Tetrahedron Letters, Vol.27, No.3, pp 377-380, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

Ruthenium Complex Catalyzed N-Heterocyclization. Indoles from Aminoarenes and Glycols.

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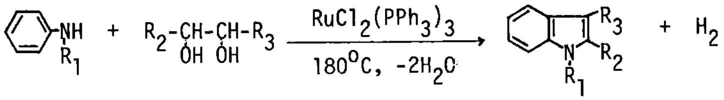
Summary: N-Methylaniline reacted with ethylene glycol in the presence of a homogeneous ruthenium catalyst (1 mol% based on ethylene glycol) to give 1-Methylindole in 51% yield. Similarly, aniline reacted with 2,3-butanediol affording 2,3-dimethylindole in 58% yield. The yields of indoles were affected by the molar ratio of aminoarene to glycol.

Indole derivatives have long been prepared by the well-known Fischer indole synthesis[1)], using a phenylhydrazine and an aldehyde or a ketone. However, the most simple way to build up a indole ring might be an use of C_2-fragment and aminoarene. Recently, such synthetic methods have been attempted, mostly from an industrial point of view. In these reactions, acetaldehyde[2)], ethylene oxide[3)], and ethylene glycol[4)] were used as the C_2-fragment with aminoarenes. However, all these reactions were carried out over heterogeneous catalyst under very severe reaction conditions, at 300-700°C, and in some cases yields were not so satisfactory.

This communication deals with the first example of a homogeneously catalyzed N-heterocyclization to indole derivatives using aminoarenes (1) and glycols (2) (eq. 1).



(1)

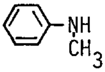
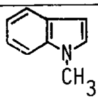
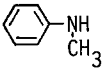
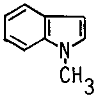
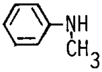
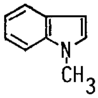
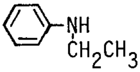
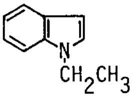
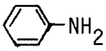
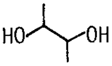
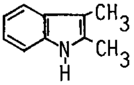
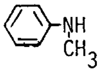
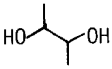
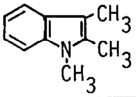
1 2 3

$R_1 = H$
$= CH_3$
$= CH_2CH_3$

$R_2 = R_3 = H$
$= CH_3$

The general experimental procedure is as follows. Into a glass liner set in a 50 ml stainless steal reactor were charged aminoarene (50 mmol), glycol (20 mmol), $RuCl_2(PPh_3)_3$ (0.2 mmol), and a solvent (5.0 ml) under argon stream. The reactor was heated to 180°C and thermostated at this temperature for 5 h with stirring.

Table 1. Synthesis of Indole derivatives from Aminoarene and Glycol using $RuCl_2(PPh_3)_3$.[a)]

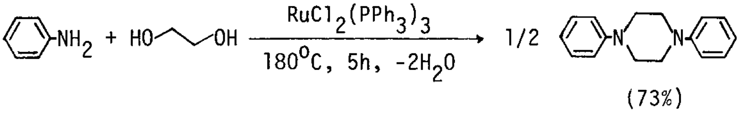
run	aminoarene	glycol	product	yield(%)[b)]
1				51
2[c)]				39
3[d)]				45
4				34
5[e)]				46
6[e)]				(58)[f)]

a) Glycol (20 mmol), aminoarene (50 mmol), $RuCl_2(PPh_3)_3$ (0.2 mmol), and dioxane (5.0 ml); at 180°C for 5h. b) Based on glycol by GLC. c) Using 1-hexene (5.0 ml) instead of dioxane. d) Using 1,3-dimethyl-2-imidazolidinone (5.0 ml) instead of dioxane. e) Reaction time 20 h. f) Isolated yield.

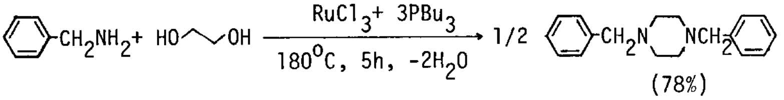
Representative results are listed in Table 1. N-Methylaniline reacted with ethylene glycol in dioxane in the presence of a catalytic amount of a ruthenium complex (1 mol% based on ethylene glycol) to give 1-methylindole in 51% yield (run 1). The yield of 1-methylindole was affected by a molar ratio of the aminoarene to ethylene glycol. The highest yield was realized at the molar ratio of 2.5(run 1); the yield of 1-methylindole was 39% at the molar ratio of 3.0, 42% at 2.0, and 16% at 1.0. The reaction proceeded similarly in other solvents such as 1-hexene (run 2)[5)], 1,3-dimethyl-2-imidazolidinone (run 3), 1-methyl-2-pyrrolidinone, and DMF. N-Ethylaniline also reacted with ethylene glycol .to give 1-ethylindole (run 4). 2,3-Butanediol could be used as a substituted C_2-fragment, and reacted with aniline or N-methylaniline to give the corresponding indoles in good yields (runs 5 and 6).

It is noteworthy that the present N-heterocyclization does not require any hydrogen acceptors. During the reaction, hydrogen was evolved into gas phase. This feature is extremely important and convenient as a synthetic method.

Indole itself was obtained in only trace yield from aniline and ethylene glycol. Instead, 1,4-diphenylpiperazine was isolated in 73% yield by column chromatography (alumina-hexane) (eq. 2)$^{6)}$. Similar reaction between benzylamine and ethylene glycol also gave 1,4-dibenzylpiperazine in 78% isolated yield (eq. 3)$^{6)}$.

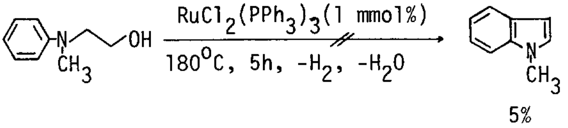


(2)



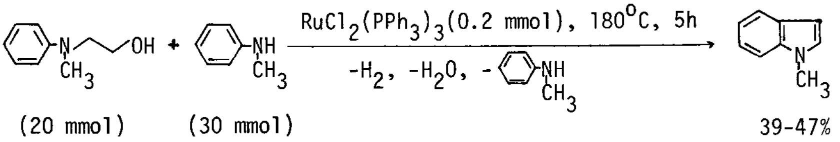
(3)

The first step in the present N-heterocyclization appeares to be formation of 2-anilinoethanol derivatives (**4**)$^{7)}$(step **a** in Scheme). Similar C-N bond formations using amine and alcohol functionalities catalyzed by the ruthenium complex have been reported recently$^{8,9)}$. In order to reveal the reaction pathway, 2-(N-methyl-N-phenylamino)ethanol (**4**: $R_1 = CH_3$, $R_2 = R_3 = H$) was allowed to react in the presence of $RuCl_2(PPh_3)_3$. However, from this aminoethanol, 1-methylindole was not substantially obtained in 1-hexene or 1,3-dimethyl-2-imidazolidinone (eq. 4). This result indicates that the



(4)

indoles are not formed directly from **4** by the intramolecular cyclization (path **d**). On the other hand, 2-(N-methyl-N-phenylamino)ethanol reacted with N-methylaniline in the presence of $RuCl_2(PPh_3)_3$ to give 1-methylindole in 47% yield in 1-hexene and in 39% yield in 1,3-dimethyl-2-imidazolidinone (eq. 5). This result suggests that an ethylenediamine type compound (**5**) is a key

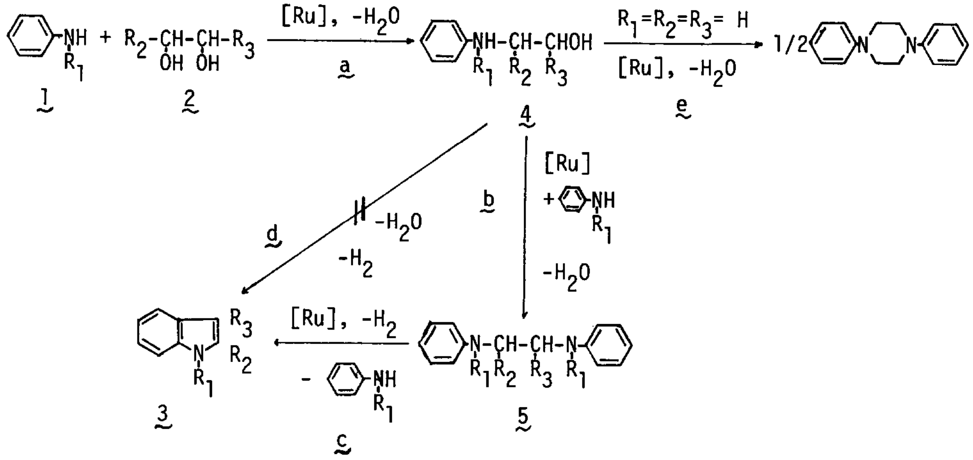


(5)

intermediate for the cyclization to the indole (3)(path **c**). In the present N-heterocyclization, yields of the indoles were good with excess of aminoarenes (vide supra). Such excess aminoarene would favor the formation of the intermediate **5** from **4**. The piperazine derivatives could be derived via bimolecular cyclization of **4** (path **e**), when primary amines reacted with ethylene glycol (eqs. 2 and 3).

Further studies on the reaction mechanism and optimization of the reaction are now in progress[10].

The present work was supported in part by Grant-in-Aid for Scientific Research No. 60119001 from the Ministry of Education, Science and Culture.



[References and Notes]

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2) Japan Kokai 72-33355; Chem. Abst. **1972**, 77, 164472.

3) Japan Kokai 81-61353; Chem. Abst. **1981**, 95, 115293.

4) U.S. Pat. **1984**, 4436917; Chem. Abst. **1984**, 101, 7024.
Japan Kokai 83-32863; Chem. Abst. **1983**, 99, 55378.
Japan Kokai 81-63958; Chem. Abst. **1981**, 95, 150441.

5) 1-Hexene was partly hydrogenated to hexane, which reduced the evolved hydrogen considerably.

6) A mixture of the amine (20 mmol), ethylene glycol (20 mmol), and dioxane 5.0 ml) was stirred at 180°C for 5 h in the presence of $RuCl_2(PPh_3)_3$ (0.20 mmol) or $RuCl_3\cdot nH_2O$ (0.20 mmol)-PBu_3 (0.60 mmol).

7) In the reaction of N-methylaniline and ethylene glycol, 2-(N-methyl-N-phenylamino)ethanol (**4**; $R_1=CH_3$, $R_2=R_3=H$) was isolated from the reaction mixture.

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9) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. J. Org. Chem. **1985**, 50, 1365.

10) Under similar reaction conditions, rhodium complexes ($RhCl(PPh_3)_3$, $RhH(PPh_3)_3$) showed only low catalytic activities; yields of 1-methylindole were 4-5% with low conversions of the substrates.

(Received in Japan 2 November 1985)