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Synthesis of 1,3-Benzothiazol-2(3*H*)-one and Some Its Derivatives

A. V. Velikorodov, A. K. Kuanchalieva, E. A. Melent'eva, and O. L. Titova

Astrakhan State University, pl. Shaumyana 1, Astrakhan, 414000 Russia
e-mail: avelikorodov@mail.ru

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Abstract—Acylation of 2-aminobenzenethiol with methyl chloroformate in pyridine gave dimethyl 2,2′-disulfanediylbis(2,1-phenylene)dicarbamate instead of expected methyl 2-suylfanylphenylcarbamate. Heating of the product with zinc dust in glacial acetic acid led to the formation of 1,3-benzothiazol-2(3*H*)-one. Alkylation of the latter with 1,2-dibromoethane and allyl bromide, as well as acylation with chloroacetyl chloride, afforded the corresponding 3-substituted derivatives. 3-[3-(Pyridin-2-yl)-4,5-dihydroisoxazol-5-ylmethyl]-1,3-benzothiazol-2(3*H*)-one was synthesized with high regioselectivity by 1,3-dipolar cycloaddition of 3-allyl-1,3-benzothiazol-2(3*H*)-one to pyridine-2-carbonitrile oxide generated from *N*-hydroxypyridine-2-carboximidoyl chloride hydrochloride by the action of triethylamine.

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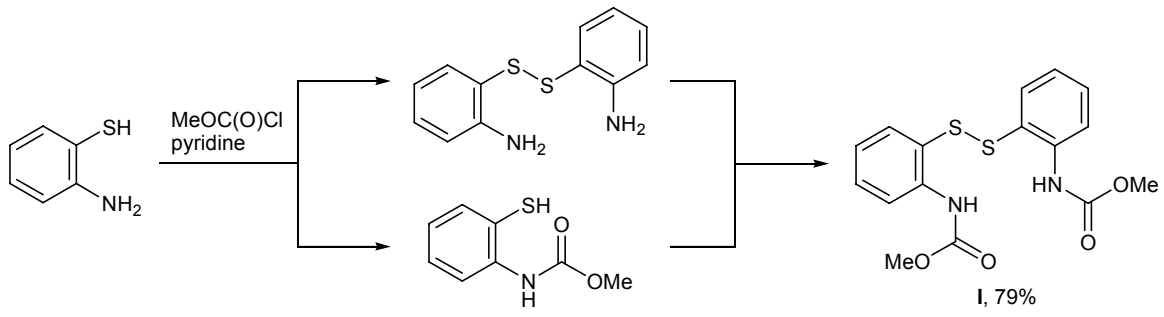
Derivatives of 2-aminobenzenethiol are widely used in the synthesis of heterocyclic compounds [1, 2]. Acylation of 2-aminobenzenethiol is not selective, and the reaction direction depends on the conditions and the nature of acylating agent. It is known that acylation of 2-aminobenzenethiol with acid chlorides in the presence of bases yields 2-substituted 1,3-benzothiazoles [3] and that the reaction with chloroacetyl chloride in methylene chloride occurs exclusively at the nitrogen atom [4]. Acylation of 2-aminobenzenethiol with acetic and propionic anhydrides in aqueous medium in the presence of sodium hydrogen carbonate was accompanied by formation of 2-methyl- and 2-ethyl-1,3-benzothiazoles, respectively (in addition to the corresponding *N*-acyl derivatives) [5]. Ethyl 3-(4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)propionate or *N*-[2-(carboxyethylsulfanyl)phenyl]-β-alanine were formed in the reaction of acrylic acid with 2-aminobenzenethiol, depending on the reactant ratio [6].

We found that acylation of 2-aminobenzenethiol with methyl chloroformate in anhydrous pyridine gives dimethyl 2,2′-disulfanediylbis(2,1-phenylene)dicarbamate (**I**) instead of expected methyl 2-suylfanylphenylcarbamate (Scheme 1). Compound **I** was synthesized previously by acylation of 2,2′-disulfanediyldianiline with methyl chloroformate [7].

The structure of disulfide **I** was confirmed by the IR, ^{1}H NMR, and mass spectra. The IR spectrum of **I** lacked absorption band at 2550 cm^{-1}, which is typical of stretching vibrations of SH group but contained absorption bands at 3380 and 1740 cm^{-1} due to stretching vibrations of NH and C=O groups in addition to absorption bands corresponding to vibrations of the benzene ring. No SH signal (δ 3.27 ppm [8]) was observed in the ^{1}H NMR spectrum of **I**. In the mass spectrum of compound **I**, ion peaks with *m*/*z* 364 $[M]^+$ and *m*/*z* 182 were present, which indicated the formation of disulfide structure.

Scheme 1.

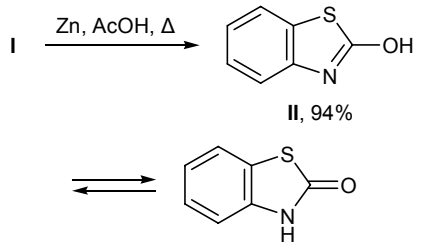


I, 79%

Presumably, disulfide **I** is formed as a result of initial oxidation of 2-aminobenzenethiol into the corresponding disulfide with atmospheric oxygen and subsequent acylation with methyl chloroformate at the nitrogen atoms. The formation of disulfide from 2-aminobenzenethiol in pyridine was confirmed by special experiment. Furthermore, compound **I** can be formed, at least in part, by oxidation of methyl 2-sulfanylphenylcarbamate. The ability of benzenethiols to undergo oxidation by the action of atmospheric oxygen in alkaline medium is well known [9].

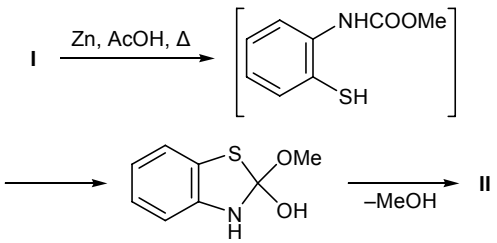
The synthesis of ethyl 2-sulfanylphenylcarbamate via reduction of the corresponding disulfide with Zn–HCl in methanol was described in [10]. With a view to obtain methyl 2-sulfanylphenylcarbamate we studied reduction of disulfide **I** with zinc dust in glacial acetic acid. However, instead of expected thiol we isolated 1,3-benzothiazol-2(3*H*)-one (**II**) which exists as two tautomers [3] (Scheme 2).

Scheme 2.



The structure of **II** was confirmed by its IR, ^{1}H NMR, and mass spectra, as well as by further chemical transformations. Compound **II** is likely to be formed via cyclization of the primary reduction product, methyl 2-sulfanylphenylcarbamate, and subsequent elimination of alkoxy group by the action of zinc(II) acetate as Lewis acid (Scheme 3).

Scheme 3.

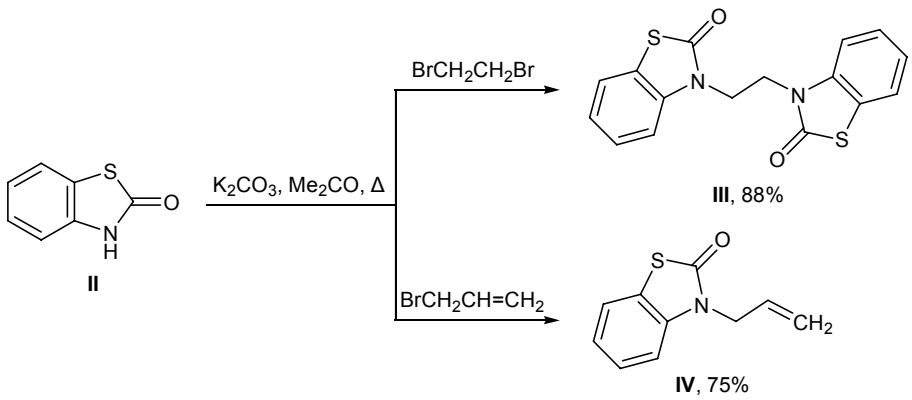


Several procedures for the preparation of 1,3-benzothiazol-2(3*H*)-ones have been reported. These include cyclization of 2-aminobenzenethiols by the action of phosgene, chloroformates, and urea [3, 11]; reductive carbonylation of substituted nitrobenzenes with sulfur, carbon(II) oxide, and water in the presence of vases [3]; cyclization of carbamothioates with subsequent cleavage of 2-alkoxybenzothiazoles thus formed [12]; oxidation of 2-sulfanyl- or 2-alkylsulfanylbenzothiazoles to the corresponding sulfones and hydrolysis of the latter; reaction of *o*-chloronitrobenzenes with 2-sulfanylacetic acid followed by cyclocondensation of 2-(*o*-nitrophenylsulfanyl)acetic acid with acetic anhydride and deacylation [3]; reaction of 1,3-benzothiazol-2-amines with alkali metal hydroxides in anhydrous medium and subsequent cyclization of *o*-sulfanylphenylureas [3, 13]; and reaction of 2-sulfanylbenzoic acid with ammonium azide and 3 equiv of the DMF–$POCl_3$ complex [14]. Various 2- and 3-substituted 1,3-benzothiazol-2(3*H*)-one derivatives exhibit a broad spectrum of biological activity, in particular herbicidal, antimicrobial, analgesic, antioxidant, anticonvulsant, antifungal, etc. [3, 14–16]. These compounds are also important as precursors of new functionally substituted derivatives [17]. In view of the above stated, synthesis of new derivatives of 1,3-benzothiazol-2(3*H*)-one and their subsequent biological screening attract strong interest.

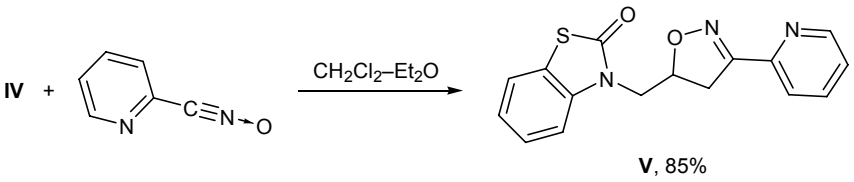
The alkylation of 1,3-benzothiazol-2(3*H*)-one (**II**) with 1,2-dibromoethane and allyl bromide in acetone in the presence of potassium carbonate occurred at the nitrogen atom and resulted in the formation of 3,3′-(ethane-1,2-diyl)bis[1,3-benzothiazol-3(2*H*)-one] (**III**) and 3-allyl-1,3-benzothiazol-2(3*H*)-one (**IV**), respectively (Scheme 4).

3-Allyl-1,3-benzothiazol-2(3*H*)-one (**IV**) may be regarded as dipolarophile; it was modified by cycloaddition of pyridine-2-carbonitrile oxide generated *in situ* from *N*-hydroxypyridine-2-carboximidoyl chloride hydrochloride [18] in diethyl ether by the action of triethylamine. The reaction was regioselective, and the product was 3-[3-(pyridin-2-yl)-4,5-dihydro-1,2-oxazol-5-ylmethyl]-1,3-benzothiazol-2(3*H*)-one (**V**) (Scheme 5). The structure of compound **V** was confirmed by the ^{1}H NMR and IR spectra. Apart from other signals, the ^{1}H NMR spectrum of **V** contained two doublets of doublets typical of protons on C^4 in 3,5-disubstituted isoxazole derivatives [19]. By acylation of 1,3-benzothiazol-2(3*H*)-one (**II**) with chloroacetyl chloride in boiling benzene (reaction time 10 h) we obtained 3-(2-chloroacetyl)-1,3-benzothiazol-2(3*H*)-one (**VI**) (Scheme 6). Our results are consistent with published data [3, 20–22], according to which 1,3-benzothiazol-2(3*H*)-one (**II**) undergoes alkylation and acylation at the nitrogen atom.

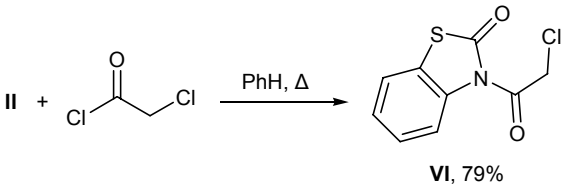
Scheme 4.



Scheme 5.



Scheme 6.



EXPERIMENTAL

The ^{1}H NMR spectra were measured on a Varian VXR-500 spectrometer (500.13 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra (4000–400 cm^{-1}) were recorded in KBr on a Specord M82 spectrometer. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS 50 instrument. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates.

Dimethyl 2,2′-disulfanediylbis(2,1-phenylene)dicarbamate (I). Methyl chloroformate, 7.7 ml (0.1 mol), was added dropwise under stirring to a solution of 10.7 ml (0.1 mol) of 2-aminobenzenethiol in 46 ml of anhydrous pyridine with protection from atmospheric moisture on cooling with ice. The mixture was stirred for 0.5 h on cooling, left to stand for 13 h at room temperature, poured onto ice, carefully acidified with concentrated hydrochloric acid (according to Congo Red), and extracted with ethyl acetate (4× 25 ml). The organic phase was washed with a saturated aqueous solution of sodium chloride (100 ml) and water (2×50 ml), dried over magnesium sulfate, and evaporated under reduced pressure, the residue was treated with 50 ml of diethyl ether and kept for 24 h in a refrigerator, and the precipitate was filtered off and recrystallized from methanol. Yield 28.8 g (79%), colorless crystals, mp 105–108°C; published data [7]: mp 108–112°C. IR spectrum, ν, cm^{-1}: 3380 (NH), 2836–3108 (CH), 1740 (C=O), 1620, 1580 (C=C, C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.68 s (6H, OMe), 7.21 t (2H, H$_{arom}$, J = 8.0 Hz), 7.29 t (2H, H$_{arom}$, J = 8.0 Hz), 7.33 d (2H, H$_{arom}$, J = 8.0 Hz), 7.54 d (2H, H$_{arom}$, J = 8.0 Hz), 9.15 br.s (2H, NH). Mass spectrum, m/z (I_{rel}, %): 364 (55) $[M]^+$, 332 (11), 306 (4), 182 (57), 166 (2), 150 (100), 136 (2.5), 124 (22), 106 (6), 96 (18), 77 (7). Found, %: C 52.57; H 4.38; N 7.39. $C_{16}H_{16}N_2O_4S_2$. Calculated, %: C 52.75; H 4.40; N 7.69.

1,3-Benzothiazol-2(3*H*)-one (II). A mixture of 4 g (0.011 mol) of disulfide **I**, 10 g (0.16 mol) of zinc dust, and 10 ml of glacial acetic acid was heated for 7 h under reflux with stirring, 2 ml of concentrated hydro-

chloric acid was added, the mixture was heated for 0.5 h more and filtered, and the filtrate was poured into 100 ml of water. The precipitate was filtered off, washed on a filter with dilute (1:1) hydrochloric acid (50 ml) and water (100 ml), dried in air, and recrystallized from ethanol. Yield 1.56 g (94%), colorless crystals, mp 138–140°C [14].

3,3′-(Ethane-1,2-diyl)bis[1,3-benzothiazol-3(2*H*)-one] (III). A mixture of 1.51 g (10 mmol) of 1,3-benzothiazol-2(3*H*)-one (**II**), 0.43 ml (5 mmol) of freshly distilled 1,2-dibromoethane, and 1.38 g (10 mmol) of anhydrous potassium carbonate in 7 ml of acetone was heated for 6 h at 70°C. The mixture was cooled, diluted with water (25 ml), and extracted with diethyl ether (3×25 ml). The extract was washed with a 10% aqueous solution of sodium hydroxide (100 ml) and water (50 ml) and dried over potassium carbonate. The solvent was removed, and the residue crystallized. Recrystallization from methanol gave 1.44 g (88%) of compound (**III**) as colorless crystals with mp 249–251°C; published data [20]: mp 250–251°C.

3-Allyl-1,3-benzothiazol-2(3*H*)-one (IV) was synthesized in a similar way from 1.51 g (10 mmol) of compound **II** and 0.87 ml (10 mmol) of allyl bromide. Yield 1.4 g (75%), yellowish oily substance, bp 162–164°C (5 mm); published data [22]: bp 155–157°C (3 mm).

3-[3-(Pyridin-2-yl)-4,5-dihydro-1,2-oxazol-5-ylmethyl]-1,3-benzothiazol-2(3*H*)-one (V). A suspension of 0.97 g (5 mmol) of *N*-hydroxypyridine-2-carboximidoyl chloride hydrochloride in 20 ml of anhydrous diethyl ether was cooled to –5°C, 1.4 ml (10 mmol) of triethylamine in 10 ml of anhydrous diethyl ether was added under vigorous stirring, the mixture was stirred for 10 min and filtered from triethylamine hydrochloride, and the filtrate was added to a solution of 0.96 g (5 mmol) of compound **IV** in 20 ml of methylene chloride on cooling to 0 to –1°C. After 48 h, the solvent was removed, and the residue was recrystallized from diethyl ether–hexane (2:1, by volume). Yield 1.3 g (85%), colorless crystals, mp 133–136°C. IR spectrum, ν, cm^{-1}: 2845–3120 (CH), 1738 (C=O), 1610, 1620, 1565 (C=C, C–C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.52 d.d (1H, 4-H, J = 6.2, 9.5 Hz), 3.87 d.d (1H, 4-H, J = 5.9, 9.3 Hz), 4.23 q (1H, NCH_2, J = 6.7 Hz), 4.51 d.d (1H, NCH_2, J = 3.4, 7.1 Hz), 5.11–5.16 m (1H, 5-H), 6.82–6.85 m (1H, H_{arom}), 7.12–7.22 m (2H, H_{arom}), 7.46–7.58 m (3H, H_{arom}), 7.68 d (1H, H_{arom}, J = 8.2 Hz), 8.44 d (1H, H_{arom}, J = 7.4 Hz). Found, %: C 61.48; H 4.16; N 13.55. $C_{16}H_{13}N_3O_2S$. Calculated, %: C 61.74; H 4.18; N 13.51.

3-(2-Chloroacetyl)-1,3-benzothiazol-2(3*H*)-one (VI). A mixture of 1.51 g (10 mmol) of compound **II**, 0.8 ml (10.5 mmol) of chloroacetyl chloride, and 5 ml of anhydrous benzene was heated for 10 h under reflux. The product was washed with a 2% aqueous solution of sodium hydroxide and extracted with benzene (2×15 ml), and the extracts were combined, washed with water, and dried over anhydrous calcium chloride. Yield 1.8 g (79%), colorless crystals, mp 111–114°C (from chloroform). IR spectrum, ν, cm^{-1}: 1672, 1665 (C=O), 1595, 1580, 1465 (C–C_{arom}), 835 (C–Cl). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 4.25 s (2H, CH_2), 7.12.t (1H, H_{arom}, J = 8.0 Hz), 7.37 d (1H, H_{arom}, J = 8.0 Hz), 7.41 d.t (1H, H_{arom}, J = 8.0, 35.0 Hz), 8.28 d (1H, H_{arom}, J = 8.0 Hz). Mass spectrum, m/z (I_{rel}, %): 229 (15.7), 227 (48.6), 152 (30.3), 151 (100), 123 (68.6), 77 (41.4). Found, %: C 47.37; H 2.55; N 6.08. $C_9H_6ClNO_2S$. Calculated, %: C 47.47; H 2.64; N 6.15.

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