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Reaction of Azolethiones with Diacetylene

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Abstract—Reactions of 2,3-dihydro-1*H*-benzimidazole-2-thione, 2,3-dihydro-1*H*-1,2,4-triazole-3-thione, 4-amino-5-phenyl-3,4-dihydro-2*H*-1,2,4-triazole, and 6-aminopurine-2-thiol with diacetylene in DMSO gave the corresponding 1-(azolylsulfanyl)but-1-en-3-ynes having *Z* configuration of the double bond.

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Azolethiones may exist as two tautomers, and they are capable of taking up acetylenes at the nitrogen or sulfur atom, depending on the conditions. For example, acetylene reacts with azolethiones in the presence of basic reagents to give the corresponding azolyl vinyl sulfides [1, 2]. Reactions with acetylenic acid esters also involve the sulfur atom [3, 4]. On the other hand, addition of activated acetylenic compounds at the nitrogen atom of the thioamide moiety was also reported [5]. Addition of phenylcyanoacetylene [6, 7] and tertiary cyanoacetylenic alcohols [8, 9] to azolethiones in the presence of KOH (or better LiOH) is accompanied by intramolecular cyclization at the cyano group to give 1,3-thiazinoazoles, indicating that the NH and SH groups in azolethiones exhibit similar reactivities. Presumably, the first reaction stage gives unstable adducts at the nitrogen atom which have *Z* configuration [6, 8], and they undergo cyclization at the exocyclic sulfur atom.

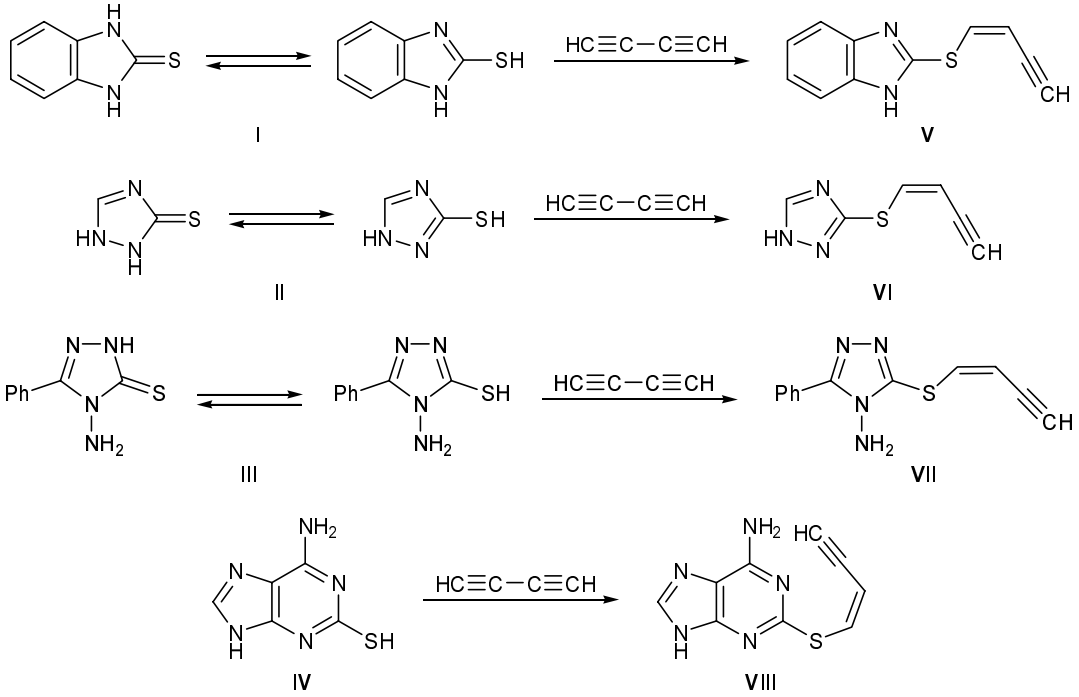
There are no published data on reactions of azolethiones **I**–**IV** with diacetylene. In the present work we examined reactions of 2,3-dihydro-1*H*-benzimidazole-2-thione (**I**), 2,3-dihydro-1*H*-1,2,4-triazole-3-thione (**II**), 4-amino-5-phenyl-3,4-dihydro-2*H*-1,2,4-triazole (**III**), and 6-aminopurine-2-thiol (**IV**) with diacetylene with the goal of obtaining new biologically active compounds. Azolethione **I** failed to react with diacetylene under mild conditions (liquid NH_3, –33°C, 7 h), while in DMSO in the presence of KOH at 20°C we isolated 2-[(*Z*)-but-1-en-3-yn-1-ylsulfanyl]benzimidazole (**V**) in 71% yield (Scheme 1).

The IR spectrum of **V** contained an absorption band at 2090 cm^{-1} due to stretching vibrations of the triple carbon–carbon bond and a band at 3270 cm^{-1} due to the ≡C–H bond. The exocyclic double bond gave rise to absorption at 1590 and 1580 cm^{-1}, and the band at 3050 cm^{-1} was assigned to =C–H stretching vibrations. In the ^{1}H NMR spectrum of **V** in DMSO-d_6, signals from the terminal acetylenic proton (δ 4.63 ppm, d, $^4J_{HH}$ ~2.3 Hz) and protons at the double bond were present (δ, ppm: 6.00 q, =CH–C≡, $^3J_{HH}$ ~10 Hz; 7.60 d, =CHS, $^3J_{HH}$ ~10 Hz). Protons in the benzimidazole ring resonated at δ 7.17 (4-H, 7-H) and 7.50 ppm (5-H, 6-H). The structure of **V** was also confirmed by the ^{13}C NMR data.

The reaction of thione **II** with diacetylene in DMSO (KOH, 20–25°C, 2 h) led to formation of a mixture of products which were difficult to separate. According to the IR and ^{1}H NMR spectra of the reaction mixture, the major product was 3-(but-1-en-3-yn-1-ylsulfanyl)-1*H*-1,2,4-triazole (**VI**), whereas no product of addition at the nitrogen atom was detected. Compound **VI** showed in the IR spectrum absorption bands at 2080 (C≡C) and 3270 cm^{-1} (≡C–H) which belong to the terminal acetylenic moiety, and stretching vibration band of the double C=C bond at the sulfur atom appeared at 1570 cm^{-1}. The ^{1}H NMR spectrum of **VI** contained the following signals, δ, ppm: 4.57 d (≡CH, $^4J_{HH}$ ~2.3 Hz), 5.89 q (=CH–C≡, $^3J_{HH}$ ~10 Hz), 7.38 d (=CHS, $^3J_{HH}$ ~10 Hz).

Triazole **III** is also capable of taking up diacetylene at the amino or sulfanyl group. However, compound **III** reacted with diacetylene in DMSO in the presence of KOH (25–27°C, 2.5 h) with high regio- and stereoselectivity, and the product was 5-[(*Z*)-but-1-en-3-yn-1-ylsulfanyl]-3-phenyl-4*H*-1,2,4-triazol-4-amine (**VII**, yield 80%). The IR spectrum of triazole **VII** contained absorption bands belonging to the amino

Scheme 1.



group (3340 cm^{-1}), ≡C–H (3275 cm^{-1}) and C≡C bonds (2090 cm^{-1}), and double C=C bond (1580 cm^{-1}). In the ^1H NMR spectrum of **VII** we observed signals at δ 4.62 (d, $^4J_{HH}$ ~2.3 Hz, ≡CH), 6.01 (q, $^3J_{HH}$ ~10 Hz, =CH–C≡), and 7.41 ppm (d, $^3J_{HH}$ ~10 Hz, =CH–S), as well as from protons of the amino group (δ 8.01 ppm, m) and aromatic protons (δ 6.24 ppm, s, *m*-H; δ 7.52 ppm, s, *o*-H, *p*-H). In the spectrum recorded at 60°C, these signals were displaced upfield by about 0.1 ppm. The structure of **VII** was also confirmed by the ^{13}C NMR spectrum.

With a view to obtain new biologically active compounds, we performed the reaction of purine **IV** with diacetylene (DMSO, KOH, 20°C, 2 h). As in the previous case, the reaction was regio- and stereoselective, and it afforded 2-[(Z)-but-1-en-3-yn-1-ylsulfanyl]-9*H*-purin-6-amine (**VIII**) in 83% yield. The structure of product **VIII** was confirmed by the IR and ^1H and ^{13}C NMR spectra (see Experimental).

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer from samples prepared as KBr pellets or thin films. The ^1H and ^{13}C NMR spectra were measured on Bruker DPX-400 (400 MHz) and Bruker DPX-250 instruments, respectively, using DMSO-d_6 as solvent and HMDS as internal reference.

2-[(*Z*)-But-1-en-3-yn-1-ylsulfanyl]-1*H*-benzimidazole (V). A stream of a diacetylene–nitrogen mixture was passed over a period of 1.5 h through a solution of 0.5 g (3.5 mmol) of benzimidazole **I** and 0.05 g of KOH in 30 ml of DMSO under stirring at 20–25°C. The mixture was diluted with water, and the precipitate was filtered off. Yield 0.47 g (71%), mp 169°C. IR spectrum, ν, cm^{-1}: 3440, 3270, 3050, 2090, 1615, 1580, 1500, 1430, 1420, 1405, 1350, 1280, 1220, 1010, 985, 950, 780, 760, 740. ^1H NMR spectrum, δ, ppm: 4.63 d (1H, ≡CH), 6.00 q (1H, =CHC≡), 7.60 d (1H, =CHS), 7.17 m (2H, 4-H, 7-H), 7.50 m (2H, 5-H, 6-H), 12.83 br (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 79.91 (**C**≡CH), 90.53 (≡CH), 107.72 (=**C**HC≡), 117.06 (C^4, C^7), 122.41 (C^5, C^6), 135.14 (CHS), 146.53 (C^{3a}, C^{7a}). Found, %: C 65.59; H 3.93; N 15.76; S 13.69. $C_{11}H_8N_2S$. Calculated, %: C 65.99; H 4.03; N 15.98; S 13.99.

3-[(*Z*)-But-1-en-3-yn-1-ylsulfanyl]-1*H*-1,2,4-triazole (VI) was identified in a mixture of products by spectral data. IR spectrum, ν, cm^{-1}: 3390, 3270, 3205, 3060, 3010, 2080, 1670, 1530, 1480, 1420, 1360, 1270, 1240, 1230, 1170, 1050, 940, 930, 850, 780, 705, 650, 620. ^1H NMR spectrum, δ, ppm: 4.57 d (1H, ≡CH), 5.89 q (1H, =CHC≡), 7.38 d (1H, =CHS), 8.50 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 79.89 (**C**≡CH), 89.71 (≡CH), 106.33 (=**C**HC≡), 118.76 (C^3), 134.63 (=CHS), 158.62 (C^5).

5-[(*Z*)-But-1-en-3-yn-1-ylsulfanyl]-3-phenyl-4*H*-1,2,4-triazol-4-amine (VII) was synthesized as described above for compound **V** from 0.5 g (2.6 mmol) of 4-amino-3-phenyl-4*H*-1,2,4-triazole-5-thiol (**III**). Yield 0.51 g (81%), mp 166°C. IR spectrum, ν, cm^{-1}: 3340, 3275, 3175, 3060, 2090, 1620, 1580, 1470, 1450, 1425, 1350, 1320, 1280, 1240, 1105, 1080, 975, 900, 770, 700, 680, 670, 625. ^{1}H NMR spectrum, δ, ppm: 4.62 d (1H, ≡CH), 6.01 q (1H, =CHC≡), 6.24 s (2H, *m*-H), 7.41 d (1H, =CHS), 7.52 m (3H, *o*-H, *p*-H), 8.01 t (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 79.34 (**C**≡CH), 90.33 (≡CH), 107.74 (=**C**HC≡), 135.55 (=CHS), 150.85 (C^5), 154.65 (C^3), 127.4–129.54 m (C_{arom}). Found, %: C 59.82; H 4.13; N 22.67; S 12.99. $C_{12}H_{10}N_4S$. Calculated, %: C 59.50; H 4.16; N 23.13; S 13.21.

2-[(Z)-But-1-en-3-yn-1-ylsulfanyl]-9*H*-purin-6-amine (VIII) was synthesized as described above for compound **V** from 1.07 g (6.4 mmol) of purine **IV**. Yield 1.15 g (89%). IR spectrum, ν, cm^{-1}: 3440, 3290, 3190, 3040, 2090, 1670, 1600, 1590, 1470, 1415, 1310, 1270, 1120, 960, 935, 850, 795, 780, 670, 625. ^{1}H NMR spectrum, δ, ppm: 4.45 d (1H, ≡CH), 5.80 q (1H, =CHC≡), 7.31 s (2H, NH_2), 7.50 d (1H, =CHS), 8.05 s (1H, 8-H), 12.91 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 80.39 (**C**≡CH), 88.75 (≡CH), 107.06 (=**C**HC≡), 117.71 (C^5), 137.33 (=CHS), 139.31 (C^8), 151.98 (C^4), 155.49 (C^6), 159.17 (C^2). Found, %: C 49.60; H 3.18; N 31.96; S 14.57. $C_9H_7N_5S$. Calculated, %: C 49.47; H 3.25; N 32.25; S 14.73.

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