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SYNTHESIS OF 1,3-BENZOTHIAZOL-2(3*H*)-ONES WITH A CARBAMATE FUNCTION AT THE C-6 ATOM

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A new method has been developed for the synthesis of 1,3-benzothiazol-2(3H)-ones with carbamate function based on the adducts of the 1,4-addition of thioacetic acid to 2-R-N,N'-dimethoxycarbonyl-1,4-benzoquinone diimines. Refluxing the 2-thioacetyl-substituted dicarbamates in ethanol in the presence of hydrochloric acid gave 1,3-benzothiazol-2(3H)-ones with methoxycarbonylamine group at the C-6 atom. Modifications of the obtained compounds were performed.

Keywords: 2-(3*H*)-benzothiazolone, *N,N'*-dimethoxycarbonyl-1,4-benzoquinone diimine, thioacetic acid, alkylation, 1,4-addition, cyclization.

A number of methods are known for the preparation of 1,3-benzothiazol-2(3*H*)-ones: 1) cyclization of 2-aminothiophenols with phosgene, chloroformates, and urea [1]; 2) reductive carbonylation of substituted nitrobenzenes using sulfur, carbon monoxide, and water in the presence of bases [1]; 3) cyclization of thiocarbamates followed by decomposition of the 2-alkoxybenzothiazoles prepared [2]; 4) oxidation of 2-mercaptobenzothiazoles or benzothiazolylalkyl thioethers with the formation of 2-sulfonyl- or 2-alkylsulfonylbenzothiazoles with their subsequent hydrolysis; 5) reaction of *o*-nitrochlorobenzenes with thioglycolic acid and subsequent cyclocondensation of the *o*-nitrophenylthioacetic acid with acetic anhydride, followed by deacylation [1]; 6) reaction of 2-aminobenzothiazoles with alkali metal hydroxides in anhydrous medium and cyclization of the *o*-mercaptophenylureas formed [1, 3]; 7) reaction of thiosalicylic acid with ammonium azide and three equivalents of DMF–$POCl_3$ complex [4].

We have shown previously that 1,3-benzothiazol-2(3*H*)-one is formed on heating bis(2,2'-dimethoxycarboxamido)phenyl disulfide in glacial acetic acid in the presence of zinc dust [5].

Various 2- and 3-substituted derivatives of 1,3-benzothiazol-2(3*H*)-ones possess a wide spectrum of biological activity. Compounds have been found among them with high herbicidal, antimicrobial, analgesic, antioxidant, anticonvulsive, antifungal, and other types of activity [1, 4, 6, 7]. They also serve as valuable precursors in the synthesis of new functionally substituted compounds [8]. In this connection the preparation of new derivatives of 2(3*H*)-benzothiazolones and their subsequent screening are of considerable interest.

It is known that reactions of quinones [9] and aroyl(sulfonyl) derivatives of benzoquinone diimines [10, 11] with mercaptans occur differently depending on the nature of the quinoid compound and mercaptan, and the reaction conditions. The products of these reactions are mercapto derivatives of diamides with aromatic

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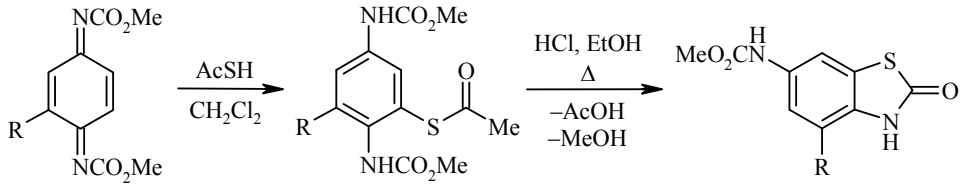
structures. However, in many cases the preferred direction of reaction is quinone imide reduction into the corresponding diamides unsubstituted in the benzene ring, while the mercaptans are oxidized to disulfides [10].

We note that the reaction of *N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine (**1**) with thioacetic acid had not been investigated previously.

We have established that the reaction of *N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine (**1**) and 2-chloro-*N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine (**2**) with thioacetic acid in methylene chloride at room temperature occurs as 1,4-addition at the N=C–C=N conjugated bond system of the quinone diimine with formation of the aromatic products **3**, **4**, the structures of which were confirmed by IR, ^{1}H NMR, and mass spectroscopy.

Refluxing the ring-substituted dicarbamates (**3**, **4**) in ethanol in the presence of concentrated hydrochloric acid for 5 h was accompanied by heterocyclization with the formation of methyl *N*-(4-R-2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)carbamates **5** and **6**. The structures of compounds **5** and **6** were confirmed by IR, as well as ^{1}H and ^{13}C NMR spectroscopy, and compound **5** also by mass spectroscopy.



1, **2** **3**, **4** **5**, **6**

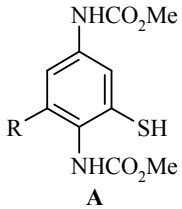
1, **3**, **5** R = H, **2**, **4**, **6** R = Cl

In the case of the unsymmetrical quinone diimine **2**, the 1,4-addition occurred regioselectively according the thin layer chromatography to give a single product, ascribed with the structure **4** on the basis of considering the ^{1}H NMR, ^{1}H–^{1}H COSY and NOESY spectra of its cyclization product.

In the ^{1}H-^{1}H COSY spectrum of 4-chloro-substituted 1,3-benzthiazol-2(3*H*)-one **6** there are nondiagonal cross peaks between the benzene ring protons (^4J = 3.0 Hz), which should be absent in the 5-chloro derivative. At the same time, in the NOESY spectrum of this compound there are two cross peaks between protons at the *ortho* position relative to the carbamate group and the NH proton of the carbamate group. In the case of the alternative product, two cross peaks would also be expected, but between protons at the *ortho* position to two different NH-groups.

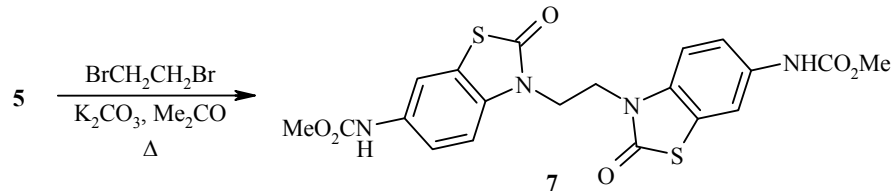
The observed direction of nucleophile addition to the unsymmetrical quinone diimine **2** is probably explained by the preferred protonation of the more basic nitrogen atom [12], which is decreased by the presence of chlorine at the *ortho* position to the *N*-methoxycarbonylimino group.

It is probable that the heterocyclization of compounds **3** and **4** occurs *via* formation of the thiol intermediate **A**.

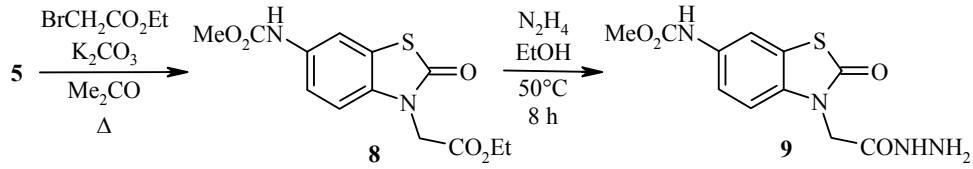


A

Alkylation of two equivalents of 1,3-benzothiazol-2(3*H*)-one **5** with 1,2-dibromoethane in acetone in the presence of potassium carbonate led to the formation of dimethyl [ethan-1,2-diylbis(2-oxo-1,3-benzothiazol-3,6-(2*H*)-diyl)]biscarbamate (**7**).



Alkylation of compound **5** with ethyl bromoacetate under analogous conditions gave ethyl 2-{6-[(methoxycarbonyl)amino]-2-oxo-1,3-benzothiazol-3(2*H*)-yl}-acetate (**8**), which was further converted into the corresponding hydrazide **9**. The synthesis of compound **9** was carried out by maintaining equimolar amounts of the reagents in absolute ethanol for 8 h at 50°C.



The structures of the new compounds **7-9** were confirmed by IR and ^{1}H NMR spectroscopy.

So we have studied for the first time the interaction of *N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine with thioacetic acid and proposed a new method for the synthesis of 1,3-benzothiazol-2(3*H*)-ones with methoxycarbonylamino group at the C-6 atom by heterocyclization of the obtained 1,4-addition adducts.

EXPERIMENTAL

IR spectra were recorded with a Specord M-80 instrument. The ^{1}H, ^{1}H–^{1}H COSY, NOESY, and ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument (500 MHz for ^{1}H nuclei, 126 MHz for ^{13}C nuclei) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded with a Finnigan MAT INCOS 50 quadrupole mass spectrometer (ionization energy 70 eV). Elemental analyses were carried out on an EuroVector EA-3000 CHNS analyzer. Melting points were determined with a Boetius hot stage apparatus. TLC was carried out on Silufol UV-254 plates with 1:1 dioxane–Et_2O as eluent.

***S*-{2,5-Bis[(methoxycarbonyl)amino]phenyl}ethanethioate (3).** Thioacetic acid (0.36 ml, 5 mmol) was added to a solution of *N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine (**1**) [13] (1.10 g, 5 mmol) in CH_2Cl_2 (10 ml), and the mixture was maintained at room temperature for 3 h. The precipitated crystalline product was filtered off, washed on the filter with Et_2O (5 ml), and recrystallized from $CHCl_3$. Yield 1.39 g (94%). Colorless crystals; mp 189-190°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1725, 1710 (C=O), 1610, 1575, 1545 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, $COCH_3$); 3.65 (3H, s, $NHCO_2C\underline{H}_3$); 3.68 (3H, s, $NHCO_2C\underline{H}_3$); 7.33 (1H, d, ^3J = 8.6, H Ar); 7.47 (1H, d, *J* = 8.6, H Ar); 7.55 (1H, s, H Ar); 8.77 (1H, br. s, NH); 9.74 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %), 300 $[M+2H]^+$ (1), 299 (2) $[M+H]^+$, 298 $[M]^+$ (17), 256 (68), 238 (17), 224 (26), 197 (31), 192 (20), 180 (12), 165 (20), 137 (9),121 (9), 109 (6), 93 (4), 79 (10), 59 (49), 52 (12). Found, %: C 48.12; H 4.55; N 9.21. $C_{12}H_{14}N_2O_5S$. Calculated, %: C 48.32; H 4.73; N 9.39.

***S*-{3-Chloro-2,5-bis[(methoxycarbonyl)amino]phenyl}ethanethioate (4)** was obtained analogously from 2-chloro-*N,N*'-dimethoxycarbonyl-1,4-benzoquinone diimine (**2**) [14] (1.30 g, 5 mmol) and thioacetic acid (0.36 ml, 5 mmol). Yield 1.47 g (87%). Colorless crystals; mp 138-140°C. R_f 0.64. IR spectrum, ν, cm^{-1}: 3340 (NH), 1725, 1715 (C=O), 1610, 1580, 1555 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm: 2.24 (3H, s, $COCH_3$); 3.65 (3H, s, $NHCO_2C\underline{H}_3$); 3.73 (3H, s, $NHCO_2C\underline{H}_3$); 7.75 (1H, s HAr); 7.90 (1H, s, HAr); 8.75 (1H, br. s, NH); 9.54 (1H, br. s, NH). Found, %: C 43.27; H 3.94; N 8.32. $C_{12}H_{13}ClN_2O_5S$. Calculated, %: C 43.31; H 3.94; N 8.42.

Methyl *N*-(2-Oxo-2,3-dihydro-1,3-benzothiazol-6-yl)carbamate (5). A mixture of compound **3** (0.80 g, 2.7 mmol) and conc. HCl (1 ml) in ethanol (10 ml) was refluxed for 5 h, poured into ice water (50 ml), the precipitate was filtered off, washed with water, dried in air, and recrystallized from dioxane. Yield 0.54 g (90%). Colorless crystals; mp 256-258°C. IR spectrum, ν, cm^{-1}: 3300-3340 (NH), 1725, 1710 (C=O), 1615, 1565, 1535 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (3H, s, $NHCO_2C\underline{H}_3$); 7.03 (1H, d, ^3J = 8.7, H Ar); 7.27 (1H, d, ^3J =8.7, H Ar); 7.68 (1H, s, H Ar); 9.65 (1H, br. s, N<u>H</u>COOMe); 11.73 (1H, br. s, 1-NH). ^{13}C NMR spectrum, δ, ppm: 52.3 (OCH_3); 109.7 (C-7); 118.7 (C-4); 120.1 (C-5); 128.4 (C-8); 135.2 (C-6); 138.6 (C-9); 155.3 (NH<u>C</u>O_2Me); 170.4 (2C=O). Mass spectrum, *m/z* (I_{rel},%): 226 $[M+2H]^+$ (5), 225 $[M+H]^+$ (10), 224 $[M]^+$ (100), 192 (74), 164 (40), 137 (93), 125 (20), 119 (13), 110 (24), 93 (15), 83 (21), 79 (48), 69 (24), 59 (86), 52 (79). Found, %: C 47.98; H 3.55; N 12.28. $C_9H_8N_2O_3S$. Calculated, %: C 48.21; H 3.60; N 12.49.

Methyl *N*-(4-chloro-2-oxo-2,3-dihydro-1,3-dibenzothiazol-6-yl)carbamate (6) was prepared analogously by cyclization of adduct **4** (0.90 g, 2.7 mmol). Yield 0.60 g, (87%). Colorless crystals; mp 242-245°C (dioxane). R_f 0.81. IR spectrum, ν, cm^{-1}: 3320-3340 (NH), 1720, 1710 (C=O), 1615, 1575, 1535 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm: 3.73 (3H, s, $NHCO_2C\underline{H}_3$); 7.51 (1H, s, H Ar); 7.62 (1H, s, H Ar); 9.13 (1H, s, N<u>H</u>CO_2Me); 12.01 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 52.3 (OCH_3); 112.1 (C-7); 122.1 (C-5); 123.0 (C-4); 127.5 (C-8); 130.1 (C-9); 135.2 (C-6); 155.3 (NH<u>C</u>O_2Me); 170.5 (2C=O). Found, %: C 41.55; H 2.57; N 10.67. $C_9H_7ClN_2O_3S$. Calculated, %: C 41.79; H 2.73; N 10.83.

Dimethyl [Ethan-1,2-diylbis(2-oxo-1,3-benzothiazol-3,6(*2H*)-diyl)]biscarbamate (7). A mixture of carbamate **5** (1.12 g, 5.0 mmol) and anhydrous K_2CO_3 (0.69 g, 5.0 mmol) in acetone (7 ml) was refluxed for 10 min; freshly distilled 1,2-dibromoethane (0.22 ml, 2.5 mmol) was added, and the mixture was heated at 70°C for 6 h, cooled, poured onto ice, the crystalline precipitate was filtered off, dried in air, and recrystallized from MeOH. Yield 0.85 g (72%). Colorless crystals; mp 284-286°C. IR spectrum, ν, cm^{-1}: 3335 (NH), 1710, 1680 (C=O), 1610, 1555, 1530 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (6H, s, $2NHCO_2C\underline{H}_3$); 5.50 (4H, s, $2CH_2$); 6.89 (2H, d, ^3J = 8.7, H Ar); 7.02 (2H, d, ^3J = 8.7, H Ar); 7.36 (2H, s, H Ar); 11.53 (2H, s, 2NH). Found, %: C 50.55; H 3.92; N 11.65. $C_{20}H_{18}N_4O_6S_2$. Calculated, %: C 50.62; H 3.82; N 11.81.

Ethyl 2-{6-[(methoxycarbonyl)amino]-2-oxo-1,3-benzothiazol-3(2*H*)-yl}acetate (8) was obtained analogously using ethyl bromoacetate (0.57 ml, 5.1 mmol) as an alkylating agent. The product was recrystallized from $CHCl_3$. Yield 1.24 g (80%). Colorless crystals; mp 276-278°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1715, 1670 (C=O), 1595, 1580, 1565 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 3.71 (3H, s, $NHCO_2C\underline{H}_3$); 4.20 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 5.10 (2H, s, $C\underline{H}_2$COOEt); 6.95 (1H, d, ^3J = 8.5, H Ar); 7.14 (1H, d, ^3J = 8.5, H Ar); 7.45 (1H, s, H Ar); 11.62 (1H, s, N<u>H</u>CO_2Me). Found, %: C 50.04; H 4.20; N 8.92. $C_{13}H_{14}N_2O_5S$. Calculated, %: C 50.32; H 4.55; N 9.03.

Methyl *N*-[3-(2-Hydrazino-2-oxoethyl)-2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl]carbamate (9). A mixture of compound **8** (0.78 g, 2.5 mmol) and 99% hydrazine hydrate (0.18 g, 3.5 mmol) in EtOH (7 ml) was kept at 50°C for 8 h, cooled, the crystalline precipitate was filtered off, washed on the filter with cold EtOH, dried in air, and recrystallized from dioxane. Yield 0.70 g (94%). Colorless crystals; mp 260-262°C. IR spectrum, ν, cm^{-1}: 3340, 3400 (NH), 1715, 1680 (C=O), 1615, 1565, 1530 (C–C_{Ar}). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (3H, s, $NHCO_2C\underline{H}_3$); 5.25 (2H, s, CH_2CO); 6.95 (1H, d, ^3J = 8.5, H Ar); 7.25 (1H, d, ^3J = 8.5, H Ar); 7.48-7.52 (1H, m, N<u>H</u>NH_2); 7.69 (1H, s, H Ar); 8.23-8.27 (2H, m, NHN<u>H</u>$_2$); 11.54 (1H, s, N<u>H</u>CO_2Me). Found, %: C 44.57; H 4.00; N 18.77. $C_{11}H_{12}N_4O_4S$. Calculated, %: C 44.59; H 4.08; N 18.91.

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