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1,2-Dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one: formation from carbon disulfide and isatoic anhydride

Philipp A. Ottersbach [a], Hans-Georg Häcker [a], Paul W. Elsinghorst [a], Gregor Schnakenburg [b], Michael Gütschow [a,*]

[a] *Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany*
[b] *Institute of Inorganic Chemistry, University of Bonn, Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany*

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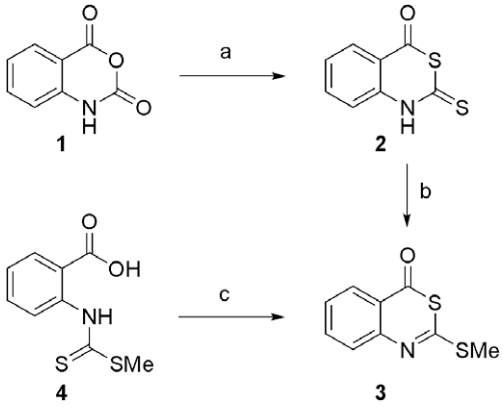
ABSTRACT

The reaction of isatoic anhydride (**1**) with carbon disulfide at room temperature unexpectedly afforded 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**). The use of ^{13}C-labeled carbon disulfide elucidated that CS_2 was entirely incorporated into the product.

Representatives of 4*H*-3,1-benzoxazin-4-ones have attracted much attention as bioactive heterocycles. For example, 2-amino-, 2-alkoxy-, and 2-alkylthio-substituted 4*H*-3,1-benzoxazin-4-ones are potent inhibitors of serine hydrolases acting through the formation of covalent acyl-enzyme intermediates.[1] Corresponding 4*H*-3,1-benzothiazin-4-ones, bearing sulfur in place of the ring oxygen, are hitherto less investigated.[2] Recently, we reported on the inhibitory activity of a series of 4*H*-3,1-benzothiazin-4-ones against a panel of proteases and esterases and identified 2-methylthio-4*H*-3,1-benzothiazin-4-one (**3**) as a selective inhibitor of human leukocyte elastase.[3]

As reported, the formation of 2-methylthio-4*H*-3,1-benzothiazin-4-one (**3**) was achieved by reacting anthranilic acid with carbon disulfide and methyl iodide to yield the dithiocarbamate **4**, which was subsequently cyclized by the use of acetic anhydride (Scheme 1).[3,4] The parent compound of this class, 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**), was recently described using a similar procedure, but was isolated only in poor yield.[5] Here we report on an improved one-step synthesis of 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**) from isatoic anhydride (**1**) and carbon disulfide. We investigated the intriguing reaction with ^{13}C-labeled carbon disulfide. Further structural evidence was obtained by a derivatization reaction and X-ray crystallographic analysis of **2**. To the best of our knowledge, the reaction



Scheme 1. Reagents and conditions: (a) CS_2 (15 equiv), Et_3N, 1,4-dioxane, rt, 120 h, 45%;[8] (b) Et_3N, MeI, 1,4-dioxane, 10 °C to rt, 24 h, 83%;[9] (c) Ac_2O, reflux, 30 min, 91%.[3]

of carbon disulfide with isatoic anhydride (**1**) has not been described before.[6,7]

The reaction was performed at room temperature in 1,4-dioxane in the presence of 2 equiv of triethylamine and excess of carbon disulfide. The procedure afforded a product with a molecular weight of 195 g mol^{-1} as detected by mass spectrometry.[8] In comparison with isatoic anhydride (**1**), the molecular mass differed by 32 g mol^{-1} indicating an unexpected twofold oxygen–sulfur exchange. Only very few cases of thionation reactions with carbon disulfide have been reported until today.[10]

* Corresponding author. Tel.: +49 228 732317; fax: +49 228 732567.
E-mail address: guetschow@uni-bonn.de (M. Gütschow).

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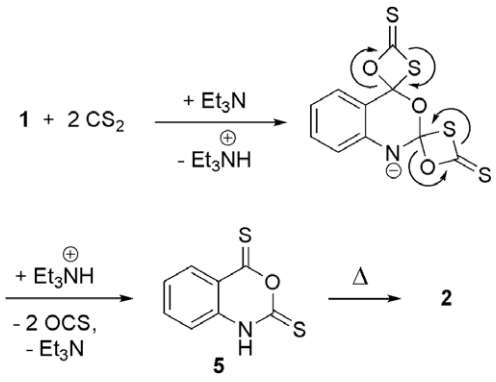
Thus, in first instance we assumed a twofold, carbon disulfide-promoted cycloaddition–elimination at the carbonyl functions in positions 2 and 4 of isatoic anhydride (**1**) to give the 2,4-dithio analog **5** (Scheme 2).

For structure verification, the product of this reaction was alkylated with methyl iodide, to give, however, the unexpected, though known[3] compound 2-methylthio-4*H*-3,1-benzothiazin-4-one (**3**). This led us to the hypothesis that not the benzoxazine **5** was isolated after the reaction of isatoic anhydride (**1**) with carbon disulfide, but the isomeric benzothiazine **2** (Scheme 1). The structure of **2** was confirmed by X-ray crystallographic analysis (see Supplementary data, S17, S18). A preliminary assumption to explain the formation of the benzothiazine **2** was a Dimroth rearrangement of **5** as a consequence of thermal exposure through solvent evaporation during workup (Scheme 2). To further elucidate the mechanism of the oxygen–sulfur exchange, we repeated the conversion with ^{13}C-labeled carbon disulfide and subjected the product to ^{13}C NMR analysis.

If thionation proceeded according to Scheme 2, the product would not be ^{13}C-labeled, because only sulfur would be donated by carbon disulfide. Unexpectedly, the ^{13}C NMR spectrum showed a strong signal at 188 ppm demonstrating that the $^{13}CS_2$ carbon was incorporated into isatoic anhydride (**1**) (Fig. 1; assignment to the thiocarbonyl carbon at position 2 is supported by HMQC and HMBC spectra; see Supplementary data, S15, S16). Thus, carbon disulfide did not act as a thionation reagent and the reaction afforded the labeled [2-^{13}C]-1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**6**) (Fig. 2).



Scheme 2. Initially assumed thionation mechanism for the reaction of isatoic anhydride (**1**) with carbon disulfide.

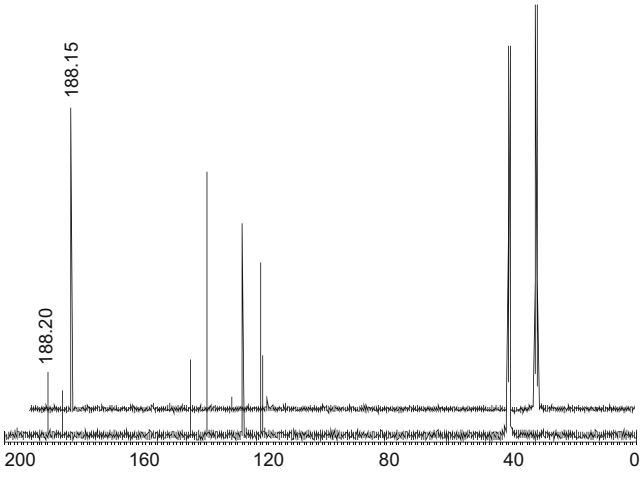


Figure 1. ^{13}C NMR spectra of 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**) (bottom) and the ^{13}C-labeled analog **6** (top).

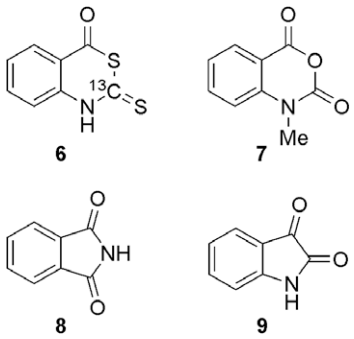


Figure 2. Products isolated after reaction with carbon disulfide.

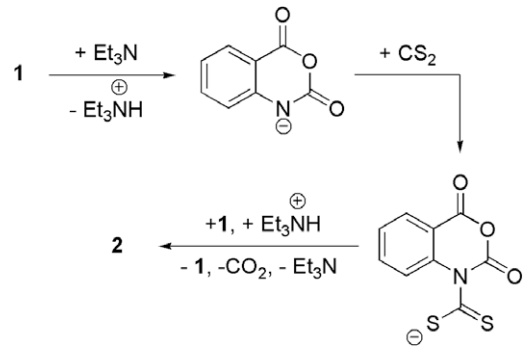
Furthermore, it is known that isatoic anhydrides can form iminoketene intermediates by thermal loss of carbon dioxide.[11,12] These heterodienes can react with dienophiles such as iso(thio)cyanates in a Diels–Alder type reaction to yield the corresponding quinazolines (see Supplementary data, S8).[13] One might assume that **1** similarly reacts with carbon disulfide in a [4+2] cycloaddition to give **2**.

To prove this hypothesis, the denoted iminoketene was generated according to a literature procedure[14] and reacted with carbon disulfide. As compound **2** was not obtained, the iminoketene mechanism cannot be applied to the reaction of isatoic anhydride (**1**) with carbon disulfide. This conclusion is corroborated by the finding that *N*-methylisatoic anhydride (**7**) did not react with carbon disulfide (see below), though iminoketene formation from **7** can be anticipated.[12]

With respect to the aforementioned results, another mechanism can be postulated (Scheme 3). In a first step, the nitrogen of isatoic anhydride (**1**) is deprotonated by triethylamine and attacks the electrophilic carbon of CS_2. Then, the resulting dithiocarbamate undergoes a subsequent intermolecular nucleophilic attack on the carbonyl carbon at position 4 of another isatoic anhydride molecule. Finally, 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**) is formed by release of isatoic anhydride (**1**) and CO_2.

There are several literature reports on the activation of carbon disulfide by basic catalysts[15] or salts of NH-acidic compounds[7] and subsequent reactions of the sulfur-based nucleophiles with electrophiles, for example, oxiranes.[15]

Obviously, the acidic NH moiety of **1** is necessary for the reaction to proceed. To provide further evidence for this prerequisite, *N*-methylisatoic anhydride (**7**) was treated in place of **1** under the same reaction conditions and, indeed, no conversion was observed. Furthermore, the less NH-acidic phthalimide (**8**) and isatine (**9**) were reacted in the same way and, again, only educts were recovered from the reaction mixtures. Thus, we conclude that the



Scheme 3. Putative mechanism for the formation of 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**).

NH acidity of the educt is a precondition for the conversion and assume that carbon dioxide elimination is its driving force.

Alternative reaction conditions for the conversion of **1** to **2**, that is, microwave irradiation or elevated temperature, did not improve the yield (see Supplementary data, S1, S2). However, as indicated by TLC, more by-products were produced in these cases. Additionally, 5-methyl- and 5-chloroisatoic anhydride were reacted with carbon disulfide applying the abovementioned reaction conditions (1,4-dioxane, rt). Indeed, the expected 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-ones were formed and recovered in traces (see Supplementary data, S4, S5).

In summary, we have introduced a new and unexpected synthetic entry to 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**) from isatoic anhydride (**1**) and carbon disulfide. It was demonstrated that carbon disulfide is entirely incorporated into the heterocyclic product and does not act as a thionation reagent. The scope and limitations of this reaction are still under investigation in our laboratories.

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Supplementary data

Supplementary data (crystallographic data, HMQC and HMBC spectra of **2**, ^{1}H NMR and ^{13}C NMR data of **2**, **3** and of the ^{13}C-labeled analog **6**, alternative synthetic procedures for **2**, preparation of 5-methylisatoic anhydride, as well as reaction of 5-methyl- and 5-chloroisatoic anhydride with carbon disulfide, and experiments regarding the iminoketene mechanism) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.042.

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8. *Preparation of 1,2-dihydro-2-thioxo-4H-3,1-benzothiazin-4-one (2)*: To a suspension of isatoic anhydride (**1**; 1.63 g, 10 mmol) and Et_3N (2.02 g, 20 mmol) in 1,4-dioxane (70 mL), CS_2 (11.42 g, 150 mmol) was added. The mixture was stirred for 120 h at room temperature. The meanwhile formed orange-brown solution was evaporated to dryness and the residue was taken up in EtOAc (400 mL) and washed with HCl (0.2 M, 3 × 150 mL), H_2O (1 × 150 mL), and brine (1 × 150 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain a brownish crude product that was subjected to column chromatography (petroleum ether/EtOAc/AcOH 80:20:1) to obtain a yellow solid, yield 0.88 g (45%), mp 217–218 °C (lit.[5] 270–271 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.39 (ddd, J = 1.3, 7.3, 7.6 Hz, 1H, H-6), 7.56 (dd, J = 1.0, 8.2 Hz, 1H, H-8), 7.82 (ddd, J = 1.6, 7.3, 8.2 Hz, 1H, H-7), 7.90 (dd, J = 1.6, 7.9 Hz, 1H, H-5), 13.71 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 118.97 (C-4a), 119.74 (C-8), 125.52, 125.79 (C-5, C-6), 137.07 (C-7), 142.21 (C-8a), 183.86 (C-4), 188.20 (C-2); MS ESI+ (*m/z*, ion, rel. intensity %): 196.0 ($[C_8H_6NOS_2]^+$, 43), 162.0 ($[C_8H_4NOS]^+$, 100); Anal. Calcd for $C_8H_5NOS_2$: C, 49.21; H, 2.58; N, 7.17. Found: C, 49.61; H, 2.91; N, 7.25.
9. *Preparation of 2-methylthio-4H-3,1-benzothiazin-4-one (**3**)*: 1,2-Dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**; 0.74 g, 3.8 mmol) and Et_3N (0.38 g, 3.8 mmol) were dissolved in dry 1,4-dioxane (20 mL). The orange solution was cooled to 10 °C with a water bath, followed by the dropwise addition of methyl iodide (0.54 g, 3.8 mmol) in dry 1,4-dioxane (10 mL). The reaction mixture was allowed to warm to room temperature and after 30 min a white precipitate was formed. After additional 23.5 h, the solvent was evaporated and the residue was taken up in EtOAc (100 mL) and washed with HCl (0.2 M, 3 × 100 mL), H_2O (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield a brown oil. Purification by column chromatography (petroleum ether/EtOAc/AcOH 80:20:1) provided a yellow solid, yield 0.66 g (83%), mp 53–55 °C (lit.[3] 54–56 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.72 (s, 3H, SCH_3), 7.57 (ddd, J = 1.3, 7.3, 7.9 Hz, 1H, H-6), 7.71 (dd, J = 1.3, 8.2 Hz, 1H, H-8), 7.91 (ddd, J = 1.6, 7.3, 8.1 Hz, 1H, H-7), 8.05 (dd, J = 1.6, 8.2 Hz, 1H, H-5); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.91 (SCH_3), 118.62 (C-4a), 124.66 (C-5), 128.31 (C-6), 129.84 (C-8), 136.81 (C-7), 147.47 (C-8a), 163.44 (C-2), 182.30 (C-4); MS ESI+ (*m/z*, ion, rel. intensity %): 264.0 ($[C_9H_7NOS_2 + Na^+CH_3OH]$, 15), 232.0 ($[C_9H_7NOS_2 + Na^+]$, 15), 210.0 ($[C_9H_8NOS_2]^+$, 7), 162.0 ($[C_8H_4NOS]^+$, 100); Anal. Calcd for $C_9H_7NOS_2$: C, 51.65; H, 3.37; N, 6.69. Found: C, 51.78; H, 3.57; N, 6.71.
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