Synthesis and Reactions of 2*H*-Benzothieno[3,2-*d*] [1,3]oxazine-2,4(1*H*)-dione

Gary M. Coppola*, Goetz E. Hardtmann and Oskar R. Pfister

Chemistry Research Department, Pharmaceutical Division,
Sandoz, Inc., Route 10, East Hanover,
New Jersey 07936

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The title compound **5** is synthesized by the reaction of the potassium salt of 3-aminobenzo[*b*]thiophene-2-carboxylic acid with phosgene. Compound **5** is readily alkylated to give **6** with methyl iodide, benzyl bromide, or propargyl bromide in the presence of sodium hydride. Reaction of **5** and **6** with nucleophiles follows specifically different pathways. Compound **5** is readily ionized to the isocycanate species **13** and subsequently reacts with methanol or methylamine to produce exclusively the carbamate **7** or ureido acid **9**. The *N*-substituted derivative **6**, in analogous reactions with methanol or methylamine, produce exclusively the amino ester **8** or the amino amide **10**. The N-benzyl derivative **6b** reacts with the cyclic *S*-methylthiopseudourea **11** to give the tetracycle **12**, a new ring system.

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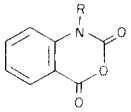
Isatoic anhydride and its *N*-substituted derivatives (**1**) have been shown to be extremely versatile intermediates in the construction of a wide variety of heterocyclic systems (1,2). The ease of attack of an external nucleophile at the C-4 carbonyl of the oxazine ring followed by ring closure (after loss of carbon dioxide) of the resulting internal electrophile with the unmasked anilino function is ideal for the heteroannelation of the benzene ring. The analogous 3-azaisatoic anhydride (**2**) has been shown to react similarly (3-7) while the recently reported furan analog **3** exhibited reversed reactivity with reaction occurring exclusively at the corresponding C-2 carbonyl of the oxazine ring (8).



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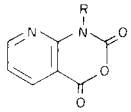

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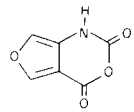

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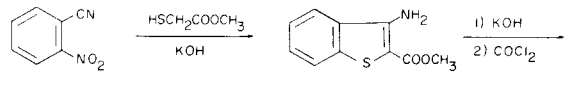
It became of interest to us to expand the variety of heterocyclic molecules derived from ring fused oxazines by investigating the analogous benzo[*b*]thiophene system fused to an oxazine-2,4-dione (**5**, **6**) and to explore their reactivity profile with a variety of nucleophiles.

The synthetic strategy for the preparation of the desired benzothienooxazine parallels the methodology for the formation of isatoic anhydrides *via* cyclization of the sodium or potassium salt of the corresponding 2-aminobenzoic acid with phosgene. The required 3-aminobenzo[*b*]thiophene-2-carboxylic acid methyl ester (**4**) was readily obtained in 67% yield from the reaction of *o*-nitrobenzonitrile with methyl thioglycolate in the presence of potassium hydroxide as described by Beck (9). The ester **4** was hydrolysed with potassium hydroxide and the resulting potassium salt was treated with phosgene to give the desired benzothienooxazine **5** in 90% yield.



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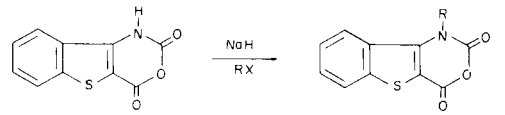
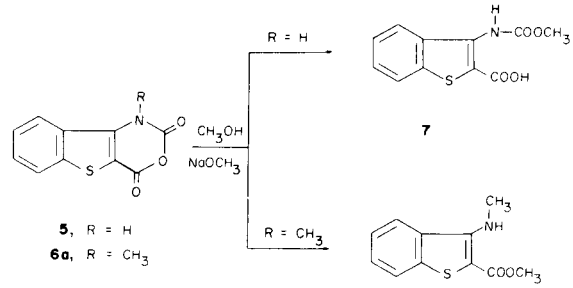


5

6a, R = CH_3
b, R = CH_2
c, R = $CH_2C{\equiv}CH$

Alkylation of **5** with methyl iodide, benzyl bromide, or propargyl bromide in the presence of sodium hydride proceeded smoothly, as in the cases of **1** and **2**, and furnished the *N*-substituted derivatives **6** in 70%, 49%, and 65% yields, respectively.

With the required intermediates **5** and **6** in hand, their reactivity with several nucleophiles was investigated. The first chosen was methanol because if nucleophilic attack occurs at the carbonyl at position 4 of the oxazine ring, regeneration of the known amino ester **4** will occur and immediate comparisons can be made. Thus, when **5** was stirred in methanol at room temperature for 24 hours, no reaction occurred. Upon raising the temperature to the

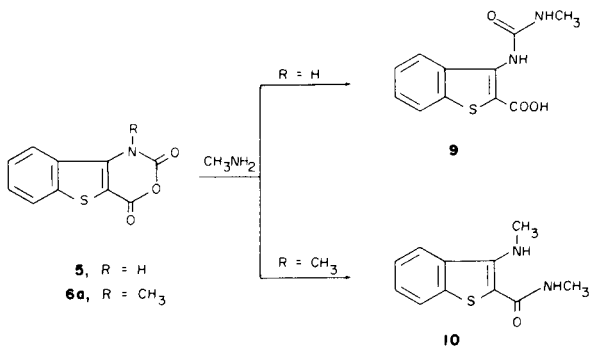


5, R = H
6a, R = CH_3

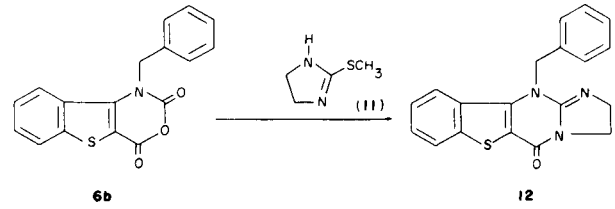
reflux point of the methanol, after 24 hours, some reaction was noticed with a more polar material (as observed by thin layer chromatography) being formed. The remainder of the reaction mixture was unreacted **5**. When a catalytic amount of sodium methoxide was added to the mixture, complete conversion occurred within 18 hours at reflux. The new material, isolated in 60% yield, was clearly different from **4** and was found to be base soluble. Its ir spectrum exhibits absorptions at 3370 (N-H), 1745 (ester C=O), and 1630 cm^{-1} (COOH). In the nmr spectrum a singlet at δ 3.7 (three protons) is seen which is attributable to a methyl ester. Data such as this suggests structure **7**. Additional corroboration of the structure is furnished by carbon-13 data which show two carbon shifts at 163.39 and 154.51 ppm which correspond to the acid and carbamate carbonyls. The mass spectrum gives a molecular ion of 251 which corresponds to the molecular weight of compound **7** and elemental analysis is in full accord with the empirical formula of **7**. Additionally, the chemical precedent for this type of transformation is known in the isatoic anhydride series (10) and furan analog **3** series (8).

When an analogous reaction was performed with the *N*-methyl derivatives **6a** and methanol, no reaction was observed under neutral conditions. Upon addition of a catalytic amount of sodium methoxide, partial reaction occurred at room temperaute (18 hours) but when the mixture was refluxed for one hour, complete consumption of **6a** was observed. In this reaction, no base soluble compound was formed and the only product isolated was the amino ester **8** (86% yield) which indicates that reaction occurred at the C-4 carbonyl of the starting material.

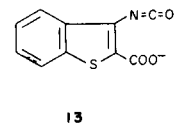
The investigation was then extended to include amines. When anhydrous methylamine was introduced into a suspension of **5** in dioxane, the known 3-aminobenzo[*b*]thiophene-2-(*N*-methylcarboxamide) (11), resulting from nucleophilic ring opening at the C-4 carbonyl of **5**, was not formed. The only isolable product from the reaction was determined to be the ureido acid **9** arising from an "apparent" attack at the C-2 carbonyl. In the nmr spectrum the *N*-methyl signal appears as a doublet centered at δ 2.67 which collapses to a singlet upon deuterium exchange. The carbon-13 spectrum reveals the presence of the acid carbonyl carbon at 164.91 ppm and the ureido carbonyl at 155.32 ppm. The mass spectrum exhibits a molecular ion of 250 which corresponds to the molecular weight of **9**. Again when the *N*-methyl analog **6a** was allowed to react with methylamine in a similar fashion, the amino amide **10** was isolated in 63% yield with no trace of a ureido acid being formed. Chemical precedent also exists for this type of transformation (8,12).



Analogous to the isatoic anhydride series, the reaction of the *N*-benzyl derivative **6b** with the cyclic thiopseudourea **11** afforded the tetracycle **12**, a new ring system.



It is apparent that the course of the reaction of **5** or **6** with nucleophiles is controlled by the ability of the molecule to form the ionized species **13**. The additional strain exerted on the oxazine ring of **5** by the fused five membered thiophene ring may assist the molecule into the ionized state **13** under very mild reaction conditions as observed by the fact that partial reaction of **5** occurs with refluxing methanol under neutral conditions, and with methylamine at room temperature. In fact, this effect is so pronounced that the reported reaction of **3** with ethanol or benzyl alcohol occurs completely at room temperature (8) whereas reaction of isatoic anhydrides (**1**) with alcohols to form isatoates requires elevated temperatures (99-170°) (10).



Subsequent to the formation of **13**, reaction of the nucleophile with the isocyanate directly forms **7** or **9**. The complete absence of any benzothiophene-2-carboxylic acids in the reaction mixture when analogous reactions are performed with the *N*-alkylated substrate **6a** support the isocyanate theory because the nitrogen substitution precludes any isocyanate formation. Although no hard evidence has been obtained for the existence of the isocyanate function in **13**, this similar type of intermediate has been proposed by Staiger and Miller (12) in the isatoic anhydride series and anlogous conclusions were drawn about the effect of *N*-alkylation *vs.* unsubstitution on the outcome of the reaction.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60, EM-360, and JEOL FX-90-Q spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on an LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-90-Q spectrometer system. The spectra were obtained at an observing frequency of 22.5 MHz. Sample concentrations were *ca.* 0.1 molar in 5 or 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5000 Hz; a pulse width of 6 μs corresponding to a 45° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ± 0.05 ppm.

Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

2*H*-Benzothieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-dione (**5**).

To a solution of 60.0 g of **4** (9) in 400 ml of ethanol was added a solution of 38.5 g of potassium hydroxide in 150 ml of water and the mixture was heated on a steam bath for 1 hour. The solvent was removed under reduced pressure and the residue was dissolved in 1000 ml of water. To this rapidly stirred solution was added dropwise over a period of 1 hour 300 ml of a 12.5% solution of phosgene in benzene then the mixture was stirred an additonal 3 hours. Excess benzene was removed by bubbling air through the reaction mixture. The resulting precipitate was filtered, washed with water and dried *in vacuo* at 60°. The solid was dissolved in 450 ml of warm dimethylacetamide and the solution was poured into 2000 ml of water. The precipitate was filtered, washed with water and dried to give 57.5 g (90%) of **5**, mp 267-272° dec; ir (potassium bromide): 3300, 1770, 1710, 1660 cm^{-1}; nmr (DMSO-d_6): δ 10.3-9.1 (broad, 1), 8.5-7.85 (m, 2), 7.8-7.3 (m, 2).

Anal. Calcd. for $C_{10}H_5NO_3S$: C, 54.8; H, 2.3; N, 6.4; S, 14.6. Found: C, 54.6; H, 2.4; N, 6.3; S, 14.6.

1-Methyl-2*H*-benzothieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-dione (**6a**).

To a solution of 19.0 g of **5** in 250 ml of dimethylacetamide was added 5.0 g of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 1 hour, then 14.0 g of methyl iodide was added and stirring was continued for 4 hours. The mixture was concentrated to one-third volume and was poured into 400 ml of cold water. The precipitate was filtered, washed with water and then dried under reduced pressure. The solid was triturated with hot chloroform to give 14.2 g (70%) of **6a**, mp 280-282° dec; ir (potassium bromide): 1750, 1700 cm^{-1}; nmr (DMSO-d_6, 110°): δ 8.5-8.35 (m, 1), 8.2-8.05 (m, 1), 7.75-7.4 (m, 2), 3.93 (s, 3).

Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.6; H, 3.0; N, 6.0; S, 13.7. Found: C, 56.4; H, 3.1; N, 6.1; S, 13.7.

1-Benzyl-2*H*-benzothieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-dione (**6b**).

To a solution of 7.5 g of **5** in 100 ml of dimethylacetamide was added 1.8 g of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 1 hour, then 6.5 g of benzyl bromide was added and stirring was continued for 18 hours. The mixture was concentrated to one-third volume and was poured into 250 ml of cold water. The resulting precipitate was filtered, washed with water and dried by suction. The solid was dissolved in chloroform and dried over magnesium sulfate. The solution was concentrated, ether was added, and the resulting solid was filtered then washed with ether to give 6.7 g (49%) of **6b**, mp 218-220°; ir (potassium bromide): 1780, 1720 cm^{-1}; nmr (DMSO-d_6): δ 8.25-7.1 (m, 9), 5.65 (s, 2).

Anal. Calcd. for $C_{17}H_{11}NO_3S$: C, 66.0; H, 3.6; N, 4.5; S, 10.4. Found: C, 65.7; H, 3.6; N, 4.5; S, 10.2.

1-(2-Propynyl)-2*H*-benzothieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-dione (**6c**).

To a solution of 19.0 g of **5** in 250 ml of dimethylacetamide was added 5.0 g of sodium hydride (50% in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 1 hour, then 12.0 g of propargyl bromide was added and stirring was continued for 18 hours. The mixture was concentrated to one-third volume and was poured into 500 ml of cold water. The precipitate was filtered, dried and recrystallized from methylene chloride/ether to give 14.5 g (65%) of **6c**, mp 233° dec; ir (potassium bromide): 3280, 1770, 1720 cm^{-1}; nmr (DMSO-d_6): δ 8.6-8.0 (m, 2), 7.8-7.4 (m, 2), 5.2 (d, J = 4 Hz, 2), 3.6 (t, 1).

Anal. Calcd. for $C_{13}H_7NO_3S$: C, 60.7; H, 2.7; N, 5.4; S, 12.5. Found: C, 60.4; H, 2.9; N, 5.5; S, 12.3.

3-(*N*-Carbomethoxy)aminobenzo[*b*]thiophene-2-carboxylic Acid (**7**).

A mixture of 2.2 g of **5** and 0.15 g of sodium methoxide in 50 ml of methanol was refluxed for 18 hours then was poured into cold water. The mixture was basified with 2*N* sodium hydroxide and was washed with ether. The aqueous phase was acidified with 2*N* hydrochloric acid and the organic material was extracted (2×) into methylene chloride. Removal of the solvent under reduced pressure furnished 1.5 g (60%) of **7**. An analytical sample was crystallized from methylene chloride, mp 208-211° dec; ir (potassium bromide): 3370, 1745, 1630 cm^{-1}; nmr (DMSO-d_6): δ 9.5 (s, 1, exchangeable), 8.1-7.75 (m, 2), 7.7-7.3 (m, 2), 3.7 (s, 3); ^{13}C-nmr (DMSO-d_6): δ 166.39 (COOH), 154.51 (*C*OOCH$_3$), 137.61 (C-N), 135.44 (*C*$_{arom}$-C-N), 135.17 (C-S)$_{arom}$, 128.13 (C)$_{arom}$, 127.48 (C)$_{arom}$, 124.61 (C)$_{arom}$, 123.79 (C)$_{arom}$, 122.01 (*C*-COOH), 52.18 (COO*C*H$_3$); ms: (70 eV) m/e 251 (M^+).

Anal. Calcd. for $C_{11}H_9NO_4S$: C, 52.6; H, 3.6; N, 5.6; S, 12.8. Found: C, 52.3; H, 3.2; N, 5.7; S, 12.7.

3-Methylaminobenzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (**8**).

A mixture of 233 mg of **6a** and 15 mg of sodium methoxide in 5 ml of methanol was refluxed for 1 hour. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform to elute the product, 190 mg (86%) of **8**. An analytical sample was crystallized from pentane, mp 82-85°; ir (potassium bromide): 3360, 1650, cm^{-1}; nmr (deuteriochloroform): δ 8.15 (m, 1), 7.8-7.15 (m, 4), 3.87 (s, 3), 3.42 (s, 3); ^{13}C-nmr (deuteriochloroform): δ 166.33 (*C*OOCH$_3$), 152.90 (C-N), 140.98 (C-S)$_{arom}$, 131.88 *C*$_{arom}$-C-N), 127.60 (C)$_{arom}$, 125.27 (C)$_{arom}$, 123.54 (C)$_{arom}$, 123.37 (C)$_{arom}$, 97.26 (*C*-COOCH$_3$), 51.27 (COO*C*H$_3$), 33.28 (N-CH$_3$); ms: (70 eV) m/e 221 (M^+).

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.7; H, 5.0; N, 6.3. Found: C, 59.7; H, 4.9; N, 6.0.

3-[Methyl(aminocarbonyl)amino]benzo[*b*]thiophene-2-carboxylic Acid (**9**).

Into a suspension of 2.0 g of **5** in 50 ml of dioxane was bubbled anhydrous methylamine for 20 minutes, then the mixture was stirred at room temperature for an additional 30 minutes. The insoluble material was filtered and washed with 1*N* hydrochloric acid. Recrystallization from methylene chloride/methanol gave 0.75 g (33%) of **9**, mp 209-210° dec; ir (potassium bromide): 3320, 1645 cm^{-1}; nmr (DMSO-d_6): δ 8.9 (s, broad, 1), 8.1-7.8 (m, 2), 7.65-7.35 (m, 2), 7.3-7.1 (m, 1, exchangeable), 2.67 (d, J = 4.5 Hz, 3), acid proton seen as broadening of the base line; ^{13}C-nmr (duteriochloroform/DMSO-d_6): δ 164.91 (COOH), 155.32 (O=C-N), 139.78 (C-N), 138.15 (C-S)$_{arom}$, 133.87 (*C*$_{arom}$-C-N), 126.56 (C)$_{arom}$, 126.29 (C)$_{arom}$, 123.04 (C)$_{arom}$, 121.74 (C)$_{arom}$, 114.26 (*C*-COOH), 26.12 (N-CH$_3$); ms (70 eV) m/e 250 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.8; H, 4.0; N, 11.2. Found: C, 52.8; H, 4.0; N, 10.2 (reanalysis of nitrogen did not improve the value).

3-Methylaminobenzo[*b*]thiophene-2-(*N*-methylcarboxamide) (**10**).

Into a suspension of 8.0 g of **6a** in 250 ml of dioxane was bubbled anhydrous methylamine for 20 minutes, then the mixture was stirred at room temperature for an additional 30 minutes. The dioxane was removed under reduced pressure and methylene chloride was added to the residue. Any insoluble material was filtered and the solvent was removed under reduced pressure. The residue was crystallized from ether to give 4.8 g (63%) of **10**, mp 108-111°; ir (chloroform): 3460, 3310, 1615 cm^{-1}; nmr (deuteriochloroform): δ 8.05 (m, 1), 7.75-7.1 (m, 4), 6.05 (d, broad, exchangeable, 1), 3.2 (s, 3), 2.88 (d, J = 4 Hz, 3) (see lit 13); ms: (70 eV) m/e 220 (M^+).

11-Benzyl-2,3-dihydro[1]benzothieno[3,2-*d*]imidazo[1,2-*a*]pyrimidin-5-(11*H*)-one (**12**).

A mixture of 6.5 g of **6b**, 2.5 g of **11** and one sodium hydroxide pellet in 100 ml of dioxane was refluxed for 5 hours. The mixture was concentrated and the restulting precipitate was filtered and washed with ether. Recrystallization from methylene chloride/ether gave 4.5 g (64%) of **12**, mp 226-229°; ir (potassium bromide): 1670, 1625 cm^{-1}; nmr (DMSO-d_6): δ 8.1-7.0 (m, 9), 5.6 (s, 2), 4.2-3.5 (m, 4).

Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.4; H, 4.5; N, 12.6; S, 9.6. Found: C, 68.7; H, 4.8; N, 12.8; S, 9.6.

Acknowledgement.

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(13) A possible explanation for the observance of a singlet and a doublet for the *N*-methyl signals is the hydrogen bonded species shown below. Hindered rotation of the 3-methylamino group on the nmr time scale results in a doublet while the freely rotating *N*-methylamide group is seen as a singlet.