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SYNTHESIS OF 4,5-BIFUNCTIONALLY SUBSTITUTED IMIDAZOLIDIN-2-ONES

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It is shown that the reaction of readily available 4,5-dihydroxyimidazolidin-2-ones with hydrazoic or p-toluenesulfinic acid takes place stereo- and regioselectively and leads to the formation of 4,5-diazido- or 4,5-di(p-tolylsulfonyl)imidazolidin-2-ones. The example of 4,5-diazidoimidazolidin-2-one is used to demonstrate the possibility of using compounds of this type for stereoselective introduction of substituents into the 4 and 5 positions of the imidazole ring.

A convenient method of constructing the imidazolidine ring is to use α-oxoaldehydes or α-oxoketones with ureas [1, 2]. The 4,5-dihydroxyimidzolidin-2-ones [1] obtained as a result of this reaction are polyfunctional compounds and can be used as the parent substances for preparing various imidazole derivatives. However, thus far, only a small number of example of synthetic use of compounds I have been described, in particular, for the preparation of 4,5-bifunctionally substituted imidazolidin-2-ones, which are of considerable interest in connection with their various useful properties. Discovered among the indicated compounds have been tranquilizers [3], sedatives and soporifics [4], anticonvulsants [5], herbicides [6], steel corrosion inhibitors [7], components of explosives [8], cotton fabric modifiers [9, 10], etc.

The synthesis of 4,5-bifunctionally substituted imidazolidin-2-ones is based on the reaction of compounds I with nucleophilic reactants in the presence of acid catalysts. Thus, the reaction of imidazolidines I with alcohols or with difluoramine forms 4,5-dialkoxy- [2, 4, 11] or 4,5-bis(difluoramino)imidazolidin-2-ones [12], respectively, and the reaction with ureas forms substituted 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones [2, 13]. It should be noted that the series of 4,5-bifunctionally substituted imidazolidin-2-ones, which can be obtained by the reaction described, is very limited, this being due to frequently occurring side reactions, in particular, conversion of compounds I to the corresponding hydantoins [14] or aromatization of the reaction products with the formation of substituted imidazolidin-2-ones [2]. It was of interest to study the possibility of using compounds I to synthesize new types of 4,5-bifunctionally substituted imidazolidin-2-ones. Some of the results obtained are presented in this report.

We showed that 4,5-dihydroxyimidazolidin-2-one (Ia) reacts with excess hydrazoic acid, generated in situ from sodium azide and hydrochloric acid, in water at 20°C, resulting in the formation of trans-4,5-diazidoimidazolidin-2-one (IIa) in diastereomerically pure form in up to 90% yields. The yield of compound IIa depends on the duration of the reaction and is 49% when the reaction is carried out for 6.5 days, 55% for 12.5 days, 61% for 14.5 days, 77% for 17.5 days, and 90% for 24 days. Similarly, the reaction of 4,5-dihydroxy-1,3-dimethylimidazolidin-2-one (Ib) with excess hydrazoic acid yields trans-4,5-diazido-1,3-dimethylimidazolidin-2-one (IIb) with complete stereoselectivity. It should be noted that in the case of compound Ib, the reaction with HN_3 takes place much faster than in the case of imidazolidine Ia, and the yield of product of IIb is 67% after 5 days.

Diazidoimidazolidin-2-one IIa with a total yield of 44% was also obtained by reacting glyoxal with urea in water (50°C, 7 h, pH 6.5) with subsequent addition of sodium azide and hydrochloric acid to the reaction mixture containing dihydroxymidazolidin-2-one Ia and holding of the mixture at 20°C for 13 days.

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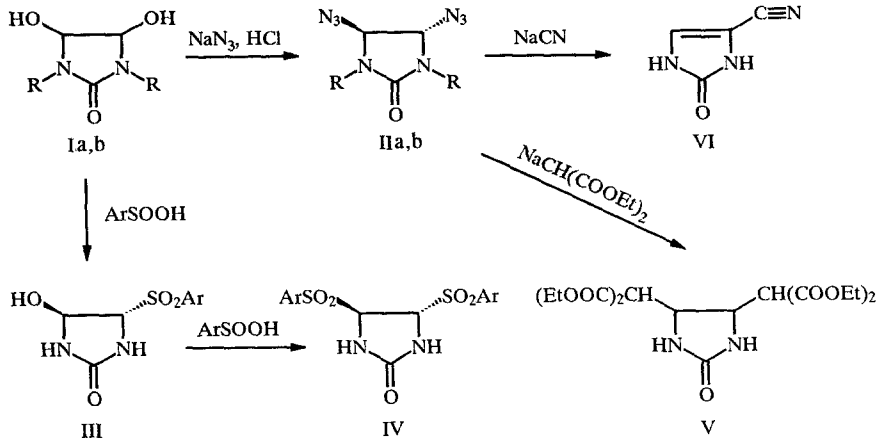

Ar = 4-$CH_3C_6H_4$; I, II a R = H, b R = CH_3

When imidazolidinone Ia is reacted with excess p-toluenesulfinic acid in water (20°C), successive stereoselective replacement of both hydroxyl groups of compound Ia is observed, resulting in the formation of trans-4,5-di(p-tolylsulfonyl)imidazolidin-2-one (IV) in 85% yield. It was found that the rate of the first step of the reaction, leading to the monosubstitution product, i.e., trans-4-hydroxy-5(p-tolylsulfonyl)imidazolidin-2-one (III), appreciably exceeds the rate of the second step, and hence, compound III can easily be separated, particularly if the reaction is carried out in the presence of insufficient sulfinic acid. Both steps of the reaction take place not only with complete stereoselectivity, but also very regioselectively: the nucleophilic center of p-toluenesulfinic acid is the sulfur atom alone.

The synthesized imidazolidinones IIa, b, III, IV contain at the $C_{(4)}$ and $C_{(5)}$ atoms an azide or p-tolylsulfonyl group, both of which, as was established earlier in the series of hexahydropyrimidin-2-ones (thiones) [15-17], are easily removed in nucleophilic substitution reactions. It may be assumed, therefore, that compounds of types II-IV can be used as the starting substances for introducing various groups into positions 4 and 5 of the imidazole ring. Indeed, diazidoimidazolidin-2-one IIa readily reacts with excess sodium malonate in DMFA (20°C, 1 h) and as a result, the bisubstitution product, 4,5-bis[di(ethoxycarbonyl)methyl]imidazolidin-2-one (V), is formed in 45% yield in the form of a single diastereoisomer. Somewhat different is the reaction of compound IIa with excess sodium cyanide in acetonitrile (20°C, 1.5 h), when 4-cyanoimidazoline-2-one (VI) is formed as the end product of the reaction. Formation of this compound is apparently due to elimination of hydrazoic acid from the initially obtained monosubstitution product, i.e., 4-azido-5-cyanoimidazolidin-2-one.

The IR spectra of the synthesized compounds show several strong absorption bands due to vibrations of the atoms of the ureide molecular fragment, in particular, the absorption bands of the stretching vibrations of the carbonyl group in the 1679-1730-cm^{-1} region (for compounds IIa, b, III-VI) and broad bands of the stretching vibrations of the N−H groups in the 3085-3238-cm^{-1} region (for compounds IIa, III-VI). In addition, absorption bands due to the presence of substituents at the $C_{(4)}$ and $C_{(5)}$ atoms are present in the spectra of imidazolidines IIa, b, III-V. For example, the IR spectra of azidoimidazolidines IIa, b show two strong absorption bands of the stretching vibrations of the azide groups in the intervals 2067-2070 (ν_{as} N_3) and 1236-1244 (ν_s N_3), the spectra of sulfones III, IV have two strong bands of the stretching vibrations of the SO_2 group(s) in the regions 1279-1316 cm^{-1} (ν_{as} SO_2) and 1137-1138 (ν_s SO_2), and the spectrum of compound V has the band of the stretching vibrations of the carbonyl group at 1738 cm^{-1}.

The presence of a cyano group in the molecule of imidazoline VI causes the presence of the band of stretching vibrations of the C≡N group at 2202 cm^{-1} in the IR spectrum of this compound. The position of this band and its comparatively high intensity indicate that the cyano group is linked to the C=C bond [18]. The latter in the IR spectrum of compound VI is manifested in the form of an absorption band with a maximum at 1597 cm^{-1}.

The 4-H and 5-H protons in the molecules of symmetrically substituted imidazolidines IIa, b, IV, V are magnetically equivalent, and as a result, these protons in the PMR spectra of compounds IIa, b, IV are manifested in the form of a singlet signal in the region of 4.74...5.18 ppm, and in the PMR spectrum of compound V, in the form of a 4.04 ppm doublet due to the presence of spin−spin interaction with protons of adjacent methine groups. Owing to the magnetic equivalence of the 4-H and 5-H protons, the J_{45} coupling constants are not manifested in the PMR spectra of compounds IIa, b, IV, V. These constants for compounds IIa, b, IV, which we determined from an analysis of the ^{13}C satellites of the 4-H and 5-H protons, as described

in [19], were found to be zero. On this basis, it was concluded that compounds IIa, b, IV had a trans configuration. Disubstituted imidazolidinone V apparently also is a pure trans diastereoisomer. From an analysis of the PMR spectrum of the asymmetric compound III we found the coupling constant $J_5 = 0$ Hz, which indicates the trans configuration of this substance.

The PMR spectrum of cyanoimidazoline VI shows a broadened singlet signal of the protons of N−H groups at 10.86 ppm and a singlet signal of the 5-H proton at 7.51 ppm with an intensity ratio of 2:1, respectively. The UV spectrum of imidazoline VI is characterized by the presence of a strong absorption band with a maximum at 251 nm (log ε 4.04).

EXPERIMENTAL

The IR spectra were recorded with a Shimadzu IR-435 instrument with the compounds in the form of suspensions in vaseline oil. The PMR spectra were recorded with a Bruker MSL-200 (200 MHz) spectrometer, with HMDS as the internal standard. The UV spectra were obtained with a Specord M-40 spectrophotometer in methanol. The course of the reactions and the purity of the compounds obtained were checked by TLC on Silufol UV-254 plates in a 7:1 chloroform−methanol system; the spots of the substances were detected by spraying the chromatograms with Ehrlich's reagent or with a mixture of 0.1 N $KMnO_4$−2N CH_3COOH (1:1) with subsequent heating.

Data of the elemental analysis for C, H, N, S for compounds IIa, b, IV-VI correspond to the calculated data.

trans-4,5-Diazidoimidazolidin-2-one (IIa, $C_3H_4N_8O$). A. To a mixture of 6.73 g (57 mmoles) of imidazolidine Ia [2], 13.00 g (200 mmoles) of sodium azide, and 10 ml of water is added a cold (−15°C) solution of 17.2 ml (200 mmoles) of conc. hydrochloric acid in 10 ml of water, and the mixture is allowed to stand in an open container at room temperature. Approximately 24 hours later, crystals of compound IIa* begin to precipitate from the reaction mixture. The mixture is kept standing for 24 hours, cooled to 0°C, and the precipitate is filtered off, thoroughly washed with ice water, and dried. Compound IIa, obtained in chromatographically pure form, is recrystallized from dry acetonitrile. mp 139...139.5°C (dec.). IR spectrum: 3195, 3085 sh (ν N−H), 2070 ($\nu_{as}N_3$), 1711 (amide I), 1236 cm^{-1} (ν_sN_3). PMR spectrum (DMSO-D_6): 8.21 (2H, br.s. $N_{(1)}H$ and $N_{(3)}$−H), 5.18 ppm (2H, s, $J_{45} \sim 0$, $J_{NH,CH} \sim 0$, $J_{13C-H} = 172.5$ Hz, 4-H and 5-H). Yield, 8.60 g (89.8%).

Compound IIa is similarly obtained in 49.2, 54.6, 61.1, and 77.3% yields when the reaction is carried out for 6.5, 12.5, 14.5, and 17.5 days, respectively.

B. To 19.28 g (99.7 mmoles) of a 30% aqueous solution of glyoxal (Merck), neutralized with a 2 N NaOH solution to pH 6.5, 5.98 g (99.6 mmoles) of urea is added, and the mixture is stirred for 7 h at 50°C. After the reaction mixture is cooled to room temperature, 25.90 g (398.5 mmoles) of sodium azide and 11 ml of water are added, the mixture is cooled to −15°C, and a cold (−15°C) solution of 34.2 ml (398.5 mmoles) of conc. hydrochloric acid in 10 ml of water is poured in. The mixture is kept in a closed container at room temperature for 13 days, cooled to 0°C, and the precipitate is filtered off, thoroughly washed with ice water, and dried. Compound IIa in chromatographically pure form is obtained in the amount of 7.28 g (43.5% in terms of urea).

trans-4,5-Diazido-1,3-dimethylimidazolidin-2-one (IIb, $C_5H_8N_8O$). A mixture of 8.16 g (55.8 mmoles) of imidazolidine Ib [2], 14.52 g (223.4 mmoles) of sodium azide, and 20 ml of water is cooled to −15°C, and a cold (−15°C) solution of 19.2 ml (223.8 mmoles) of conc. hydrochloric acid in 15 ml of water is added. The solution obtained, from which a heavy oil begins to separate as early as 5 min after the start of the reaction, is kept in a closed container at room temperature for 5 days, the product is extracted with ether (5 × 100 ml), and the extract is dried with anhydrous magnesium sulfate. After the solvent is driven off in a vacuum, 15 ml of ether is added to the residue, the solution is cooled to 0°C, and the precipitate is filtered off, washed with cold ether on a filter, and dried. Compound IIb is obtained in the amount of 6.75 g. Treatment of the ether mother liquor yields an additional 0.58 g of product. The total yield of chromatographically pure compound IIb is 7.33 g (67.0%). mp 94-95°C (3:2 hexane−ethyl acetate). IR spectrum: 2067 (ν_{as} N_3), 1710 (amide I), 1244 cm^{-1} (ν_s N_3). PMR spectrum ($CDCl_3$): 4.74 (2H, s, $J_{45} \sim 0$, $J_{13_{C-H}} = 139.7$ Hz, 4-H and 5-H), 2.95 ppm (6H, s, $N_{(1)}-CH_3$ and $N_{(3)}-CH_3$).

trans-4-Hydroxy-5-(p-tolylsulfonyl)imidazolidin-2-one (III, $C_{10}H_{12}N_2O_4S$). A mixture of 0.40 g (3.35 mmoles) of imidazolidine Ia, 0.26 g (1.68 mmoles) of p-toluenesulfinic acid, and 4 ml of water is agitated for 3 h at room temperature,

*The start of crystallization can be accelerated by adding a seed of compound IIa.

and the precipitate is filtered off, washed with cold water on a filter, and dried. Compound III is obtained in the amount of 0.29 g (68.0%) with an admixture of imidazolidine IV (5% from data of PMR spectroscopy). IR spectrum: 3397, 3371, 3238 (ν O-H, ν N-H), 1723, 1693 (amide-I), 1596 (ν C=C), 1279 (ν_{as} SO_2), 1137 (ν_s SO_2), 814 cm^{-1} (δ C-H_{arom}). PMR spectrum (DMSO-D_6): 7.85 (1H, br.s., N−H), 7.48 (1H, br.s., N−H), 7.65-7.82 (2H, m, CH_{arom}), 7.38-7.56 (2H, m, CH_{arom}), 6.63 (1H, d, $J_{4\text{-H, OH}}$ = 7.2 Hz, O−H), 5.14 (1H, d, J_{45} = 0 hz, 4-H), 4.55 (1H, d, $J_{5\text{-H, NH}}$ = 1.5 Hz, 5-H), 2.42 ppm (3H, s, CH_3).

trans-4,5-Di(p-tolylsulfonyl)imidazolidin-2-one (IV, $C_{17}H_{18}N_2O_5S_2$). A mixture of 0.78 g (6.59 mmoles) of imidazolidine Ia, 2.16 g (13.83 mmoles) of p-toluenesulfinic acid, and 20 ml of water is kept at room temperature for 25 days with periodic agitation of the creamy mass formed. The precipitate is filtered off, thoroughly washed with cold water, and dried. Compounds IV are obtained in the amount of 2.21 g (85.1%), and they are recrystallized from dry acetonitrile. mp 146-147°C (dec.).* IR spectrum: 3178 (ν N−H), 3061 (ν C−H_{arom}), 1730 (amide I), 1593 (ν C=C), 1316 (ν_{as} SO_2), 1138 (ν_s SO_2), 813 cm^{-1} (δ C-H_{arom}). PMR spectrum (DMSO-D_6): 8.25 (2H, br.s., N−H), 7.72-7.81 (4H, m, CH_{arom}), 7.39-7.49 (4H, m, CH_{arom}), 5.03 (2H, d, J_{45} ~ 0, $^3J_{NH,CH}$ = 0.8, $J_{13_{C\text{-}H}}$ = 162.0 Hz, 4-H and 5-H), 2.45 ppm (6H, s, CH_3).

4,5-Bis[di(ethoxycarbonyl)methyl]imidazolidin-2-one (V, $C_{17}H_{26}N_2O_9$). To a suspension of 0.13 g (5.30 mmoles) of sodium hydride in 0.8 ml of dry DMFA with stirring and cooling on a water bath is added dropwise a solution of 0.85 g (5.29 mmoles) of malonic ester in 1.50 ml of DMFA. To the sodium malonate solution obtained is added 0.40 g (2.41 mmoles) of imidazolidine IIa, and the mixture is stirred at room temperature for 1 h. Then, 8 ml of ice water is added to the reaction mixture, the temperature is lowered to 0°C, and the precipitate formed is filtered off, washed with ice water, and dried. Compound V is obtained in the amount 0.44 g (45.1%)† in chromatographically pure form, then recrystallized from a 1:4 alcohol−hexane mixture. mp 127.5-128.5°C. IR spectrum: 3188, 3108 (ν N−H), 1738 (ν C=O), 1721 (amide I), 1229, 1200, 1026 cm^{-1} (ν C−O). PMR spectrum: (DMSO-D_6): 6.64 (2H, br.s., $N_{(1)}$−H and $N_{(3)}$−H), 4.13 (8H, q, J = 7.1 Hz, OCH_2), 4.04 (2H, d, 4-H and 5-H), 3.62 (2H, d, J = 6.0 Hz, 4-CH and 5-CH), 1.18 ppm (12H, t, CH_3).

4-Cyanoimidazolin-2-one (VI, $C_4H_3N_3O$). A mixture of 0.62 g (3.71 mmoles) of azidoimidazolidinone IIa, 0.54 g (11.13 mmoles) of sodium cyanide and 8 ml of dry acetonitrile is stirred at room temperature for 1.5 h, evaporated under vacuum to dryness, and the residue is extracted with ethanol (3 × 10 ml). The extract is filtered off, the solvent is driven off under vacuum, the residue is dissolved in 5 ml of methanol, and 3 g of silica gel L40/100 μ is added. After the solvent is driven off under vacuum, the powder obtained is poured into a chromatographic column containing 14 g of silica gel L40/100 μ (2 × 7.5 cm) and eluted with a 7:1 chloroform−methanol system. Compound VI is obtained in the amount of 0.15 g (38.3%) and recrystallized from acetonitrile. mp > 270°C (dec.). IR spectrum: 3158 sh, 3133 (ν N−H), 2202 (ν C≡N), 1710, 1679 (amide-I), 1597 cm^{-1} (ν C=C). UV spectrum, λ_{max} (log ε): 251 nm (4.04). PMR spectrum (Jeol FX-90 Q); DMSO-D_6: 10.86 (2H, br.s., $N_{(1)}$−H and $N_{(3)}$−H), 7.51 ppm (1H, s, 5−H).

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*In this temperature range, the substance turns wet and begins to decompose; it melts over a wide temperature range.
†The yield was not optimized.

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