Radical Chemistry Associated with the Thiocarbonyl Group

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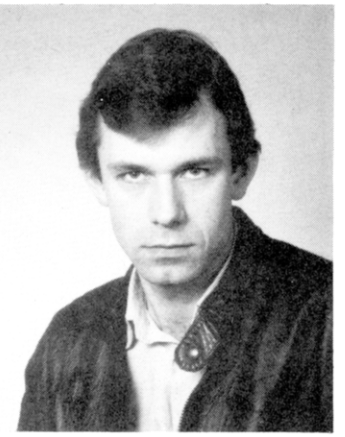
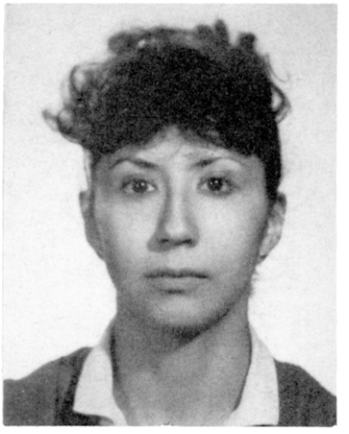


David Crich was born in Chesterfieid, England, in 1959 and obtained his B.Sc. from the University of Surrey in 1981. He then moved to the Institut de Chimie des Substances Naturelles in Gif sur Yvette, France, where he worked under the supervision of Professor Sir Derek Barton, obtaining the degree of Docteur ès Sciences in 1984. After a further period in Gif as a postdoctoral research worker, Dr. Crich was appointed to his present position as lecturer at University College London in 1985. His major research interests are in the area of synthetic methodology.



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I. Introduction

The inherent weakness of the thiocarbonyl bond with its low coefficient of $C2p^{\pi}$–$S3p^{\pi}$ orbital overlap leads to a rich and varied chemistry, photochemical[1] and nonradical[2] aspects of which have been reviewed recently. This article reviews the still-developing field of synthetic aspects of thiocarbonyl group chemistry arising from addition of so-called thiophilic radicals to the sulfur of the thiocarbonyl bond. The addition of electrons to thiocarbonyl esters[3] in single-electron-transfer reactions is not within the scope of this review.

The attachment of a thiocarbonyl moiety, with its extensive associated free-radical chemistry, to various functional groups, for instance, as thiocarbonyl esters to alcohols and as mixed anhydrides to carboxylic acids, can considerably broaden and enhance the chemistry of those groups. Maximum advantage of thiocarbonyl groups and their radical-trapping capabilities is taken when the trapping step is designed to be one step in a chain sequence, so enabling the radical concentration

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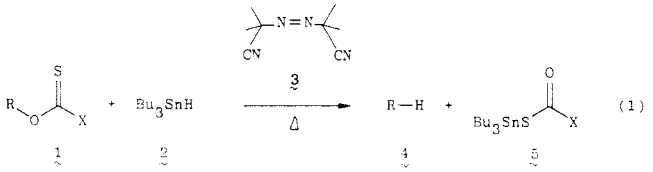
to be maintained at a minimum and effectively eliminating wasteful and unwanted radical–radical reactions.

II. Generation and Trapping of Alkyl Radicals from Alcohols via Thiocarbonyl Esters

1. Introduction

The deoxygenation of secondary alcohols by means of the azobis(isobutyronitrile) (AIBN) (3) initiated reaction of tri-*n*-butyltin hydride (TBTH) (2) with derived thiocarbonyl esters 1 (eq 1) is widely known as the

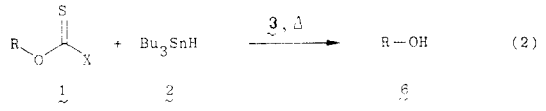


(1)

Barton–McCombie reaction. The early development of this extremely useful reaction, first described[4] in 1975, has been discussed[5] in several reviews. Nevertheless this is a continually evolving area and as such we deal here first with mechanistic aspects of the reaction and go on to present an overview of its utility as a tool for the removal and/or manipulation of hydroxyl groups in organic synthesis.

2. Mechanistic Aspects

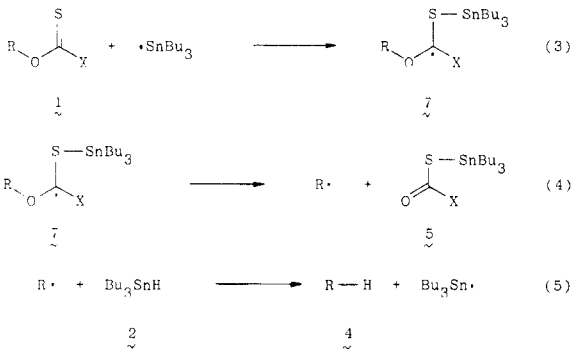
As indicated by eq 1 a variety of readily derived thiocarbonyl esters of secondary alcohols have been treated with 2 in attempts to bring about efficient high-yielding deoxygenation. A considerable range of X groups has been studied in order to find a derivative that satisfies three main criteria, viz., ease of preparation, crystallinity, and, most importantly, clean deoxygenation. It has been found that the following X groups give good yields of deoxygenation according to eq 1 when R is a secondary alkyl group: X = SMe,[4] SPh[5,6] (dithiocarbonates or xanthates); X = Ph[4] (thiobenzoates); X = OMe,[7] OPh[8] (thiocarbonates); X = 1-imidazolyl,[4] X = 1-pyrrolyl,[9] X = 1-(1*H*)pyridin-2-onyl[10] (thiocarbamates with delocalization of an N lone pair). Various X groups have also been found that do not give deoxygenation under typical conditions and can be subdivided into several classes: those undergoing reaction with TBTH but refurnishing the starting alcohol 6 (eq 2) (X = H,[4,11] Me[4]); those recovered un-



(2)

changed after heating with TBTH and AIBN (X = NR_2, aliphatic thiocarbamates[4]); and a third category, the thiocinnamates[4] (X = CH=CHPh), which are simply reduced to the dihydrothiocinnamates and do not react further.

A radical chain mechanism (eq 3–5) was originally proposed[4] by Barton and McCombie to account for the successful deoxygenation reactions. This mechanism allows for all the variations of X. In the most common case (X = SMe) it is assumed[4] that the initial byproduct 5 decomposes in situ according to eq 6 to give the ob-



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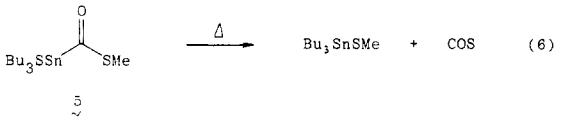
served byproducts (methylthio)tributylstannane and carbon oxysulfide. ESR studies have been published[13]



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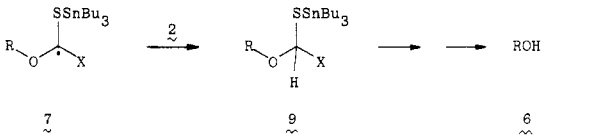
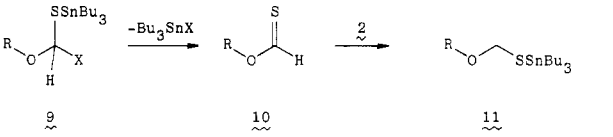
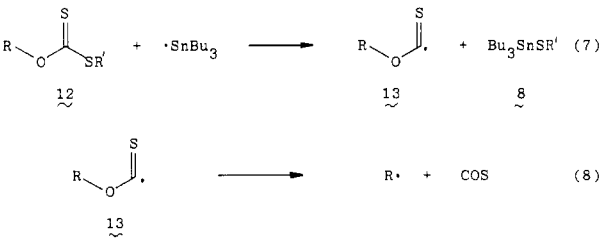
in support of an initial adduct radical 7 when X = H or Me, i.e., for those cases in which efficient fragmentation is not observed, but not for the xanthates, thiocarbonates, or (thiocarbonyl)imidazolides. According to this chain mechanism, the formation of alcohols (X = H, Me) is accounted for by inefficient fragmentation of adduct radical 7, which is trapped by the stannane, giving an orthoester 9, which eventually leads to the alcohol 6. Subsequent work[14] has clearly shown that



such orthoester derivatives 9 are not observable under typical conditions and if present must decay further to thioformates 10, which react to give hemithioacetals 11, resulting in hydrolysis back to the alcohol on workup.



An alternative chain mechanism for the deoxygenation reaction, based on ESR observations of alkoxythiocarbonyl radicals 13, was subsequently proposed[15,16] by Beckwith and Barker for xanthates 12 (X = SMe, SPh) (eq 5, 7, and 8).



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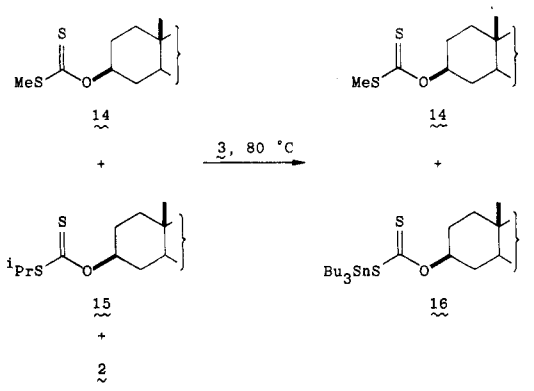
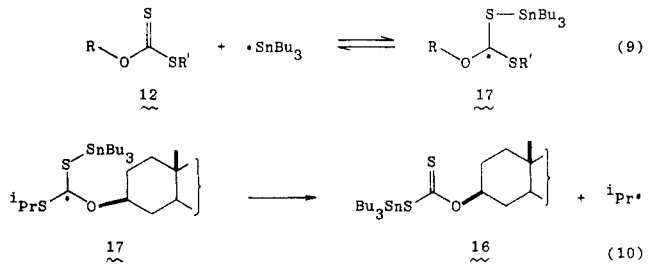
This proposal stimulated the Barton group to carry out a further series of experiments[14] designed to differentiate between stannyl radical attack at thiocarbonyl sulfur (eq 3) or sulfide sulfur (eq 7) under the typical deoxygenation conditions. The majority of these experiments, and indeed later experiments involving cyclizable probes by Bachi and Bosch,[18,19] provided useful information on the temperature dependence of

the reaction and on the formation of side products due to inefficient deoxygenation but proved unable to differentiate unambiguously between the two mechanisms. Nevertheless one series of experiments[14] involving competitive reductions of different xanthates was highly informative. Thus AIBN-initiated reaction of equimolar quantities of the *S*-methyl (**14**) and *S*-isopropyl (**15**) xanthates of cholestanol and TBTH in deuterio-

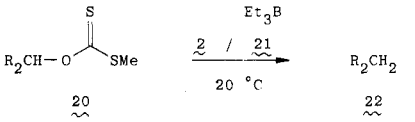


benzene at 80 °C led to the recovery (78%) of the *S*-methyl xanthate **14**, consumption of the *S*-isopropyl xanthate **15**, and formation of an *S*-stannyl xanthate **16** and presumably propane. These results can only be satisfactorily explained in terms of a reversible addition of the stannyl radical to the thiocarbonyl sulfur of both xanthates (eq 9) and preferential cleavage of the weaker *S*-isopropyl bond in the adduct **17** from **15** and the stannyl radical (eq 10).



Further supportive evidence for the reversibility of stannyl radical addition to xanthate thiocarbonyl groups was provided by competitive reductions of the *S*-methyl (**14**), *S*-phenyl (**18a**), and *S*-mesityl (**18b**) xanthates in benzene at 80 °C and toluene at 110 °C in which the relative rates of consumption were found to be different at 80 and 110 °C. Furthermore, in separate reductions of **14**, **18a**, and **18b** with TBTH at 80 °C, the partitioning of the reaction products between cholestane **19a** and the hemithioacetal **19b** was different for each xanthate. These latter experiments conclusively rule out a common intermediate **19c** in the reductions of the various xanthates **14**, **18a**, and **18b** and so invalidate the mechanism proposed by Beckwith.

Given the assumption that the Barton mechanism (eq 3, 9, 4, and 5) holds for all thiocarbonyl esters, it is clear that the overall efficiency of the reaction is related to the efficiency of the cleavage step (eq 4). As stated above, inefficient cleavage of **7** in the case of xanthates and (thiocarbonyl)imidazolides leads eventually to hemithioacetals **11** and so to alcohols on workup. In the case of thiobenzoates inefficient cleavage results in reduction to the benzyl ethers.[4,8] It will be noted that both reduction of xanthates and (thiocarbonyl)-imidazolides to hemithioacetals and reduction of thiobenzoates to benzyl ethers consumes further TBTH and hence is not only detrimental to the deoxygenation yield but also further complicates product isolation. Clean high-yielding deoxygenation reactions are observed by operating under conditions such that fragmentation (eq 4) is much more rapid than adduct quenching (**7** → **9**). For secondary alcohol derivatives this is best achieved[20] by carrying out the reaction in toluene at reflux. For primary alcohols efficient fragmentation is achieved[21] by working in xylenes at reflux, although there has been a report[22] of primary alcohol deoxygenation in benzene at reflux. Deoxygenation at lower temperatures is observed[23] when fragmentation is accelerated by the presence of a β C–O bond. The deoxygenation of tertiary alcohols is hampered by difficulties in the preparation of and isolation of suitable thiocarbonyl derivatives as well as by their thermal instability[24] with respect to the Chugaev reaction, although exceptions to this rule are known. Thus an isolated example of the high-yielding deoxygenation of a tertiary xanthate in toluene at reflux has been published[25] but Barton and co-workers prefer[12] the more stable thioformate esters, which are reduced in benzene at reflux. With respect to the more usual case of secondary alcohol deoxygenation, a recent paper[26] has disclosed that secondary xanthates **20** can be efficiently deoxygenated to alkanes **22** in benzene at 20 °C when triethylborane (**21**) is added to the usual reaction mixture (≥80%). This



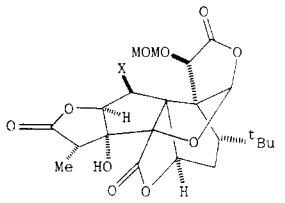
observation is obviously of some considerable importance insofar as it will allow deoxygenation of thermally unstable secondary alcohols; however, it should be noted that the effect did not extend to primary alcohols. Finally in this section it is interesting to note a report of the successful deoxygenation[27] of a secondary alcohol by treatment of its derived (thiocarbonyl)imidazolide with sodium borohydride in dimethyl sulfoxide at 90 °C.

3. Reductive Deoxygenations

The deoxygenation of secondary alcohols by the Barton–McCombie procedure is an extremely wide-ranging reaction and is compatible with many functional groups encountered in natural and nonnatural product chemistry. The examples illustrating the text are chosen to portray the multiplicity of functional groups and skeletal types consistent with this reaction.

A first important point to note is the fact that the reaction proceeds via free-radical intermediates and, due to the low solvation of these neutral species compared to charged intermediates, is considerably less susceptible to steric hindrance. An early example of this property is provided[28] by the obtention of 1,1,3,3-

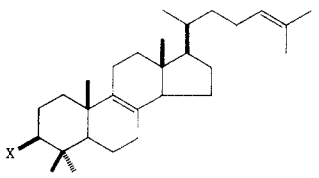
tetramethylcyclopentane in 52% yield from the reaction of *O*-2,2,5,5-tetramethylcyclopentyl *S*-methyl dithiocarbonate with TBTH at 110 °C. A more graphic example of this insensitivity to steric hindrance is taken from Corey's work[29] in the ginkgolide field (**23a** → **23b**, 90%).



23a X = OCSN

23b X = H

Barton's application[4] to lanosterol deoxygenation (**24a** → **24b**, 88%) demonstrates a further principle: namely, that unlike the corresponding carbocationic intermediates, skeletal rearrangement of the intermediate radical is not normally a problem. Application to er-

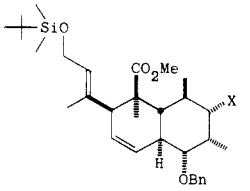


24a X = OCSSMe

24b X = H

gosterol[4] demonstrates that even this sensitive cyclohexa-1,3-diene system is stable under the standard Barton–McCombie conditions. In the steroid area monothiocarbonates have been used[8,30] for the removal of oxygen from the 3-position, and a variety of thiocarbonyl esters have been employed in the deoxygenation of 11α-[31] and 16-ols[32] and several side chain[33] hydroxylated products. In the related pentacyclic triterpene field the final step in a preparation[34] of 30-norhopane was a Barton–McCombie deoxygenation sequence.

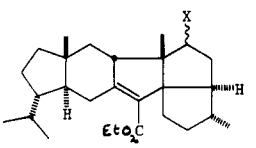
In the vast field of decalinoid and perhydroindanoid natural products there are many examples of the successful deoxygenation of secondary alcohol groups by the Barton–McCombie reaction; a single example from the work of Roush[35] on the synthesis of the octahydronaphthalene unit common to the antitumor antibiotics kijanolide and tetronolide is illustrative (**25a** → **25b**, 82%).



25a X = OCSN

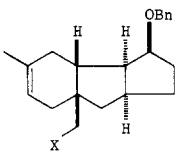
25b X = H

Extensive use has been made of Barton–McCombie deoxygenation for the removal of surplus secondary hydroxyl groups in the popular polyquinane area; examples are to be found in the hirsutene series,[36] the capnellene series,[37] in the angular triquinanes,[38] and in the closing stages of a synthesis[39] of retigeranic acid (**26a** → **26b**, 72%). A further interesting example in this area, particularly in view of the fact that it was carried out at 110 °C, is the selective removal of a neopentylic primary hydroxyl group in a triquinane synthesis[40] (**27a** → **27b**, 60%).



26a X = OCSSMe

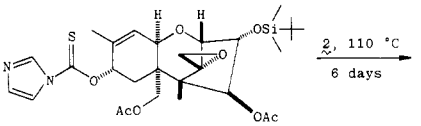
26b X = H



27a X = OCSOPh

27b X = H

Applications of the Barton–McCombie reaction have been found in the gibberelin[41] and tricothecene[42] fields. The formation **29** from **28** (50%), taken from the latter



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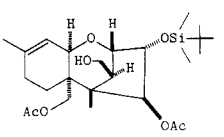
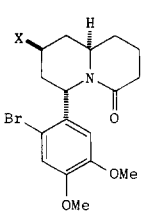


29

field, serves to illustrate how prolonged heating with tin hydrides may be detrimental:[43] Almost certainly opening of the spirocyclic epoxide moiety could have been averted by heating for a shorter time, particularly given the allylic nature of the unwanted secondary hydroxyl group.

Thiobenzoates have been used[44] by Noyori in the prostaglandin field for the deoxygenation of secondary propargylic hydroxyl groups and other thiocarbonyl esters for deoxygenation of the related carbacyclins.[45] In the alkaloid field the Barton–McCombie sequence has served for the removal[46] of unwanted secondary hydroxyl groups from a variety of different skeletons. A particularly interesting example from a synthesis of the quinolizidinone alkaloid vertaline shows[47] how a secondary xanthate **30a** → **30b** is attacked preferentially to an aryl bromide by stannyl radicals (47%).

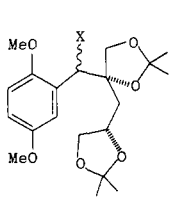


30a X = OCSSMe

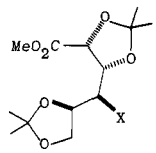
30b X = H

Perhaps the most extensive use of the Barton–McCombie reaction has been in the deoxygenation of

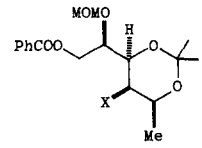
polyhydroxylated compounds where ionic alternatives often fail due to steric hindrance or competing elimination of neighboring groups. Application to carbohydrate-like acyclic polyhydroxylated molecules is widespread as illustrated by **31a** → **31b** (86%),[48] **32a** → **32b** (>70%),[49] and **33a** → **33b** (55%),[50] but the most important application is in the deoxygenation of furanoses, pyranoses, aminoglycosides, and nucleosides, which we now discuss sequentially.

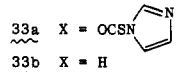


31a X = OCSSMe
31b X = H



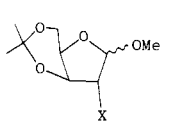
32a X = OCSSMe
32b X = H



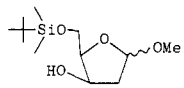


33a X = OCSN
33b X = H

The Barton–McCombie reaction has been successfully applied many times for the preparation of both 2- and 3-deoxyfuranosides. A recent example[51] of such a reaction at the 2-position is the formation of **35** from **34a** by reaction with TBTH followed by exchange of blocking groups (55%). Interestingly, it was found[51] that the dithiocarbonate **34a** gave a much better yield than the thiocarbonate **34b**. A further example,[52] **36a** → **36c** (11%), **36b** → **36c** (67%), draws attention to the fact that dithiocarbonates are better substrates for deoxygenation than thiobenzoates under otherwise identical conditions. Deoxygenation at the furanose 3-position was first demonstrated for the dithiocarbonate **37a** of diisopropylideneglucose by Barton and McCombie;[4,53] further work[54] by Stick demonstrated that the same 3-deoxyfuranose **37c** could be obtained in comparable yield (80–90%) from the equivalent allose derivative **37b**. Moreover, replacement of TBTH by tributyltin deuteride led in both cases to an identical 85:15 ratio of β:α 3-deuterated product, so implying a common radical intermediate. Stick then went on to study[55] deoxygenation at the 3-position of the remaining six isomeric 1,2:5,6-diisopropylidene-D-hexofuranoses and the stereochemistry of quenching with tributyltin deuteride. An example of application to a furanose side chain is provided[56,57] by the work of Vasella, **38a** → **38b** (79%), in which the compatibility of α-phosphonates is also underlined. Vasella has also successfully applied the Barton–McCombie reaction to the deoxygenation of carbocyclic furanose analogues.[58]



34a X = OCSSMe
34b X = OCSOPh



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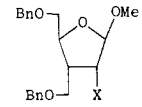
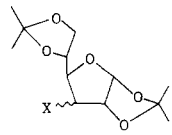
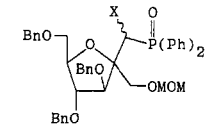
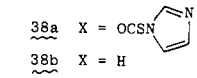


36a X = OCSPh
36b X = OCSSMe
36c X = H



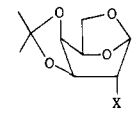
37a X = β-OCSSMe
37b X = α-OCSSMe
37c X = H



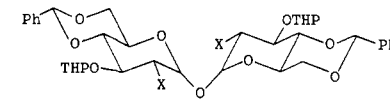


38a X = OCSN
38b X = H

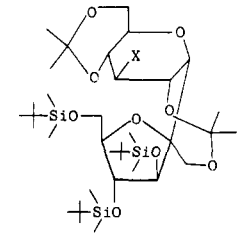
In the pyranose area a good illustration, **39a** → **39b**, of deoxygenation at the 2-position is again provided by the original work[4] by Barton and McCombie (94%). A slightly different procedure was adopted by Thiem in his work[59] on the synthesis of oligo-2-deoxysaccharides; thus various derivatives of 2-deoxyglucose were prepared by reaction of the appropriate 2-dithiocarbonates with tributyltin hydride prepared in situ from bis(tributyltin) oxide and poly(hydromethylsiloxane). A further elegant example,[60] **40a** → **40b**, of the preparation of 2-deoxypyranoses is the simultaneous dideoxygenation of a suitably protected α,α'-trehalose derivative (89%).



39a X = OCSSMe
39b X = H



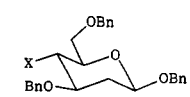
40a X = OCSSMe
40b X = H



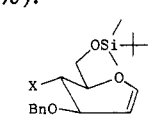
41a X = OCSSMe
41b X = H

Deoxygenation of sucrose at the 3-position of the pyranose ring, **41a** → **41b** (93%), serves as an example[61] of the preparation of 3-deoxypyranoses by this method. A further example is to be found[62] in the deoxygenation of the spiroketal moiety of a milbemycin derivative.

Many examples are known of the preparation of 4-deoxypyranoses by application of the Barton–McCombie reaction to the corresponding hydroxylated molecules. A range of examples using 4-(thiocarbonyl)-imidazolides in the galactose, glucose, and mannose series has been reported[63] by Rasmussen. Other illustrative examples are given by deoxygenation of **42a** to **42b** (75%)[64] and **43a** to **43b** (72%).[65]



42a X = OCSN
42b X = H

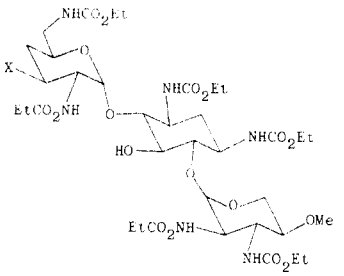


43a X = OCSSMe
43b X = H

An elegant departure from the usual procedure of selective protection followed by thiocarbonyl ester formation at remaining unprotected hydroxyl groups

has been reported.[66] Thus treatment of methyl α-D-xylopyranoside with dibutyltin oxide and subsequently with phenyl chlorothiocarbonate followed by acetylation of the remaining hydroxyl groups and deoxygenation with TBTH in the usual manner gave methyl per-*O*-acetyl-4-deoxy-α-D-xylopyranoside in high yield. Application of the same sequence to methyl glucopyranoside gave 2-deoxy products. As with the furanosides applications of the Barton–McCombie reaction have been found in the field of carbocyclic pyranoses[67] and the related inositols.[68]

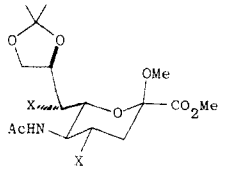
From the very beginning[4] it was realized that the Barton–McCombie sequence would be of value in the modification of aminoglycoside antibiotics. One example, **44a** → **44b**, the deoxygenation of seldomycin factor **5** via a derived (thiocarbonyl)imidazolide, is particularly noteworthy insofar as it was performed on a 12.5-g scale (90%). Deoxygenation of the related molecules epifortimicin[70] and butirosin[71] has also been reported.



44a X = OCSN

44b X = H

In the course of a synthesis of L-vancosamine Brimacombe attempted[72] deoxygenation of the 2-position of a 3-acetamidopyranose by addition of the derived thiobenzoate to TBTH in toluene at reflux. The low yield obtained (30–40%) is probably a further reflection of the lower efficiency of fragmentation of the tributyltin/thiobenzoate radical adduct, especially given the success of other workers with closely related molecules but using dithiocarbonates[72] and monothiocarbonates.[73] More recently, application of the Barton–McCombie procedure in the aminoglycoside area has expanded to include sialic acid derivatives. An elegant example is furnished[74] by the 4,6-dideoxygenation of *N*-acetylneuraminic acid conducted by Zbiral, **45a** → **45b**; examples of the dideoxygenation of neuraminyl disaccharides have also been published.[75]

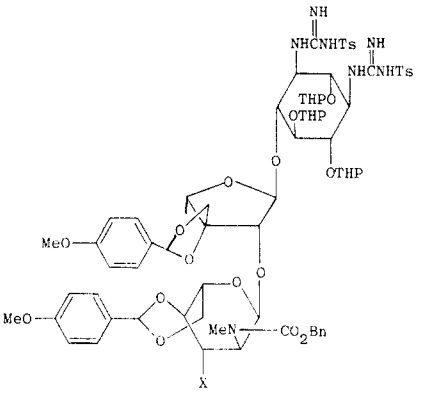


45a X = OCSPh

45b X = H

A final example in the aminoglycoside domain concerns the deoxygenation (68%)[76] of a streptomycin derivative, **46a** → **46b**, and serves to further illustrate the tolerance of the Barton–McCombie procedure toward complex functional groups.

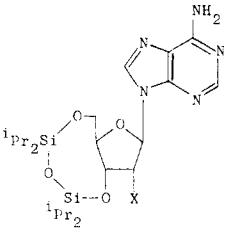
In the nucleoside field the Barton–McCombie reaction has been of immense value in the preparation of



46a X = OCSN

46b X = H

2′-deoxyribonucleosides from ribonucleosides. The groundwork was laid by Robins, who demonstrated[8] that 3′,5′-protection by the tetraisopropyldisiloxyl group followed by treatment with phenyl chlorothiocarbonate and 4-(dimethylamino)pyridine enabled selective formation of a 2′-thiocarbonate **47a**. Conditions required



47a X = OCSOPh

47b X = H

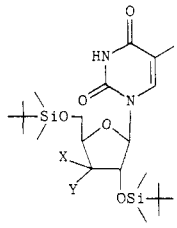
for xanthate formation were incompatible with the 3′,5′-disiloxane group. Deoxygenation to **47b** was then achieved by heating to reflux with TBTH in toluene (78%). This procedure is compatible with both pyrimidine and purine nucleosides; no protection of the base groups is required.

Initial stereochemistry at the 2′-position is of no consequence; both ribo- and arabinonucleosides gave 2′-deoxyribonucleosides in good yield. Reduction with tributyltin deuteride permitted the stereoselective introduction of deuterium onto the α face of ribonucleosides.[8,77] Robins has also demonstrated[78] the applicability of his sequence to the preparation of 2′-deoxyxylonucleosides from xylonucleosides. This sequence has become the method of choice for the preparation of 2′-deoxynucleosides; however, it has been demonstrated that 2′-(thiocarbonyl)imidazolides[80,81] can be used.

Examples of other 2′-deoxynucleosides bearing nonstandard base groups prepared in this manner are to be found in the work of Tamm[82] (benzimidazole) and of Zbiral[83] (aminotetrazoles). 3′-Fluoro-2′-deoxynucleosides have also been prepared[84,85] from the corresponding 3′-fluoronucleosides by the Barton–McCombie procedure.

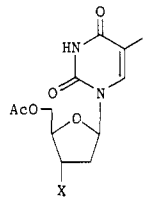
Deoxygenation at the 3′-position of 2′,5′-diprotected nucleosides has been achieved[86] by treatment with (thiocarbonyl)diimidazole followed by TBTH; once again both pyrimidine and purine bases are compatible. Recently, Spanish workers have carried out[87] the deoxygenation of a 3′-cyanohydrin **48a**, so providing an

entry into the 3′-cyano-3′-deoxynucleosides **48b** of interest in the antiviral field (55%).



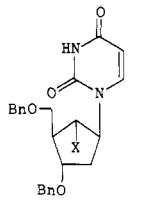
48a X = OCSOPh , Y = CN
48b X = CN , Y = H

Further deoxygenation of 2′-deoxynucleosides can be brought about by the Barton–McCombie procedure to give 2′,3′-dideoxynucleosides; both (thiocarbonyl)-imidazolides and phenyl thiocarbonates have been used[88] successfully for this purpose. In a recent modification[7] a 3′-OH moiety was removed from a 2′-deoxynucleoside by in situ treatment of the (thiocarbonyl)imidazolide with methanol, leading to a methyl thiocarbonate **49a** followed by reduction with poly(methylhydrosiloxane) and a catalytic amount of dibutyltin oxide to **49b**, the evident advantage being found in the isolation procedure. 2′,3′-Dideoxynucleosides have also been prepared[85] by 2′-deoxygenation of 3′-deoxynucleosides.

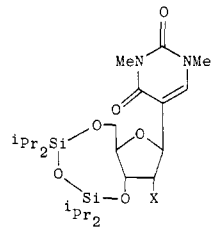


49a X = OCSOMe
49b X = H

Various preparations of carbocyclic nucleoside analogues involve[89] deoxygenation by the Barton–McCombie reaction; an example[90] is given by reduction of **50a** to **50b** (54%). Finally, *C*-ribonucleosides have also been subject to deoxygenation at the 2-position; both (thiocarbonyl)imidazolides, as in **51a** going to **51b** (74%), and phenyl thiocarbonates[92] have been used in this context.



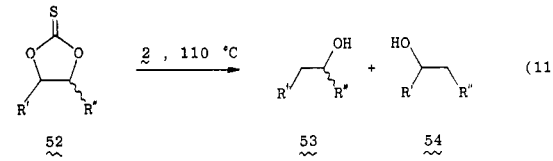
50a X = OCSOPh
50b X = H



51a X = OCSN
51b X = H

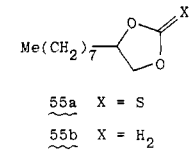
4. Reductive Deoxygenations of Diols via Cyclic Thiocarbonates

Treatment of a cyclic thiocarbonate **52**, formed from a diol and (thiocarbonyl)diimidazole with TBTH and AIBN at the correct temperature for fragmentation to occur (eq 11), results[93] in monodeoxygenation to one or



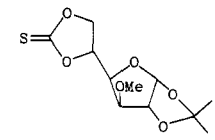
52 53 54 (11)

the other (or both) of two monools **53** + **54**, as first reported by Barton and Subramanian. When the reaction is carried out at too low a temperature, reduction of the thiocarbonyl group to a methylene group can take place[94] as in **55a** going to **55b** (65%).

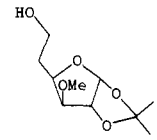


55a X = S
55b X = H_2

Given the difference in efficiency of deoxygenation of primary and secondary thiocarbonyl esters in toluene at reflux, it was originally envisaged[93] that cyclic thiocarbonates formed from primary/secondary diols would allow the selective deoxygenation of the secondary alcohol moiety. The viability of this hypothesis was established by the clean reduction of **56** to **57** (57%) and is confirmed[95] by other workers.



56

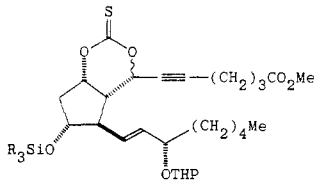


57

When the cyclic thiocarbonate is derived from two primary or two secondary alcohols, there is no reason to expect any significant regioselectivity of deoxygenation in the absence of other radical-stabilizing effects. This is readily confirmed[96] by various studies on the monodeoxygenation of secondary/secondary diols. Several examples in the carbohydrate field with some slight regioselectivity were reported[93] by Barton, but a more systematic investigation in that area was carried out by Stick.[97] Treatment of ribonucleoside 2′,3′-cyclic thiocarbonates with TBTH leads to a slight preference for 2′-deoxygenation,[98] with similar results being observed for related carbocyclic nucleosides.[6]

The reaction has been extended[99] by Noyori to include a cyclic thiocarbonate **58** derived from a 1,3-diol; as expected fragmentation gave exclusively the more stabilized propargylic radical and after chain transfer the prostaglandin **59** (77%). A further elegant example of the use of cyclic thiocarbonates for diol monodeoxygenation is the preparation[100] of dimethyl (*R*)-malate (**61**) from a cyclic thiocarbonate **60** derived from (*R*,*R*)-tartaric acid and TBTH.

Dideoxygenation of triols has been achieved[101,102] by reaction with excess (thiocarbonyl)diimidazole followed by reduction of the resulting thiocarbonate/(thiocarbonyl)imidazolide. The example[102] of **62a** giving **63**



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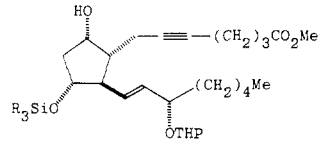

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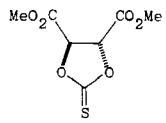
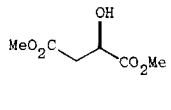


60



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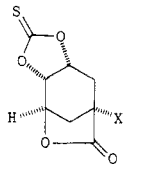
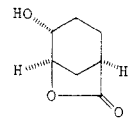


62a X = OCSN

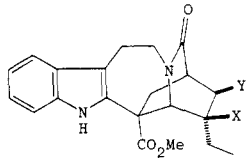
62b X = H



63

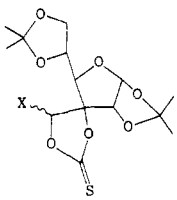
(40%) is unusual insofar as it contains a tertiary thiocarbonyl ester, obviously stabilized due to the anti-Bredt nature of its elimination product. It was reported that deoxygenation at the tertiary center to **62b** preceded cleavage of the cyclic thiocarbonate.

Cyclic thiocarbonates derived from secondary/tertiary diols are expected to result in preferential deoxygenation of the tertiary alcohol, and this has been demonstrated to be the case by Kutney[103] working with the catharanthine group of indole alkaloids (**64a** → **64b**). However, it has been shown[104] by Redlich that



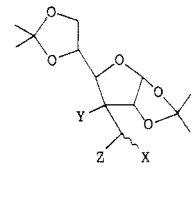
64a X = Y = OCSO

64b X = H, Y = OH



65a X = H

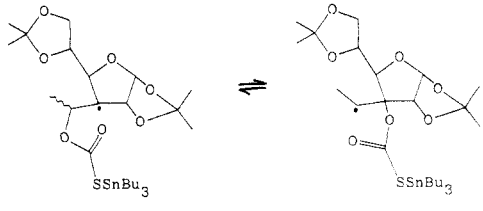
65b X = Me



66a X = Y = H, Z = OH

66b X = Me, Y = OH, Z = H

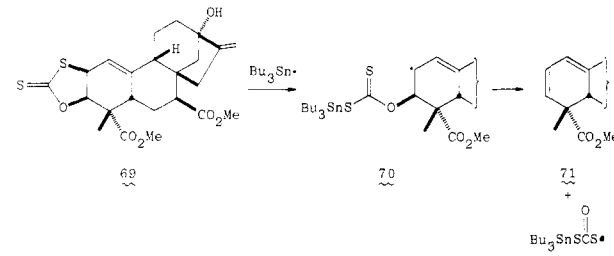
66c X = Me, Y = H, Z = OH



67 ⇌ 68

selective cleavage of the tertiary C–O bond is not an inviolable rule. Thus, although treatment of the primary/tertiary cyclic thiocarbonate **65a** followed expectations and gave **66a** by regioselective deoxygenation of the tertiary alcohol moiety (53%), the related secondary/tertiary cyclic thiocarbonate **65b** exhibited cleavage of both the secondary and tertiary C–O bonds, giving **66b** and **66c**, respectively, with a significant preference for the former. These results are suggestive of an equilibrium situation, **67** ⇌ **68**, with migration of an ester function, not unlike acetoxyl group migration in β-acetoxyl radicals[105] or allyl migration in allylhydroperoxy radicals,[106] with quenching of the less hindered radical **68** by the stannane.

Finally, interesting observations have been made by MacMillan[107] on the reaction of other cyclic thiocarbonyl derivatives with TBTH. Thus a cyclic dithiocarbonate **69** on treatment with TBTH under



69 70 71

standard conditions underwent overall elimination to give an alkene **71**, a result reminiscent of the Corey–Winter reaction.[108] In the light of the mechanistic studies[14] of Barton with the *S*-isopropyl dithiocarbonate **15** and the elimination[6,109] of 1,2-bis(dithiocarbonates) with TBTH, it is most likely that this reaction proceeds by initial cleavage of the allylic C–S bond to radical **70** followed by a radical elimination step.

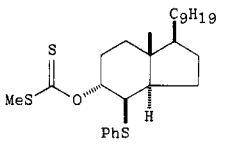
5. Eliminations from β-Functionalized Thiocarbonyl Esters

One of the major advantages of the Barton–McCombie reductive deoxygenation method is the avoidance of possible β-elimination reactions. However, certain groups that form stabilized free radicals are capable of undergoing β-elimination with the resultant formation of carbon–carbon double bonds (eq 12). Such a process

72 73 (12)

was first noted[110] by Lythgoe in the course of his studies in the vitamin D_3 field. It was recorded that β-phenylthio xanthate **74** underwent elimination on treatment with TBTH to give alkene **75** (65%). Given the known[111] low reactivity of simple alkyl phenyl sulfides toward stannyl radicals, it is likely that this reaction proceeds by attack at the thiocarbonyl sulfur followed by C–O bond cleavage, as for simple xanthates (eq 3 and 4), and finally β-elimination of the phenylthio radical.

Lythgoe further demonstrated[110] that thiobenzoates were also successful triggers for such elimination reactions and that the phenylsulfonyl radical was a useful leaving group. Such β-elimination reactions may ac-



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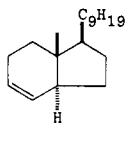
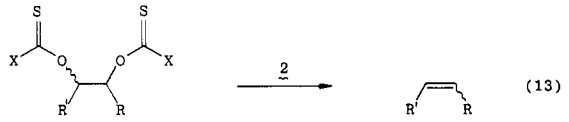


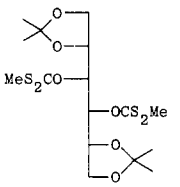
75

count for the observations[112] by Fraser-Reid that reduction of xanthates α to dithiolanes is a complex reaction but that prior hydrolysis of the dithiolane permits clean deoxygenation. The elimination of vicinal diols by means of the treatment of their derived bis(thiocarbonyl) esters with TBTH (eq 13) was described[6,109] independently by two groups. The mechanism of this reaction is considered[113] to involve discrete radical intermediates as the dixanthates of both *meso*- and (±)-dihydrobenzoin lead exclusively to the more stable *trans*-stilbene. In open-chain compounds preferential formation of the more stable *trans*-alkene appears to be the rule as illustrated by the formation of 78[113] from 1,2:5,6-diisopropylidenemannitol dixanthate 77.[113] Double elimination of 1,2-bis(thiocarbonyl) esters



(13)

76 73



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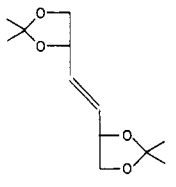
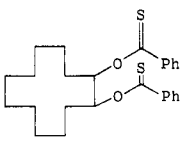


78

with tributyltin hydride is, however, not always successful as demonstrated[114] by the work of Sano involving isolation of **80** from reaction of **79** with TBTH. Higher reaction temperatures and lower stannane concentrations must favor more efficient fragmentation and limit such reactions.



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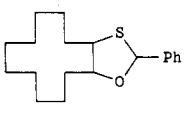
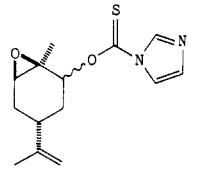


80

Eliminations from β-isocyano xanthate esters are considered[115] to occur by stannyl radical attack at the isocyano group followed by fragmentation and subsequent β-elimination of the xanthate radical due to the fact that 1,2-diisocyano compounds undergo double reductive deamination and not elimination.

The formation of carbon–carbon double bonds by reaction of a β-epoxy thiocarbonyl ester with TBTH has been described[116] by the Barton group as an alternative method of carrying out the Wharton reaction. Thus treatment of a diastereoisomeric mixture of epoxy carveol (thiocarbonyl)imidazolides **81** with TBTH in benzene at reflux yielded carveol (**82**) (65%). In certain cases the alkoxy radical formed on epoxide opening



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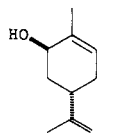

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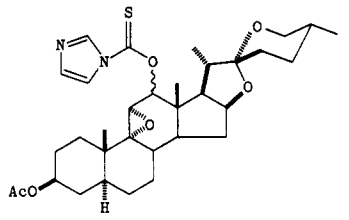

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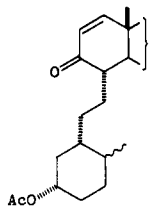
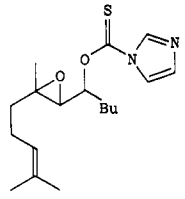


84

itself undergoes further rapid fragmentation to give a stabilized carbon radical. An example of this kind with fragmentation to a tertiary carbon radical[116] is the formation of secosteroid **84** from **83** (82%). The maintenance of a high stannane concentration in the reaction mixture can be used to limit such alkoxy fragmentations.

A further possibility for alkoxy radicals generated in the course of radical Wharton reactions is cyclization onto an appropriately placed double bond. Such reactions, first observed by Barton,[116] have been extended[117] by Murphy into a synthesis of tetrahydrofurans **86** (63%) and **87** (22%) from **85**. Murphy has also



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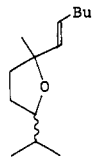

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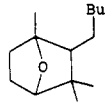

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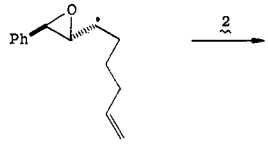
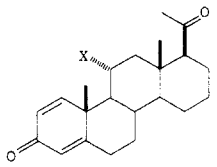


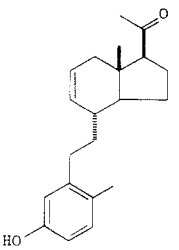
88 89

observed[118] an interesting dichotomy in his study of homolytic epoxide cleavage reactions insofar as γ-aryl-substituted β,γ-epoxyalkyl radicals as in **88**, derived from inter alia (thiocarbonyl)imidazolides, undergo preferential cleavage of the epoxide C–C bond rather than the C–O bond, leading to stabilized benzylic radicals **89**. Furthermore, this C–C cleavage is more rapid than the well-known 5-hexenyl type radical cyclization reaction.

Cleavage of C–C bonds in radical eliminations is not limited to strained rings but may also be achieved when other stabilized radicals such as phenoxy,[31] **90a** → **90b** + **91** (50% 1/1), or allyl[119] are formed. Finally in this section we draw attention again to the work of Nozaki,[26] where triethylborane (**21**) has also been used in conjunction with TBTH to drastically reduce the temperature required to bring about elimination of 1,2-bis(thiocarbonyl) esters.



90a X = OCSSMe
90b X = H



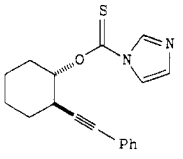
91

6. Carbon–Carbon Bond Formation from Thiocarbonyl Esters

Although the Barton–McCombie deoxygenation reaction has been mainly used in conjunction with TBTH as a radical trap resulting in overall reductive deoxygenation, recent years have seen its use as a source of carbon radicals for carbon–carbon bond formation by addition to C–C multiple bonds. The working principles of radical addition to C–C multiple bonds as a means of C–C bond formation are now well established[120] and hence not further reviewed here. The use of thiocarbonyl esters as radical sources in C–C bond-forming reactions may be divided into three classes: (i) trapping of the initial adduct radical **7** in an intramolecular fashion; (ii) and (iii) trapping of the alkyl radical generated on fragmentation (eq 4) either intra- or intermolecularly. The three classes will be dealt with in this order.

(i) Intramolecular Trapping of the Initial Adduct

The first reported example of this class is due to Clive[121] and involves cyclization onto an appropriately placed triple bond, **92** → **93**. After cyclization the



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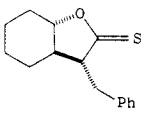

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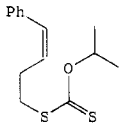

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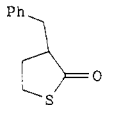
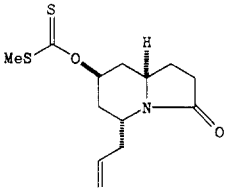


95

resulting exocyclic double bond is reduced in situ by excess TBTH. Similar cyclizations onto double bonds in the *O*-alkyl chain of (thiocarbonyl)imidazolides have been reported[122] by Snider. Bachi has followed up these observations and developed them with slight modifications into a synthesis[123] of δ-lactones. In agreement with the work of Clive, Bachi noted that exocyclic methylene groups of thiolactones were reduced by excess TBTH; this finding is obviously related to the reduction of thiocinnamates to dihydrothiocinnamates recorded[4] by Barton and McCombie. Subsequently Bachi studied[18,19] trapping of the initial adduct radical **7** with double bonds in the *S*-chain of dithiocarbonates **94** and was able to obtain a good yield of thiolactone **95** after hydrolysis, although it should be noted that the substrate was used in excess and the yield based on the stannane. Recently, Japanese chemists have reproduced the Bachi lactone work but at temperatures as low as −78 °C for addition to triple bonds and 0 °C for addition to double bonds[124] by an extension of their studies[26] on the use of triethylborane (**21**) in conjunction with TBTH.

(ii) Intramolecular Trapping of Radicals Generated on Fragmentation

The intramolecular trapping of carbon radicals generated by stannyl radical induced fragmentation of thiocarbonyl esters has been exploited by various authors. An early example[125] of this type is cyclization of **96** to **97** with TBTH (75%). Similar 5-exo-mode



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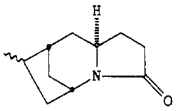

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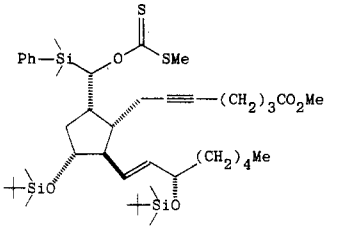

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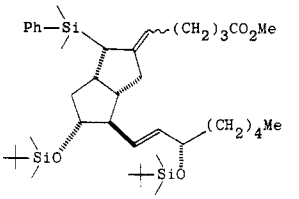

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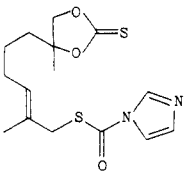

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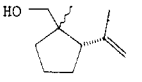
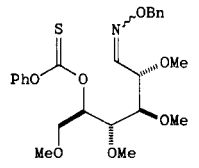


101

cyclizations are commonplace[126] but the work of Noyori, **98** → **99**, is especially interesting insofar as it involves an α-silyl-substituted radical in a high-yielding (86%) cyclization reaction.[127] The work of Ziegler,[128] **100** → **101** (98%) is distinguished by the fact that chain transfer is not by the more usual hydrogen abstraction from TBTH but by β-elimination of a sulfur-centered radical.

Six-membered rings can also be formed by 6-exo-mode cyclizations of radicals generated by the Barton–McCombie procedure, provided that the double bond acting as radical trap is activated with an electron-withdrawing group.[129] Clive has shown[130] how alkyl radicals, generated by stannyl radical induced fragmentation of thiocarbonyl esters, may be cyclized efficiently onto nitriles in the 5-exo-dig mode giving cyclopentanones after hydrolysis. In a similar vein Bartlett has cyclized alkyl radicals onto oximes, **102** → **103** (93%).[131] Finally, Motherwell has employed[132] (thiocarbonyl)imidazolides as radical sources in his elegant preparation of spirocyclic molecules **105** (71%) by a (thiocarbonyl)imidazolide **104**/TBTH initiated tandem cyclopropylmethyl opening/5-hexenyl closure sequence.



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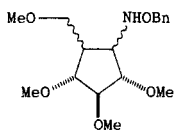

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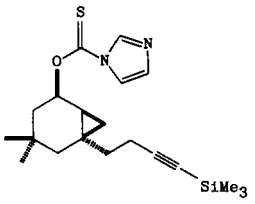

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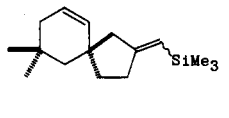

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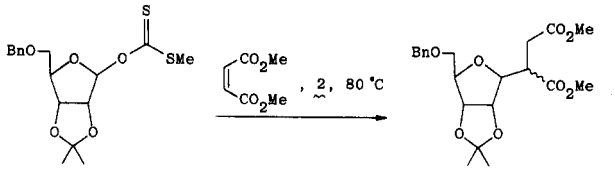
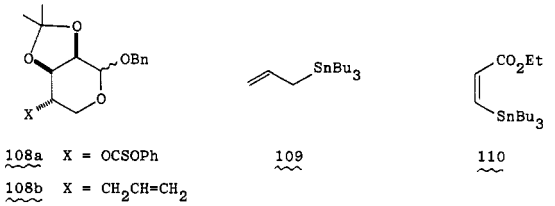
(iii) Intermolecular Trapping of Radicals Generated on Fragmentation

Intermolecular radical C–C bond-forming reactions have been much less commonly used in organic synthesis than their intramolecular counterparts. This is largely due to the extra variable introduced in the form of alkene concentration, which renders optimization of conditions for each specific reaction necessary. Nevertheless exploratory work by Giese revealed[133] that moderate yields of addition to acrylonitrile could be obtained with several *sec*-alkyl dithiocarbonates and TBTH in toluene at reflux. Araki took this concept and used it in a synthesis of showdomycin, during the course of which he discovered that although it proved possible to generate and trap 1-furanosyl radicals in this manner, **106** → **107** (62%), 1-pyranosyl radicals could not be prepared in the same way.[134]



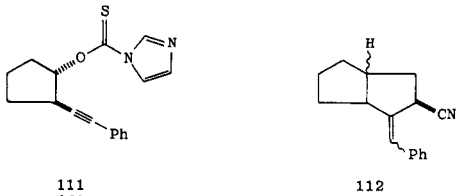
106 107

Polymerization of the alkene used as a trap is a particular problem in reactions of this kind, with the result that much effort has been put into the design of alternative sequences. Thus Keck has introduced[135] allyltributylstannane **109** as a combined non-



108a X = OCSOPh
108b X = $CH_2CH{=}CH_2$

109 110

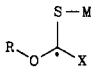


111 112

polymerizable radical trap and stannyl radical source for use with inter alia thiocarbonyl esters. It was found that monothiocarbonates gave better yields than dithiocarbonates and (thiocarbonyl)imidazolides when used in conjunction with this latter reagent. Surprisingly, especially given the temperature requirement for efficient fragmentation of thiocarbonyl ester/stannyl adducts **7**, the best yields of **108b** from **108a** and **109** were obtained photochemically at 25 °C (80%). Baldwin has published[136] a variant of this methodology using β-(tributylstannyl)acrylates **110**. Finally, a conceptually different solution to the polymerization problem is due to Clive[121] and involves cyclization of the initial adduct in an intramolecular manner as in formation of **112** from **111** with triphenyltin hydride and acrylonitrile. Unfortunately, yields in this multistep reaction were only low (26).

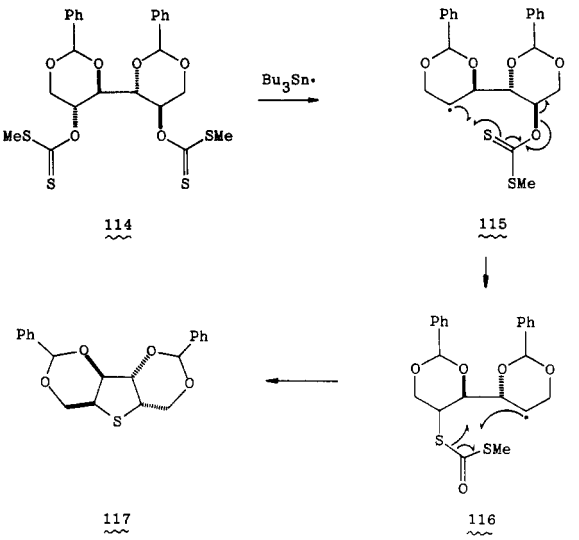
7. Addition of Radicals Other Than Stannyl Radicals to Thiocarbonyl Esters

Perhaps the major factor limiting the further development of the Barton–McCombie reaction currently is the necessity of using stannyl or, possibly, germyl radicals. An alternative radical capable of attacking at the thiocarbonyl sulfur to give an adduct susceptible to fragmentation would be of great potential. Unfortunately the problem is not limited to finding a radical M• that will add to the thiocarbonyl group to give an adduct **113**; it is also a requirement that the reverse reaction (elimination of M• from **113**) be slower than the adduct fragmentation to give the alkyl radical. With stannyl radicals this delicate balance of requirements is attained usually between 80 and 110 °C.



113

Much unpublished and unsuccessful work has been directed toward identifying a suitable radical M• in **113**, and Cristol has reported[17] on the inadequacy of the trichloromethyl radical, almost certainly due to the ease of the reverse reaction. Nevertheless recent results in this field are encouraging, particularly concerning alkyl radicals. Thus it has been reported[137] that treatment of the bis(dithiocarbonate) **114** derived from 1,3:4,6-



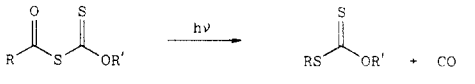
114 115

117 116

dibenzylidenemannitol with TBTH in the usual manner

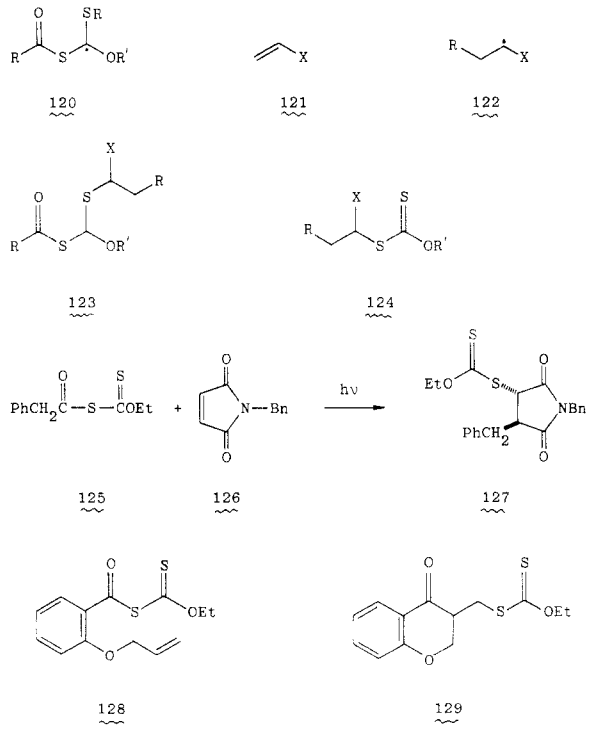
led to the isolation of a single crystalline product, which was identified as the tetrahydrothiophene **117** (80%). The formation of this product was explained by the sequence **114** → **115** → **116** → **117** and necessitates migration of a dithiocarbonate group by intramolecular attack of a carbon-centered radical at the thiocarbonyl sulfur (cf. **79** → **80**[114]).

In a further development Zard has designed[138] a system making use of the *S*-acyl xanthates **118** based on initial observations[139] by Barton of their decarbonylative rearrangement to alkyl xanthates **119**. This



118 **119**

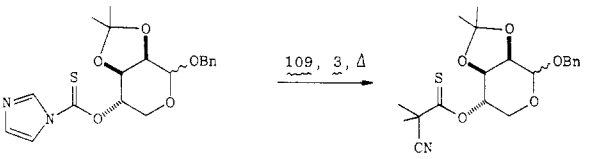
rearrangement is best explained[138] by addition of an alkyl radical, R•, to **118** giving an adduct radical **120** that fragments to form the product **119** and an acyl radical RĊO. Decarbonylation of R-ĊO gives R• which propagates the chain. In the Zard chemistry an alkene **121** is added to the reaction mixture such that the radical R• can now add and form an adduct **122**. This



120 **121** **122** **123** **124** **125** **126** **127** **128** **129**

adduct radical **122** carries the chain by addition to **118**, forming a new adduct **123** that on fragmentation generates the product **124** and the acyl radical RĊO so propagating the chain. An example is the formation of **127** from the *O*-acyl xanthate **125** and *N*-benzylmaleimide (**126**) (70%). An intramolecular version with an *S*-acyl xanthate **128** derived from *O*-allylsalicylic acid was also shown to proceed in good yield (70%) to the chromanone **129**.

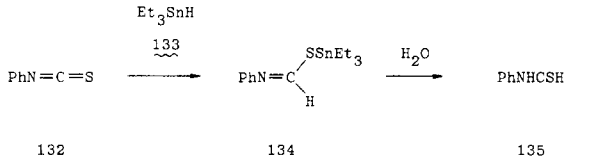
Finally, we note an interesting, although as yet unexplained, observation recorded[135] by Keck during his study of the reaction of thiocarbonyl esters with allyltributylstannane (**109**) in which an initiator-derived 2-cyanopropyl radical appears to have added to the carbon, rather than sulfur, of a (thiocarbonyl)-imidazolide **130** with expulsion of an imidazole group and formation of the thiocarbonyl ester **131**.



130 **131**

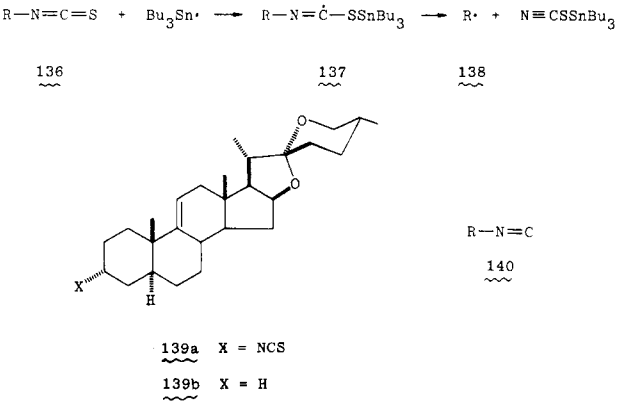
III. Generation and Trapping of Radicals from Amines via Isothiocyanates

The reaction of tin hydrides with isothiocyanates was first reported[140] in 1963 by Lorenz and Becker, who noted that triphenyltin hydride and phenyl isothiocyanate gave, on heating to 90 °C, a mixture of aniline, *N*-methylaniline, and phenyl isocyanide. In a more complete study Noltes and Janssen subsequently reported[141] that triethyltin hydride (**133**) and phenyl isothiocyanate (**132**) react together in benzene at reflux to give an adduct **134** resulting from addition of the Sn–H bond across the thiocarbonyl bond. This adduct was unstable and on exposure to moist air decomposed to thioformanilide (**135**).



132 **134** **135**

Application to aliphatic isothiocyanates was left to Barton, who conceived the idea[115] that the initial adduct radical **137** formed on addition of a stannyl radical to **136** would fragment to give an alkyl radical **138** resulting, after chain transfer with TBTH, in the overall radical chain deamination of the isothiocyanate. In practice, an isothiocyanate **139a** derived from Δ^9-tigogenin reacted with TBTH and AIBN in benzene at reflux to give the deaminated product **139b** (89%).



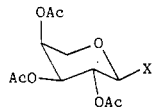
136 **137** **138** **140**

139a X = NCS

139b X = H

However, it was soon realized that the true course of the reaction involves stannyl radical mediated desulfurization of the isothiocyanate **136** to the isonitrile **140** and deamination by reaction of the latter with further TBTH. A direct consequence of this realization is that the isonitrile can be advantageously used, particularly in view of the fact that less stannane is required. Indeed subsequent papers[142] preferred the isonitrile as starting material. However, a recent paper has drawn attention to the fact that by operating at lower tem-

peratures the reaction can be diverted to provide isonitriles. Thus treatment of a carbohydrate isothiocyanate **141a** with TBTH and AIBN in ether at 25 °C gave the corresponding isonitrile **141b** (69%) and only a trace of the deaminated product **141c** (<2%) whereas the situation was completely reversed in toluene at 110 °C, with **141c** as the major product.[143]

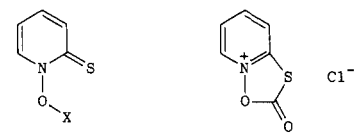


141a X = NCS
141b X = NC
141c X = H

IV. Generation and Trapping of Radicals from Derivatives of Thiohydroxamic Acids

1. General

The realization[144] in 1983 by the Barton group that *O*-acyl derivatives **142b** of the thiohydroxamic acid *N*-hydroxypyridine-2-thione **142a** undergo facile reac-



142a X = H
142b X = COR

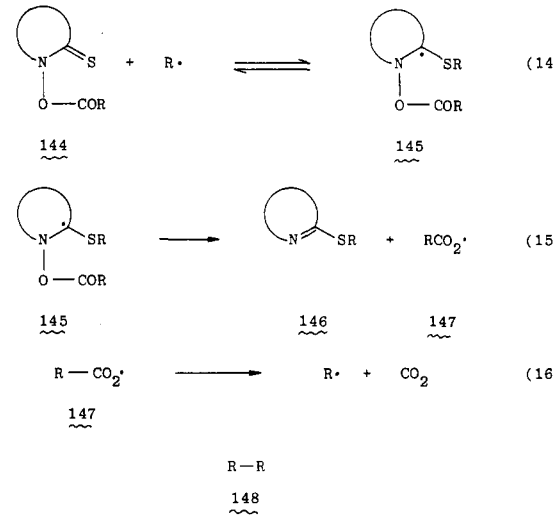
143

tion not only with stannyl radicals but also with thiyl, alkyl, and many other thiophilic radicals brought a new dimension to preparative free-radical chemistry and in particular to that of the thiocarbonyl group. This new radical chemistry has now developed[145] into one of the most important facets of thiohydroxamic acid chemistry, which had previously been limited[146] to the area of polar mechanisms.

The *O*-acyl thiohydroxamates **142b** are readily prepared by the reaction of **142a** with an activated acyl derivative such as the chloride[144,147] or a mixed anhydride prepared from the carboxylic acid and isobutyl chloroformate.[148] Alternative preparations involve coupling **142a** and a carboxylic acid by means of dicyclohexylcarbodiimide[147] and reaction of the carboxylic acid, or better its triethylammonium salt,[149,150] with the heterocyclic salt **143**, which itself is prepared in essentially quantitative yield from **142a** and phosgene.

2. Decarboxylative Rearrangement

The most elementary radical reaction undergone by the *O*-acyl thiohydroxamates is their decarboxylative rearrangement to alkyl 2-pyridyl sulfides. This transformation takes place via a radical chain mechanism[151] (eq 14–16). Crossover experiments showed this chain mechanism to be the only one operating under photolytic conditions, but under thermal conditions there is a competing cage mechanism. The reversibility of alkyl radical addition to the thiocarbonyl group (eq 14) was proposed[152] in order to explain the formation of significant amounts of dimer **148** when the reaction is carried out photochemically at low temperatures.



144 **145** (14)

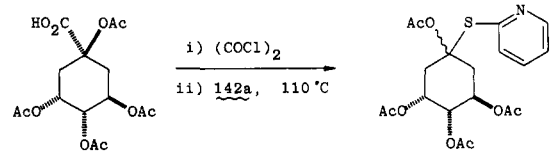
145 **146** **147** (15)

147 (16)

148

It has also been suggested[152] that the fragmentation of **145** and of the ensuing carboxyl radical **147** takes place in a concerted manner although there is at present no compelling evidence in support of this hypothesis. The presence of radicals in this decarboxylative rearrangement has been confirmed[153] by ESR; furthermore, it was reported that spectra of benzyl radicals obtained in this manner were of exceptionally high quality.

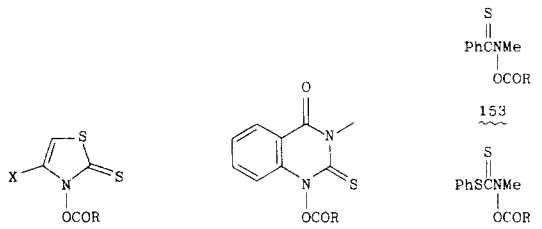
Decarboxylative rearrangement of *O*-acyl thiohydroxamates, either photochemically or thermally, is an expeditious entry into alkyl pyridyl sulfides and functions well whatever the nature, primary, secondary, or tertiary, of the intermediate radical as illustrated by **149** → **150** (72%).[147]



149 **150**

For simple primary alkyl radicals Newcomb has measured[154] the rate of decarboxylative rearrangement (R• = *n*-octyl; $k = 2.2 \times 10^6$ M^{-1} s^{-1}) and made use[155] of the reaction as a radical clock for the determination of the rate of iodine atom transfer reactions. In a similar vein Ingold has employed[156] the decarboxylative rearrangement as a clock for the determination of rate of hydrogen atom transfer to alkyl radicals from tributylgermanium hydride. Attention was drawn, however, to the possibility of cage recombination products distorting the measured rates.

This novel chemistry is not limited to *O*-acyl derivatives of the commercial thiohydroxamic acid **142a**. The Barton group has synthesized a number of other thiohydroxamic acids[151,157] and their corresponding *O*-acyl derivatives and have demonstrated that they undergo identical chemistry albeit under different conditions. Thus while the *O*-acyl thiohydroxamates **142b** are a beautiful lemon yellow color and are readily rearranged photochemically with a simple tungsten lamp, **151a**, **152**, **153**, and **154** are essentially colorless and require medium-pressure UV photolysis to initiate reaction. Compound **151b** with its extended conjugation can be rearranged, albeit slowly, on photolysis with a tungsten lamp. The *O*-acyl thiohydroxamates **142b**,



151a X = Me
151b X = Ph

152

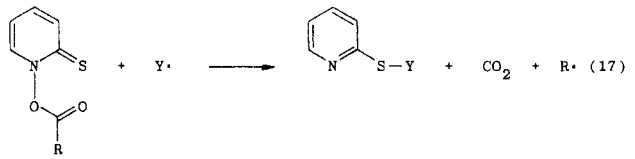
153

154

151a, and **151b** can also be induced to suffer smooth decarboxylative rearrangement on heating to reflux in benzene or better toluene but **152**, **153**, and **154** are for all practical purposes stable up to 130 °C.

3. Atom- or Group-Transfer Trapping

Perhaps the most useful type of reaction undergone by the *O*-acyl thiohydroxamates is with a molecule X–Y **155**, which serves the dual purpose of donor of an atom or group X quenching the alkyl radical to the product **156** and of a thiophilic radical Y• capable of chain propagation by addition to the thiocarbonyl group. A general chain mechanism (eq 17 + 18) can be written.



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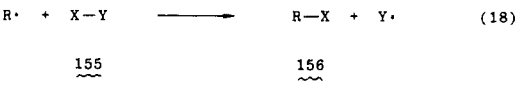
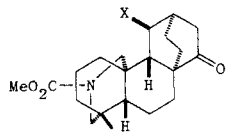


(18)

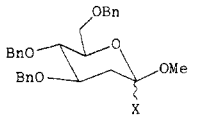
155 156

(i) Reductive Decarboxylation

In reductive decarboxylation[144,147] the molecule X–Y **155** is a stannane, as, for example, in the work[158] of Kametani (**157a** → **157b** (48%)) or a tertiary thiol[147,148,159] as in **158a** → **158b** (40%),[149] the latter being preferred for reasons of simplicity of workup. This reaction is an excellent means of removing a carboxyl group from aliphatic carboxylic acids and can be carried out by tungsten photolysis at or below room temperature.



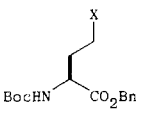
157a X = CO_2H
157b X = H



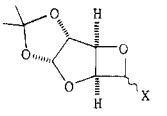
158a X = α-CO_2H
158b X = α-H

(ii) Decarboxylative Halogenation

Decarboxylative chlorination of *O*-acyl thiohydroxamates is achieved when X–Y **155** is Cl–CCl_3 and results in formation of the norchloride **156** (X = Cl). For practical purposes tetrachloromethane is used as solvent and the reaction is initiated by tungsten photolysis or by heating to reflux.[147] Analogous decarboxylative bromination is achieved with bromotrichloromethane as solvent and iodination with iodoform in benzene or, better, cyclohexene.[147] Decarboxylative halogenation by the *O*-acyl thiohydroxamate method has been applied with excellent yields to various primary, secondary, and tertiary acids.[147,160] An example of application to amino acids[148] is the formation of bromide **159b** from the glutamic acid **159a** (82%). The formation, albeit in low yield (18%), of an α-chlorooxetane **160b** from the acid **160a** is particularly noteworthy.[161]

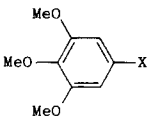


159a X = CO_2H
159b X = Br
159c X = SeMe



160a X = CO_2Na
160b X = Cl

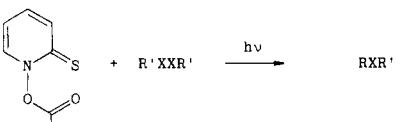
This method for decarboxylative halogenation presents many advantages over the classical Hunsdiecker reactions and its many variants insofar as it uses no heavy-metal salts or strongly electrophilic species. Applications to vinyl and aryl acids, as, for example, in **161a** → **161b** (62%), with the use of stoichiometric quantities of AIBN by Vogel[162] and subsequently Barton[163] make this point particularly well.



161a X = CO_2H
161b X = Br

(iii) Decarboxylative Chalcogenation

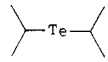
The use of disulfides, diselenides, and ditellurides **162** as X–Y **155** with *O*-acyl thiohydroxamates results in the formation of thio-, seleno-, and telluroethers **163**, respectively. Originally these reactions were carried out



142b

X = S, Se, Te R' is alkyl or aryl

by heating to reflux in toluene and required a large amount of dichalcogenide to minimize competing basic decarboxylative rearrangement to alkyl pyridyl sulfides.[164] However, it was subsequently found[165] that by operating under photolytic conditions at low temperatures clean reactions were obtained by using only a slight excess of reagents. The use of dimethyl diselenide as trap in conjunction with the *O*-acyl thiohydroxamate derived from **159a** enabled the Barton group to prepare a selenomethionine **159c** in good yield (78%).[166] Dicyanogen triselenide is also a suitable radical trap/propagator in *O*-acyl thiohydroxamate chemistry.[166] In a different context diisopropyl telluride (**164**) has been used in conjunction with an *O*-acyl thiohydroxamate as a source of isopropyl radicals although no advantage over the more straightforward use of the *O*-acyl thiohydroxamate from isobutyric acid was observed.[167]



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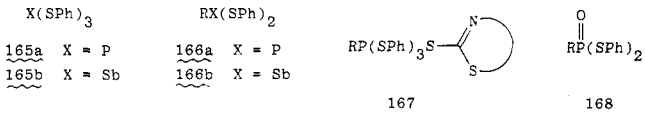
(iv) Trapping with Phosphorus and Antimony Reagents

Phosphoric acid analogues of carboxylic acids are readily prepared by reaction of *O*-acyl thiohydroxamates with tris(phenylthio)phosphorus[168] (**165a**)

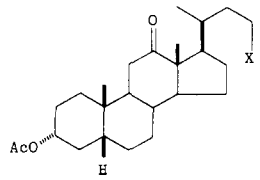


165a X = P
165b X = Sb

166a X = P
166b X = Sb

167

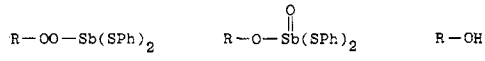
168



169a X = CO_2H
169b X = P(O)(SPh)$_2$

in which $(PhS)_2P$–SPh is X–Y. The radical step results in an alkylbis(phenylthio)phosphine **166a** which undergoes addition of the disulfide byproduct to give a pentavalent phosphorus species **167** which is hydrolyzed to an *S,S*-diphenyl dithiophosphonate **168** on workup. The formation of the bile acid analogue **169b** from the 12-ketolithocholic acid ester **169a** is illustrative of this reaction sequence (60%).[168]

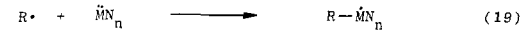
In a similar manner tris(phenylthio)antimony **165b** reacts with *O*-acyl thiohydroxamates to give alkylbis(phenylthio)antimony derivatives[169] **166b**. These derivatives are, however, very air sensitive and undergo oxygen insertion into the carbon–antimony bond giving **170**, which rearranges to **171**, yielding the alcohol **172** on hydrolysis. The overall process therefore provides a method for the formation of noralcohols from carboxylic acids.



170 **171** **172**

4. Valence Shell Expansion Trapping (Sulfur Dioxide + Isonitriles)

This particular type of radical chain mechanism is described in general terms by eq 19 and 20, where M in MN_3 **173** is an atom whose valence increases by two in the course of the reaction to form **174**.



(19)

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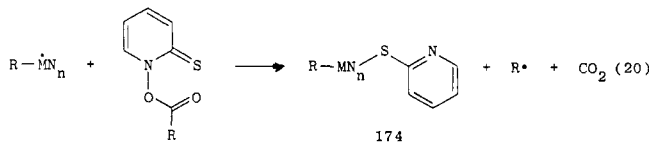
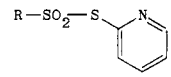


(20)

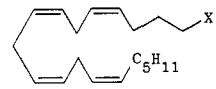
174

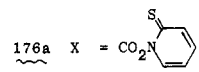
A simple illustration of this concept is the use of sulfur dioxide as a radical trap in conjunction with an *O*-acyl thiohydroxamate leading to the formation of *S*-pyridyl alkylthiosulfonates **175** (30–90%).[170] For practical reasons this reaction is carried out at −10 °C in a mixture of dichloromethane and liquid sulfur dioxide.



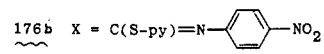
175

Isonitriles have also served as valence expansion type radical traps: it was found[171] that the most efficient isonitriles were those bearing electron-withdrawing groups, in particular, 4-nitrophenyl isocyanide, as in **176a** → **176b** (35%), and *protonated* 3-pyridyl isocyanide. The attraction of this methodology lies in the possibility of using isotopically labeled isonitriles and so of preparing labeled carboxylic acids by decarboxylation, trapping with the labeled isonitrile, and hydrolysis of the adduct. Enabling methodology for the hydrolysis was reported[171] by the Barton group.





176a X = CO_2



176b X = C(S-py)=N–NO_2

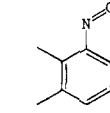
5. Decarboxylative Oxygenation and Amination

An alternative method for the formation of noralcohols from *O*-acyl thiohydroxamates to that employing **165b** involves reaction of **142b** with triplet oxygen and a tertiary thiol.[147] The initial product of the reaction is a hydroperoxide **177**, and it is possible to

177

isolate these from the reaction mixture in moderate to good yield.[147,172] However, the Barton group found it convenient either to reduce in situ with trimethylphosphine to the noralcohol or, where appropriate, to convert to the corresponding aldehyde or ketone with toluenesulfonyl chloride and pyridine. The presence of a tertiary thiol was found to be essential for the maintenance of clean reactions and the obtention of high yields.

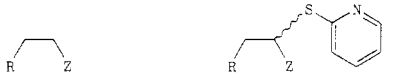
Efforts to construct radical chain reactions with *O*-acyl thiohydroxamates and nitrogen-centered radical traps, leading eventually to the formation of noramines have been thwarted inter alia by rapid polar reactions between the trap and the *O*-acyl thiohydroxamate.[173] However, Ingold has succeeded in forming carbon–nitrogen bonds in a nonchain manner with the aid of nitrosodurene (**178**) as a highly reactive radical trap.[153]



178

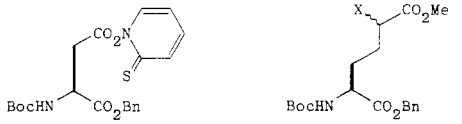
6. Trapping with C–C Multiple Bonds

In parallel with thiocarbonyl esters the fragmentation of *O*-acyl thiohydroxamates in the presence of electron-deficient terminal alkenes leads to the formation of new carbon–carbon bonds. Chain transfer, however, is achieved not by hydrogen atom abstraction from TBTH but by attack of the adduct radical **179** on the thiohydroxamate thiocarbonyl bond to give the product **180**.[157] Useful stereoselectivity is sometimes observed at the newly generated asymmetric carbon.[174]



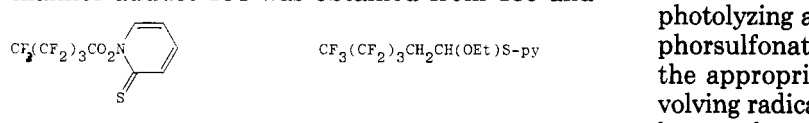
179 180

This general reaction is illustrated by the formation of an α-aminoadipic acid derivative **182** from the aspartic acid **181** and methyl acrylate (62%).[175] The pyridylthio residue can be removed either by oxidation to the sulfoxide followed by syn elimination or reductively with Raney nickel or TBTH.



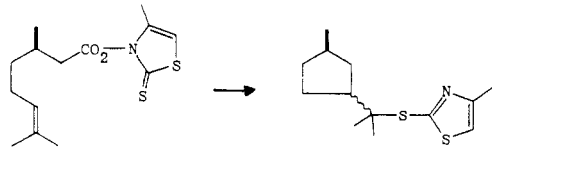
181 182 X = S-py

Radical addition to less standard traps such as nitroalkenes, vinyl sulfones, and vinyl phosphonium salts by the *O*-acyl thiohydroxamate method is also efficient.[176] However, use of the much discussed captodative alkenes as radical traps leads to complex reaction mixtures.[177] Addition to electron-deficient alkynes is also moderately effective.[157] *O*-Acyl thiohydroxamates derived from perfluoroalkanoic acids react with electron-rich alkenes to give adducts in moderate yields. In this manner adduct **184** was obtained from **183** and

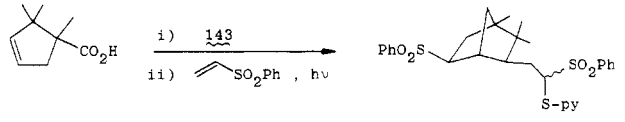


183 184

ethyl vinyl ether (58%).[178] *O*-Acyl thiohydroxamate mediated radical cyclization can also be achieved as, for example, in **185** → **186** (82%).[157,179] An elegant mul-



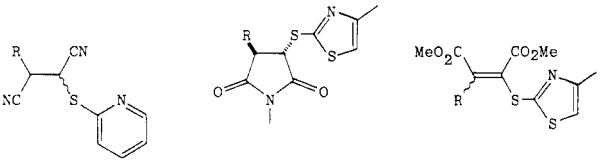
185 186



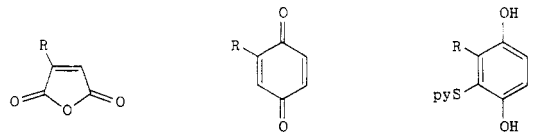
187 188

tiple radical addition/cyclization/addition sequence has been reported[180] by Zard, allowing the formation of complex bicyclic systems from simple γ,δ-unsaturated acids and 2 equiv of an electron-deficient alkene as, for example, in the formation of **188** from **187** by reaction with heterocyclic salt **143** and phenyl vinyl sulfone (59%). This reaction is not unlike that employed by Clive (**111** → **112**) insofar as polymerization of the initial radical adduct is prevented by cyclization.

With the exception[176] of nitroalkenes in order to add radicals from *O*-acyl thiohydroxamates to nonterminal double bonds, it is necessary for the alkene to be doubly activated. With fumarodinitrile, *N*-methylmaleimide, and even the internal alkyne dimethyl butynedioate, the reaction proceeds smoothly to give the expected adducts **189**, **190**, and **191**, respectively.[157] However,



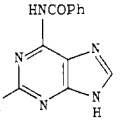
189 190 191



192 193 194

with maleic anhydride[157] and quinones[157,181] as radical traps, spontaneous in situ elimination of the heterocyclic thiol group leads to isolation of alkylated maleic anhydrides **192** and quinones **193**. In the case of quinones this elimination can be avoided by working at lower temperatures when the isolated product is a 2-alkyl-3-(pyridylthio)hydroquinone (**194**).

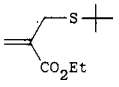
A further extension of the method involves *O*-acyl thiohydroxamate decomposition in the presence of *protonated* heterocyclic bases permitting radical aromatic substitution. This reaction is carried out by photolyzing a solution of the aromatic base, as its camphorsulfonate, in dichloromethane in the presence of the appropriate thiohydroxamate. A mechanism involving radical addition, proton loss, and chain transfer by attack at the *O*-acyl thiohydroxamate thiocarbonyl group and elimination of 2-mercaptopyridine was invoked.[182] In accordance with the nucleophilic nature of alkyl radicals, pyridinium and lepidinium salts were alkylated primarily at the ortho- and para positions. Reaction of the 1-adamantanyl radical with benzoyladenine (**195a**) under these conditions gave a single product **195b** and serves as an example (60%).[182]



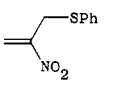
195a X = H
195b X = 1-adamantanyl

Finally, as with the thiocarbonyl esters, alkenes incorporating radical leaving groups in the allylic position have been designed for use with *O*-acyl thiohydroxamates. In order to compete effectively with simple decarboxylative rearrangement, it was found necessary to activate the alkene as in **196** and **197**.[176,183]

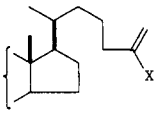
Reaction of either of these two allylic sulfides with *O*-acyl thiohydroxamates derived from cholanic acids, e.g., **169a**, permits entry into side chain functionalized cholestane derivatives **198** in a single step.



196



197

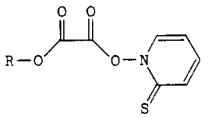


198a X = CO_2Et

198b X = NO_2

7. Deoxygenation of Alcohols

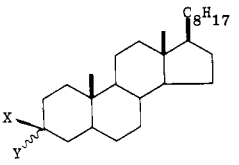
Although initially designed for the generation of alkyl radicals from carboxylic acids, the radical chemistry of thiohydroxamic acid derivatives is by no means limited to that domain. The formation and decomposition of an *O*-acyl thiohydroxamate **199** from **142a** and hemi-



199

oxalate esters is, in principle, an entry into the generation of alkyl radicals from alcohols by sequential loss of two molecules of carbon dioxide.

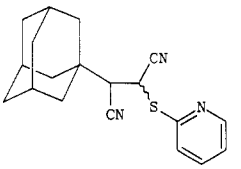
This possibility was investigated[184] as an alternative to the Barton–McCombie reaction avoiding the use of TBTH. In practice, it was found that the slow fragmentation of primary and secondary alkoxycarbonyl radicals limited application to tertiary alcohols. Given the difficulties in preparing thiocarbonyl esters of such alcohols, this process nicely complements the Barton–McCombie procedure. Thus it proved possible to treat a variety of tertiary alcohols or, for practical reasons, their trimethylsilyl ethers with excess oxalyl chloride followed by **142a** and a tertiary thiol in benzene at reflux and obtain the product of reductive deoxygenation as, for example, in **200a** → **200b** (80%).



200a X = β-$OSiMe_3$, Y = α-Me
200b X = β-Me, Y = H
200c X = βα-Me, Y = αβ-Cl
200d X = αβ-$CH_2(=CH_2)CO_2Et$, Y = βα-Me

In direct parallel with the decarboxylative halogenation of acids, tertiary alkyl chlorides were prepared from the corresponding tertiary alcohols by heating of the derivatives **199** in tetrachloromethane as illustrated by **200a** → **200c** (95%).[185] Unfortunately, however, extension to the formation of tertiary bromides was excluded by the action of the byproduct trichloromethyl 2-pyridyl sulfide as a base causing in situ elimination of hydrogen bromide.

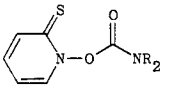
Furthermore, it proved possible[184] to trap radicals generated from tertiary alcohols by this hemioxalate/thiohydroxamate chemistry by addition to electron-deficient alkenes, providing a concise entry into quaternary carbon centers. Thus the 1-adamantanyl radical, generated from **199** (R = 1-adamantanyl), reacted with fumarodinitrile to give the adduct **201** after chain transfer with **199** (32%). Decomposition of **199** in the presence of radical traps **196** and **197** is also feasible as illustrated by the formation of **200d** from **200a** (52%).[184]



201

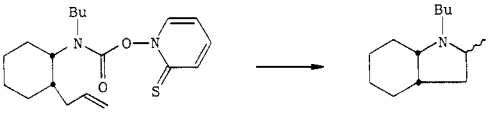
8. Aminyl Radical Generation

Mixed anhydrides **202** of carbamic acids with **142a** provide a useful source of aminyl radicals on tungsten photolysis.[186] In the absence of a hydrogen donor



202

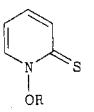
disproportion of the aminyl radical occurs, leading to the conclusion that aminyl radicals are not thiophilic with respect to thiocarbonyl groups. However, in the presence of thiols efficient chain reactions are established. This method for aminyl radical generation has been used to study the ring opening of cyclopropyl- and cyclobutylaminyl radicals. It was also reported that but-4-enaminyl radicals generated in this manner cyclized efficiently in the presence of acetic acid and a thiol, so providing a useful synthesis of pyrrolidines as, for example, in the formation of **204** from **203** (60%).[186]



203 204

9. Alkoxy Radical Generation

Alkoxy radicals can be generated by heating *O*-alkyl thiohydroxamates **205** to reflux in benzene in the presence of TBTH.[187] This fragmentation is initiated

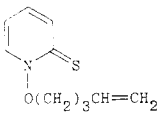


205

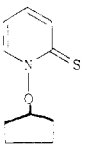
by addition of the stannyl radical to the thiocarbonyl moiety of **205** analogously to the reductive decarboxylation procedure.

The alkoxyl radical precursors **205** were prepared by heating **142a** with a suitable alkyl halide in dimethylformamide, the use of this solvent being critical as it has previously been demonstrated[157,188] that **142a** or its sodium salt undergoes S-alkylation in less polar solvents. The formation (80%) of 2-methyltetrahydro-

furan from **206** and TBTH at 80 °C was used to estimate the rate of ring closure of the 4-pentenyloxy radical (6×10^{-8} s^{-1}). However, decomposition of **207** in bromotrichloromethane at reflux gave a high yield (95%) of 5-bromopentanal, so demonstrating that the product obtained from cyclizable alkoxyl radical probes is highly dependent on the nature of the chain-transfer reagent.



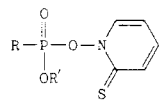
206



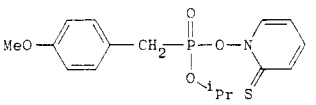
207

10. Dephosphorylation

Finally, it has been demonstrated[189] that mixed anhydrides **208** of phosphonic acids and **142a** react in a chain sequence with thiols, TBTH, and tetrachloromethane to give dephosphorylated products. For simple primary and secondary alkylphosphonates, yields were low (≤3%), indicating inefficient fragmentation and/or competing polar reactions, but for allyl- or benzylphosphonates, moderate yields of dephosphonylated products were obtained. Thus p-methoxytoluene and p-methoxybenzyl chloride were obtained from **209** by heating to reflux in benzene with TBTH and tetrachloromethane, respectively.



208



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