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REACTIONS OF α-ACETYLENIC KETONES WITH N-3-AMIDINOTHIOUREAS. 1. SYNTHESIS AND PROPERTIES OF NEW DERIVATIVES OF 1,3-THIAZINE

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[4-Phenyl-2H-1,3-thiazin]-2-ylideneguanidinium perchlorate or acetoxytrifluoroborate respectively was obtained from the reaction of benzoylacetylene with N-amidinothiourea in glacial AcOH in the presence of an equimolar quantity of $HClO_4$ or $BF_3 \cdot Et_2O$. These compounds underwent hydrolysis at the amidine unit on treatment with acid or base. For example, the perchlorate on heating in $HClO_4$ was converted into 2-imino-4-phenyl-2H-1,3-thiazinium perchlorate, while treatment with aqueous NaOH in DMSO gave the free base – 6-phenyl-1,2-dihydropyrimidine-2-thione.

Keywords: N-amidinothiourea, benzoylacetylene, 4-phenyl-1,2-dihydropyrimidine-2-thione, [4-phenyl-2H-1,3-thiazin]-2-ylideneguanidinium perchlorate and acetoxytrifluoroborate, heterocyclization.

In a continuation of the study of the reactions of α-acetylenic ketones with sulfur- and nitrogen-containing ambident nucleophiles [1-3] as a suitable method for the synthesis of N,S-containing heterocyclic compounds, we have investigated the reaction of benzoylacetylene **1** with N-amidinothiourea **2**.

The choice of compound **2** as the subject for this investigation is because it contains both thioamide and guanidine units, is a potential polydentate nucleophile with several reaction centers arising from intramolecular mesomorphic interactions. Condensation of thioamides and thiourea with α,β-unsaturated ketones, esters of propiolic and acetylenedicarboxylic acids [4-7] is one of the basic methods for the preparation of substituted 1,3-thiazines which are used as fungicides, pharmaceuticals, and vulcanizing agents [8]. Moreover guanidine is involved in the classical heterocyclization reaction which leads to biologically important derivatives of pyrimidine, and guanidine is a structural fragment of nucleic acids and streptomycin.

The reaction of benzoylacetylene **1** with N-amidinothiourea **2** (**1** : **2** = 1:1) was carried out in glacial acetic acid at 20°C with the addition of an equimolar quantity of $HClO_4$ or $BF_3 \cdot Et_2O$. Under these conditions the reaction proceeded directly to [4-phenyl-2H-1,3-thiazin]-2-ylideneguanidinium perchlorate or acetoxy-trifluoroborate (**3a** and **3b** respectively). The formation of the substituted 1,3-thiazines **3a,b** probably occurs via the intermediate formation the benzoylvinylisothiouronium salts **4** which were not isolated under these conditions. However when the reaction of benzoylacetylene **1** with 3-amidino-2-thiourea **5** (specially synthesized by us) was carried out in glacial acetic acid at 20°C 3-amidino-2-benzoylvinylisothiourea perchlorate **4a** was obtained, which on heating in acetic acid was converted in high yield to the corresponding 1,3-thiazine **3a** as a result of attack by the nitrogen atom of the thioamide unit on the electron poor carbon atom of the carbonyl group.

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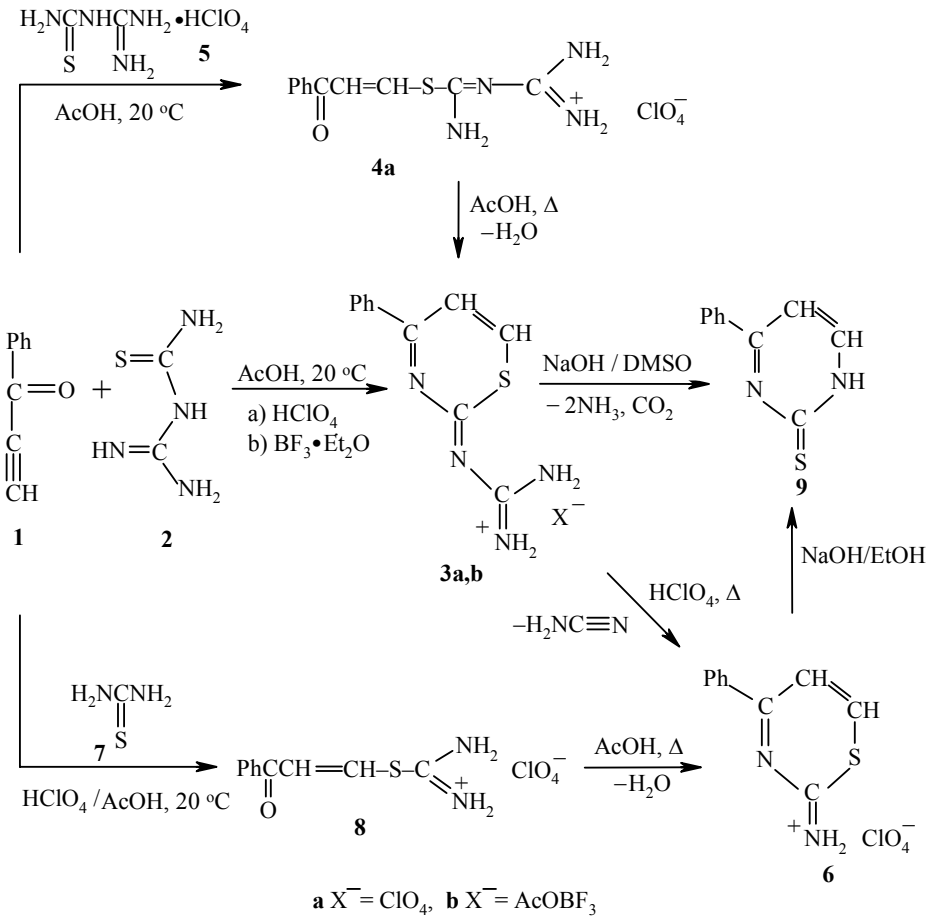


a $X^- = ClO_4$, **b** $X^- = AcOBF_3$

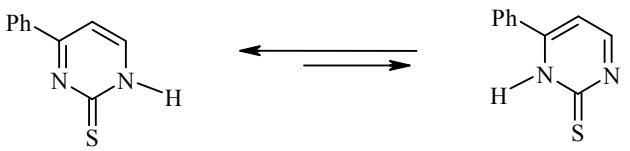
According to their ^1H NMR spectra, the synthesized 1,3-thiazines **3a,b** are immonium salts as indicated by the presence of two signals of the NH_2 group. The proton donor in the formation of the immonium salts was either $HClO_4$ or the solvent molecule (AcOH) when the reaction was carried out with $BF_3 \cdot Et_2O$.

When the perchlorate **3a** was heated with perchloric acid cyanamide was evolved and the reaction product was 2-imino-4-phenyl-2H-1,3-thiazinium perchlorate (**6**). We carried out a retrosynthesis of this compound by the reaction of benzoylacetylene **1** with thiourea **7** in acetic acid in the presence of $HClO_4$ at 20°C with the isolation of the intermediate S-(benzoylvinyl)isothiouronium perchlorate (**8**) using a published method [8].

Treatment of the perchlorate **3a** with 0.1 N NaOH in DMSO led to complete hydrolysis of the amidine unit (with evolution of ammonia and carbon dioxide) and recyclization of the 1,3-thiazine ring into pyrimidine-2-thione **9**. This compound is completely identical with the free base which we obtained by the analogous treatment of 2-imino-4-phenyl-2H-1,3-thiazinium perchlorate **6**.

The structure **9** is in agreement with the results of [8] where the isolated compound was identified as 4-phenyl-1,2-dihydropyrimidine-2-thione (**9**).

Second tautomeric form is possible for compound **9** – 1,2-dihydro-6-phenylpyrimidine-2-thione (**9A**).



9 **9A**

According to our *ab initio* (RHF/6-31G*) [9] calculations on the two tautomers, the phenyl and pyrimidine rings are at 18° and 42° to each other in molecules **9** and **9A** respectively. The experimentally observed shift of the equilibrium towards structure **9** may be explained by its greater stability on account of increased conjugation between the two rings.

EXPERIMENTAL

IR spectra of KBr disks were recorded with Bruker-25 instrument. ^{1}H and ^{13}C NMR spectra of DMSO-d_6 solution were recorded with a Bruker DPX-400 instrument (400 and 100 MHz respectively).

N-amidinothiourea **2** was prepared according to [10].

[4-Phenyl-2H-1,3-thiazin]-2-ylideneguanidinium Perchlorate (3a). Benzoylacetylene **1** (0.65 g, 5 mmol) and $HClO_4$ (58%, 0.58 ml) in glacial AcOH (10 ml) was added to a solution of N-amidinothiourea **2** (0.59 g, 5 mmol) in glacial AcOH (10 ml) and the mixture was stirred for 1 h at 20°C and kept for 24 h. The precipitate was filtered off, washed with glacial AcOH (5 ml) and absolute ether until the smell of acetic acid disappeared, and dried in vacuum to give compound **3a** (1.19 g, 72%) as lemonish crystals; mp 165-167°C (AcOH). IR spectrum, ν, cm^{-1}: 3216-3379 (NH, N$^+$H), 1658 (NH def.) 1534 -1576 (C=C, C=N), 1053-1120 (ClO_4^-). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.57- 8.12 (5H, m, C_6H_5); 8.02 (1H, d, ^3J = 5.30, $C_{(6)}H$); 8.82 (1H, d, ^3J = 5.30, $C_{(5)}H$); 9.49 (2H, br. s, NH_2); 10.00 (2H, br. s, N$^+H_2$). ^{13}C NMR spectrum, δ, ppm; 116.25 ($C_{(5)}$); 127.69, 129.66, 132.63, 134.79 (C_6H_5); 159.68 ($C_{(6)}$); 164.71 ($C_{(4)}$); 165.00 ($C_{(2)}$); 165.04 ($C_{amidine}$). Found, %: C 39.68; H 3.45; Cl 10.63; N 16.82; S 9.45. $C_{11}H_{10}N_4S{\cdot}HClO_4$. Calculated, %: C 39.94; H 3.33; C 10.74; N 16.94; S 9.68.

[4-Phenyl-2H-1,3-thiazin]-2-ylideneguanidinium Acetoxytrifluoroborate (3b) was obtained analogously to compound **3a** from compound **2** (0.59 g, 5 mmol), benzoylacetylene **1** (0.65 g, 5 mmol), and $BF_3{\cdot}Et_2O$ (0.63 ml) in glacial AcOH (20 ml). Yield of compound **3b** 1.2 g (67%), colorless crystals; mp 145-146°C. IR spectrum, ν, cm^{-1}: 3240-3370 (NH, N$^+$H); 1660 (NH def.); 1534-1575 (C=C, C=N); 1000-1102 (B–F). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.91 (3H, s, CH_3); 7.61-8.16 (5H, m, C_6H_5); 7.96 (1H, d, ^3J = 5.34, $C_{(6)}H$); 8.86 (1H, d, ^3J = 5.34, $C_{(5)}H$); 9.51(2H, br. s, NH_2); 9.98 (2H, br. s, N$^+H_2$). ^{13}C NMR spectrum, δ, ppm: 21.08 (CH_3); 115.91 ($C_{(5)}$); 127.44, 129.35, 132.30, 134.60 (C_6H_5); 159.50 ($C_{(6)}$); 164.13 ($C_{(4)}$); 164.73 ($C_{(2)}$); 164.77 ($C_{amidine}$). Found, %: C 43.30; H 3.58; F 15.55; N 15.83; S 8.79. $C_{11}H_{10}N_4S{\cdot}CH_3COOH{\cdot}BF_3$. Calculated, %: C 43.58; H 3.91; F 15.92; N 15.64; S 8.94.

N-Amidinothiourea Perchlorate (5). N-amidinothiourea **2** (3 g, 25 mmol) was heated in 58% $HClO_4$ (30 ml) for 15 min, the solution was cooled, the precipitate was filtered off and washed with cold EtOH (5 ml) and absolute ether and dried in vacuum to give colorless crystals of perchlorate **5** (5 g, 92%); mp 140-141°C. ^{13}C NMR spectrum, δ, ppm: 156.10 (C=N); 180.74 (C=S). Found, %: C 10.93; H 3.35; Cl 16.38; N 25.18; S 14.83. $C_2H_6N_4S{\cdot}HClO_4$. Calculated, %: C 10.99; H 3.23; Cl 16.22; N 25.63; S 14.67.

3-Amidino-2-benzoylvinylisothiourea Perchlorate (4a) and [4-Phenyl-2H-1,3-thiazin]-2-ylideneguanidinium Perchlorate (3a). A solution of benzoylacetylene **1** (0.65 g, 5 mmol) in AcOH (10 ml) was added slowly to a suspension of the perchlorate of N-amidionthiourea **5** (1.09 g, 5 mmol) in glacial AcOH (10 ml), the mixture was stirred for 2h, the precipitate was filtered off, washed with AcOH (5 ml) and absolute ether, and dried in vacuum to give compound **4a** (1.4 g, 80%) as a yellow powder; mp 148-150°C. IR spectrum, ν, cm^{-1}: 3216-3411 (NH, N$^+$H); 1642 (br, C=O, NH def.); 1538-1599 (C=C, C=N); 1060-1119 (ClO_4^-). ^{1}N NMR spectrum, δ, ppm (*J*, Hz): 7.48 (1H, d, ^3J = 9.68, *cis*-isomer, $C_\alpha H$); 8.15 (1H, d, ^3J = 9.68, $C_\beta H$); 7.59-8.07 (5H, m, C_6H_5); 7.83 (2H, br. s, NH_2); 8.25 (2H, br. s, NH_2); 8.40 (2H, br. s, N$^+H_2$). ^{13}C NMR spectrum, δ, ppm: 118.44 (C_α); 128.43, 129.24, 133.71, 136.80 (C_6H_5); 141.96 (C_β); 161.28, 163.07 (2C, 2C=N); 189.10 (C=O). Found, %: C 38.22; H 3.82; Cl 10.18; N 16.27; S 9.06. $C_{11}H_{12}N_4OS{\cdot}HClO_4$. Calculated, %: C 37.88; H 3.73; Cl 10.19; N 16.07; S 9.18.

Compound **4a** (1.05 g, 3 mmol) was dissolved in glacial acetic acid (10 ml), the temperature was slowly increased to 50°C and kept at the temperature for 0.5 h. The reaction mixture was then kept at 20°C for 24 h. The precipitate was filtered off, washed with absolute ether and dried in vacuum to give compound **3a** (0.83 g, 84%) identical to that prepared previously.

S-(Benzoylvinyl)isothiuronium Perchlorate (8) and 2-Imino-4-phenyl-2H-1,3-thiazinium Perchlorate (6). A solution of benzoylacetylene **1** (0.65 g, 5 mmol) and 58% $HClO_4$ (0.58 ml) in AcOH (10 ml) was added to a stirred solution of thiourea **7** (0.38 g, 5 mmol) in glacial AcOH (10 ml). The reaction mixture was stirred for 1 h at 20°C, the precipitate was filtered off, washed with AcOH and absolute ether and dried in vacuum to give yellow crystals of perchlorate **8** (1.0 g, 65%); mp 156-158°C. IR spectrum, ν, cm^{-1}: 3178-3386 (NH, N^+H); 1675 (NH def.); 1638 (C=O, conj.); 1552-1594 (C=C, C=N); 1048-1118 (ClO_4^-). ^{1}N NMR spectrum, δ, ppm (*J*, Hz): 7.71 (1H, d, ^3J = 9.42, *cis*-isomer, $C_\alpha H$); 7.84 (1H, d, ^3J = 9.42, $C_\beta H$); 7.59-8.08 (5H, m, C_6H_5); 9.30 (2H, br. s, NH_2); 9.70 (2H, br. s, N^+H_2). ^{13}C NMR spectrum, δ, ppm: 120.32 (C_α); 128.57, 129.26, 134.09, 136.05 (C_6H_5); 139.26 (C_β); 168.74 (C=N); 189.52 (C=O). Found, %: C 39.38; H 3.37; Cl 11.75; N 9.29; S 10.37. $C_{10}H_{10}N_2OS\cdot HClO_4$. Calculated, %: C 39.15; H 3.59; Cl 11.58; N 9.13; S 10.44.

After removal of compound **8** the mother liquor was reduced to about half by passage of nitrogen and was kept at 20° for 24 h. The additional precipitate was filtered off, washed with AcOH and absolute ether, and dried in vacuum to give lemonish crystals of 1,3-thiazinium perchlorate **6** (0.29 g, 20%); mp 162-164°C. IR spectrum, ν, cm^{-1}: 3192-3376 (NH, N^+H); 1628 (NH def.); 1573-1590 (C=C, C=N); 1077-1121 (ClO_4^-). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, d, ^3J = 9.84, $C_{(6)}H$); 8.92 (1H, d, ^3J = 9.84, $C_{(5)}H$); 7.67-8.30 (5H, m, C_6H_5); 10.94 (2H, br. s, N^+H_2). ^{13}C NMR spectrum, δ, ppm: 115.48 (C_5); 129.53, 129.57, 134.83, 135.13 (C_6H_5); 149.73 (C_6); 171.27 (C_4); 172.87 (C_2). Found, %: C 41.32; H 3.01; Cl 12.54; N 9.71; S 11.21. $C_{10}H_8N_2S\cdot HClO_4$. Calculated, %: C 41.59; H 3.12; Cl 12.30; N 9.70; S 11.09.

By increasing the time of reaction at 20°C to 6 h or by carrying it out at 50°C for 1 h increased the content of compound **6** in the reaction mixture to 40-50%.

On recrystallizing perchlorate **8** from AcOH it was partially converted to compound **6**.

Reaction of [4-Phenyl-2H-1,3-thiazin]-2-ylideneguanidinium Perchlorate (3a) with Perchloric Acid. Compound **3a** (0.3 g, 0.91 mmol) was heated in 58% $HClO_4$ to 50°C, kept at that temperature for 0.5 h, the solution was then cooled, the precipitate was filtered off, triturated, dried in vacuum to give 1,3-thiazinium perchlorate (0.15 g, 58%) identical to that prepared previously.

Reaction of Perchlorate 3a with Alkali. A solution of perchlorate **3a** (0.33 g, 1 mmol) in DMSO (5 ml) was cooled to 8-10°C and 0.1 N NaOH (12 ml) was added with vigorous stirring, the stirring was continued for 0.5 h, distilled water (25 ml) was added, the temperature of the mixture was raised to 20°C, the precipitate was filtered off, washed with water and dried in vacuum over $CaCl_2$ to give 1,2-dihydro-4-phenylpyrimidine-2-thione (**9**) as yellowish crystals (0.14 g, 76%); mp 158-160°C (water). IR spectrum, ν, cm^{-1}: 3123 (NH); 1558-1605 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.43 (1H, d, ^3J = 6.52, $C_{(4)}H$); 8.07 (1H, d, ^3J = 6.52, $C_{(5)}H$); 7.55-8.15 (5H, m, C_6H_5); 13.73 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 105.70 ($C_{(5)}$), 128.03, 129.08, 132.41, 135.23 (C_6H_5), 146.90 ($C_{(6)}$), 166.11 ($C_{(4)}$), 180.92 (C=S). Found, %: C 63.64; H 4.39; N 14.98; S 16.89. $C_{10}H_8N_2S$. Calculated, %: C 63.80; H 4.28; N 14.88; S 17.03.

Reaction of Perchlorate 6 with Base. 0.1 N NaOH (45 ml) was added to a stirred solution 1,3-thiazinium perchlorate **6** (1.22 g, 4.2 mmol) in EtOH (20 ml) and the mixture was stirred for 3 h at 20°C. The precipitate was filtered off, washed with water, and dried in vacuum over $CaCl_2$ to give pyrimidine-2-thione **9** (0.67 g, 85%), identical to that obtained previously from perchlorate **3a**.

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