

N-Alkylation of Indole and Pyrroles in Dimethyl Sulphoxide

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The potassium salts of indole, pyrrole, and 2,5-dimethylpyrrole were converted into *N*-alkyl derivatives in high yield in dimethyl sulphoxide by use of iodomethane, iodoethane, 1-iodopropane, and benzyl bromide. Dehydrohalogenation occurred when 2-iodo- and 2-bromo-2-methylpropane were used; when 2-iodopropane was employed alkylation and dehydrohalogenation were observed.

We required a high yield route to certain *N*-alkylpyrrole derivatives in connection with another study.¹ The alkylation of pyrrolylmagnesium bromide is complex; both 2- and 3-alkylpyrroles are formed and polyalkylation is observed when equivalent quantities of alkyl halide are used.² The reactions of alkali metal salts of pyrroles³ and indole⁴ with alkyl halides are complex but alkylation at nitrogen is usually predominant in strongly ionising solvents. The use of dimethyl sulphoxide as a dipolar aprotic solvent is well known⁵ and excellent results have been obtained, for example in the methylation of phenols.⁶ Dimethyl sulphoxide has been used as a solvent for pyrrolyl-

potassium in a study of the reactions of the anion with allylic halides,^{7,†} and the use of sodium hydroxide in dimethylformamide has been described,⁸ as has the use of hexamethylphosphoramide.⁹

We now report an extremely convenient method for the preparation of *N*-*n*-alkyl-indoles and -pyrroles in high yield, involving the formation of the potassium salts of indole and pyrroles by interaction with powdered potassium hydroxide in dimethyl sulphoxide at room temperature. Alkylation is then achieved without the isolation of the potassium salts by addition of an excess of the appropriate *n*-alkyl halide, also at room temperature (Table). Our results should be compared with those recently reported for the alkylation of pyrrolyllithium (I)¹⁰ and the *N*-methylation of indole in liquid

† Note added in proof. Professor A. H. Jackson has recently informed us of his similar work on the *N*-alkylation of pyrroles and indoles in dimethyl sulphoxide using either potassium *t*-butoxide (D. J. Newman, M.Sc. Thesis, Liverpool, 1963) or sodium hydride (B. Naidoo and P. P. Lynch, Ph.D. Theses, Liverpool, 1969 and 1970, respectively) as the base.

¹ H. Heaney, S. V. Ley, A. P. Price, and R. P. Sharma, *Tetrahedron Letters*, 1972, 3067.

² P. S. Skell and G. P. Bean, *J. Amer. Chem. Soc.*, 1962, **84**, 4655.

³ K. Schofield, 'Heteroaromatic Nitrogen Compounds, Pyrroles and Pyridines,' Butterworths, London, 1967, p. 66.

⁴ L. R. Smith in 'Indoles, Part Two,' ed. W. J. Houlihan, 'The Chemistry of Heterocyclic Compounds,' Wiley-Interscience, New York, 1972, p. 72.

⁵ L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, vol. 1, 1968, pp. 296—318; vol. 2, 1969, pp. 157—173; D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, 1960, **82**, 6412; D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *ibid.*, 1961, **83**, 3678.

⁶ R. G. Gillis, *Tetrahedron Letters*, 1968, 1413.

⁷ C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1962, **84**, 43.

⁸ Belg. P. 621,047/1963.

⁹ See for example, J. A. Joule and G. F. Smith, 'Heterocyclic Chemistry,' Van Nostrand-Reinhold, London, 1972, p. 208; H. Normant, *Angew. Chem. Internat. Edn.*, 1967, **6**, 1046.

¹⁰ C. F. Candy and R. A. Jones, *J. Org. Chem.*, 1971, **36**, 3993.

ammonia¹¹ and are in accord with the rationalisation of the results of the reactions of allylic halides with alkali metal salts of pyrrole in various solvents.^{7,12}

Reactions of indole and pyrroles with potassium hydroxide in dimethyl sulphoxide and then with alkyl halides at room temperature

Heterocycle	Alkyl halide (mol)	Products (isolated yield %)
Indole	Iodomethane (2)	1-Methylindole (95)
Indole	Benzyl bromide (2)	1-Benzylindole (95)
Pyrrole	Iodomethane (2)	1-Methylpyrrole (86)
2,5-Dimethylpyrrole	Iodomethane (2)	1,2,5-Trimethylpyrrole (86)
Pyrrole	Iodoethane (2)	1-Ethylpyrrole (85)
Pyrrole	1-Iodopropane (2)	1-n-Propylpyrrole (85)
Pyrrole	2-Iodopropane (2)	1-Isopropylpyrrole (60), Pyrrole (15)
Pyrrole	2-Bromo-2-methylpropane (3)	Pyrrole (85)

Although no attempt has been made to optimise the yields obtained it is clear that the ease with which the reactions can be carried out makes this a valuable method for the preparation of n-alkyl-pyrroles and -indoles. A very high yield of *N*-benzylindole was obtained even though benzyl bromide is known to react with dimethyl sulphoxide.¹³ This result is presumably due to the fact that the reaction between the indolyl anion and benzyl bromide is carried out at a low temperature. In each of the reactions we analysed the crude mixtures of products by g.l.c. before distillation. In the reactions with primary alkyl halides no pyrrole was detected and no other products were present in excess of 5%.

In the reaction of pyrrolyl potassium with 2-iodopropane g.l.c. showed the presence of pyrrole (20%) in addition to *N*-isopropylpyrrole (67%) and in the reactions with 2-bromo- and 2-iodo-2-methylpropane the

¹¹ K. T. Potts and J. E. Saxton, *Org. Synth.*, 1960, **40**, 68.

¹² P. A. Cantor and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1958, **80**, 970.

only major product was pyrrole (>90%). In each of these last three reactions a brisk evolution of gas was observed immediately after the addition of the alkyl halide. These results strongly support the view that dehydrohalogenation is efficiently effected by the pyrrolyl anion in dimethyl sulphoxide with tertiary halides and to a lesser extent with secondary halides.

EXPERIMENTAL

Crude reaction mixtures were analysed by g.l.c. with a Pye (series 104) instrument fitted with a flame ionisation detector and a 5 ft \times $\frac{3}{8}$ in column of polypropylene glycol on Chromosorb W (15:85 w/w) at 106° with a nitrogen flow rate of 50 ml min⁻¹.

Typical Procedures.—(a) Dimethyl sulphoxide (200 ml) (dry) was added to potassium hydroxide (22.4 g, 0.4 mol) (crushed pellets) and the mixture was stirred for 5 min. Indole (11.7 g, 0.1 mol) was then added and the mixture was stirred for $\frac{3}{4}$ h. Benzyl bromide (34.2 g, 0.2 mol) was added and the mixture was cooled briefly and stirred for a further $\frac{3}{4}$ h before water (200 ml) was added. The mixture was extracted with ether (3 \times 100 ml) and each extract was washed with water (3 \times 50 ml). The combined ether layers were dried (CaCl₂) and the solvent and excess of benzyl bromide was removed finally under reduced pressure (15 mmHg). The residue was distilled and gave 1-benzylindole (19.6 g, 95%), b.p. 133–138° at 0.3 mmHg, m.p. 43° (from ethanol) (lit.,¹⁴ 45°); τ (CDCl₃) 2.25–2.50 (1H, m), 2.6–3.1 (9H, m), 3.48 (1H, d, *J* 3.4 Hz), and 4.79 (2H, s).

(b) A similar method was used with pyrrole except that that the products were distilled through a 2½ ft Vigreux column fitted with an electrically heated jacket.

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¹³ H. R. Nace and J. J. Monagle, *J. Org. Chem.*, 1959, **24**, 1792.

¹⁴ H. Plieninger, *Chem. Ber.*, 1954, **87**, 127; H. Normant and T. Cuvigny, *Bull. Soc. chim. France*, 1965, 1866.