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New 1,3,4-Thiadiazole Derivatives from 1-Benzylidene-thiocarbonohydrazides and 3-Bromo-1-phenylprop-2-yn-1-one

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Abstract—3-Bromo-1-phenylprop-2-yn-1-one reacted with 1-benzylidenethiocarbonohydrazones in acetic acid or acetonitrile at room temperature (reaction time 3 h) to give in good yields the corresponding benzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromides which were converted into the free bases by treatment with aqueous ammonia.

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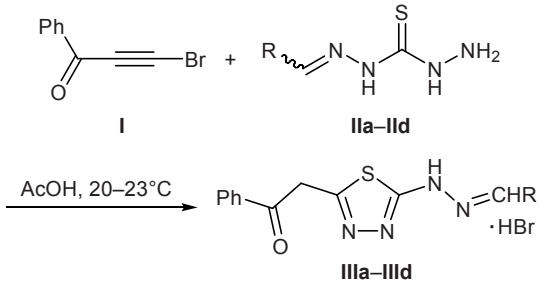
Depending on the substrate structure and conditions, reactions of bielectrophilic α-acetylenic ketones with multident N,S-centered nucleophiles could take different paths, giving rise to N,S-containing heterocycles possessing a broad spectrum of useful properties. From this viewpoint, the most interesting are thiocarbonohydrazones derived from aromatic and aliphatic aldehydes and ketones, which were found to exhibit strong biological activity (antituberculostatic, antitumor, antiviral, and fungicidal) [1–5] and act as quite efficient complexing agents [3–8].

Aromatic aldehyde thiocarbonohydrazones were reported to react with terminal α-acetylenic ketones exclusively at the triple bond to give, depending on the reactant ratio, 2-(2-acylvinyl)- or 2,2-bis(2-acylvinyl)-thiocarbonohydrazones [9]. The reactions of benzaldehyde thiocarbonohydrazone with 1-benzoyl- and 1-(2-thenoyl)-2-phenylacetylenes involved both the triple bond and the carbonyl group in the latter, yielding functionally substituted dihydropyrazoles [10].

With the goal of further studying reactions of α-acetylenic ketones with thiocarbonohydrazones and extending synthetic potential of these reactions, in the present work we examined reactions of 1-bromo-2-benzoylacetylene (**I**) with thiocarbonohydrazones **IIa**–**IId** derived from benzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, and 4-dimethylaminobenzaldehyde. Acetylenic ketone **I** reacted with an equimolar amount of compounds **IIa**–**IId** in acetic acid at 20–23°C to give in 3 h the corresponding benzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromides **IIIa**–**IIId** in 73–84% yield (Scheme 1). Compounds **IIIa**–**IIId** were also obtained when the reaction was carried out in acetonitrile (20–23°C, 3 h), but their yields were slightly lower (63–70%).

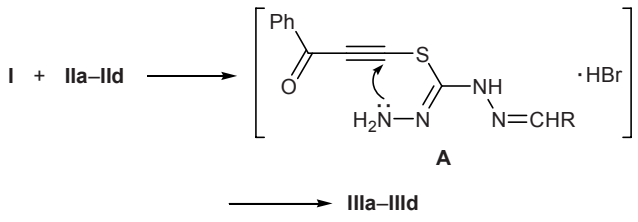
Scheme 1.



R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$O_2NC_6H_4$ (**c**), 4-$Me_2NC_6H_4$ (**d**).

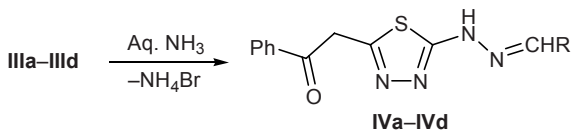
Presumably, the reaction involves nucleophilic replacement of the bromine atom at the triple-bonded carbon atom with intermediate formation of benzoylethynyl sulfides **A** [11] (Scheme 2) and intramolecular

Scheme 2.



cyclization of the latter via addition of the NH_2 group at the electron-deficient β-carbon atom at the triple bond leads to *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazones **IIIa**–**IIId**. By treatment of hydrobromides **IIIa**–**IIId** with 12% aqueous ammonia we obtained the corresponding free bases **IVa**–**IVd** in 89–93% yield (Scheme 3).

Scheme 3.



IVa–IVd

R = Ph (**a**), 4-ClC_6H_4 (**b**), 4-$O_2NC_6H_4$ (**c**), 4-$Me_2NC_6H_4$ (**d**).

The structure of compounds **IIIa**–**IIId** and **IVa**–**IVd** was proved by their elemental analyses and IR and ^1H and ^{13}C spectra. The IR spectra of hydrobromides **IIIa**–**IIId** and free bases **IVa**–**IVd** contained absorption bands arising from stretching vibrations of the NH group (3158–3284 cm^{-1}), unconjugated carbonyl group (1668–1694 cm^{-1}), and C=C and C=N bonds (1508–1622 cm^{-1}); in addition, hydrobromides **IIIa**–**IIId** displayed in the IR spectra broadened bands due to NH^+ group in the region 2739–3002 cm^{-1}.

In the ^1H NMR spectra of **IIIa**–**IIId** and **IVa**–**IVd** we observed singlets from protons of the CH_2 group (δ 4.78–4.92 ppm) and CH=N group (δ 8.05–8.14 ppm) and multiplets from aromatic protons in the region δ 6.71–8.29 ppm. In the spectra of hydrobromides **IIIa**–**IIId**, signals from the NH and NH^+ protons appeared as strongly broadened singlets in the region δ 9–10 ppm. The ^{13}C NMR spectra were consistent with the assumed structure of compounds **IIIa**–**IIId** and **IVa**–**IVd** as 1,3,4-thiadiazole derivatives. Signals in the ^{13}C NMR spectra were assigned using two-dimensional HSQC [12] and HMBC techniques [13].

We previously reported that 1-bromo-2-acylacetylenes react with thiobenzohydrazide [14] and thiosemicarbazides [15] to give 2-acylmethyl-1,3,4-thiadiazole derivatives. Therefore, reactions of 1-bromo-2-acylacetylenes with multicenter N,S-nucleophiles possessing a thiocarbonohydrazine fragment may be regarded as a general synthetic route to functionally substituted 1,3,4-thiadizoles.

Compounds **III** and **IV** are new highly functionalized representatives of pharmacophoric 1,3,4-thiadiazoles [16–18]; they can be used as precursors of drugs of new generation. In addition, their molecules possess a set of potential O-, N-, and S-electron-donating centers, so that thiadiazoles **III** and **IV** are promising as multidentate ligands in the synthesis of metal complexes with different coordination modes [19–22].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75-IR spectrometer. The ^1H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker DPX 400 spectrometer (400.13 MHz for ^1H and 100.61 MHz for ^{13}C) using hexamethyldisiloxane as internal reference.

Substituted benzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromides IIIa–IIId (*general procedure*). Thiocarbonohydrazone **IIa**–**IId**, 2.5 mmol, was added in portions to a solution of 2.5 mmol of 3-bromo-1-phenylprop-2-yn-1-one (**I**) in 10 ml of acetic acid, and the mixture was stirred for 3 h at 20–23°C. The precipitate was filtered off, washed with 40 ml of anhydrous diethyl ether, and dried under reduced pressure. The reaction in acetonitrile was carried out in a similar way. Compounds **IIIa**–**IIId** were thus isolated as analytically pure substances.

Benzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromide (IIIa). Yield 0.81 g (80%, in AcOH), 70% (in MeCN); mp 191–194°C. IR spectrum, ν, cm^{-1}: 3230, 2749–3002, 1670, 1553–1619. ^1H NMR spectrum, δ, ppm: 4.92 s (2H, CH_2), 7.40–7.95 m (10H, H_{arom}), 8.13 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 41.42 (CH_2); 126.62, 127.03, 128.53, 128.98, 130.28, 133.68, 134.07, 135.48 (C_{arom}); 146.30 (CH=N); 153.43 (C^5); 169.52 (C^2); 194.89 (C=O). Found, %: C 50.98; H 3.65; Br 19.58; N 13.94; S 7.72. $C_{17}H_{14}N_4OS \cdot HBr$. Calculated, %: C 50.63; H 3.75; Br 19.81; N 13.89; S 7.95.

4-Chlorobenzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromide (IIIb). Yield 0.80 g (73%, in AcOH), 66% (in MeCN); mp 178–181°C. IR spectrum, ν, cm^{-1}: 3212, 2747–3001, 1672, 1552–1619. ^1H NMR spectrum, δ, ppm: 4.88 s (2H, CH_2), 7.49–8.11 m (9H, H_{arom}), 8.14 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 39.53 (CH_2); 128.57, 128.68, 129.11, 129.21, 133.06, 134.19, 134.51, 135.69 (C_{arom}); 144.13 (CH=N); 153.35 (C^5); 170.19 (C^2); 195.17 (C=O). Found, %: C 46.22; H 3.32; Br 18.06; Cl 8.36; N 12.65; S 7.29. $C_{17}H_{13}ClN_4OS \cdot HBr$. Calculated, %: C 46.64; H 3.22; Br 18.25; Cl 8.10; N 12.80; S 7.33.

4-Nitrobenzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromide (IIIc).

Yield 0.94 g (84%, in AcOH), 63% (in MeCN); mp 192–194°C. IR spectrum, ν, cm^{-1}: 3161, 2739–3001, 1671, 1517–1622. ^1H NMR spectrum, δ, ppm: 4.87 s (2H, CH_2), 7.47–8.29 m (10H, H_{arom}, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 39.70 (CH_2); 124.65, 127.74, 128.94, 129.18, 134.40, 136.11, 147.84, 142.01 (C_{arom}); 141.10 (CH=N); 153.69 (C^5); 171.15 (C^2); 195.52 (C=O). Found, %: C 45.35; H 3.28; Br 17.48; N 15.92; S 7.26. $C_{17}H_{13}N_5O_3S \cdot HBr$. Calculated, %: C 45.55; H 3.15; Br 17.82; N 15.62; S 7.15.

4-Dimethylaminobenzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromide (IIId). Yield 0.87 g (78%, in AcOH), 66% (in MeCN); mp 191–193°C. IR spectrum, ν, cm^{-1}: 3216, 2750–2996, 1668, 1537–1612. ^1H NMR spectrum, δ, ppm: 3.00 s (6H, Me), 4.87 s (2H, CH_2), 6.88–8.04 m (9H, H_{arom}), 8.08 s (1H, CH=N). ^{13}C NMR spectrum, δ_C, ppm: 39.55 (CH_2); 39.80 (Me); 112.76, 128.02, 128.38, 128.81, 133.83, 135.52, 150.56 (C_{arom}); 145.66 (CH=N); 152.16 (C^5); 171.91 (C^2); 194.95 (C=O). Found, %: C 51.23; H 4.78; Br 17.44; N 15.37; S 7.02. $C_{19}H_{19}N_5OS \cdot HBr$. Calculated, %: C 51.12; H 4.52; Br 17.90; N 15.69; S 7.18.

Substituted benzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazones IVa–IVd (*general procedure*). Hydrobromide **IIIa**–**IIId**, 1 mmol, was added in portions to 30 ml of 12% aqueous ammonia, and the mixture was stirred for 1 h at 20–23°C. The precipitate was filtered, washed with distilled water, dried over $CaCl_2$ under reduced pressure, and recrystallized from ethanol or acetonitrile.

Benzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone (IVa). Yield 0.295 g (92%), mp 177–180°C. IR spectrum, ν, cm^{-1}: 3202, 1691, 1555–1612. ^1H NMR spectrum, δ, ppm: 4.84 s (2H, CH_2), 7.40–8.06 m (10H, H_{arom}), 8.08 s (1H, CH=N), 12.30 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.22 (CH_2); 126.35, 128.37, 128.80, 128.92, 129.42, 133.75, 134.17, 135.62 (C_{arom}); 143.46 (CH=N); 152.49 (C^5); 170.68 (C^2); 195.04 (C=O). Found, %: C 63.15; H 4.25; N 17.42; S 9.72. $C_{17}H_{14}N_4OS$. Calculated, %: C 63.33; H 4.38; N 17.38; S 9.95.

4-Chlorobenzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone (IVb). Yield 0.325 g (91%), mp 148–150°C. IR spectrum, ν, cm^{-1}: 3284, 1694, 1563–1611. ^1H NMR spectrum, δ, ppm: 4.84 s (2H, CH_2), 7.43–8.06 m (9H, H_{arom}), 8.08 s (1H, CH=N), 11.47 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.02 (CH_2); 128.52, 128.94, 129.14, 129.38, 129.44, 133.71, 134.38, 136.15 (C_{arom}); 141.20 (CH=N); 153.23 (C^5); 171.21 (C^2); 195.60 (C=O). Found, %: C 57.04; H 3.53; Cl 9.67; N 15.98; S 8.68. $C_{17}H_{13}ClN_4OS$. Calculated, %: C 57.22; H 3.67; Cl 9.94; N 15.70; S 8.99.

4-Nitrobenzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone (IVc). Yield 0.33 g (89%), mp 176–178°C. IR spectrum, ν, cm^{-1}: 3158, 1688, 1508–1592. ^1H NMR spectrum, δ, ppm: 4.87 s (2H, CH_2), 7.47–8.29 m (10H, H_{arom}, CH=N), 11.72 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.14 (CH_2); 123.70, 127.13, 128.12, 128.84, 133.85, 135.58, 140.86, 147.41 (C_{arom}); 139.25 (CH=N); 153.40 (C^5); 175.70 (C^2); 194.99 (C=O). Found, %: C 55.74; H 3.42; N 19.14; S 8.40. $C_{17}H_{13}N_5O_3S$. Calculated, %: C 55.58; H 3.57; N 19.06; S 8.73.

4-Dimethylaminobenzaldehyde *N′*-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone (IVd). Yield 0.33 g (90%), mp 162–164°C. IR spectrum, ν, cm^{-1}: 3197, 1691, 1524–1607. ^1H NMR spectrum, δ, ppm: 2.93 s (6H, Me), 4.78 s (2H, CH_2), 6.71–7.93 m (9H, H_{arom}), 8.05 s (1H, CH=N), 11.96 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 39.85 (Me); 39.95 (CH_2); 111.84, 121.61, 127.66, 128.36, 128.78, 133.71, 135.65, 151.11 (C_{arom}); 144.50 (CH=N); 151.71 (C^5); 170.57 (C^2); 195.09 (C=O). Found, %: C 62.78; H 5.09; N 19.08; S 8.53. $C_{19}H_{19}N_5OS$. Calculated, %: C 62.44; H 5.24; N 19.16; S 8.77.

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