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An Expedient Route to Dihydrothiazines, a Virtually Unknown Class of Heterocycles

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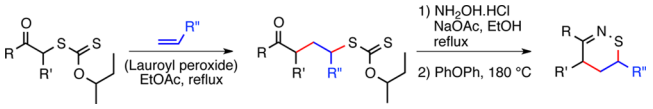
ABSTRACT

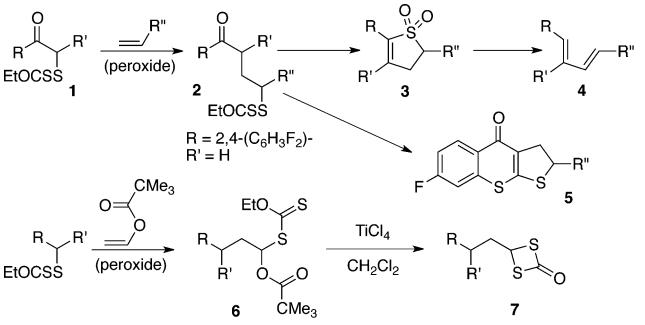


Upon heating at 180−200 °C in diphenyl ether, *S*-(4-oximinoalkyl)xanthates with a secondary isopropyl or isobutyl group on the oxygen undergo a Chugaev elimination followed by ring closure onto the oxime to give dihydrothiazines, a virtually unknown class of heterocycles.

Heterocycles and heteroaromatics constitute the backbone of the majority of medicinally useful compounds.[1] The search for practical synthetic routes to new or rare heterocyclic structures hence remains a worthwhile endeavor. From this perspective, radical reactions remain grossly underutilized despite their immense potential for creating new structures. While we have, over the years, exploited the unique power of the degenerative radical addition−transfer of xanthates[2] for the creation of new carbon−carbon bonds to construct or to modify heterocyclic and heteroaromatic derivatives,[3] we have only seldom taken advantage of the presence of the xanthate group in the adducts to access sulfur containing heterocycles. Indeed, the degenerative xanthate addition allows the bringing together of various functional groups, which can then be made to react not only just with each other but also with the xanthate under suitable conditions. Our main contributions in the latter respect are summarized in Scheme 1.

We have, in particular, established a practical access to dihydrothiophene *S*,*S*-dioxides **3**, which are convenient

Scheme 1



precursors to dienes **4**.[4] In the case where the radical adduct is derived from a 2-fluoroarylketone, heating with potassium carbonate provides an unusually short route to 2,3-dihydrothieno[2,3-*b*]thiopyran-4-ones **5**, a rare class of sulfur heterocycles.[5] We also accidentally discovered an expedient synthesis of dithietanones **7** by the action of $TiCl_4$ on adducts **6** derived from vinyl pivalate.[6] Dithietanones also represent a rare family of sulfur compounds, and preliminary work indicates them to be useful

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(3) For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

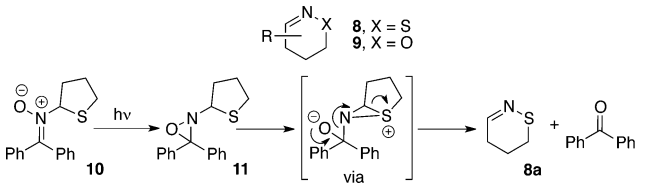
(4) Lusinchi, M.; Stanbury, T.; Zard, S. Z. *Chem. Commun.* **2002**, 1532.

(5) (a) Boutillier, P.; Quiclet-Sire, B.; Zafar, S. N.; Zard, S. Z. *Tetrahedron: Asymmetry* **2010**, *21*, 1649. (b) Boivin, J.; Boutillier, P.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2529.

(6) Quiclet-Sire, B.; Sanchez-Jimenez, G.; Zard, S. Z. *Chem. Commun.* **2003**, 1408.

10.1021/ol402973q

Scheme 2

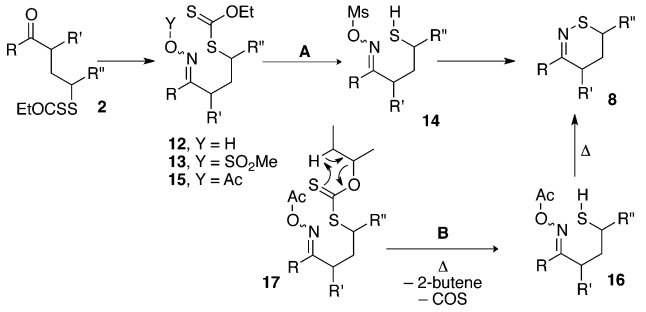


precursors of thioaldehydes. In continuation of our work on xanthates, we have now discovered an expedient route to the virtually unknown dihydrothiazines **8** (Scheme 2).

In contrast to dihydrooxazines **9**, their oxygen analogs, which are well-known and popular among medicinal chemists,[7] dihydrothiazines are extremely rare heterocyclic compounds. Indeed, only the parent compound **8a** has been reported.[8,9] This substance was discovered serendipitously when nitrone **10** was irradiated with UV light (Scheme 2), which caused its isomerization into oxaziridine **11**.[8] This compound is unstable and spontaneously collapses into dihydrothiazine **8a** and benzophenone. Despite its mechanistic elegance, this approach cannot be easily generalized because of the major difficulties associated with the synthesis of substituted nitrone precursors.

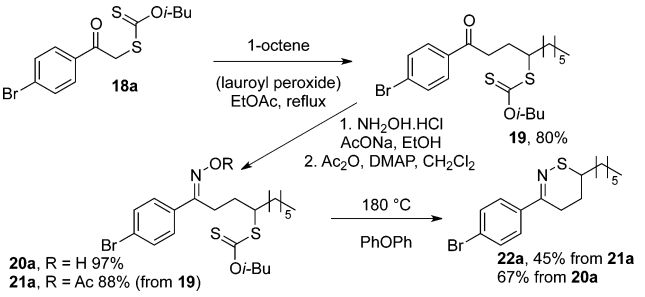
Our initial synthetic plan, outlined in Scheme 3 (route **A**), relied on the ready accessibility of adducts **2**, which appeared to be logical precursors to dihydrothiazines **8** via the corresponding activated oxime derivatives. However, our attempts at implementing what looked like a trivial sequence were frustrated by competition from a Beckmann rearrangement upon conversion of oximes **12** into the corresponding mesylate **13**. We could not therefore reach the desired intermediate thiol **14**, which we hoped would evolve spontaneously into dihydrothiazines **8** under the mildly basic conditions used to cleave the xanthate group. Introduction of a poorer ester type leaving group on the oxime, such as an acetate (e.g., **15**), would alleviate complications from the Beckmann rearrangement but would raise the problem of how to accomplish selective cleavage of the xanthate to form the required thiol acetate **16**.

Scheme 3



A solution to this difficulty presented itself in the guise of the Chugaev elimination (Scheme 3, route **B**). This classical reaction is seldom applied in synthesis, but then usually as a method for generating alkenes from alcohols by thermolysis of the corresponding *S*-methyl xanthates. Xanthates derived from tertiary alcohols decompose under very mild conditions, often at, and sometimes even below, room temperature. Indeed, it is usually difficult to handle xanthates prepared from tertiary alcohols. Xanthates derived from secondary alcohols start decomposing at temperatures around 150 °C whereas those made from primary alcohols require drastic temperatures in excess of 200 °C and are not normally useful precursors of alkenes. The methanethiol coproduced in the process is discarded or destroyed because of its stench.

Scheme 4



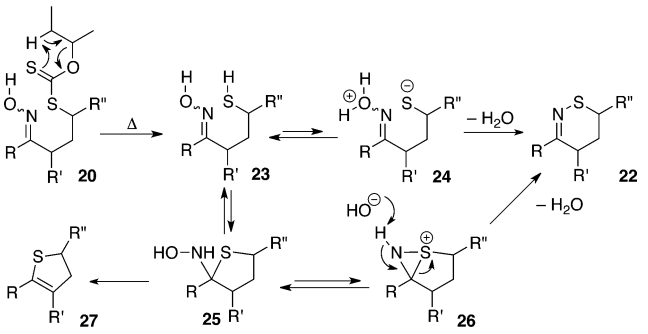
In our case, *the thiol is the valuable product*, and by starting with a xanthate derived from a simple secondary alcohol such as **17**, thermolysis would lead to the formation of a volatile alkene and leave behind the desired thiol **16**. To test this approach, compound **21a** was prepared by addition of xanthate **18a** to 1-octene and the ketone group in the resulting adduct **19a** was converted into its oxime acetate **21a** using standard reactions (Scheme 4). We were pleasantly surprised to find that heating a solution of **21a** in diphenyl ether at 180 °C for 120 min resulted in a reasonably clean reaction to give directly dihydrothiazine **22a** in 45% yield. Even more interesting, a blank experiment on free oxime **20a** also furnished dihydrothiazine **22a** in a slightly higher yield (67%). It is clearly not necessary to go through the acetate, and this results in a very significant simplification of the synthesis.

(7) For a recent review on six-membered ring cyclic oxime ethers, see: Sukhorukov, A. Y.; Ioffe, S. L. *Chem. Rev.* **2011**, *111*, 5004.

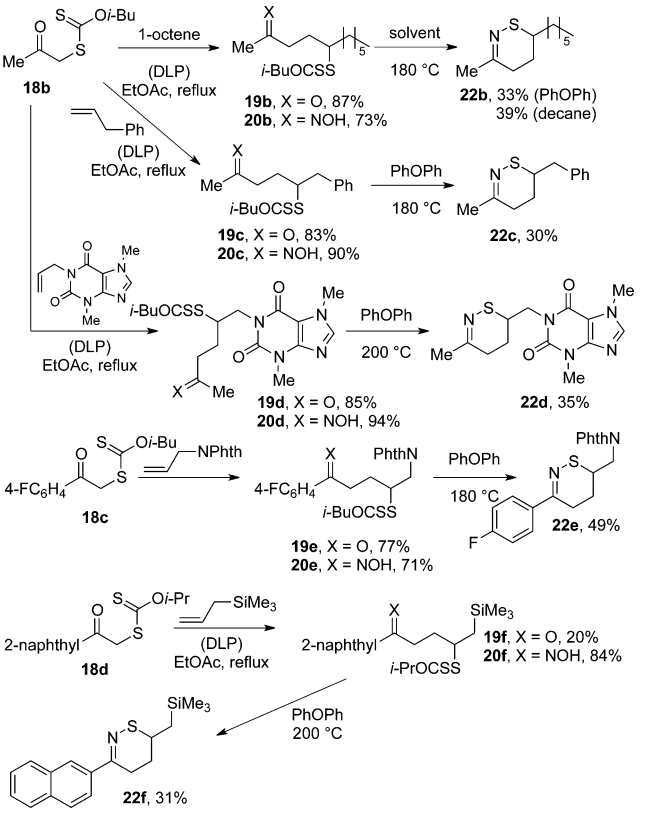
(8) (a) Leyshon, W. M.; Wilson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1925. (b) Leyshon, W. M.; Wilson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1929.

(9) Benzothiazines are more robust substances and are better documented: (a) Grant, R. D.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc., Chem. Commun.* **1982**, 884. (b) Gairns, R. S.; Grant, R. D.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 491. (c) Jones, S.; Kennewell, P. D.; Westwood, R.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1990**, 498. (d) Shimazu, H.; Ikedo, K.; Hamada, K.; Ozawa, M.; Matsumoto, H.; Kamata, K.; Nakamura, H.; Ji, M.; Kataoka, T.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1733. (e) King, J. F.; Yuyitung, G.; Gill, M. S.; Stewart, J. C.; Payne, N. C. *Can. J. Chem.* **1998**, *76*, 164. (f) Piatek, A.; Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **2002**, *85*, 1973.

Scheme 5



Scheme 6



A plausible mechanism for this transformation is depicted in Scheme 5. Chugaev fragmentation of xanthate **20** leads to thiol **23**, which can then proceed to dihydrothiazine **22** by ring closure of protonated oxime intermediate **24**. Alternatively, *reversible* cyclization onto to the carbon of the oxime first takes place to give hydroxylamine **25** followed by formation of bicyclic intermediate **26**, which should rapidly collapse into the same dihydrothiazine **22**. These two mechanistic variants are not mutually exclusive and could operate simultaneously under the reaction conditions. We did not observe a clear dependence on the initial geometry of the oxime, suggesting at least an equilibration between the *E* and *Z* isomers. Furthermore, we found that the main side product in these reactions is dihydrothiophene **27** and/or the isomeric exoalkylidene tetrahydrothiophene, with the double bond outside the ring (not shown). Such compounds could be observed in the NMR of the crude reaction mixtures once the diphenyl ether solvent was removed and, in a few cases, could even be isolated (see for example compound **27i** in Scheme 8).

With an expedient route to this family of heterocycles in hand, we explored its scope. Despite the somewhat drastic conditions, many functional groups are tolerated as indicated by the examples displayed in Schemes 6–9 (in all these schemes, DLP is lauroyl peroxide). The yields are generally moderate, partly because of the competitive formation of dihydrothiophenes in 10–35% yield and because of the relative fragility of the dihydrothiazines to chromatographic purification. In some instances, deactivation of the silica with triethylamine proved beneficial.

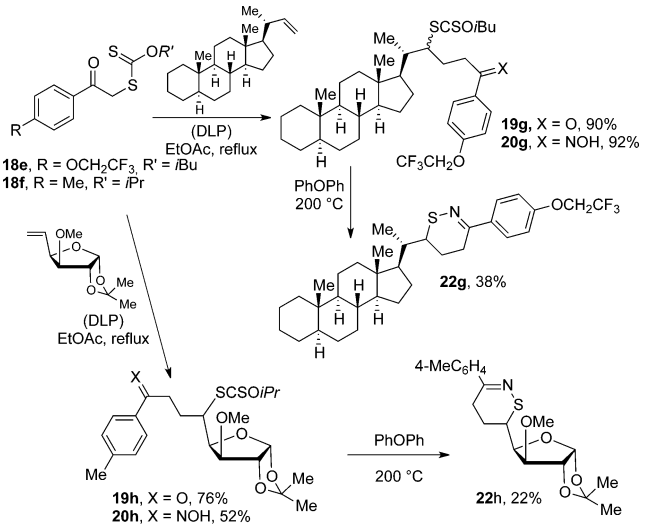
In our initial experiments, *O*-isobutyl xanthates such as **18a–c** were used, as they were available from another study (Scheme 6); however, we soon switched to *O*-isopropyl xanthates (e.g., **18d**), since these could be thermolyzed at similar temperatures, do not introduce a cumbersome extra chiral center, and exhibit simpler NMR spectra. The reaction leading to dihydrothiazines could also be accomplished starting with aliphatic ketones (e.g., **18b**), and even adducts prepared from relatively complex alkenes such as 2-allyl-3,7-dimethyl xanthine underwent the expected transformation (example **22d** in Scheme 6).

Two further examples using relatively complex alkenes are displayed in Scheme 7. The first, **22g**, results from addition to a steroid alkene, whereas the second, **22h**, arises from a glucose derived alkene. Both of these dihydrothiazines, and especially the latter, would be exceedingly difficult to access by more conventional routes. In the case of ketone **19h**, a precursor of **22h**, the radical addition gave two separable epimers and only the major epimer was processed further. It is nevertheless remarkable that the carbohydrate derivative reasonably withstood the thermally harsh experimental conditions. This is due to the fact that the heating is done under strictly neutral conditions. Most of the material loss is caused by the unwanted formation of the dihydrothiophene side product and partial destruction of the dihydrothiazine on silica during purification rather than through decomposition during thermolysis.

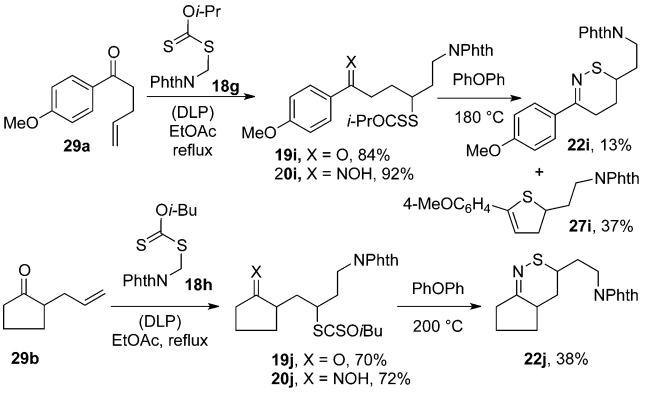
One feature of this approach is the fact that the ketone can be present on the alkene partner and not necessarily on the xanthate, as illustrated by the two examples depicted in Scheme 8. Starting from 1-(*p*-methoxyphenyl)-buten-4-ene **29a** leads to dihydrothiazine **22i** in a rather disappointingly low yield, with the major side product being dihydrothiophene **27i**, isolated in this case in 37% yield. A better outcome was observed with 2-allyl-cyclopentanone **29b**, which furnished the corresponding dihydrothiazine **22j** in 38% yield. The reason underlying the difference in efficiency between the two reactions is not clear at the moment.

The possibility of having the ketone in either the xanthate or the alkene partner reflects the high degree of flexibility of this approach. This versatility is further increased by the important observation that the radical

Scheme 7

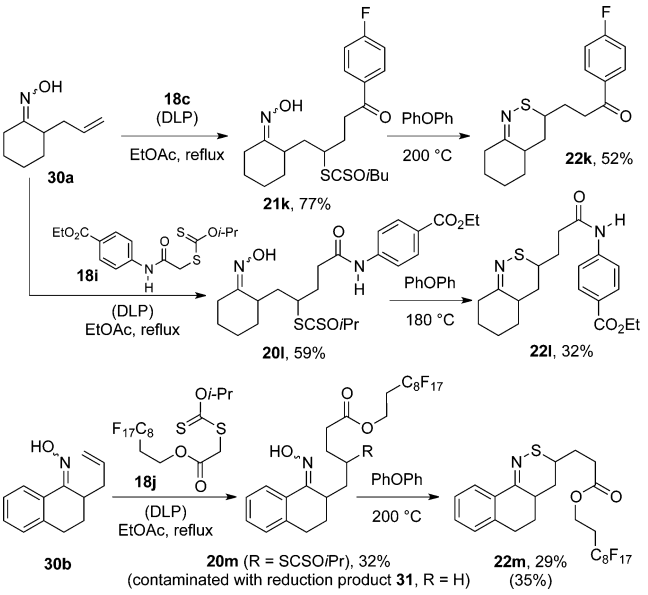


Scheme 8



addition of the xanthate *can be accomplished on the preformed oxime*. This avoids problems of regioselectivity in the formation of the oxime intermediate when both the alkene and xanthate partners bear a ketone group. Thus xanthyl ketone **18c** could be added efficiently to the oxime of 2-allylcyclohexanone **30a** to give adduct **21k**, which furnished dihydrothiazine **22k** in 52% yield (Scheme 9). Two other examples of additions to allyl substituted oximes **30a** and **30b** leading ultimately to dihydrothiazines

Scheme 9



22l and **22m** respectively are pictured in the same scheme. In the case of the latter, the intermediate adduct **20m** was contaminated with a small amount of the inseparable reduced material **31**, so that the corrected yield (35%) of dihydrothiazine **22m** is slightly higher.

These preliminary results demonstrate the viability of our approach to this virtually unknown class of heterocyclic compounds. While the yields are mostly modest and much optimization work remains to be done, this route nevertheless offers tremendous versatility. It is convergent, is concise, and tolerates a broad range of functional groups. The chemical reactivity of dihydrothiazines and their potential in medicinal chemistry can now be more conveniently and systematically studied.

Acknowledgment. We dedicate this paper with respect to the memory of Professor Serge David (Université Paris XI, Orsay).

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.