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Reactions of Aliphatic, Aromatic, and Heterocyclic Aminothiols with Diacetylene

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Abstract—Reactions of aliphatic, aromatic, and heterocyclic aminothiols with diacetylene in liquid ammonia or methanol furnished the corresponding aminoorganylsulfanylbutenynes of predominantly *Z*-configuration.

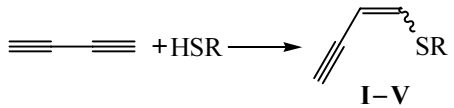
Diacetylene opens up new fields for preparation versatile unsaturated heteroatomic compounds with specific characteristics [1, 2]. Reactions of diacetylene with thiols and hydrogen sulfide in various media [3], in particular, in liquid ammonia [4], gave rise to enyne sulfides [5] and thiophene [6].

We report here on the study of nucleophilic addition of 1,2-aminothiols to diacetylene in liquid ammonia or in methanol aimed at elucidation of the reaction direction and at preparation of new biologically active compounds. The combination in a single molecule of acid and base properties makes it possible for the compound to exist in a form of an internal salt (zwitter-ion). By changing the pH of the medium the ammonium salt $HSCH_2CH_2^+NH_3$ can be converted through $^-SCH_2CH_2^+NH_3$ into a free base $^-SCH_2CH_2NH_2$ [7].

The nucleophilic ability of 1,2-aminothiols in reactions with activated unsaturated compounds is well consistent with the acidity of the mercapto and amino groups in aminothiols [7]. According to [8] at comparable values of the medium p*K* and comparable spatial surrounding the HS^- anions are 280 times more active than NH_2^- anions. Therefore the proton elimination from the β-aminoethanethiol occurred exclusively from the SH groups. The analysis of published data [9–12] revealed that sometimes NH_2 groups are involved, and cyclization also may happen. For instance, the reaction of α-acetylene ketones with β-aminoethanethiol hydrochloride in methanol solution in the presence of sodium methylate resulted in bis(acylvinylaminoethyl) disulfides, i.e., only amino group was involved into the process. At excess initial ketone (2:1) alongside the disulfides formed also 1,4-bis-(acylvinyl)-1-thia-4-azabutanes [9].

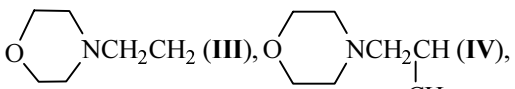
Taking into account the presence of two reaction sites in aminothiol molecules and the thiols ability to be oxidized into disulfides it was presumable that the reaction would give rise to several products. However the use of mild conditions (liquid ammonia) prevented participation in the reaction of the amino group and also disulfides formation. The basic quality of ammonia favors thiolate ion formation, and the high reactivity of the latter is ensured by its weak solvation with the ammonia molecules. Therefore the reaction begins by a nucleophilic attack of the thiolate ion on the triple bond and affords the corresponding enyne sulfides **I–V** that were isolated in high yields (78–98%).

The diacetylene reaction with the β-aminoethanethiol in methanol in the presence of alkali also resulted in sulfide **I** but in a lower yield (52%).



I–V

R = $NH_2CH_2CH_2$ (I), $(C_2H_5)_2NCH_2CH_2$ (**II**),



o-$NH_2C_6H_4$ (**V**).

In the IR spectra of compounds **I–V** appear the absorption bands of the triple bond at 2060–2100 cm^{-1} and of ≡CH group at 3250–3290 cm^{-1}. To the vibrations of S–C=C and C–S bonds belong the absorption bands at 1550–1600 cm^{-1} and 690–710 cm^{-1} respectively. The following resonances were observed in the ^1H NMR spec-

tra of compounds **I–V** recorded in CD_3OD, δ, ppm: 3.17–3.75 d (≡CH, $^4J_{HH}$ ~2.3 Hz), 5.33–5.16 q (=CHC≡, $^3J_{HH}$ ~10 Hz), 6.39–6.76 d (=CHS, $^3J_{HH}$ ~10 Hz). Enyne sulfides **III–V** were obtained as *Z*-isomers, and sulfides **I** and **II** as mixtures of *Z*- and *E*-isomers in a ratio 3:1 and 6:1 respectively. The lack of stereospecificity in addition of β-aminoethanethiol and β-(*N,N*-diethylamino-ethanethiol to diacetylene is in agreement with the formerly obtained data on the partial deviation from the rule of the *trans*-nucleophilic thiol addition to diacetylene occurring in liquid ammonia [4]. In the ^{13}C NMR spectrum of sulfide **I** were found the signals belonging to the *Z*- and *E*-isomers ($CDCl_3$), δ, ppm: 78.30 and 76.81 (–C≡), 84.85 and 82.09 (≡CH), 103.92 and 104.05 (=CHC≡), 141.30 and 140.25 (=CHS), 41.75 and 40.74 (CH_2N), 37.46 and 36.04 (CH_2S) respectively.

The presence of amino group in sulfide **I** may lead to intramolecular cyclization into a 1,3-thiazole. However the heating of sulfide **I** in dioxane (90°C, 10 h) did not result in the cyclization. The reaction of sulfide **I** with acetic acid afforded 2-(but-1-en-3-yn-1-ylsulfanyl)-ethylammonium acetate (**VI**), mp 105–106°C.

Note that the acetylene proton in the ^1H NMR spectrum of compound **I** is the most shielded (3.35 ppm) in $CDCl_3$ solution and the least shielded (4.28 ppm) in DMSO-d_6 environment. The downfield shift of the acetylene proton (~1 ppm) is presumably caused by formation of a relatively strong associate of the enyne compound with DMSO-d_6.

In the case of *o*-aminothiophenol the formation of sulfide **V** was less predictable for the thiophenols (pK_a 7–8) formed stronger ammonium salts with ammonia. However the structure of sulfide **V** is unambiguously confirmed by its ^1H NMR spectrum (δ, ppm) where appear signals of NH_2 protons(4.08), and also of olefin protons (5.49 q and 6.74 d, $^3J_{HH}$ ~10 Hz) corresponding to *Z*-isomer.

EXPERIMENTAL

^1H NMR spectra of compounds **I–V** were registered from solutions in $CDCl_3$ on spectrometer Bruker DPX-400 (400 MHz), ^1H and ^{13}C NMR spectra of compound **I** were taken on spectrometer Bruker DPX-250 (250.1 and 62.4 MHz), internal reference HMDS. IR spectra were recorded on spectrometer Specord 751R from thin films.

2-(But-1-en-3-yn-1-ylsulfanyl)ethylamine (I). (a) To a solution of 0.56 g (4.9 mmol) of β-aminoethanethiol hydrochloride in 100 ml of liquid NH_3 was added at stirring a solution of 2 g (40 mmol) of diacetylene in 50 ml of liquid NH_3. The mixture was stirred for 3 h at –33°C, NH_3 was evaporated, the residue was extracted with ethyl ether, dried on $MgSO_4$, and dilstilled. Yield 0.53 g (77.8%), bp 92–95°C (2 mm Hg), n_D^{20} 1.5724. IR spectrum, cm^{-1}: 3350, 3280, 3020, 2080, 1655, 1550, 1410, 1370, 1330, 1210, 1065, 1010, 960, 830, 770, 700, 640. ^1H NMR spectrum, δ, ppm: (*Z*, $CDCl_3$) – 3.35 d (1H, ≡CH), 5.44 q (1H, =CHC≡), 6.51 d (1H, =CHS), 2.86 m (2H, CH_2N), 2.79 m (2H, CH_2S); (*Z*, CD_3OD) – 3.75 d (1H, ≡CH), 5.58 q (1H, =CHC≡), 6.76 d (1H, =CHS); (*Z*, DMSO-d_6) – 4.28 d (1H, ≡CH), 5.52 q (1H, =CHC≡), 6.85 d (1H, =CHS), 2.79 m (2H, CH_2N), 2.73 m (2H, CH_2S), 1.97 br (2H, NH_2); (*E*, CD_3OD) – 3.68 d (1H, ≡CH), 5.47 q (1H, =CHC≡), 6.68 d (1H, =CHS); (*E*, DMSO-d_6) – 3.84 d (1H, ≡CH), 5.56 q (1H, =CHC≡), 6.93 d (1H, =CHS), 2.82 m (2H, CH_2N), 2.70 m (2H, CH_2S). Found, %: C 57.01; H 7.02; N 10.73; S 24.97. C_6H_9NS. Calculated, %: C 56.68; H 7.09; N 11.02; S 25.19.

(b) To a solution of 0.91 g (8 mmol) of β-aminoethanethiol in 35 ml of methanol was added 0.32 g (70 mmol) of NaOH, 3.61 g (72 mmol) of diacetylene was passed through, and the reaction mixture was stirred for 3 h and then distilled. Yield 0.45 g.

2-(But-1-en-3-yn-1-ylsulfanyl)ethyldiethylamine (II) was prepared similarly from 2.54 g (19 mmol) β-(*N,N*-diethylamino)ethanethiol in 50 ml of liquid NH_3 and 1.6 g (3.2 mmol) of diacetylene in 50 ml of liquid NH_3 at –33°C within 5 h. Yield 3.42 g (98%), bp 83–84°C (2 mm Hg), n_D^{20} 1.5260. IR spectrum, cm^{-1}: 3310, 3270, 2100, 1500, 1460, 1385, 1310, 1300, 1200, 1150, 1115, 1070, 1040, 1020, 1000, 960, 915, 840, 790. ^1H NMR spectrum, δ, ppm: (*Z*, CCl_4) – 3.17 d (1H, ≡CH), 5.33 q (1H, =CHC≡), 6.50 d (1H, =CHS), 2.56 m (2H, CH_2N), 2.42 m (2H, CH_2S), 0.93 t (3H, CH_3); (*E*, CCl_4) – 3.09 d (1H, ≡CH), 5.07 q (1H, =CHC≡), 6.67 d (1H, =CHS). Found, %: C 65.20; H 9.44; N 7.63; S 17.60. $C_{10}H_{17}NS$. Calculated, %: C 65.54; H 9.35; N 7.64; S 17.46.

N-[2-(But-1-en-3-yn-1-ylsulfanyl)ethyl]-morpholine (III) was prepared similarly from 1.74 g (12 mmol) of 2-(morpholino)ethanethiol in 4 ml of CH_3OH and 100 ml of liquid NH_3, and 1.15 g (23 mmol) of diacetylene in 50 ml of liquid NH_3. The mixture was stirred for 5 h at –33°C. Yield 2.03 g (87%), bp 118°C (3 mm Hg), n_D^{20} 1.5540. IR spectrum, cm^{-1}: 3290, 3040, 2095, 1690, 1600, 1580, 1450, 1370, 1330, 1275, 1200, 1120, 1010, 910, 870, 750, 690. ^1H NMR spectrum, δ, ppm: (*Z*, CD_3OD) – 3.25 d (1H, ≡CH), 5.88 q (1H, =CHC≡),

6.70 d (1H, =CHS), 2.82 t (2H, CH_2N), 2.47 m (2H, CH_2S), 3.68 t (2H, CH_2O). Found, %: C 60.69; H 7.69; N 7.36; S 15.83. $C_{10}H_{15}NOS$. Calculated, % : C 60.89; H 7.67; N 7.10; S 16.16.

N-[2-(But-1-en-3-yn-1-ylsulfanyl)propyl]-morpholine (IV) was prepared similarly from 4.63 g (29 mmol) of 1-morpholinopropane-2-thiol in 100 ml of liquid NH_3 and 4.38 g (88 mmol) of diacetylene in 70 ml of liquid NH_3. Yield 5.93 g (97%), bp 145–149°C (1 mm Hg), n_D^{20} 1.6695. IR spectrum, cm^{-1}: 3250, 3050, 2060, 1560, 1450, 1350, 1310, 1300, 1200, 1100, 1060, 1040, 1020, 1000, 960, 850, 790, 775, 700. ^1H NMR spectrum, δ, ppm: (*Z*, $CDCl_3$) – 3.40 d (1H, ≡CH), 5.49 q (1H, =CHC≡), 6.74 d (1H, =CHS), 2.95 d (2H, CH_2N), 2.44 m (2H, CH_2S), 3.66 t (2H, CH_2O), 1.34 d (3H, CH_3). Found, %: C 62.69; H 8.39; N 6.93; S 15.07. $C_{11}H_{17}NOS$. Calculated, %: C 62.54; H 8.11; N 6.63; S 15.15.

2-(But-1-en-3-yn-1-ylsulfanyl)aniline (V) was prepared similarly from 3.21 g (24 mmol) of *o*-aminothiophenol in 50 ml of liquid NH_3 and 1.51 g (30 mmol) of diacetylene in 50 ml of liquid NH_3. Yield 3.5 g (79 %), bp 116°C (1 mm Hg) IR spectrum, cm^{-1}: 3460, 3365, 3280, 3040, 3015, 2100, 1610, 1565, 1555, 1480, 1445, 1330, 1310, 1250, 1160, 1080, 1030, 970, 800, 770, 720. ^1H NMR spectrum, δ, ppm: (*Z*, CCl_4) – 3.26 d (1H, ≡CH), 5.43 q (1H, =CHC?), 6.39 d (1H, =CHS), 7.12 m (4H, C_6H_4), 4.08 br (2H, NH_2). Found, %: C 68.80; H 5.37; N 7.87; S 17.90. $C_{10}H_9NS$. Calculated, %: C 68.56; H 5.18; N 8.00; S 18.27.

2-(But-1-en-3-yn-1-ylsulfanyl)ethylammonium acetate (VI). To a solution of 0.25 g (1.97 mmol) of compound **I** in 10 ml of dioxane was added dropwise 0.12 g (2 mmol) of acetic acid; the mixture was maintained for 15 min at 25–30°C, and dioxane was evaporated. Yield 0.33 g (89.6%). IR spectrum, cm^{-1}: 3440, 3170, 3050, 2080, 1630, 1560 sh, 1520, 1450, 1390, 1330, 1280, 1240, 1120, 1030, 1000, 970, 920, 890, 740, 690, 640, 620. ^1H NMR spectrum, δ, ppm: (*Z*, DMSO-d_6) – 4.32 d (1H, ≡CH), 5.55 q (1H, =CHC≡), 6.87 d (1H, =CHS), 2.89 m (2H, CH_2N), 2.81 m (2H, CH_2S), 1.80 s (3H, CH_3), 6.00 (3H, NH_3^0). ^{13}C NMR spectrum, δ, ppm : (*Z*, DMSO-d_6) – 80.62. (–C≡), 88.08 (HC≡), 103.65 (=CH–C≡), 142.63 (=CH–S), 41.34 (NCH_2), 34.15 (SCH_2), 22.62 (CH_3CO).

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