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RESEARCH IN THE IMIDAZOLE SERIES. 95.* SYNTHESIS OF DERIVATIVES OF IMIDAZO[1,5-a]IMIDAZOLE

P. M. Kochergin and V. A. Lifanov

The interaction of 1-acylmethyl-2-methyl-4-nitro-5-bromoimidazoles with ammonia or primary amines, followed by cyclization of the 1-acylmethyl-2-methyl-4-nitro-5-alkyl(aryl)aminoimidazoles in a medium of lower organic acids, leads to the formation of derivatives of imidazo[1,5-a]imidazole.

Substituted heteroaromatic systems of imidazo[1,5-a]imidazole were not known before the publication of our brief communications [2, 3]. A few polycyclic compounds had been reported — derivatives of hexahydroimidazo[1,5-a]imidazole [4] and 2,3-dihydro-2-oxo-5-methyl-7-nitroimidazo[1,5-a]imidazole [5].

In extending our studies [6-10] on the synthesis of condensed imidazole systems with a common nitrogen atom, we investigated reactions of the accessible 1-acetonyl- and 1-phenacyl-2-methyl-4-nitro-5-bromoimidazoles (II, III) [10, 11] with ammonia, and also with primary amines of the aliphatic, aliphatic-aromatic, and aromatic series; dialkylaminoalkylamines; amino alcohols; and amino acids. It was established that this reaction proceeds readily upon heating the reactants in alcohols (methanol–butanol), hydrocarbons (xylene), DMF, lower organic acids (HCOOH, CH_3COOH), or in an excess of high-boiling amine. In these reactions, derivatives of imidazo[1,5-a]imidazole VIII-XIX are obtained in a single stage (Table 1). The yields of these compounds, depending on the character of the initial substance and the conditions of the reaction and the recovery and purification of the substances, vary from 20% to 86%. In a number of experiments we observed considerable tar formation in the reaction mixture, which can probably attributed to the formation of Schiff bases that polymerize upon heating.

Excess amine was used in order to bind the hydrogen bromide evolved in the reaction; in the case of amino acids, their potassium salts were used.

It was shown that the first stage of this process is a nucleophilic replacement of the bromine atom by an ammonia or amine residue, forming intermediate 1-acylmethyl-2-methyl-4-nitro-5-amino(alkylamino, arylamino)imidazoles. Thus, upon heating the ketones II and III with methylamine in methanol at 65-75°C, we recovered 1-acetonyl- and 1-phenacyl-2-methyl-4-nitro-5-methylaminoimidazoles (VI, VII). The latter compounds, upon further heating of the reaction mixture, and even better at a higher temperature (for example, by refluxing in formic acid), readily split out a molecule of water and are cyclized to form derivatives of imidazo[1,5-a]imidazole (IX, XVI).

The structure of the intermediate compounds (VI, VII) was confirmed by their IR spectra, which contained bands of stretching vibrations of the CO group in the 1680-1740 cm^{-1} region and of the NH group in the 3280-3400 cm^{-1} region.

The second method for obtaining derivatives of imidazo[1,5-a]imidazole, which can be regarded as a counter-synthesis, consists of the reaction of 2-methyl-4(5)-nitro-5(4)-bromoimidazole I with ammonia or a primary amine, followed by alkylation of the 2-methyl-4(5)-nitro-5(4)-aminoimidazoles by α-haloketones in an alkaline medium and cyclization of the resulting 1-acylmethyl-2-methyl-4-nitro-5-aminoimidazoles by heating in a high-boiling solvent or in HCOOH. Thus, from the nitrobromoimidazole I, aniline, and phenacyl bromide, we obtained in three stages 1,2-diphenyl-5-methyl-7-nitroimidazo[1,5-

*For communication 94, see [1].

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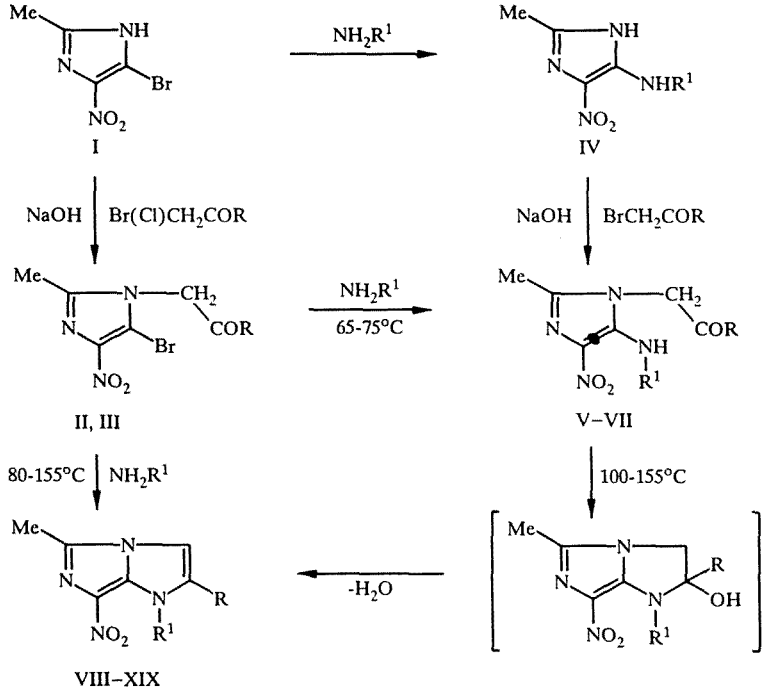
TABLE 1. Derivatives of Imidazo[1,5-a]imidazoles (VIII-XIX)

Compound	R	R^1	Empirical formula	mp, °C (decomp)	Yield, %
VIII	Me	H	$C_7H_3N_4O_2$	237...238*	42
IX	Me	Me	$C_8H_{10}N_4O_2$	270...271*	53...62
X	Me	$(CH_2)_2OH$	$C_9H_{12}N_4O_3$	241...243	86
XI	Me	$(CH_2)_2N(C_2H_5)_2$	$C_{13}H_{21}N_5O_2$	143...144	20
XII	Me	*i*-C_4H_9	$C_{11}H_{16}N_4O_2$	174...175	80
XIII	Me	Ph	$C_{13}H_{12}N_4O_2$	258...259	76
XIV	Me	CH_2COOH	$C_9H_{10}N_4O_4$	242...245*	71
XV	Me	$(CH_2)_3COOH$	$C_{11}H_{14}N_4O_4$	236...237	20
XVI	Ph	Me	$C_{13}H_{12}N_4O_2$	279...281	23...90
XVII	Ph	$(CH_2)_2OH$	$C_{14}H_{14}N_4O_3$	254...255	21
XVIII	Ph	Ph	$C_{18}H_{14}N_4O_2$	271...272	37...80
XIX	Ph	$PhCH_2$	$C_{19}H_{16}N_4O_2$	244...245	66...69

*According to [3], the melting points of compounds VIII, IX, and XIV are 238, 270-271, and 242-245°C, respectively.

a]imidazole XVIII, which proved to be identical to the product from the reaction of the ketone III with aniline. It should be noted that this method of synthesis of derivatives of imidazo[1,5-a]imidazole is less convenient than the method described above.



The individuality of the synthesized bicyclic compounds VIII-XIX was confirmed by TLC, and their composition and structure were confirmed by elemental analysis and by IR and PMR spectroscopy. In the IR spectra of these compounds, in contrast to those of the original nitrobromoketones (II, III) or the intermediate nitroaminoketones (V-VII), there are no bands corresponding to absorption by CO and NH groups. In the PMR spectra, as reported previously [3], there are distinct signals from protons of the 5-CH_3 group in the 2.31-2.49 ppm region, and of the aromatic proton in position 3 in the 7.38-7.48 ppm region.

EXPERIMENTAL

The IR spectra of the compounds were obtained in a UR-10 instrument in white mineral oil. TLC of the compounds was performed on Silufol UV-254 plates, development by iodine vapor. The liquid amines (isobutylamine, monoethanolamine, etc.) were freshly distilled for use in the reactions. The characteristics of the synthesized derivatives of imidazo[1,5-a]imidazole (VIII-XIX) are listed in Table 1.

Elemental analyses of compounds IV, V, and VIII-XIX for C, H, and N matched the calculated values.

2-Methyl-4(5)-nitro-5(4)bromoimidazole (I) was obtained by bromination of 2-methyl-4(5)-nitroimidazole by bromine, following a procedure given in [12].

1-Acetonyl- and 1-phenacyl-4-nitro-5-bromoimidazoles (II, III) were obtained by alkylation of compound I by α-haloketones, following a procedure given in [10, 11].

2-Methyl-4(5)-nitro-5(4)-phenylaminoimidazole (IV). A solution of 10.3 g (0.05 mole) of compound I and 10.2 g (0.11 mole) of aniline in 200 ml of n-butanol was refluxed for 8 h and then cooled; the precipitate was filtered off, washed with petroleum ether and water, and dried; mp 211-213°C (decomp.), from methanol. IR spectrum, cm^{-1}: 3280 (NH). Yield of compound IV 6.2 g (57%).

1-Phenacyl-2-methyl-4-nitro-5-phenylaminoimidazole (V). To a solution of 0.4 g (0.01 mole) of NaOH in 50 ml of anhydrous alcohol, 2.38 g (0.012 mole) of phenacyl bromide was added.* The mixture was refluxed for 2 h and then cooled; the precipitate was filtered off, washed with ether and water, and dried; mp 203-204°C (decomp.), from methanol. IR spectrum, cm^{-1}: 1680 (CO), 3280 (NH). Yield of compound V 2.4 g (71%).

1-Acetonyl-2-methyl-4-nitro-5-methylaminoimidazole (VI). A. A mixture of 2.62 g of the ketone II, 45 ml of ethanol, and 25 ml of a 25% aqueous solution of methylamine was heated in an autoclave for 3 h at 65°C. The solvent was removed under vacuum, and the oily residue was crystallized by trituration with ethanol. The precipitate was filtered off, washed with water, and chilled with ethanol, acetone, and ether; mp 175-179°C (decomp.). IR spectrum, cm^{-1}: 1740 (CO), 3400 (NH). Yield of compound VI 0.6 g (28%).

B. A mixture of 2.62 g of the ketone II and 15 ml of a 20% solution of methylamine in methanol was refluxed for 2 h, while monitoring the reaction mass by means of TLC up to the point of disappearance of the original ketone II. The preci-pitate was filtered off and washed with water and then with chilled ethanol, acetone, and ether; mp 175-177°C (decomp.); after crystallization from ethanol, mp 175-177°C (decomp.). The water–ethanol–acetone filtrates were evaporated down, the residue was dissolved in water and extracted with chloroform, the extract was dried with Na_2SO_4, the solvent was driven off, and the residue was crystallized from methyl ethyl ketone, recovering 0.49 g (25%) of the bicyclic compound IX with mp 270-271°C (decomp.). Yield of compound VI 0.54 g (25%).

1-Phenacyl-2-methyl-4-nitro-5-methylaminoimidazole (VII). A mixture of 6.48 g of the ketone III and 80 ml of an 8% solution of methylamine in methanol was heated in an autoclave for 4 h at 70-75°C, after which most of the solvent was driven off and the small amount of residue was cooled; the precipitate was filtered off, washed with water, acetone, and chloroform, and dried; mp 182-183°C (decomp.), from methanol. IR spectrum, cm^{-1}: 1680 (CO), 3280 (NH). Yield of compound VII 2.95 g (54%).

2,5-Dimethyl-7-nitroimidazo[1,5-a]imidazole (VIII). A mixture of 5.24 g of the ketone II and 80 ml of a 15% solution of ammonia in methanol was heated in an autoclave for 5 h at 70-75°C; the solvent was removed under vacuum, the oily residue was triturated with acetone, and the precipitate was filtered off, washed with water, and dried. Yield of compound VIII 1.5 g.

1,2,5-Trimethyl-7-nitroimidazo[1,5-a]imidazole (IX). A. Into a solution of 2.62 g of the ketone II in 15 ml of 96% CH_3COOH, a stream of gaseous methylamine was passed for 5 min, during which time the solution became dark and heated up. A precipitate formed very shortly in the reaction mass, which was then diluted with water; the precipitate was filtered off, washed with water, and dried. Yield of compound IX 1.2 g (62%).

B. A solution of 0.21 g of compound VI in 2 ml of 99.7% HCOOH was refluxed for 5 min, cooled, and diluted with 8 ml of water; the precipitate was filtered off, washed with water, and dried. A mixed melting point determination with a sample of IX obtained by method A did not show any depression. Yield of compound IX 0.1 g (53%). Analogously, from the

*As in Russian original; something has evidently been omitted, probably in regard to the use of compound IV as the starting material – Translator.

monocyclic compounds V and VII, the corresponding bicyclic compounds XVIII and XVI were obtained with yields of 80% and 90%.

1-Hydroxyethyl-2,5-dimethyl-7-nitroimidazo[1,5-a]imidazole (X). A solution of 13.1 g (0.05 mole) of the ketone II and 9.2 g (0.15 mole) of monoethanolamine in 30 ml of DMF was heated 5 h at 110-115°C and 8 h at the refluxing temperature. The mass was cooled and poured into 20 ml of water; the precipitate was filtered off, washed with water, and dried. Yield of compound X 4.8 g.

1-Diethylaminoethyl-2,5-dimethyl-7-nitroimidazo[1,5-a]imidazole (XI). A mixture of 5.24 g (0.02 mole) of the ketone II, 5.81 g (0.05 mole) of diethylaminoethylamine, and 15 ml of ethanol was refluxed 2 h and then cooled to 0-2°C; the precipitate was filtered off, washed with chilled ethanol, and dried. Yield of compound XI 1.52 g.

1-Isobutyl-2,5-dimethyl-7-nitroimidazo[1,5-a]imidazole (XII). To a solution of 2.62 g (0.01 mole) of the ketone II in 20 ml of 99% HCOOH, 14.6 g (0.2 mole) of isobutylamine was added. The mixture was refluxed for 1 h and then cooled, 50 ml of water was added, and the mixture was extracted with chloroform; the extract was washed with water and dried with Na_2SO_4; the solvent was driven off, and the residue was washed with ether and dried. Yield of compound XII 1.9 g. Compound XVI was obtained analogously, with the only difference that gaseous methylamine was passed into a solution of the ketone III in HCOOH. A mixed sample of compound XVI with a sample of this substance prepared by cyclization of the intermediate compound VII in HCOOH did not show any depression of the melting point.

1-Phenyl-2,5-dimethyl-7-nitroimidazo[1,5-a]imidazole (XIII). A solution of 2.62 g (0.01 mole) of the ketone III and 4.64 g (0.05 mole) of aniline in 15 ml of DMF was refluxed 5 h and then cooled; 15 ml of water was added; and the precipitate was filtered off, washed with water, and dried. Yield of compound XIII 1.94 g. Compounds XVII and XIX were obtained analogously.

1-Carboxymethyl-2,5-dimethyl-7-nitroimidazo[1,5-a]imidazole (XIV). To a solution of 1.12 g (0.02 mole) of KOH in 50 ml of water, 1.5 g (0.02 mole) of glycocoll and 2.62 g (0.01 mole) of the ketone II were added. The mixture was refluxed 2 h, cooled, and acidified with dilute HCl to pH 5; the precipitate was filtered off, washed with water, and dried. Yield of compound XIV 1.7 g. Compound XV was obtained analogously.

1,2-Diphenyl-5-methyl-7-nitroimidazo[1,5-a]imidazole (XVIII). A solution of 1.62 g (0.005 mole) of the ketone III and 1.16 g (0.0125 mole) of aniline in 30 ml of n-butanol was refluxed 10 h and then cooled; the precipitate was filtered off, washed with 2-propanol and water, and dried. Yield of compound XVIII 0.64 g (40%). When this reaction was carried out in xylene (8-h refluxing), the yield of compound XVIII was 37%; and in excess aniline (6-h refluxing) the yield was 70%. A mixed sample of compound XVIII with the substance obtained by cyclization of compound V in HCOOH did not show any depression of melting point, and the IR spectra of the samples were identical.

Properties of compounds VIII-XIX (Table 1): Light-yellow crystalline substances, difficultly soluble in water and in most organic solvents, readily soluble with heating in CH_3COOH and DMF; do not form hydrochlorides or picrates (with the exception of compound XI). For analysis, the substances were purified by crystallization from water (IX, X), methanol (VIII, XIII), aqueous methanol (XII, XV), ethanol (XIX), benzene (XI), glacial acetic acid (XVI), DMF (XVII), or aqueous DMF (XVIII).

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