# SYNTHESIS OF 1,2,4-TRIAZOLO[3,4-b]-1,3,4-THIADIAZEPINES AND 4-AMINO-3-ACYLVINYLTHIO-1,2,4-TRIAZOLES BY REACTION O ACYLACETYLENES WITH 4-AMINO-3-MERCAPTO-1,2,4-TRIAZOLE

**T. E. Glotova, A. S. Nakhmanovich, L. S. Romanenko, and M. V. Sigalov**

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*1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazepines have been prepared by treating α-acetylenic ketones with 4-amino-3-mercapto-1,2,4-triazole in glacial acetic acid. Terminal acetylenic ketones react with the triazole to form 4-amino-3-acylvinylthio-1,2,4-triazoles. Heating the latter with hydrazine hydrate in alcohol yields substituted pyrazoles.*

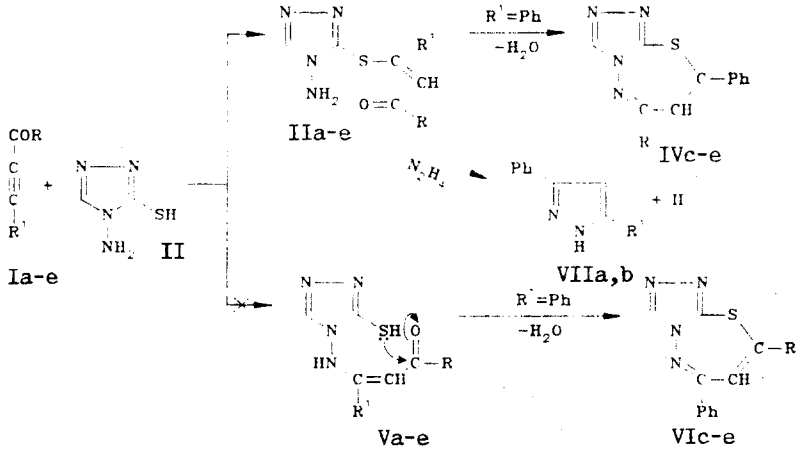
Heating 5-substituted 4-amino-3-mercapto-1,2,4-triazoles with methyl propiolate in methanol gives cis-4-amino-3-carbomethoxyvinylthio-1,2,4-triazoles [1]. Similar reactions with phenyl- and p-bromophenylpropiolic aldehydes have given 8-aryl-1,2,4-triazolo-3,4-b]-1,3,4-thiadiazepines [1].

Depending on conditions, α-acetylenic ketones react with 5-substituted 1,2,4-triazol-3-thiones to give 3-acylvinylthio-1,2,4-triazoles, 2-benzoylvinyl-1,22,4-triazol-3-thiones, or 2-benzoylvinyl-3-benzoylvinylthio-1,2,4-triazoles [3, 4].

Reaction of 1-bromo-2-acylacetylenes with 4-amino-3-mercapto-5-phenyl-1,2,4-triazole in acetonitrile gives 2-acylmethylene-5-phenyl-3H-1,3,4-thiadiazolo]2,3-d]-1H(2H)-1,2,4-triazolium bromides [3].

It is known that certain substituted triazoles and condensed heterocyclic compounds containing the triazole ring are biologically active [5-8].

In a search for novel biologically active 1,2,4-triazoles we have studied the reaction of acylacetylenes Ia-e with an equimolar amount of 4-amino-3-mercapto-1,2,4-triazole (II) in MeOH, MeCN, glacial AcOH, or DMSO at 20°C or upon heating.




I—III, V, VII a R=Ph, R¹=H; I—III, V, VI b R=α-$C_4H_5S$, R¹=H; I—VII c R=R¹=Ph; I—VI d R=α-$C_4H_3S$, R¹=Ph; e R=Me, R¹=Ph

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033.
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Terminal α-acetylenic ketones Ia, b in MeOH, MeCN, glacial AcOH, or DMSO at 20°C react with an equimolar ratio of triazole II to form 4-amino-3-acylvinylthio-1,2,4-triazoles IIIa, b in 69-80% yields. When the reaction of Ia with II was carried out in MeOH or glacial AcOH at 60°C the S-mono adduct IIIa was obtained in yields of 73 and 70%, respectively.

Prolonged heating of the α-acetylenic ketones Ic, d with II in glacial AcOH at 60°C gives the corresponding S-mono adducts IIIc, d in 29-69% yield.

The reaction of ketones Ic-e with II in glacial AcOH at 60°C occurs quite differently. In this case the only reaction products were 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazepines IVc-e in 50-59% yields. Evidently the latter is formed by an intramolecular dehydrative cyclization of the S-mono adducts IIIc-e in the presence of glacial AcOH.

It was also found that 2-acetyl-1-phenylacetylene (Ie) with II (in contrast to ketones Ic, d) readily forms IVe upon heating in protonic solvent (MeOH). The intermediate S-mono adduct IIIe could not be isolated.

The IR spectra of IIIa-d show absorption bands for C—S at 690-740 $cm^{-1}$, C=C at 1530-1560 $cm^{-1}$, ring C=N at 1580-1585, C=O at 1630-1645 $cm^{-1}$, and two bands for $NH_2$ at 3180-3200 and 3305-3310 $cm^{-1}$.

The IR spectra of the condensed heterocycles IVc-e show bands for C—S at 704-720 $cm^{-1}$, ring C=N and C=C at 1420-1470 and 1520-1595 $cm^{-1}$, and CH at 2980-3050 $cm^{-1}$.

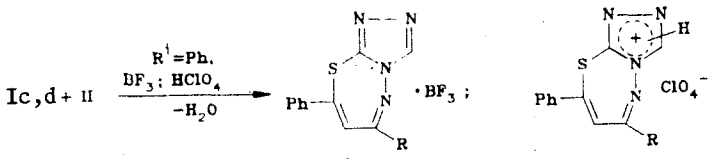
Reaction of ketones Ia-e with II might also be expected to occur via the alternate N-mono adducts Va-e through nucleophilic addition of the triazole $NH_2$ to the activated acetylenic bond of Ia-e. Carrying out the reaction in glacial AcOH at 60°C could give the triazolo[3,4-b]-1,3,4-thiadiazepines VIc-e from Vc-e. However, we have already shown that prolonged refluxing of 4-amino-5-phenyl-3-ethylthio-1,2,4-triazole (in which the nucleophilic center at the sulfur atom is blocked) with benzoylacetylene (Ia) in methanol without catalyst or in the present of triethylamine did not react by addition at the amino group [3]. This observation may be explained by the significant decrease in the basicity of the $NH_2$ due to the conjugation of the amino nitrogen unshared electron pair within the aromatic ring system.

We have previously shown that the proton signals of the COCH= in aminovinylketones [9, 10] are shifted to much higher field than those of COCH= in thiovinylketones [11] and are seen at 5.5-6.1 and 7.0-7.6 ppm, respectively. Taking into account the observed shift in our compounds of 7.3-8.2 ppm this is a further basis for proposing that acetylenes Ia-e react with II to give exclusively IIIa-e and not Va-e. Finally, we observe peaks in the mass spectrum of IVd for the fragments $[C_6H_5C\equiv CH]^{+\cdot}$ with m/z 102 and $[C_4H_3S—C\equiv N]^{+\cdot}$ with m/z 109 which could not be explained by fragmentation of VId.

Heating of acylvinylsulfides IIIa, c with hydrazine hydrate in ethanol caused separation of a molecule of triazole II and formation of pyrazoles VIIa, c.

TABLE 1. Parameters for Synthesized Compounds

| Compound | Empirical formula | Mp, °C | PMR spectrum, ppm (in DMSO-$D_6$) | Yield, % |
|---|---|---|---|---|
| IIIa | $C_{11}H_{10}N_4OS$ | 135...137 | 6,3 (2H, s, $NH_2$); 7,7...8,1 (6H, m, $C_6H_5$, COCH=); 8,3 (1H, d, SCH=; $J$=9,4 Hz); 8,7 (1H, s, CH=N) | 80 |
| IIIb | $C_9H_8N_4OS_2$ | 160...161 | 6,2 (2H, s, $NH_2$); 7,3...8,1 (4H, m, $C_4H_3S$, COCH=); 8,2 (1H, d, SCH=; $J$=9,9 Hz); 8,6 (1H, s, CH=N) | 80 |
| IIIc | $C_{17}H_{14}N_4OS$ | 168...170 | 6,1 (2H, s, $NH_2$); 7,3...8,2 (11H, $C_6H_5$, COCH=); 8,4 (1H, s, CH=N) | 62 |
| IIId | $C_{15}H_{12}N_4OS_2$ | 188...190 | 6,0 (2H, s, $NH_2$); 7,3...8,2 (10H, m, $C_6H_5$, $C_4H_3S$, COCH=); 8,3 (1H, s, CH=N) | 69 |
| IVe | $C_{17}H_{12}N_4S$ | 196...197 | 6,9 (1H, s, CH=); 7,5...7,9 (10H, m, $C_6H_5$); 8,5 (1H, s, CH=N) | 53 |
| IVf | $C_{15}H_{10}N_4S_2$ | 214...216 | 7,0 (1H, s, CH=); 7,5...7,8 (8H, m, $C_6H_5$, $C_4H_3S$); 8,5 (1H, c, CH=N) | 50 |
| IVg | $C_{12}H_{10}N_4S$ | 132...134 | 2,4 (3H, s, $CH_3$); 7,0 (1H, s, CH=); 7,5...7,9 (5H, m, $C_6H_5$); 9,0 (1H, s, CH=N) | 59 |
| VIIIi | $C_{17}H_{12}BF_3N_4S$ | 226...227 | 7,4 (1H, s, CH=); 7,6...8,0 (10H, m, $C_6H_5$); 9,1 (1H, s, CH=N) | 65 |
| VIIIj | $C_{15}H_{10}BF_3N_4S_2$ | 235...238 | 7,3 (1H, s, CH=); 7,5...7,9 (8H, m, $C_6H_5$, $C_4H_3S$); 9,0 (1H, s, CH=N) | 65 |
| IXk | $C_{17}H_{13}ClN_4O_4S$ | 138...140 | — | 64 |
| IXl | $C_{15}H_{11}ClN_4O_4S_2$ | 135...138 | — | 67 |



VIIIc,d IXc,d

Reaction of ketones Ic, d with triazole II in glacial AcOH at 60°C in the presence of an equimolar amount of $BF_3$-etherate or perchloric acid led to formation of the corresponding 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine trifluoroborates VIIIc, d or perchlorates IXc, d. Heating the latter in aqueous alcohol readily gave high yields (84-85%) or the free bases IVc, d.

## EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer for KBr tablets and $^1H$ and $^{13}C$ NMR spectra on a Tesla-BS 567 A (100 MHz) instrument using DMSO-$D_6$ solvent and HMDS internal standard. Mass spectra were recorded on an MK-1303 instrument with direct introduction of the sample into the ion source and ionization intensity of 30 eV.

Parameters and PMR spectral details for the synthesized compounds are given in Table 1.

Elemental analytical data for C, H, Cl, F, N, and S for IIIa-d, IVc-e, VIIIc, d, and IXc, d were in agreement with those calculated.

**4-Amino-3-benzoylvinylthio-1,2,4-triazole (IIIa).** Triazole II (0.58 g, 5 mmoles) was added with stirring to a solution of benzoylacetylene Ia (0.65 g, 5 mmoles) in MeOH (20 ml). After stirring for 1 h at 20°C the precipitate was filtered off and dried in vacuo to give 0.98 g (80%) of colorless crystals with mp 135-137°C (from ethanol).

When the reaction was carried out in MeOH at 60°C for 4 h the yield was 0.9 g (73%), in MeCN at 20°C for 1 h 0.84 g (68%), in glacial AcOH at 20°C for 2 h 0.95 g (77%), in glacial AcOH at 60°C for 4 h 0.86 g (70%), and in DMSO at 20 °C for 24 h (with precipitation from a tenfold excess of cold water) 0.85 g (69%).

**4-Amino-3-(2-thien-2-oyl)vinylthio-1,2,4-triazole (IIIb)** was obtained similarly from thienoylacetylen Ib (1.36 g, 10 mmoles) and triazole II (1.16 g, 10 mmoles) as colorless crystals (2.05 g, 80%) with mp 160-161°C (ethanol). When carried out in MeCN the reaction yield was 1.83 g (73%).

**4-Amino-3-(2,4-diphenyl-4-oxo-1-thia-2-butenyl)-1,2,4-triazole (IIIc).** Triazole II (0.58 g, 5 mmoles) was added to a solution of 1-benzoyl-2-phenylacetylene (Ic, 1.03 g, 5 mmoles) in MeOH (20 ml) and heated to 60°C. After stirring for 5 h and standing at 0°C for 15 h the precipitate was filtered off to give colorless crystals (0.99 g, 62%) with mp 168-170°C (ethanol—water, 2:1).

**Compound IIId** was obtained similarly in 69% (MeOH) or 32% (MeCN) yields.

**5,7-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine (IVc).** Triazole II (0.58 g, 5 mmoles) was added to a solution of 1-benzoyl-2-phenylacetylene (Ic, 1.03 g, 5 mmoles) in AcOH (15 ml), heated to 60°C, and stirred for 4 h. The mixture was cooled to 20°C, water (15 ml) was added slowly, and the precipitate filtered off and recrystallized from EtOH—water (2:1) to give 0.8 g (53%) of product.

**Compound IVd** was prepared similarly. Mass spectrum, m/z: 310 ($M^+$), 201 ($M - C_4H_3S{-}C{\equiv}N)^+$, 109 ($C_4H_3S{-}C{\equiv}N)^+$, 102 ($C_6H_5{-}C{\equiv}CH)^+$, 32 $(S)^+$. Yield 0.78 g (50%).

**5-Methyl-7-phenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine (IVe).** Triazole II (1.16 g, 10 mmoles) was added to a solution of acylacetylene Ie (1.44 g, 10 mmoles)in MeOH (20 ml), heated to 60°C, and stirred for 5 h. The solvent was half evaporated and the residue cooled to 0°C and held for 24 h. The precipitate was filtered off and recrystallized from EtOH—water (1:1) to give 1.43 g (59%) of product. When glacial AcOH was used at 60°C for 4 h the yield was 1.26 g (52%). $^{13}C$ NMR spectrum (DMSO-$D_6$): 25.19 ($CH_3$), 124.95 ($C_6$), 144.52 ($C_7$), 147.51 ($C_2$), 167.26 ($C_5$), 145.10 (CH=N), 127.90, 129.09, 131.22, 136.27 ppm ($C_6H_5$).

**5-Phenylpyrazole (VIIa).** Hydrazine hydrate (6 ml) was added to a solution of triazole IIIa (0.5 g, 2 mmoles) in EtOH (30 ml), heated to 70°C, and stirred for 5 h. The solvent was half evaporated and the residue cooled to 0°C, and held for 24 h. The precipitate was filtered off and dried in vacuo to give white needles 0.2 g (69%) with mp 77-78°C (78°C according to [12]). IR spectrum (in KBr): 1465-1570 (pyrazole C=N and C=C), 3190 $cm^{-1}$ (NH).

**3,5-Diphenylpyrazole (VIIc)** was obtained similarly from triazole IIIc (0.64 g, 2 mmoles) and hydrazine hydrate (6 ml) was white needles (0.37 g, 90%), with mp 198-200°C (199-200°C according to [12]). IR spectrum (in KBr): 1470-1580 (pyrazole C=N and C=C), 3200 $cm^{-1}$ (NH).

**5,7-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepinium Trifluoroborate (VIIIc).** A solution of $BF_3 \cdot Et_2O$ (1.42 g, 10 mmoles) in glacial AcOH (30 ml) was added with stirring to a mixture of ketone Ic (2.06 g, 10 mmoles) and triazole II (1.16 g, 10 mmoles). The mixture was heated to 60°C, stirred for 4 h, cooled to 20°C, and the precipitate filtered, washed with ether, and dried in vacuo to give the product (2.4 g, 65%).

Heating VIIIc at 70°C in EtOH—water (4:1) for 1 h gave IVc in 85% yield.

**Trifluoroborate VIIId** was obtained similarly.

**5,7-Diphenyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazepine Perchlorate (IXc).** A solutn of $HClO_4$ (0.62 ml, 55%) in glacial AcOH (15 ml) was added to a mixture of ketone Ic (1.03 g, 5 mmoles) and triazole II (0.58 g, 5 mmoles), heated to 60°C, and stirred for 4 h. The mixture was cooled to 20°C, poured into cold ether (60 ml), and triturated with a glass stirring rod until precipitation occurred. The solid was filtered off, washed with ether, and dried in vacuo to give 1.35 g (64%).

Heating **perchlorate IXc** at 60°C in MeOH—water (2:1) for 1 h gave IVc in 84% yield.

**Perchlorate IXd** was obtained similarly.

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