

Notes

New C₂-Fragment for Ruthenium-Catalyzed Synthesis of IndolesChan Sik Cho,^{*,*} Dong Cheon Park, and Sang Chul Shim^{*}[†]Research Institute of Industrial Technology, Kyungpook National University, Daegu 702-701, Korea. *E-mail: cscho@knu.ac.kr
Department of Applied Chemistry, College of Engineering, Kyungpook National University, Daegu 702-701, Korea

*E-mail: scshim@knu.ac.kr

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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 reaction²) (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 C₂-fragment leading to indoles (Scheme 1, route c).⁶ In these regards, it was suggested that these reactions proceed *via* a sequence involving an initial formation of 2-anilinoalkanol shown in Scheme 1 and *N*-alkylation of anilines by 2-anilinoalkanol to form 1,2-dianilinoalkanes.⁷ These circumstances led us to seek a new C₂-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 C₂-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 RuCl₃(PPh₃)₃ or RuCl₃·*m*H₂O/3PPh₃ 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

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 · <i>m</i> H ₂ O/3PPh ₃	20	19	8
2	8	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	39	9
3 ^c	8	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	22	35
4 ^d	8	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	38	4
5	20	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	67	7
6	30	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	85	9
7	40	(0.1) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	93	7
8	40	(0.05) RuCl ₃ · <i>m</i> H ₂ O/3PPh ₃	20	48	49
9	40	(0.05) RuCl ₃ · <i>m</i> H ₂ O/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 · <i>m</i> H ₂ O/3PPh ₃	20	33	0

^aReaction conditions: 2a (1 mmol), dioxane (10 mL), 180 °C, under argon. ^bDetermined by GLC. ^cSnCl₂ (1 mmol) was used as hydrogen acceptor. ^d1-Hexene (10 mmol) was used as hydrogen acceptor. ^eWithout dioxane.

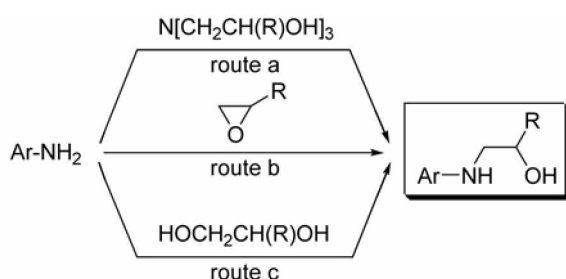
**Scheme 1**

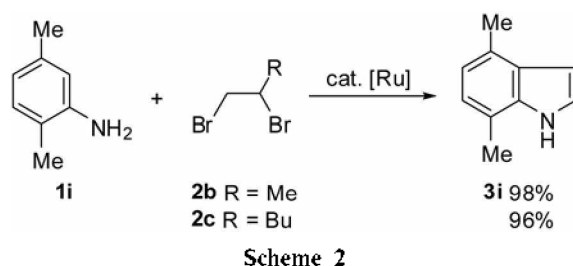
Table 2. Ruthenium-catalyzed synthesis of **3** from **1** and **2**^a

Anilines	Indoles	Yield (%) ^b
		78
		75
		72 ^c
		45
		25
		26
		54
		94
		96
		95
		20

^aReaction conditions: **1** (40 mmol), **2** (1 mmol), RuCl₃·nH₂O (0.1 mmol), PPh₃ (0.3 mmol), dioxane (10 mL), 180 °C, for 20 h, under argon. ^bIsolated yield. ^c4-Methylindole: 6-methylindole = 1:2.

(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 C₂-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 C₂-fragment. However, treatment of **1a** (1 mmol) in the absence of **2a** under the conditions of RuCl₃·nH₂O (0.1 mmol)/PPh₃ (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 C₂-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 N₂ as carrier gas. The isolation of pure products was carried out via thin layer (silica gel 60 GF₂₅₄, 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), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (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 °C 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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- 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.
- Besides alkanolamine, ethylene glycol and ethylene oxide, acetaldehyde is also used as C₂-fragment for the synthesis of indoles: ref. 6.
- Except for indoles, we could not isolate any identifiable products.
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