

## Heterogeneously Catalysed Alkylations of Indole and 2,3-Dihydroindole \*

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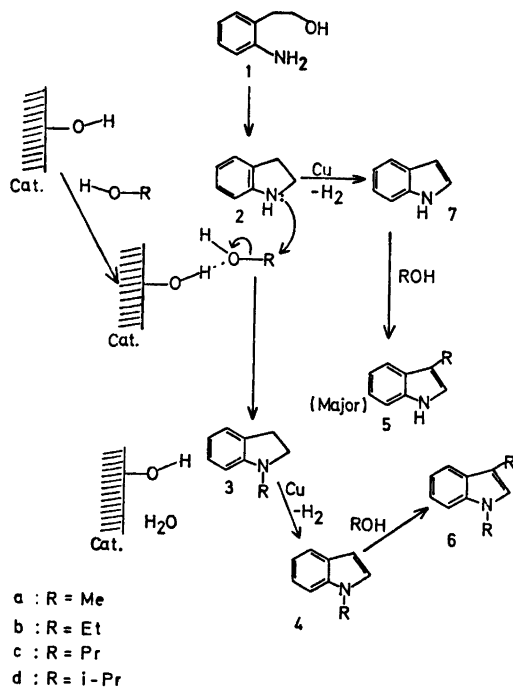
2,3-Dihydroindole (2) from 2-(*o*-aminophenyl)ethanol (1) is a readily available intermediate for the synthesis of indole and indoles substituted in the benzene ring.<sup>1</sup> We now report heterogeneously catalysed syntheses of 1-alkylated dihydroindoles (3) and 1- and 3-alkylated indoles (4 and 5). Other syntheses of alkylindoles have been reported.<sup>2-5</sup> However, 1-alkyldihydroindoles, if readily available, would be valuable in the preparation of indoles substituted in the benzene ring. Silica gel, alumina and alumina-silica have been used as catalysts for the alkylation of amines with alcohols and also for the formation of ethers and alkenes from alcohols.<sup>1,6-9</sup>

Compound 2 and a series of four alcohols were passed over an alumina-silica catalyst at 250 °C. Good yields of 1-alkyl-2,3-dihydroindoles (3) were obtained (Table 1) when primary alcohols were used as the alkylating agents. A by-product was the 1-alkylindole which which must have been formed by dehydrogenation of 3 (see below). The method compares favourably with the ones reported earlier for the synthesis of 3.<sup>10,11</sup> The reaction with propanol gave 3c and that with 2-propanol 3d together with unreacted 2.

When a solution of 1 in methanol or 1,2-dimethoxyethane was passed over various catalysts at 250 °C,<sup>1</sup> 3a was obtained in good to excellent yields (87 %, run 9). The activity of the catalysts was in the order silica gel < alumina < alumina-silica. 1,2-Dimethoxyethane did methylate the amino nitrogen, but those runs gave lower yields than the corresponding ones with methanol. No other alkyldihydroindoles were identified from the reactions with 1,2-dimethoxyethane.

Passing 1 and methanol over a copper-containing catalyst (run 10),<sup>1</sup> gave 4a, but it was accompanied by 5a and indole. However, it was possible to obtain 4a in high yield (87 %) by passing 3a over the same catalyst; 4a was thus obtained in two operations from 1 and in a 74 % overall yield. When indole and methanol were reacted, 5a (20 %) and 4a (2 %) were obtained. From this observation it appears that when 1 and methanol were passed over the copper catalyst, dehydrogenation of 2 to give indole competed successfully with alkylation of 2. Alkylation of the indole then gave 5a. Reaction of 3a and methanol gave a mixture of 4a (17 %) and 6a (14 %).

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Scheme 1.

The results in Table 1 and 2 also give indications of the mechanisms for the formation of 3 from 2 or 1. The acidity of the catalysts<sup>12</sup> increases in the same order as their activity in the alkylation reaction (Table 2). Further, the primary alcohols were better alkylating agents than the secondary one, and the product from the reaction with propanol was 1-propyldihydroindole and not the isopropyl isomer (run 3). These facts together suggest that the alkylation goes by an  $S_N2$ -like mechanism catalysed by the acidic groups of the catalyst (Scheme 1). A similar mechanism has been proposed for the intramolecular alkylation of 1 and 2.<sup>1</sup>

The hydrogens of the amino groups of 1 and 2 may have been hydrogen bonded to the surface during the reaction. The exact mode of attachment of the alcohol to the catalyst is not known. It may be a hydrogen bond as in Scheme 1 or as an alkoxy group.<sup>13</sup> Further, the reaction of 1 and methanol over the copper-containing alumina-silica catalyst (run 10) did not give 1-methylindole as the major product. The reaction of 1 with methanol has therefore probably proceeded as shown in Scheme 1, and not by alkylation of 1 to 2-(*o*-methylaminophenyl)ethanol followed by cyclisation of this to 3a.

*Experimental.* The system for the catalysed reactions has been described.<sup>1</sup> The reactor was heated in an oven with forced air circulation and a "Euroterm" temperature controller

Table 1. Reaction of 2,3-dihydroindole (2) with alcohols over alumina-6% silica at 250°C. Details in experimental.

Run	Alcohol	Yields, % of charged 2		
		Re- covered 2	1-Alkyl- dihydro- indole	1-Alkyl- indole
1	Methanol	4	95	2
2	Ethanol	7	70	10
3	Propanol	4	45	17
4	2-Propanol	55	20	2

which kept the reactor at  $250 \pm 1^\circ\text{C}$ . The reactants were condensed in a series of three cold traps, the last of which contained methanol at  $-75^\circ\text{C}$ . All reactions were run over 10 g of catalyst. The combined condensates were analysed by GC (Varian Aerograph 1200, Column 10% OV17, 90 cm) with nitrobenzene as internal standard. The reported yields are from these analyses. Control experiments with only quartz chips in the reactor gave no reaction.

The catalysts used were silica gel (Schuchardt), alumina (Harshaw 1404T, surface area  $200 \text{ m}^2 \text{ g}^{-1}$ ) and alumina with 6% silica (Harshaw 1602T, surface area  $240 \text{ m}^2 \text{ g}^{-1}$ ). The preparation of the copper-containing catalysts has been described.<sup>1</sup> All products were identified by comparing their GC retention times, IR, NMR and mass spectra with those

of authentic samples. Both 4a and 5a were stable under the reaction conditions.

*Alkylations of 2,3-dihydroindole (2) with alcohols.* A solution of 2 (10%) in the appropriate alcohol was passed over alumina-6% silica catalyst at  $250^\circ\text{C}$  at a rate of  $5 \text{ g h}^{-1}$ . The rate of flow of nitrogen was  $100 \text{ ml min}^{-1}$  (Table 1).

*Alkylation of 2-(o-aminophenyl)ethanol (1).* (a) By dimethoxyethane: A mixture of 1 (6 g) and dimethoxyethane (4 g) was passed over the appropriate catalyst at  $250^\circ\text{C}$  at a rate of  $7 \text{ g h}^{-1}$  with nitrogen ( $150 \text{ ml min}^{-1}$ ). (b) By methanol: A solution of 1 (20%) in methanol was passed over the appropriate catalyst at  $250^\circ\text{C}$  at a rate of  $20 \text{ g h}^{-1}$  with nitrogen ( $100 \text{ ml min}^{-1}$ ) (Table 2).

*Alkylation of indole.* A solution of indole (20%) in methanol was passed over the catalyst at  $250^\circ\text{C}$  at a rate of  $20 \text{ ml h}^{-1}$  with nitrogen ( $100 \text{ ml min}^{-1}$ ). Over alumina-6% silica, alumina-6% silica-3% copper, and silica gel-3% copper catalysts, 1-methylindole (2%), 3-methylindole (20%) and 1,3-dimethylindole (1%) were obtained together with unreacted indole (45%).

*Dehydrogenation of 1-methyl-2,3-dihydroindole (3a).* 3a (3.3 g) was injected during 1 h over a copper-containing (3%) alumina-6% silica catalyst together with nitrogen ( $100 \text{ ml min}^{-1}$ ) at  $250^\circ\text{C}$  to give 4a (2.8 g, 85%).

*Reaction of 1-methyl-2,3-dihydroindole (3a) with methanol.* 3a (2.3 g) in methanol (9.2 g) was passed over the same catalyst as used above during 1 h with nitrogen ( $100 \text{ ml min}^{-1}$ ) at  $250^\circ\text{C}$  to give 4a (0.38 g, 17%) and 6a (0.35 g, 14%).

Table 2. Alkylation of 2-(o-aminophenyl)ethanol (1) over different catalysts at  $250^\circ\text{C}$ . Details in experimental.

Run	Catalyst	Yields, % of charged 1	
		Dihydro- indole	1-Me-dihydro- indole
Alkylating agent: Dimethoxyethane			
5 <sup>a</sup>	Silica gel	65	3
6	Alumina	75	6
7	Alumina- 6% silica	13	48
Alkylating agent: Methanol			
8	Silica gel	51	15
9	Alumina- 6% silica	0.3	87
10 <sup>b</sup>	Alumina- 6% silica- 3% copper	0	8

<sup>a</sup> Recovered 1, 14%; none or traces only in the other runs. <sup>b</sup> Carrier gas hydrogen. Other products: indole (21%), 1-methylindole (4a, 17%), 3-methylindole (5a, 19%), 1,3-dimethylindole (6a, 2%).

- Bakke, J., Heikman, H. and Hellgren, E. B. *Acta Chem. Scand. B* 28 (1974) 393.
- Sundberg, R. J. *The Chemistry of Indoles*, Academic, New York 1970.
- Houlihan, W. J., Ed., *Indoles*, Wiley, New York 1972.
- Barco, A., Benetti, S., Pollini, G. P. and Barandi, P. G. *Synthesis* 2 (1976) 124.
- Bocchi, V., Casnati, G., Dossena, A. and Villani, F. *Synthesis* 2 (1976) 414.
- Sabatier, P. and Mailhe, A. *C. R. Acad. Sci.* 150 (1910) 823.
- Hayami, H., Yoda, S. and Shimizu, H. *Japan Kokai*: 78 09, 725; *Chem. Abstr.* 88 (1978) 190362h.
- Decker, M., Hoffmann, H., Hupfer, L. and Toussaint, H. *Ger. Offen.*, 2,646,379.
- Winfield, M. E. In Emmet, P. H., Ed., *Catalysis*, Reinhold, New York 1960, Vol. 7, Chapter 2.
- Behringer, H. and Duesberg, P. *Chem. Ber.* 96 (1963) 377.
- Albrecht, H. and Farnung, W. *Synthesis* 3 (1977) 335.
- Boehm, H. P. *Adv. Catal.* 16 (1966) 179.
- Knözinger, H. *Adv. Catal.* 25 (1976) 184.

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