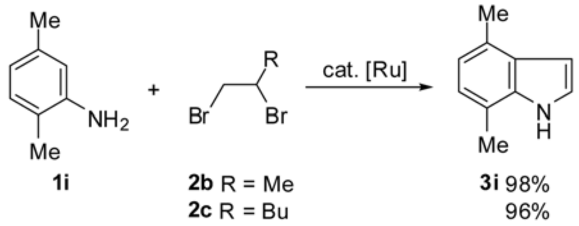
| Entry | Molar ratio [**1a**]/[**2a**] | Ruthenium catalysts (mmol) | Time (h) | Yield (%)[b] | |
|---|---|---|---|---|---|
| | | | | **3a** | **4** |
| 1 | 4 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 19 | 8 |
| 2 | 8 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 39 | 9 |
| 3[c] | 8 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 22 | 35 |
| 4[d] | 8 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 38 | 4 |
| 5 | 20 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 67 | 7 |
| 6 | 30 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 85 | 9 |
| 7 | 40 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 93 | 7 |
| 8 | 40 | (0.05) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 48 | 49 |
| 9 | 40 | (0.05) $RuCl_3\cdot nH_2O/3PPh_3$ | 40 | 45 | 52 |
| 10 | 40 | (0.05) $RuCl_2(PPh_3)_3$ | 20 | 53 | 39 |
| 11 | 40 | (0.05) $RuCl_2(PPh_3)_3$ | 40 | 54 | 44 |
| 12[e] | 50 | (0.1) $RuCl_3\cdot nH_2O/3PPh_3$ | 20 | 33 | 0 |

[a]Reaction conditions: **2a** (1 mmol), dioxane (10 mL), 180 °C, under argon. [b]Determined by GLC. [c]$SnCl_2$ (1 mmol) was used as hydrogen acceptor. [d]1-Hexene (10 mmol) was used as hydrogen acceptor. [e]Without dioxane.

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

| Anilines | | Indoles | | Yield (%)[b] |
|---|---|---|---|---|
|  | **1a** |  | **3a** | 78 |
|  | **1b** |  | **3b** | 75 |
|  | **1c** |  | **3c** | 72[c] |
|  | **1d** |  | **3d** | 45 |
|  | **1e** |  | **3e** | 25 |
|  | **1f** |  | **3f** | 26 |
|  | **1g** |  | **3g** | 54 |
|  | **1h** |  | **3h** | 94 |
|  | **1i** |  | **3i** | 96 |
|  | **1j** |  | **3j** | 95 |
|  | **1k** |  | **3k** | 20 |

[a] Reaction conditions: **1** (40 mmol), **2** (1 mmol), $RuCl_3{\cdot}nH_2O$ (0.1 mmol), $PPh_3$ (0.3 mmol), dioxane (10 mL), 180 °C, for 20 h, under argon. [b] Isolated yield. [c] 4-Methylindole: 6-methylindole = 1:2.



**Scheme 2**

(entries 8-11). When the reaction was carried out in the absence of solvent, **3a** was formed at most 33% yield without any other identifiable products (entry 12).

Given the controlled conditions, various anilines **1** were subjected to react with **2a** in order to investigate the reaction scope and feature. Table 2 shows that this reaction can be extended to a wide range of anilines with the range of 20-96% of indole yields. Here again, the production of 1,2-dianilinoethanes remains similar as is the case for the reaction between **1a** and **2a**. The product yield was considerably affected by the position of the substituent on anilines. The indole yield from *ortho*- and *meta*-substituted anilines (**1b** and **1c**) was higher than that when *para*-substituted anilines (**1d** and **1g**) were used. In the case of *m*-toluidine (**1c**), the corresponding indoles **3c** were obtained as a regioisomeric mixture, favoring cyclization at less-hindered position. As has been observed in our recent report,[3] lower reaction rate and yield were observed with anilines having methoxy and chloro functional groups (**1e** and **1f**).[9] The reaction of two methyl substituted anilines (**1h-1j**) with **2a** also proceeds likewise to give the corresponding indoles in quantitative yields. However, the indole **3k** was produced at most 20% yield with 2,5-dimethoxyaniline (**1k**). As a result, it appears that an appropriate electronic density of aromatic ring of anilines is necessary for a successful formation of indoles.

Next, several 1,2-dibromoalkanes as $C_2$-fragment were applied to the present reaction in order to extend reaction scope. However, similar treatment of 2,5-dimethylaniline (**1i**) with 1,2-dibromopropane (**2b**) and 1,2-dibromohexane (**2c**) under the same conditions afforded 4,7-dimethylindole (**3i**) in 98% and 96% yields, respectively, irrespective of the starting bromoalkanes (Scheme 2). No 2- and/or 3-substituted indoles as expected products were formed. Although the exact function of mechanism is not fully understood, these results indicate that a carbon-carbon bond cleavage occurs during the course of reaction.[10] The another explanation that rationalizes such an experimental result is the incorporation of dioxane as a $C_2$-fragment. However, treatment of **1a** (1 mmol) in the absence of **2a** under the conditions of $RuCl_3{\cdot}nH_2O$ (0.1 mmol)/$PPh_3$ (0.3 mmol)/dioxane (10 mL)/180 °C/20 h/Ar resulted in only 1% yield of **3a**.

In summary, we have demonstrated that anilines are cyclized with 1,2-dibromoethane in the presence of a ruthenium catalyst to give the corresponding indoles in moderate to good yields. The present reaction is an alternative synthetic approach for indoles from anilines and 1,2-dibromoethane as a new $C_2$-fragment.

## Experimental Section

GLC analyses were carried out with Shimadzu GC-17A (FID) equipped with CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using $N_2$ as carrier gas. The isolation of pure products was carried out via thin layer (silica gel 60 $GF_{254}$, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification.

**Typical experimental procedure for ruthenium-catalyzed cyclization of anilines with 1,2-dibromoethane.** A mixture of **1a** (3.725 g, 40 mmol), **2a** (0.188 g, 1 mmol), $RuCl_3 \cdot nH_2O$ (0.026 g, 0.1 mmol), and $PPh_3$ (0.079 g, 0.3 mmol) in dioxane (10 mL) was placed in a 50 mL pressure vessel. After the system was flushed with argon, the mixture was allowed to react at 180 $^oC$ for 20 h. Excess aniline was recovered by vacuum distillation and the residue was separated by thin layer chromatography (ethyl acetate:hexane = 1:5) to give **3a** (0.091 g, 78%).

All indoles prepared by the above procedure were characterized by GLC and spectroscopic comparison with authentic samples synthesized by our recent report.[3c]

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4. Cho, C. S.; Kim, J. H.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett*. **2003**, *44*, 2975.
5. For our recent report on the synthesis of quinolines *via* a ruthenium-catalyzed alkyl group transfer from alkylamines to N-atom of anilines, see: (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett*. **1999**, *40*, 1499. (b) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2000**, *56*, 7747. (c) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun*. **2000**, 1885. (d) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organomet. Chem*. **2002**, *650*, 65.
6. (a) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *Tetrahedron Lett*. **1986**, *27*, 377. (b) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem*. **1987**, *52*, 1673.
7. Although no intermediates were formed, both groups confirmed the evidence for the formation and pathway for 2-anilinoalkanol and 1,2-dianilinoalkane via a separate experiment.
8. Besides alkanolamine, ethylene glycol and ethylene oxide, acetaldehyde is also used as $C_2$-fragment for the synthesis of indoles: ref. 6.
9. Except for indoles, we could not isolate any identifiable products.
10. *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999.