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A novel synthesis and transformations of isothiochroman 2,2-dioxide

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ABSTRACT

A convenient synthesis of isothiochromen-4-one 2,2-dioxide was carried out via cyclisation of *o*-cyanobenzyl thioacetate by a Thorpe reaction. The reactions of isothiochromen-4-one 2,2-dioxide with nitrogen-containing nucleophilic reagents have been investigated.

Sulfones are an important class of compounds that have attracted considerable attention.[1] Isothiochromen-4-one 2,2-dioxide is an interesting compound, the chemistry of which has proved useful because thiochromanones and isothiochromanones are reported as valuable biological agents[2–9] and are useful precursors in the synthesis of steroid heterocycles.[10–12] Only a few isothiochromanones and their dioxides are described in the literature[2,3,5,7,9–14] which were prepared by cyclocondensation of arylmethylthioacetic acids,[2,5,7,13–16] by oxidative cleavage of oximes[17] or by cyclisation of 1-*o*-alkylphenylpropane-1,2-diones.[18,19] All previously known methods for obtaining the isothiochromen-4-one 2,2-dioxide system have several disadvantages including multi-step processes and low yields of target product (up to 60%).

There is no generally accepted method for obtaining isothiochromen-4-one. Earlier, the isothiochromanone system was prepared via Friedel–Crafts cyclisation of benzylthioacetic acid or its chloride,[14] however, the authors were unable to obtain any isothiochromen-4-one by way of this method, using a wide range of catalysts and experimental conditions.

In this Letter, we introduce a novel method for the synthesis of isothiochromen-4-one 2,2-dioxide in high yield. Also, we consider some of the chemical properties of this compound.

The novel synthesis of isothiochromen-4-one 2,2-dioxide is depicted in Scheme 1. Initially, 2-(chloromethyl)benzonitrile was reacted with alkyl mercaptoacetate in the presence of K_2CO_3 in CH_3CN at reflux to afford quantitative yields of **1a,b**. Oxidation of the sulfur under standard conditions (33% H_2O_2, AcOH, ice-bath) resulted in the corresponding sulfone **2a,b**. Cyclisation of the sulfone **2** into isothiochromen-4-one 2,2-dioxide (**3**) in 93% yield via a Thorpe reaction was effected with NaOR[1] (R[1]:Et, *i*-Pr) in a polar solvent (absolute EtOH, *i*-PrOH) at reflux (10 h) with. The structure of isothiochromen-4-one 2,2-dioxide (**3**) was proved by X-ray diffraction (Fig. 1).

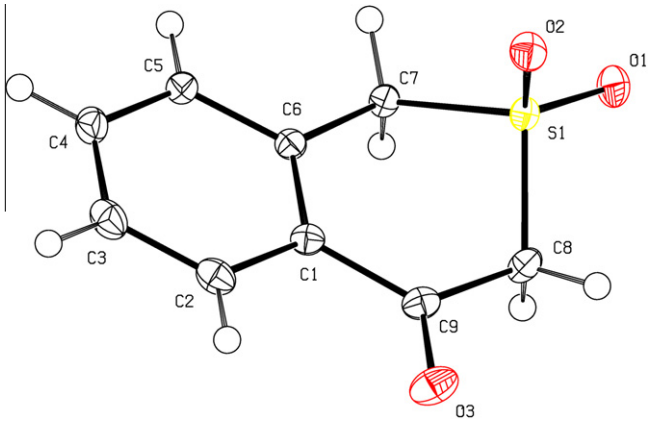

Figure 1. Molecular structure of isothiochromen-4-one 2,2-dioxide according to X-ray diffraction data (ORTEP).

We found that enamine **4** was obtained in the presence of NaOR[1] (R[1]:Et, *i*-Pr) in a polar solvent (absolute EtOH, *i*-PrOH) on

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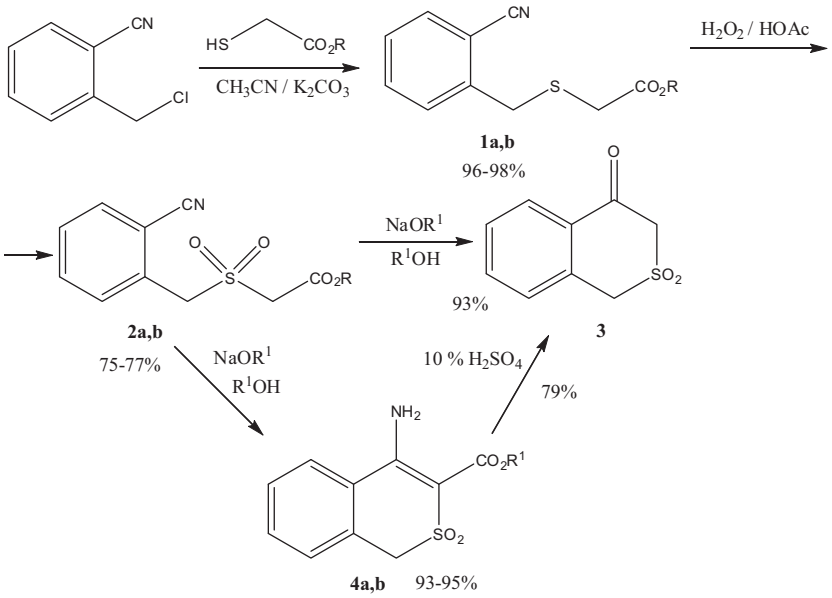


1,**2**: **a** R=Me; **b** R=Et; **4**: **a** R^1=Et; **b** R^1=*i*-Pr

Scheme 1. Synthesis of isothiochromen-4-one 2,2-dioxide (**3**).

short reflux (3 h).[20] Enamine **4** gave the desired product **3** in 79% yield on boiling in 10% H_2SO_4. The structure of enamine **4a** was proved by X-ray diffraction (Fig. 2).

Therefore the direct synthesis of **3** is more preferable. Isothiochromen-4-one 2,2-dioxide **3** and enamines **4a,b** are colorless crystalline substances.

In contrast to the synthesis of isothiochromen-4-one 2,2-dioxide (**3**), its transformations are scarcely reported in the literature.[2,7,16]

We used enamine **4** to prepare isothiochromen-4-amine 2,2-dioxide (**5**). Compound **5** was formed by vigorous stirring of enamine **4** in 20% sodium hydroxide solution as a consequence of decarboxylation (Scheme 2). The structure of compound **5** was proved by X-ray diffraction (Fig. 3).

John et al.[7] prepared 3,4-dihydroisothiochromen-4-amine 2,2-dioxide which is an analogue of compound **5**. The keto group was converted into an amino group directly via reductive amination, or indirectly through the generation of an oxime, which was then reduced to form the amine. Transition metal catalysis and hydrogen or another reducing agent, such as $NaBH_4$, $LiAlH_4$ or $NaCNBH_3$, can be used to effect the reduction.

Earlier,[21–24] it was demonstrated that thiapyran-3-one 1,1-dioxide underwent reactions with nitrogen-containing nucleophilic reagents. Taking into account the similarity in structure of this compound and isothiochromen-4-one 2,2-dioxide (**3**) it is possible to suppose that similar reactions may occur with compound **3**. Isothiochromen-4-one 2,2-dioxide (**3**) was found to react with compounds containing an amino group in a polar solvent (MeOH, *i*-PrOH) at reflux giving colorless oxime **6a**, hydrazone **6b** and NPh-hydrazone **6c**, respectively (Scheme 3). The structure of oxime **6a** was proved by an X-ray diffraction study (Fig. 4).

Boiling a solution of isothiochromen-4-one 2,2-dioxide (**3**) with excess pyrrolidine in toluene resulted in yellow crystals of 1-(2,2-dioxide-3,4-dihydroisothiochromen-4-yl)pyrrolidine (**7**) (Scheme 4) as was established by an X-ray diffraction study (Fig. 5).

As expected, the reactivity of isothiochromen-4-one 2,2-dioxide (**3**) with nitrogen-containing nucleophilic reagents was similar to that of thiapyran-3-one 1,1-dioxide.

The structures of all the compounds were proved by IR and NMR spectroscopy (^{1}H and ^{13}C), mass spectrometry and elemental analysis. (see Supplementary data). According to X-ray diffraction

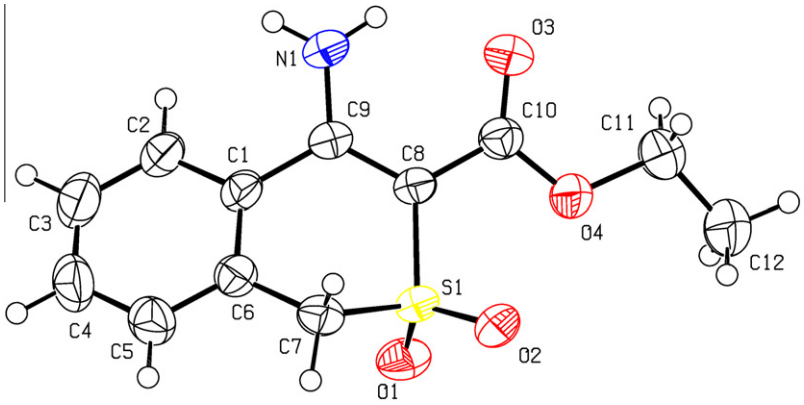
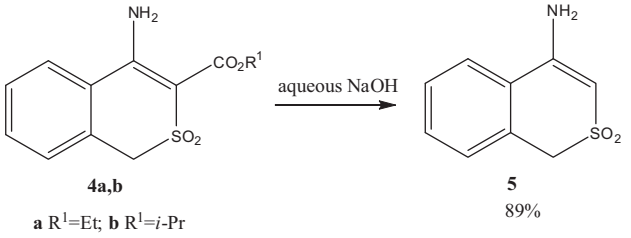


Figure 2. Molecular structure of **4a** according to X-ray diffraction data (ORTEP).



Scheme 2. Synthesis of isothiochromen-4-amine 2,2-dioxide (**5**).

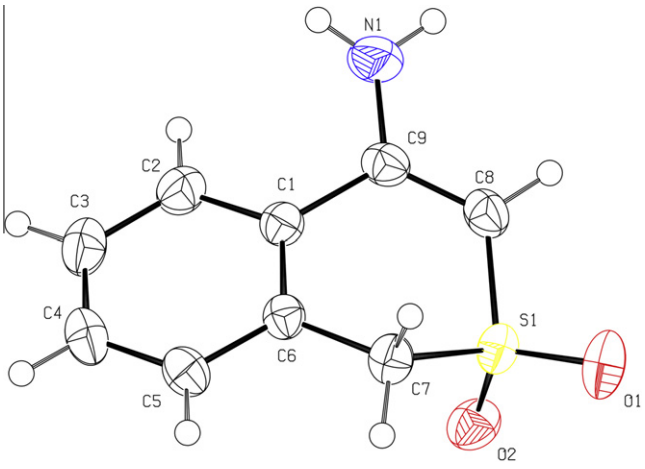
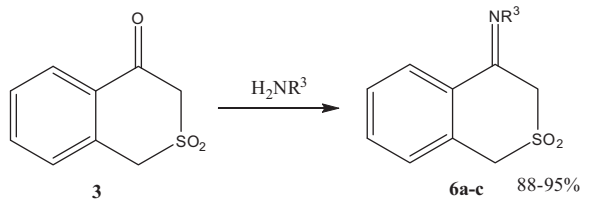


Figure 3. Molecular structure of compound **5** according to X-ray diffraction data (ORTEP).



Scheme 3. Synthesis of novel compounds **6a–c**.

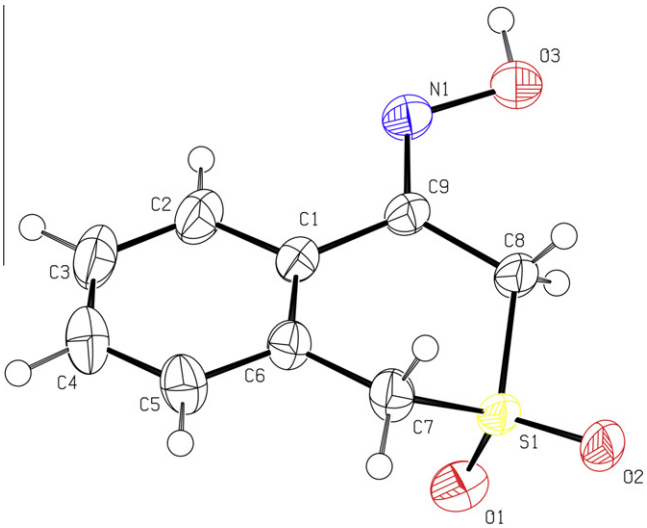
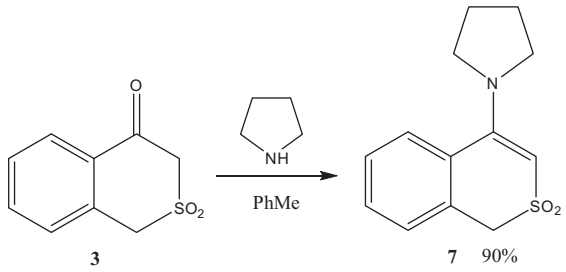


Figure 4. Molecular structure of **6a** according to X-ray diffraction data (ORTEP).



Scheme 4. Synthesis of 1-(2,2-dioxide-3,4-dihydroisothiochromen-4-yl)pyrrolidine (**7**).

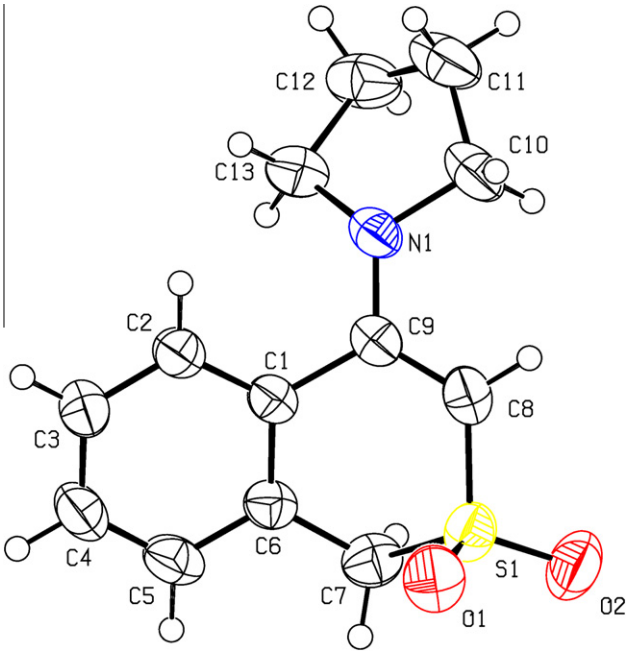


Figure 5. Molecular structure of **7** according to X-ray diffraction data (ORTEP).

data, the six-membered ring in molecules **4a**, **5** and **7** adopts a twist-boat conformation with the value of the C6-C7-S1-C8 torsion angle being within 52.0–54.3°. The presence of both strong electron-donating (amino group) and electron-withdrawing (COOEt) groups at the endocyclic double bond in molecule **4a** results in considerable elongation of the C8–C9 bond [1.388(3) Å] and shortening of the C9–N1 bond [1.324(2) Å] as compared to structures **5** and **7** where these bond lengths are 1.355(2) Å, 1.367(4) Å and 1.359(2) Å, 1.365(3) Å, respectively. In contrast, the conformation of the six-membered ring in molecules **3** and **6a** is considerably different. The sulfone ring in **3** adopts a sofa conformation with deviation of the S1 atom from the mean plane of the remaining atoms of the ring by 0.88 Å. In the case of **6a**, the sulfone ring has a twist-boat conformation [the value of the C6-C7-S1-C8 torsion angle is 57.9(1)°].

In summary, we have identified a novel and simple method for the synthesis of isothiochromen-4-one 2,2-dioxide **3** in high yield (93%) from easily accessible reagents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.163. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Simpkins, N. S. In *Sulfones in Organic Synthesis*; Magnus, P., Baldwin, J. E., Eds.; Pergamon Press: Oxford, 1993; p 381.
2. Peixoto, Ch.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Tetrahedron Lett.* **2000**, *41*, 1741–1745.
3. Pfizer Corporation, Patent Specification, USA, 1259415, **1972**; *Chem. Abstr.* **1972**, *76*, 92907.
4. Toshima, K.; Ohta, K.; Ohtasuka, A.; Matsumura, Sh.; Nakata, M. *J. Chem. Soc. Chem. Commun.* **1993**, 1406–1407.
5. Sohda, T., Tsuda, M., Yamazaki, I., US Pat. 5071841, 1991; Chem. Abstr. 1991, 114, 23804.
6. Ohta T., Komoriya S., Yoshino T., Uoto K., Nokomoto Y., Naito H., Mochizuki A., Nagata T., Kanno H., Haginoya N., Yoshikawa K., Nagamochi M., Kobayashi S., Ono M., EP 1405852, **2004**; *Chem. Abstr*. **2004**, *138*, 73271.
7. John V., Maillard M., Fang L., Tucker J., Brogley L., Aquino J., Bowers J., Probst G., Tung J., Patent WO 2005/087714, **2005**; *Chem. Abstr*. **2005**, *143*, 326226.
8. Zhu, Q.; Fang, L.; Zhang, G. *Zhongguo Yaowu Huaxue Zazhi* **2000**, *10*, 1–4.
9. Dey, D., Neogi, P, Sen, A., Sharma, S. D., Nag, B., Patent WO 02/30888, 2002; Chem. Abstr. 2002, 136, 309858.
10. Krishna, M. V.; Ramadas, S. R. *Heterocycles* **1981**, *16*, 405–409.
11. Ramadas, S. R.; Chenchaiah, C. *Steroids* **1981**, *37*, 353–359.
12. Terasawa, T.; Okada, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 990–1003.
13. Reddy, N. S.; Reddy, E. P.; Reddy, M. V. R. *Synth. Commun.* **2004**, *34*, 2691–2695.
14. Pulman, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 410–418.
15. Bose, D. S.; Srinivas, P. *Synlett* **1998**, 977–978.
16. Still, I. W. J.; Wilson, D. K. T. *Can. J. Chem.* **1992**, *70*, 964–973.
17. Hill, R. K.; Cullison, D. A. *J. Am. Chem. Soc.* **1973**, *95*, 2923–2927.
18. Hamer, N. K. *J. Chem. Soc., Chem. Commun.* **1975**, *8*, 557–558.
19. Hamer, N. K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 508–511.
20. Smith, M. B.; March, J. *March's advanced organic chemistry*, fifth ed.; John Wiley & Sons: New York, 2001. p. 2083.
21. Fatutta, S.; Pitacco, G.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2735–2738.
22. Fatutta, S.; Pitacco, G.; Valentin, E. *J. Heterocycl. Chem.* **1989**, *26*, 183–187.
23. Fatutta, S.; Pitacco, G.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2111–2115.
24. Fatutta, S.; Pitacco, G.; Russo, C.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2045–2050.