DERIVATIVES OF IMIDAZOLE CONTAINING POTENTIALLY LABILE GROUPINGS AT THE N-ATOM

IV. A New Method of Preparing 1, 6-Disubstituted Derivatives of Benzimidazole

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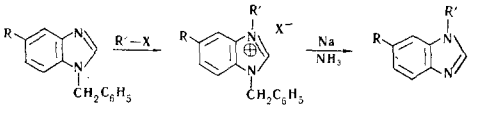
By the action of alkyl halides the 5-substituted derivatives of 1-benzylbenzimidazole were converted into salts of benzimidazole, debenzylation of which in liquid ammonia with sodium leads to the formation of the less readily available 6-derivatives of 1-alkylbenzimidazoles. This method gives good results during the synthesis of 6-alkyl-, 6-alkoxy-, and 6-aminobenzimidazoles, but because of secondary processes it cannot be used for the production of 6-bromo and 6-nitro derivatives.

It is well known that alkylation of 5(6)-substituted derivatives of benzimidazole leads to the formation of a mixture of 1, 5- and 1, 6-disubstituted derivatives formed in approximately a 1 : 1 ratio [1]. Thus the synthesis of 1, 5-disubstituted derivatives of benzimidazole is conducted according to a well elaborated scheme from the 4-derivatives of o-nitroaniline [3]. The 6-substituted derivatives of benzimidazole are much less readily available. In order to obtain such compounds, two multistage methods have been proposed, although they are of somewhat limited use [4, 5].

We have elaborated a simple method for obtaining 6-alkyl-, 6-alkoxy-, and 6-aminobenzimidazoles containing the alkyl radical in position 1. According to our scheme the readily available 5-substituted derivatives of 1-benzylbenzimidazole [6] (I) are converted into alkyl halides (II), the debenzylation of which gives rise to the 6-derivatives of 1-alkylbenzimidazoles (III).



I IIa–з III

Quaternization of 5-alkyl- and 5-alkoxy-1-benzylbenzimidazoles proceeds readily in a medium of absolute toluene, whereas 5-amino-1-benzimidazole is most conveniently alkylated in acetone because of side reactions. On debenzylation the best results are obtained when a solution of sodium in liquid ammonia is used. During the procedure 80% yields of the 6-substituted derivatives of compound III are achieved. Cleavage of the benzyl radical proceeds markedly less readily on reaction of salts of compound II with sodium amalgam or hydrogen in the presence of Raney nickel [7].

We propose that our method can be used for the synthesis of 6-bromo- and 6-nitro-substituted derivatives of benzimidazole. During the action of sodium in liquid ammonia on the salt of 1-benzyl-3-ethyl-5-bromobenzimidazole bromine is cleaved and an 80% yield of 1-ethylbenzimidazole is obtained. Salts of 5-nitrobenzimidazole interact with solutions of sodium liquid ammonia with the formation of a mixture of various products which are difficult to identify.

EXPERIMENTAL

Formation of Benzimidazole Salts (II). A solution of 0.01 mole of compound I and 0.04 mole of the alkyl halide in 40 ml absolute toluene were boiled for several hours (table). The crystals which separated out were removed by filtration, washed with acetone and then ether, and recrystallized from alcohol. Yield, 85–95%. The salt IIf was obtained in a medium of acetone. Yield, 53%.

1-Methyl-6-methoxybenzimidazole (III, R' = CH_3; R = CH_3O). A 0.92 g quantity (0.04 mole) of sodium was added

*For part III, see [9].

stepwise with stirring to a suspension of 7.4 g (0.02 mole) of the salt IIe in 75 ml liquid ammonia. The ammonia was removed by evaporation, the residue was extracted with chloroform and the product obtained was isolated from the extract by distillation under vacuum. The latter consisted of colorless crystals with a mp of 66–67° C, which is in accordance with data in the literature. Bp, 185–190° C (15 mm). Yield, 2.05 g (60%).

Salts of Benzimidazole (II)

Compound	R′	R	X	M.P., °C	Empirical formula	N, % Found	N, % Calculated	Duration of the reaction, hr
IIa	C_2H_5	H	I	173—174*	$C_{16}H_{17}JN_2$	—	—	2
IIb	C_2H_5	CH_3	I	173—174	$C_{17}H_{19}JN_2$	33.28	33.52	3
IIc	C_2H_5	CH_3O	Br	172—173	$C_{17}H_{19}BrN_2O$	23.28	23.01	2
IId	C_2H_5	CH_3O	I	151—152	$C_{17}H_{19}JN_2O$	32.30	32.52	5
IIe	CH_3	CH_3O	I	240—241	$C_{16}H_{17}JN_2O$	33.08	33.37	3
IIf	CH_3	NH_2	I	166—167	$C_{15}H_{16}JN_3$	34.98	34.74	38
IIg	C_2H_5	NO_2	I	169—169.5	$C_{16}H_{16}JN_3O$	30.88	31.01	36
IIh	C_2H_5	Br	I	201—202	$C_{16}H_{16}BrJN_2$	28.40	28.64	5

*According to data in the literature, mp is 173.5–174.5° C [8].

1-Ethyl-6-methoxybenzimidazole (III; R′ = C_2H_5; R = CH_3O). A) This compound is obtained in an analogous manner from the salt of IIc. Yield, 62%. Yellowish oil with a bp of 180–185° C (13 mm). Found, %: C 68.6; H 6.6; N 15.7. Calculated for $C_{10}H_{12}N_2O$, %: C 68.3; H 6.9; N 15.9. Picrate, yellow needles with a mp of 215–216° C (from alcohol). Found, %: N 17.0. Calculated for $C_{10}H_{12}N_2O \cdot C_6H_3N_3O_7$, %: N 17.3.

B) A 15.3 g quantity of 6% sodium amalgam was transferred stepwise with mixing into a solution of 3.43 g (0.014 mole) of a salt of compound IIc in 30 ml water. On the following day the mixture was extracted with chloroform, the extract was dried with potash and after removal of the solvent the residue was distilled under vacuum. Bp 162–167° C (9mm). Yield, 0.9 g (32%).

1-Ethyl-6-methylbenzimidazole (III, R′ = C_2H_5; R = CH_3). This compound was obtained by the action of sodium in liquid ammonia on the salt of IIb according to the above-described method. Yield, 53%. Yellowish oil with a bp of 205–210° C (2 mm). Found, %: C 74.8; H 7.6; N 17.2. Calculated for $C_{10}H_{12}N_2$: 75.0; H 7.5; N 17.5. Picrate, yellow needles (from alcohol) with a mp of 256–257° C. Found, %: N 18.2. Calculated for $C_{10}H_{12}N_2 \cdot C_6H_3N_3O_7$: N 18.0.

1-Benzyl-6-aminobenzimidazole (I, R = NH_2). A mixture of 3.2 (0.013 mole) of 1-benzyl-5-nitrobenzimidazole [9], 12 g (0.05 mole) $SnCl_2 \cdot 2H_2O$ and 15 ml conc HCl was stirred at 100° C for 1.5 hr. The precipitate was removed by filtration, dissolved in 10 ml water and treated with excess of 40% sodium hydroxide. The resulting precipitate was again filtered, dried, and the amine was extracted with hot benzene. Yield, 1.8 g (67%) Colorless needles (from benzene) with a mp of 155–156° C, Found, %: C 75.1; H 5.7; N 18.6. Calculated for $C_{14}H_{13}N_3$, %: C 75.3; H 5.9; N 18.8%.

1-Methyl-6-aminobenzimidazole (III, R′ = CH_3; R = NH_2). This compound was obtained by the action of metallic sodium in liquid ammonia on the salt of IIf according to the above-mentioned method. Light-yellow oil with a bp of 180–185° C (4 mm), readily soluble in alcohol, acetone, and chloroform. On heating it dissolves in benzene but does not dissolve in petroleum ether. Yield, 70%. Picrate, yellow prisms (from alcohol) with a mp of 225–227° C. Found, %: C 44.6; H 3.2; N 22.2. Calculated for $C_8H_9N_3 \cdot C_6H_3N_3O_7$, %: C 44.8; H 3.2; N 22.4.

Interaction between the iodide of 1-benzyl-3-ethyl-5-bromobenzimidazole (IIh) and sodium in liquid ammonium. A 0.4 g (0.0176 mole) quantity of sodium was added in small portions with mixing to a suspension of 3.9 g (0.088 mole) of the salt of IIh in 75 ml liquid ammonia. After evaporation of the ammonia the residue was extracted with chloroform, the extract was dried with potash, the solvent was removed by distillation, and the residue was sublimed under vacuum. A 0.9 g (80%) quantity of a light yellow oil was obtained, the picrate of which had a mp of 217–218° C (from alcohol) and the sample mixed with a known sample was identical to the picrate of 1-ethylbenzimidazole [8].

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