BENZIMIDAZOLE DERIVATIVES

XXXI.* REACTION OF BENZIMIDAZOLE AND ITS DERIVATIVES WITH PROPARGYL BROMIDE

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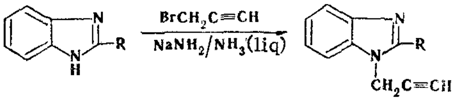
The alkylation of benzimidazole and its derivatives with propargyl bromide was studied. 1-(2'-Propynyl)benzimidazoles are readily formed in liquid ammonia in the presence of sodium amide. The alkylation of 1-ethyl-2-aminobenzimidazole leads to a mixture of 2-(N-mono)- and 2-(N,N-2'-propynyl)amino-1-ethylbenzimidazoles.

Very little study has been devoted to the alkylation of benzimidazole with unsaturated alkyl halides, and only the synthesis of 1-allylbenzimidazole has been described [2]. Continuing our investigation of ethynyl-substituted compounds of this series [3, 4], we have synthesized some 1-(2'-propynyl)benzimidazoles (IIa-d).

We were unable to introduce a propynyl group into the 1 position of benzimidazole by refluxing its sodium or potassium salts with propargyl bromide in alcohol because of side reactions of the reaction products (II), which are unstable in the presence of alkalis. The silver salts of benzimidazole are alkylated with difficulty by propargyl bromide (the yield is 30%), while the alkylation of Ia-d, as in the pyrazole [5] and imidazole [6] series, in liquid ammonia in the presence of sodium amide proceeds readily to give N-substituted compounds (IIa-d) in yields up to 75%.



I II

I, II a R=H; b R=CH_3; c R=C_6H_5; d R=$CH_2C_6H_5$

It is known that the amino derivatives of nitrogen heterocycles, for example, 4-aminoquinoline [7], are alkylated by propargyl bromide in liquid ammonia in the presence of alkali-metal halides at the exocyclic nitrogen atom. A mixture of 2-(N-mono)- (IV) and 2-(N,N-2'-dipropynyl)amino-1-ethylbenzimidazole (V) in a ratio of 1 : 2 is formed in the reaction of 1-ethyl-2-aminobenzimidazole with propargyl bromide (1 mole) under these conditions. The use of a twofold excess of alkynyl halide (2 mole) gives only disubstituted V in 80% yield. The IR spectra confirm the structures of the compounds obtained (IIa-d, IV, V) (see scheme on following page).

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer.

1-(2'-Propynyl)benzimidazole (Ia). A. A 1.2-g (0.01 mole) sample of propargyl bromide was added to a suspension of 2.25 g (0.01 mole) of the silver salt of benzimidazole in 20 ml of absolute xylene, and the mixture was refluxed for 4 h. The precipitate was removed by filtration, the solvent was removed by

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*See [1] for communication XXX.

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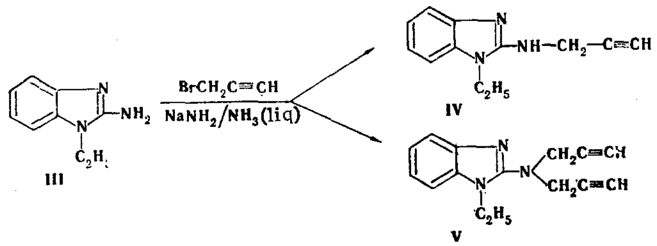

vacuum distillation, and the residue was chromatographed on aluminum oxide with ether to give 0.47 g (30%) of a colorless hygroscopic oil that was readily soluble in organic solvents. IR spectrum, ν 3310 cm^{-1} (≡ C−H). The picrate was obtained as yellow prisms with mp 202-203° (from alcohol). Found: C 50.4; H 2.9; N 17.5%. $C_{10}H_8N_2 \cdot C_6H_3N_3O_7$. Calculated: C 50.0; H 2.8; N 18.0%. The hydrochloride had mp 197-198° (from alcohol) and was quite soluble in water. Found: C 62.3; H 4.5; N 14.9; Cl 18.3%. $C_{10}H_8N_2 \cdot HCl$. Calculated: C 62.5; H 4.7; N 14.6; Cl 18.5%.

B. A 1.18-g (0.01 mole) sample of thoroughly ground Ia was added to a solution of 0.23 g (0.01 g-atom) of sodium metal in 50 ml liquid ammonia, and the mixture was stirred for 1 h. A solution of 1.2 g (0.01 mole) of propargyl bromide in 10 ml of absolute ether was added by drops, and the mixture was held at −70° for 2 h and allowed to stand with stirring until the ammonia had evaporated. The residue was treated with 30 ml of water and extracted with ether. The solvent was removed by distillation, and the residue was chromatographed on Al_2O_3 with ether to give 1.17 g (74.8%) of product.

2-Methyl-1-(2'-propynyl)benzimidazole (IIb). This compound was similarly obtained in 71% yield as colorless prisms with mp 43-44° (from ether) that were soluble in alcohol, chloroform, and benzene. Found: C 77.2; H 5.7; N 16.5%. $C_{11}H_{10}N_2$. Calculated: C 77.6; H 5.9; N 16.4%. IR spectrum: ν 3310 cm^{-1} (≡ C−H).

2-Phenyl-1-(2'-propynyl)benzimidazole (IIc). This compound was similarly obtained in 20.3% yield as colorless needles with mp 72° (from ether−petroleum ether). The product was soluble in alcohol, benzene, and chloroform. Found: C 82.5; H 5.0; N 11.5%. $C_{16}H_{12}N_2$. Calculated: C 82.7; H 5.2; N 12.0%. IR spectrum: ν 3310 cm^{-1} (≡ C−H).

2-Benzyl-1-(2'-propynyl)benzimidazole (IId). This compound was similarly obtained in 67% yield as a colorless oil that was soluble in alcohol, acetone, benzene, and chloroform. IR spectrum: ν 3310 cm^{-1} (≡C−H). The picrate was obtained as yellow needles with mp 164-165° (from alcohol). Found: C 58.3; H 3.9; N 15.1%. $C_{17}H_{14}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 58.1; H 3.6; N 14.7%.

Reaction of Propargyl Bromide with 1-Ethyl-2-aminobenzimidazole. A. A 1.61-g (0.01 mole) sample of III was added to a solution of 0.23 g (0.01 g-atom) of sodium metal in 50 ml of liquid ammonia, and the mixture was stirred for 1 h. A solution of 1.2 g (0.01 mole) of propargyl bromide in 10 ml of absolute ether was then added by drops, and the mixture was held at −70° for 1-2 h and then allowed to stand until the ammonia had evaporated. The residue was treated with 40 ml of water, and the mixture was extracted with chloroform. The reaction products (IV and V) were separated by chromatography on Al_2O_3 with ether to give 0.38 g (19%) of IV as colorless needles with mp 149° (from benzene). The product was quite soluble in alcohol, chloroform, ether, and acetone. Found: C 72.8; H 6.6; N 21.6%. $C_{12}H_{13}N_3$. Calculated: C 72.4; H 6.3; N 21.2%. IR spectrum: ν 3310 (≡ C−H), 3450 cm^{-1} (N−H). The yield of V, which was obtained as colorless prisms with mp 143° (from benzene), was 0.94 g (40%). The product was soluble in ether, alcohol, chloroform, and acetone. Found: C 76.2; H 6.7; N 17.8%. $C_{15}H_{15}N_3$. Calculated: C 76.0; H 6.3; N 17.7%. IR spectrum: ν 3310 cm^{-1} (≡ C−H).

B. A 1.61-g (0.01 mole) sample of III was treated with 2.4 g (0.02 mole) of propargyl bromide in the presence of 0.46 g (0.02 g-atom) of sodium metal as in A to give 1.9 g (80%) of product.

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