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# Direct Formation of Ring-Fused 1,3-Thiazine-2,4-dithiones from Aromatic *o*-Amino Carboxylic Acids: Observation of a Carbon Disulfide Mediated Thionation

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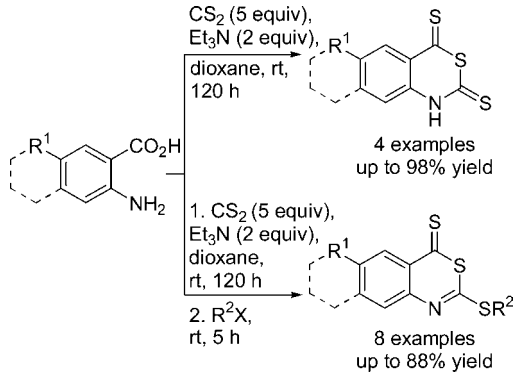
## ABSTRACT




**A facile synthesis of 2*H*-3,1-benzothiazine-2,4(1*H*)-dithiones (trithioisatoic anhydrides) or 2*H*-naphtho[2,3-*d*][1,3]thiazine-2,4(1*H*)-dithione solely from anthranilic acids or 3-amino-2-naphthoic acid and carbon disulfide, performed at room temperature in 1,4-dioxane in the presence of $Et_3N$, is reported. Corresponding 2-alkylsulfanyl derivatives were obtained in one-pot reactions under the same conditions after addition of alkyl halides. The mechanism of the thiazine cyclization was investigated using $^{13}C$-labeled carbon disulfide to reveal that carbon disulfide was incorporated into the heterocycle and additionally acted as a thionation reagent.**

Thionation, the conversion of a carbonyl to a thiocarbonyl group, is a commonly used procedure for the preparation of organosulfur compounds that are valued for their rich and varied chemistry, as well as many important biological activities.[1,2] Usually, thionation reactions are performed with phosphorus pentasulfide[1,3] or Lawesson's reagent.[4] Elemental sulfur has also been employed for this purpose,[1,5] and novel thionation protocols have been discovered to overcome

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(1) For reviews on thionation reactions, see: (a) Polshettiwar, V.; Kaushik, M. P. *J. Sulfur Chem.* **2006**, *27*, 353. (b) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297.

(2) Zang, Y.; Munday, R. *Mol. Cancer Ther.* **2008**, *7*, 3470.

(3) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461.

(4) For reviews on the use of Lawesson's reagent, see: (a) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929. (b) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210.

(5) For recent examples, see: (a) O-Yang, C.; Rotstein, D. M.; Labadie, S. S.; Walker, K. A. M. *Synlett* **1995**, 655. (b) Janosik, T.; Bergman, J.; Stansland, B.; Stålhandske, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 330. (c) Shibahara, F.; Sugiura, R.; Murai, T. *Org. Lett.* **2009**, *11*, 3064.

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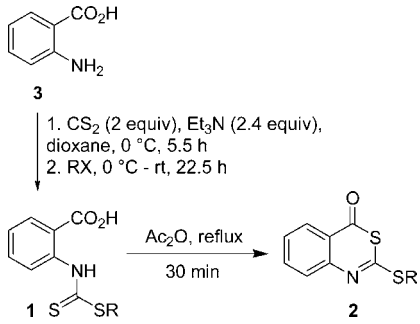
disadvantages of the common thionation reagents.[3,6] Herein, we report that carbon disulfide unexpectedly facilitates a carbonyl oxygen−sulfur exchange at room temperature. A convenient one-pot procedure to directly form trithioisatoic anhydride derivatives from commercially available aromatic *o*-amino carboxylic acids and carbon disulfide in moderate to excellent yields is presented. The mechanism of the 1,3-thiazine-2,4-dithione formation has been elucidated using $^{13}$C-labeled carbon disulfide.

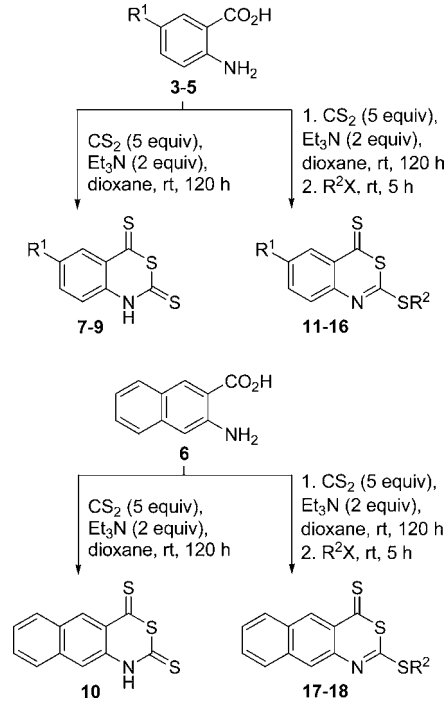
Anthranilic acid (**3**) can be transformed into alkylated dithiocarbamates **1** by the reaction with carbon disulfide and alkyl halides (Scheme 1). In a second, separate step, compounds **1** can undergo cyclocondensation in refluxing acetic anhydride to yield 2-alkylsulfanyl-4*H*-3,1-benzothiazin-4-ones **2** as colorless or yellow compounds.[7]

**Scheme 1.** Preparation of 2-Alkysulfanyl-4*H*-3,1-benzothiazin-4-ones[7b]




Surprisingly, when **3** is reacted with 5 equiv of carbon disulfide in the presence of triethylamine in dioxane at room temperature and iodomethane is added after an extended reaction time of 120 h, the corresponding yellow *S*-methyl dithiocarbamate **1** (R = Me) was not obtained. Instead, a bright red product was isolated with a $^{13}$C NMR resonance at 210 ppm, whereas in **1** (R = Me) the most downfield signal appears at 198 ppm.[7b] As a result of the prolonged reaction time, a spontaneous cyclocondensation of the corresponding dithiocarbamate followed by alkylation at the exocyclic sulfur was considered to form the 2-methylsulfanyl-4*H*-3,1-benzothiazin-4-one (**2**, R = Me). However, the most downfield signal of **2** (R = Me) would appear at 182 ppm,[7b] not at 210 ppm. This indicated an unexpected course of the reaction. The comparison of our product's melting point with literature values,[8a,b] its striking red color, and the NMR and MS data revealed that the 4-thioxo analogue of **2** (R = Me) bearing a sulfur in place of an oxygen at C-4 was formed, and the structure was assigned as 2-methylsulfanyl-4*H*-3,1-benzothiazine-4-thione (**11**, Table 1). The organosulfur compound **11** is a derivative of trithioisatoic anhydride. The parent compound **7**, exhibiting a benzo-condensed cyclic NH−C(=S)−S−C(=S) moiety, is shown in Table 1.[9,10]

**Table 1.** Synthesis of Ring-Fused Thiazine-4-thiones **7**−**18**




| compound | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|
| **7** | H | | 84 |
| **8** | Me | | 82 |
| **9** | Cl | | 98 |
| **10** | | | 24 |
| **11** | H | Me | 88 |
| **12** | H | Bn | 45 |
| **13** | Me | Me | 46 |
| **14** | Me | Bn | 58 |
| **15** | Cl | Me | 63 |
| **16** | Cl | Bn | 35 |
| **17** | | Me | 71 |
| **18** | | Bn | 72 |

Trithioisatoic anhydrides are usually obtained from isatoic anhydrides and phosphorus pentasulfide in high-boiling solvents (e.g., xylene, 1,2,4-trimethylbenzene) in moderate yields.[9−11] These attractive heterocycles possess a wide range

(6) For examples, see: (a) Srinivas Rao, S.; Chowdary, K. S.; Prashant, A.; Krishnan, V. S. H. *Synth. Commun.* **2001**, *31*, 3469. (b) Polshettiwar, V.; Nivsarkar, M.; Paradashani, D.; Kaushik, M. P. *J. Chem. Res.* **2004**, 474. (c) Krstić, N. M.; Bjelaković, M. S.; Dabović, M. M.; Pavlović., V. D. *Molecules* **2010**, *15*, 3462. (d) Pathak, U.; Pandey, L. K.; Tank, R. *J. Org. Chem.* **2008**, *73*, 2890. (e) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697. (f) Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625.

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(8) (a) Leistner, S.; Wagner, G.; Iffland, E. *Z. Chem.* **1972**, *12*, 289. (b) Takahashi, M.; Gunji, T.; Ichikawa, A. *J. Heterocycl. Chem.* **2002**, *39*, 1029. (c) Abdel-Megeed, M. F.; Saleh, M. A.; Aly, Y. L.; Abdo, I. M. *Nucleosides, Nucleotides* **1995**, *14*, 1985. (d) Wagner, G.; Rothe, L. *Pharmazie* **1971**, *26*, 271. (e) Leistner, S.; Wagner, G. *Z. Chem.* **1973**, *13*, 135. (f) Leistner, S.; Wagner, G. *Pharmazie* **1980**, *35*, 582. (g) Walter, W.; Fleck, T.; Voβ, J.; Gerwin, M. *Liebigs Ann. Chem.* **1975**, 275. (h) Leistner, S.; Hentschel, K.; Wagner, G. *Monatsh. Chem.* **1983**, *114*, 915.

(9) Wagner, G.; Rothe, L. *Z. Chem.* **1967**, *7*, 339.

(10) (a) Copolla, G. M. *Synthesis* **1980**, 505. (b) Kappe, T.; Stadlbauer, W. *Adv. Heterocycl. Chem.* **1981**, *28*, 127.

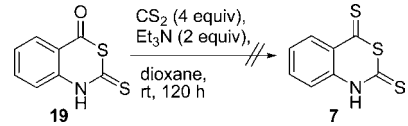
of preparative applications, e.g., to form *S*-glycosides,[8c] *o*-aminothiobenzamides,[8b,d,11] *o*-(thioureido)thiobenzoic acids,[8b] 2-amino-4-thioxo-4*H*-3,1-benzothiazines,[8e] and in the course of ring transformation reactions, imidazo[1,2-*c*]quinazolines,[8a] quinazoline-2,4-dithiones,[8d−g] and guanidino- and triazolo[1,5-*c*]quinazolines[8f] or thiadiazoles.[8h]

We decided to evaluate the applicability of the conditions leading to **11** for the synthesis of trithioisatoic anhydride (**7**) and further analogues by reacting aromatic *o*-amino carboxylic acids with carbon disulfide (Table 1). Indeed, the trithioisatoic anhydrides **7**−**9** and the naphtho[2,3-*d*][1,3]thiazine derivative **10** were readily obtained by this facile synthetic procedure. Additionally, one-pot, two-step reactions with alkyl halides conveniently afforded a series of *S*-alkylated derivatives **11**−**18** (Table 1). Noteworthy, the easy access to **7**−**18** does not require the preparation of intermediate isatoic anhydrides[10,12] and proceeds under mild conditions.[13]

The unexpected formation of trithioisatoic anhydrides solely from *o*-amino carboxylic acids and carbon disulfide raised the question whether carbon disulfide, besides its obvious role as a donor for the C(2)S−S unit, acts as a thionation agent to form the C(4)-S group. Only very few cases of a thionation promoted by carbon disulfide have been reported until today.[1] The reaction of *N*-methyl-2-pyrrolidinone and carbon disulfide at elevated temperatures (>200 °C) to *N*-methylpyrrolidine-2-thione[14a] was shown to proceed *via* a cycloaddition−elimination mechanism.[14b]

For a mechanistic investigation of the observed 1,3-thiazine-2,4-dithione formation, anthranilic acid (**3**) was used as a representative educt. A ring closure of the anthranilic acid derived dithiocarbamate to 1,2-dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one **19** (for structure, see Scheme 2) was assumed. As a possible intermediate, **19** could then react at the C-4 carbonyl function with carbon disulfide in a cycloaddition−elimination mechanism *via* a 1,3-oxathietane[15] to produce **7**.[16] Corresponding Wittig-type 1,3,2-oxathiaphosphetane intermediates have been considered for the thionation of esters, thioesters, and carboxamides with Lawesson's reagent.[4] Moreover, a carbon disulfide addition to the phosphorus−nitrogen double bond of 1,2-azaphospholes has been reported.[17] Hence, **19** was prepared[18] and subjected to the reaction with carbon disulfide (Scheme 2)

**Scheme 2.** Reaction of 1,2-Dihydro-2-thioxo-4*H*-3,1-benzothiazin-4-one (**19**) with Carbon Disulfide

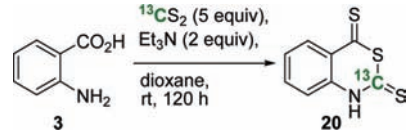



to test it as a possible intermediate in the conversion of **3** to **7**. However, as only unthionated educt was isolated, this route to introduce the thiocarbonyl sulfur at C-4 was excluded.

2-(Trifluoromethyl)aniline, when reacted with sodium sulfide, gave the corresponding dithiocarboxylic acid, which in turn produced trithioisatoic anhydride (**7**) upon reaction with carbon disulfide.[19] Thus, we next supposed a dithiocarboxylic acid intermediate in the course of the transformation of anthranilic acid (**3**) to **7**. A thionation of the carboxylic acid to the dithiocarboxylic acid function was hereby assumed *prior* to cyclization to **7** and the simultaneous release of hydrogen sulfide. Benzoic acid was reacted under the same conditions as before anthranilic acid ($CS_2$ (5 equiv), $Et_3N$ (2 equiv), 1,4-dioxane, 120 h, rt). Instead of dithiobenzoic acid (or thiobenzoic acid), again only unreacted educt was recovered, indicating that this mechanism did not occur.

It is known that a dithiocarboxylic acid moiety may originate from carbon disulfide, for example, in reactions with cyclic enamines,[20a] ketones,[20b] or *m*-phenylendiamine.[20c] Thus, the reaction of carbon disulfide with the amino group of **3**, accompanied by decarboxylation and immediate electrophilic substitution with carbon disulfide,[21] followed by thiazine cyclization to trithioisatoic anhydride (**7**) was considered. This hypothesis prompted us to react anthranilic acid (**3**) with $^{13}C$-labeled carbon disulfide (Scheme 3). If the decarboxylation mechanism was correct, both thiocarbonyl carbons of **7**

**Scheme 3.** Reaction of Anthranilic Acid (**3**) with $^{13}C$-Labeled Carbon Disulfide

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(12) Gütschow, M. *J. Org. Chem.* **1999**, *64*, 5109.

(13) A similar conversion of **3** ($CS_2$, KOH, MeOH, 65 °C, 4 h) to trithioisatoic anhydride (**7**) has been reported; see: Abdel-Megeed, M. F.; Aly, Y. L.; Saleh, M. A.; Abdo, I. M.; El-Hiti, G. A.; Smith, K. *Sulfur Lett.* **1995**, *19*, 129. However, the compound characterization by NMR clearly indicates that not the postulated, three-sulfur-containing compound but the 4-*oxo* analogue **19** was obtained; see ref 18.

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(15) For the formation of 1,3-oxathiethanes by intramolecular cycloaddition, see: (a) Ishii, A.; Ding, M.-X.; Nakayama, J.; Hoshino, M. *J. Chem. Soc., Chem. Commun.* **1992**, 7. (b) Ishii, A.; Akazawa, T.; Maruta, T.; Nakayama, J.; Hoshino, M.; Shiro, M. *Angew. Chem.* **1994**, *106*, 829. (c) Ishii, A.; Akazawa, T.; Ding, M.-X.; Honjo, T.; Maruta, T.; Nakamura, S.; Nagaya, H.; Ogura, M.; Teramoto, K.; Shiro, M.; Hoshino, M.; Nakayama, J. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 509.

(16) For an *ab initio* study of the [2 + 2] cycloaddition of X=C=Y molecules, see: Rode, J. E.; Dobrowolski, J. C. *J. Phys. Chem. A* **2006**, *110*, 207.

(17) von Criegern, T.; Polborn, K.; Schmidpeter, A. *Heteroat. Chem.* **1999**, *10*, 167.

(18) Ottersbach, P. A.; Häcker, H.-G.; Elsinghorst, P. W.; Schnakenburg, G.; Gütschow, M. *Tetrahedron Lett.* **2010**, *51*, 2727.

(19) Jourdan, G. P.; Dreikorn, B. A. *J. Org. Chem.* **1982**, *47*, 5255.

(20) For examples to generate a dithiocarboxylic acid moiety with carbon disulfide, see: (a) Gompper, R.; Wetzel, B.; Elser, W. *Tetrahedron Lett.* **1968**, *9*, 5519. (b) Bordás, B.; Sohár, P.; Matolcsy, G.; Berenesci, P. *J. Org. Chem.* **1972**, *37*, 1727. (c) Yu, Y.; Zhong, H.-P.; Yang, K.-B.; Huang, R.-B.; Zheng, L.-S. *Acta Crystallogr.* **2005**, *E61*, o387.

at position 2 and 4 would be donated by carbon disulfide and would be $^{13}$C-labeled. However, the $^{13}$C NMR spectrum of the $^{13}$C-labeled trithioisatoic anhydride (**20**) showed one strong signal at 187 ppm (Figure 1, NMR assignment of the carbons is supported by HMQC and HMBC spectra; see Supporting Information). This clearly proves that only the C-2 thiocarbonyl carbon originated from carbon disulfide, while C-4 derived from the carbon of the carboxylic acid function of **3**.

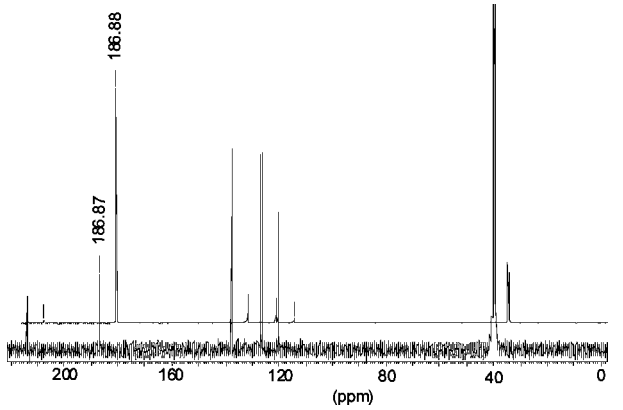
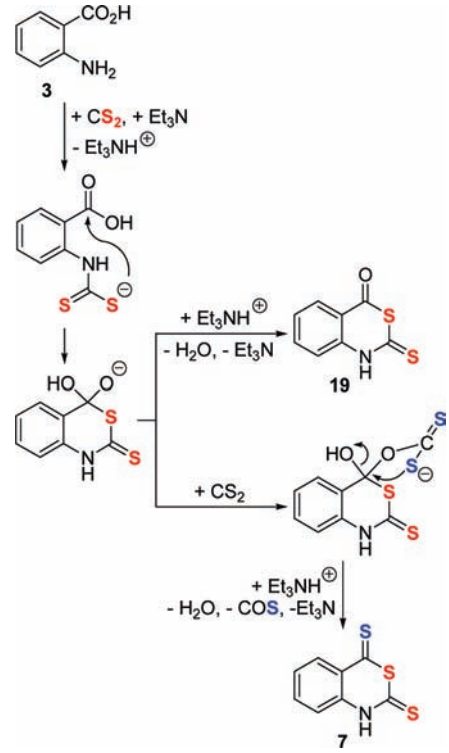



**Figure 1.** $^{13}$C NMR Spectra of trithioisatoic anhydride (**7**) (bottom) and the $^{13}$C-labeled analogue **20** (top).

These results led us to the conclusion that yet another mechanism for the formation of trithioisatoic anhydride (**7**) from anthranilic acid (**3**) should be proposed as follows (Scheme 4). After formation of the dithiocarbamate and subsequent cyclization, a geminal diol is trapped by the electrophilic attack of carbon disulfide. The intermediate dithiocarbonate sulfur attacks C-4, and finally, the three-sulfur-containing compound **7** is formed along with the release of water and carbonyl sulfide. The formation of the latter product was, however, not verified. The fact that the oxo compound **19** could be identified in traces by NMR and LC/MS analysis of the crude product corroborates the mechanism, in that the formation of **19** and **7** represents competing branches in the reaction course. Compound **19** might either result from the dehydratization of the diol intermediate (Scheme 4) or from the loss of unstable[22] hydrogen dithiocarbonate after attack of carbon disulfide. When the reaction of **3** was performed with only 1 equiv of $CS_2$ (with $Et_3N$ (2 equiv) in 1,4-dioxane, 120 h, rt), the amount of **19** was not enhanced and a mixture was formed containing **7** and further products besides unreacted educt **3**.

**Scheme 4.** Proposed Mechanism for the Formation of Trithioisatoic Anhydride (**7**) from Anthranilic Acid (**3**)




In conclusion, we present a one-pot procedure to produce trithioisatoic anhydride derivatives with easy workup in moderate to excellent yields. The method is superior to the common one using isatoic anhydrides and phosphorus pentasulfide. The mechanism underlying the formation of ring-fused 1,3-thiazine-2,4-dithiones was investigated using $^{13}$C-labeled carbon disulfide to reveal that carbon disulfide indeed acted as a thionation reagent, which has been rarely observed before.

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**Supporting Information Available:** Experimental procedures, analytical data, $^1$H NMR and $^{13}$C NMR spectra of compounds **7**−**18** and **20**, HMQC spectra of **7** and **11**, and HMBC spectrum of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For decarboxylation and trapping with carbon disulfide to generate a dithiocarboxylate from pyridinium-2-carboxylates or 1,2-dimethylimidazolium-2-carboxylate *via* an *N*-heterocyclic carbene, respectively, see: (a) Katritzky, A. R.; Cozens, A. J.; Ossana, A.; Rubio, O.; Dabbas, N. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2167. (b) Schmidt, A.; Beutler, A.; Albrecht, M.; Snovydovych, B.; Ramírez, F. J. *Org. Biomol. Chem.* **2008**, *6*, 287.

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