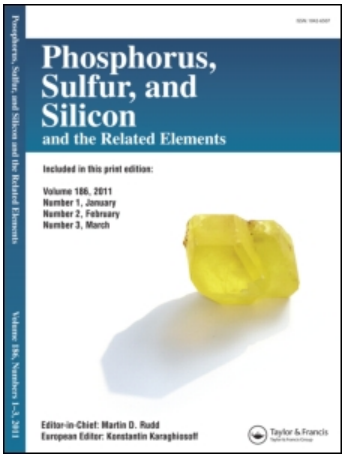

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REACTIONS OF N-ARYL-N-(4,5-DIHYDRO-1*H*-IMIDAZOL-2-YL)-HYDROXYLAMINES WITH CARBON DISULFIDE. A POSSIBLE ROUTE TO 1-(1,3-BENZOTHIAZOL-2-YL)-2-IMIDAZOLIDINETHIONES

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REACTIONS OF N-ARYL-N-(4,5-DIHYDRO-1*H*-IMIDAZOL-2-YL)-HYDROXYLAMINES WITH CARBON DISULFIDE. A POSSIBLE ROUTE TO 1-(1,3-BENZOTHIAZOL-2-YL)-2-IMIDAZOLIDINETHIONES

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A series of 1-(1,3 -benzothiazol-2-yl)-2-imidazolidinethiones **3a-d** was prepared from the reaction of N-aryl-N-(4,5-dihydro-1*H*-imidazol-2-yl)hydroxylamines **1a-d** with carbon disulfide. The key step of the reaction involves [3,3] sigmatropic shift of the 1-thia-3-oxa-4-aza-Cope system. Reactivity of **3** was further examplified by the acetylation reaction as well as Mannich type reaction leading to the derivatives **4** and **5** respectively.

Keywords: N-aryl-N-(4,5-dihydro-H-imidazol-2-yl)hydroxylamines; 1-thia-3-oxa-4-aza-Cope reaction; 1-(1,3-benzothiazol-2-yl)-2-imidazolidinethiones; acetylation; Mannich type reaction.

INTRODUCTION

Carbon disulfide has been commonly used by organic chemists working in areas of pharmaceuticals and agrochemicals and its synthetic applications are covered in comprehensive manner in monographs and review articles[1,2].

Recently we have become interested in the reactivity of N-aryl-N-(4,5-dihydro-1H.-imidazol-2-yl)hydroxylamines **1**, and especially those involving polihetero-Cope rearrangements[3,4].

We reasoned that the construction of useful type of polihetero-Cope system, namely the 1-thia-3-oxa-4-aza-Cope system of type **A** could be

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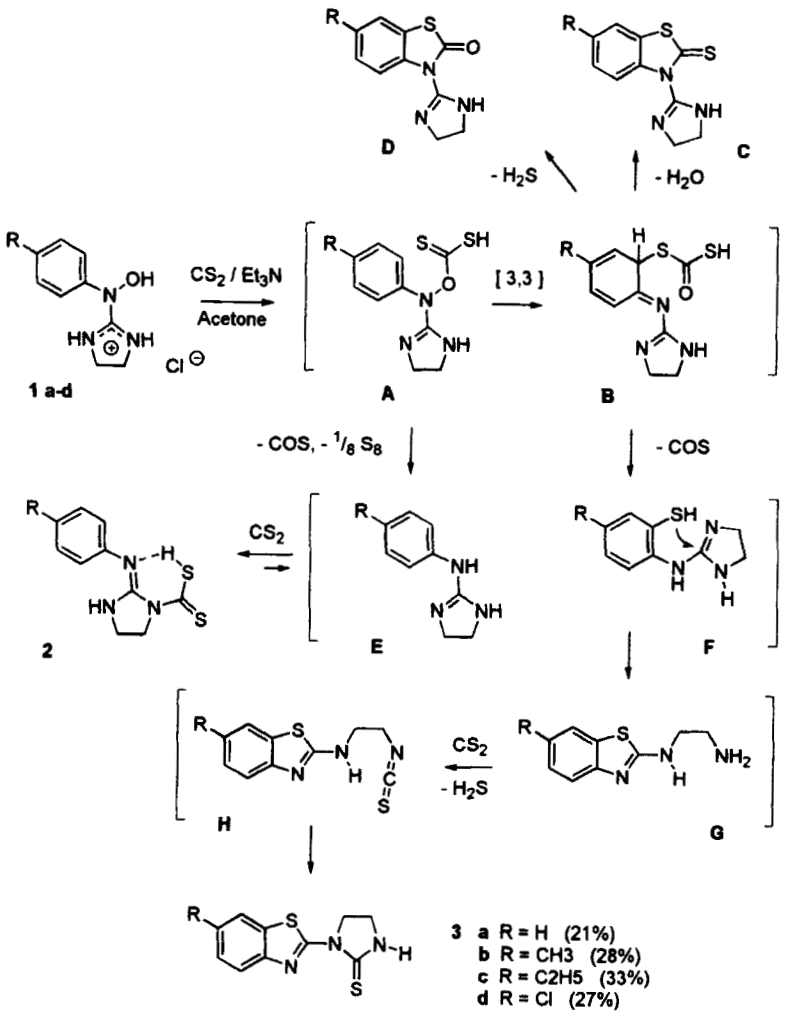
achieved by reacting hydroxylamines **1** with carbon disulfide (Scheme 1). Under mild conditions a [3,3] sigmatropic rearrangement of **2** could occur giving rise to the formation of dithiocarbonic acid derivative **3** which, in turn, could be stabilized by rearomatization process and intramolecular cyclocondensation reaction leading to the final benzothiazole derivatives of type **C** or benzoxazoles **D**.

It should be noted, that the unstable species of structure analogous to **A** were previously found to be the key intermediates in the deoxygenation processes of both tertiary amine oxides[5] and aromatic nitrones[6] as well as the dehydration of oximes by means of carbon disulphide[7]. In latter reaction, such an unstable species were stable enough to be captured by methylation with methyl iodide.

RESULTS AND DISCUSSION

When a mixture of hydroxylamine **1** (1 equivalent) and carbon disulfide (10 equivalents) in dry acetone was treated with triethylamine (2 equivalents) a slightly exothermic reaction took place and after 24 h at room temperature the following products were isolated from the reaction mixture: triethylamine hydrochloride, elemental sulfur, 2-(arylimino)-1-imidazolidine-carbodithioic acid **2** and 1-(1,3-benzothiazol-2-yl)-2-imidazolidinethione **3** in low yields (21–33 %) (Scheme 1).

The mechanism of the reaction pathway was not investigated but it can be mechanistically explained as follows. First, a portion of the transiently formed adduct of the hydroxylamine **1** to carbon disulfide (intermediate **A**) decomposes with evolution of COS molecule and elemental sulfur to yield the arylaminoimidazoline **E**, which, in turn, reacts with a second molecule of carbon disulfide resulting in the formation of a yellow coloured carbodithioic acid **2**. Simultaneously, the adduct **A** undergoes a [3,3] sigmatropic shift to give the dithiocarbonic acid **B** which, as evidenced from spectroscopic data, does not form the expected benzothiazole derivative **C** or **D**. Instead, the intermediate **B** stabilizes by loss of COS molecule and successive or simultaneous rearomatization process leading to the thiophenol **F**. Under alkaline conditions, the intramolecular nucleophilic attack of sulfur atom at the C-2 carbon atom of the imidazoline moiety takes place followed by imidazoline ring opening. The ethylene diamine



derivative **G** thus formed reacts further with an excess carbon disulfide to give the isothiocyanate **H**. This process is completed by 2-imidazolidine ring closure giving rise to the final product **3**.

The free acids of type **2** are stabilized by an intramolecular hydrogen bonding, and therefore, in solid state they proved to be stable for several days. In solution, however, ^{1}H- and ^{13}C-NBMR spectra of the freshly pre-

pared compound **2a** run in DMSO-d_6 revealed a mixture, consisting of the adduct **2a** (85 %), and phenyliminoimidazoline **E** (15 %) and carbon disulfide.

The structures of the compounds **3** are based upon a satisfactory elemental analyses and appropriate IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral characteristics.

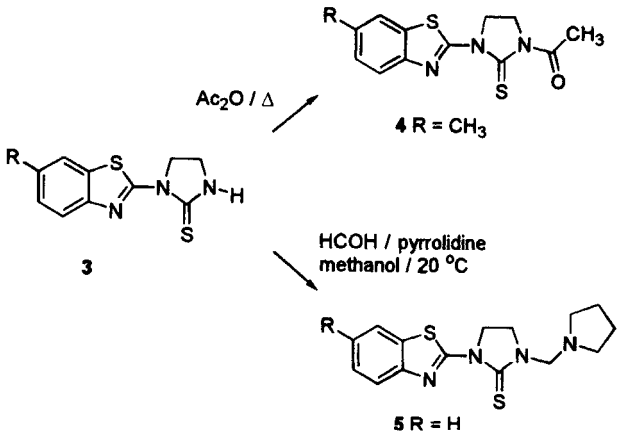
The IR spectra of the 2-imidazolidinethione derivatives **3a-d** exhibit absorptions at 3215–3230 cm^{-1} corresponding to N-H stretching vibrations and strong bands at 1232–1236 cm^{-1}characteristic of exocyclic C=S double bonds. In the ^{1}H-NMR spectra the methylene protons of the imidazoline moiety appear as two separate triplets confirming the substitution at the N-1 nitrogen atom. The mass spectra of the compounds **3** were also revealing. Thus, the molecular ion M^+ for the compound **3b** appears at $m/z = 249$ and is accompained by the base peak at $m/z = 177$ resulting from elimination of the [CH2NCS] radical. A similar fragmentation pattern was observed in mass spectrum of **3d**.

It should be mentioned that the compound **3a** was previously obtained by Beer and co-workers by bromine oxidation of 1-phenylthiocarbamoyl-2-imidazolidinethione[8]. The spectroscopic data of **3a** obtained by us are in agreement with those described by Beer.

As the synthetic potential of the 2-imidazolidinethiones of type **3** had not been explored, we performed some representative reactions (Scheme 2). Thus, the acetylation of the compound **3b** was completed by refluxing in acetic anhydride for 2h giving rise to the product **4.** Moreover, the Mannich type reaction of **3a** with pyrrolidine in the presence of formaldehyde carried out according to the procedure described earlier for 1-(arylthiocarbamoyl)-2-imidazolidinethiones[9] furnished the expected product **5.**

EXPERIMENTAL

Melting points were taken on a Boetius apparatus and are uncorrected. IR spectra were obtained on a Specord 80M. spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (200 MHz) and Varian Unity 500 Plus (500 MHz) instruments using TMS as an internal standard. MS spectra were recorded on a LKB 9000S spectrometer.



Reaction of N-phenyl-N-(4,5-dihydro-1*H* -imidazol-2-yl) hydroxylamine (1a) with carbon disulfide. Preparation of 2-(phenylimino)-1 -imidazolidine-carbodithioic acid (2a) and 1-(1,3 -benzothiazol-2-yl)-2-imidazolidinethione (3a)

To a suspension of the hydroxylamine **1a**[10] (1 g, 4.7 mmol) and carbon disulfide (2.8 ml, 49 mmol) in dry acetone (10 ml) was added dropwise triethylamine (1.3 ml, 9.4 mmol) with stirring. After 24 h the solid that precipitated was filtered off (triethylamine hydrochloride and elemental sulfur) and the filtrate was concentrated to dryness under reduced pressure. Then, the residue was treated with aqueous 5% NaOH (20 ml) followed by extraction with CH_2Cl_2 (3 X 20 ml). The organic layer was dried with anhydrous $MgSO_4$ and the solvent was evaporated to dryness. The crude product **3a** thus obtained was purified by crystallization from DMF/H_2O; yield: 0.23 g (21 %), m.p. 242–244 °C (lit [8] m.p. 225–227 °C). – IR (KBr): ν = 3230, 1608, 1504, 1440, 1408, 1344, 1232. – ^{1}H-NMR ($CDCl_3$) δ = 3.85 (t, 2H, CH2), 4.65 (t, 2H, CH2), 6.65 (s, 1H, NH), 7.3–7.9 (m., 4H, aromat.). – ^{13}C-NMR (DMSO-d_6): δ = 41.48, 49.78, 120.27, 121.4, 123.43, 125.9, 132.12, 148.08, 158.5, 177.89. – $C_{10}H_9N_3S_2$ (235.31): calcd. C 51.04, H 3.85, found: C 51.12, H 3.71.

The alkaline aqueous phase was neutralized with 10% HCl The yellow adduct **2a** that precipitated was collected by filtration, washed with water

and purified by dissolving it in 5% NaOH and reprecipitation with 10% HCl. Yield: 0.23 g (21%), m.p. 87–90 °C (dec). – IR (KBr): ν = 3296, 1664, 1568, 1488, 1248, 1136, 1072. – MS (70 eV) *m/z* (relative intensity): 161 ($M^+ - CS_2$, 36), 160 (16), 104 (11), 77 (8), 76 (100).

Analogously were prepared compounds **3b** and **3c** from the hydroxylamine derivatives **1b** and **1c** respectively.

1-(6-methyl-1,3-benzothiazol-2-yl)-2-imidazolidinethione (3b)

Yield: 28 %, m.p. 265–267 °C (DMF/H_2O). – IR (KBr): ν = 3216, 1600, 1584, 1536, 1432, 1408, 1344, 1296, 1232. – ^{1}H-NMR (DMSO-d_6): δ = 2.4 (s, 3H, CH_3), 3.7 (t, 2H, CH_2), 4.45 (t, 2H, CH_2), 7.2 (dd, 1H, aromat.), 7.6 (d, 1H, aromat.), 7.7 (d, 1H, aromat.), 9.7 (br s, 1H, NH) – ^{13}C-NMR (DMSO-d_6): δ = 21.0, 41.45, 49.8, 119.93, 121.0, 127.2, 132.29, 132.87, 146.06, 157.7, 177.8.- MS (70 eV) *m/z* (relative intensity): 249 (M^+, 77), 177 (100), 164 (42), 150 (14), 123 (3). – $C_{11}H_{11}N_3S_2$ (249.34): calcd C 52.98, H 4.45, found: C 52.61, H 4.11.

1-(6-ethyl-1,3-benzothiazol-2-yl)-2-imidazolidinethione (3c)

Yield: 33 %, m.p. 243–245 °C (EtOH). – IR (KBr): ν = 3215, 1640, 1584, 1504, 1424, 1344, 1296, 1236. – ^{1}H-NMR (DMSO-d_6): δ = 1.1 (t, 3H, CH_3), 2.7 (q, 2H, CH_2), 3.7 (t, 2H, CH_2), 4.4 (t, 2H, CH_2), 7.25 (dd, 1H, aromat.), 7.65 (d, 1H, aromat.), 7.75 (d, 1H, aromat.), 9.6 (br s, 1H, NH). – ^{13}C-NMR (DMSO-d_6): δ = 15.97,28.18,41.58,49.81, 119.89, 120.03, 126.12, 132.34, 139.37, 146.3, 157.87, 177.76. – $C_{12}H_{13}N_3S_2$ (263.36): calcd. C 54.72, H 4.97, found: C 55.02, H 4.88.

Preparation of 1-(6-chloro-1,3-benzothiazol-2-yl)-2-imidazolidinethione (3d)

To a suspension of N-(4-chlorophenyl)-N-(4, 5-dihydro-1*H*-imidazol –2-yl)hydroxylamine hydrochloride **1d**[10] (1 g, 4 mmol) and carbon disulfide (2.44 ml, 40 mmol) in dry acetone (10 ml) triethylamine (1.1 1 ml, 8 mmol) was added dropwise with stirring. After 24 h the solid that precipitated was separated by suction, washed thoroughly with water, dried and purified by recrystallization from DMF/H_2O; yield: 0.29 g (27

%), m.p. 273–276 °C. IR (KBr): ν = 3224, 1584, 1536, 1504, 1472, 1440, 1408, 1344, 1236. – ^{1}H-NMR (DMSO-d_6): δ = 3.72 (t, 2H, CH_2), 4.46 (t, 2H, CH_2), 7.42 (dd, 1H, aromat.), 7.72 (d, 1H, aromat.), 8.08 (d, 1H, aromat.), 9.8 (br s, 1H, NH). – ^{13}C-NMR (DMSO-d_6): δ = 41.56, 49.76, 121.09, 121.44, 126.18, 127.37, 133.76, 146.95, 159.24, 177.77. – $C_{10}H_8ClN_3S_2$ (269.75): calcd. C 44.52, H 2.98, found: C 44.81, H 3.17.

1-acetyl-3-(6-methyl-1,3-benzothiazol-2-yl)-2-imidazolidinethione (4)

The compound **3b** (1 g, 4 mmol) was suspended in acetic anhydride (10 ml) and the reaction mixture was refluxed for 2h. After cooling to 15°C in a refrigerator, the crude product **4** that deposited was collected by filtration and purified by recrystallization from MeOH. Yield: 0.68 g (58 %), m.p. 225–228 °C. – IR (KBr): ν = 2940, 1684, 1644, 1504, 1392, 1252. – ^{1}H-NMR (DMSO-d_6): δ = 2.5 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 4.25 (t, 2H, CH_2), 4.57 (t, 2H, CH_2), 7.3 (dd, 1H, aromat.), 7.62 (d, 1H, aromat.), 7.78 (d, 1H, aromat.). – ^{13}C-NMR (DMSO-d_6): δ = 21.55, 26.91, 44.03, 46.97, 120.82, 127.73, 127.84, 132.26, 134.63, 145.53, 156.6, 171.56, 175.08. – MS (70 eV) *m/z* (relative intensity): 291 (M^+, 25), 178 (12), 177 (100), 175 (61).- $C_{13}H_{13}N_3S_2$ (291.37): calcd. C 53.58, H 4.49, found: C 53.78, H 4.73.

1-(1,3-benzothiazol-2-yl)-3-(1-pyrrolidinmethyl)-2-imidazolidinethione (5)

To a suspension of the compound **3a** (0.5 g, 2.1 mmol) in methanol (5 ml) was added dropwise 38% formaldehyde (0.16 ml, 2.1 mmol) and the reaction mixture was stirred at room temperature for 3h. The crude product **5** that precipitated was collected by filtration, washed with water and purified by recrystallization from DMF/H_2O. Yield: 0.42 g (62 %), m.p. 153–156 °C. – IR (KBr): ν = 2960, 1472, 1372, 1232, 1120. – ^{1}H-NMR (DMSO-d_6): δ = 1.83 (m, 4H, CH_2), 2.77 (m, 4H, CH_2), 3.87 (t, 2H, CH_2), 4.52 (t, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.26–7.8 (m, 4H, aromat.). – ^{13}C-NMR (DMSO-d_6): δ = 24.52, 46.76, 48.18, 52.64, 67.63, 121.42, 121.73, 124.34, 126.56, 132.96, 148.91, 160.05, 178.48. – $C_{15}H_{18}N_4S_2$ (318.44): calcd. C 56.57, H 5.69, found: C 56.77, H 5.84.

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