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A CONVENIENT PROCEDURE FOR THE N-ALKYLATION OF COMPOUNDS CONTAINING MULTIPLE BENZIMIDAZOLE FUNCTIONALITIES

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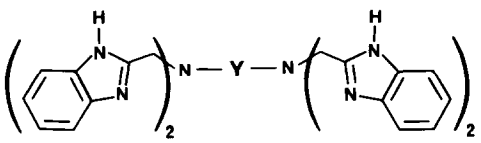
SUMMARY: A facile and efficient method for the N-alkylation of ligand systems containing multiple benzimidazole groups has been developed, involving a basic media of powdered KOH in dimethylsulfoxide and alkyl halides as alkylating agents.

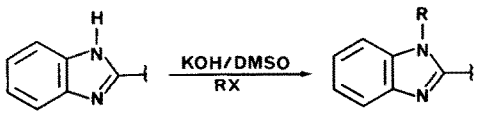
In the course of our work on the synthesis of binucleating ligands for biomimetic studies on dinuclear copper proteins[1] we have found a need to N-alkylate a variety of ligands containing up to four 2-substituted benzimidazole groups (1).



(1)

Although several efficient methods have been reported for the N-alkylation of simple benzimidazoles,[2-4] we have found that these methods are generally unsuitable for the alkylation of our more complex systems because of (a) poor solubility of the starting materials in the solvents commonly used, (b) incomplete alkylation, despite the use of excess alkylating agent, and subsequent separation difficulties, and (c) overreaction to form quaternary ammonium salts at the elevated temperatures often required.[5,6] This probably explains why there are several reports of multi-benzimidazole ligands[7] but only sporadic examples of successful alkylation. Methylation in 77% yield of the tetra-benzimidazole **1** with Y = $-CH_2CH_2-$ has been reported[8] using powdered KOH in acetone and ethylation of **1** with Y = $-CH_2CH(OH)CH_2-$ in basic tetrahydrofuran proceeds in 83% yield.[1]

Powdered KOH in dimethylsulfoxide has been shown to be a successful medium for the N-alkylation of a variety of functional groups[9] including indoles and pyrroles.[10] Alkyl halides are the alkylating agents. We have found that this procedure can be adapted to a range of tetrabenzimidazole ligands (Table I) using a variety of alkyl halides (Table II):



The reaction is extremely facile, being complete within 1 hr at room temperature, and no special precautions are needed to ensure dryness of the reagents. Moderate to excellent isolated yields were consistently obtained obviating the need for yield optimization. The yields and scope of the reaction investigated to date are listed in the following tables. In addition, one ligand system with 5,6-dimethylbenzimidazoles (Y = -m-$CH_2C_6H_4CH_2$-) has been methylated in 64% yield. We expect the method will have wide generality.

Table I. METHYL- and ETHYLATION OF TETRABENZIMIDAZOLES

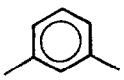
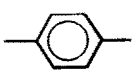
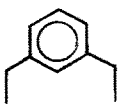
Y	RX	Yield (%)
	MeI	63
〃	EtI	40
	MeI	44
	MeI	72
〃	EtI	50
	MeI	68

Table II. ALKYLATION OF 1 WHERE Y = $-CH_2CH_2-$

RX	Yield (%)
MeI	81
EtI	92
n-PrBr	100
n-BuBr	93
$CH_2=CHCH_2Br$	86
BzBr	87

TYPICAL PROCEDURE

To a stirred suspension of powdered KOH (1.2 g, 19 mmol) in DMSO (30 ml) was added the benzimidazole (1.6 mmol) followed immediately by methyl iodide (1.4 g, 9.6 mmol). The reaction was stirred at room temp. for 1 hr and then poured into water (80 ml). The resultant flocculant precipitate was extracted into chloroform (3 x 80 ml) and the combined organic extracts were washed with water (5 x 40 ml) to remove the bulk of the DMSO, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was titurated with a minimum amount of acetone and the product collected by filtration and vacuum dried. Products were characterized by ^1H NMR and LSIMS.

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7. See for example M. Suzuki & A. Uehara, Inorg. Chim. Acta, 87, L29, (1984); Y. Nishida, K. Takahashi, H. Kuramoto & S. Kida, Inorg. Chim. Acta, 54, L103, (1981); L. K. Thompson, B. S. Ramaswang & R. D. Dawe, Can. J. Chem., 56, 1311, (1978).

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