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Recent Developments in the Area of Thionation Methods and Related Synthetic Applications

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RECENT DEVELOPMENTS IN THE AREA OF THIONATION METHODS AND RELATED SYNTHETIC APPLICATIONS†

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This review article represents a collection of references explicit to all thionation methods and related thiocarbonyl derivatives found and described in the literature during the period 1985 to mid-1991. The classification of this review is based on the thionation reagent in the first instance and then on the type of transformation and the type of thiocarbonyl obtained. Special emphasis was also put on new thionation reagents which are described in Section 2. The synthetic applications of previously known thionation reagents, such as Lawesson's reagent and tetraphosphorus decasulfide for example, are presented separately through Sections 3 to 8 with as much experimental details as available. This collection of references was performed with the Chemical Abstract and the CAS on-line system with key words such as *thioamide, thiolactam, thiopeptide, thionoester, dithioester* or *thioaldehyde* and those given below. Other references were found by screening (1) synthetic organic chemistry book series, (2) the issues of several journals for the year 1991 and (3) the reference sections of the articles found.

Key words: Lawesson's reagent, sulfuration, thio analogs, thiocarbonyl, thionation.

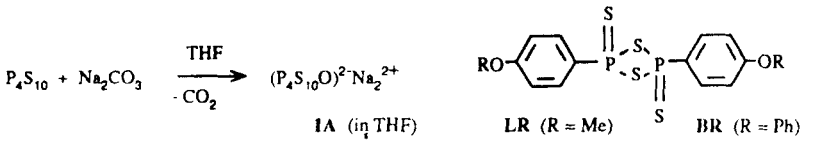
CONTENTS

† This paper is dedicated to the memory of Professor Bernard Belleau.

1. INTRODUCTION

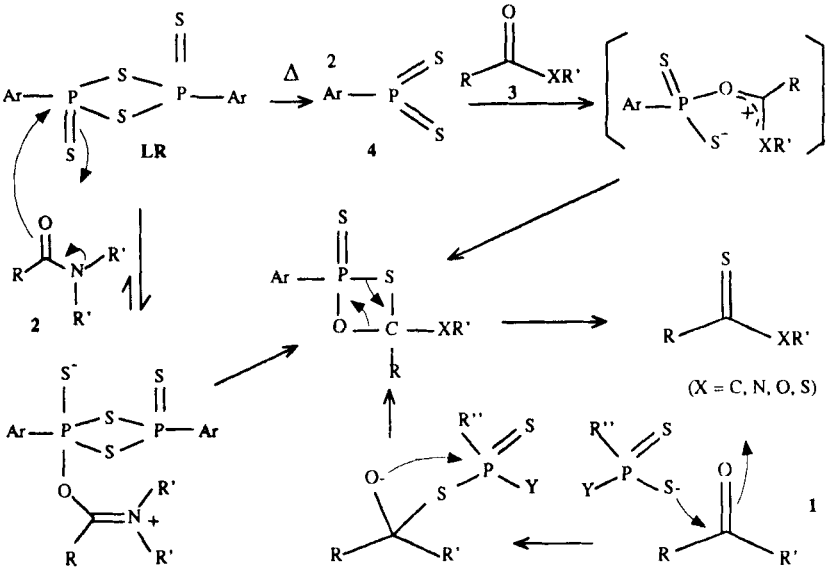
The preparation of thiocarbonyl compounds via *O*,*S*-exchange reagents or reactions has been an interesting area of research for more than a century now. Preparation of a thiocarbonyl- or sulfur-containing derivative can be a challenge for the synthetic chemist, but it is a functionality which has found wide uses for example as an isosteric group of the peptidic bond in endothionopeptides[1,2] and in other areas as indicated by patent filings describing thio analogs.

In recent years (1985 onwards) several new thionation reagents have been described. The most recent example is an *in situ* reagent **1A**[3] easily prepared from phosphorus pentasulfide/sodium carbonate (1 : 1) in THF (Scheme 1). This reagent has been found useful for thionation of the R–C=O–NR′R″ moiety in general.[3] There are, as might be expected, a large number of papers dealing with the use of the efficient Lawesson's reagent[4] (**LR**) (Scheme 1), now sold by Aldrich Chemical Co. There are also other dithiaphosphetane analogs such as Belleau's reagent **BR**.[5] However, the majority of publications deal with more conventional reagents which are more economical and accessible, such as phosphorus pentasulfide or derivatives, sulfur, and hydrogen sulfide/acid.



Scheme 1.

The mechanism of thionation may vary from one type of carbonyl to another and certainly from one reagent to another. In this regard, Lawesson's reagent[4] and organothiophosphorus[6] thionation mechanisms are understood and depend on the carbonyl type. Generally speaking, the choice of a reagent can be made (Scheme 2) by countermatching the electrophilic (ketone **1**) or nucleophilic (amide **2**, lactam) character of the carbonyl with that of the reagent. Combining for example the solubility of *in situ* reagent **1A**[3] in THF and its mainly electrophilic character, the thionation of several



Scheme 2.

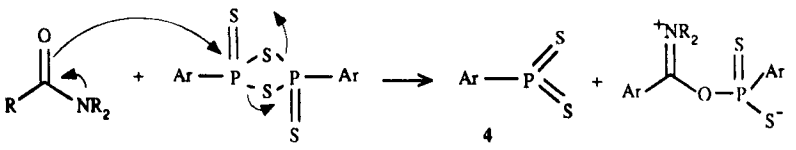


Figure 1

R–C=O–NR′R″ (nucleophilic) containing compounds has been achieved at room temperature and below. However, the direct thionation of an ester and thioester **3** with **LR** requires high temperatures[4] because of the presumed formation of the reactive dipolar intermediate Ar-PS_2,[7,8] **4**, at high temperatures. A study[9] performed using ^{31}P NMR spectroscopy shows that all carbonyl thionations with **LR** and dithiaphosphetane reagents likely occur as an attack of the carbonyl on an *in situ* generated tricoordinated phosphorus species **4** (Scheme 2). Also, to explain the low temperature associated with the thionation of amides, intermediate **4** is likely to be *in situ* generated[9] by the rearrangement of **LR** (Figure 1) during an attack by the more nucleophilic amide oxygen.

This report focuses on the use of thionation reagents, as listed in the contents section, and thionation methods published subsequent to 1984. The related synthetic applications of these thionation methods are described in the following order through Sections 2–8: (a) the direct thionation of carbonyls (*R–C=O–X → R–C=S–X*), (b) thionation of a carbonyl to give a modified thiocarbonyl compound (*R–C=O–X → R–C=S–Y*), (c) thionation of an electrophilic functional group to give a thiocarbonyl compound (*not carbonyl → C=S*), (d) the thionation of a carbonyl to give a product containing no thiocarbonyl group (*C=O → not thiocarbonyl*) and (e) sulfuration without involving a carbonyl and a thiocarbonyl in the reaction (*not carbonyl → not thiocarbonyl*).

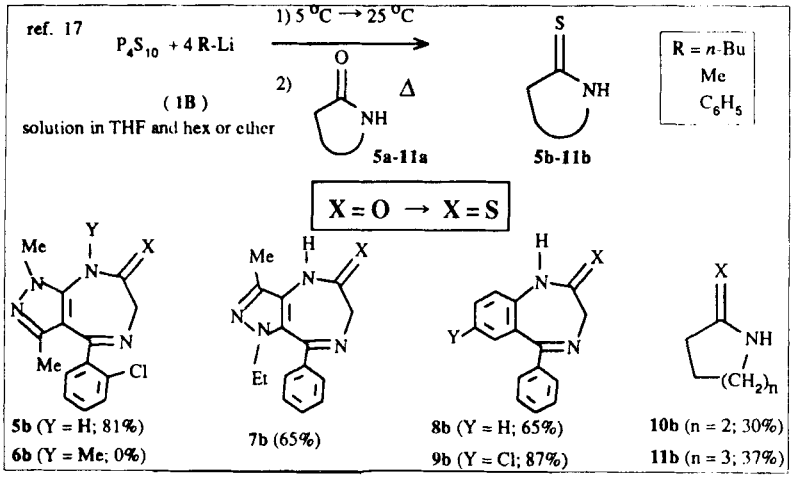
Finally, the reader must be aware that other transformations provide better access to thioaldehydes.[10] These have recently been prepared through elimination or rearrangement reactions which are beyond the scope of this review. There are also new synthetic methods for thiocarbonyl preparation, not mentioned here, described in review articles on dithioesters[11–14] and thionoesters,[11,13] to mention a few. Thioacylating reagents (references 1, 54, 62, 96–98, 129) are also being developed as an approach to the preparation of thiocarbonyls.

2. NEW THIONATION REAGENTS

(*a*) (*R–C=O–X → R–C=S–X*)

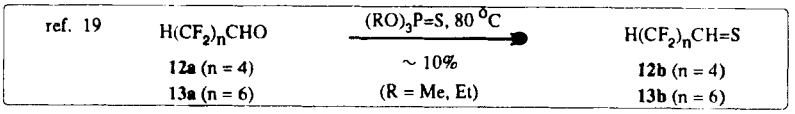
2.1. ***1B****:* P_4S_{10} *+ 4 n-BuLi* The first reagent in this section is another example of the addition of nucleophiles to phosphorus pentasulfide to afford a more soluble *in situ* thionation reagent through phosphorus-sulfur bond breaking.[15,16] Goel and Krolls[17] showed that phosphorus pentasulfide reacts with organolithiums, mainly *n*-BuLi, (Scheme 3) to give a mixture which thionates lactams **5a–11a** once brought to reflux in THF. As explained by the authors, this *in situ* reagent **1B** is a mixture of several reactive species. Despite no real improvements over previous methods for thiolactam formation,[4,18] the reagent is selective and the interesting new thiolactams **5b–11b** (30–87%)

have been described. For example, 0% of the *N*-substituted thiolactam **6b** was obtained compared to 81% of the unsubstituted **5b**.



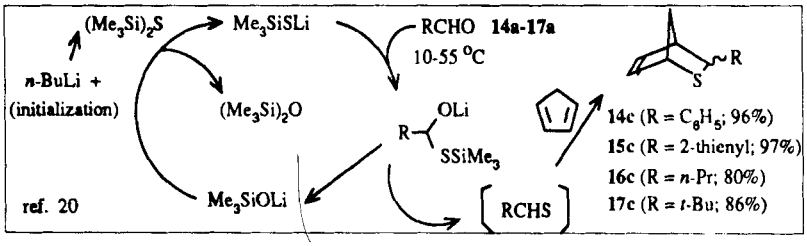
Scheme 3.

2.2. $(RO)_3P{=}S$ Shermolovich *et al.*[19] reported the use of *O,O,O*-triethyl or -trimethyl thiophosphate $(RO)_3P{=}S$ (Scheme 4) for the thionation at 80 °C of aldehydes **12a** and **13a** to give 10% of the ω-hydroperfluorothioaldehydes **12b–13b**. Despite much polymeric material in the crude mixture, these thioaldehydes with electron-withdrawing groups are quite unique and were readily used for cycloadduct formation with dienes.



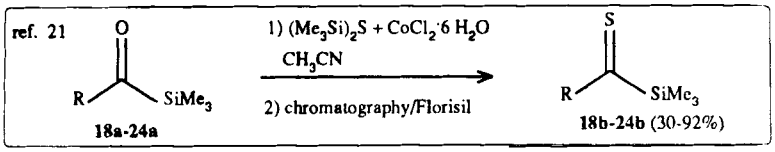
Scheme 4.

2.3. $(Me_3Si)_2S$ + *n-BuLi* (*cat.*) This method developed by Segi *et al.*[20] is one of the most original in this Section in that it demonstrates for the first time that an organosilicon sulfide derivative can be used directly as a thionation reagent. Furthermore, an analogous seleno reagent was used for the preparation of selenoaldehydes.[20] Thus, in the presence of a catalytic amount of *n*-BuLi (Scheme 5) in THF, bis(trimethylsilyl) sulfide converted at 10–55 °C the aldehydes **14a–17a** into the corresponding thioaldehydes **14b–17b**. These were trapped with cyclopentadiene to give the cycloadducts **14c–17c** (80–97%) (Scheme 5) in excellent yields. The nucleophilic character of this reagent derives from the *in situ* reactive species $Me_3SiS^-Li^+$.



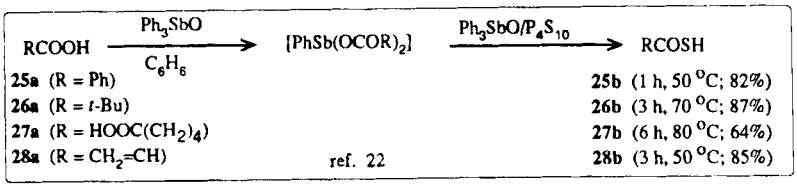
Scheme 5.

2.4. $(Me_3Si)_2S/CoCl_2 \cdot 6\,H_2O$ Use of $(Me_3Si)_2S$[21] in the presence of $CoCl_2 \cdot 6\,H_2O$ as a catalyst also results in thionation of aldehydes in acetonitrile to give the thioaldehydes **14b–15b** which can be trapped with 2,3-dimethylbutadiene to give cycloaddition analogs of **14** and **15**: **14c′** (94%) and **15c′** (91%). An interesting application of these conditions is the thionation of the acylsilanes[21] **18a–24a** to give the thioacylsilanes R–C=S–$SiMe_3$ (Scheme 6): **18b** (R = Me; 30%), **19b** (R = $Me(CH_2)_5$; 64%), **20b** (R = Ph; 92%), **21b** (R = 3-MeO–C_6H_4; 74%), **22b** (R = 4-MeO–C_6H_4; 66%), **23b** (R = 2-furyl; 68%), **24b** (R = 2-thienyl; 59%).



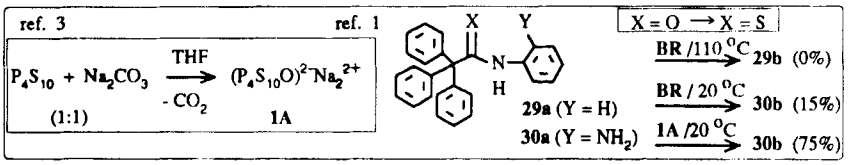
Scheme 6.

2.5. Ph_3SbO/P_4S_{10} Triphenylstibine oxide reacts with carboxylic acids in the presence of tetraphosphorus decasulfide to give directly the corresponding thioacids[22] (Scheme 7). This work is an extension of a procedure for the preparation of dipeptides[23] under these conditions. For example, the carboxylic acids **25a–28a** were converted to the thiocarboxylic acids **25b–28b** (64–84%) after 1–6 h at 50–80 °C in benzene. The *in situ* formed stibine diacetate is the reactive intermediate.



Scheme 7.

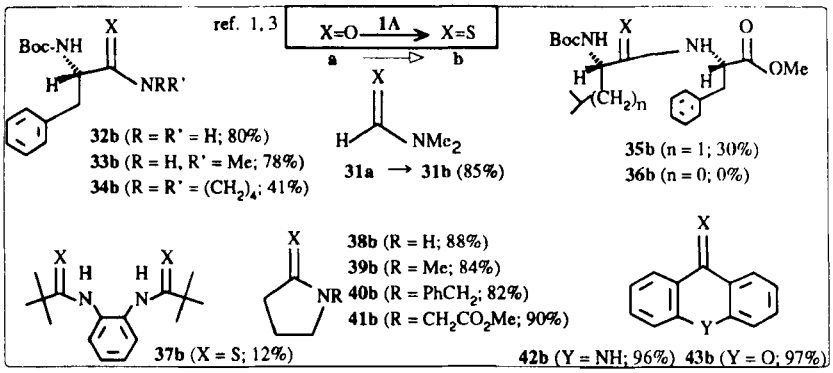
2.6. 1A: P_4S_{10} + Na_2CO_3 (1 : 1) in THF This *in situ* reagent **1A** (Schemes 1 and 8) was developed by us[3] during the course of the thionation of *o*-aminoacetanilides[1] as synthetic intermediates. The thionation of triphenylacetanilide **29a** with Belleau's reagent **BR** was found not to proceed, possibly due to steric reasons (0% **29b**) (Scheme 8). However, we found that the introduction of an *o*-amino group, as in **30a**, lowers the activation energy of the thionation process since **30a** and **BR** seem to complex together through donor/acceptor (amine + carbonyl/phosphorus) interactions[1] allowing the thionation to take place and giving 15% of **30b** at 20 °C! The low yield was again rationalized in terms of steric interactions between the aryl groups of **30a** and **BR**. To prevent also the possibility of a nucleophilic attack by the amino group on the electrophilic organophosphorus thionation reagent,[4,16] we replaced the two aryl groups in **BR** and **LR** by two sodiothiophosphate groups in **1A**. This was easily achieved by treating P_4S_{10} with Na_2CO_3 (1 : 1 ratio) in THF at 20 °C (10–15 min) to give an *in situ* reagent **1A** (empirical formula: $(P_4S_{10}O)^{2-}$ Na_2^{2+}) by modification of Scheeren's procedure.[15] The thionation of **30a** with **1A** indeed reached completion at 20 °C giving 75% of **30b**.[1]



Scheme 8.

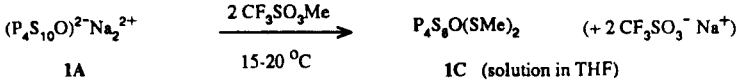
The main advantages[3,1] of this *in situ* reagent **1A** are: (1) its increased electrophilic character (see **31a**[15]) for the thionation of amides or carbonyls which are nucleophilic (Scheme 2) due to the presence of donor groups such as a nitrogen attached to or conjugated with the carbonyl; (2) its preparation can be scaled up; it is economically and rapidly prepared (10–20 min, 20 °C) as a perfectly clear solution in THF, so that the thionation does not proceed under basic[16] or heterogeneous conditions;[15] (3) it is water soluble so that the work-up is very easy. The main disadvantage is that it precipitates on standing (> 24 h) or upon heating,[15,17] after which the thionation stops. However, filtration of the solution and heating below 50 °C generally eliminates the precipitation if heating is required.[3] Compared to Scheeren's reagent[15] (85% of **31b** after 5 h in refluxing ether), thionation of DMF **31a** with the more electrophilic reagent **1A** was accomplished within 5 min at 20 °C giving **31b** (89%) (Scheme 9). We also found that **1A** is convenient for the thionation of amide derivatives of amino acids[3] **32a–34a** which affords thioamides **32b** (80%/0 °C), **33b** (78%/20 °C) and the more sterically hindered thioamide[3] **34b** (41%/50 °C), respectively. Probably due to ionic/hydrophobic repulsive interactions, the *in situ* reagent **1A** is less efficient for the thionation of peptidic bonds.[3] Thus, Boc–Leu–Phe–OMe **35a** gave Boc–Leu–ψ–(CS–NH)–Phe–OMe **35b** (30%/20 °C) and dipeptide Boc–Val–Phe–OMe **36a** was not thionated at all. However, reagent **1A** did thionate the crowded bis-acetanilide[3] **37a** to give the bis-thioamide **37b** in 12% yield at 25 °C.

Interestingly, lactams are easily thionated with **1A**. Thiolactam **10b**[3] (Scheme 3) was obtained in 85% yield with **1A** after 2 h at 25 °C. The thiopyrrolidones[3,1] **38b** (88%/25 °C), **39b** (84%/25 °C), **40b** (82%/25 °C) and **41b**[1,3] (90%/50 °C) were, respectively, obtained from the lactams **38–41a** (Scheme 9). Some aromatic thioketones were also obtained; the *in situ* reagent **1A** thionated acridone **42a** and xanthen-9-one **43a** at 25 °C to give, respectively, the thioketones **42b**[3] (96%) and **43b**[1] (97%). The *in situ* reagent **1A** also afforded thiobenzamides,[3] other thioamides[1] and thiolactams[1] in good yields at 20–25 °C.



Scheme 9.

2.7. 1C: Reagent 1A + CF_3SO_3Me (1:2) in THF Our observation that some R′–C=O–NR_2 compounds were inefficiently thionated by the *in situ* reagent **1A** led us to further increase its electrophilic character[3] in accordance with a mechanism involving nucleophilic attack of an amide oxygen on an electrophilic phosphorus center[9] (Scheme 2). We achieved this by methylating **1A** with methyl trifluoromethanesulfonate in THF[3] at 15 °C (Scheme 10). We thus obtained a clear solution of a new *in situ* reagent **1C**,[3] distinct from **1A** by ^{31}P NMR, but still being a complex mixture (25–120 ppm).

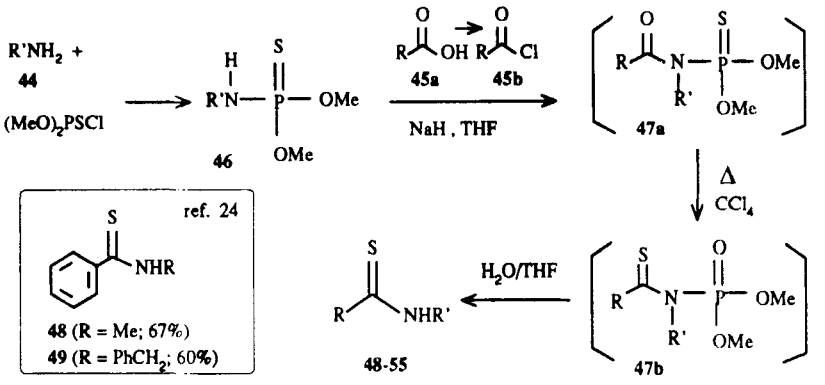


Scheme 10.

Despite the fact that the *in situ* reagent **1C** is unstable, or very stable in the presence of **34a**, and that therefore the solution must generally be filtered to prevent precipitation induced by remaining solid particles, this new *in situ* reagent is the most potent we know for thionation of the R′–C=O–NR_2 moiety. It allowed us to complete on a small scale the thionation of some compounds previously described[3] with **1A** (Scheme 9). For example, the peptides **34b** (72%), **35b** (75%) and **36b** (28%) were obtained with **1C** at 25 °C; the bis-thioamide **37b** (80%) was obtained after 10 h at 25 °C.

(*b*) (*R–C=O–X → R–C=S–Y*)

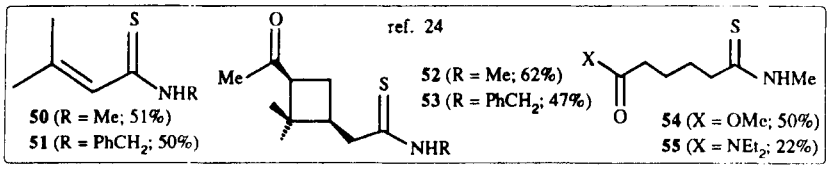
2.8. (*MeO*)$_2$*P=S–Cl* (*multistep*) A two-step sequence was developed by DeBruin and Boros[24] for conversion of acyl chlorides into the *N*-monosubstituted thioamides **48–55** (Scheme 11). This indirect procedure requires treatment of an amine **44** (R′=Me, $PhCH_2$, allyl) with dimethyl chlorothiophosphate to give a thiophosphoramide intermediate **46**. The intermediate **46** is then coupled with an acyl chloride **45b** in the presence of sodium



Scheme 11.

hydride in THF to give an *in situ* intermediate **47a** in which the sulfur migrates upon heating to give a thioacylphosphoramide **47b** which is hydrolyzed easily to a thioamide.

Interesting applications of this methodology[24] are illustrated in Schemes 11 and 12. The thioamides **48** (67%), **49** (60%), **50** (51%), **51** (50%), **52** (62%), **53** (47%), **54** (50%) and **55** (22%) were obtained in fair to good yield from the corresponding acyl chlorides. Some of the overall yields given were better if the synthetic derivatives **47b** were purified by chromatography prior to the hydrolysis.

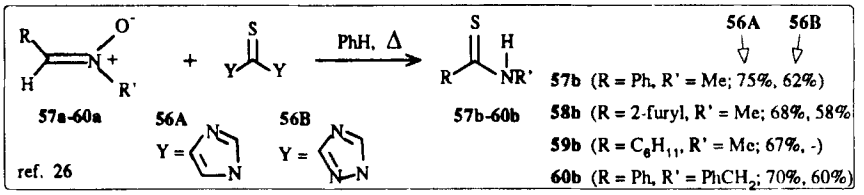


Scheme 12.

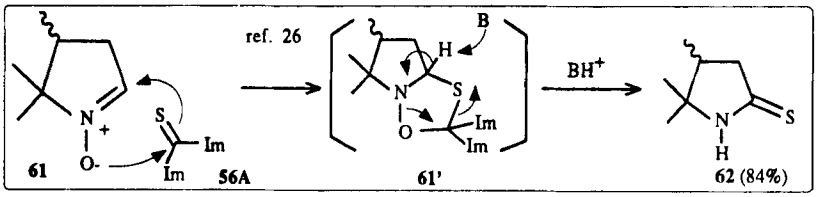
(*c*) (*Not carbonyl → C=S*)

2.9. *Im*$_2$*C=S or Tri*$_2$*C=S* The work of Harpp *et al.*[25,26] has shown that aldonitrones **57a–60a** react with the thiocarbonyl transfer reagent (Scheme 13) 1,1′-thiocarbonyldiimidazole **56A** and the 1,2,4-triazole analog **56B** in refluxing benzene to give the

corresponding *N*-substituted thioamides. Reagent **56A** gives better yields than **56B**. A cyclic aldonitrone **61** (Scheme 14) also reacted with **56A** to give the thiolactam **62** (84%). The reaction is accelerated by pyridine in accordance with a base-catalyzed rearrangement of an intermediate cyclic adduct **61'**.

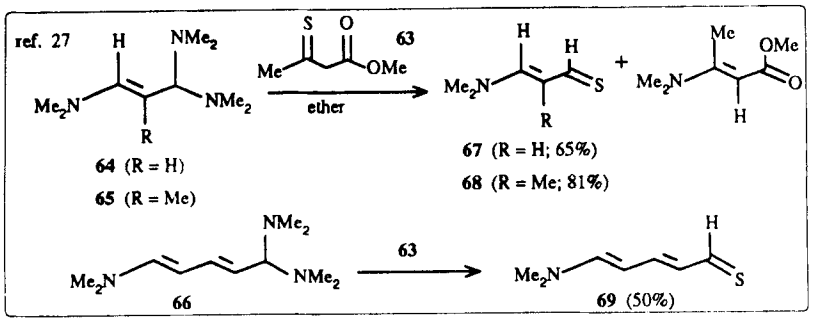


Scheme 13.



Scheme 14.

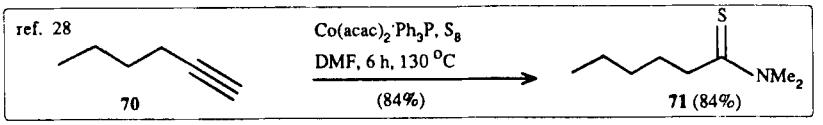
2.10. $CH_3CSCH_2CO_2CH_3$ Krasnaya[27] has demonstrated the use of methyl thioacetoacetate **63** as a thionation reagent. This compound **63** reacts with aminals (Scheme 15) in diethyl ether to give conjugated ω-dimethylamino thioaldehydes in good yields. Thus, the aminals **64**, **65** and **66** gave the thioaldehydes **67** (65%), **68** (81%) and **69** (50%), respectively.



Scheme 15.

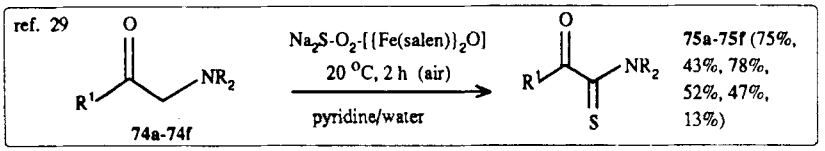
2.11. *Co(acac)₂ · Ph₃P/S₈ in DMF* Dzhemilev *et al.*[28] have developed a new approach for *N,N*-dimethylthioamide synthesis by using the catalyst $Co(acac)_2 \cdot Ph_3P$ for the

aminosulfuration of terminal alkynes (Scheme 16) with elemental sulfur in DMF. For example, 1-hexyne **70** gave $C_5H_{11}CSNMe_2$ **71** in 84% yield after 6 h at 130 °C. Other alkynes **72a–72d** such as 1-decyne, 1-pentyne, phenylacetylene and 1-octyne were also transformed to the *N,N*-dimethylthioamides **73a–73d**.



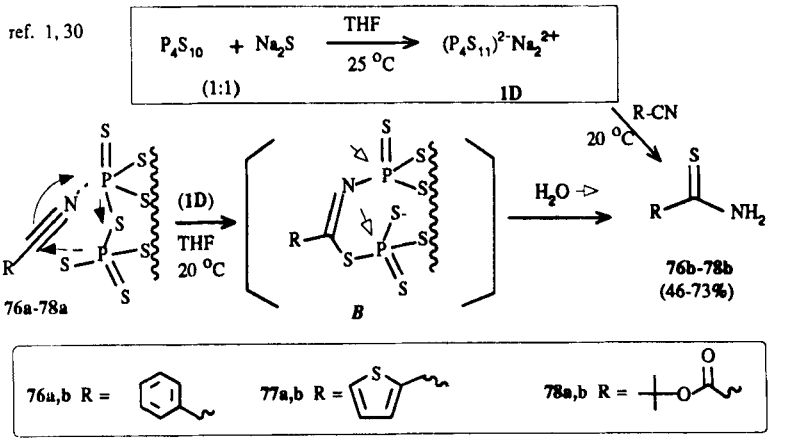
Scheme 16.

2.12. [{Fe(salen)}$_2$O]/$Na_2S \cdot 9\ H_2O$ Miura *et al.*[29] have used the iron complex [{Fe(salen)}$_2$O] (salen = *N,N*-bis(salicylidene)ethylenediaminato) for the α-oxidation of six acylmethylamines **74a–74f** (R^1, R = **a** Ph, $(CH_2)_5$; **b** 4-MeC_6H_4, $(CH_2)_5$; **c** 4-ClC_6H_4, $(CH_2)_5$; **d** Ph, $(CH_2)_4CHMe$; **e** Ph, Et; **f** Me, $(CH_2)_5$) (Scheme 17) in the presence of sodium sulfide nonahydrate in pyridine/water under air and obtained the α-keto thioamides **75a–75f** (13–78%). The thioamide **75a** was also obtained with elemental sulfur alone but in low yield. It is believed that an active sulfur species is generated by reaction of the S^{2-} anion with O_2 mediated by the iron complex.



Scheme 17.

2.13. 1D: P_4S_{10} + Na_2S (1 : 1) in THF We developed this new *in situ* reagent **1D**[1,30] while improving the yield of thionation of phenylacetonitrile **76a** to the corresponding primary thioamide **76b** (27%/**1A**; 19%/**1C**) with reagent **1A**[1,30] at 20 °C. By optimizing the conditions of the thionation of the nitrile at 20 °C, we found that phosphorus pentasulfide reacts with sodium sulfide[15] in THF to give a very stable clear solution of an *in situ* reagent assigned **1D** and having the empirical formula $(P_4S_{11})^{2-}Na_2^{2+}$ based on the stoichiometric amount of reagents used. This new *in situ* reagent exists as a mixture of species, but gives the best yields for this thionation of nitriles. We required its ambivalent electrophilic (2 neutral phosphorus centers) and nucleophilic (2 sodiothiophosphates) character in accordance with a possible mechanism involving nucleophilic attack of a thiophosphate on the nitrile to give an intermediate ***B*** (cyclic or acyclic) obtained after trapping of a thioimidate with a neutral phosphorus center. Intermediate ***B*** should hydrolyze[62] easily with water in the work-up to give a thioamide (Scheme 18). We were able to thionate nitriles[30] after 3.5 h at 20 °C using 5 equivalents of this reagent **1D** (0.4 M). For example, the nitriles **76a**, **77a** and **78a** were transformed into the corresponding primary thioamides **76b** (73%), **77b** (72%) and **78b** (46%) at 20 °C.



Scheme 18.

In summary, this section illustrates the use of the first organosilicon sulfide derivative, $(Me_3Si)_2S$, for direct nucleophilic[20] thionation of carbonyls.[20,21] Three new *in situ* reagents **1A**,[3] **1C**[3] and **1D**,[30] easily prepared from P_4S_{10} in THF at 25 °C and soluble in water for easy work-up, were also shown to be convenient for the thionation of amides, lactams and nitriles at 20–25 °C.

3. ORGANOTHIOPHOSPHORUS REAGENTS

Lawesson's reagent **LR** (Scheme 1) [2,4-bis(4-methoxyphenyl)-2,4-dithioxo-P^v,P^v-1,3,2,4-dithiaphosphetane] is a very versatile and efficient organothiophosphorus reagent for the preparation of thiocarbonyls[4,31] in toluene, THF, xylene, HMPT, *o*-dichlorobenzene, benzene or DME. As previously mentioned, the mechanism of thionation with **LR** (Scheme 2) and analogs is well documented,[4,9] and it is therefore not surprising that analogs such as **BR** perform similar transformations[1] although **BR** is slightly more bulky and selective than **LR** for endothionopeptide[5] preparation. Numerous other synthetic applications related to thionated heterocycles, thiones and others are presented here in Sections 3.1–3.4.

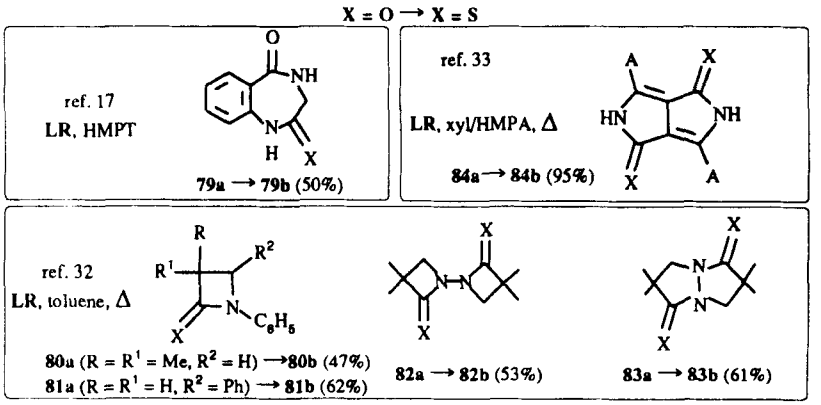
(*a*) (*R–C=O–X* → *R–C=S–X*)

3.1. Thionated Heterocycles The previously mentioned work on thiolactams with *in situ* reagent **1B**[17] (Scheme 3) also showed that **LR** gives better yields. For example, the thiolactams **5b** (90%/pyridine) and **6b** (10%/HMPT) could be obtained with **LR**. Similarly, a cyclic dioxo compound **79a** was converted by **LR** to **79b** (50%; 25%/**1B**)[17] (Scheme 19).

Rademacher and Verkoyen[32] have obtained the β-thiolactams **80b** (47%), **81b** (62%), **82b** (53%) and a bis-thiolactam **83b** (61%) using **LR** in refluxing toluene for the thionation of the lactams **80a–83a**.

Rochat *et al.*[33] have obtained the pyrrolopyrroledithiones **84b** (95%) by thionation of **84a** with **LR** in refluxing xylene. Several analogs of **84a** with different substituents

(A = alkyl, aralkyl, cycloalkyl, carbocyclic or heterocyclic aromatic group) were successfully thionated; **84b** and analogs were developed as photoconductors.

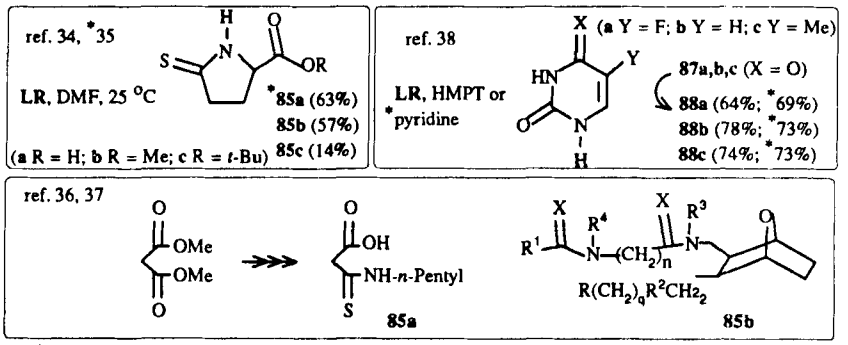


Scheme 19.

Lawesson *et al.*[34] have thionated esters and unprotected (R = H) 5-oxoproline derivatives (Scheme 20) with **LR** and obtained the corresponding 5-thioxoprolines **85a** (R = H; 50%) **85b** (R = Me; 57%) and **85c** (R = *t*-Bu; 14%). Senning *et al.*[35] have recently improved the thionation process of 5-oxo-L-proline with **LR** using DME as solvent and obtained 63% of 5-thioxo-L-proline **85a**.

Several bis-thioamide prostaglandin analogs **86b** (n = 1–5, q = 1–12) with several different groups R, R^1–R^4 have been prepared as antithrombotic agents[36,37] by use of the thioamide **86a** prepared in three steps from dimethyl malonate.

The thionation of uracil derivatives **87a–87c** to give the monothionation products **88a–88c** (64%, 78%, 74%) with **LR** in HMPT (10–120 °C) or in pyridine (140 °C) was also accomplished by Kaneko *et al.*;[38] dithionated analogs were also obtained.



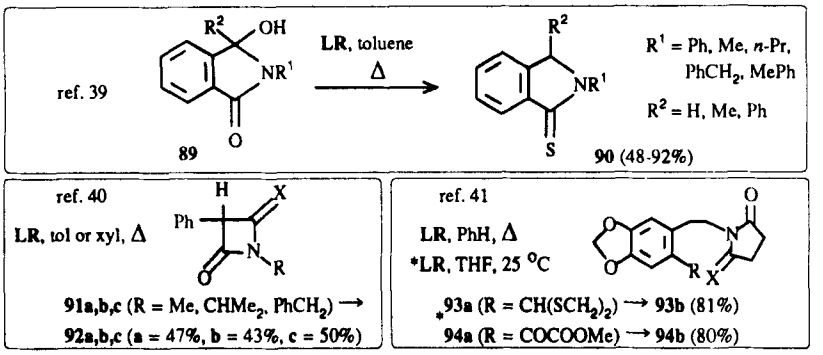
Scheme 20.

Nishio *et al.*[39] have thionated 3-hydroxyisoindolin-1-ones **89** (Scheme 21) with **LR** and obtained the corresponding thiolactam derivatives **90** (48–92%) in good yields by thionation also of the OH group in **89**, followed by reduction of the thiol formed.

Aoyama *et al.*[40] have obtained the products **92a–92c** (43–50%) (Scheme 21) by monothionation of three azetidine-2,4-diones **91a–91c** using **LR** in refluxing toluene or xylene.

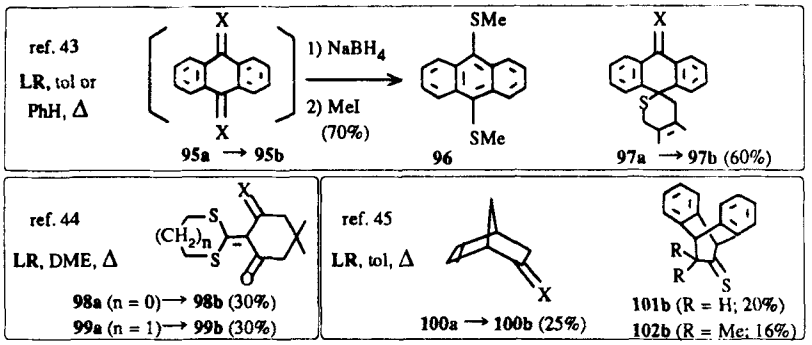
This was also observed by Danishefsky *et al.*[41] during the thionation of **93a** and **94a** (Scheme 21) which gave the thioimides **93b** (81%) and **94b** (80%).

The last example in this section is the use of **LR** for the thionation of polyamide polymers in toluene at 100 °C for 2 h to give polythioamides.[42]



Scheme 21.

3.2. Thiones and Thionolactones Cava *et al.*[43] have thionated anthraquinone **95a** with **LR** obtaining the dithione **95b** (Scheme 22) which is unstable. However, treatment of the crude mixture of **95b** with sodium borohydride/methyl iodide gave the methylated dithio derivative **96** in an overall yield of 70%. A potential precursor, **97b** (60%), of **95b** was also obtained by thionation of **97a** with **LR** in refluxing benzene.



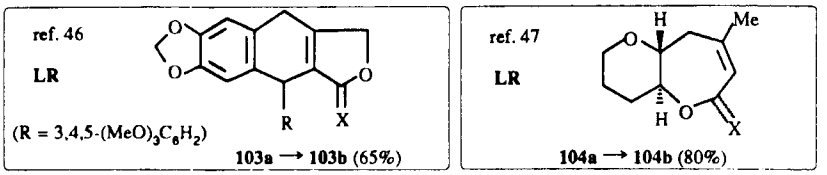
Scheme 22.

Sandström and Khan[44] have obtained, with **LR** in refluxing DME, the selectively monothionated derivatives **98b** (30%) and **99b** (30%) (Scheme 22) only from the diacylketene thioacetals **98a** and **99a**.

A route developed by Ripoll *et al.*[45] for the preparation of thioketenes involved the thionation of the cyclic ketones **100a–102a** (Scheme 22) to give the thioketones **100b–102b** (16–25%) using **LR** in refluxing toluene.

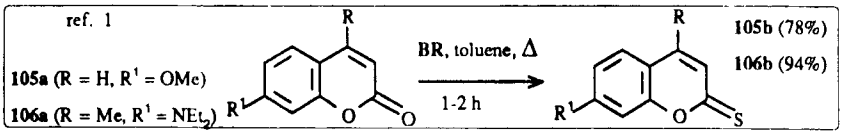
An interesting application of **LR** is in the thionation of β-apopicropodophyllin **103a**[46] (Scheme 23) to the thionolactone **103b** (65%).

Nicolaou *et al.*[47] have reported the preparation of thionolactones with **LR**, **BR** and four other dithiaphosphetanes. In a comparative study, **BR** gave a slightly better yield than **LR**. The lactone **104a** was converted among others to the thionolactone **104b** (80%) with **LR**; the authors decided to choose **LR** because of its commercial availability.



Scheme 23.

We have also used **BR** (Scheme 1) for the thionation of coumarins **105a–106a**[1] (Scheme 24) in refluxing toluene and have obtained the benzopyran-2-thiones **105b** and **106b** in yields of 78% and 94%, respectively.

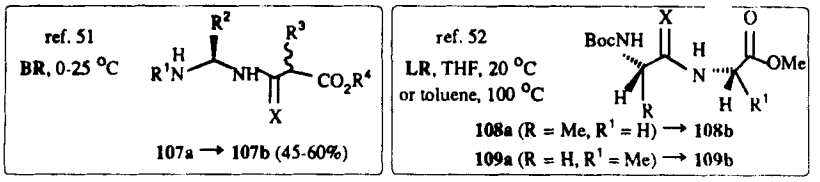


Scheme 24.

3.3. Endothionopeptides Several studies deal with the use of **BR**[5] for the thionation of the peptidic bond by stirring a solution of a peptide and **BR** in THF[5] which is one of the best solvents for the thionation of carbonyls at 20 °C. The work of Lajoie[5,48] and of Lépine[5,49] is most illustrative of the use of **BR** for the preparation of endothionopeptides. The work of Belleau *et al.*[5,50] also shows that **BR** is a selective peptide thionation reagent and that thiopeptidic analogs can be potent derivatives which resist the proteolytic process.[50]

The reagent **BR** was used by Campbell *et al.*[51] to prepare the retroinverso endothionopeptide analogs **107b** (45–60%) (Scheme 25) by thionation of **107a**. They have also shown that **107b** can be chain elongated on both the amino and carboxyl side, which is not the case with endothionopeptides.[5]

However, most thiopeptides have been prepared simply by thionation of a dipeptide with **LR**[4] as reported by Lawesson *et al.*[52] with Boc–Ala–ψ-(CSNH)–Gly–OMe **108b** and Boc–Gly–ψ-(CSNH)–Ala–OMe **109b** in THF (20 °C) or in toluene (100 °C).



Scheme 25.

Cho[53] has prepared fluorescent thiopeptidic derivatives such as Z–Arg–ψ-(CSNH)–(Mtr)–AIE **110**; this was obtained in a yield of 39% by treatment of the parent peptide with **LR** in refluxing benzene.

Other endothionopeptides that have been prepared by thionation of peptides with **LR** are: Boc–Leu–ψ-(CS–NH)–Asp–OMe[54] **111**, Z–Gly–ψ-(CSNH)–Gly–ψ-(CSNH)–Phe–OMe[55] **112** (65%), Boc–Pro–ψ-(CSNH)–Gly–OEt[56] **113** (63%).

In an interesting new application for terminal thioamide peptide synthesis, Majer *et al.*[57] have shown that an amino acid linked to a resin, by an amide linkage, can be thionated with **LR** in toluene at 90–100 °C. This can then be utilized in a normal Merrifield solid phase synthesis of peptides; the yield of thionation was 92% based on weight changes.

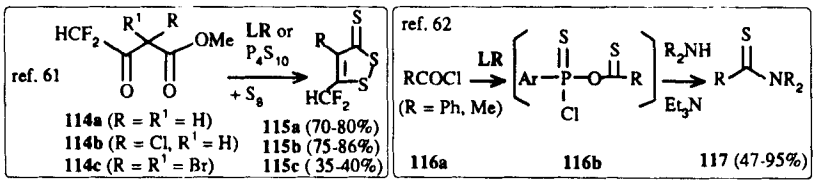
A similar terminal thioamide modification has been applied to pentagastrin analogs by Kruszynski *et al.*[58]

Finally, general results on endothionopeptide preparation and their use as synthetic intermediates have also been reported by Wasmund[59,60] and by us.[1,48-49]

(*b*) (*R–C=O–X → R–C=S–Y*)

3.4. Miscellaneous Pashkevich *et al.*[61] have thionated methyl esters of the fluorinated β-keto acids **114a, b, c** (Scheme 26) with **LR** or P_4S_{10}/sulfur to obtain the 1,2-dithiole-3-thiones **115a** (70–80%), **115b** (75–86%) and **115c** (35–40%).

Yousif and Salama[62] have obtained the intermediate **116b**, from acyl chloride **116a** and **LR**, which reacts as a thioacylating reagents with secondary amines to give thioamides. Thiobenzamides and thioacetamides **117** (47–95%) have been prepared.



Scheme 26.

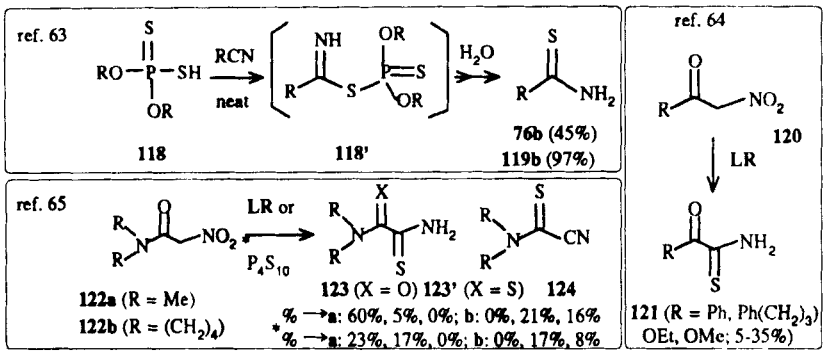
Davy used his reagent $(RSPS_2)_2$ (R = Me, alkyl) **DR**[68,84] for the preparation of dithioesters from carboxylic acids:

$$(RSPS_2)_2 + R^1COOH \rightarrow R^1CSSR$$
DR

(c) (not carbonyl → C=S)

Shabana *et al.*[63] have thionated the nitriles **76a** (22 °C) and **119a** (R = 4-O_2NC$_6$H$_4$; 80 °C) (Scheme 27) with *O,O*-diethyldithiophosphoric acid **118**,[6] in the presence of 1–2 eq. of water and in the absence of solvent, and obtained the thioamides **76b** (45%) and **119b** (97%), although in substantially lower yield than with the *in situ* reagent **1D** (73%/**76b**). Reagent **118** likely reacts through concerted protonation and thiophosphate attack[6] on the nitrile to give the intermediate **118′** which rearranges to a thioacylamidothiophosphate and then hydrolyses.

Joule *et al.*[64] have obtained the α-keto thioamides **121** (5–35%) (Scheme 27) from 2-nitro ketones and nitroacetates **120** (R = Me, Ph, OEt, OMe) with **LR** or P_4S_{10}; the corresponding acylthiourethanes (28–72%) were also obtained along with **121**. The same authors have also obtained thionated derivatives of oxalic acid[65] **123**, **123′** and α-cyano thioamides **124** from the thionation of nitroacetamides **122a,b** with **LR** in toluene or with P_4S_{10} in dioxane at 80–100 °C.

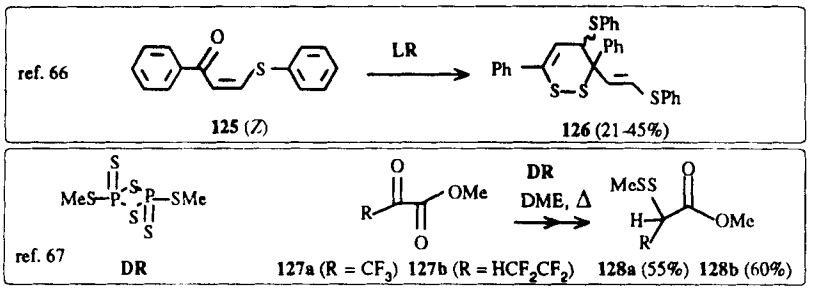


Scheme 27.

(d) (C=O → not thiocarbonyl)

Karakasa[66] obtained the products of sulfuration/cyclodimerization **126** (*E*) (21–45%) (Scheme 28) by thionation of 3-phenyl-2-propen-2-one **125** (*E* or *Z*) with **LR**.

Bobrov *et al.*[67] have used Davy's reagent,[68] **DR** $(MeSPS_2)_2$, in refluxing DME for the thionation of the fluorinated α-keto esters **127a** and **127b**. No thionation took place with **LR** and P_4S_{10} below 140 °C but the most electrophilic carbonyl was thionated with **DR**, which probably acts as a better nucleophilic reagent with methylthio groups, giving the methyldithio derivatives **128a** (55%) and **128b** (60%) as the isolated products.



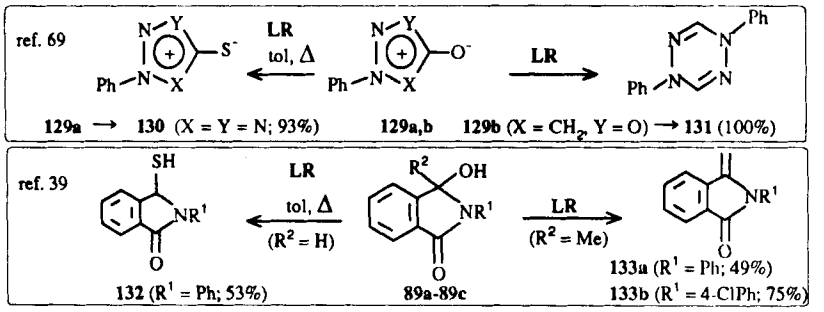
Scheme 28.

(*e*) (*not carbonyl → not thiocarbonyl*)

Araki *et al.*[69] have thionated the mesoionic olates **129a, b** with **LR** in refluxing toluene (Scheme 29). This afforded the thiolate **130** (98%) from **129a**, while **129b** gave exclusively the tetrazine **131** (100%).

The work of Nishio[39] (Scheme 21) also shows that the hydroxyl group in **89a** (R^2 = H) can be converted to a thiol **132** (53%) (Scheme 29). However, if the thiol formed is tertiary, an elimination can occur from group R^2. Compounds **89b** (R^1 = Ph, R^2 = Me) and **89c** (R^1 = 4-ClC_6H_4, R^2 = Me) were thus converted to the products **133a** (49%) and **133b** (75%) with less **LR** than for the preparation of the derivatives **90** (Scheme 21).

Finally, Levinson[70] used the thionating properties of **LR** for preparing C–S analogs of sulfur nitride $(SN)_x$.



Scheme 29.

This Section demonstrates that **BR** and **LR** are particulary useful for endothionopeptide synthesis and that **LR** is even compatible with Merrifield's method.[57] The electrophilic character of **LR** also allows thionation of weak nucleophiles such as olate[69] and hydroxyl[39] groups. *O,O*-Diethyldithiophosphoric acid **118**[6] was used in the presence of water for the first time to thionate nitriles.[63] Finally, **DR**[68] was found more potent than **LR** for the thionation of electrophilic ketones[67] although the thionation products were not thiocarbonyls.

4. TETRAPHOSPHORUS DECASULFIDE AND *IN SITU* DERIVATIVES

The use of the electrophilic P_4S_{10} for thionation is well documented. However, P_4S_{10} is poorly soluble in organic solvents at 25 °C and a thionation with P_4S_{10} thus generally requires high temperature and a polar solvent such as HMPT or pyridine; it has, however, been reported by Davy[83] that *o*-dichlorobenzene partially solubilizes P_4S_{10}. The addition of nucleophiles to break P–S bonds allows partial or complete[3] solubilization of this reagent making it more reactive mainly for that reason. These *in situ* derivatives are commonly obtained by the reaction of $NaHCO_3$[15] with P_4S_{10} in CH_3CN and Na_2CO_3 in THF[3] (**1A**) and the thiophosphate[3,15,16] groups so obtained can also be further useful for nucleophilic thionations especially of ketones[15] (Scheme 2). The recent applications of P_4S_{10} are related mainly to the thionation of heterocycles.

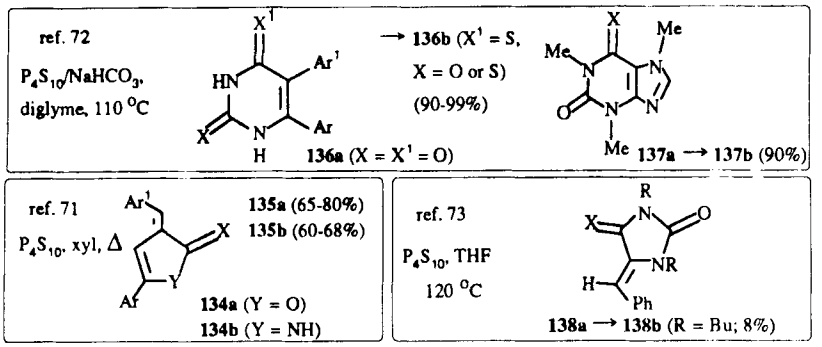
(*a*) (*R*–C=O–*X* → *R*–C=S–*X*)

The work of Rademacher and Verkoyen[32] involves the use of P_4S_{10} for the thionation of the lactams **80a–83a** (Scheme 19) to give the thiolactams **80b–83b** (21–42%). **LR** is better, but with P_4S_{10} the β-lactam **82a** was transformed into the thiolactam **83b** (35%) with no formation of **82b** observed.[32]

Work by Hashem *et al.*[71] shows that the butenolides **134a, b** (Scheme 30) with different aryl groups can be thionated with P_4S_{10} in refluxing xylene to give the thiono derivatives **135a** (65–80%) and **135b** (60–68%).

Thionation of the pyrimidine bases **136a** with many different aryl substituents, and of **137a** has been accomplished in high yield by Lapucha[72] with P_4S_{10} + 4-$NaHCO_3$ in diglyme at 110 °C to give **136b** (90–99%) and **137b** (90%).

Süss-Fink and Schmidt[73] have thionated the more electrophilic carbonyl group in the 5-benzylidenehydantoins **138a** (R = Me, Et, Pr, Bu) (Scheme 30) with P_4S_{10} in THF at 120 °C; **138b** (R = Bu) was obtained in 8% yield.



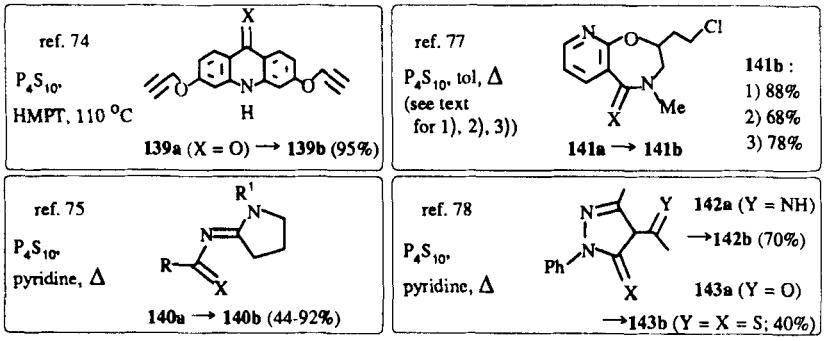
Scheme 30.

The acridone **139a** (Scheme 31) was thionated by Lehn *et al.*[74] with P_4S_{10} in HMPT at 110 °C giving **139b** (95%).

Liebscher *et al.*[75] have thionated,[76] with P_4S_{10} in refluxing pyridine, nine acylamidines **140a** with different aryl groups R. This resulted in the isolation of the thionated products **140b** (44–92%).

Stahly[77] have thionated the lactam **141a** with P_4S_{10} in toluene in the presence of different additives such as $NaHCO_3$,[15] diatomaceous earth and CaF_2 and obtained the thiolactam **141b** in respective yields of 88%, 68% and 78%; this is the first reported use of CaF_2 for a thionation with P_4S_{10} but it appears to offer no advantages over $NaHCO_3$.

Awad and Hassan[78] have thionated the pyrazolin-5-ones **142a** (Y = NH) and **143a** (Y = O) with P_4S_{10} in pyridine and obtained the thioxo derivatives **142b** (70%) and **143b** (40%).

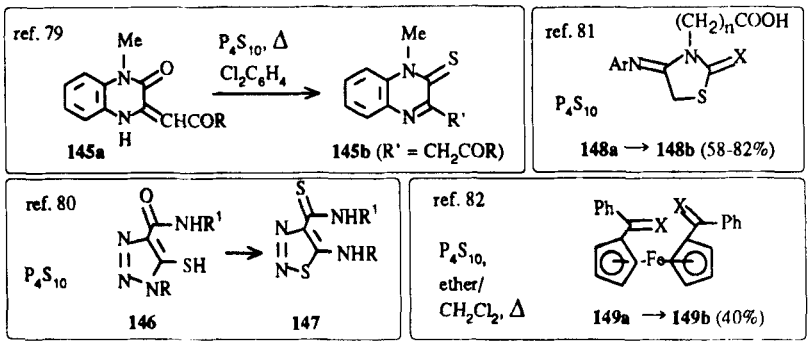


Scheme 31.

Douglas *et al.*[54] have also obtained the derivatives Boc–Phe–ψ-(CSNHR) **32b**, **33b** and Ac–Trp–Leu–Asp–ψ-($CSNH_2$) **144** via thionation with P_4S_{10}.

Toman and Klicnar[79] obtained the thiolactams **145b** (10–61%) (Scheme 19) by thionation of the lactams **145a** with P_4S_{10} in hot *o*-dichlorobenzene.

Dankova *et al.*[80] have achieved the thionation of the carboxamide group in **146** to yield **147** (Scheme 32). P_4S_{10} is furthermore a ring-opening/recyclization catalyst in this transformation since the 5-mercapto-1,2,3-triazole **146** heterocycle is converted to a thiadiazole **147** during the thionation.



Scheme 32.

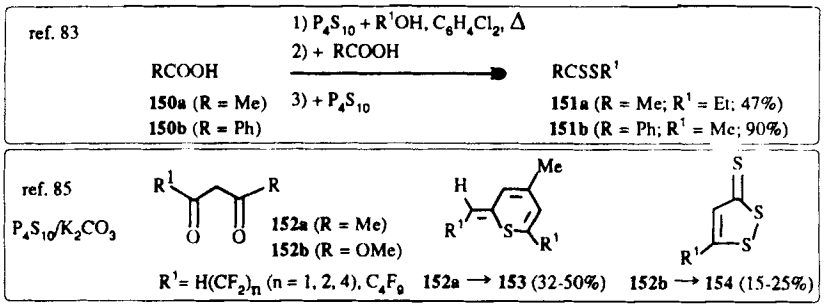
Ganitkevich[81] has obtained several thiazolidine-2-thiones **148b** (58–82%) by thionation of the derivatives **148a** (R = $(CH_2)_nCOOH$; n = 1, 2, 3, 5) with P_4S_{10}.

An interesting thionation of 1,1′-dibenzoylferrocene **149a** to give the dithioxo derivative **149b** (40%) has been achieved by Glidewell *et al.*[82] with P_4S_{10} alone or with $NaHCO_3$ (no improvement) in refluxing CH_2Cl_2/ether. They also obtained a low yield (1%) of a 1,2,4-trithiolane as a by-product.

(*b*) ($R-C=O-X \rightarrow R-C=S-Y$)

Davy and Metzner[83,84] have designed a one-pot preparation of dithioesters from carboxylic acids with P_4S_{10} (Scheme 33). Thus, P_4S_{10} is first treated with an alcohol R^1OH to generate an *in situ* trialkyl tetrathiophosphate $(R^1S)_3PS$ which in turn reacts with acetic acid **150a** or benzoic acid **150b**. Addition of more P_4S_{10} converts an *in situ* thioester intermediate to the dithioesters **151a** (47%) and **151b** (90%).

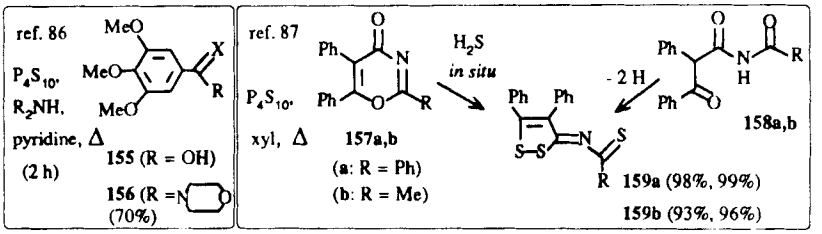
Bobrov *et al.*[61] have used a P_4S_{10}/S_8 mixture to prepare the 1,2-dithiole-3-thiones **115a, b, c** (Scheme 26). The same team[85] also treated the fluorinated acetoacetones **152a** (Scheme 33) and the fluorinated β-keto esters **152b** with P_4S_{10}/K_2CO_3 and obtained dimerization products such as the thiopyrans **153** (32–50%) and the dithiolenethiones **154** (15–25%), respectively.



Scheme 33.

Blade Font *et al.*[86] have used P_4S_{10} to convert carboxylic acids to thioamides or thiolactams (Scheme 34) in the presence of a secondary amine. For example, the benzoic acid **155** was converted to the thiobenzamide **156** (70%) in the presence of morpholine after 2 h in refluxing pyridine.

Capuano *et al.*[87] have obtained the rearrangement products **159a, b** (93–99%) in similar high yields by thionation of either the oxazinones **157a, b** or the trioxo derivatives **158a, b** with P_4S_{10} in refluxing xylene.

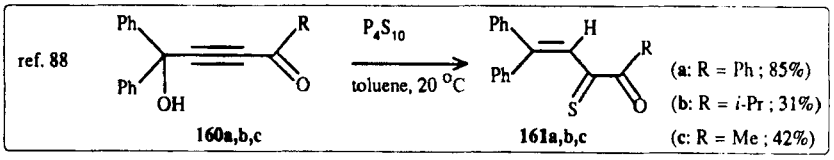


Scheme 34.

(*c*) (*not carbonyl* → *C=S*)

The work of Harris *et al.*[65] also features the use of P_4S_{10} for the thionation of the nitroacetamides **122** (Scheme 27).

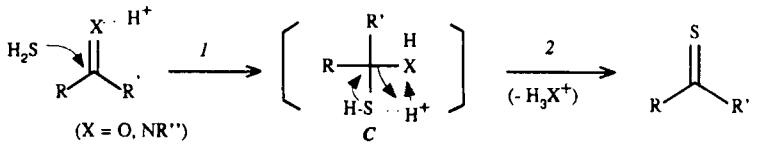
An interesting rearrangement was observed when the propargylic alcohols **160a, b, c** (Scheme 35) were treated with P_4S_{10} in toluene at 25 °C. As noted by Toda and Tokunaga,[88] the exact mechanism is not clear but the α-thioxo ketones **161a, b, c** (85%, 31%, 42%) are rapidly formed.



Scheme 35.

5. HYDROGEN SULFIDE

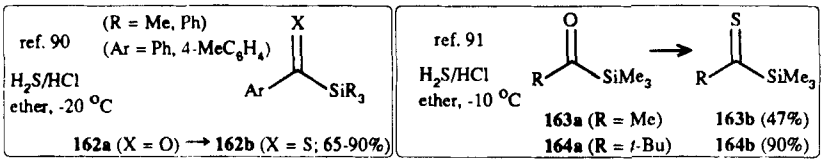
Hydrogen sulfide (H_2S) was one of the first thionating reagents ever reported and is still being employed. However, due to polymerization problems during some thionations and development of alternatives (Sections 1–3), it is often no longer the reagent of choice. Distinct from **LR**, **BR** and P_4S_{10}, it is a weakly nucleophilic and acidic thionation reagent. Thus it adds to a carbonyl group with formation of a mercapto hydroxy hemiketal *C* (X=O in Scheme 36) which eliminates to a thiocarbonyl. Further addition can give a *gem*-dithiol. This exchange process is acid-catalyzed (Scheme 36) in both steps *1* and *2* and the equilibrium is driven by the stronger hydrogen bond formed with an oxygen[89] or a nitrogen which favors the elimination of H_3O^+ or $R''NH_3^+$ from the intermediate. Hydrogen sulfide is particularly useful for the sulfuration of stable imidate salts and gives good yields of thiono derivatives.



Scheme 36.

(*a*) (*R–C=O–X* → *R–C=S–X*)

The recent thionations with H_2S all involve carbonyls attached to heteroatoms. Particularly interesting was the first use of H_2S for the preparation of the aromatic thioacylsilanes **162b** (Scheme 37); these compounds are unstable and had to be used immediately



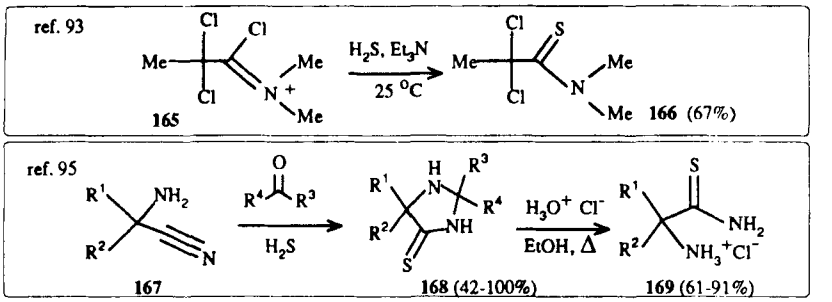
Scheme 37.

for further transformations. Bonini *et al.*[90] have thus obtained the silyl thioketones **162b** (65–90%) with H_2S/HCl at −20 °C from **162a** (R = Me, Ph; Ar = Ph, 4-MeC_6H_4) (see **20b**[21]). More recently[91] they obtained the thioacyltrimethylsilanes **163b** (47%; = **18b**,[21] 30%), **164b** (90%) from **163a** (R = Me) and **164a** (R = *t*-Bu) using identical conditions at −10 °C. They observed that a *gem*-dithiol derivative can be isolated in quantitative yield prior to its transformation to **163b** by use of an alkaline work-up; thione **163b** is, however, unstable while **164b** is much more stable than the arylthiones **162b**.

Eastman *et al.*[92] have used γ-alumina for the sulfuration of methylpyrrolidone **39a** (26.4% conversion) with H_2S at 725 °C and 15 psi to obtain **39b** (see Scheme 9).

(*c*) (*not carbonyl → C=S*)

Viehe *et al.*[93,94] have performed the thionation of the chloroiminium salt **165** (Scheme 38) with H_2S in the presence of Et_3N at 25 °C and obtained the 2,2-dichloropropanethioamide **166** (67%).

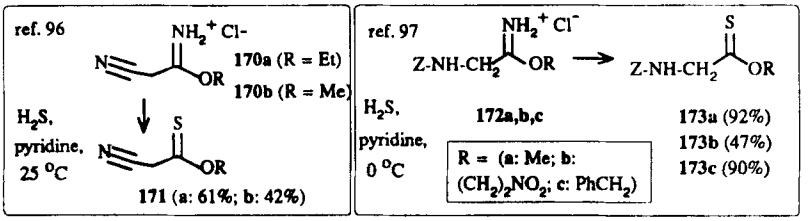


Scheme 38.

Edward and Paventi[95] have thionated several α-amino nitriles **167** (Scheme 38) with H_2S/Et_3N in the presence of a ketone at 0–65 °C and isolated the corresponding imidazolidine-4-thiones **168** (42–100%). Compounds **168** were then hydrolyzed with HCl in refluxing ethanol to give the hydrochlorides of the α-amino thioamides **169** (61–91% in the amino acid series).

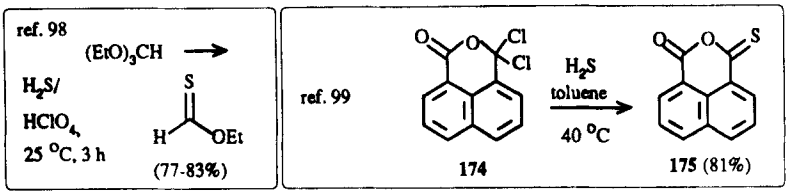
Hartke and Müller[96] treated the hydrochlorides of the malononitrile imidoesters **170a, b** (Scheme 39) with H_2S/pyridine at 25 °C and obtained the corresponding cyanoacetic thionoesters **171a** (61%) and **171b** (42%).

Williams *et al.*[97] have used this transformation for the preparation of six thionoester derivatives of glycine (*N*-Z or -Fmoc), and also one phenylalanine and one Tyr–Gly–Gly thionoester. For example, the hydrochlorides of the glycine imidoesters **172a, b, c** gave the thionoesters **173a, b, c** (92%, 47%, 90%) upon teatment with H_2S in pyridine.



Scheme 39.

Some interesting transformations with H_2S are possible at centers supporting the formation of an oxonium[95] ($R-O^+=R'$) or carbonium[99] intermediate. An improved preparation of ethyl thionoformate (77–83%) (Scheme 40) has been achieved by Stowell *et al.*[98] using $H_2S/HClO_4$ for the hydrothiolysis of triethyl orthoformate at 20 °C.

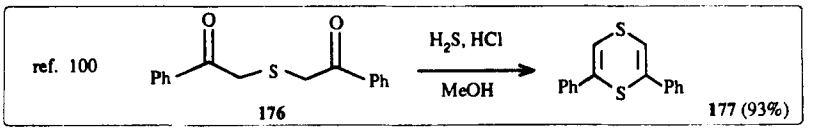


Scheme 40.

Cava *et al.*[99] have obtained the thionoanhydride **175** (81%) (Scheme 40) by treatment of the 6,6-dichloropyran-2-one **174** in toluene with H_2S at 40 °C.

(d) (C=O → not thiocarbonyl)

Voronkov *et al.*[100] have shown that the diketone **176** (Scheme 41) is converted to the dithiin **177** (93%) by H_2S/HCl in methanol.



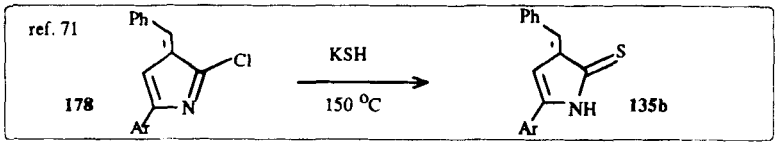
Scheme 41.

6. POTASSIUM HYDROSULFIDE AND SODIUM HYDROSULFIDE

The hydrosulfide anion is strictly a nucleophilic source of sulfur S^{II} for the introduction of the SH group. For example, displacements of labile halides such as in α-halo imines followed by tautomerization give thioamides.

(*c*) (*not carbonyl → C=S*)

6.1. KSH Hashem *et al.*[71] have also used potassium hydrosulfide for converting the benzylidene-2-chloro-3*H*-pyrroles **178** (Scheme 42) to the thioxopyrrolines **135b** (Scheme 30) after 2 h at 150 °C (neat).



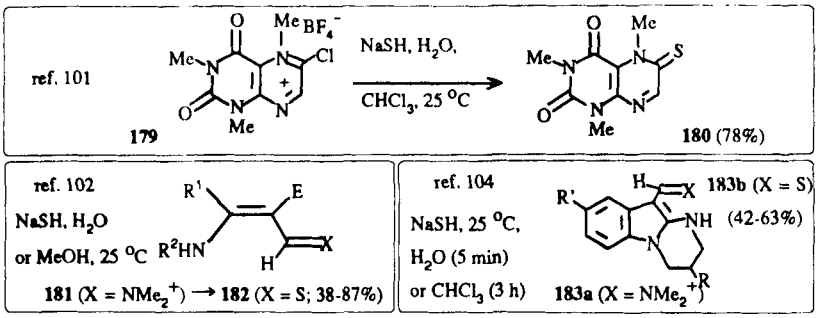
Scheme 42.

6.2. NaSH Pfleiderer and Heckel[101] have converted the chloroiminium salt **179** (Scheme 43) to the thioxo derivative **180** (78%) within 10 min at 25 °C with aqueous NaSH.

Enamino thioaldehydes **182** (38–87%) with several substituents (E = CO_2R^3, H, Ph; R = alkyl, aryl) have been prepared by Muraoka *et al.*[102] Most of the thiono derivatives **182** were prepared by hydrothiolysis of the Vilsmeier salts **181** with aqueous or methanolic NaSH solutions. Muraoka and Yamamoto[103] also prepared similar thioaldehydes from enamines by hydrothiolysis of *in situ* formed Vilsmeier salts with sodium hydrosulfide.

Sviridova *et al.*[104] have similarly hydrothiolyzed the Vilsmeier salts **183a** (R = H, Me; R^1 = H, Br) to give the 2-aminoindolethiocarbaldehydes **183b** (42–63%). The reaction is much faster in water than in chloroform; this is probably related to the solubility difference of NaSH in each solvent.

An extensive review on enamino thioaldehydes and thioketone analogs has also been written by Pulst, Greif and Kleinpeter.[105]



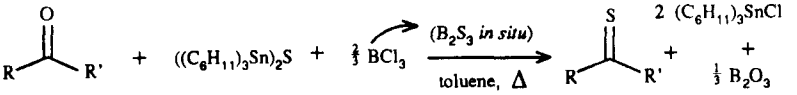
Scheme 43.

7. OTHER REAGENTS

Combined in this section are thionation reagents or conditions which have been of limited use in recent years.

(a) *(R–C=O–X → R–C=S–X)*

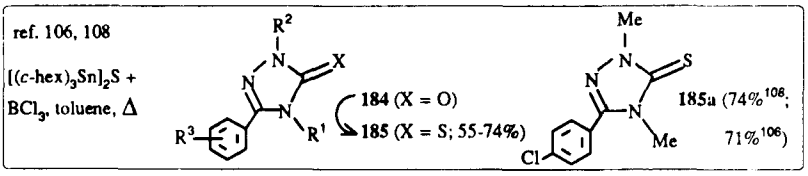
7.1. $[(C_6H_{11})_3Sn_2]S + BCl_3$ This *in situ* reagent has been described by Steliou *et al.*[18] In refluxing toluene the very reactive B_2S_3 is formed by a reaction between bis(tricyclohexylstannyl) sulfide and BCl_3 (Scheme 44) and reacts with carbonyls to give thiocarbonyl derivatives. Due to the Lewis acid character of the boron, the thionation mechanism with B_2S_3 is expected to be similar to that with intermediate **4** (Scheme 2). This involves attachment of the carbonyl oxygen to the B^{III} (P^{V} in **4**[9]) electrophilic center.[18]



Scheme 44.

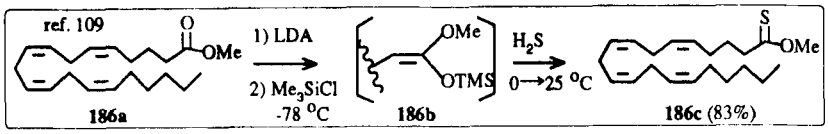
Kane[106] has used these conditions for the thionation of several 1,2,4-triazol-3-one derivatives[107] **184** (R^1 and R^2 = Me, Et; R^3 = H, 4-Cl, 4-F) in refluxing toluene and obtained the thiono compounds **185** (55–74%) (Scheme 45) which can be used as antidepressants. For example, derivative **184a** gave 71% of **185a**.

Compound **185a** was also prepared in 74% yield by Merrell Dow Pharmaceuticals[108] under the same conditions. They also prepared several other analogs of **185** (R^3 in *o*-, *m*- or *p*-position = halo, C_{1-6} alkyl, alkoxy, OH, CF_3; R^1 and R^2 = C_{1-6} alkyl).



Scheme 45.

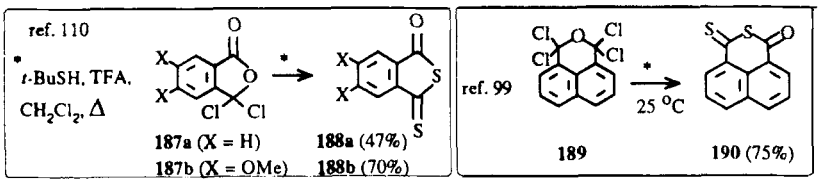
7.2. 1) LDA, 2) Me_3SiCl, 3) H_2S This indirect thionation method was developed by Corey and Wright[109] and involves the *in situ* preparation of a silyl enol ether by treatment of an ester with LDA and Me_3SiCl at −78 °C. The enol ether is then hydrothiolyzed with H_2S at 0 → 25 °C. For example, the ester **186a** (Scheme 46) was transformed to the thionoester **186c** (83%) via formation of the silyl enol ether **186b** in this one-pot sequence.



Scheme 46.

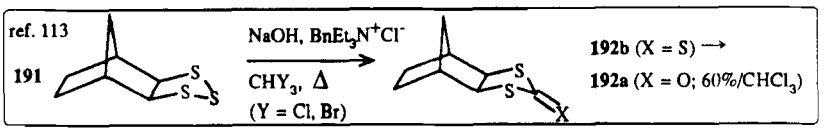
(*c*) (*not carbonyl → C=S*)

7.3. t-BuSH/TFA In an extension of the reaction of *gem*-dichloro[111] compounds with SH^- anion, Cava *et al.*[110] have applied the conditions developed by Lawesson *et al.*[112] (for thiobenzophenone) to the hydrothiolysis of *gem*-dichlorobenzyl derivatives of phthalic anhydride. They thus treated **187a, b** (Scheme 47) with *t*-butyl mercaptan in the presence of trifluoroacetic acid in refluxing CH_2Cl_2 and obtained the thiothionoanhydrides **188a** (47%) and **188b** (70%). They recently[99] converted the tetrachloronaphthopyran **189** to the thiothiononaphthalic anhydride **190** (75%) using identical conditions at 25 °C. These reactions with *t*-BuSH proceed under extremely acidic conditions, which are sufficient to remove the *t*-butyl group, since the by-products are 2 to 4 eq. of HCl and *t*-BuCl or isobutene.



Scheme 47.

7.4. R–S–S–S–R′ Ghosh[113] has demonstrated that the trithiolane **191** (Scheme 48) reacts with both dichloro- and dibromocarbene to give the trithiocarbonate **192b** which reacts further to give the dithiocarbonate **192a** as the major product. The trithiolane can thus be considered as a thionation reagent for carbenes by insertion of the latter into the trithiolane moiety.



Scheme 48.

8. ELEMENTAL SULFUR

Like H_2S and P_4S_{10}, elemental sulfur (S_8) has been utilized for thionation for over a century. It is nevertheless distinct from other thionation reagents (Sections 2–7) since a

change of its oxidation state occurs during a thionation. Some additives improve its reactivity by sulfur-sulfur bond breaking[114] (Scheme 49) and S_8 thus becomes a nucleophilic/reducing oxidizing thionation reagent in the presence of a nucleophile such as a tertiary amine[121] or methoxide.[129]

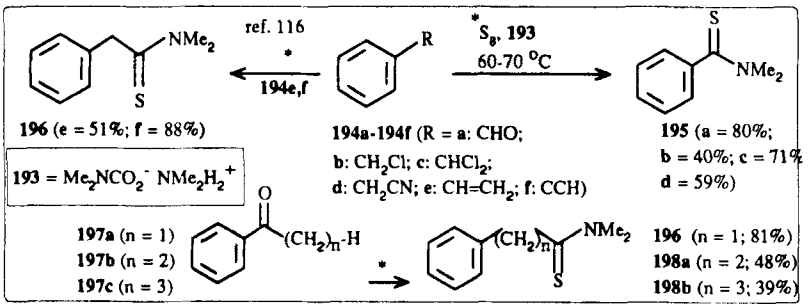
$$S_8 + \text{Base} \longrightarrow \text{Base}^+\text{-}S_7\text{-}S^- \qquad \text{(nucleophilic/oxidizing)}$$

Scheme 49.

(*b*) (*R–C=O–X → R–C=S–Y*)

(*c*) (*not carbonyl → C=S*)

8.1. Willgerodt-Kindler reaction In the Willgerodt-Kindler reaction[115] a terminal thioamide is formed from a reaction between an aryl alkyl ketone and a *sec*-amine in the presence of sulfur through an oxidation/rearrangement process (aminosulfuration of ketones or aldehydes). Schroth and Andersch[116] recently obtained *N,N*-dimethylthiobenzamide **195** (49–80%) (Scheme 50) by treating benzaldehyde **194a**, benzyl

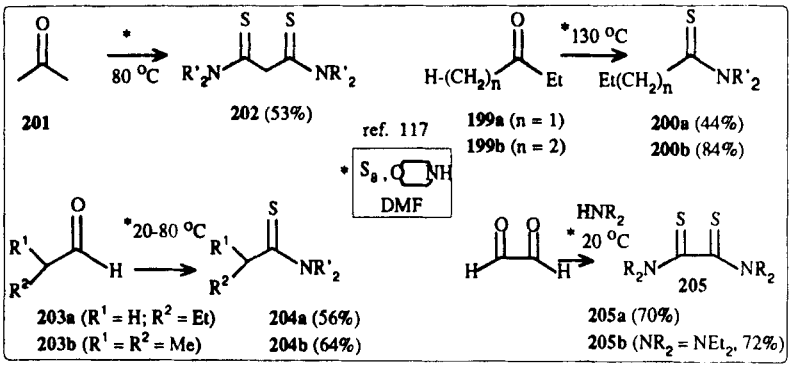


Scheme 50.

chloride **194b**, benzal dichloride **194c** and benzyl cyanide **194d** with S_8 in the presence of dimethylammonium dimethylcarbamate **193** (source of $HNMe_2$) at 65–68 °C. They also obtained the thioamide **196**[116] (51%, 88%) from styrene **194e** and phenylacetylene **194f**. The migration of the sp^2 center is well illustrated in the preparation of the thioamides **196** (81%), **198a** (48%) and **198b** (39%) from **197a–197c**.

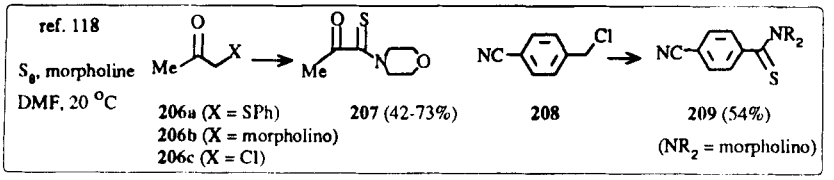
Viehe *et al.*[117–120] have made a seminal contribution in broadening the use of the Willgerodt-Kindler[115] reaction. They have extended the Willgerodt-Kindler reaction to the aliphatic series by use of capto-dative methylene groups (donor→CH_2→EWG)[117] and have thereby prepared mono- and dithioamide derivatives of oxalic **205** (Scheme 51), malonic **202** and succinic acid. Using sulfur and morpholine in DMF at 130 °C they converted the ethyl ketones **199a, b** into the thioamides **200a** (44%) and **200b** (84%); acetone **201** gave the dithioamide of malonic acid **202** (53%) at 80 °C; the aldehydes

203a–b gave the thioamides **204a** (56%) and **204b** (65%) at 20–80 °C; glyoxal gave the dithioamides **205a** (70%) and **205b** (72%) with morpholine and diethylamine, respectively.



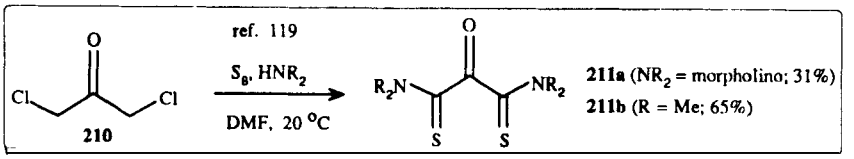
Scheme 51.

In closely related work with carbonyl groups adjacent to an α-donor group (Scheme 52), Viehe *et al.*[118] converted 1-phenylthio- **206a**, 1-morpholino- **206b** and 1-chloroacetone **206c** to the pyruvic thioamide **207** (42–73%) using sulfur with morpholine in DMF at 20 °C. If a nitrile instead of a ketone is used this transformation still takes place. For example, the 4-(chloromethyl)-benzonitrile **208** was converted to the 4-cyanothiobenzamide **209** (54%).



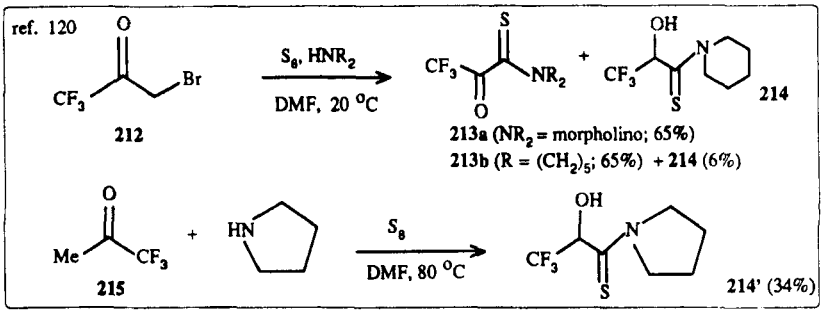
Scheme 52.

Viehe *et al.*[119] also have shown that α,α′-dichloroacetone **210** (Scheme 53) reacts similarly with either morpholine or dimethylamine to give, respectively, the 1,3-dithiomesoxalamides **211a** (31%) and **211b** (65%).



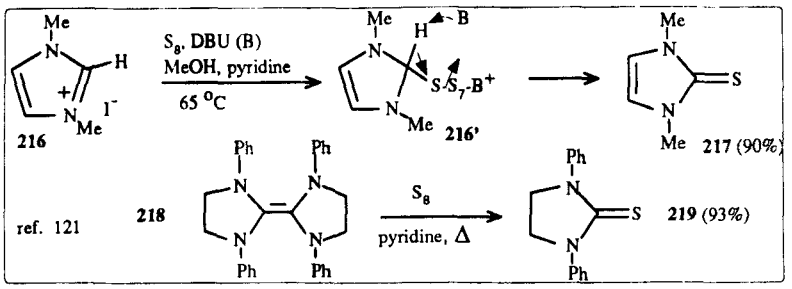
Scheme 53.

Viehe and Maliverney[120] recently prepared trifluoropyruvic and lactic thioamides using the Willgerodt-Kindler reaction applied to bromotrifluoroacetone **212** (BTFA). They obtained the β-oxo thioamide **213a** (65%) (Scheme 54) from **212** and morpholine; with piperidine they obtained the α-hydroxy thioamide **214** (6%) in addition to **213b** (65%). Furthermore, the trifluoroacetone **215** gave exclusively the hydroxy derivative **214′** (34%) with pyrrolidine at 80 °C.



Scheme 54.

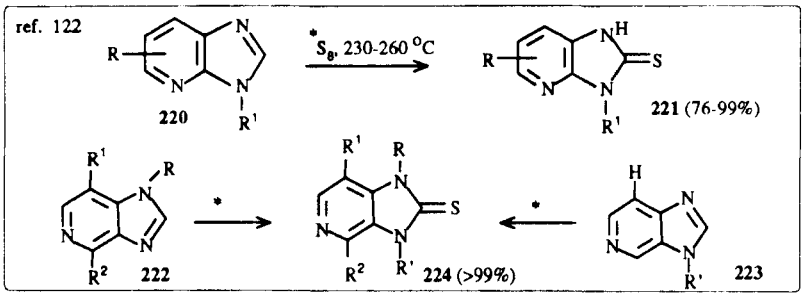
8.2. Imidazole oxidation Field and Karkhanis[121] thionated the imidazolium iodide salt **216** (Scheme 55) with elemental sulfur in the presence of 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) and obtained the cyclic thiourea **217** (90%) at 65 °C. The oxidation of the imidazolium moiety occurs through the adduct **216′**. The imidaz ylidene **218** was also thionated in refluxing pyridine to give the imidazolidine-2-thione **219** (93%).



Scheme 55.

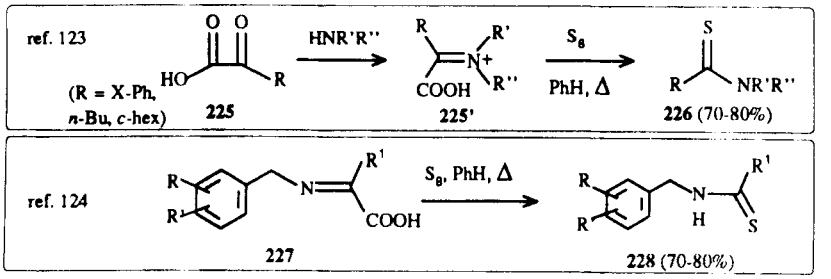
Yutilov and Svertilova[122] have sulfurated several imidazopyridines to obtain imidazopyridinethiones (Scheme 56) with sulfur at 230–260 °C. Thus they obtained the thiones **221** (76–99%) from **220** (R = H, Cl, Br; R^1 = H, Me, Ph, Br) and the thiones

224 (>99%) from **222** (R = H, *i*-Pr, Bu, *c*-Hex, Ph, $PhCh_2$; R^1 = H, Br, NO_2; R^2 = H, Cl, OMe) and **223** (R = Me, Et, Ph, CH_2).



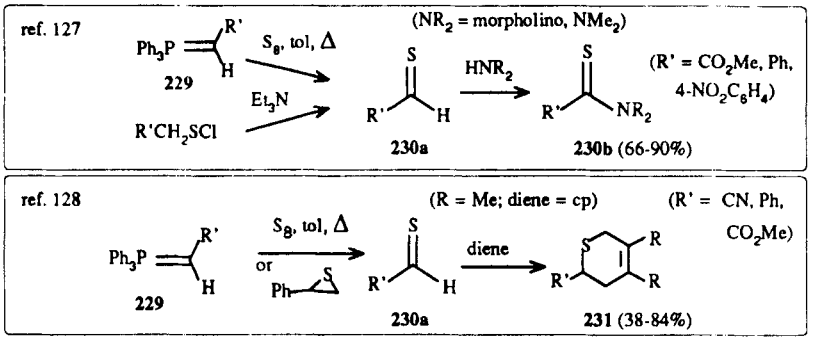
Scheme 56.

8.3. α-Imino acid decarboxylation Grigg and Aly[123,124] have synthesized several thioamides **226** (70–80%) (Scheme 57) by the decarboxylative sulfuration of the α-imino acids **225′**, isolated or generated *in situ* from the α-keto acids **225**. The reactive species is an azolium ylide $R_2C{=}NH^+{-}C^-HR'$ which is trapped by sulfur.[125] For example, reaction of benzoylformic acid[123] with pyrrolidine in the presence of sulfur in refluxing benzene gave the thioamide **226** in quantitative yield. They have also extented their work[124] and converted, for example, the benzylimino acids **227** (R = H, OMe, Me, NO_2; R′ = H, OMe; R^1 = Ph, 2-thienyl) to the *N*-benzylthioamides **228** (70–80%) by treatment with sulfur in refluxing benzene.



Scheme 57.

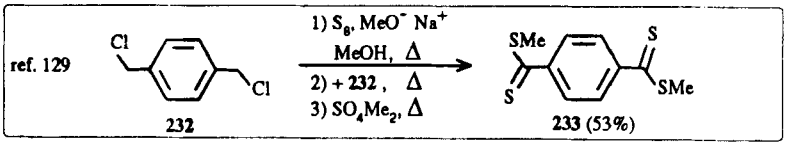
8.4. Phosphonium ylides It is known that phosphonium ylides react with sulfur to afford thiocarbonyl compounds.[126] Okuma *et al.*[127] have applied this transformation to the generation of the thioaldehydes **230a** (Scheme 58) from the ylides **229** by treatment with sulfur in refluxing toluene. In the presence of $HNMe_2$ or morpholine those are transformed directly into the thioamides **230b** (66–90%) (R′ = CO_2Me, Ph, 4-$O_2NC_6H_4$); the thioaldehydes were also prepared by base-induced elimination of sulfenyl chlorides.



Scheme 58.

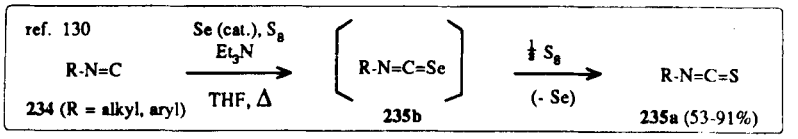
The thioaldehydes have also been trapped as the cycloadducts[128] **231** (38–84%) with dienes. In this instance the thioaldehydes were prepared by treatment of the phosphonium ylides **229** with either phenylthiirane[128] or elemental sulfur.

8.5. Miscellaneous Levesque and Delfanne[129] have treated sulfur with sodium methoxide in refluxing methanol generating an *in situ* thionation reagent. This mixture was allowed to react with the benzyl chloride **232** (Scheme 59) under reflux to give a dithioacid which was methylated with dimethyl sulfate to yield the bisdithioester **233** (53%). Dimethyl tetrathioterephthalate (DMTT) **233** was used for a polythioamide polymer synthesis; this was accomplished by thioacylation of diamines with **233**.



Scheme 59.

Fujiwara *et al.*[130] observed that a catalytic amount of selenium promotes a new oxidative sulfuration of isocyanides **234** (R = alkyl, aryl) (Scheme 60) with sulfur in the presence of triethylamine in refluxing THF to give isothiocyanates **235a** (53–91%). This reaction was based on the observation that isoselenocyanates **235b** gave quantitatively **235a** in the presence of NR_3 and S_8.

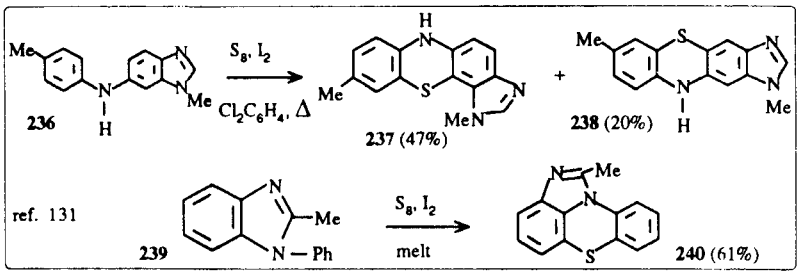


Scheme 60.

(*e*) (*not carbonyl → not thiocarbonyl*)

Avendaño *et al.*[131] have used sulfur and a trace of iodine (Bernthsen conditions[132]) for

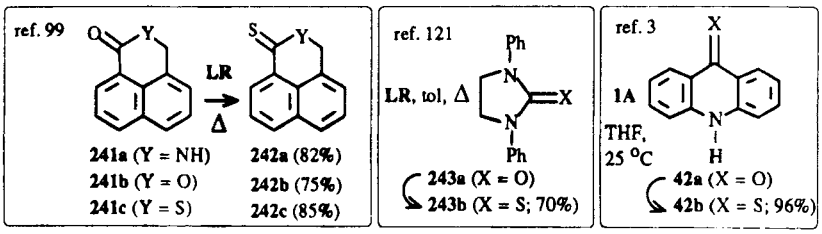
the sulfuration of aromatic heterocycles. They thus obtained a mixture of the imidazophenothiazines **237** (46%) and **238** (20%) (Scheme 61) from **236** in refluxing *o*-dichlorobenzene. They also thionated the benzimidazole **239** without solvent; this resulted in the formation of the phenothiazine **240** (61%).



Scheme 61.

9. CONCLUSIONS

A substantial number of new reagents and experimental conditions have been developed since 1985, most notably the first organosilicon sulfide ($(Me_3Si)_2S$),[20,21] for direct thionation of carbonyls. Also, the development of soluble derivatives of phosphorus pentasulfide is clearly of synthetic and experimental value. In this regard, the organothiophosphorus reagents such as **LR** and **BR**, which are more soluble than P_4S_{10} in organic solvents (THF, toluene for example) and thus more reactive, are especially useful. The following examples illustrate this versatility: a thiolactam **242a** (82%) (Scheme 62), a thionolactone **242b** (75%) and a dithiolactone **242c** (85%) were, respectively, obtained from **241a–241c**[99] in the presence of **LR** in refluxing toluene (**242a**) or *o*-dichlorobenzene (4–6 h, **242b, c**). We have also observed and rationalized[1,3] the fact that **BR** and **LR** with their solubilising aryl groups can be sterically hindered reagents for some thionations[1] (Scheme 8). We have eliminated both solubilization and steric hindrance problems by using thiophosphate groups as in **1A**;[3] this *in situ* phosphorus pentasulfide derivative is not only soluble in THF and water (easy work-up) but also very reactive. For example, the thionation of acridone **42a** with **1A** was accomplished within 2 h at 25 °C to give the thioacridone **42b**[1,3] (96%).



Scheme 62.

Some unique thionations have also been described recently (1985 onwards). The cyclic thiourea **243b**[121] (70%) was obtained by thionation of the imidazol-2-one **243a** with **LR** in refluxing toluene. Thioacylsilanes (Schemes 6 and 37) have also been prepared by direct thionation methods based upon bis(trimethylsilyl) sulfide[20,21] or with H_2S.

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