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SHORT COMMUNICATIONS

Synthesis of 3-Chloromethyl-5,6-dihydroimidazo-[2,1-*b*]thiazole— A Convenient Synthon for the Preparation of Biologicaly Active Substances

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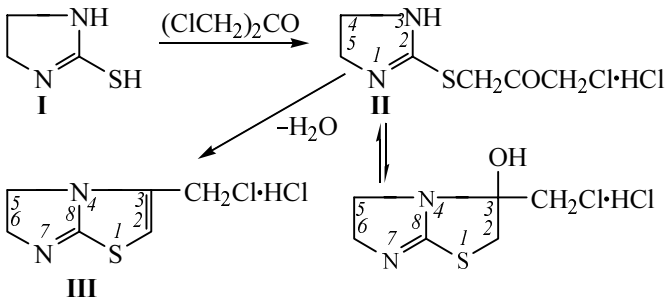
We prevously showed [1, 2] that reactions of 1,3-dichloro-2-propanone with heterocyclic thiols can involve substitution of both one and two chlorine atoms in the former to afford the corresponding 1-heterylsulfanyl-3-chloro-2-propanone and 1,3-bis(heterylsulfanyl)-2-propanone which can be separated by fractional crystallization. In the present work we examined the reaction of 4,5-dihydro-1*H*-imidazole-2-thiol (**I**) with 1,3-dichloro-2-propanone. The alkylation was carried out in ethanol on heating to 65–70°C under continuous stirring. As a result, we isolated 1-chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylsulfanyl)-2-propanone (**II**). According to spectral data, the product recrystallized from ethanol contained imidazothiazole derivative **III**. Presumably, the latter was formed due to easy dehydration of compound **II**. Imidazothiazole **III** was also formed on prolonged heating of a mixture of 4,5-dhydro-1*H*-imidazole-2-thiol (**I**) and 1,3-dichloro-2-propanone in boiling ethanol.

The IR spectrum of **II** lacked absorption bands in the region 1650–1730 cm^{-1}, which are typical of carbonyl stretching vibrations, whereas an absorption was present at 2700–3200 cm^{-1}, presumably due to stretching vibrations of the hydroxy group in the corresponding tautomeric ring structure. As shown in [3, 4], analogous dihydroimidazolyl sulfides tend to undergo ring–chain tautomerism. The structure of **II** was also confirmed by the ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum of **II** we observed a clearly defined two-proton singlet belonging to the CH_2Cl group (δ 4.1 ppm), while pseudoaxial and pseudoequatorial protons in the C^2H_2, C^5H_2, and C^6H_2 methylene groups gave two multiplets at δ 3.97–4.12 and 4.37–4.55 ppm, respectively.

Compound **III** is the key intermediate product in the synthesis of 3-methyl-substituted 2,3-dihydroimidazo-[2,1-*b*]thiazoles. It was obtained by heterocyclization of ketone **II** on heating for 2 h in boiling anhydrous ethanol in the presence of a catalytic amount of hydrochloric acid. Compound **III** showed in the ^1H NMR spectrum two triplets at δ 4.10 and 4.50 ppm, which correspond to methylene protons in the imidazole ring, a two-proton singlet at δ 4.15 ppm from the chloromethyl group, and a one-proton singlet at δ 5.72 ppm from the 2-H proton. The mass spectrum of **III** contained $[M - Cl]^+$ and $[M - CH_2Cl]^+$ ion peaks; in addition, peaks from the $[M - CHN]^{+\cdot}$ ion and that formed by elimination of neutral sulfur-containing fragments (SRR') were present. These data indicate that the thiazole ring in **III** is relatively unstable under electron impact.

Compound **III** possesses a readily departing chlorine atom, and it should react with nucleophiles such as amines,



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phenols, and alcohols. These reactions are expected to produce various 3-methyl-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles which are promising from the viewpoint of biological activity.

1-Chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylsulfanyl)-2-propanone hydrochloride (II). 4,5-Dihydro-1*H*-imidazole-2-thiol, 6 g, was added in portions over a period of 1 h to a solution of 12 g of 1,3-dichloro-2-propanone in 120–150 ml of ethanol. The solvent was removed under reduced pressure, the residue was treated with acetone, and the precipitate was filtered off. Yield 90–99%, mp 125–128°C (crude product). IR spectrum, ν, cm^{-1}: 1600 (C=N), 2700–3200 (OH). ^1H NMR spectrum, δ, ppm: 4.1 s (2H, CH_2Cl), 3.94–4.12 m (3H, 6-H_b, 5-H_b, 2-H_b), 4.37–4.55 m (3H, 6-H_a, 5-H_a, 2-H_a). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 45.02 (C^2), 48.13 (C^5), 48.66 (CH_2Cl), 53.95 (C^6), 92.68 (C^3), 178.48 (C^8). Found, %: C 31.85; H 4.63; Cl 30.16; N 12.40; S 14.45. $C_6H_9ClN_2OS \cdot HCl$. Calculated, %: C 31.45; H 4.40; Cl 30.95; N 12.22; S 13.99.

3-Chloromethyl-5,6-dihydroimidazo[2,1-*b*]-thiazole hydrochloride (III). A mixture of 10 g of compound **II**, 100 ml of anhydrous ethanol, and 3–4 drops of hydrochloric acid was heated for 2 h under reflux. The precipitate was filtered off. Yield 98%, mp 222–224°C. ^1H NMR spectrum (D_2O), δ, ppm: 4.10 t (2H, C^6H_2), 4.15 s (2H, CH_2Cl), 4.50 t (2H, C^5H_2), 7.08 s (1H, 2-H). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 37.78 (CH_2Cl), 48.55 (C^5), 53.35 (C^6), 112.57 (C^2), 135.78 (C^3), 173.77 (C^8). Mass spectrum, *m*/*z* (I_{rel}, %): 174 $[M]^{+\cdot}$ (18), 147 (24), 139 (100), 138 (12), 125 (25), 112 (32), 45 (8), 38 (14), 27 (10). Found, %: C 34.85; H 3.63; Cl 33.76; N 13.22; S 15.85. $C_6H_7ClN_2S \cdot HCl$. Calculated, %: C 34.14; H 3.82; Cl 33.59; N 13.27; S 15.19.

The IR spectra were recorded on a UR-20 instrument from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured from solutions in D_2O on a Bruker AM-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) using DSS as internal reference. The mass spectra (electron impact, 70 eV) were run on an MKh-1320 spectrometer with direct sample admission into the ion source (65–100°C). The progress of reactions was monitored by TLC on Silufol UV-254 plates (1-butanol–acetic acid–water, 4 : 1 : 2).

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