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SYNTHESIS OF INDOLES FROM *N*-SUBSTITUTED ANILINES AND TRIETHANOLAMINE BY A HOMOGENEOUS RUTHENIUM CATALYST

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ABSTRACT: *N*-substituted anilines react with triethanolamine in the presence of a catalytic amount of a homogeneous ruthenium catalyst to give the corresponding 1-substituted indoles in good yields.

The chemistry of indoles has been widely investigated from both an industrial point of view and a physiological activity. The Fischer indole synthesis is the most commonly used route and has been extensively reviewed.[1] Bischler synthesis[2] and Madelung synthesis[3] are also popular routes to the indole synthesis. However, these precedents are restricted to the particular substrates, which are not easily accessible. The simplest way to build up an indole skeleton might be an intermolecular reaction between *N*-substituted anilines and C_2-fragments such as acetaldehyde,[4] ethylene glycol,[5] and ethylene oxide.[6] However, all these reactions were carried out over heterogeneous catalyst under very severe reaction

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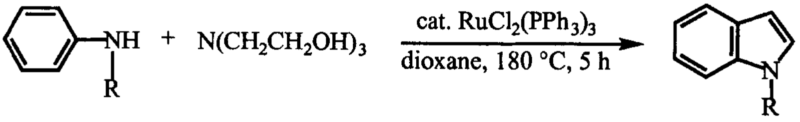
conditions and in some cases yields were not so satisfactory. Recently, one of us reported on the facile synthesis of indoles from *N*-substituted anilines and ethylene glycols by introducing a homogeneous ruthenium catalyst.[7] We here report the first synthesis of indoles from *N*-substituted anilines and triethanolamine as a new C_2-fragment by the ruthenium catalyst.



Treatment of *N*-methylaniline (50 mmol) with triethanolamine (5 mmol) in dioxane in the presence of a catalytic amount of tris(triphenylphosphine)-ruthenium(II) chloride [$RuCl_2(PPh_3)_3$, 2 mol % based on the amine] at 180 °C for 5 h afforded 1-methylindole in 78% yield (Table). The yield of 1-methylindole was considerably affected by the molar ratio of *N*-methylaniline to triethanolamine. The highest yield was optimized at a molar ratio of 10.0. The reaction also proceeded using primary- or secondary ethanolamines in place of triethanolamine, but the product yield was generally lower (runs 2 and 3). On the other hand, the reaction using *N*-benzyldiethanolamine showed nearly the same yield of 1-methylindole as triethanolamine (run 4). The reaction could also be applied to many *N*-substituted anilines such as *N*-ethyl-, *N*-*n*-propyl-, *N*-*n*-butyl-, *N*-benzyl-, and *N*-phenylanilines, the yields of the corresponding *N*-alkylindoles being always good (runs 6-10). Typical results are summarized in Table. However, treatment of aniline with triethanolamine under the conditions described so far resulted in only a trace amount of 1-methylindole together with the formation of many unidentified compounds.

Although the details of the reaction scheme are not certain, we presume the formation of 2-(*N*-alkyl-*N*-phenylamino)ethanol obtained from an intermolecular

Table

run	anilines	amines	isolated yield (%)
1	*N*-methylaniline	triethanolamine	78
2	*N*-methylaniline	diethanolamine	29
3	*N*-methylaniline	ethanolamine	13
4	*N*-methylaniline	*N*-benzyldiethanolamine	70
5	*N*-methylaniline	*N*-dibenzylethanolamine	19
6	*N*-ethylaniline	triethanolamine	76
7	*N*-*n*-propylaniline	triethanolamine	75
8	*N*-*n*-butylaniline	triehanolamine	70
9	*N*-benzylaniline	triethanolamine	71
10	*N*-phenylaniline	triethanolamine	63

alkyl group transfer between *N*-substituted aniline and triethanolamine. The detailed mechanism of this reaction and application of other alkanolamines for synthetic utility are in progress.

EXPERIMENTAL

General procedure for the synthesis of indoles: A mixture of *N*-substituted aniline (50 mmol), triethanolamine (0.746g, 5 mmol), and $RuCl_2(PPh_3)_3$ (0.096g, 0.1 mmol) in a stainless steel autoclave was stirred magnetically in dioxane (10 mL) at 180 °C for 5 h under argon atmosphere. The reaction mixture was filtered and evaporated under reduced pressure. To the residual oily material was added 100 mL of diethyl ether and washed three times with 50 mL of aqueous 5% HCl solution to remove excess *N*-alkylaniline. The organic phase was separated and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure left an oil which was separated by TLC using ethyl acetate/hexane (1/30) mixture as an eluent to give the indoles.

1-Methylindole: 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.50-7.60 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.7, 100.6, 119.1, 120.7, 121.4, 128.4, 128.6, 136.6; Ms *m/z* (relative intensity) 131 (M+, 92.5), 130 (100), 129 (76), 128 (4), 103 (14), 102 (14).

1-Ethylindole: 76% yield; ^{1}H NMR (60 MHz, CCl_4) δ 1.4 (t, *J* = 7 Hz, 3H), 4.1 (q, *J* = 7 Hz, 2H), 6.4-7.7 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.3, 40.7, 100.9, 109.2, 119.1, 120.9, 121.2, 126.8, 128.6, 135.6.

1-*n*-propylindole: 75% yield; ^{1}H NMR (60 MHz, CCl_4) δ 0.8 (t, *J* = 7 Hz, 3H), 1.5-1.9 (m, 2H), 3.9 (t, *J* = 7H, 2H), 6.4-7.7 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3, 23.3, 47.7, 100.7, 109.3, 119.0, 120.8, 121.1, 127.6, 128.5, 135.9.

1-*n*-butylindole: 70% yield; ^{1}H NMR (60 MHz, CCl_4) δ 0.9 (t, *J* = 7 Hz, 3H), 1.0-1.4 (m, 2H), 1.6-1.9 (m, 2H), 4.0 (t, *J* = 7 Hz, 2H), 6.4-7.1 (m, 11H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 20.1, 32.2, 45.9, 100.8, 109.3, 119.0, 120.8, 121.2, 127.6, 128.5, 135.9.

1-phenylindole: 63% yield; ^{1}H NMR (60 MHz, CCl_4) δ 6.5-7.5 (m, 11H).

1-benzylindole: 71% yield; ^{1}H NMR (60 MHz, CCl_4) δ 4.7 (s, 2H), 6.0-7.1 (m, 11H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 54.3, 101.7, 109.6, 119.5, 120.9, 121.6, 126.8, 127.6, 128.2.

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