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Review

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The xanthate radical addition route to sulfur heterocycles

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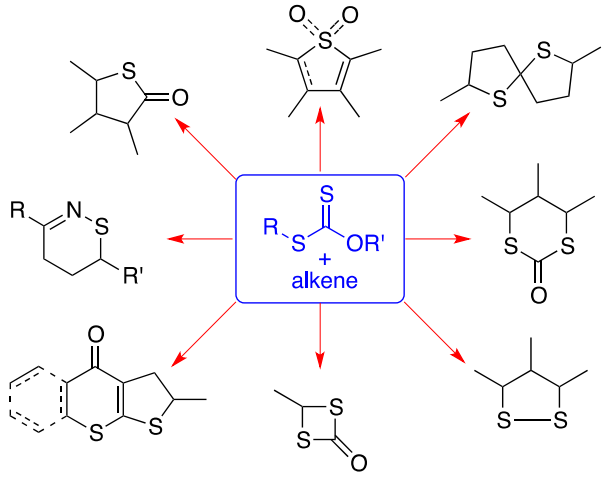
Dedicated with respect and admiration to Professor Léon Ghosez

Received 03-20-2024 **Accepted** 04-25-2024 **Published on line** 05-15-2024

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

Cite as *Arkivoc* **2024** (5) 202412199

DOI: https://doi.org/10.24820/ark.5550190.p012.199

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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 **1** reacts with alkene **2** to give adduct **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 **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.

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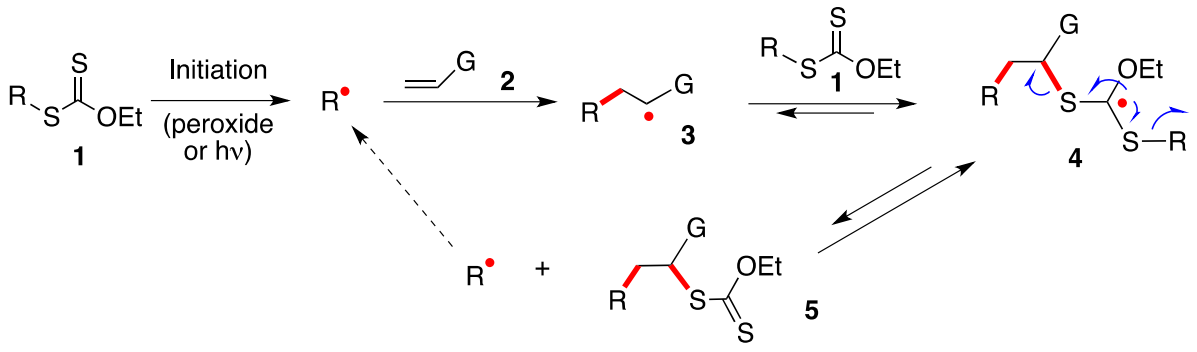

Scheme 1. Radical addition of xanthates to alkenes.

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, because 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.[5] 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 dideoxy-thiadifluoro nucleoside **10**.[6] 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.[7] Such bis-thiolactones are

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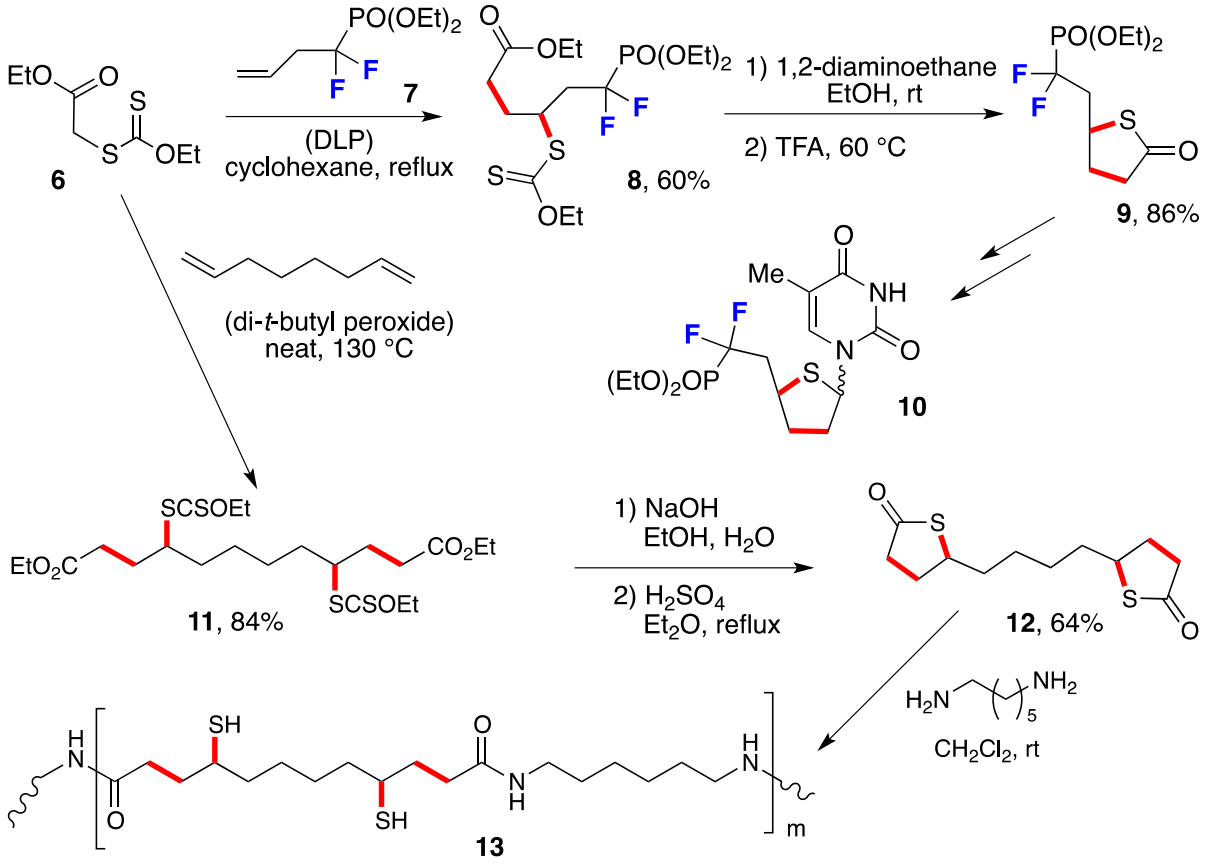
interesting novel monomers for ionic polymerization since they readily react under mild conditions with diamines to give thiol-substituted polyamides such as **13**.



Scheme 2. Synthesis of γ-thiolactones.

Destarac and co-workers extended this strategy to numerous other thiolactones and bis-thiolactones (Schemes 3 and 4).[8-10] 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.

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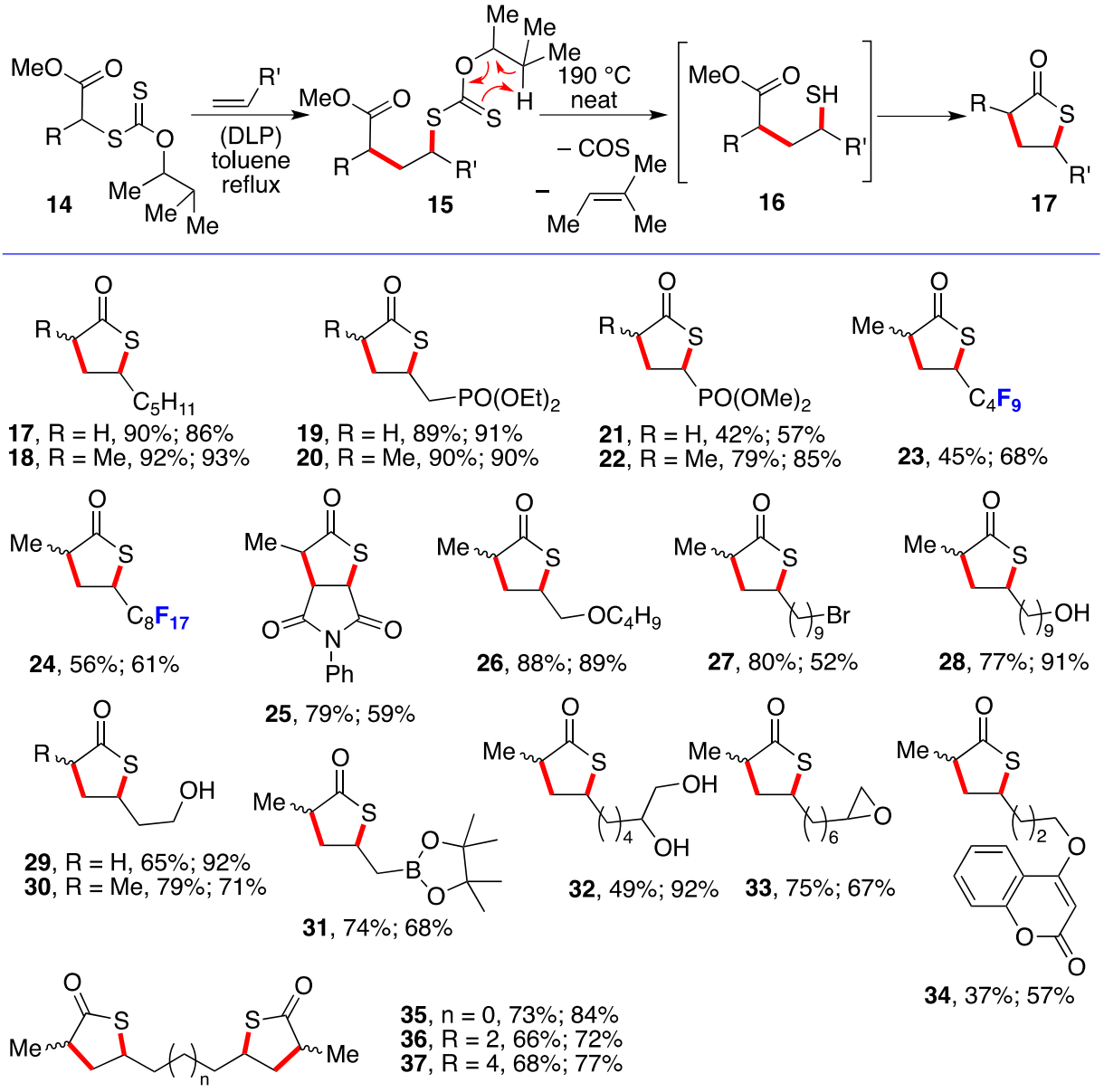

Scheme 3. Further examples of γ-thiolactones.

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).[10] Bis-γ-thiolactones **41**-**43** were prepared by the same two-step sequence.

An alternative route to γ-thiolactones described by the same group, is outlined in Scheme 5.[9] In this variant, the ester function used to construct the thiolactone motif is now located on the alkene partner **44**. Radical addition of xanthates **45**, **48**, and **51** places the xanthate group in the correct position to form the corresponding thiolactones **47**, **50**, and **53** by thermolysis of intermediate adducts **46**, **49**, and **52**, respectively.

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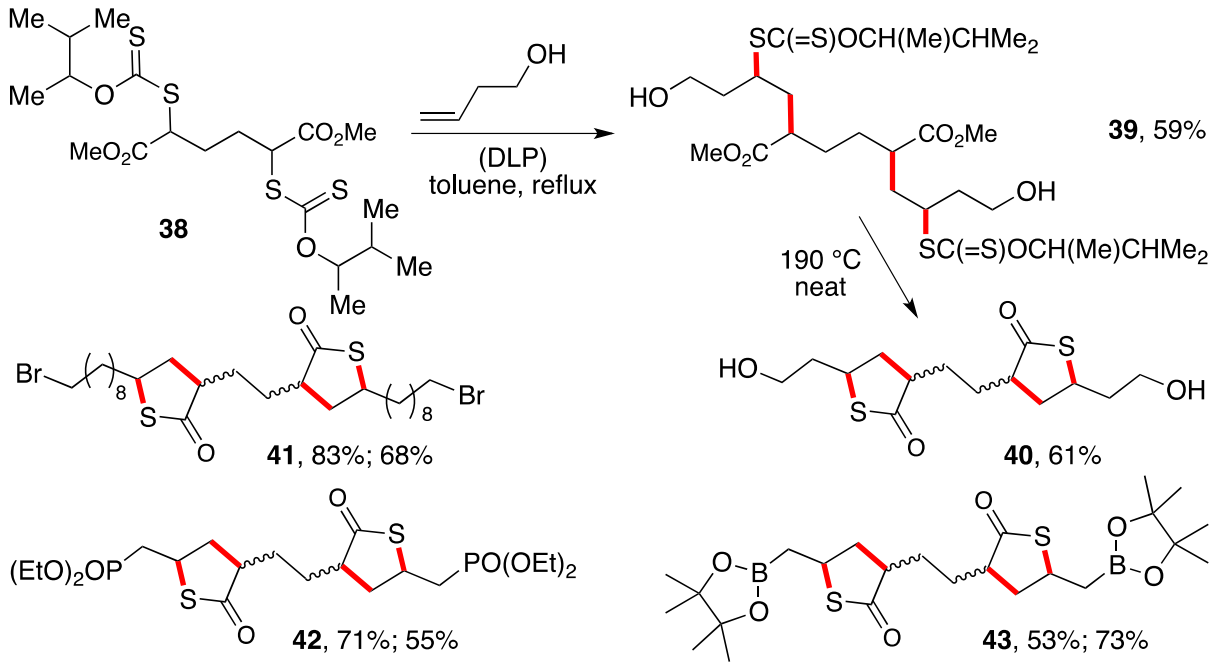
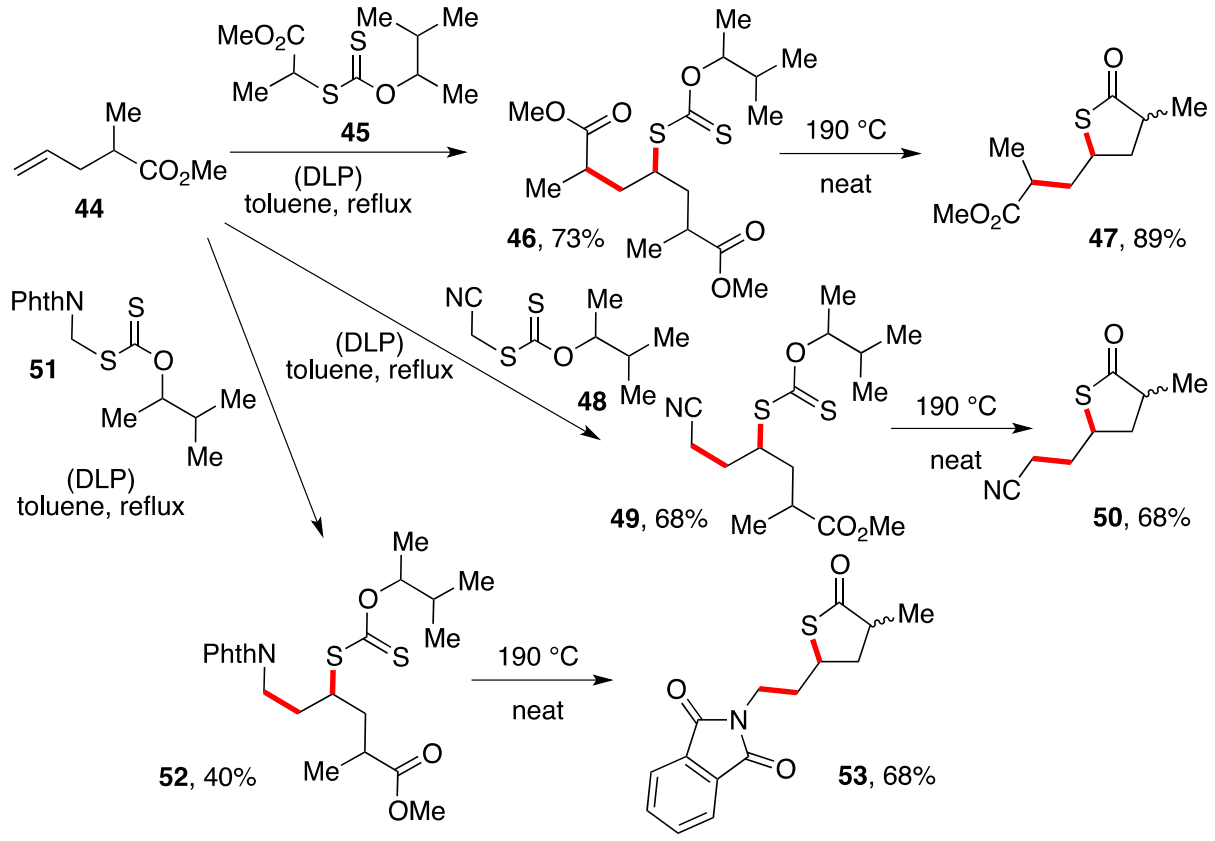


Scheme 4. A further route to bis-γ-thiolactones.



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

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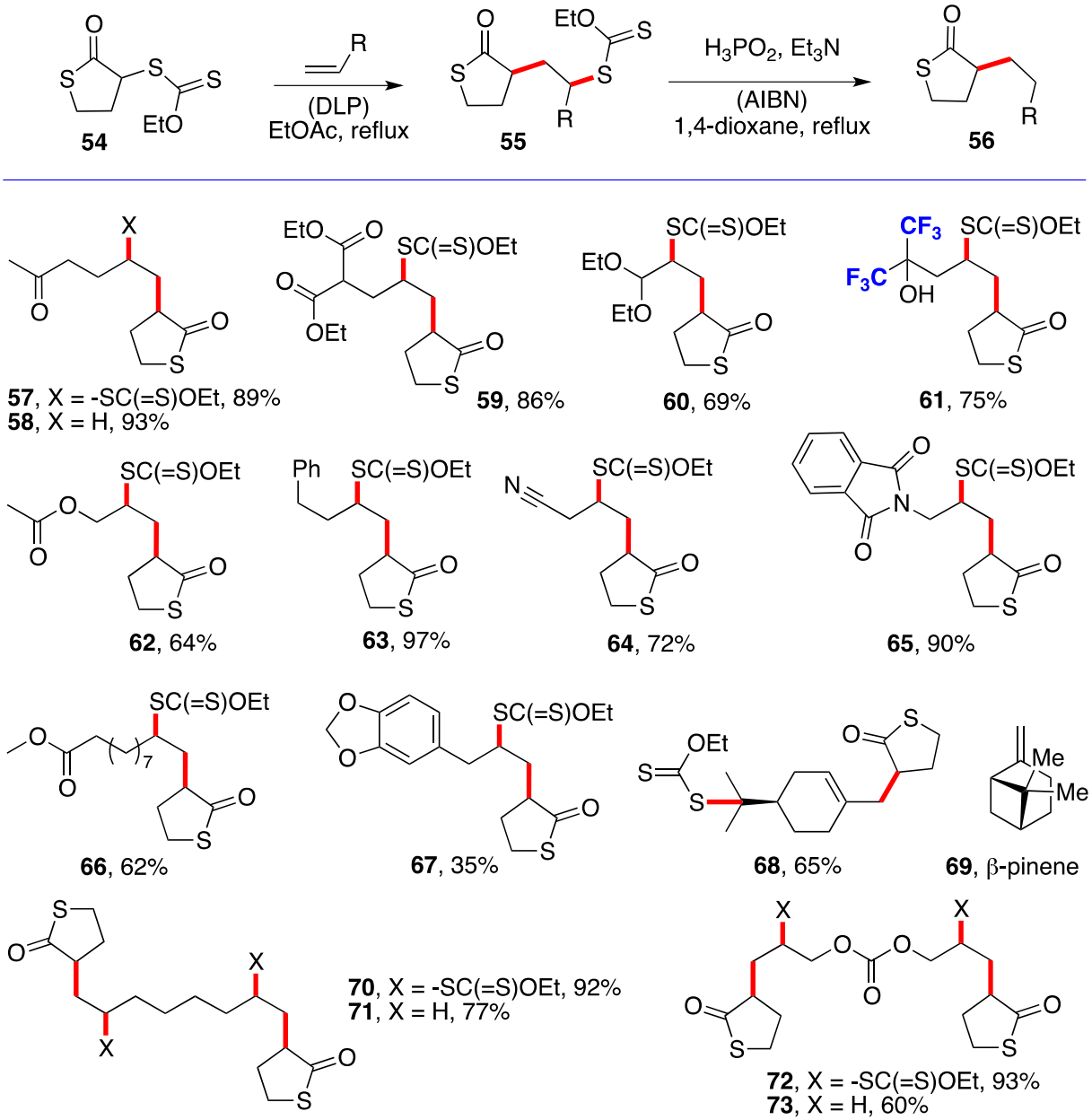
introduces a substituent on the carbon adjacent to the carbonyl (Scheme 6).[11] In this case, the γ-thiolactone moiety is already formed and the xanthate group in the adduct can be simply reductively removed using, for example, hypophosphorous salts according to the procedure of Barton.[12,13] Again, 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 γ-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.[14] Thus, exposure of xanthate **74** to the action of DLP in cyclohexane

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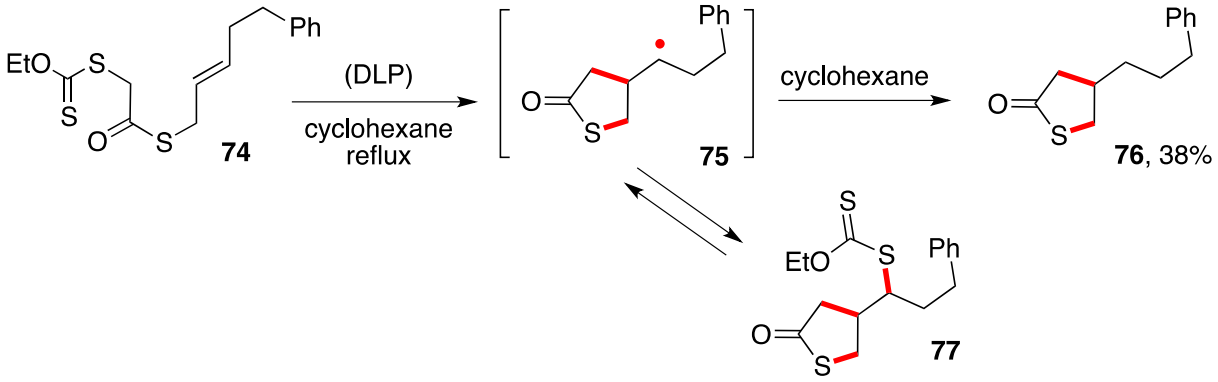
resulted in the formation of thiolactone **76** in moderate yield. The normal product is, in fact, **77**; however, since the fast exchange of the xanthate group regenerates intermediate radical **75** continuously, hydrogen abstraction from the solvent ultimately gives the observed reduced product **76**.



Scheme 7. A γ-thiolactone by radical cyclization.

The preceding methods allow the synthesis of γ-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 γ-thiolactone **80** by thermolysis of adduct **78**, obtained by addition of xanthate **45** to 1-bromo-pent-4-ene (Scheme 8).[9] 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**.[6] 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.

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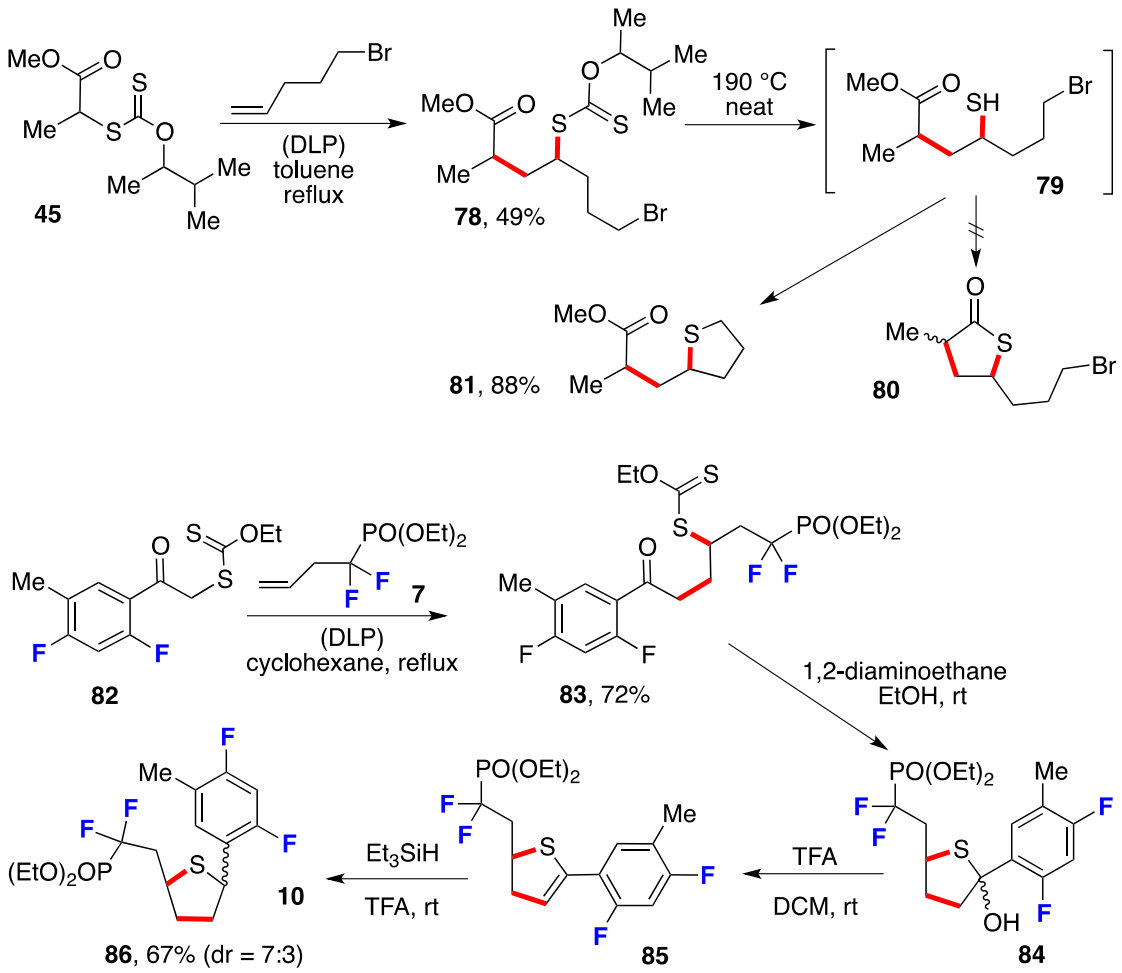
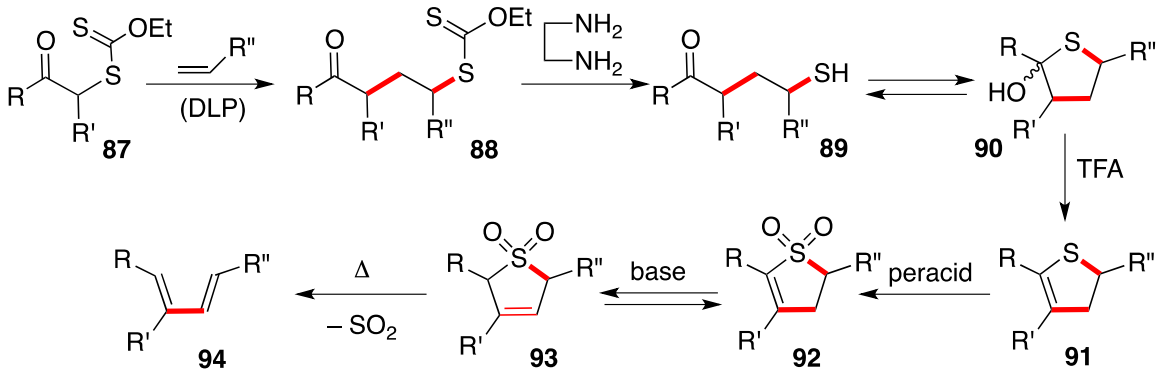


Scheme 8. Synthesis of tetrahydro- and dihydro-thiophenes.



Scheme 9. A synthesis of sulfolenes and dienes.

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.[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^2-sulfolenes **92**. Finally, heating with a base such as DBU induces an equilibrium with the isomeric

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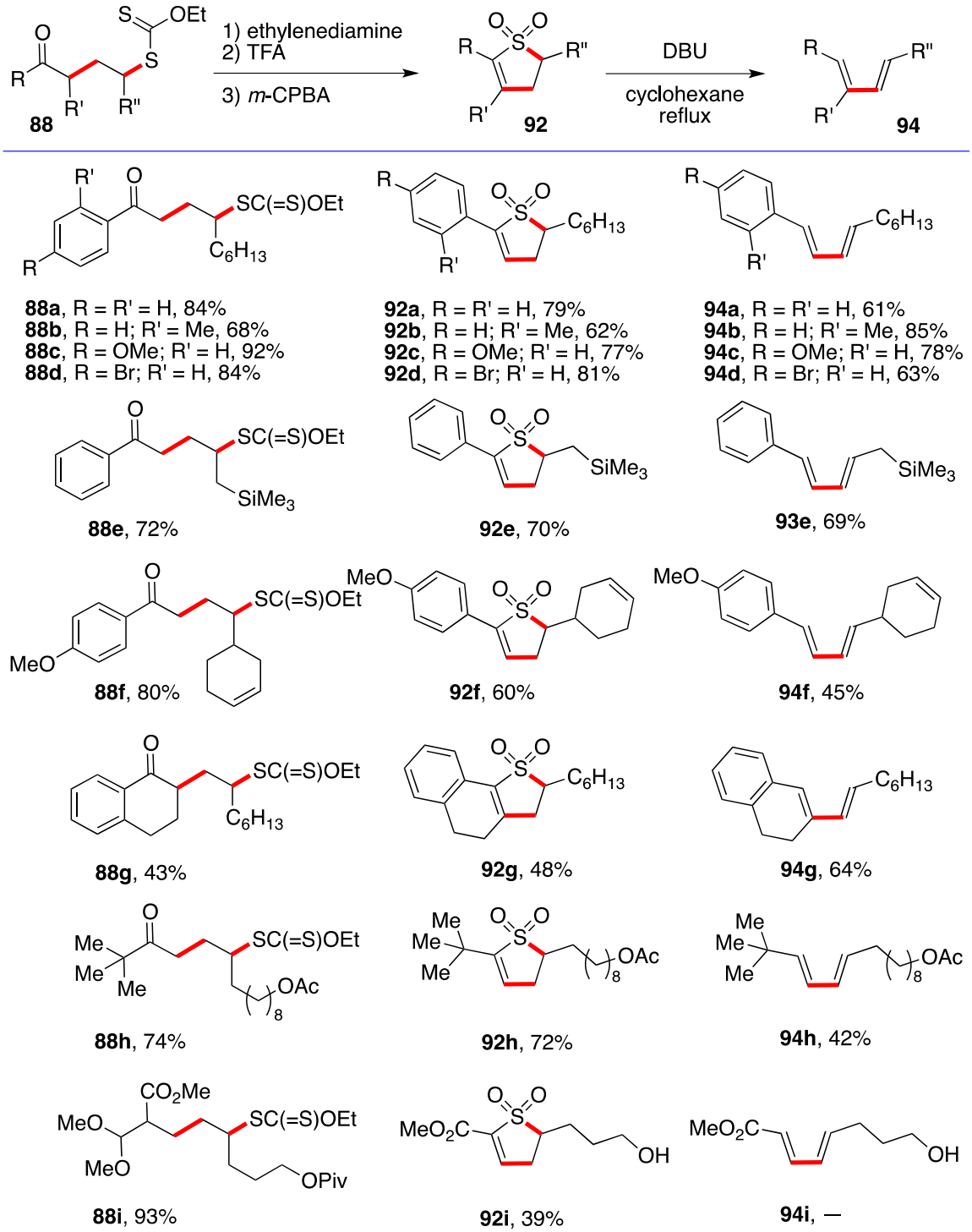
Δ^3-sulfolenes **93**; the latter then extrude sulfur dioxide by a retro-cheletropic cycloaddition to give the desired dienes **94**.

Examples of this approach to dienes are assembled in Scheme 10.[15] The conversion of adducts **88a-f** of various α-ketonyl xanthates **87** and alkenes into the corresponding Δ^2-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,[16] which was not transformed into diene **94i**.



Scheme 10. Examples of sulfolenes and dienes.

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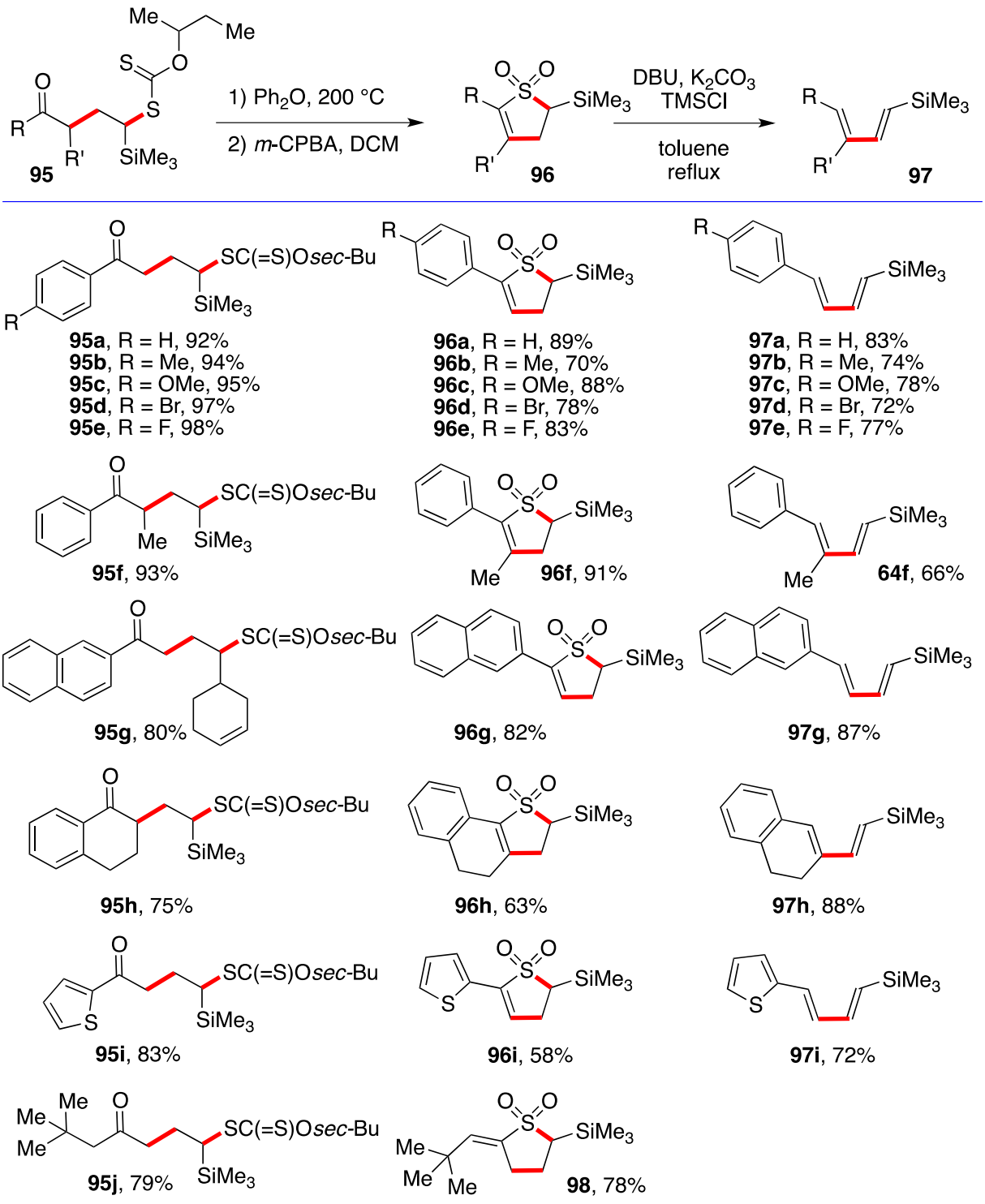

Scheme 11. Examples of TMS-substituted sulfolenes and dienes.

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).[17] 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 Δ^2-sulfolenes **96a-i** in the indicated overall yields. The conversion of

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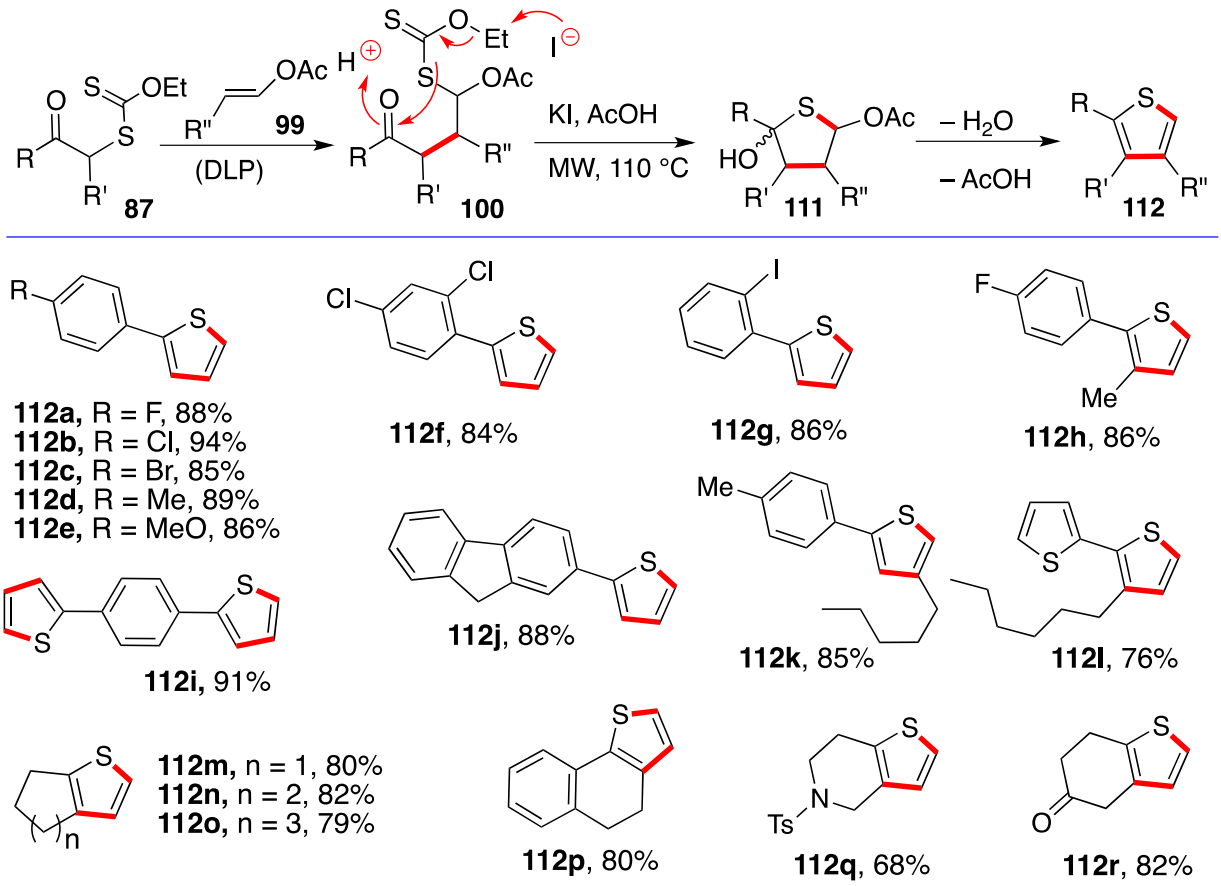
the latter into the corresponding dienes **97a-i** required a significant modification of the experimental conditions. Simple heating with DBU as in the previous examples in Scheme 10 resulted in extensive desilylation of the Δ^2-sulfolenes. This was assumed to be caused by hydroxide ions generated from 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-l** 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.

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.[18,19] 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).[20] 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**.



Scheme 12. Synthesis of thiophenes.

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

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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. Dithiospiroketals

As previously shown in Section 3, the addition of the α-ketonyl xanthates **87** to an alkene gave rise to adducts **88**. The subsequent thiols, **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 α-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 dithiospiroketals **116** with loss of water.[21]

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 dithiospiroketals **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 dithiospiroketals 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 dithiospiroketals 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 dithiospiroketals **116a,c,d** could be readily desulfurized using Raney nickel to give 25-carbon long-chain monomers in high yield. Polyamides derived from such monomers have physico-chemical properties in between those of non-polar polyethylene and polar 6,6-nylon.[25]

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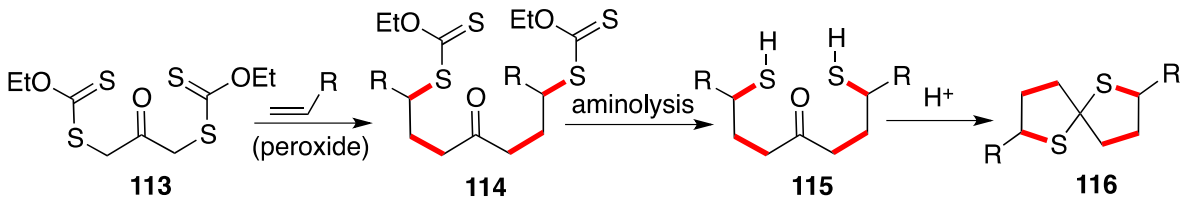

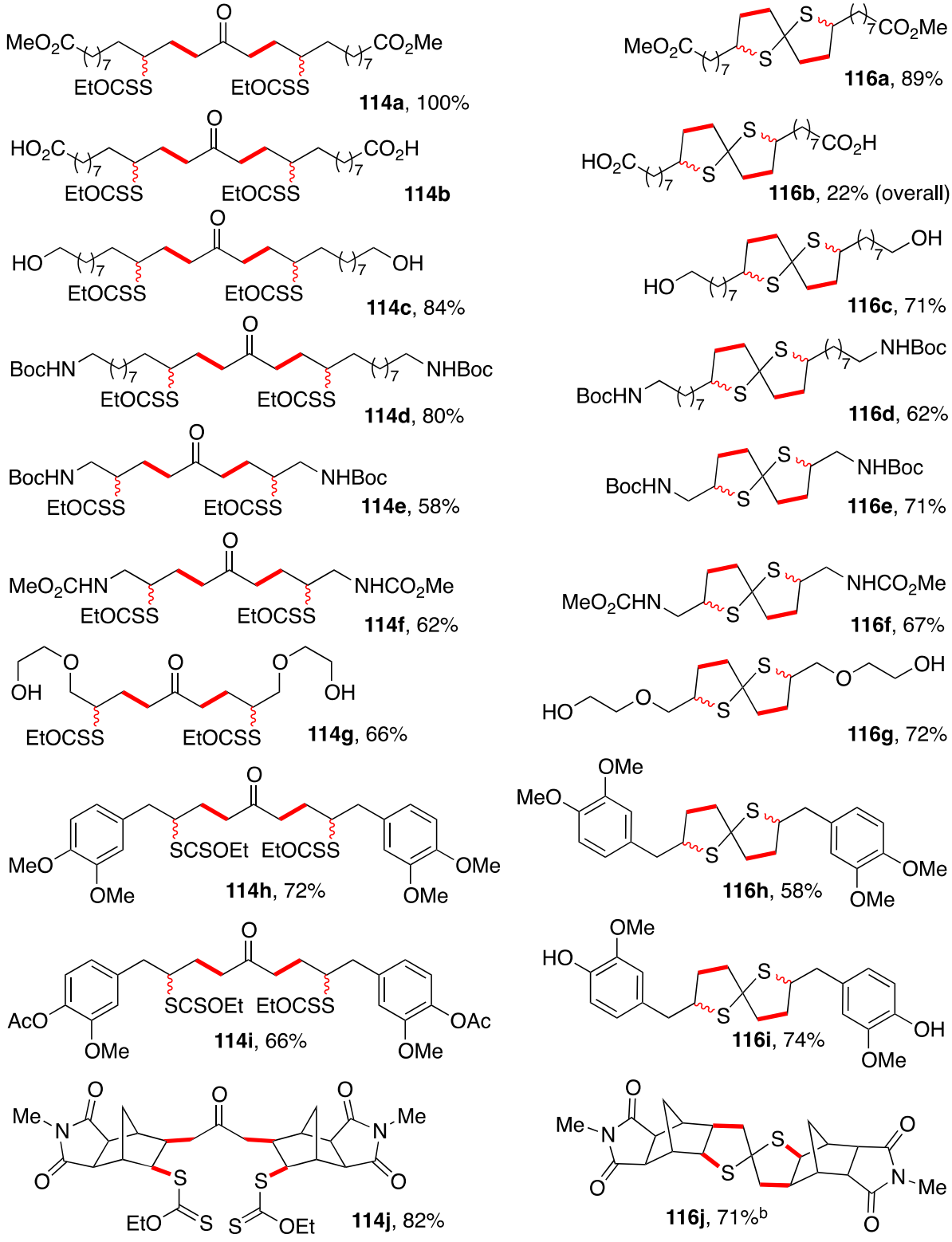

Scheme 13. Synthesis of dithiospiroketals.

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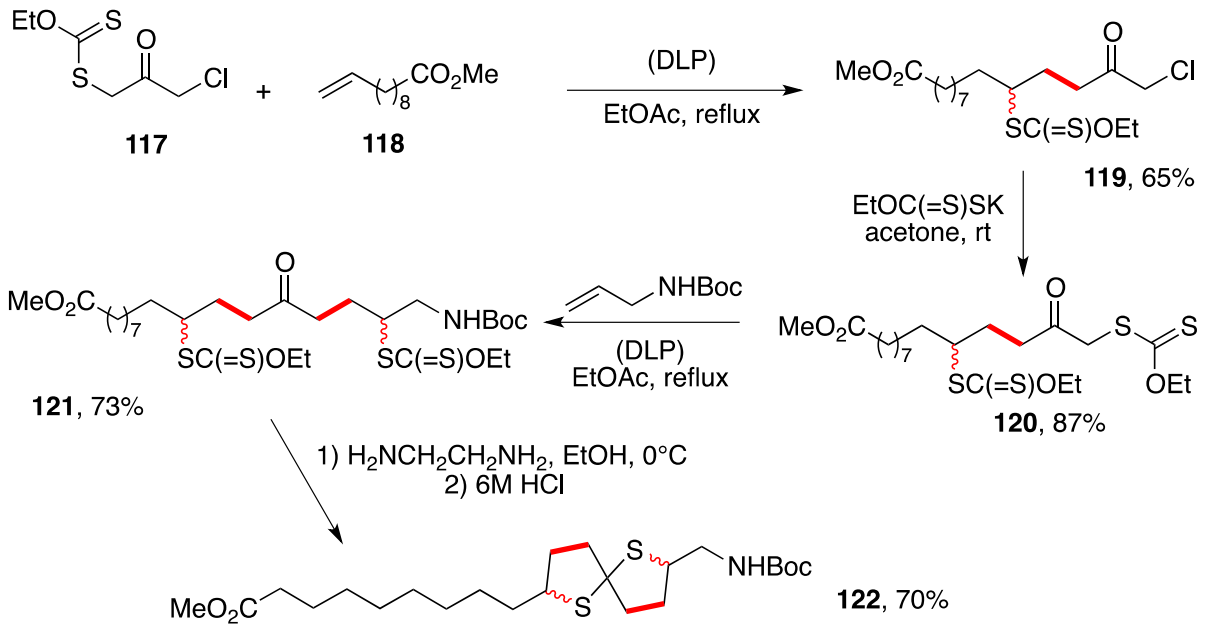
Non-symmetrical dithiospiroketals are simply obtained by a variation of the above route, as outlined in Scheme 14 for compound **122**.[21] Chloroketonyl xanthate **117** adds cleanly to methyl 10-undecylenate **118** to give adduct **119**, from which the chlorine can be substituted with a xanthate. 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.



Scheme 14. Synthesis of an unsymmetrical dithiospiroketal.

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**.[26] 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.[27, 28] 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 **125o**, which combines a thiolactone and a 1,3-dithian-2-one motif, are quite unusual derivatives worth underlining.

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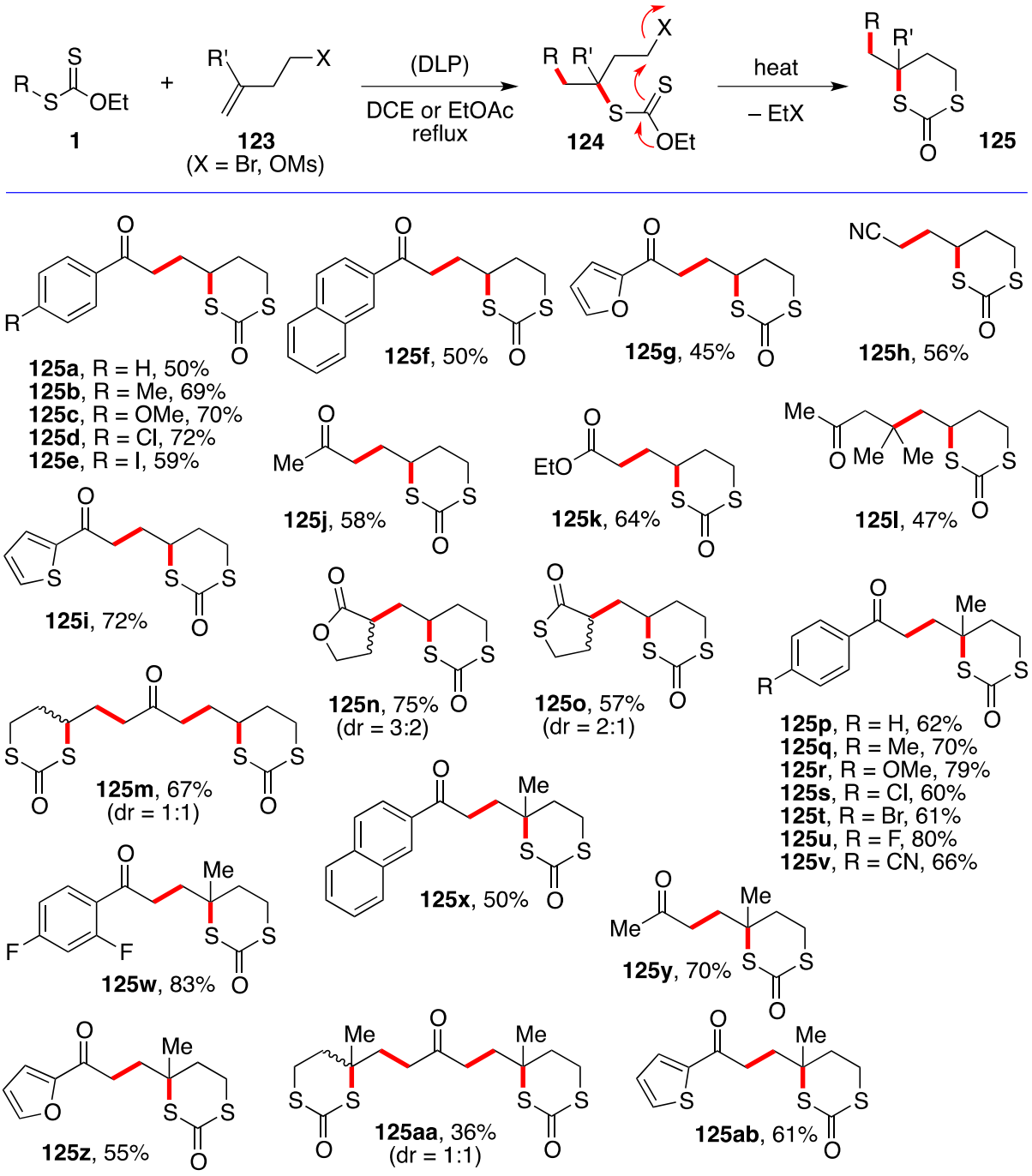

Scheme 15. Synthesis of 1,3-dithian-2-ones.

Homoallylic tertiary alcohols **126** are also suitable precursors (Scheme 16).[26] 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.

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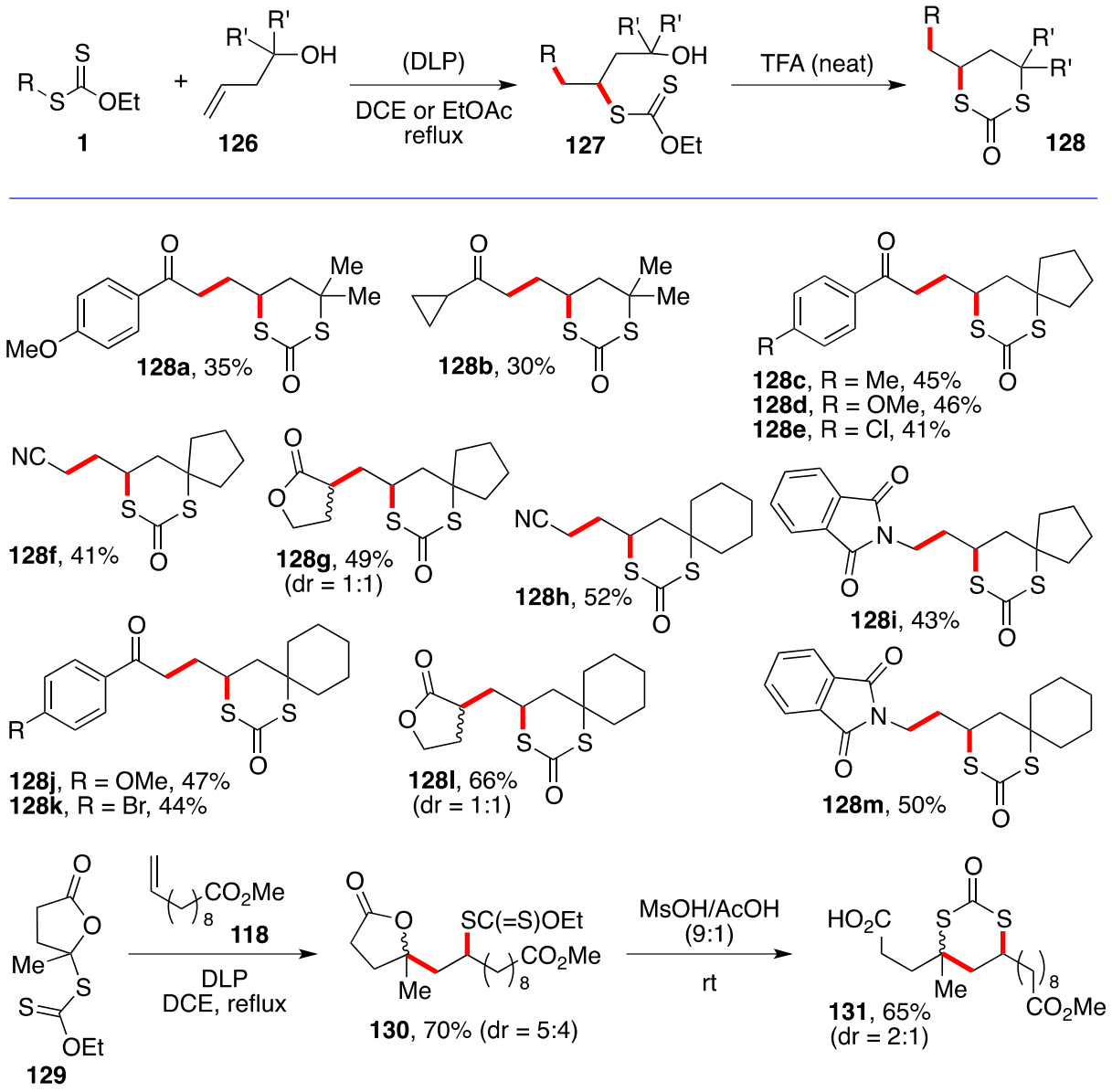

Scheme 16. Further examples of 1,3-dithian-2-ones.

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.

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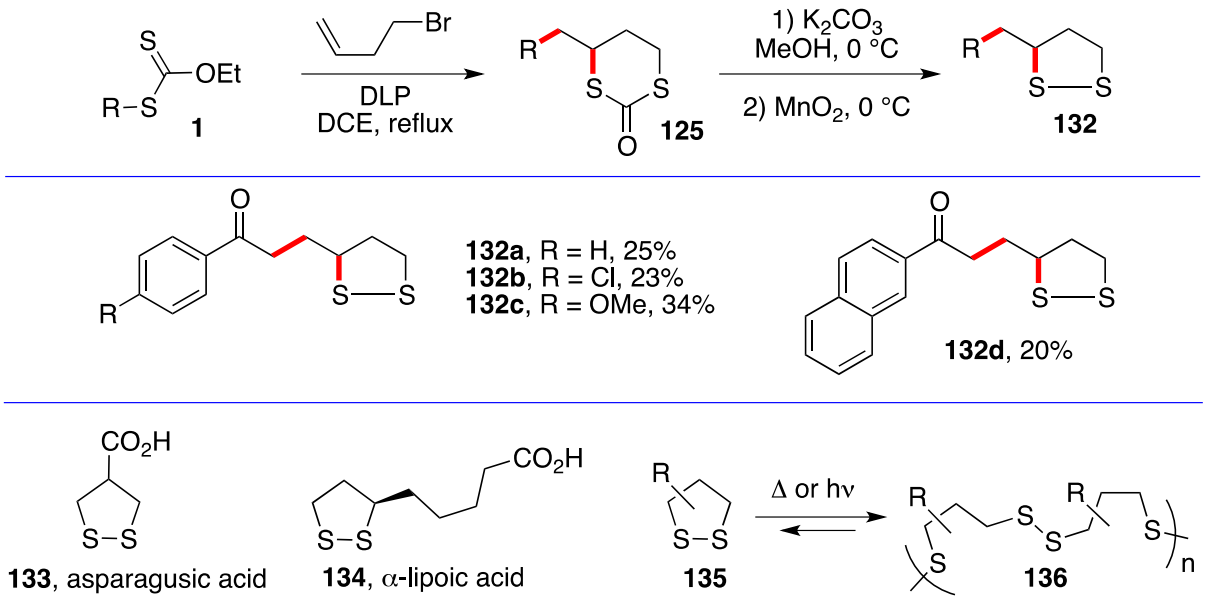

Scheme 17. Synthesis of 1,2-dithiolanes.

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 allylic 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.

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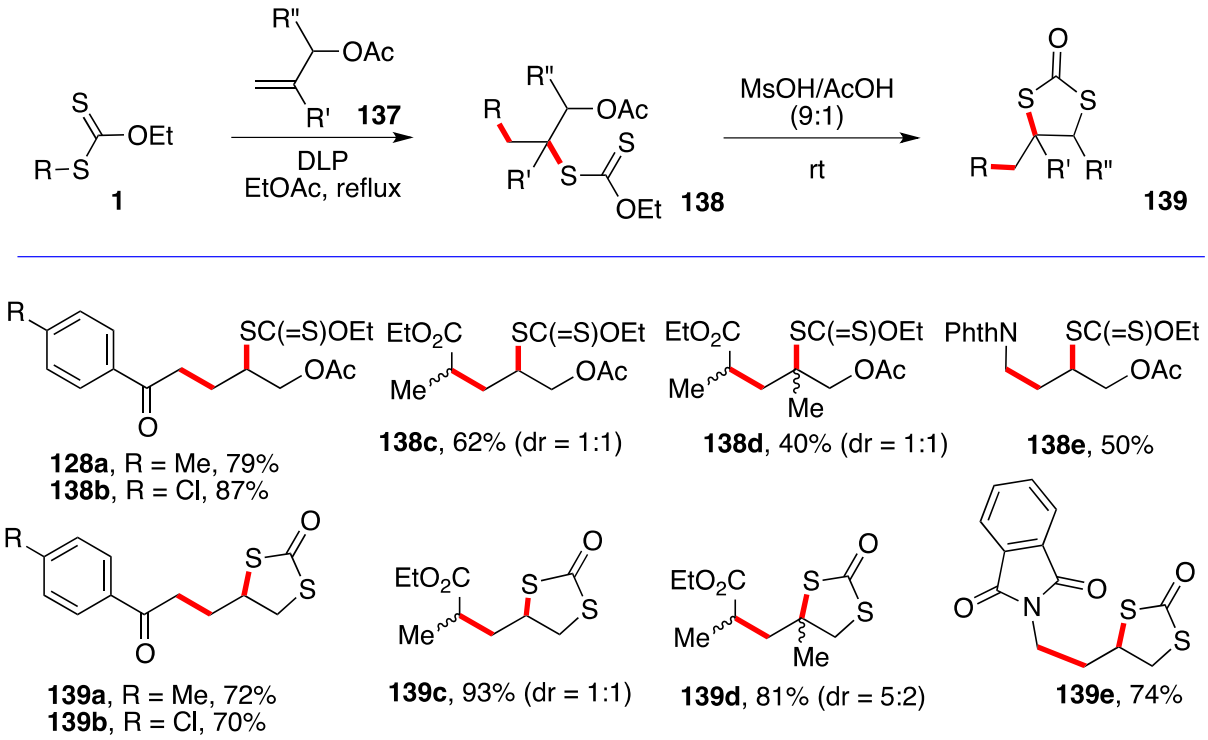

Scheme 18. Synthesis of 1,3-dithiolanones.

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-fluoroacetophenyl 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

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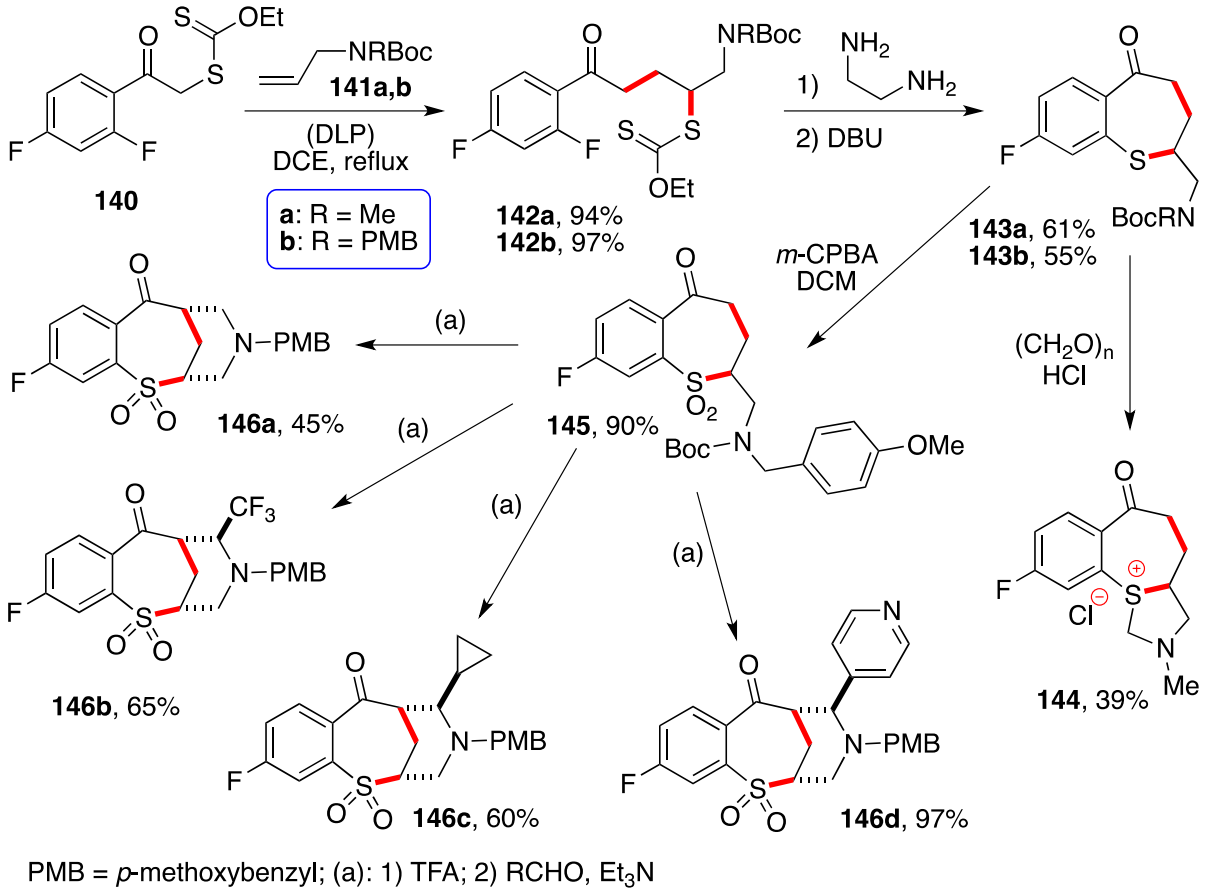
p-fluorine atom. The latter is activated by the electron-withdrawing ketone and is, therefore, easily substituted by various nucleophiles.[31]



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**.[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.

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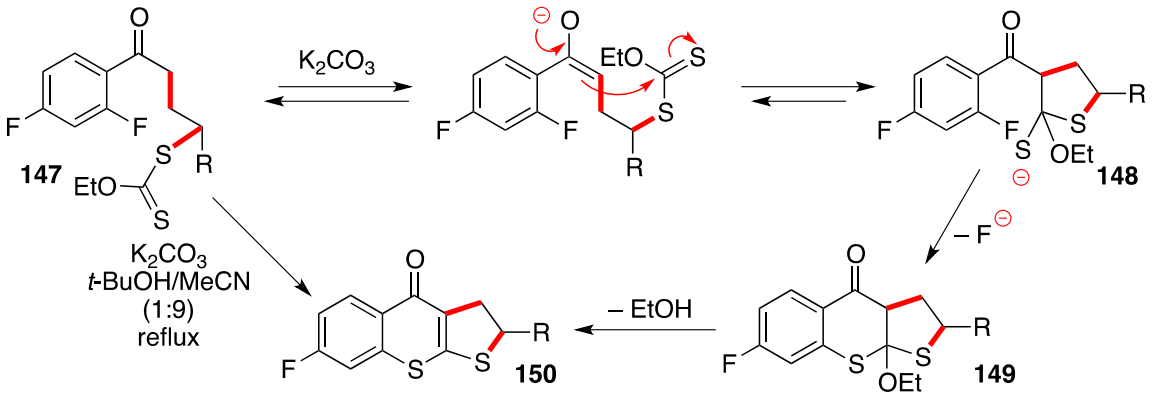
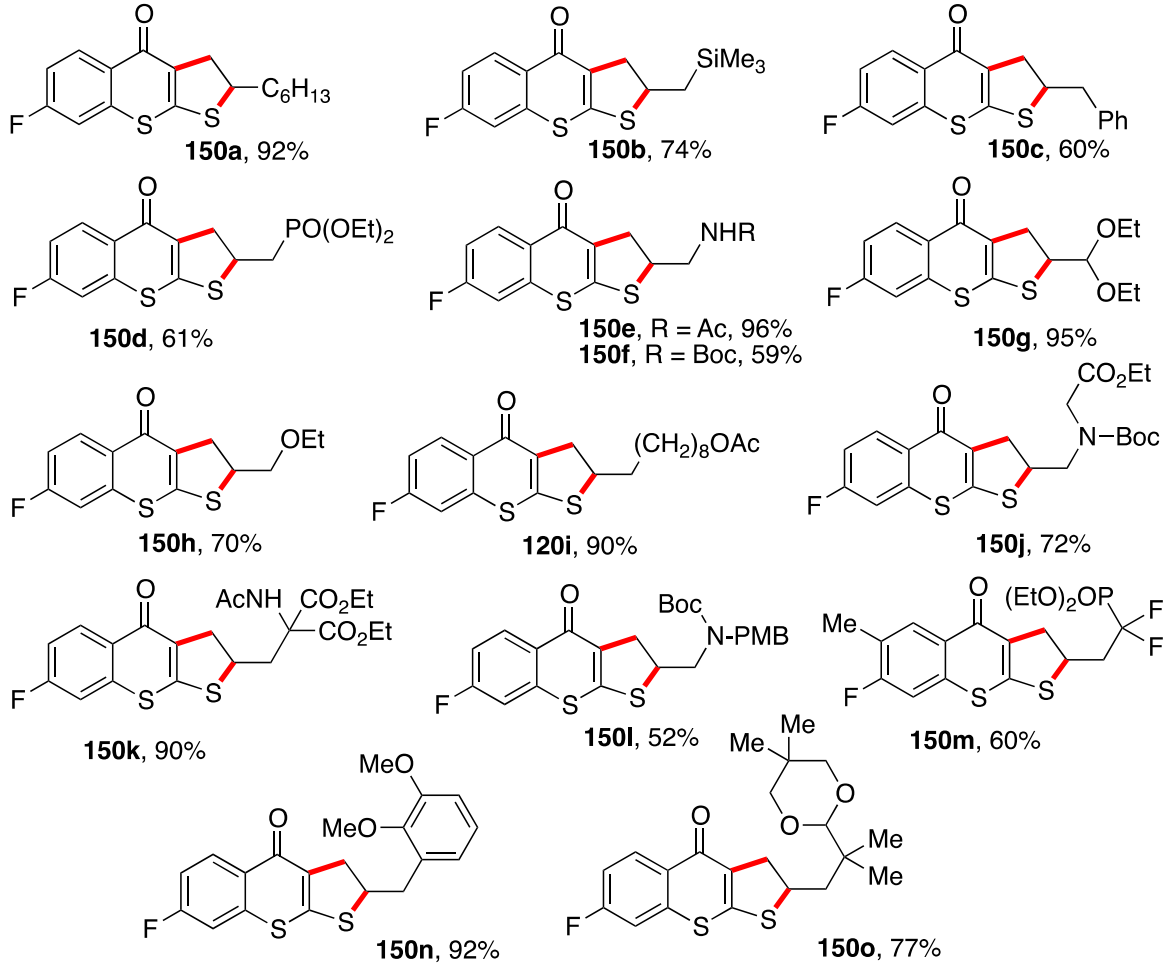


Scheme 20. An unusual route to 2,3-Dihydrothieno[2,3-b]thiopyran-4-ones.

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.

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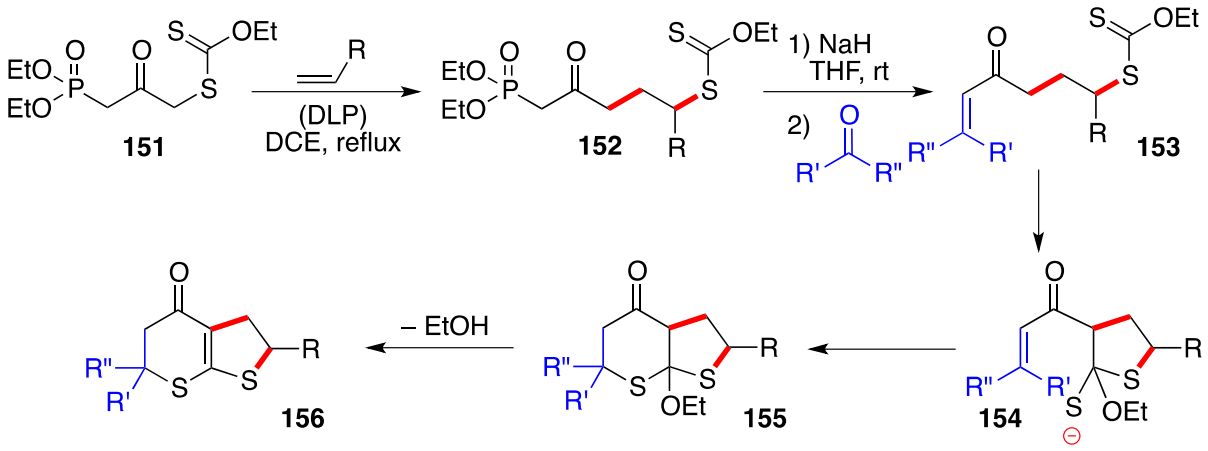
A conceptually-related approach to aliphatic analogues was also uncovered using xanthate **151** (Scheme 22). The xanthate in this reagent allows a radical addition on one side of the ketone to give adducts **152**, and the phosphonate mediates an ionic Horner-Wadsworth-Emmons on the other side to give finally enones **153**.[32] 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-tetrahydro-thieno[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.[32] 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.

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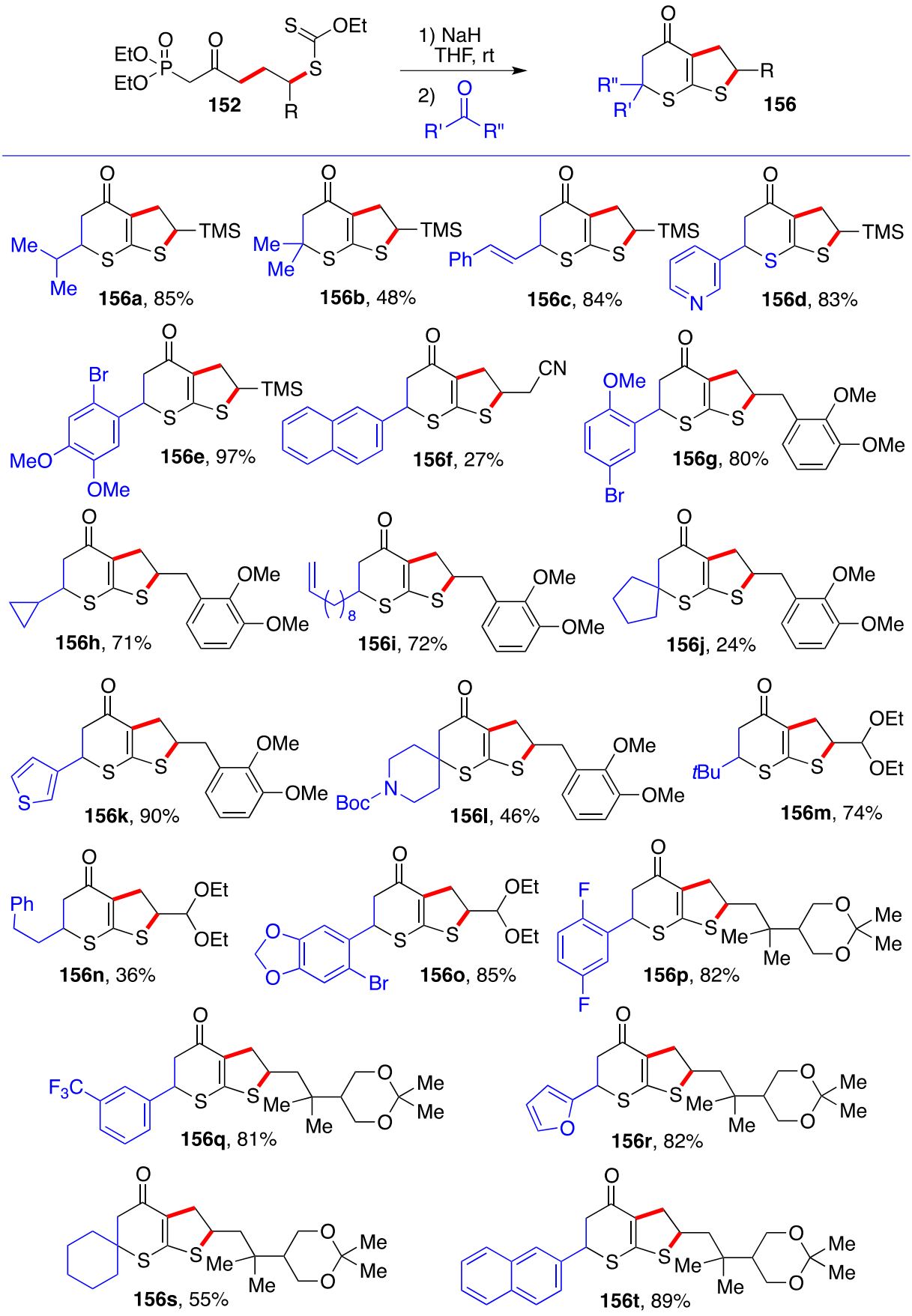

Scheme 23. Examples of 2,3,5,6-tetrahydro-thieno[2,3-b]thiopyran-4-ones.

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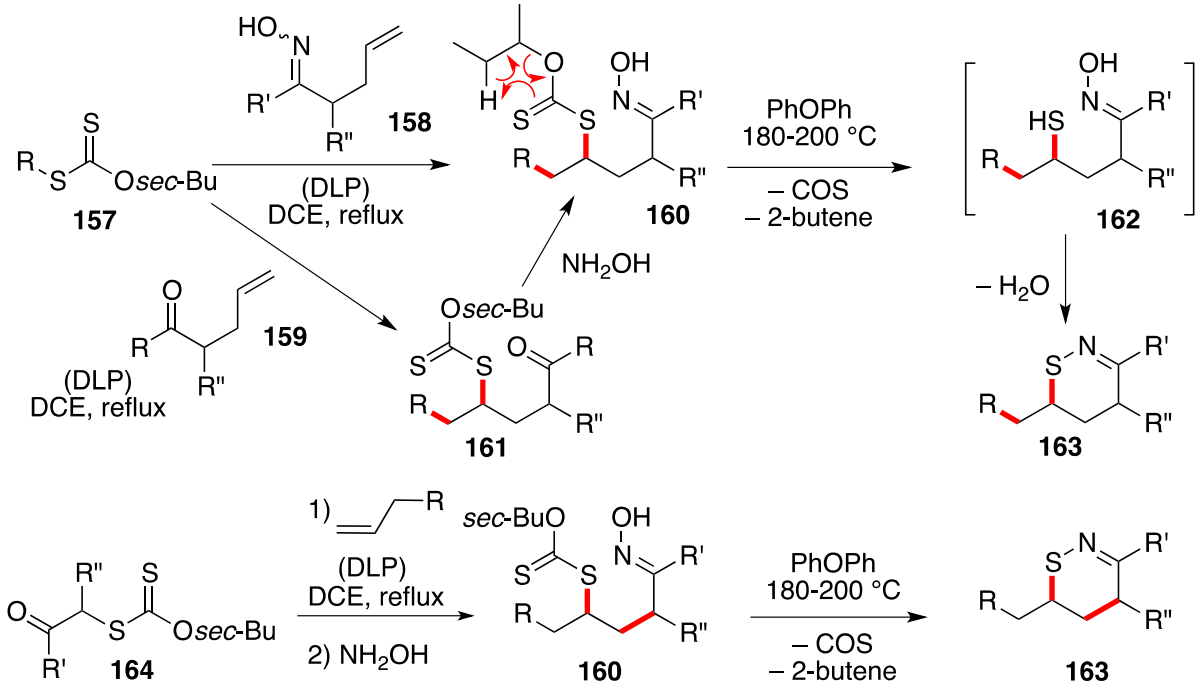
7. Dihydrothiazines and Difluorothiochromanes

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.

Dihydrothiazines **163a-l**, 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**).[34] Despite the modest yields, this approach remains so far the only reported access to substituted members of this family of heterocycles.

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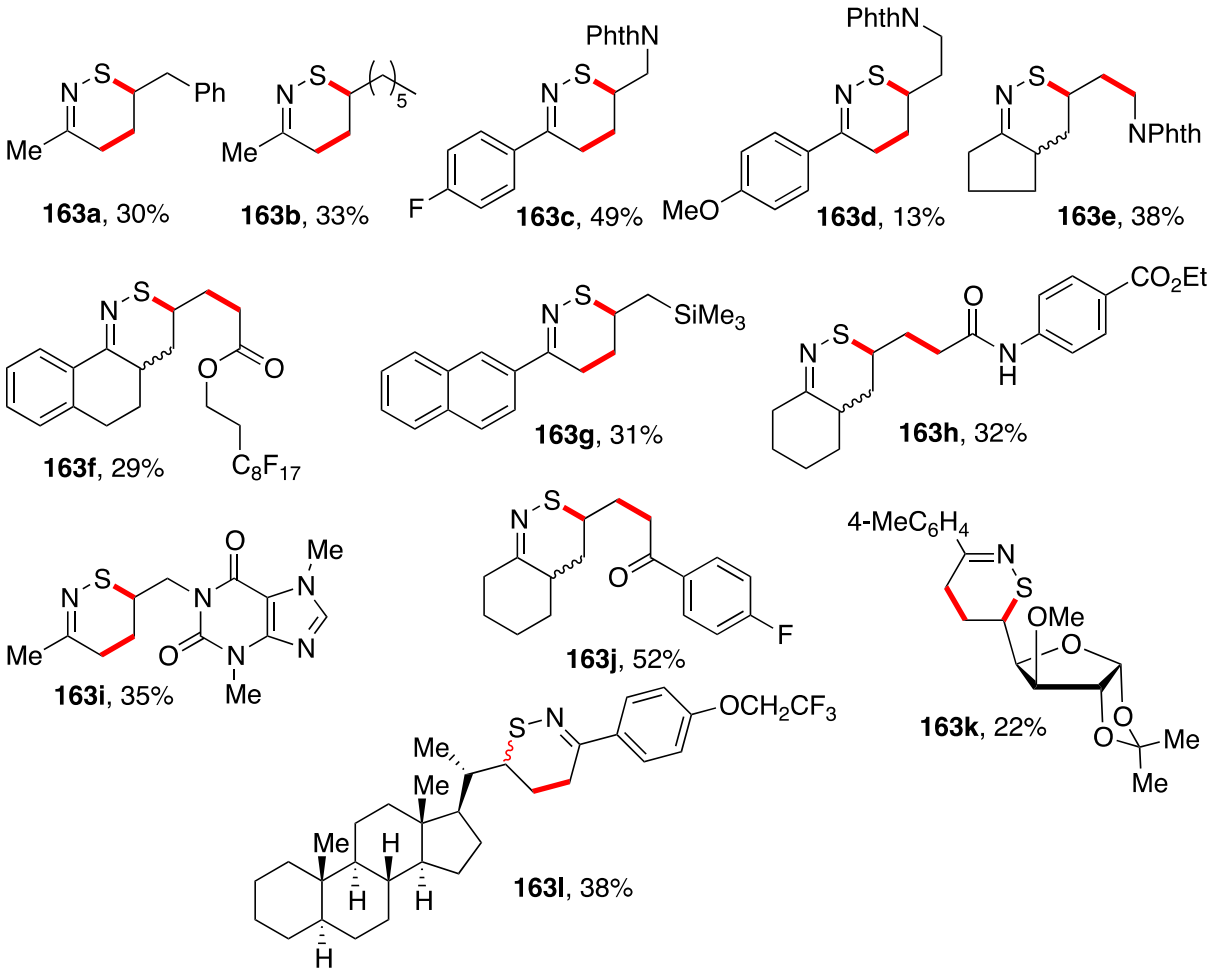

Scheme 25. Examples of dihydrothiazines.

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.[34] 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 difuorothiochromanes 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.

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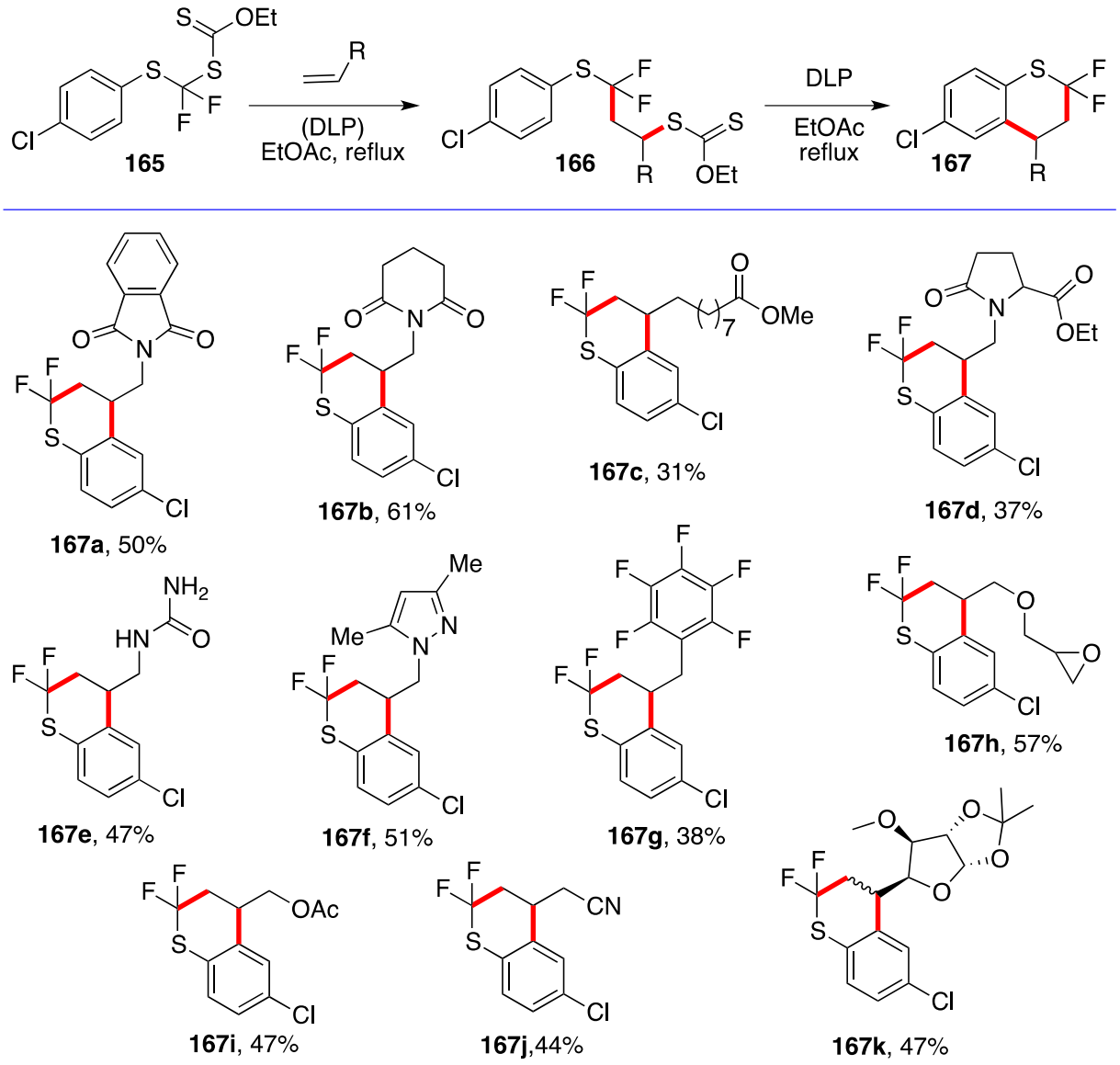

Scheme 26. Synthesis of difluorothiochromanes.

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 heterocyles 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.

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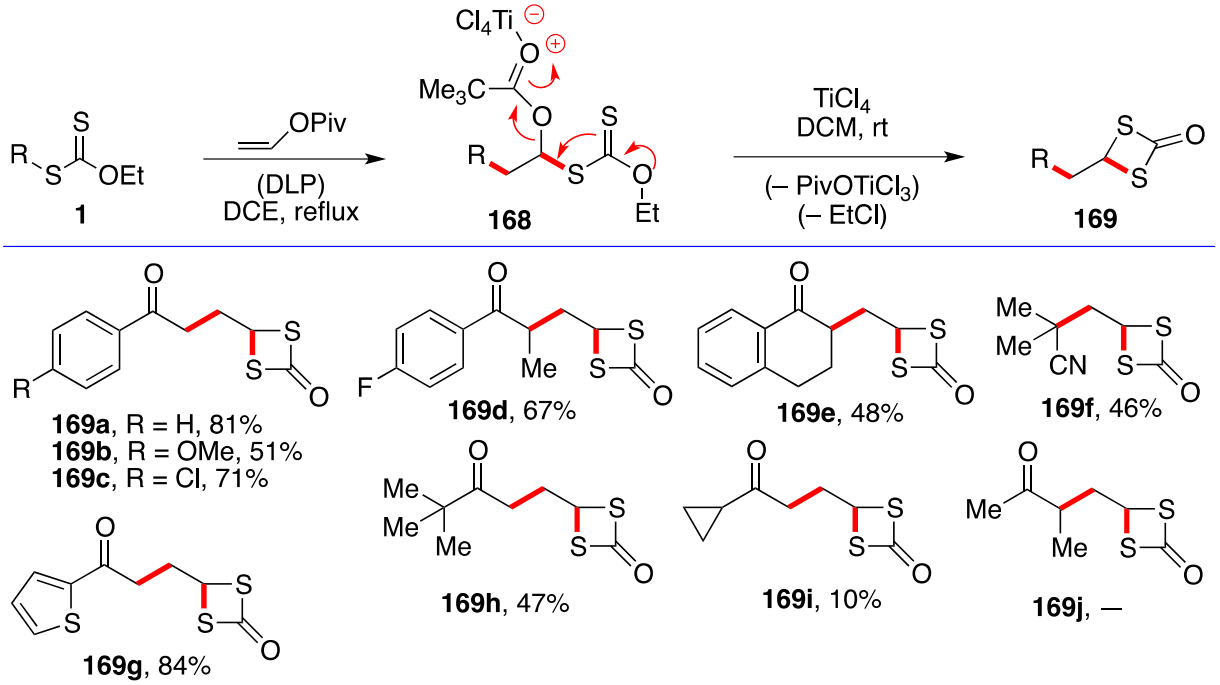
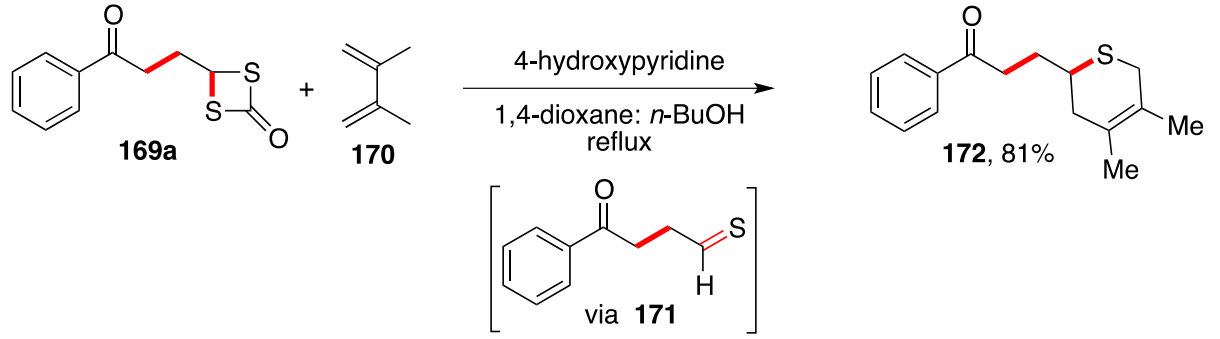
This is shown in a generic way for adducts **168** derived from xanthates **1** and vinyl pivalate (Scheme 27).[35] The Lewis acid complexes with the oxygen of the ester group and activates it toward substitution by the thiono-sulfur of the xanthate as indicated on structure **168**.



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.

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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.[37] This chemistry will no doubt see further important developments in the future.

Acknowledgements

No chemistry laboratory can function without dedicated and talented younger colleagues. We, therefore, wish to express our sincere thanks to our students and post-doctoral collaborators for making this chemistry possible. We are also very grateful to all the institutions, agencies, and industries that have funded our laboratory over the years.

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Authors' Biographies

Béatrice Sire (née Quiclet) obtained her MSc in biochemistry in 1976 from Université Paris-Sud, Orsay, France. She then completed her PhD thesis in 1980 at the same university under the supervision of Dr Stéphene Géro, working on the synthesis of pseudo-disaccharides related to the aminoglycoside antibiotics. In 1981, she obtained a position as a Chargée de Recherches at the CNRS within the research group of Dr Stéphene Géro at the Institut de Chimie des Substances Naturelles (ICSN) in Gif-sur-Yvette where she also collaborated with Professor Sir Derek Barton. In 1993, she joined the group of Professor Samir Z. Zard, first at the ICSN, then at Ecole Polytechnique.

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Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received the Croix de Chevalier de la Légion d'Honneur in 2007. He is currently an emeritus professor at Ecole Polytechnique, and an emeritus Director of Research Exceptional Class in the CNRS

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