A Facile *N*-Alkylation of Imidazoles and Benzimidazoles

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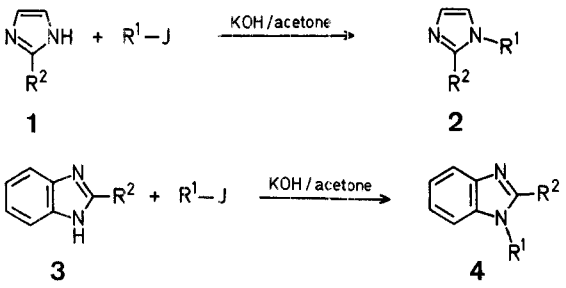
The most general method for the *N*-alkylation of imidazoles is the alkylation in the presence of alkaline reagents[1]. Nevertheless, the reaction of imidazoles with alkyl halides does not proceed satisfactorily when carried out in the presence of an alkali metal hydroxide due to the recovery of the starting imidazole and the formation of quarternary salts[2,3]. 2-Methylbenzimidazole has been methylated to give the 1,2-dimethyl compound (48%) using methyl iodide and sodium in liquid ammonia[4]; less satisfactory results were reported for the use of methyl iodide or dimethyl sulfate and potassium hydroxide. Recently, the *N*-alkylation of benzimidazoles in the presence of a phase-transfer catalyst, 18-crown-6, was reported[3].

I now report a new convenient method for the *N*-alkylation of imidazoles (**1**) and benzimidazoles (**3**) in high yield in which the potassium salts of **1** or **3** are first prepared by reaction with powdered potassium hydroxide in acetone at room temperature and then, without previous isolation, submitted to the reaction with a slight excess of the alkyl halide at room temperature to give the monoalkylated products **2** or **4**, respectively.



1 2

3 4

The use of powdered potassium hydroxide is essential for the alkylation to proceed satisfactorily. When the reaction was performed using potassium carbonate instead of potassium hydroxide the starting imidazole was recovered in high yield. With benzimidazole, the best yield (89%) of 1-methylbenzimidazole is obtained using a two- or threefold molar excess of methyl iodide. In the case of 2-aminobenzimidazole, the use of excess alkylating agent leads to side reactions and to a decrease in yield of the desired 2-amino-1-methylbenzimidazole.

1,2-Dimethylbenzimidazole; Typical Procedure:

Powdered potassium hydroxide (910 mg, 16.25 mmol) is added to a stirred suspension of 2-methylbenzimidazole (429 mg, 3.25 mmol) in acetone (13 ml). After a few min, methyl iodide (507.7 mg, 3.58 mmol) is added to the reaction mixture with vigorous stirring. After 10 min, the acetone solution is transferred to a separating funnel containing benzene (120 ml). The organic layer is washed with water (1 × 20 ml) and saturated sodium chloride solution (20 ml) and is dried with sodium sulfate. Benzene is evaporated and the residue is submitted to column chromato-

Table. Alkylation of Imidazoles (**1**) and Benzimidazoles (**3**)[a]

Educt	R^2	Alkylating Agent	Product	R^1	R^2	Yield[b] [%]	m.p. [°C] (solvent) found	m.p. [°C] (solvent) reported
1	CH_3	C_2H_5—J	**2**	C_2H_5	CH_3	70	[picrate: 171–173° (ethanol)]	[picrate: 168–169°][5]
1	C_6H_5	H_3C—J	**2**	CH_3	C_6H_5	80[c]	[picrate: 131–133° (ethanol)]	[picrate: 132°][6]
3	H	H_3C—J	**4**	CH_3	H	85; 89[d]	[picrate: 247–249° (dec) (ethanol)]	[picrate: 248°][7]
3	CH_3	H_3C—J	**4**	CH_3	CH_3	91	111–112° (benzene/pet. ether)	112°[4]
3	NH_2	H_3C—J	**4**	CH_3	NH_2	75	202–204° (benzene/chloroform)	201–202°[8]
3	H	$C_6H_5CH_2$—Br	**4**	$C_6H_5CH_2$	H	80	114–115° (ethanol)	115–115.5°[9]

[a] Reaction conditions: alkyl iodide/**1** (or **3**) = 1.1; potassium hydroxide/**1** (or **3**) = 5.0; reaction time 10 min.

[b] Yield of isolated product.

[c] The product was contaminated by an acetone dimer (probably 4-hydroxy-4-methyl-2-pentanone) which could not be removed by column chromatography. To eliminate this contamination, the reaction mixture obtained before column chromatography was acidified with aqueous 10% hydrochloric acid, and extracted with chloroform, and then the solution was made alkaline with aqueous 10% sodium hydroxide and extracted with benzene. Benzene was evaporated and the residue was submitted to column chromatography on silica gel using chloroform/ethanol (7/1) for elution.

[d] Ratio methyl iodide/benzimidazole = 2.0.

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graphy on silica gel (Merck) using chloroform/ethanol (9/1) for elution; yield: 432.5 mg (91%); m.p. 110–111 °C (Ref.[4], m.p. 114 °C).

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