The xanthate radical addition route to sulfur heterocycles

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Dedicated with respect and admiration to Professor Léon Ghosez

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Abstract

This account summarizes the application of the degenerative addition-fragmentation of xanthates for the synthesis of various sulfur heterocycles. Many of the structures obtained in this manner are difficult or tedious to obtain by more conventional routes. These include γ-thiolactones, tetrahydrothiophenes, dihydrothiophenes, thiophenes, dithiospiroketals, 1,3-dithian-2-ones, 1,2-dithiolanes, 1,3-dithiolan-2-ones, benzothiepinones, 2,3-dihydrothieno[2,3-b]thiopyran-4-ones, dihydrothiazines, difluorothiochromanes, and 1,3-dithietan-2-ones. The mechanistic rationales and occasional serendipitous observations undergirding these methods are discussed briefly.

Keywords: Xanthates, γ-thiolactones, thiophenes, dithiospiroketals, 1,2-dithiolanes, dihydrothiazines
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1. Introduction

One of the earliest, and perhaps conceptually simplest, strategies for the synthesis of heterocycles is to place nucleophilic and electrophilic centers at a suitable distance in the same molecule, and then allow them to interact in a ring-closing mode. This is seldom trivial to implement in practice, however, especially in multifunctional structures, because the reactive entities must often be introduced in a latent form, and other functional groups present that might interfere at each of the steps, require temporary masking. Such regioselective protection-deprotection operations can rapidly become a costly burden on synthetic efficiency. Many years ago, we discovered the addition-transfer of xanthates and related dithiocarbonyl derivatives (dithioesters, dithiocarbamates and trithiocarbonates) to unactivated, electronically-unbiased alkenes.\(^1\)\(^-\)\(^3\) This transformation, whereby xanthate \(\textbf{1}\) reacts with alkene \(\textbf{2}\) to give adduct \(\textbf{5}\), proceeds by the radical chain sequence outlined in a simplified form in Scheme 1. The new carbon-carbon and carbon-sulfur bonds formed in this process are highlighted in red. The ability to bring together diverse functional groups present on either the xanthate, the alkene partner, or both, opens numerous avenues for the assembly of a range of heterocyclic structures. Since sulfur is naturally present in adducts \(\textbf{5}\), this chemistry is ideally suited for the synthesis of a broad variety of sulfur heterocycles. The general use of xanthates for the preparation of sulfur-containing heterocycles has very recently been reviewed by Mahdavi and co-workers, but only a tiny fraction of the possibilities provided by the present process has been covered.\(^4\) This brief overview will, therefore, describe more comprehensively how the radical addition of xanthates can be exploited to provide a remarkable diversity of sulfur heterocycles, many of which are not readily accessible by other more conventional routes.
The actual mechanistic manifold for the radical addition of xanthates 1 to alkenes 2 is more complex and subtle than is conveyed by the minimal outline in Scheme 1. The reader is directed to reference 3 for a more detailed discussion. Suffice it to say, that, owing to the reversibility of the addition-fragmentation of radicals R• and adduct radical 3 with any xanthate in the medium is fast and reversible, their average lifetime is significantly extended. Furthermore, their absolute concentration is considerably lowered because they are, most of the time, sequestered as relatively unreactive, and generally more stable, adducts such as 4; hence, the unequal lengths of the forward and reverse arrows connecting intermediates 3, 4, and 5 in Scheme 1. At the same time, radicals R• and 3 are in equilibrium via adduct 4 and their relative concentration is, therefore, controlled by their relative thermodynamic stability. This provides a simple, yet powerful, control handle, neglecting for simplicity the possible influence of polar effects. Thus, by selecting the partners such that radical R• is more stable than adduct radical 3, the forward process is favored over the formation of oligomers by further addition of adduct radical 3 to alkene 2.

This method of producing and capturing radicals offers many advantages from a practical standpoint. It can be conducted at high concentrations, and even neat without solvent, it is easily scalable, and the starting materials and reagents are readily available, non-toxic, and inexpensive. Importantly, numerous functional groups are tolerated, especially polar groups that often need protection when using ionic or organometallic methods. This opens vast possibilities for the construction of a diversity of molecular architectures, and especially sulfur heterocycles.

### 2. γ-Thiolactones

In contrast to lactones, which have been extensively studied and employed in syntheses, thiolactones have attracted hardly any attention. Thiolactones are rarely found in natural products and their synthesis using traditional methods is usually a multi-step process, except for the simplest members. The radical chemistry of xanthates offers straightforward routes to this family of compounds, permitting a better study of their properties. The first application is depicted in Scheme 2. Its ultimate aim was the synthesis of dideoxythiadifluoro nucleoside 10. The required precursor thiolactone 9 was simply prepared by adding acetate-derived xanthate 6 to alkene 7 using dilauroyl peroxide (DLP; also sold under lauroyl peroxide, Luperox® or Laurox®) as the initiator, followed by aminolysis of the xanthate group in adduct 8, and heating of the resulting thiol in trifluoroacetic acid to induce ring closure. Later, a similar approach was applied to the formation of bis-thiolactones such as 12 by cyclisation of the bis-adduct 11 to 1,7-octadiene. Such bis-thiolactones are...
interesting novel monomers for ionic polymerization since they readily react under mild conditions with diamines to give thiol-substituted polyamides such as 13.

Scheme 2. Synthesis of γ-thiolactones.

Destarac and co-workers extended this strategy to numerous other thiolactones and bis-thiolactones (Schemes 3 and 4). They applied a slight modification which consisted of using xanthates 14, where the ubiquitous ethyl moiety is replaced with a sec-butyl group. The corresponding adducts 15 could now be subjected to the thermal Chugaev elimination (190 °C, neat); the thiols 16, thus generated, underwent spontaneous ring closure to the desired thiolactones 17. In the examples displayed in Scheme 3, two yields are given. The first corresponds to the intermediate addition product (not shown) and the second to the thiolactone. A broad variety of substituents can be present. These include fluorinated side chains (23 and 24), phosphonates (19-22), imide (25), boronate (31), diol (32), and epoxide (33). Bis-thiolactones 35-37 were also prepared by this method.
Scheme 3. Further examples of γ-thiolactones.

Bis-γ-thiolactones can also be obtained by adding adipic-acid-derived bis-xanthate 38 to a simple alkene such as 3-buten-1-ol, to give bis-adduct 39 which, under the Chugaev thermolysis conditions, furnishes bis-γ-thiolactone 40 (Scheme 4).\textsuperscript{10} Bis-γ-thiolactones 41-43 were prepared by the same two-step sequence.
Scheme 4. A further route to bis-γ-thiolactones.

An alternative route to γ-thiolactones described by the same group, is outlined in Scheme 5. In this variant, the ester function used to construct the thiolactone motif is now located on the alkene partner. Radical addition of xanthates places the xanthate group in the correct position to form the corresponding thiolactones by thermolysis of intermediate adducts, respectively.
**Scheme 5.** An alternative synthesis of γ-thiolactones.

In the approaches described in the previous schemes, the radical addition introduces a substituent on C-5 of the γ-thiolactones, i.e., on the carbon bearing the sulfur atom. By starting with xanthate 54, the addition introduces a substituent on the carbon adjacent to the carbonyl (Scheme 6). In this case, the γ-thiolactone moiety is already formed and the xanthate group in the adduct can be simply reductively removed using, for example, hypophosphorous salts according to the procedure of Barton. Again, a variety of functional groups can be present on the alkene partner, as demonstrated by the examples pictured in Scheme 6, and bis-γ-thiolactones can be prepared, as exemplified by compounds 71 and 73. Thiolactone 68 derives from the addition-fragmentation of xanthate 54 to β-pinene 69.

**Scheme 6.** A direct route to γ-thiolactones.
The routes discussed above are convergent, modular, and highly flexible, providing access to a plethora of $\gamma$-thiolactones, including many that would be very tedious to obtain by other chemistries. A less general approach was described by Scanlan and co-workers in one example, whereby, the thiolactone ring is constructed by a radical cyclisation. Thus, exposure of xanthate 74 to the action of DLP in cyclohexane resulted in the formation of thiolactone 76 in moderate yield. The normal product is, in fact, 77; however, since the fast exchange of the xanthate group regenerates intermediate radical 75 continuously, hydrogen abstraction from the solvent ultimately gives the observed reduced product 76.

![Scheme 7. A $\gamma$-thiolactone by radical cyclization.](image)

The preceding methods allow the synthesis of $\gamma$-thiolactones with almost any substitution pattern, and constitute, by far, the most powerful routes to this family of compounds. Furthermore, there is every reason to believe that they could be adapted to access higher thiolactones, especially 6- and 7-membered derivatives, albeit with lesser flexibility and generality. Hopefully, this will eventually lead to a better understanding of their chemistry and encourage their practical application to problems in various domains. The synthesis of sulfur-bearing polymers, in particular, appears to be extremely promising.

### 3. Tetrahydrothiophenes, Dihydrothiophenes, and Thiophenes

The addition of xanthates to alkenes provides various opportunities for the synthesis of thiophenes and their reduced congeners. One simple approach to tetrahydrothiophenes was found by Destarac and co-workers when attempting to prepare $\gamma$-thiolactone 80 by thermolysis of adduct 78, obtained by addition of xanthate 45 to 1-bromo-pent-4-ene (Scheme 8). In this case, thiol 79, arising from the Chugaev elimination, displaced the bromine atom to give tetrahydrothiophene 81 in high yield, instead of undergoing the desired ring closure onto the ester group.

A potentially more general route is exemplified by the synthesis of the dideoxynucleoside thia-analogue 86. It consists of adding phenacyl xanthate 82 to difluoroalkene 7 to give the corresponding adduct 83, followed by aminolysis of the xanthate group. The resulting thiol spontaneously adds to the ketone to afford thiohemiketal 84, which is readily dehydrated with trifluoroacetic acid (TFA) into dihydrothiophene 85. Reduction finally provides tetrahydrothiophene 86, where the 2,4-difluorotoluene moiety mimics the thymine base present in natural nucleosides.

The ready formation of dihydrothiophene 85 is of particular synthetic interest because it can be easily generalized to other combinations of α-ketonyl xanthates 87 and alkenes, and used to prepare dienes, as outlined in Scheme 9.\textsuperscript{15} Thus, aminolysis of the xanthate in adducts 88 leads to thiols 89, which are in equilibrium with thio-hemiketals 90. Dehydration into dihydrothiophenes 91 and oxidation with peracid then provides Δ\textsuperscript{2}-sulfolenes 92. Finally, heating with a base such as DBU induces an equilibrium with the isomeric Δ\textsuperscript{3}-sulfolenes 93; the latter then extrude sulfur dioxide by a retro-cheletropic cycloaddition to give the desired dienes 94.
Scheme 9. A synthesis of sulfolenes and dienes.

Examples of this approach to dienes are assembled in Scheme 10. The conversion of adducts 88a-f of various α-ketonyl xanthates 87 and alkenes into the corresponding Δ²-sulfolenes 92a-f was accomplished without purification of the intermediates. The formation of dienes 94a-h was achieved by heating with DBU in refluxing cyclohexane, except for sulfolene 92i, reported by Wilkinson and co-workers, which was not transformed into diene 94i.
Scheme 10. Examples of sulfolenes and dienes.

By using O-sec-butyl instead of the ubiquitous O-ethyl xanthates, the intermediate thiol (cf. 89 in Scheme 9) can be generated through the Chugaev elimination under conditions in which cyclization and elimination of water take place, spontaneously, to give the desired dihydrothiophene directly (cf. 91 in Scheme 9). This variation was applied to the synthesis of TMS-substituted dienes 97 (Scheme 11). Thus, heating adducts 95a-i bearing an O-sec-butyl xanthate group at 200 °C in diphenyl ether gave the expected dihydrothiophenes (not shown), which were directly oxidized into Δ2-sulfolenes 96a-i in the indicated overall yields. The conversion of
the latter into the corresponding dienes 97a-i required a significant modification of the experimental conditions. Simple heating with DBU as in the previous examples in Scheme 10 resulted in extensive desilylation of the Δ2-sulfolenes. This was assumed to be caused by hydroxide ions generated from adventitious water. To circumvent this unwanted side-reaction, an excess of trimethylsilyl chloride was, therefore, added to react irreversibly with hydroxide ions and any other nucleophiles present in the medium. The incorporation of solid anhydrous potassium carbonate as both a base and dehydrating agent was also found to be beneficial. Under these conditions, no desilylation was observed and the TMS-substituted dienes 97a-I were obtained in good yields.17 Interestingly, when aliphatic adduct 95j was subjected to thermolysis and oxidation, the alkylidene sulfolane 98 was formed in high yield, indicating that the exo isomer is more stable than the desired endo isomer in this case.
Scheme 11. Examples of TMS-substituted sulfolenes and dienes.

The easy access to dihydrothiophenes 91 (Scheme 9) also constitutes, in fact, a synthesis of thiophenes, since it has long been known that the former can be efficiently dehydrogenated with oxidants such as chloranil. A more direct route to thiophenes can be envisaged by starting with the addition products 100 of α-ketonyl xanthates 87 to enol esters 99 (Scheme 12). These adducts possess the correct oxidation level, and simple heating with potassium iodide and acetic acid in a microwave oven for a few minutes is sufficient to bring about the desired ring closure into thiophenes 112 via intermediate 111.
Examples of thiophenes \(112a-r\) prepared by this method are displayed in Scheme 12. For the vinyl ester partner \(99\), both vinyl acetates and vinyl pivalates were used, even if only acetates are shown for clarity. Obviously, other vinyl esters could be equally employed. Thiophenes of various types and substitution patterns are readily accessible. The diversity can be further increased by post-functionalization of the thiophene ring (halogenation, Friedel-Crafts reaction, lithiation, etc.) or by exploiting the presence of various groups such as the bromide in \(112c\), the iodide in \(122g\) or the ketone in \(112r\). Note, further, that the thiophene rings in example \(112i\) were prepared through a double radical addition.

### 4. Dithiospiroketalts

As previously shown in Section 3, the addition of the \(\alpha\)-ketonyl xanthates \(87\) to an alkene gave rise to the adducts \(88\). The subsequent thiol s, \(89\), resulting from cleavage of the xanthate group, were ideally placed to cyclize onto the ketone to give a tetrahydrothiophene \(90\) (Scheme 9). Similarly (or analogously), by starting with the \(\alpha\)-ketonyl bis-xanthate \(113\), the double radical addition leads to the formation of the bis-adducts \(114\), the precursor of the bis-thiols \(115\). Acidification of the latter now furnishes dithiospiroketalts \(116\) with loss of water.21
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**Scheme 1**

The reaction of 113 with a peroxide results in the formation of 114, which undergoes aminolysis to give 115. Acid treatment of 115 leads to the formation of 116.

- **114a**, 100% yield:
  - 
  - MeO\(_2\)C
  - EtOCSS
  - CO\(_2\)Me

- **114b**, 22% overall yield:
  - HO\(_2\)C
  - EtOCSS
  - CO\(_2\)H

- **114c**, 84% yield:
  - HO
  - EtOCSS
  - OH

- **114d**, 80% yield:
  - BocHN
  - EtOCSS
  - NHBOc

- **114e**, 58% yield:
  - BocHN
  - EtOCSS
  - NHBOc

- **114f**, 62% yield:
  - MeO\(_2\)CHN
  - EtOCSS
  - NHCO\(_2\)Me

- **114g**, 66% yield:
  - OH
  - EtOCSS
  - OH

- **114h**, 72% yield:
  - Me\(_2\)O
  - OMe
  - SCSOEt
  - EtOCSS
  - OMe

- **114i**, 66% yield:
  - AcO
  - OMe
  - SCSOEt
  - EtOCSS
  - OMe

- **114j**, 82% yield:
  - Me
  - N
  - S
  - S
  - O
  - EtO
  - S
  - S
  - O

- **116a**, 89% yield:
  - MeO\(_2\)C
  - EtOCSS
  - CO\(_2\)Me

- **116b**, 22% overall yield:
  - HO\(_2\)C
  - EtOCSS
  - CO\(_2\)H

- **116c**, 71% yield:
  - HO
  - EtOCSS
  - OH

- **116d**, 62% yield:
  - BocHN
  - EtOCSS
  - NHBOc

- **116e**, 71% yield:
  - BocHN
  - EtOCSS
  - NHBOc

- **116f**, 67% yield:
  - MeO\(_2\)CHN
  - EtOCSS
  - NHCO\(_2\)Me

- **116g**, 72% yield:
  - HO
  - EtOCSS
  - OMe

- **116h**, 58% yield:
  - MeO
  - OMe
  - SCSOEt
  - EtOCSS
  - OMe

- **116i**, 74% yield:
  - HO
  - OMe
  - SCSOEt
  - EtOCSS
  - OH

- **116j**, 71% yield:
  - Me
  - N
  - S
  - S
  - O
  - EtO
  - S
  - S
  - O
  - Me

In contrast to the very common spiroketals, their sulfur analogues are virtually unknown. Only two members have been previously described, the parent dithiospiroketal (116, R = H) and the dibenzo-fused derivative.22,23 Interestingly, the former was prepared accidentally by a rather unusual reaction in 1901.22 The xanthate route provides simple access to these compounds and will, hopefully, encourage a better study of their chemistry. A variety of examples 116a-j are collected in Scheme 13.21 The intermediate dithiols 115 were not isolated since simple acidification of the crude product following aminolysis caused spontaneous ring closure to the corresponding dithiospiroketal 116. The dicarboxylic acid bis-adduct 114b was transformed directly into dithiospiroketal 116b without prior purification. In the case of bis-adduct 114i, the acetates did not survive the aminolysis step, and the final product 116i is a bis-phenol.

With the exception of compound 116h, all the dithiospiroketales in Scheme 13 constitute an interesting family of novel monomers for condensation-type polymerisations. Thus, they can be used to prepare polyamides, polyesters, polyurethanes, polyimides, etc. The presence of the globular dithiospiroketal introduces a kink in the chains, and could impart interesting properties to the derived polymers, such as an increased refractive index and perhaps a better biodegradability, since many soil microorganisms are known to metabolize organosulfur compounds.24 Furthermore, many of the dithiospiroketal in Scheme 13 are derived from bio-sourced alkenes. Thus, compounds 116a-d derive ultimately from 10-undecylenic acid, a substance obtained by degradation of cheap castor oil, whereas 116h and 116i were prepared from eugenol, the main constituent of clove oil. It is also worth noting that dithiospiroketales 116a,c,d could be readily desulfurized using Raney nickel to give 25-carbon long-chain monomers in high yield. Polymides derived from such monomers have physico-chemical properties in between those of non-polar polyethylene and polar 6,6-nylon.25

Non-symmetrical dithiospiroketal are simply obtained by a variation of the above route, as outlined in Scheme 14 for compound 122.21 Chloroketonyl xanthate 117 adds cleanly to methyl 10-undecylenate 118 to give adduct 119, from which the chlorine can be substituted with a xanthate. A second addition from dixanthate 120 can be accomplished, regioselectively, to Boc-protected allylamine to furnish the unsymmetrical bis-adduct 121. Because the reversible exchange of xanthates is much faster than the addition to the alkene, it is, ultimately, the more stable radical, located adjacent to the ketone carbonyl, that participates in the addition. Finally, aminolysis of both xanthates in product 121, and acidification, affords the unsymmetrical dithiospiroketal 122. This compound is also an interesting monomer for polyamide synthesis since it contains, in a conveniently protected form, the requisite amino and carboxylic-acid groups at its extremities.

5. Dithianones and Dithiolanones

Both sulfur atoms present in the xanthate group can end up in the sulfur heterocycle. This is the case when the alkene bears a suitably positioned leaving group as, for example, olefin 123 pictured in Scheme 15. This results in the synthesis of another little-known family of sulfur heterocycles, namely 1,3-dithian-2-ones 125. Thus, addition of xanthates 1 to homoallylic bromides or mesylates 123 furnishes adducts 124 which, upon further heating, undergo a slow intramolecular substitution to give 1,3-dithian-2-ones 125. The rare 1,3-dithian-2-ones, hitherto described, were obtained by treating 1,3-dithiols with 1,1'-carbonyldiimidazole, a safer synthetic equivalent of phosgene. This past approach is severely constrained by the limited availability of 1,3-dithiols. The present one-pot transformation expands considerably the pool of accessible structures, as demonstrated by the numerous examples displayed in Scheme 15. Essentially, any xanthate capable of adding cleanly to an alkene can potentially afford a 1,3-dithian-2-one. Bis-(1,3-dithian-2-ones) 125m and 125aa, as well as compound 125c, which combines a thiolactone and a 1,3-dithian-2-one motif, are quite unusual derivatives worth underlining.
Scheme 15. Synthesis of 1,3-dithian-2-ones.

Homoallylic tertiary alcohols 126 are also suitable precursors (Scheme 16). Treatment of the corresponding adducts 127 with a strong acid such as trifluoroacetic acid (TFA) generates a stabilized tertiary cation, which is captured by the thiocarbonyl sulfur of the xanthate to give 1,3-dithian-2-ones of general structure 128. This alternative route is showcased by the examples in Scheme 16. The synthesis of dithianone 131 illustrates the possibility of using a tertiary lactone 130 as a substrate, even if a stronger acidic medium is needed (a 9:1 combination of methanesulfonic and acetic acids). Dithianone 131 bears a carboxylate and a free carboxylic acid at its extremities, and is, therefore, a novel potential monomer in condensation-type polymerizations. Furthermore, all the carbons in this compound derive from the biomass: xanthate 129 is prepared from levulinic acid, and, as stated above, methyl 10-undecenylate 118 is obtained from castor oil.
Scheme 16. Further examples of 1,3-dithian-2-ones.

1,3-Dithian-2-ones are useful as latent 1,3-dithiols which, upon mild oxidation, give rise to 1,2-dithiolanes of structure 132 (Scheme 17). For example, methanolysis under mild basic conditions of dithiolanes 125, derived from the radical xanthate addition/ionic cyclization to 1-bromo-3-butene, followed by exposure to manganese dioxide, provides the corresponding 1,2-dithiolanes 132a-d in modest overall yield from the starting xanthate, without isolation of the intermediates.
Scheme 17. Synthesis of 1,2-dithiolanes.

The 1,2-dithiolane motif is found in a few natural products, such as asparagusic acid 133, isolated from asparagus (as the name implies), and α-lipoic acid 134. The latter is present in essentially all organisms and is an over-the-counter drug with various medical applications. Interestingly, the eclipsed disposition of the sulfur lone pairs results in a strong repulsion that weakens the S—S bond quite significantly, allowing the easy establishment, under photochemical or mild thermal conditions, of an equilibrium between the monomeric closed form 135 and the polymeric modification 136. Indeed, the ready formation of oligomers 136 explains, in part, the modest yields of 1,2-dithiolanes 132a-d. At any rate, this unusual property, not observed with open-chain or higher cyclic disulfides, is the subject of extensive studies by polymer and material scientists. 29

For the synthesis of 1,3-dithiolanone congeners 139, the radical addition of the xanthates is performed on an allyl acetate 137; the resulting adduct 138 is then subjected to the stronger combination of methanesulfonic and acetic acids to force the ionic ring closure (Scheme 18). 30 In this manner, dithiolanones 139a-e were prepared from adducts 138a-d additions to allyl and methallyl acetates. The transformation is somewhat less general than for the higher homologue, and unusual side reactions, such as the formation of lactones, were observed in some cases. These are not discussed as they lie outside the scope of the present overview.
Scheme 18. Synthesis of 1,3-dithiolanones.

6. Benzothiepinones and 2,3-Dihydrothieno[2,3-b]thiopyran-4-ones

In the sequence displayed in Scheme 8, when aminolysis of the xanthate in adduct 83 is followed by treatment with acid, dihydrothiophene 85 is produced following dehydration of thiohemiketal 84. However, when the aminolysis is followed by exposure to a moderately strong base, the intermediate thiol displaces the ortho-fluorine to give a benzothiepinone instead. This is outlined in Scheme 19 for adducts 142a,b derived from the radical addition of xanthate 140 to protected allylamines 141a,b. Cleavage of the xanthate with 1,2-ethylenediamine followed by addition of DBU gives the corresponding fluorobenzothiepinones 143a,b.31 Such compounds are sulfur analogues of the medicinally-important benzazepinones. Indeed, numerous benzothiepinones could be prepared by simply modifying the alkene partner and by employing S-2-fluoracetophenyl xanthates with different substitution patterns. In the present case, the purpose of using protected allylamines 141a,b was to create further diversity by associating the radical addition and ionic fluorine displacement with a Mannich reaction, to construct another ring bridging the amine nitrogen and the carbon adjacent to the ketone.

When benzothiepinone 143a was treated with paraformaldehyde and HCl, compound 144 with a novel sulfonium-containing skeleton was produced in moderate yield.31 This unwanted, but, nevertheless, interesting, pathway could be shut down by converting sulfide 143b into sulfone 145b, where the sulfur atom can no longer act as a nucleophile. Thus, removal of the Boc protecting group with TFA, followed by addition of an aldehyde, leads to the desired bridged tricyclic derivative, as illustrated by examples 146a-d. The p-methoxybenzyl (PMB) group was selected because it can be easily removed, revealing a secondary amine that would constitute an extra point of diversification, in addition to the ketone group and the remaining aromatic.
p-fluorine atom. The latter is activated by the electron-withdrawing ketone and is, therefore, easily substituted by various nucleophiles.\textsuperscript{31}

**Scheme 19.** Synthesis of benzothiepinones and further elaboration.

Another novel sulfur heterocyclic structure can be produced from the very same generic adducts 147 derived from S-2-fluoroacetophenyl xanthates (Scheme 20). Merely refluxing with potassium carbonate in a 1:9 mixture of t-butanol and acetonitrile, cleanly converts these adducts into novel 2,3-dihydrothieno[2,3-b]thiopyran-4-ones 150.\textsuperscript{31} Under these different basic conditions, the enolate of the ketone is generated, and reacts with the neighboring xanthate to give intermediate 148. Substitution of the fluorine then leads to tricyclic derivative 149, from which loss of ethanol finally affords the observed product.
Scheme 20. An unusual route to 2,3-Dihydrothieno[2,3-b]thiopyran-4-ones.

It is possible that the loss of ethanol precedes the ring closure step; however, these mechanistic variations are not mutually exclusive, and could be operating simultaneously. Various examples are presented in Scheme 21. The process tolerates a broad range of functional groups and provides a particularly concise route to a novel family of compounds of potential interest to medicinal chemists and materials scientists. Moreover, post-modification of the side chain, the ketone group or the aromatic ring — especially through substitution of the remaining activated fluorine — provides additional handles for increasing the diversity.

Scheme 21. Examples of 2,3-Dihydro-thieno[2,3-b]thiopyran-4-ones.

A conceptually-related approach to aliphatic analogues was also uncovered using xanthate 151 (Scheme 22). The xanthate in this reagent allows a radical addition on one side of the ketone to give adducts 152, and the phosphonate mediates an ionic Horner-Wadsworth-Emmons on the other side to give finally enones 153. However, under the strong basic conditions sometimes employed for the latter transformation, e.g., NaH/THF, the reaction can proceed further to intermediates 154, and, thence, to 2,3,5,6-tetrahydrothieno[2,3-b]thiopyran-4-ones 156 by elimination of ethanol from the cyclic dithio-orthoformate 155.
Scheme 22. Synthesis of 2,3,5,6-tetrahydro-thieno[2,3-b]thiopyran-4-ones.

In this sequence, three components are brought together in a modular fashion, namely xanthate 151, the alkene, and the aldehyde or ketone. Vast libraries of novel tetrahydrothienothiopyranones 156 can, thus, be readily constructed by this convergent two-step approach. A few examples are presented in Scheme 23. They give an idea of the possibilities and the broad functional group tolerance. Yields are mostly high and generally better with aldehydes as condensation partners. Many of the compounds in Schemes 21 and 23 would be very difficult to attain by other chemistries, again underscoring the unique advantages offered by the xanthate group.
Scheme 23. Examples of 2,3,5,6-tetrahydro-thieno[2,3-b]thiopyran-4-ones.
7. Dihydrothiazines and Difluorothiochromanes

The high nucleophilicity of the sulfur can be exploited to create a sulfur-nitrogen bond and construct yet another family of a little-known heterocyclic system. It is, thus, possible to place a xanthate and an oxime at the correct distance to ultimately generate a dihydrothiazine of generic structure 163 from precursor 160 (Scheme 24).33 Thiol 162, produced by Chugaev elimination from xanthate 160, attacks the nitrogen of the oxime and causes rupture of the weak N—O bond with elimination of water. The requisite adduct 160 can be accessed, either directly by addition of xanthate 157 to alkenyl oxime 158 or by radical addition to γ,δ-unsaturated ketone 159, followed by reaction of ketone 161 with hydroxylamine. Yet another route involves addition of α-ketonyl xanthate 164 to an alkene prior to oxime formation. This latter method is by far the more flexible, since both the alkene and the α-ketonyl xanthate 164 are readily available and can bear various other functional groups. The choice of the approach will, therefore, depend on the particular substitution pattern desired in the final dihydrothiazine 163. Notice, however, that the position of the new carbon-carbon bond formed in the radical addition step (colored in red) in compounds 160 and 163 depends on the method employed.

![Scheme 24. Synthesis of dihydrothiazines.](image)

Dihydrothiazines 163a-I, pictured in Scheme 25, illustrate the scope of both alternative routes to these compounds. The modest yields reflect the rather harsh thermal conditions and the relative fragility of the dihydrothiazines because of the weakness of the N—S bond due to lone-pair repulsion. Indeed, much of the driving force in the conversion of oximethiols 162 into dihydrothiazines 163 arises from the gain of energy derived by replacing the S—H bond in thiol 162 with the stronger O—H bond in the expelled water molecule, and the large positive entropic term in the Gibbs free energy change since two molecules (163 and water) are
generated from one precursor (162). Despite the modest yields, this approach remains so far the only reported access to substituted members of this family of heterocycles.

Scheme 25. Examples of dihydrothiazines.

The formation of a sulfur heterocycle can be accomplished by applying two successive radical additions. This is illustrated in Scheme 26 for the synthesis of difluorothiochromanes 167 through, first, an intermolecular addition of xanthate 165 to an alkene, followed by ring closure to the aromatic ring. The latter step is achieved by taking advantage of the presence of a xanthate group at a suitable position in adduct 166 to regenerate the intermediate carbon radical under conditions conducive to cyclization, i.e., by exposure to stoichiometric amounts of DLP in refluxing ethyl acetate. A few examples of difluorothiochromanes are deployed in Scheme 26. The variety arises from the substituents on the alkene partner, even though the aromatic ring in the starting xanthate 165 could be modified if so desired, albeit less conveniently (xanthate 165 is prepared in two steps from p-chlorothiophenol). The ease of introducing a sugar motif, as in compound 167k, is particularly noteworthy because two carbon-carbon bonds are created without harm to the carbohydrate structure. In the case of thiochromanes 167e and 167f, a stoichiometric amount of camphorsulfonic acid was added to the reaction mixtures of both steps in order to neutralize the nucleophilicity of the nitrogen atoms present on the alkene partners.

8. Dithietanones

The bimolecular addition to alkenes allows the introduction of various functional groups into the same molecule, which can then be used to fashion various sulfur heterocycles, especially through the exploitation of the sulfur present in the xanthate group itself. Furthermore, by changing the experimental conditions, completely different sulfur heterocycles can be obtained, in some cases from the same precursors, e.g., adducts from S-ortho-fluorophenacyl xanthates can be converted into dihydrothiophenes, into benzothiepinones or into 2,3-dihydrothieno[2,3-b]thiopyran-4-ones depending on whether or not the xanthate group in the adducts is aminolysed.

Another instance of such bifurcating pathways is with addition products to vinyl esters. In the case of adducts 100 in Scheme 12, these could be converted into thiophenes 112 by heating with potassium iodide and acetic acid for a few minutes in a microwave oven. However, when such adducts are exposed to titanium tetrachloride in dichloromethane (DCM) at room temperature, 1,3-dithietan-2-ones 169 are formed instead. This is shown in a generic way for adducts 168 derived from xanthates 1 and vinyl pivalate (Scheme 27). The
Lewis acid complexes with the oxygen of the ester group and activates it toward substitution by the thiono-sulfur of the xanthate as indicated on structure 168.

Scheme 27. A route to 1,3-dithietan-2-ones.

The best yields are observed with adducts of (hetero)aromatic ketonyl xanthates. Adducts bearing aliphatic ketones provide the corresponding 1,3-dithietan-2-ones with modest efficiency or not at all, as in the case of 169j (Scheme 27). These 4-membered sulfur-containing structures are quite rare. Interestingly, they act as latent thioaldehydes under certain conditions. Thus, heating dithietanone 169a with 4-hydroxypyridine produces thioaldehyde 171, which is captured in situ by an excess of 2,3-dimethyl-butadiene to give, in good yield, yet another sulfur heterocycle, namely dihydrothiopyran 172 (Scheme 28).36

Scheme 28. Generation and capture of a thioaldehyde.

9. Conclusions

Xanthates enable radical processes too slow to be accomplished by more traditional methods. This unique feature results from their ability to increase the lifetime of the active intermediate radicals and, at the same
time, regulate their absolute and relative concentrations in the medium. From a synthetic standpoint, it is the ability to achieve intermolecular additions to ordinary, unactivated alkenes, and to perform unusual ring closures that are most useful. The transformations discussed in this brief overview give only a small glimpse of the vast possibilities offered by the present radical chemistry of xanthates. Many other sulfur heterocycles could be constructed by placing the requisite functional groups at the correct distance through the radical addition to alkenes. Alternatively, existing sulfur heterocycles could be modified by appending additional functional groups using xanthate-mediated additions. This is especially useful in the case of thiophenes, which constitute a fundamental class of heteroaromatics. This chemistry will no doubt see further important developments in the future.

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References


   https://doi.org/10.1021/ol02432610

   https://doi.org/10.3390/molecules23040897

   https://doi.org/10.1039/b203975c

   https://doi.org/10.1016/j.tetlet.2005.09.058

   https://doi.org/10.1021/jo402169v

   https://doi.org/10.1139/v75-029

   https://doi.org/10.1021/ol403310f

   https://doi.org/10.1021/acs.orglett.2c00855

   https://doi.org/10.1021/ja01565a058

   https://doi.org/10.1021/acs.orglett.2c02215

   https://doi.org/10.1021/acs.orglett.2c02214

   https://doi.org/10.1111/j.1365-2672.2005.02723.x

   https://doi.org/10.1016/S0957-4166(96)00463-6

   https://doi.org/10.1021/jacs.1c08706

   https://doi.org/10.1021/acs.orglett.2c02215

   https://doi.org/10.1021/ol801033e

   https://doi.org/10.1021/ol402169v
   https://doi.org/10.1021/ol402973g
   https://doi.org/10.1039/b302434b
   https://doi.org/10.1055/s-0037-1611638
   https://doi.org/10.1039/B306966D

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