REACTION OF METHYL BROMOPROPIOLATE WITH DIAMINES AS A METHOD OF SYNTHESIS OF IMIDAZOLIDINE DERIVATIVES

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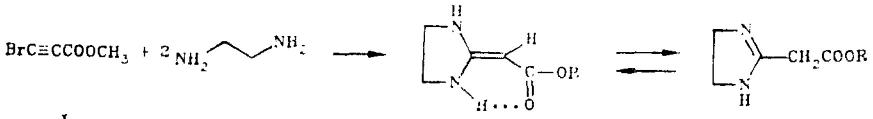
A convenient method of synthesis of 2-(methoxycarbonylmethylene)-substituted imidazolidines and imidazolidinium bromides, and also of bicyclic diazo compounds has been developed starting from methyl bromopropiolate and ethylenediamine and its derivatives.

Carbonyl-containing haloacetylenes containing an activated triple bond and a labile halogen atom are promising compounds for organic synthesis [1]. However, the possibilities of their application and their properties have not yet been sufficiently investigated and they are limited mainly to ketones of haloacetylene series. We have previously [2] synthesized 2-functionally substituted 1,3-oxazolines and oxazolidines from methyl bromopropiolate and β-amino alcohols. In continuation of this work we now have studied the reaction of methyl bromopropiolate with certain diamines.

The reaction of 1-chloro-3,3,3-trifluoropropyne with ethylene diamine has been described in the literature [3]. It was found that in this case the diamine does not enter into the nucleophilic substitution reaction of the halogen with the subsequent intramolecular cyclization, but acts as a dehalogenating agent. Contrary to this, methyl propiolate (I) reacts readily with two equivalents of ethylene diamine with formation of compound II.



I II A II B

Two tautomeric forms are possible for compound II — the enamine (**A**) and the imine (**B**). Tautomer **A** seemed to be the correct form on the basis of the analysis of the data of PMR and IR spectroscopy. Thus, the presence in the PMR spectrum (Table 1) of two different signals of NH protons, and also of a methine proton singlet, indicates the absence of the imine form (**B**). The existence of tautomer **A** is also supported by the characteristic absorption bands of the conjugated C=O bond at 1642 cm^{-1} and two bands of NH stretching vibrations at 3240 and 3305 cm^{-1}. These data conform with the spectral characteristics of an analog of compound II ($R = C_2H_5$) obtained by the reaction of ethoxycarbonylmethylimidate with ethylenediamine [4] and existing in the form of tautomer (**A**).

Thus, the only product of the reaction of methyl bromopropiolate with ethylenediamine is 2-(methoxycarbonylmethylene)-1,3-imidazolidine (II), the enamine form of which is stabilized by an intramolecular hydrogen bond.

Methyl bromopropiolate reacts similarly with diethylenetriamine with the formation of imidazolidine III with a free amino group in the side chain. The structure of compound III was confirmed by the data of the IR and PMR spectroscopy (see Table 1). The high hygroscopicity of imidazolidine III does not permit a satisfactory performance of the elemental analysis, but it was determined for the corresponding imine IV obtained by the reaction of III with 4-nitrobenzaldehyde (see below).

2-(Aminomethyl)aziridine (V) can be regarded as a derivative of ethylenediamine, in which one of the nitrogen atoms is part of a three-membered ring. The reaction of methyl bromopropiolate with two equivalents of

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	IR spectrum ν, cm^{-1}		PMR spectrum, δ, ppm (in $CDCl_3$)*								yield, %
			C=O	NH	OCH_3, s	=CH–, s	NH, br.s	NCH_2	OCH_2	CH	NH_2	CH_2	
II	$C_6H_{10}N_2O_2$	100 . . . 102	1642	3240, 3305	3,62	4,11	4,40	3,53 br.s	—	—	—	—	57
III	—	—	1650	3305, 3355	3,60	4,02	7,47	2,84 m; 3,13 m; 3,49 m	—	—	1.38 br.s	—	76
IV	$C_{15}H_{18}N_4O_4$	122 . . . 124	1650	3355									80
VI	$C_7H_{10}N_2O_2$	90 . . . 92	1660	3310	3,67	4,82	7,40	1,71 d; 2,42 d; 3,76 d	—	2,96 m	—	—	41
VIII	$C_{10}H_{17}BrN_2O_3$	103 . . . 105	1742	3240	3,75	—	7,40	3,67 br.s; 3,86 m	4,09 m	3,10 t	—	2,60 m	84

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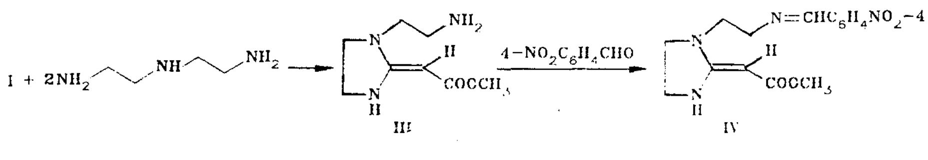
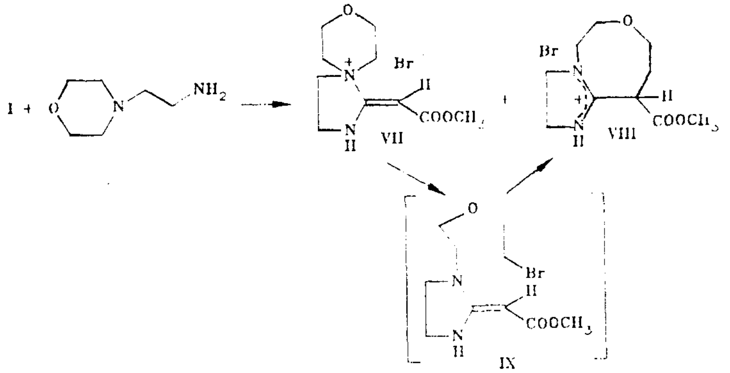
*The spectrum of compound VII was run in D_2O.

aziridine V gave us a new derivative of 1,3-diazabicyclo[3.1.0]hexane VI.



The structure of compound VI is confirmed by the presence in the PMR spectrum of a weak-field signal of the NH proton characteristic for an intramolecular hydrogen bond, and also of a methine proton signal at 4.82 ppm.

It is noteworthy that in compounds II, III, and VI, together with NH protons, the methine proton =CH— also completely or partially enters into a deutero exchange, which indicates its fairly high mobility.



4-(2-Aminomethyl)morpholine is a diamine, in the molecule of which there are both primary and tertiary amino groups which are free to participate in the reaction with methyl bromopropiolate. We found that in the reaction of propiolate I with 4-(2-aminoethyl)morpholine in ether, a crystalline product is formed, which comprises a mixture of quaternized salts VII and VIII with the latter predominating.

This is indicated by the presence of a singlet of the methine proton of compound VII in the PMR spectrum at 5.35 ppm, as well as strong-field triplets of the CH proton and a multiplet of the CH_2 group of compound VIII. A brief heating of the mixture of the salts obtained in acetonitrile is accompanied by the conversion of VII into VIII. It is possible that in the primarily formed spirobromide VII a cleavage occurs of the C—N bond of the morpholine ring with the formation of an intermediate compound IX, the intramolecular C-alkylation in which gives product VIII.

Thus, a convenient path is opened starting from methyl bromopropiolate and ethylenediamine derivatives for the synthesis of 2-functionally substituted imidazolidines and other heterocyclic compounds.

EXPERIMENTAL

The IR spectra were run in Nujol on a Perkin—Elmer 580-B spectrophotometer. The PMR spectra were recorded in $CDCl_3$ on a Bruker WH-90 spectrometer, using TMS as internal standard. The preparative HPLC was carried out on a Du Pont 830 Prep LC chromatograph, using a UV-spectrophotometer detector, and a Zorbax SIL column (22.7 × 250 mm). The course of the reaction and the purity of the products was monitored by means of TLC on Silufol UV-254 plates in ethanol.

2-(Methoxycarbonylmethylene)imidazolidine (II). A 300-mg portion (1.8 mmoles) of propiolate I in 30 ml of acetonitrile was added dropwise at —5°C, with stirring, to 216 mg (3.6 mmoles) of ethylenediamine in 40 ml of acetonitrile. The reaction mixture was stirred at room temperature for 4 h. Acetonitrile was evaporated, and ethylenediamine hydrobromide was washed with ethyl acetate. The solution of ethyl acetate was evaporated, and the residue was dissolved in acetonitrile and passed through a column with aluminum oxide. Yield 146 mg (57%) of a crystalline imidazolidine II.

1-(2-Aminomethyl)-2-(methoxycarbonylmethylene)imidazolidine (III). A 250-mg portion (1.5 mmoles) of propiolate I in 5 ml of acetonitrile was added dropwise at —5°C, with stirring, to 316 mg (3.1 mmoles) of diethylenetriamine in 10 ml of acetonitrile. The reaction mixture was stirred at room temperature for 5 h. The precipitate of diethylenetriamine hydrobromide was filtered off, the filtrate was evaporated, and the residue was washed with ether. The ether evaporated to yield 210 mg (76%) of a colorless hygroscopic crystalline imidazolidine III.

2-(Methoxycarbonylmethylene)-1-[2-(4-nitrobenzylideneamino)ethyl]imidazolidine (IV). A 100-mg portion (0.54 mmole) of compound III and 80 mg (0.54 mmole) of 4-nitrobenzaldehyde in 5 ml of methanol were mixed together. After 3 h methanol was evaporated, and the residue was crystallized from acetonitrile. Yield 137 mg (80%) of yellow crystalline compound (IV).

2-(Methoxycarbonylmethylene)-1,3-diazabicyclo[3.1.0]hexane (VI). A 330-mg portion (2 mmoles) of propiolate I in 8 ml of THF was added dropwise at —5°C, with stirring, to 288 mg (4 mmoles) of compound V in 15 ml of THF. The reaction mixture was stirred at room temperature for 12 h. The precipitate was filtered off, THF was evaporated from the filtrate, and the residue (an oily material) was chromatographed by HPLC (hexane–2-propanol, 2.5:1). Yield 126 mg (41%) of a light-yellow crystalline compound VI.

Reaction of Methyl Bromopropiolate with 4-(2-Aminoethyl)morpholine. A 156-mg portion (1.2 mmoles) of 4-(2-aminoethyl)morpholine in 10 ml of ether was added at —5°C, with stirring, to 195 mg (1.2 mmoles) of propiolate I in 15 ml of ether. The temperature was raised to room temperature and the mixture was stirred for 30 min. The crystalline product that separated out is a mixture of compounds VII and VIII in a ratio of 1:2. It was dissolved in 15 ml of acetonitrile, and the solution was heated for 30 min at 60°C. Acetonitrile was evaporated, and the residue was crystallized from ether. Yield 295 mg (84%) of compound VIII in the form of a yellow crystalline substance.

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