



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

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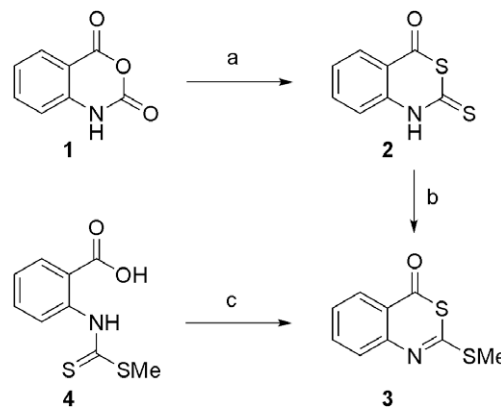
ABSTRACT

The reaction of isatoic anhydride (**1**) with carbon disulfide at room temperature unexpectedly afforded 1,2-dihydro-2-thioxo-4H-3,1-benzothiazin-4-one (**2**). The use of ¹³C-labeled carbon disulfide elucidated that CS₂ was entirely incorporated into the product.

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Representatives of 4H-3,1-benzoxazin-4-ones have attracted much attention as bioactive heterocycles. For example, 2-amino-, 2-alkoxy-, and 2-alkylthio-substituted 4H-3,1-benzoxazin-4-ones are potent inhibitors of serine hydrolases acting through the formation of covalent acyl-enzyme intermediates.¹ Corresponding 4H-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 4H-3,1-benzothiazin-4-ones against a panel of proteases and esterases and identified 2-methylthio-4H-3,1-benzothiazin-4-one (**3**) as a selective inhibitor of human leukocyte elastase.³

As reported, the formation of 2-methylthio-4H-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-4H-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-4H-3,1-benzothiazin-4-one (**2**) from isatoic anhydride (**1**) and carbon disulfide. We investigated the intriguing reaction with ¹³C-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) CS₂ (15 equiv), Et₃N, 1,4-dioxane, rt, 120 h, 45%;⁸ (b) Et₃N, MeI, 1,4-dioxane, 10 °C to rt, 24 h, 83%;⁹ (c) Ac₂O, 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

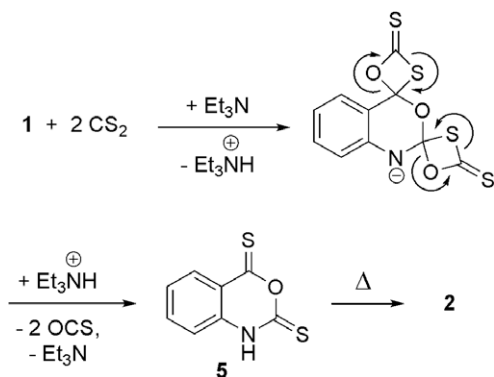
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Thus, in first instance we assumed a twofold, carbon disulfide-promoted cycloaddition–elimination at the carbonyl functions in positions 2 and 4 of isatoic anhydride (**1**) to give the 2,4-dithio analog **5** (Scheme 2).

For structure verification, the product of this reaction was alkylated with methyl iodide, to give, however, the unexpected, though known³ 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 ¹³C-labeled carbon disulfide and subjected the product to ¹³C NMR analysis.

If thionation proceeded according to Scheme 2, the product would not be ¹³C-labeled, because only sulfur would be donated by carbon disulfide. Unexpectedly, the ¹³C NMR spectrum showed a strong signal at 188 ppm demonstrating that the ¹³CS₂ 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 [2-¹³C]-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.

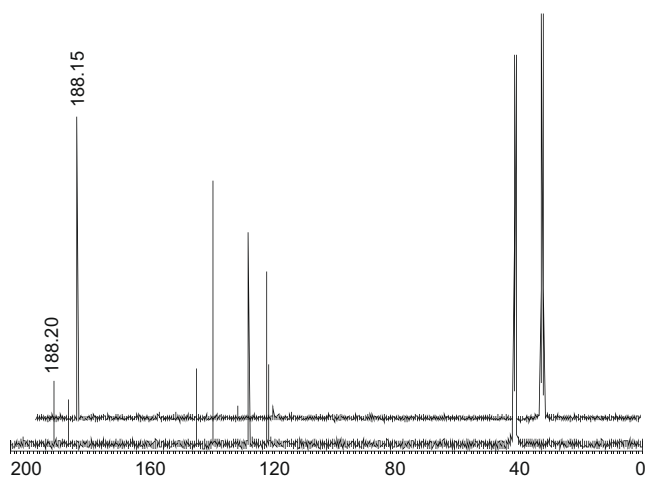


Figure 1. ¹³C NMR spectra of 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**2**) (bottom) and the ¹³C-labeled analog **6** (top).

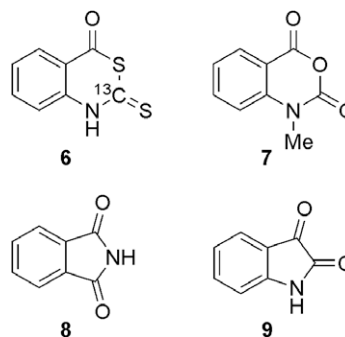


Figure 2. Products isolated after reaction with carbon disulfide.

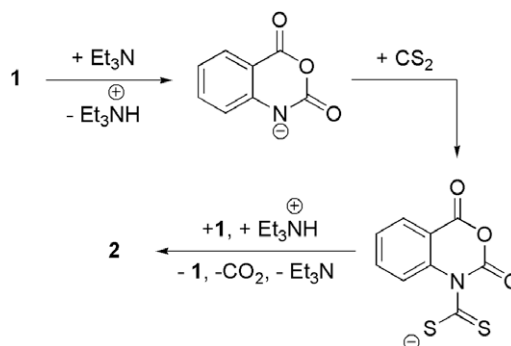
Furthermore, it is known that isatoic anhydrides can form iminoketene intermediates by thermal loss of carbon dioxide.^{11,12} These heterodienes can react with dienophiles such as iso(thio)cyanates in a Diels–Alder type reaction to yield the corresponding quinazolines (see Supplementary data, S8).¹³ 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 procedure¹⁴ 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 CS₂. 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 CO₂.

There are several literature reports on the activation of carbon disulfide by basic catalysts¹⁵ or salts of NH-acidic compounds⁷ 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-4H-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-4H-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**, ^1H 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.

References and notes

- (a) Pietsch, M.; Gütschow, M. *J. Biol. Chem.* **2002**, *277*, 24006–24013; (b) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464–479; (c) Uejima, Y.; Oshida, J.; Kawabata, H.; Kokubo, M.; Kato, Y.; Fujii, K. *Biochem. Pharmacol.* **1994**, *48*, 426–428; (d) Gütschow, M.; Kuerschner, L.; Pietsch, M.; Ambrozak, A.; Neumann, U.; Günther, R.; Hofmann, H. *J. Arch. Biochem. Biophys.* **2002**, *402*, 180–191.
- (a) Matysiak, J. *Bioorg. Med. Chem.* **2006**, *14*, 2613–2619; (b) Besson, T.; Rees, C. W.; Cottenceau, G.; Pons, A.-M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2343–2348; (c) Alexandre, F.-R.; Berecibar, A.; Wigglesworth, R.; Perreux, L.; Guillon, J.; Léger, J.-M.; Thiéry, V.; Besson, T. *Tetrahedron* **2005**, *61*, 8288–8294; (d) Neumann, U.; Gütschow, M. *Bioorg. Chem.* **1995**, *23*, 72–88.
- Häcker, H.-G.; Grundmann, F.; Lohr, F.; Ottersbach, P. A.; Zhou, J.; Schnakenburg, G.; Gütschow, M. *Molecules* **2009**, *14*, 378–402.
- Matsuoka, M.; Segawa, J.; Makita, Y.; Ohmachi, S.; Kashima, T.; Nakamura, K. I.; Hattori, M.; Kitano, M.; Kise, M. *J. Heterocycl. Chem.* **1997**, *34*, 1773–1779.
- Lin, L.-R.; Fang, W.; Huang, R.-B.; Zheng, L.-S. *Chin. J. Struct. Chem.* **2008**, *27*, 1059–1064.
- (a) Copolla, G. M. *Synthesis* **1980**, 505–535; (b) Kappe, T.; Stadlbauer, W. *Adv. Heterocycl. Chem.* **1981**, *28*, 127–182; (c) Brouillette, Y.; Martinez, J.; Lisowski, V. *Eur. J. Org. Chem.* **2009**, 3487–3503.
- Rudolf, W.-D. *J. Sulfur Chem.* **2007**, *28*, 295–339.
- 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); ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 ($[\text{C}_8\text{H}_6\text{NOS}_2]^+$, 43), 162.0 ($[\text{C}_8\text{H}_4\text{NOS}]^+$, 100); Anal. Calcd for $\text{C}_8\text{H}_5\text{NOS}_2$: C, 49.21; H, 2.58; N, 7.17. Found: C, 49.61; H, 2.91; N, 7.25.
- Preparation of 2-methylthio-4H-3,1-benzothiazin-4-one (**3**): 1,2-Dihydro-2-thioxo-4H-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); ^1H NMR (500 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 ($[\text{C}_9\text{H}_7\text{NOS}_2 + \text{Na}^+\text{CH}_3\text{OH}]$, 15), 232.0 ($[\text{C}_9\text{H}_7\text{NOS}_2 + \text{Na}^+]$, 15), 210.0 ($[\text{C}_9\text{H}_6\text{NOS}_2]^+$, 7), 162.0 ($[\text{C}_8\text{H}_4\text{NOS}]^+$, 100); Anal. Calcd for $\text{C}_9\text{H}_7\text{NOS}_2$: C, 51.65; H, 3.37; N, 6.69. Found: C, 51.78; H, 3.57; N, 6.71.
- (a) Zong, Z.-M.; Peng, Y.-L.; Liu, Z.-G.; Zhou, S.-L.; Wu, L.; Wang, X.-H.; Wei, X.-Y.; Lee, C. W. *Korean J. Chem. Eng.* **2003**, *20*, 235–238; (b) Fu, X.; Zhang, C.; Zhang, D.; Yuan, S. *Chem. Phys. Lett.* **2006**, *420*, 162–165; (c) Polshettiwar, V.; Kaushik, M. P. *J. Sulfur Chem.* **2006**, *27*, 353–386.
- (a) Ziegler, E.; Kappe, T.; Steiger, W. Z. *Naturforsch.* **1965**, *20b*, 812–813; (b) Smalley, R. K.; Suschitzky, H.; Tanner, E. M. *Tetrahedron Lett.* **1966**, *7*, 3465–3469.
- Zhou, C.; Birney, D. M. *J. Org. Chem.* **2004**, *69*, 86–94.
- Reddy, C. K.; Reddy, P. S. N.; Ratnam, C. V. *Indian J. Chem.* **1987**, *26B*, 882–883.
- Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306–2309.
- (a) Kihara, N.; Nakawaki, Y.; Endo, T. *J. Org. Chem.* **1995**, *60*, 473–475; (b) Maggi, R.; Malmassari, C.; Oro, C.; Pela, R.; Sartori, G.; Soldi, L. *Synthesis* **2008**, 53–56; (c) Halimehjani, A. Z.; Ebrahimi, F.; Azizi, N.; Saidi, M. R. *J. Heterocycl. Chem.* **2009**, *46*, 347–350; (d) North, M.; Villuendas, P. *Synlett* **2010**, 623–627.