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Recent advances in thionating reagents for the synthesis of organosulfur compounds

Vivek Polshettiwar[a]; M. P. Kaushik[b]
[a] Ecole Nationale Supérieure de Chimie, Montpellier, Cedex 05, France [b] Process Technology Development Division, Defence R & D Establishment, Gwalior, MP, India

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REVIEW ARTICLE

Recent advances in thionating reagents for the synthesis of organosulfur compounds

VIVEK POLSHETTIWAR†* and M. P. KAUSHIK‡

†Ecole Nationale Supérieure de Chimie, 8, rue de l'Ecole Normale,
34296 Montpellier Cedex 05 France
‡Process Technology Development Division, Defence R & D Establishment,
Jhansi Road, Gwalior-474002 (MP), India

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Thionation is the most suitable and efficient method for the synthesis of organosulfur compounds. Thio-compounds are important intermediates in the synthesis of various biologically active molecules and are also of importance from an industrial point of view. They have various applications in fields such as pharmaceutical, polymer and pesticide industries. Several methods are reported in the literature for the thionation which makes use of a variety of thionating reagents (either alone or in combination) such as elemental sulfur, phosphorus pentasulfide and Lawesson's reagent (LR). This report focuses on the thionation method for the synthesis of organosulfur compounds developed after 1991.

Keywords: Thionation; Organosulfur compounds; Lawesson's reagent; Curphey's reagent (P_4S_{10}/HMDO); Kaushik's reagent (P_4S_{10}/Al_2O_3); Bernthsen reagent (S_8/I_2); HMDST; Heimgartner's reagent; Davy's reagent; *In situ* and supported thionating reagents

1. Introduction

Organosulfur compounds are valued not only for their rich and varied chemistry, but also for many important biological properties [1]. This subject presents us with examples of sulfur compounds with striking physiological activity as well as culinary appeal. Novel organosulfur compounds also show notable spectroscopic properties. The reactions involving sulfur radicals, sulfur stabilized carbocations and noteworthy organosulfur rearrangements are important in synthetic organic chemistry. The scope and applications of organosulfur chemistry have increased tremendously as sulfur containing groups continue to serve an important auxiliary function in synthetic sequences [2].

Organosulfur compounds present in *allium* vegetables, which are either lipid or water soluble, are considered responsible for the beneficial effects of allium species such as garlic, onion, leeks, and chives. Various *allium* species have been shown to have beneficial effects against several diseases such as stomach and colorectal cancers. These protective effects appear to be related to the presence of organosulfur compounds such as sulfines and sulfinates. The exact mechanisms of the cancer-preventitive effects are not known so far, although several

*Corresponding author. Email: vivekpol@yahoo.com; mpkaushik@rediffmail.com

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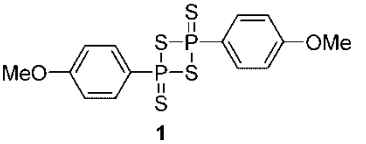
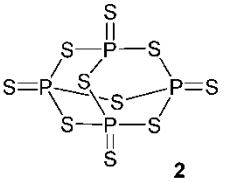
hypotheses have been proposed. One of the hypothesis is that organosulfur compounds modulate the activity of several metabolizing enzymes that activate or detoxify carcinogens and inhibit the formation of DNA adducts in several target tissues [3].

The large scale manufacture of organosulfur compounds has assumed great importance after the Second World War because of the development of effective and persistent drugs. There are other industrially useful organosulfur compounds as both the element and its compounds have a wide range of applications in the agriculture, glass, ceramic, rubber industry, as insulators, vulcanizers and lubricants [4].

Thionation is the most suitable and efficient method for the synthesis of a variety of organosulfur compounds. Thio-compounds are important intermediates in the synthesis of various biologically active molecules and are of importance also from industrial point of view. Several methods are reported in the literature for the thionation of organic compounds [5, 6], which make use of various thionating agents (either alone or in combination) such as phosphorus pentasulfide **2** [6], elemental sulfur [7], and Lawesson's reagent (LR) **1** [8, 9].



1
Lawesson's Reagent (LR)



2
Phosphorus Pentasulfide (P_4S_{10})

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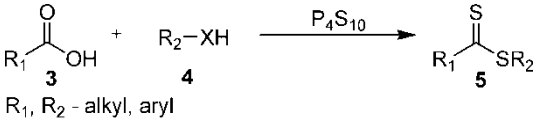
Brillon has published an excellent report about thionating reagents up to 1991 [5]; however in recent years several new and efficient thionating reagents have been developed. This report focuses on the thionation method for synthesis of organosulfur compounds developed after 1991.

2. Thionating reagents

2.1 *Phosphorus pentasulfide (P_4S_{10})*

Introduced as early as in 1892 by Hoffman [10], the thionation by means of P_4S_{10} was the most utilized method for preparing thiocarbonyl compounds. Phosphorous pentasulfide is a very useful and versatile reagent for the synthesis of various organosulfur compounds. It is widely available as a light yellow crystalline solid. It is highly flammable and decomposes in the presence of moisture. P_4S_{10} has been extensively used as a thionating agent for the conversion of carbonyls into thiocarbonyls in the preparation of organosulfur compounds. It also activates the free hydroxyl group of an acid or an alcohol to create a good leaving group. P_4S_{10} can also be used as a deoxygenating and dehydrating agent [11, 12].

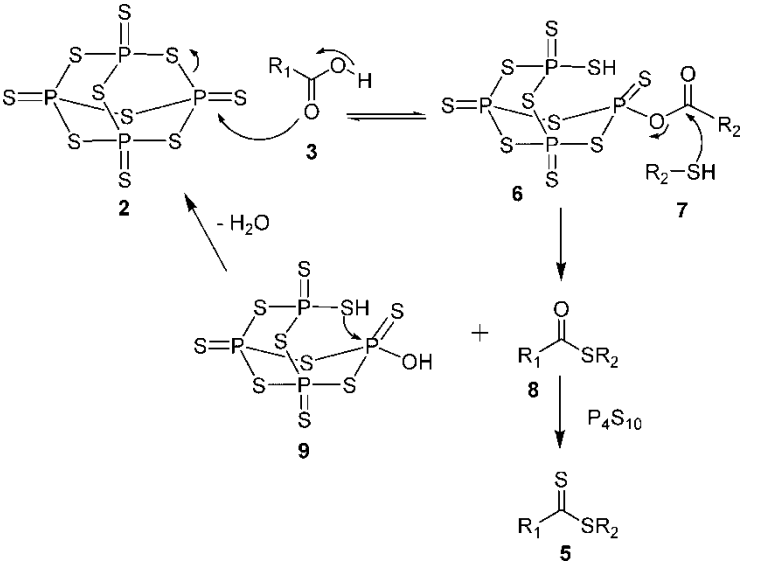
Recently dithiocarboxylic esters were prepared in one step from carboxylic acid and thiol using phosphorous pentasulfide (P_4S_{10}) as a thionating reagent [13] (scheme 1).



R_1, R_2 - alkyl, aryl
X - O, S

SCHEME 1

The reaction of carboxylic acids with a variety of thiols or alcohols in the presence of phosphorus pentasulfide (P_4S_{10}) as a catalyst and reagent (20–40 mol%) proceeded effectively to afford the corresponding dithiocarboxylic esters in high yields. One of the most important features of this methodology is that P_4S_{10} can be used in reduced amounts (20 mol%). A novel feature of this system is the unexpected reactivity shown by the tertiary as well as secondary alcohols affording good yields of the corresponding dithioesters without undergoing dehydration. The probable mechanism for the formation of dithioester is believed to take place in two steps as shown in scheme 2.



SCHEME 2

In step 1, P_4S_{10} activates carboxylic acid through its electrophilic phosphorus center to give an active species **6**. The evidence in favour of formation of such a species can be deduced from the GC-MS analysis of the reaction mixture, in which the complete conversion of carboxylic acid and the simultaneous formation of active species **6** (R^1CO^+, base peak in MS) can be seen when the reactions were done at lower temperature. The nucleophilic attack of thiol **7** on the species **6** generates **9** and thiocarboxylic S-ester, **8**. Such condensation reactions with the use of phosphorus reagents are well established in the literature. It is also possible that both the species **6** and **9** are in equilibrium (at different time intervals of the reaction mixture, appearance and disappearance of thiol can be seen in GC-MS). The formation of the intermediate thiocarboxylic S-ester, **8** was confirmed from GC-MS analysis and by isolating and characterizing it when 15 mol% of P_4S_{10} was employed. However, further addition of 5 mol% of P_4S_{10} transformed the species **8** completely to the corresponding dithioester **5**. It is also quite likely that **9** might undergo dehydration to regenerate P_4S_{10}. In step 2, the intermediate **8** undergoes thionation of carbonyl group with P_4S_{10} readily to yield dithioesters **5**.

The thionation of cage ketones, such as pentacyclo[5.4.0.02,6.03,10.05,8]undecane-8-one (**10**) was achieved by P_4S_{10} in pyridine affording the corresponding thione in good yields (70%) [14] (scheme 3).

In contrast to this result, the P_4S_{10} promoted thionation of pentacyclo[5.4.0.02,6.03,10.05,8] undecane-8,11-dione (**12**) did not afford the expected dithiocarbonyl derivative and alternatively, reaction with H_2S(g)/HCl(g) in methanol led to the two different (**13a** and **13b**)

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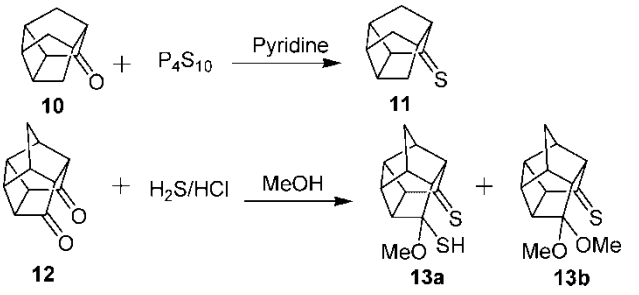

SCHEME 3

thiocarbonyl derivatives. Thus, this method is suitable for cage ketones and not for cage diones. However, this drawback was overcome by Artyukhova and Patsenker group [15]. They have treated N-methyl- and N-phenylnaphthalimide derivatives with phosphorus pentasulfide. The mixture of mono- and dithionaphthalimides was formed regardless of reaction conditions. Mono-/dithio derivative ratio depends on the amount of the thionating reagent and the reaction time (scheme 4).

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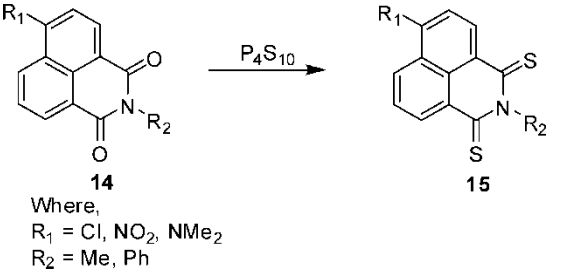
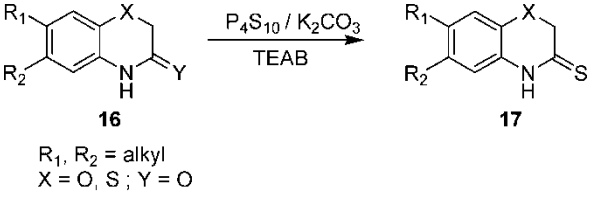


SCHEME 4

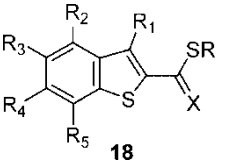
Phosphorus pentasulfide was also used in combination with phase transfer catalyst (PTC) for thionation of amide carbonyl of **16** [16]. Thus, 2H-1,4-benzoxa/thiazine-3(4H)-ones can be easily converted into their respective thiones by using P_4S_{10}/TEAB. The use of PTC makes the method efficient with good to excellent product yield (scheme 5).



SCHEME 5

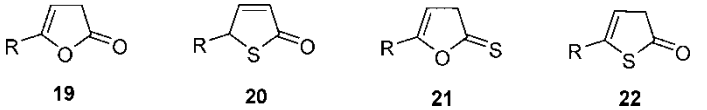
The above protocol was also used for thionation of thiolester carbonyl groups [17]. Benzo[b]thiophenecarbodithioic esters **18** [X = S; R = alkyl; R_1 = H, halo or alkyl; R_2-R_5 are independently H, halo, alkyl, alkoxy, alkylthio, trifluoromethyl, cyano or aryl] were prepared by treating one equivalent of an S-thiol ester **18** (X = O) with 1/3 equivalent of P_4S_{10}, 2 equivalents of alkali metal carbonate, about 2.5 mol% of phase transfer catalyst, and

a catalytic amount of water in hot toluene.



18

The comparative study between LR and P_4S_{10} was reported, for the thionation of carbonyl group [18]. The thionation of 5-substituted 3H-furan-2-ones **19**, using LR and P_4S_{10}, yields various products including 5-substituted 5H- and 3H-thiophen-2-ones and 3H-furan-2-thiones (**20–22**) (R = Et, Bu, i-Bu, pentyl, isohexyl). It was found that the structure of the reaction products depends mainly on the thionating reagent used.



19 **20** **21** **22**

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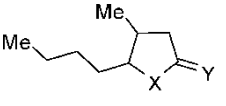
Biologically active Whiskey lactone can also be converted into its thio-derivative using phosphorus pentasulfide [19]. The *cis*- and *trans*-3-methyl-4-octanolides (Whiskey lactones) were converted into their thio-, thiono-, and dithio- derivatives **23** (X = S, Y = O; X = O, Y = S; X = Y = S, respectively) by the reaction with phosphorus pentasulfide. In this study, two-dimensional NOESY spectra showed that sulfur is incorporated into the ring with reversal of the absolute configuration at C-4, whereas substitution of the keto-oxygen atom by sulfur occurs with retention of ring configuration. The *cis*- and *trans*-pairs of **23** were separated into enantiomers by GC on heptakis(2,3-di-O-methyl-6-O-*tert*-butyldimethylsilyl)-β-cyclodextrin and heptakis(2,3-di-O-acetyl-6-O-*tert*-butyldimethylsilyl)-β-cyclodextrin as chiral stationary phases. GC-olfactometry revealed a sweet coconut-like odour for the *cis*-thio- and pleasant mushroom-like flavours for the *cis*-thiono- and *trans*-dithio-derivatives of Whiskey lactone.

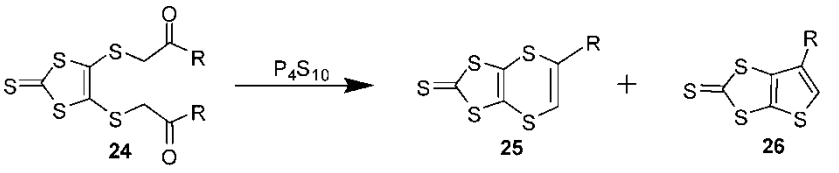


23

In similar way, flavones can also be converted to thioflavones using phosphorus pentasulfide and sodium hydrogen carbonate [20]. This method is advantageous in terms of rapid reaction rate and high product yield.

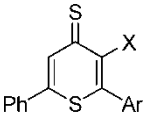
The 1,2-dithiole-3-thiones can be synthesised from β-enaminonitriles and phosphorus pentasulfide [21]. Reactions of β-enaminonitriles $H_2NCR{:}CR_1CN$ [R = Me, (un)substituted Ph; R_1 = H, Me, Ph] with sulfur and Lawesson's reagent or phosphorus pentasulfide in 1:2:2 molar ratio in refluxing pyridine afforded 1,2-dithiole-3-thiones in 19–23% yield. A better yield (25–36%) was achieved in the reaction with sulfur and phosphorus pentasulfide without solvent.

A new series of tetrathiafulvalene derivatives can be synthesised from 1,8-diketones using P_4S_{10} as a thionating reagent. A detailed study of the reactions of phosphorus pentasulfide and Lawesson's reagent with a series of 4,5-bis($RCOCH_2S$)-1,3-dithiole-2-thiones (R = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, Me) (**24**) was reported [22]. These reactions lead to the fusion of either an unsaturated 1,4-dithin ring or a thiophene to the dithio; the former in higher yield, while the latter is a significant product in the reactions with Lawesson's reagent; as well as small amounts of minor products were also produced (scheme 6).



SCHEME 6

A mechanistic rationalization of these products is discussed in some detail. The new fused dithiols have been converted to novel series of fused derivatives. Diketones can also be converted into 4H-thiopyran-4-thiones derivative using P_4S_{10} [23]. 2,6-Diaryl-4H-thiopyran-4-thiones **27** (Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, X = H; Ar = Ph, 4-ClC_6H_4, X = Cl) have been synthesized in excellent yields by the reaction of 1-aryl-5-phenyl-4-pentyne-1,3-diones (PhCCCOCHXCOAr) with phosphorus pentasulfide in dry pyridine at room temperature and were converted into the corresponding hydrazones and oximes. This is an excellent method for the synthesis of such thiopyran derivatives.



27

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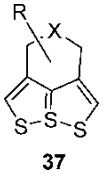
Paulussen and group studied mechanistic aspects on the formation of poly(isothianaphthene) (**36**) from P_4S_{10} and phthalic anhydride derivatives [24] (scheme 7).

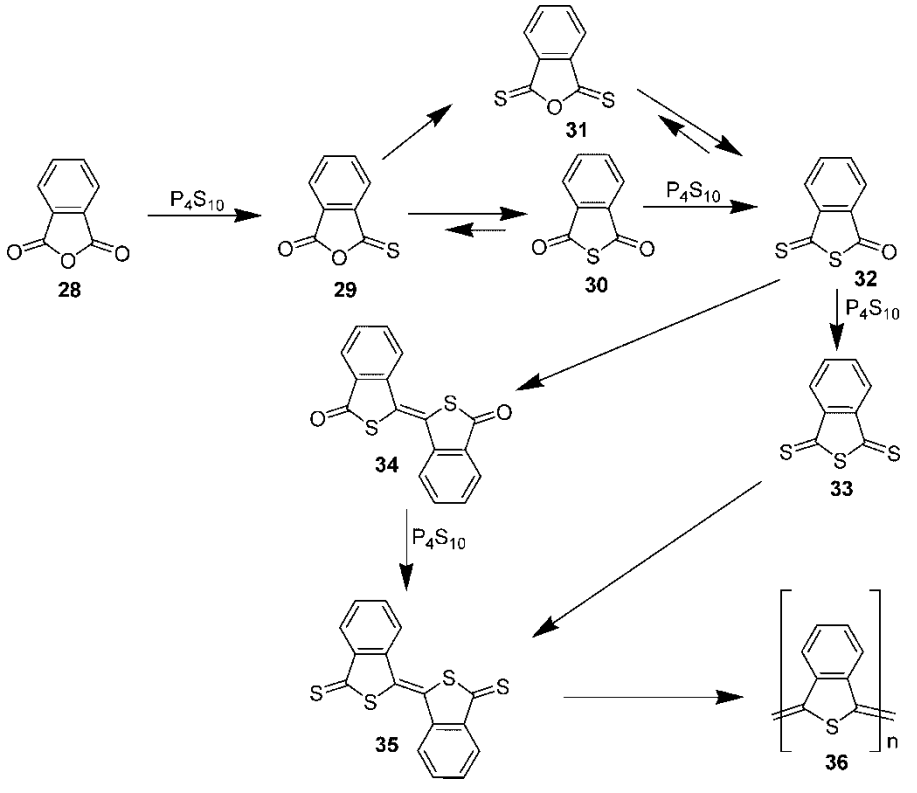
Mechanistic studies on the formation of poly(isothianaphthene) (**36**) (PITN) from phthalic anhydride (**28**) and a thionating reagent (phosphorus pentasulfide or Lawesson's reagent) have shown that the thionating reagent is not crucial in the polymerisation reaction itself; it only plays a role in the synthesis of the actual monomer, the tristhiophthalic anhydride (**33**). The polymerisation process is not a classical polycondensation, but a process by which the very reactive tristhiophthalic anhydride monomer repeatedly attaches to the growing chain under expulsion of sulfur.

Trithiapentalenes such as 3,4-bridged 1,6,6aλ4-trithiapentalenes, **37** (R = H, Me, Et, CF_3, t-Bu, EtO_2C, Ph; X = CH_2, O, S), can be synthesised based on reactions of cyclic ketones with Bredereck's reagent followed by thionation of the resulting keto dienamines with phosphorus pentasulfide [25].



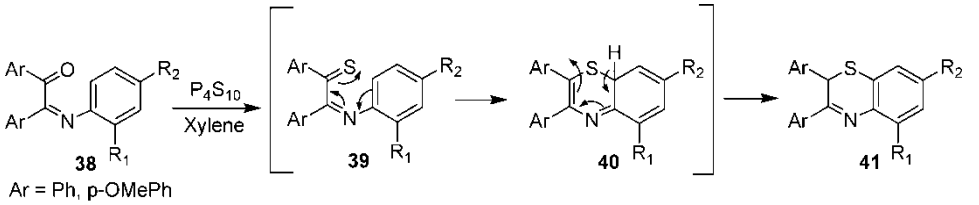
37

Benzothiazines and benzothiazoles can be synthesised by thionation of benzil aryl imines using phosphorus pentasulfide in refluxing toluene or xylene [26]. Thionation of benzil monoarylimines occurred readily to afford either 2H-benzo-1,4-thiazines or indoles via



SCHEME 7

annulation reactions, depending strongly on the nature of the meta substituants of the arylamino group. Furthermore, subsequent oxidation of 2H-benzo-1,4-thiazines provided benzothiazoles (scheme 8).



SCHEME 8

p-Quinone monoimines react with LR and P_4S_{10} to yield various products, whose structures depend upon the thionating reagent used [27]. 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide [Lawesson's reagent] reacts with p-quinone monoimine **42** (X = Me) to give the novel 5-(methanesulfonamido)-2-(4-methoxyphenyl)benzo-1,3,2-oxathiaphosphole 2-sulfide (**43**). On the other hand, the reaction of **42** (X = Ph) or 1,4-naphthoquinone monoimine **44** with LR forms the corresponding benzo-1,3,2-dithiaphosphole 2-sulfide **45** or the naphtho analogues. Thionation of **42** (X = Me, Ph) and **43** with P_4S_{10} yields phenoxathiin derivatives **46** (X = Me, Ph) and **47**, respectively. This study clearly

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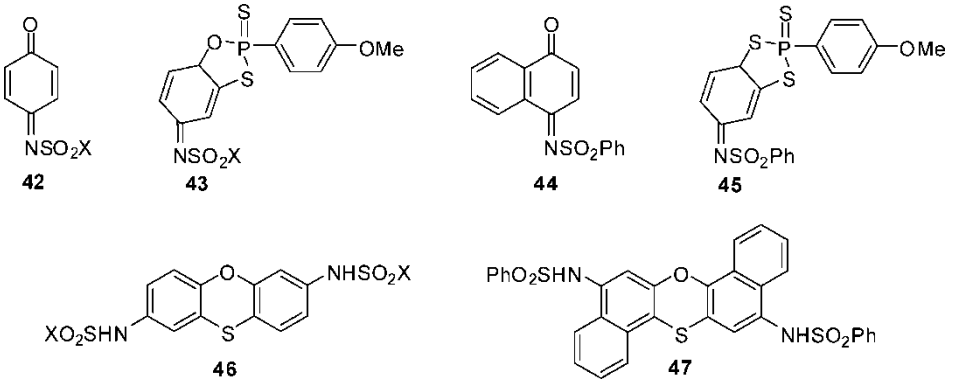
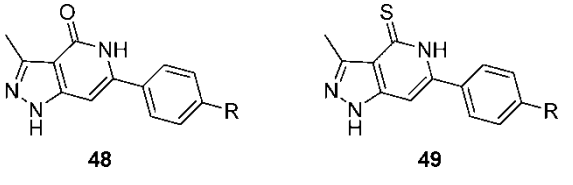
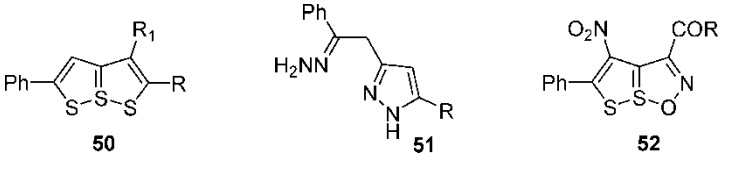
demonstrates the different reactivity of the thionating reagent towards particular substrates.



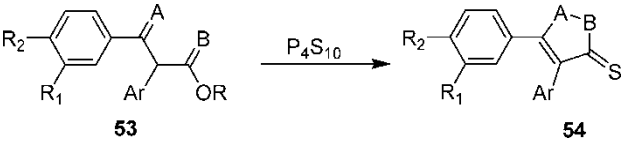
Thioanalog (**49**) of pyrazolo[4,3-c]pyridin-4(5H)-ones (R = Me, Cl) (**48**) can also be prepared on reaction with phosphorus pentasulfide. This is a useful method for thionation of heterocyclic compound to prepare its new thio analogues [28].



A new method for the synthesis of 2,5-diaryl-6-thiathiophthenes **50** (R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, R_1 = H, Cl) were also reported involving the reaction of 1,5-diarylpent-1-yne-3,5-diones (PhCCCOCHR$_1$COR) with P_4S_{10}. The reaction of **50** (R = Ph, 4-ClC_6H_4, R_1 = Cl) with N_2H_4 gave pyrazole derivatives **51**. Nitration of **50** (R = Ph, 4-MeC_6H_4, 4-BrC_6H_4, R_1 = H) afforded the corresponding 4-nitro-1-oxa-6,6a-dithia-2-azapentalenes **52** [29].



Pharmaceutically active heterocyclic thione derivatives (**54**) can be prepared by thionation of various heterocyclic substrates using phosphorus pentasulfide as a thionating agent [30]. The compounds, where Ar = (un)substituted aryl or heteroaryl; R_1 = H, alkyl, alkoxy, halo, etc.; A and B independently = O, S, NR_2; R_2 = H, alkyl, alkenyl, or aryl, or a non-toxic salt thereof, are prepared and disclosed as COX-1 or COX-2 inhibitors (scheme 9).



SCHEME 9

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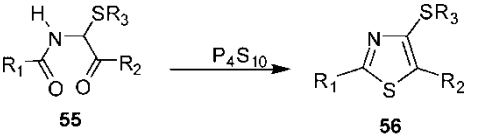
The S-amidophenacylation products of thiols and sulfanylphenols on treatment with phosphorus pentasulfide convert into the corresponding 1,3-thiazole-4-thiol derivatives, which are easily oxidized with hydrogen peroxide [31]. The latter reaction was used to introduce a series of alkyl- or arylsulfonyl groups in the 4 position of the thiazole ring. This general approach significantly extends the limited range of synthetic procedures for 1,3-thiazole-4-thiol derivatives (scheme 10).

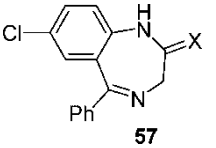


55 **56**

Where,
R_1,R_2, R_3 = alkyl or aryl

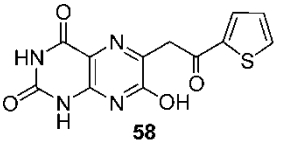
SCHEME 10

An alprazolam intermediate such as 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepine-2-thione, can be prepared by using P_4S_{10} as a thionating reagent [32]. Title compound **57** (X = S), an intermediate for the anxiolytic alprazolam, is prepared by thionation of **57** (X = O) with P_4S_{10} at 40–150 °C in an aromatic hydrocarbon, PhCl, or $PhNO_2$ solvents, or their mixtures. The invention solvents are superior to pyridine, used in known methods, for a variety of reasons, including cost, odour, and regenerability. In a typical example, 50 g **57** (X = O) and 27 g P_4S_{10} were heated 4 h in 330 mL PhMe at 110 °C, and the mixture was worked up by pouring into aq. NH_3 (1:4), filtration, washing with H_2O and EtOH, and drying, to gave 85% **57** (X = S).



57

Thionation of pteridine was also achieved by P_4S_{10} [33]. 7-Hydroxypteridine **58** and its isomeric 6-hydroxypteridine **59** were prepared by condensation of 5,6-diaminouracil with ethyl thienoylpyruvate in pyridine and hydrochloric acid, respectively. Compounds **58** and **59** were converted into the corresponding thienopteridines **60** and **61** on treatment with phosphorus pentasulfide.



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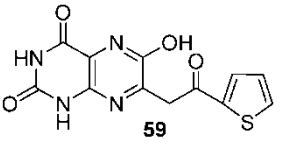

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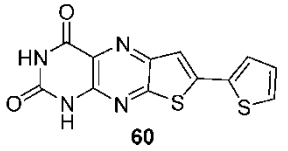

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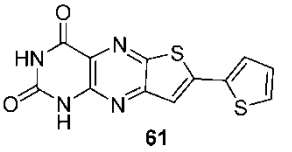

61

Janosik *et al.* synthesised thioanalog of bisindole derivatives using P_4S_{10} in pyridine [34]. Thionation reactions of several bisindole derivatives using elemental sulfur or P_4S_{10} in pyridine have been studied, leading to the formation of several novel structures. The reaction of indigo

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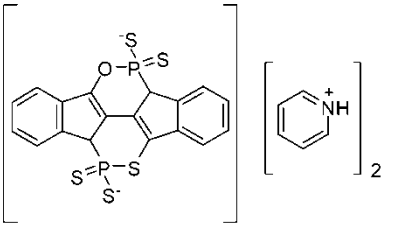
or isatin with P_4S_{10} gave structurally new salt **62**. The first example of a thionated indigo derivative, monothioindigo, was isolated in low yield from the thionation of isatin. Treatment of 3,3′-biindolyl with sulfur in hot DMF produced the previously known tetrasulfide **63**, which was studied by X-ray crystallography, thus also establishing that **63** is chiral in the crystaline state. The structure of an additional thionated product, the thienoindole derivative **64** was also solved by using X-ray crystallography.



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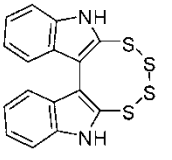

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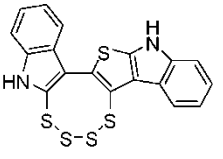
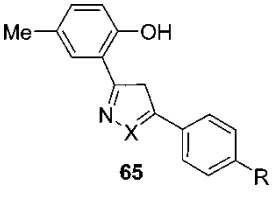


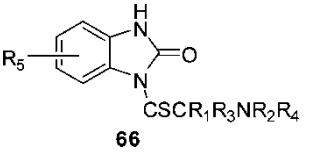
64

The direct synthesis of isothiazoles and isothiazolines from isoxazoles and isoxazolines by reaction with phosphorus pentasulfide in pyridine has been achieved using P_4S_{10} [35]. Isoxazoles **65** (R = H, MeO; X = O) were treated with P_4S_{10} in pyridine to give 80% isothiazoles **65** (X = S).



65

In recent years, various new thionating reagents were developed, however key components of most of the reaction/reagent was P_4S_{10}. Brillon *et al.* prepared a new thionating agent (aminothioacyl)benzimidazolones whose synthesis also requires the use of phosphorus pentasulfide as a thionating reagent [36]. (Aminothioacyl)benzimidazolones **66** [R_1 = (protected) amino acid side chain; R_2 = amino protecting group; R_3 = H, Me, Et, $R_1R_3 = (CH_2)_n$, n = 2–4; R_4 = H, $R_1R_4 = (CH_2)_m$, m = 1–5; R_5 = H, halogen, amido, amino, guanidino, CO_2H, CO_2Me, CN, OH, CH_2OH, SH, NO_2] were prepared as thioacylating agents, intermediates in the preparation of thiopeptides. Thus, condensation of 1,2-$(H_2N)_2C_6H_4$ with Boc-Ser(CH_2Ph)-OH (Boc = Me_3CO_2C) gave aminoanilide Boc-Ser(CH_2Ph)-$NHC_6H_4NH_2$-2 in 97% yield, which on thionation by P_4S_{10} gave thioamide Boc-L-NHCH(CH_2OCH_2Ph)$CSNHC_6H_4NH_2$-2. This product on cyclocondensation with carbonyl ditriazole gave **66** ($R_1 = CH_2OCH_2Ph$, R_2 = Boc, R_3–R_5 = H) in 91% yield. Several derivatives of **66** underwent solution and solid-phase peptide coupling reactions to give thioamide analogues of tuftsin and thymopentin.



66

P_4S_{10} can also be used for thionation of organo-phosphorus compounds [37]. Phosphite or phosphonate esters can be converted into their corresponding thiophosphites or thiophosphonates using P_4S_{10} in benzene (scheme 11).

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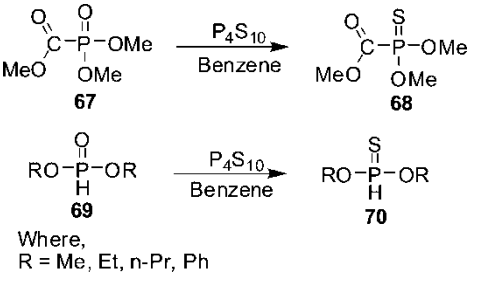

SCHEME 11

The methods start from phosphite diesters using P_4S_{10} as the thionation reagent. The reaction mixture is refluxed until the reaction is complete and may be followed by separation and chloroformate ester phosphonation steps to produce pure thiophosphonocarboxylate triesters. Alternatively, these esters may be prepared directly by action of P_4S_{10} on the corresponding phosphonocarboxylate esters.

Savran and Andronnikov also prepared O,O-dialkyl dithiophosphates using phosphorus pentasulfide [38]. O,O-Dialkyl dithiophosphates, useful as flotation agents in the preparation of nonferrous, rare and precious metal ores, are prepared by an improved process involving O,O-dialkyl dithiophosphoric acid by reaction of phosphorus pentasulfide with an aliphatic alcohol, in a mass ratio of P_4S_{10} to dialkyl dithiophosphoric acid $\geq$1:0.2, followed by treatment with an alkaline agent. This invention provides a simplified process, reducing waste in manufacturing and enhanced yield of the end product.

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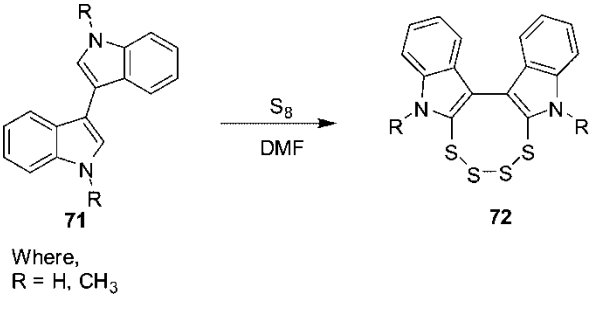
2.2 *Elemental sulfur (S_8)*

Elemental sulfur alone is also used for thionation reaction. Recently few reports have been found in the literature describing use of elemental sulfur as a thionating agent. Thionation of 3,3′-biindolyl derivatives (**71**) can be achieved using elemental sulfur [34], which produced a moderate yield of the tetrasulfide (**72**) (scheme 12).

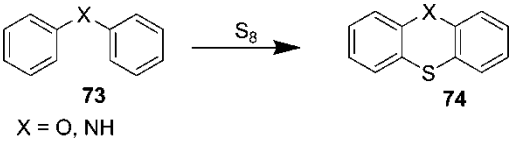


SCHEME 12

Anthrone can also be thionated by elemental sulfur [39]. The reaction of anthrone with S_8 at room temperature in DMF in the presence of catalytic amounts of pyridine afforded monothioanthraquinone, besides oxidation and dimerization products.

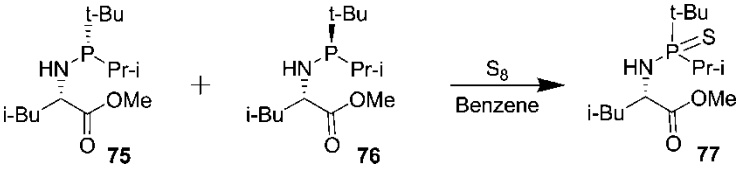
Thionation of diphenyl-type compounds using elemental sulfur and zeolite is an efficient process for the synthesis of cyclic thioether [40]. Phenothiazine and phenoxathine were very efficiently synthesised by the thionation of diphenylamine and di-Ph ether, respectively with

elemental sulfur using hydrothermally treated HY zeolites as catalysts. It was found that, the nature of the active-sites of the zeolites plays an important role in this type of thionation reaction (scheme 13).



SCHEME 13

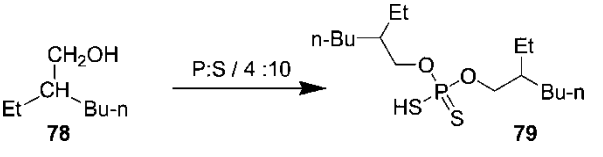
Interestingly, an asymmetric induction was found in thionation of aminophosphine diastereomers with elemental sulfur [41]. Aminophosphine diastereomers, $tBuP(R_1)NHCHR_2R_3$ [R_1 = Ph, R_2 = CHMeEt, R_3 = CO_2Me; R_1 = $CHMe_2$, R_2 = CHMeEt, R_3 = CO_2Me; R_1 = Ph, R_2 = Me, R_3 = Ph] (**75**,**76**) react with elemental sulfur non stereospecifically but stereoselectively, *i.e.*, with asymmetric induction at phosphorus atom, resulting in predominant formation of one of two possible diastereomers of the phosphinothioic amides, $tBuP(S)(R_1)NHCHR_2R_3$ (**77**) (scheme 14).



SCHEME 14

Holzner and co-workers developed a process for the preparation of thiophosphoric acid O,O′-diesters and their salts by thionation using elemental sulfur [42]. Thiophosphoric acid O,O′-diesters, thiophosphoric acid O-monoesters, or thiophosphoric acid and their salts were prepared via the reaction of phosphoric acid diesters, phosphoric acid monoesters, or phosphoric acid with sulfur followed by reaction with ammonia for the preparation of salts. Thus, thionation of di-Et phosphite with sulfur followed by reaction with ammonia in H_2O gave 92% thiophosphoric acid O, O′-diethyl ester ammonium salt.

Organophosphorus compounds and their thioanalogs can be prepared using elemental sulfur in combination with phosphorus [43]. Dialkyl phosphorodithioates, 3-mercaptopyridazine, can be prepared by the reaction of elemental S and elemental P together with an organic compound wherein the ratio of P and S generally corresponding to P_4S_{10}. The process obviates the need for separation of P_4S_{10} to prepare thionated and organophosphorus compounds (scheme 15).



SCHEME 15

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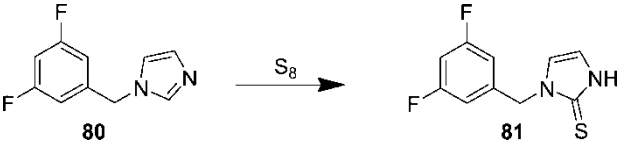
Elemental sulfur has also been used for the synthesis of 1-substituted 1,3-dihydroimidazole-2-thione (**81**) derivatives by thionation of corresponding imidazoles (**80**) using S_8 [44]. This is an excellent method for the synthesis of heterocyclic compounds containing thiocarbonyl functional group (scheme 16).

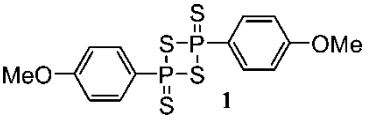


80 **81**

SCHEME 16

2.3 *Lawesson's reagent (LR)*

Phosphorus pentasulfide has been generally used as a thionation reagent for transformation of carbonyl group into the corresponding thiocarbonyl group. These reactions are normally performed in boiling toluene, xylene or pyridine and require large excess of reagents. Furthermore, long recation times are needed for reaction completion, with usually low and variable yield. In 1978, Lawesson and co-workers developed a new reagent commonly named as Lawesson's reagent (LR) [7, 8]. LR can be obtained readily by reaction of phosphorus pentasulfide with anisole, which is commercially available now.



1

Since 1978, increasing numbers of reports on thionation using LR have been published. High yield, convenient handling, easy work up, commercial availability, and use of mild reaction condition makes the LR popular among synthetic chemist. Cava and Levinson reviewed thionation reaction using LR in 1985 [9] and Jesberger *et al.* in 2003 [45]. In this review, we focused only on the new development in the application of LR after 2003. The mechanism of thionation reaction by LR has been well established in the literature and same is described below.

LR can be in equilibrium with highly reactive dithiophosphine ylide (**82**,**83**). Both mesomeric structures shown in scheme 17 can react with carbonyl compounds to form thiooxophosphonate (**85**), which decomposes into Wittig-analogs (**86**) reaction to the corresponding thio carbonyl compounds (**88**). Recently Przychodzen *et al.* established the mechanism of the reaction of Lawesson's reagent with N-alkylhydroxamic acids [46] through analysis of the products of the reaction.

An efficient and solvent-free microwave-accelerated synthesis of isothiocyanates using Lawesson's reagent was reported [47]. A series of iso-thiocyanates (ITC) was readily prepared from the corresponding isocyanates (IC) using Lawesson's reagent (LR) under microwave irradiation and solvent-free conditions.

LR has also been used for an efficient solid-phase synthesis of a series of 1,3,4-trisubstituted β-thiolactams, **89** [48]. The key reaction, a direct thionation of polymer-supported β-lactams,

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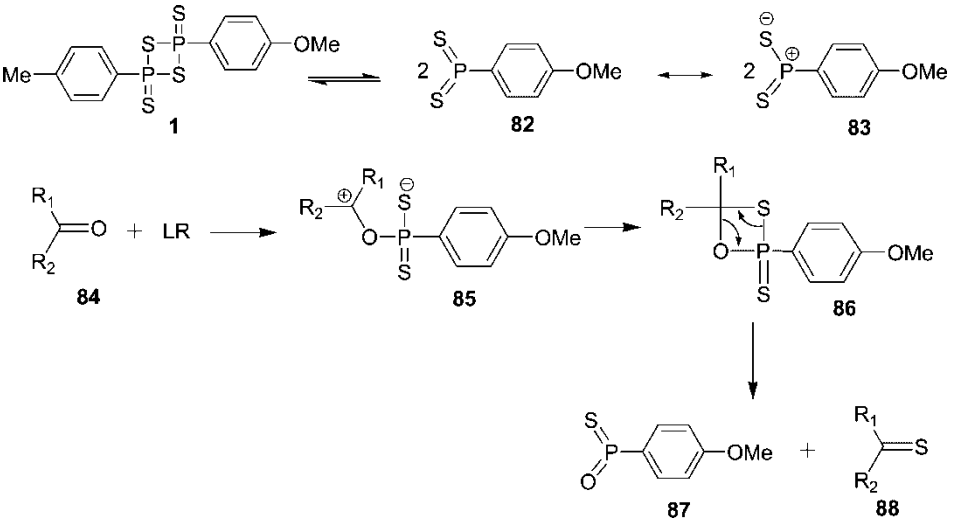

SCHEME 17

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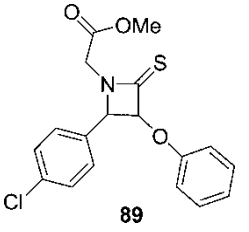
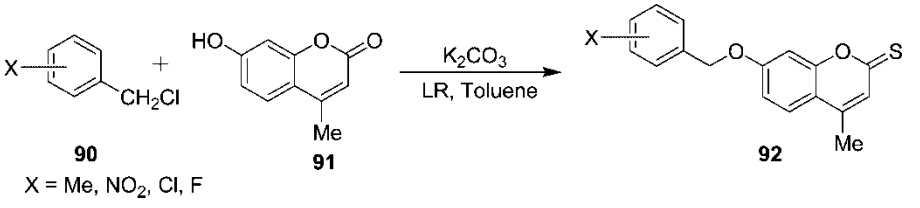
was carried out using the Lawesson's reagent to give β-thiolactams in overall good yields.



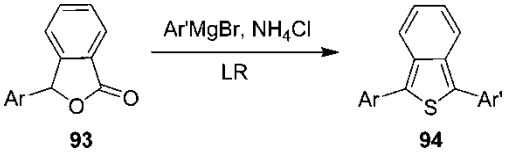
Thiocoumarins can be synthesised by using Lawesson's reagent [49]. This is a simple and convenient method for the preparation of 4-methyl-2-thiocoumarins (R = (un)substituted phenyl; X = CH_2, SO_2) (**92**) by the reaction of the appropriate 4-methylcoumarins with Lawesson's Reagent in hot anhydrous toluene (scheme 18).



SCHEME 18

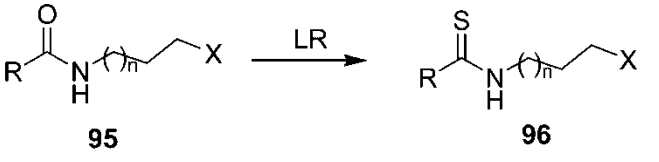
Mohanakrishnan and Amaladass used LR for the synthesis 1,3-diaryl benzo[c]thiophenes [50]. An array of 1,3-diarylbenzo[c]thiophenes (**94**) has been synthesized via the ring opening of lactones followed by thionation using Lawesson's reagent (scheme 19).

New chiral ligands, bis-thiazoline derivatives (sulfur analogs of known oxazolines) with chiral bis-(N-acylamino alcohols) have been synthesised using Lawesson's reagent [51]. Bis-thiazolines thus obtained proved to be useful chiral ligands for metal-catalyzed asymmetric Diels-Alder reactions.



SCHEME 19

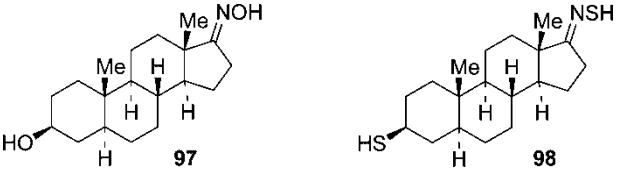
N-(ω-halogenoalkyl)-substituted amides has been thionated with Lawesson's reagent [52]. Treatment of N-[2-(chloro)ethyl]acetamide, N-[2-(bromo)ethyl]acetamide, or N-[2-(iodo)ethyl]acetamide, or N-[3-(chloro)propyl]acetamide, gave the corresponding N-[(ω-halo)alkyl]ethanethioamides in moderate to good yields. The latter, upon treatment with base, afforded, either in a separate step or in a one-pot procedure, the cyclized compounds *i.e.*, the 4,5-dihydro-1,3-thiazole or 5-6-dihydro-4H-thiazine derivatives via a dehydrohalogenation reaction (scheme 20).



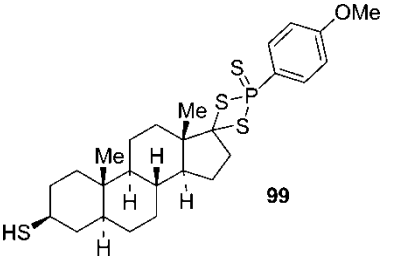
R = Ph, X-Ph, 2-Furyl, 2-Thienyl
X = Cl, Br, I

SCHEME 20

LR has also been used for the synthesis of biologically active steroid derivatives [53]. Steroid derivatives reacted with Lawesson's reagent to produce a spiro-oxazaphosphole-4′,17-androstene derivative, a diazaphospholoandrostane and thionated derivatives. Oxime **97** was refluxed in toluene for 5 h using Lawesson's reagent to form thiol **98** with 72% yield.



Lawesson's reagent (LR) is also reactive toward some steroidal hormones [54]. 4-Androsten-3,17-dione reacted with LR to produce the corresponding thioxosteroids. Epiandrosterone showed a great activity to LR and produced 3β-mercaptospiro-(androstan-17,4′dithiaphosphetan)thione **99** and a sulfide derivative. Similarly progesterone reacted with LR to yield the thiaphospholo[3′,4′:16,17]androsten-3-one and a sulfide.



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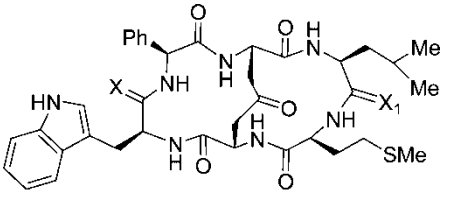
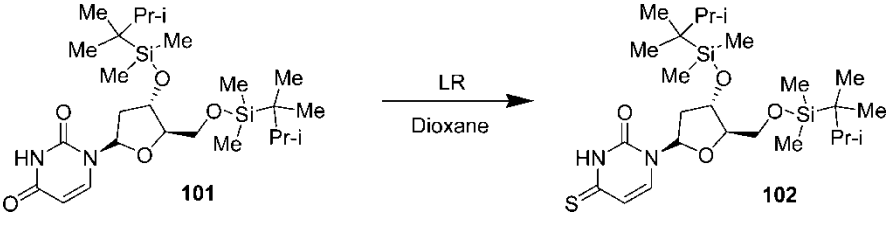
LR has also been used for the synthesis of mono thioxylated derivatives of MEN 10627 (**100**) [55]. The thioxylation of the potent neurokinin antagonist MEN 10627 **100** (X = X_1 = O) by Lawesson's reagent gave mono-sulfurated derivatives. **100** (X = O, X_1 = S; X = S, X_1 = O) and showed a potentially useful post-synthetic manipulation of the related family of structurally peculiar bicyclic hexapeptides.



100

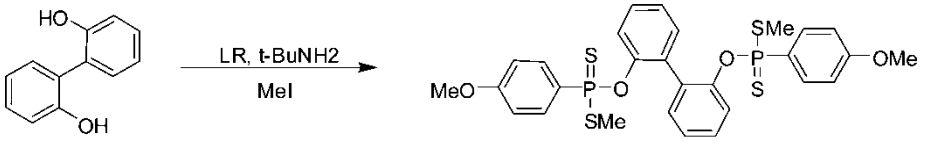
Thionation 2′-deoxy-5,6-dihydropyrimidine nucleosides was achieved with Lawesson's reagent [56]. Treatment of 2′-deoxy-3′,5′-dithexyldimethylsilyl-5,6-dihydrouridine with Lawesson's reagent led to the expected C4-thiolated derivative together with a number of oxathiaphosphepane isomers which resulted from the heat reversible incorporation of an AnPS2 unit within the 2′-deoxyribose moiety explaining the subsequent anomerization of the 5,6-dihydropyrimidine nucleosides (scheme 21).



101 **102**

SCHEME 21

Aliphatic 1,2 and 1,3-diols, as well as aromatic 2,2′-dihydroxybiphenyl, on reaction with LR led to new, stable bis(anisyldithiophosphonic acids) [57]. The bis(anisyldithiophosphonic acids) were isolated as di-*tert*-butylammonium salts and converted into unique 8-, 9-, and 10-membered cyclic disulfides and into S,S-di-Me esters (scheme 22).



103 **104**

SCHEME 22

Mehta and co-workers synthesised thiabowls using LR [58]. Trithia[3]peristylane **105**, a novel C_{3v} symmetric thiabowl, is prepared in two steps from bullvalene **106**; the photoelectron spectra calculated energies of the highest occupied MOs, calculated structure, and crystal structure of **105** were determined. Ozonolysis of **106** in methanol followed by reduction yields the all-*cis*-cyclopropane-1,2,3-tricarboxaldehyde acetal **107** in 65% yield; thionation and cyclocondensation of **107** with Lawesson's reagent then provides **105** in 25% yield. The

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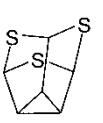
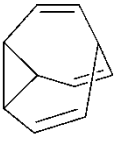
crystal structure of **105** displays an unprecedented supramolecular architecture in the solid state with each molecule of **105** involved in 12 sulfur-methine interactions involving all six of its hydrogen atoms and all of the available lone pairs on its three sulfur atoms.



105



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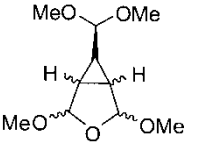
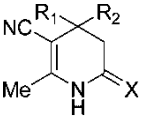


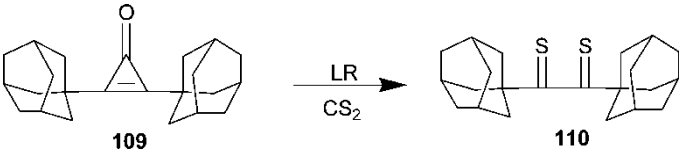
107

Polysubstituted 3,4-dihydropyridine-2(1H)-thiones can be synthesized conveniently by using LR as a thionating reagent [59]. Dihydropyridinones **108** [X = O, R_1 = (un)substituted Ph, Me, 2-furanyl, R_2 = H; $R_1 = R_2$ = Me] were converted to dihydropyridinethiones **108** (X = S; same R_1, R_2) by Lawesson's reagent.



108

LR was also used for the synthesis of aliphatic α-dithiones, di(1-adamantyl)- and di-*tert*-butylethanedithiones [60]. 2,3-Di(1-adamantyl)thirene 1-oxide quickly reacted with Lawesson's reagent in CH_2Cl_2 at room temperature to provide di(1-adamantyl)ethanedithione as thermally labile, violet crystals in 20% isolated yield. The use of CS_2 as the solvent gave product in 46% isolated yield (scheme 23).



109 **110**

SCHEME 23

N,N-Dialkyl-2-methylbenzenecarbothioamides and naphthalenecarbothioamides can be prepared by thionation of amides with Lawesson's reagent in 1,2,4-$Cl_3C_6H_3$ at 165 °C [61]. Benzylic deprotonation of thioamides bearing N,N-diisopropyl groups with sec-butyllithium was selective. The resulting anions were reacted with prochiral electrophiles (aromatic aldehydes, an unsaturated aldehyde or ketone, and an imine) to afford diastereomeric mixtures of adducts (scheme 24). The selectivity was due to the axial chirality of the thioamides.

Lawesson's reagent (LR) and hexamethyldisiloxane (HMDO) in combination with microwaves can thionate γ-lactones under solvent-free conditions [62]. This is a rapid and high yield, environmentally friendly method for the synthesis of γ-thionolactones (scheme 25).

N-Tosylamidrazones react with thionyl chloride and Lawesson's reagent to yield thiatriazoles and triazaphospholines [63]. N-Tosylamidrazones $R_1C(NHR_2)$:NNHTs (R_1 = Me, Et, R_2 = CH_2Ph, 2-furylmethyl, Cy, iBu) on reaction with LR yields, respectively 2,5-dihydro-2-tosyl-4-R_1-5-R_2-1,2,3,5-thiatriazole 1-oxides and 3,4-dihydro-3-Ar-2-tosyl-4-R_2-5-R_1-2H-1,2,4,3-triazaphosphole 3-sulfides (Ar = 4-$MeOC_6H_4$; R_1 = Me, Et, R_2 = CH_2Ph, iBu, 2-furylmethyl) (scheme 26).

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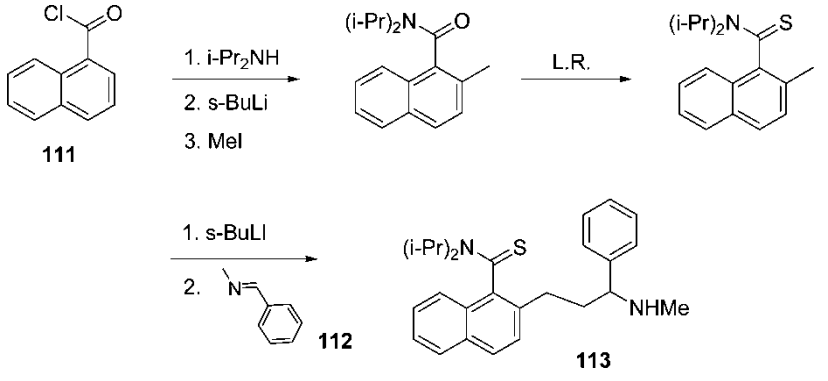
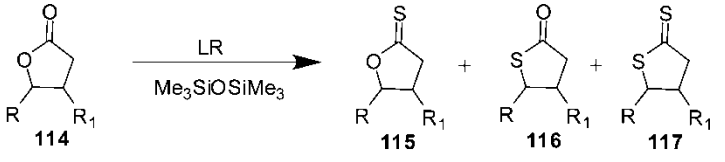
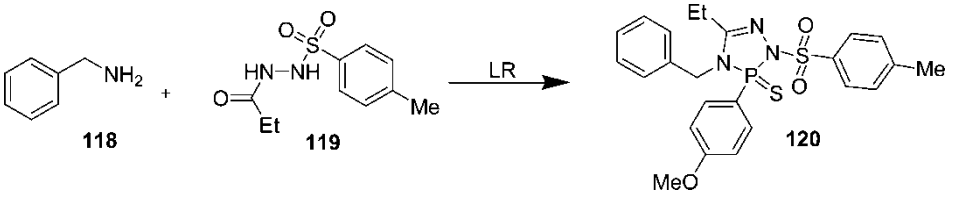


SCHEME 24



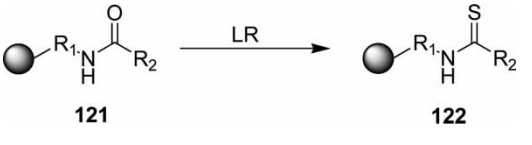
Where,
R = alkyl, aryl
R_1 = H, Me

SCHEME 25



SCHEME 26

LR can also be used for solid phase parallel synthesis of thioamides at elevated temperature, using various alternating solvents. A new class of higher-boiling solvents was investigated for elevated-temperature solid-phase parallel synthesis. Extremely low vapour pressures at high temperature and a broader range of solvent effect tuning make this new class of solvents an ideal choice for high-temperature parallel solid-phase synthesis. Benzyl benzoate is identified as a superior high-boiling solvent for parallel solid-phase Lawesson's thionation reactions [64] (scheme 27).



SCHEME 27

Ishii *et al.* deoxygenated dithirane 1-oxides with Lawesson's reagent leading to the corresponding dithiiranes. 3,3-Disubstituted dithiirane 1-oxides were efficiently reacted with LR to give

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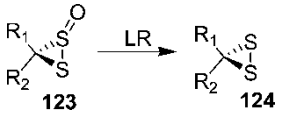
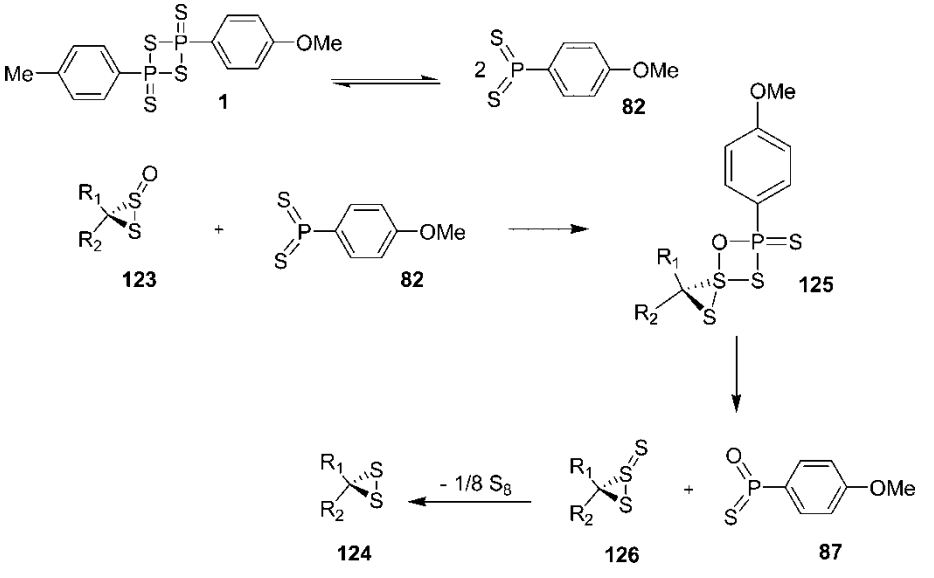
the corresponding dithiiranes [65]. X-ray diffraction analysis of 3,3-di-1-adamantyldithiirane is reported. Reaction of ^{34}S-labeled 3,3-di-1-adamantyldithiirane 1-oxide with LR produced the corresponding dithiirane in which the ^{34}S atoms were retained quantitatively (scheme 28).



SCHEME 28

The likely mechanism is as shown below (scheme 29).



SCHEME 29

A novel heterocyclic atom exchange reaction with Lawesson's reagent has been reported [66]. A one-pot reaction of maltol with Lawesson's reagent generates dithiomaltol, a thiopyran-4-thione, via an unusual heterocyclic atom exchange (HCAE) reaction; only pyrones with proton or aliphatic substituants undergo the HCAE substitution.

2.4 *Hexamethyldisilathiane (HMDST)*

Reactions of hexamethyldisilathiane (HMDST) with carbonyl compounds under the catalytic activity of $CoCl_2 \cdot 6H_2O$ or trimethylsilyl triflate lead to a simple and general access to thioaldehydes and thioketones, which could be isolated as their cycloadducts with dienes. The use of $CF_3SO_3SiMe_3$ in reactions with cyclohexadiene allows a stereo predetermined access to either the *endo*- or the *exo*-isomer. Furthermore, on using silyl-substituted acetylenic ketones, a smooth access to acetylenic thioketones can be achieved. In reactions with aromatic and heteroaromatic *o*-azido aldehydes, the reactivity of HMDST may be finely tuned toward the synthesis of *o*-azido thioaldehydes, fused isothiazole ring systems, aromatic and heteroaromatic *o*-amino aldehydes, and *o*-amino thioaldehydes. HMDST proved also very

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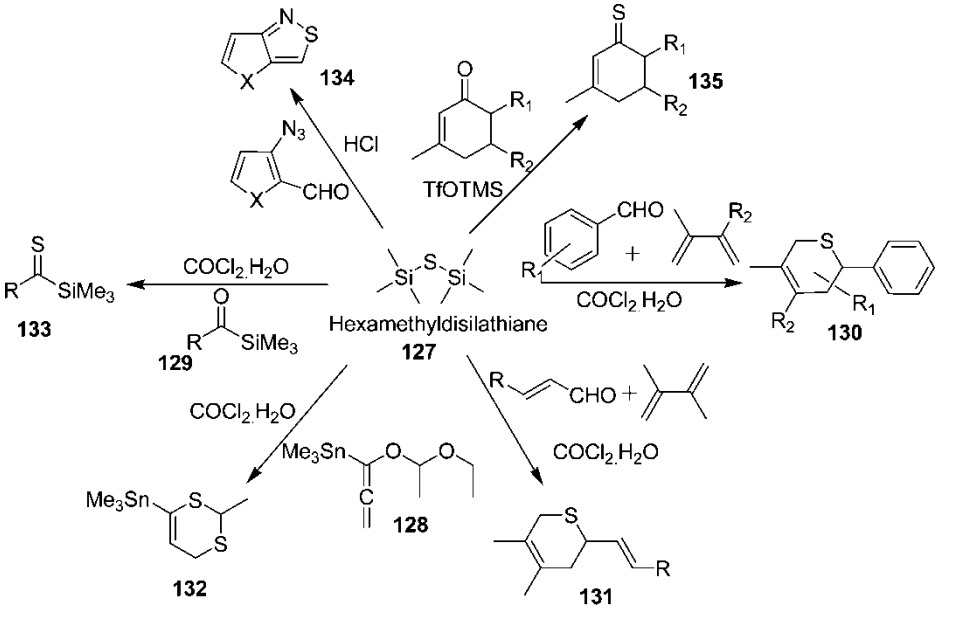
efficient in thionating more intriguing substrates such as acylsilanes. Thus, thioacylsilanes, thioformylsilanes, unsaturated thioacylsilanes and -stannanes can be obtained in good yields. Ethylenic thioacylsilanes show an interesting behaviour leading to a general synthesis of functionalized dithiins. Finally, HMDST led also to the synthesis of bis(thioacylsilanes), which in turn led to the formation of new silylated thiaheterocyclic systems as intermediates in organic synthesis.

HMDST has proved a very efficient and mild thionating agent in the synthesis of various thiocarbonyl compounds (scheme 30).



SCHEME 30

An excellent review by Degl'Innocenti *et al.* has been published very recently [67], which covers various thionation reaction mediated by HMDST, until 2005. So no more attempts have been made in this report to review this reagent.

2.5 *Curphey's thionating reagent (P_4S_{10}/HMDO)*

Thionation, the conversion of the carbonyl group to thiocarbonyl, is a commonly used procedure for the preparation of organosulfur compounds. As for many thionations, the transformation, which involves thionation of both the ketone and ester carbonyl groups of the oxoester, can be effected by P_4S_{10}, but typically in rather low yield. In recent years, LR has displaced P_4S_{10} as the reagent of choice for many thionations. This is indeed the case for the transformation where treatment of 3-oxoesters with the combination of LR and elemental sulfur produces generally excellent yields of dithiolethiones. However, aside from its high cost, LR has the major disadvantage that by-products derived from the reagent itself cannot, in general, be removed by any extractive procedure and must be separated by column chromatography on silica gel. The high equivalent weight of LR means that relatively large columns must be used, and the procedure becomes unwieldy for any but small-scale reactions or in cases where low molecular weight products may be distilled directly from the reaction mixture. Curphey developed a new thionating reagent P_4S_{10}/HMDO [68–71]. The combination of P_4S_{10}

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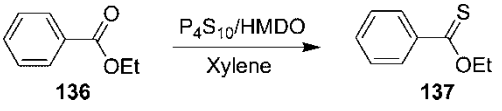
and hexamethyldisiloxane efficiently converts esters, lactones, amides, lactams and ketones to their corresponding thio analogues. In the presence of elemental sulfur, 3-oxoesters are converted to dithiolethiones by this reagent. Yields are comparable to or superior to those obtained with Lawesson's reagent. The method has the advantage that reagent-derived by-products may be removed by a simple hydrolytic workup or by filtration through silica gel, rather than by chromatography, as required for Lawesson's reagent. Curphey carried out detail study for the preparation of thioketones, thioesters, thioamides and thiolactams and demonstrated the wide utility of P_4S_{10}/HMDO as a thionating agent.

As a test case for the utility of P_4S_{10}/HMDO in the thionation of esters, the conversion of ethyl benzoate to the corresponding thionoester in refluxing xylene was studied (scheme 31).



136 **137**

SCHEME 31

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The course of the reaction was monitored by HPLC, using a photodiode array detector, which allowed both disappearance of starting material and appearance of the product to be followed. In selected runs, consumption of HMDO was measured by dilution of the final reaction mixture with xylene, codistillation of HMDO with xylene, and GC quantification of the amount of HMDO present in the distillate. These experiments established that a minimum of 0.2 mol of P_4S_{10} per mol of ester was required to achieve maximum yields of thionoester. Use of more than 0.2 mol of P_4S_{10} per mol of ester, while having little effect on the final yield of thionoester, did reduce the amount of recovered starting material. Consequently, 0.25–0.33 mol of P_4S_{10} per mol of ester was found to give the most satisfactory results.

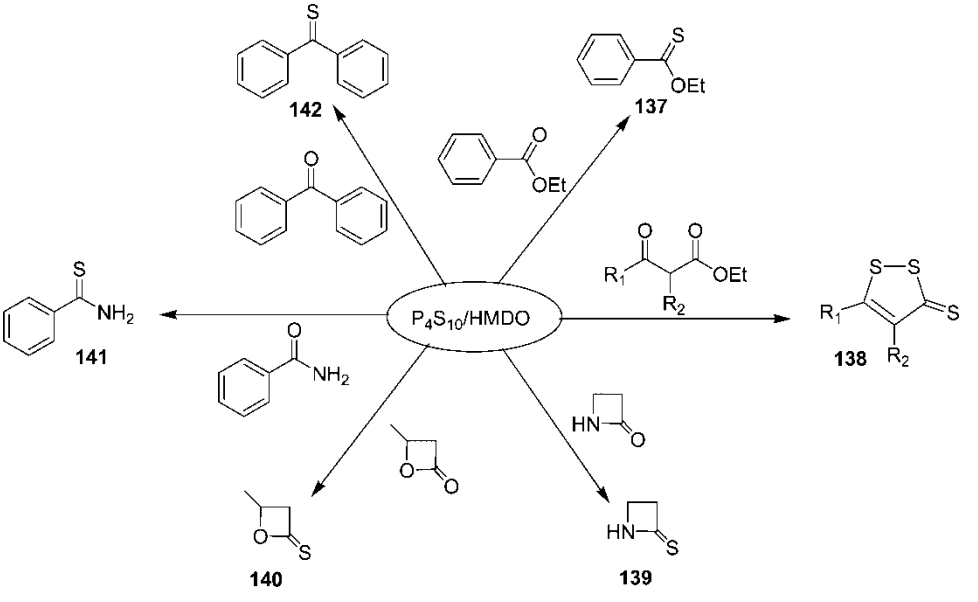
GC analysis showed that 3–4 mol of HMDO per mol of P_4S_{10} were consumed during the course of the reaction. Because some loss of the volatile HMDO is inevitable during the several hours necessary for completion of the reaction in refluxing xylene, use of 5 mol of HMDO per mol of P_4S_{10} was adopted as the standard in subsequent reactions. At a substrate concentration of 0.5–1 mmol/mL in refluxing xylene, the yield of thionoester under the optimum conditions reached a maximum of approximately 80% in 8–13 h, with the resulting solution undergoing little change upon further reaction. In the course of these experiments, it was observed that complete dissolution of the solids occurred shortly before the reaction reached its maximum yield. By allowing a further reaction time of one-third to one-half of that required for the P_4S_{10} to dissolve, one could then be assured of being at or near maximum yield without the necessity of following the reaction by HPLC or TLC.

The above study was also carried out for the conversion of ketone, amide, lactone, lactam to their corresponding carbonyl compound, and P_4S_{10}/HMDO was found to be very effective thionating reagent with high yield (scheme 32).

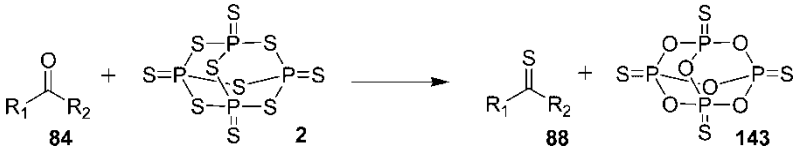
The mechanistic aspects of thionation by Curphey's reagent were also studied. In the first step the six bridging sulfur atoms of P_4S_{10} are exchanged with oxygen, converting six molecules of carbonyl to thiocarbonyl, leaving one atom of sulfur per phosphate (scheme 33).

In the second step of the reaction, five of six P-O-P units cleaved with HMDO in the manner as shown in scheme 34.

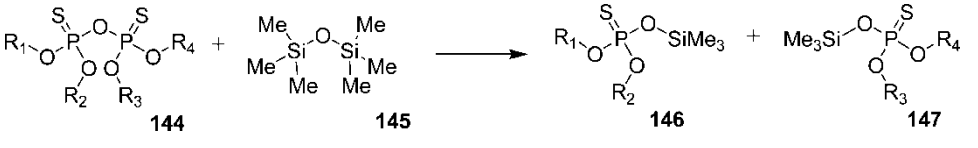
The mechanistic consideration outlined above provides a reasonable, rationalization for the beneficial effect of HMDO on thionation by P_4S_{10}. In the absence of HMDO, thionation by P_4S_{10} will of necessity produce highly condensed polythiophosphates. These species might be expected to be a potent electrophile, by analogy to P_4O_{10}, and therefore capable of promoting undesirable side reactions of both the carbonyl and thiocarbonyl derivatives. In fact, as the



SCHEME 32



SCHEME 33



SCHEME 34

reaction with P_4S_{10} proceeds in the absence of HMDO, the general reaction environment becomes increasing electrophilic with each successive replacement of sulfur on phosphorus by oxygen. However, the presence of HMDO in the reaction converts highly electrophilic species to innocuous silylated phosphates and thereby raising the yield of the thionation product.

Although Curphey's thionating reagent is good in terms of reactivity under standard conditions (dry toluene/xylene, thermal heating), the use of P_4S_{10}/HMDO under microwave irradiation has increases the reactivity and yields of the product further. Kaushik *et al.* reported thionation of carbonyl compounds by phosphorus pentasulfide and hexamethyldisiloxane under microwave irradiations [72]. Microwave irradiation improves the selectivity, reduces the reaction time from several hours to few minutes with quantitative yields (scheme 35).

For these studies a newer household MW oven (Samsung) equipped with inverter technology that provides a better control of MW power to a desired level was used. The mixture of the corresponding carbonyl compound, HMDO and P_4S_{10} was exposed to microwaves. In order to optimize the microwave power, the reaction mixture was exposed to the electromagnetic field

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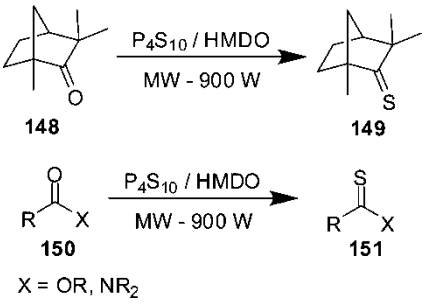
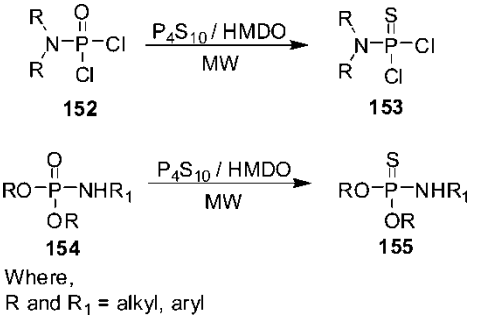


SCHEME 35

at different power levels. The experiments were conducted at three different power levels to compare reaction time and product yield. The effect of irradiation time on the yield of a product was also investigated. It was found that yields were affected by time of microwave exposure. The maximum yield was obtained at 900W. The reactions were conducted with intermittent heating at 900 W power level and mixing, to obtain better yields and clean products. The intermittent heating is basically to reduce the formation of hot spot. It has been observed that, at elevated power level, a partial decomposition or charring of reaction mixture occurred possibly due to localized overheating that creates hot spots in reaction mixture. This can be avoided by mixing the reaction mixture after every microwave exposure to delocalize the heat over reaction mixture.

To explore the utility of this methodology, thionation of the representative set of esters, amides and lactam using P_4S_{10}/HMDO under microwave were also studied [72]. Kaushik *et al.* also used this protocol for synthesis of thiophosphoramidodichloridates (**153**) and thiophosphoramidate diesters (**155**) [73] (scheme 36).



SCHEME 36

This microwave assisted protocol for the thionation of variety of carbonyl compounds *viz.* ketones, esters, amides, lactam was occurs remarkably fast. The advantages of this method are, simple reaction set up, safe, high product yields, very short reaction time as well as elimination of solvents.

2.6 *Kaushik's thionating reagent (P_4S_{10}/Al_2O_3)*

The combination of P_4S_{10}/HMDO is good in terms of reactivity but use of HMDO makes this method expensive and the removal by-products formed is cumbersome. Despite the wide range of synthetic methods for the conversion of ketones to thioketones available to synthetic

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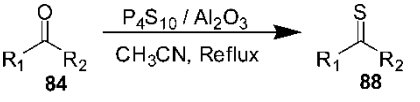
chemist, no attempt has been made to use readily accessible P_4S_{10} on solid support for the thionation of ketone. In recent years, the use of reagents and catalysts supported on solid supports has received much attention. Such reagents not only simplify purification processes but also help in preventing release of reaction residues into the environment. This leads to explosive growth especially in the field of solid supported reagents on alumina.

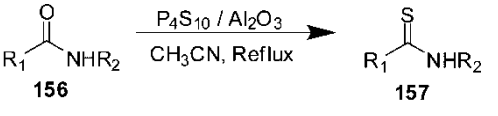
Kaushik *et al.* developed a new thionating reagent by encapsulating P_4S_{10} in basic alumina (scheme 37) [74].



Where R_1, R_2 = alkyl, aryl

SCHEME 37

The reaction was carried out by refluxing a mixture of ketone and P_4S_{10}/Al_2O_3 in acetonitrile. A series of experiments established that 0.34 moles of P_4S_{10}/Al_2O_3 per mole of ketone were required to obtain maximum yields of the thioketone. Using standard condition of 0.34 moles of P_4S_{10}/Al_2O_3 per mole of ketone, thionation of series of ketones was examined. The carbonyl substrates were chosen to reflect variety of structural types. Alkyl and aryl ketones reacted smoothly with P_4S_{10}/Al_2O_3 under these reaction conditions to produce the corresponding thioketones in good to excellent yields. The utility of this reagent was further explored for the thionation of amide to thioamides [75] (scheme 38).



Where R_1, R_2 = alkyl, aryl

SCHEME 38

The catalytic role of Al_2O_3 was also studied by carrying out the reaction in the absence of Al_2O_3 using P_4S_{10} alone. It was found that yields of thioketones/thioamides using combination P_4S_{10}/Al_2O_3 were greater than those with P_4S_{10} alone. The beneficial effect of Al_2O_3 may be due to scavenging of yield lowering intermediates formed during the course of the reaction.

Although yields and reaction time is comparable with LR, P_4S_{10}/Al_2O_3 combination still offered advantages over LR. LR needs two moles of the reagent per mole of ketone and high equivalent weight of Lawesson's reagent comprises only a small percentage by weight of the crude reaction mixture, where as P_4S_{10}/Al_2O_3 needs only 0.34 moles per mole of ketone making the method less expensive. The combination P_4S_{10}/Al_2O_3 provides clean product in comparison to that of LR which gives by-products which are difficult to remove. Also this method is economical and practical as compared to expensive P_4S_{10}/HMDO method. Use of solid support in P_4S_{10}/Al_2O_3 is advantageous over LR and P_4S_{10}/HMDO essentially because support bound reagent can be removed easily by filtration, avoiding cumbersome aqueous workup and decreasing solvent waste. Since the thiocarbonyl never covalently binds to the solid support, monitoring of the reactions and analysis can be accomplished using standard methods such as GC, TLC. The thiocarbonyls were isolated by filtration and removal of solvent makes the process simple and convenient.

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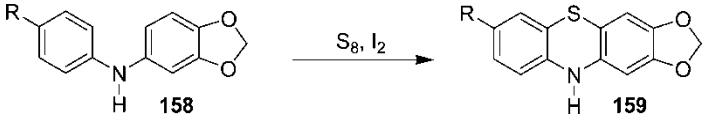
2.7 *Bernthsen's reagent*

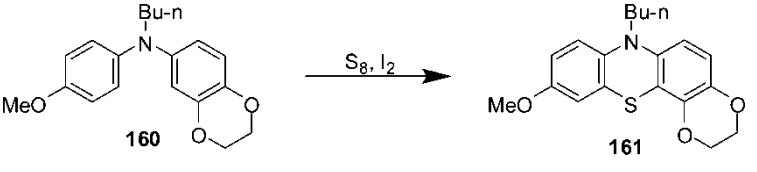
Bernthsen's thionation [76, 77] which uses elemental sulfur and iodine as a reagent was efficiently used for the regioselective synthesis of N-acyl- and N-alkyldioxolo[4,5-b]phenathiazines [78] (scheme 39).



SCHEME 39

In a typical reaction mixture of *N*-(4-alkylphenyl)[1,3]benzodioxol-5-amine, sulfur and one iodine crystal was refluxed under nitrogen in dry *o*-dichlorobenzene during 6 h. The mixture was then extracted with Et_2O. The resulting oil was chromatographed on silica gel with toluene to elute first the solvent (*o*-dichlorobenzene), and next a product as a red powder. The thionation reaction turned out to be regioselective and led to single isomer, the linear dioxolo[4,5-*b*]phenothiazine. Under the same conditions the reaction of the chloro derivative (R – Cl) was unsuccessful, leading to many side products of polymerization.

Chatel *et al.* also synthesised new N-alkyl- and N-acyldioxinophenothiazine and acridinone derivatives, where they used Bernthsen's thionation [79]. The synthesis of the new substituted dioxino[b]- and [c]phenothiazines or acridinones was reported. N-arylation of [1,4]benzodioxin-6-amine with organolead or organobismuth reagents gave N-aryl-2,3-dihydro-1,4-benzodioxin-6-amine; subsequent Bernthsen thionation led to phenothiazine ring formation, followed by N-acylation. On the other hand [1,4]benzodioxin-6-amine was first N-alkylated and the resulting alkylamines were N-phenylated before Bernthsen thionation to provide the tetracyclic phenothiazines. Alternative arylation with chlorobenzoic acid followed by cyclization under acidic conditions afforded the dioxinoacridinones, which were successfully alkylated (scheme 40).



SCHEME 40

They have also synthesized new cyclopentacridinones and cyclopentaphenothiazines by cyclization of N-aryl indane derivatives under acidic conditions or via Bernthsen's thionation [80].

This reagent has also been used for the synthesis of pyrazolo[3,4-b]- and pyrazolo[4,3-c]phenothiazine derivatives by thionation of corresponding N-arylindazoles [81]. $Cu(OAc)_2$-catalyzed reaction of 6-amino-3-chloroindazole, was prepared from 6-nitroindazole, with p-tolyl lead triacetate gave 3-chloro-6-(p-tolylamino)-1H-indazole, which on Bernthsen's thionation with S_8 and I_2 gave the pyrazolo[4,3-c]phenothiazine derivative (scheme 41).
Fused imidazole can also be thionated by Bernthsen's thionating reagent [82]. Thionation of 1-methyl-6-(p-tolylamino)benzimidazole, obtained from 1-methyl-6-aminobenzimidazole and p-tolyl lead triacetate, by sulfur and iodine, afforded a 7:3 mixture of two isomeric imidazophenothiazines, **165** and **166**, by inclusion of sulfur into the C-7 and C-2′ or C-5 and C-2′

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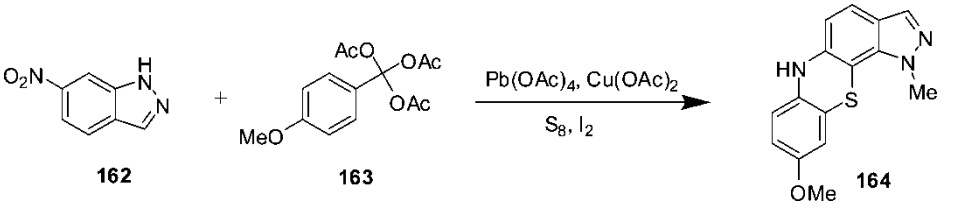
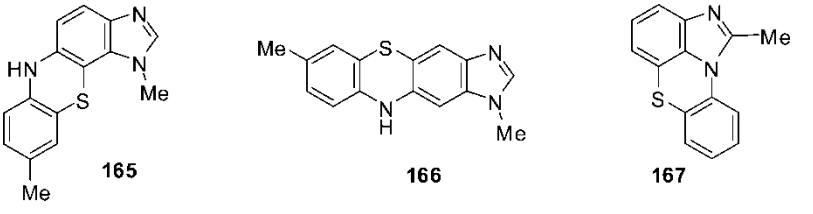


162 163 164

SCHEME 41

positions, respectively. 2-Methyl-1-phenylbenzimidazole also underwent thionation to give imidazothiazine **167**.



165 166 167

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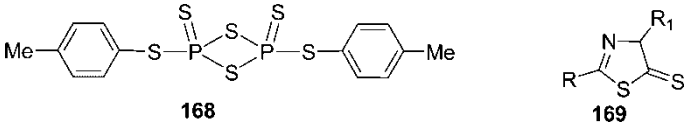
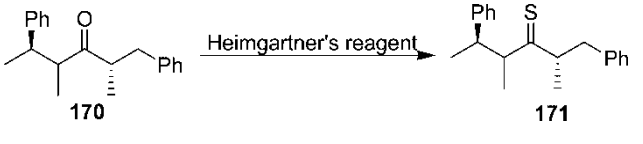
2.8 *Heimgartner's reagent*

Heimgartner *et al.* prepared a new thionating reagent 2,4-bis(4-methylphenylthio)-1,3,2λ5, 4λ5-dithiadiphosphetane-2,4-dithione; known as Heimgartner's reagent [83]. Reaction of p-thiocresol with P_4S_{10} in PhMe gave 81% bis(methylphenylthio)dithiadiphosphetanedithione **168** (Heimgartner's reagent). Reagent **168** showed a remarkable selectivity for thionation of N,N-disubstituted amides and are thus complementary to the well known Lawesson's reagent. Thus, thionation of diamides $RCONHCMeR_1CONMe_2$ (R = H, Me, Ph, $PhCH_2$, PhCH:CH; R_1 = Me, Ph, CH_2:CH) with **168** gave dithiodiamides which cyclize to give 1,3-thiazolethiones **169**.



168 169

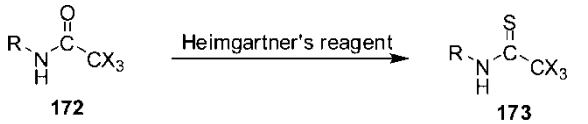
This reagent can also thionate chiral ketone **170** to its thioanalog **171** in good yield, without any racemization (scheme 42).



170 171

SCHEME 42

Several N-monosubstituted trichlorothioacetamides (**173**) has been prepared by thionation of the corresponding acetamides by Heimgartner's reagent [84]. In contrast to the corresponding amides which undergo base-induced beta-elimination of chloroform, these compounds undergo an unexpected rearrangement to thiooxamides (scheme 43).



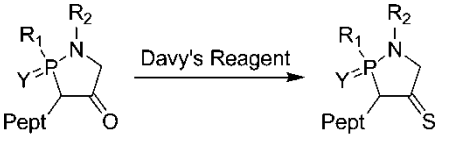
172 **173**

Where,
R = aryl, X = halide

SCHEME 43

2.9 *Davy's reagent*

2,4-Bis(methylthio)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane, $(CH_3S)_2P_2S_4$, is known as Davy's reagent. Alibert *et al.* synthesized thio-sarcosin (**175**) using Davy's reagent for the thionation step [85] as part of a new, three-step method for the synthesis of thiopeptides. Sarcosin derivative MeNHP(S)MeNMeCH_2CO_2Et underwent cyclization (DBU, BSA, DMF), thionation with Davy's reagent and reactions with water or alcohol to give thiosarcosin derivatives. With amines regioselective attack at thiocarbonyl, instead of thiophosphoryl with alcohols, is observed (scheme 44).

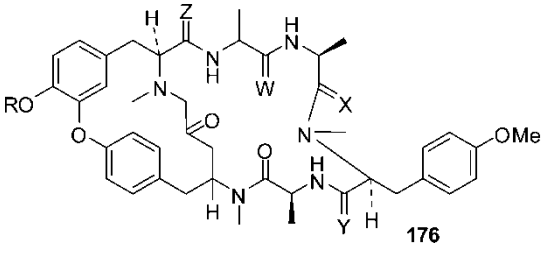


174 **175**

R_1 = Alkyl, Aryl, O-Aryl; R_2 = H, Me
Y = O, S; Pept = Peptide chain

SCHEME 44

Cyclic hexapeptide has also been thionated by Davy's reagent [86]. For example, cyclic hexapeptide **176** (R = Me; W = X = Y = Z = O) was thionated with Davy reagent **177** (R = SMe or R = S-p-C_6H_4Me) to afford novel thionopeptides **176** (R = Me; W = X = Z = O or S; Y = O, S or H_2).



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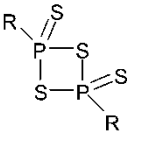
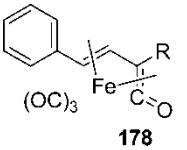


177

η4-Ketene complexes of iron **178** (R = Ph, CH:CHPh) react with Davy's reagent (2,4-bis(methylthio)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) to give ferrathiolactones **179** upon insertion of S into an Fe-C bond [87].



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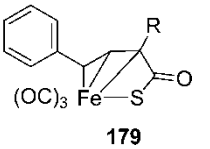

179

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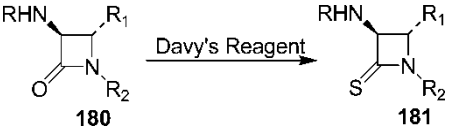
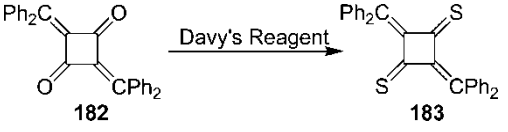
Thioanalogs of β-lactams can be synthesised using Davy's reagent [88]. Optically active β-lactams (**180**) were treated with Davy's reagent to give the β-thiolactams (**181**) (R = Boc with R_1 = H, Me; R_2 = MeO and R_1 = H, R_2 = $PhCH_2O$) (scheme 45).



180 **181**

SCHEME 45

Strelow *et al.* also achieved the synthesis of thioketyls (**183**) using Davy's reagent [89] (scheme 46).



182 **183**

SCHEME 46

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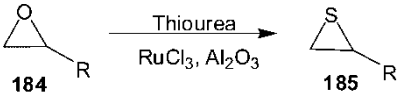
2.10 *Other thionating reagents*

In addition to these thionating reagents, as discussed above, which are generally used for various thionation reactions in organic synthesis, there are a few other molecules, which also act as thionating reagents.

2.10.1 Thiourea. Thiourea has been efficiently used for conversion of oxiranes to thiranes [90]. Oxiranes (**184**) are efficiently converted to the corresponding thiiranes (**185**) by thiourea in the presence of catalytic amounts of Ru(III) with excellent yields under mild and nonaqueous conditions. The presence of Woelm chromatographic alumina in reaction media increases the rate of reactions (scheme 47).



184 **185**

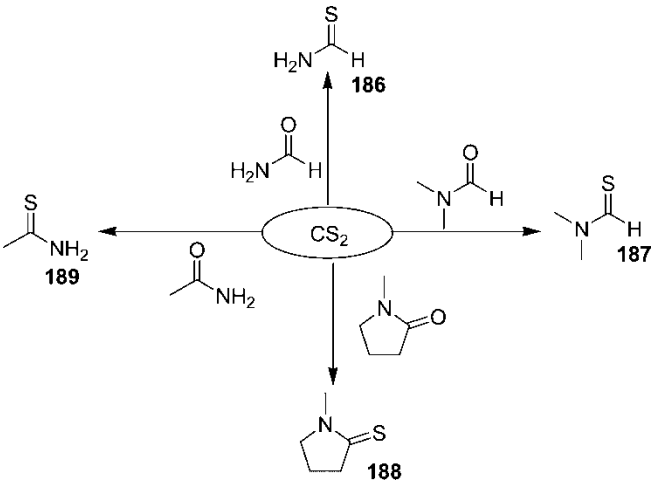
Where,
R = alkyl, aryl

SCHEME 47

This reaction can also be carried out under solvent free condition [91]. Cyclohexene oxide, styrene oxide, glycidyl Ph ether, glycidyl iso-Pr ether and allyl glycidyl ether were thionated in 65–92% yields.

2.10.2 Carbon disulfide. CS_2 was also used as a thionating reagent [92]. Zong *et al.* examined thermal reactions of CS_2 with N-methyl-2-pyrrolidinone, formamide, acetamide,

and DMF. Under optimum conditions N-methylpyrrolidine-2-thione and the corresponding thioamides can be obtained in good to excellent yields (scheme 48).



SCHEME 48

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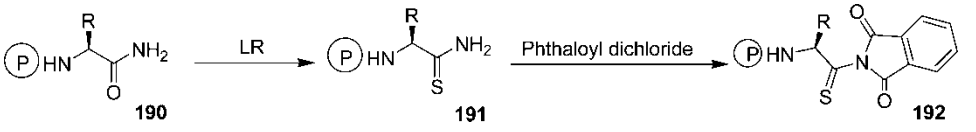
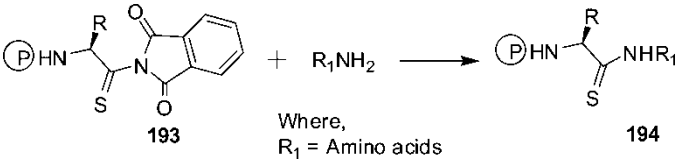
2.10.3 Thioacyl-N-pthalimides. Brain *et al.* used thioacyl-*N*-phthalimides as a thionating reagent for synthesis of thioamide [93]. A new class of N-thioacylating agents, based on thioacyl-*N*-phthalimides, was developed. Highly enantiomerically pure thioacyl-*N*-phthalimides were prepared by thionation of N-terminal protected amino acid using Lawesson's reagent, followed by activation using phthaloyl dichloride. The utility of these reagents was demonstrated by the efficient thioacylation of a range of amine nucleophiles (amino acids and peptides) under very mild conditions.

Preparation of the thioacylating agents turned out to be an experimentally facile process. Thus, thionation of the amino acid amides with Lawesson's reagent proceeded smoothly at room temperature and provided the thioamides in excellent yields. These were easily converted to the thioacyl-*N*-phthalimides in good to excellent yields by treatment with phthaloyl dichloride at 0 °C (scheme 49).



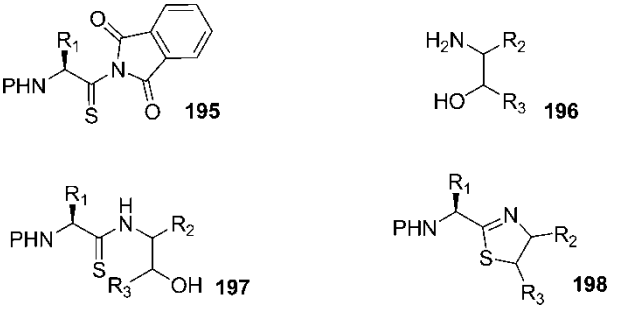
SCHEME 49

In order to assess their utility in thiopeptide synthesis, the thioacyl-*N*-phthalimides were treated with a selection of amino acids, including a dipeptide. The thioacyl-*N*-phthalimides reacted smoothly with these nucleophiles in good to quantitative yields under very mild conditions (chloroform, 0 °C, 10 min). The high reactivity of the new thioacylating agents was noteworthy: thus, sterically demanding couplings as exemplified by hindered valine nucleophiles and hindered thioacylating agent, derived from *N*-Boc-valine proceeded efficiently (scheme 50).



SCHEME 50

N-Thioacylation of β-amino alcohols by N-(thioacyl)phthalimides was also reported [94]. Amino acid-derived phthalimide thioacylation reagents, *e.g.* **195** [$R_1 = CH_2Ph$, CH_2CHMe_2, $CHMe_2$; P = 9-fluorenylmethoxycarbonyl (Fmoc), Me_3CO_2C (Boc)] react with β-amino alcohols **196** [R_1 = H, Me, $CONHCH_2Ph$, CH_2OMe, CH_2Ph; R_2 = H, Me, Ph; $R_2R_3 = (CH_2)_4$] under very mild conditions to provide N-(hydroxyethyl)thioamides **197** in high yields. Cyclodehydration with Burgess' reagent then provides α-amino acid thiazolines **198**. This approach provides a convenient alternative to those based upon thionation of preformed N-(hydroxyethyl)amide.



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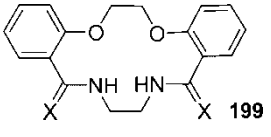
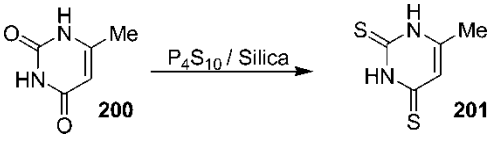
2.10.4 P_4S_{10}/Silica. P_4S_{10} in combination with silica can be used for the synthesis of macrocyclic dithiodiamides [95]. Treatment of macrocyclic diamides such as **199** (X = O) with phosphorus pentasulfide supported on silica gel under solvent-free conditions with microwave irradiation gives macrocyclic thioamides such as **199** (X = S) in 78–89% yields.

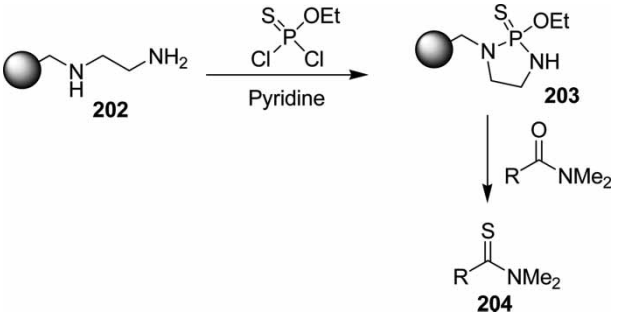


This reagent can also be used as a thionating reagent for thionation of heterocycles (**200**) under microwave irradiation [96] (scheme 51).



SCHEME 51

2.10.5 Polymer supported thionating reagent. A new polymer-supported thionating reagent has been developed and used for the conversion of carbonyls to thiocarbonyls of variety of amides [97]. The reactions can be facilitated by conventional heating. However, if microwave heating is used, in the presence of an ionic liquid, enhanced reaction rates are achieved (scheme 52).



SCHEME 52

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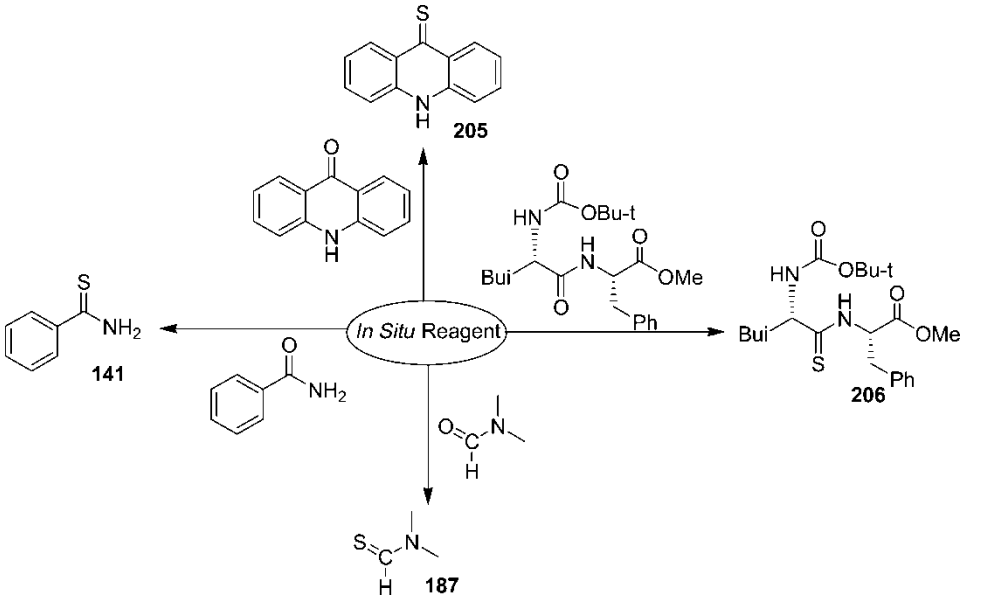
The typical reaction is carried out as follows: Et dichlorothiophosphate (90 mmol) was added drop wise to a suspension of [N-(2-aminoethyl)amino]methyl polystyrene (9.32 g; 2.8 mmol/g) in pyridine (150 mL) at 0 °C. The resulting suspension was allowed to warm to room temperature and was then shaken for 4 h, filtered and washed with dichloromethane and di-ethyl ether to give polystyrene-bound 2-ethoxy-1,3,2-diazaphospholidine 2-sulfide. Polystyrene-bound 2-ethoxy-1,3,2-diazaphospholidine 2-sulfide (466 mg; 0.84 mmol) was added in one portion to N,N-dimethylbenzamide (0.19 mmol) in toluene (3.0 mL). The resulting suspension was heated without agitation to 90 °C for 14 h; additional reagent (0.46 mmol) was added and the suspension was heated to 90 °C for and additional 16 h. The product mixture was cooled to room temperature, filtered through a silica pad and the solvent was evaporated to give N,N-dimethylbenzenecarbothioamide in 99% yield. Treatment of secondary or tertiary amides gave thioamides; however, reaction of primary amides mainly led to the formation of nitriles.

Overall this new polymer-supported thionating reagent represents an important development in that it is an easily handled, low odour alternative to Lawesson's reagent. Its use has been demonstrated in the conversion of secondary or tertiary amides to thioamides and primary amides to nitriles. Moreover, the benefits of microwave technology have been illustrated and the use of a small amount of ionic liquid to promote efficient heating in such systems has been proven to be very effective.

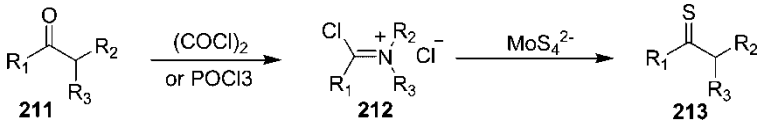
2.10.6 *In situ* thionating reagent. Brillon developed a new *in situ* thionating reagent [98]. This reagent which was prepared from 1:1 P_2S_5 and Na_2CO_3 in situ was used for the thionation of amides, amino acids, peptides, and lactams, with product yields ranging from 28–96% (scheme 53).

It was also reported that phosphorus pentasulfide reacts with sodium sulfide (1:1 ratio) in THF at 25 °C to afford an *in situ* reagent $(P_4S_{11})Na_2$ that rapidly converts nitriles into thioamides at 20 °C [99] (scheme 54).

2.10.7 Benzyltriethylammonium tetrathiomolybdate. Benzyltriethylammonium tetrathiomolybdate can be used for thionation of amides and lactams [100]. Chloroiminium salts



SCHEME 53



SCHEME 54

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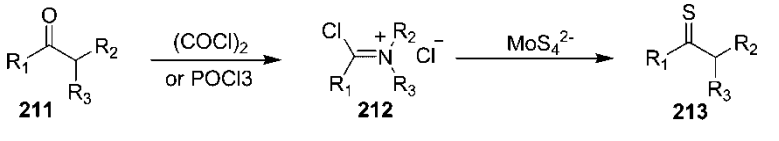
generated *in situ* from amides and lactams using $(COCl)_2$ or $POCl_3$ reacted readily with the sulfur transfer reagent, benzyltriethylammonium tetrathiomolybdate to afford the corresponding thioamides and thiolactams in excellent yields under mild reaction conditions (scheme 55).



SCHEME 55

The amides and lactams were reacted with $(COCl)_2$ or $POCl_3$ in dichloromethane to generate the chloro iminium salts in situ, which are then reacted with benzyltriethylammonium tetrathiomolybdate at −78 to 25 °C to afford the corresponding thioamide and thiolactams within 15–40 min with excellent yield. The yields of thioamides obtained using this method are comparable to those reported using LR. The advantage of this methodology is the isolation of products by simple extraction with diethyl ether compared to the tedious workup needed for LR.

3. Summary and conclusion

Various new thionating reagents have been prepared and used for synthesis of organosulfur compounds in the last few years. Curphey's thionating reagent (P_4S_{10}/HMDO) seems to be the best substitute for Lawesson's reagent. Also P_4S_{10} in combination with various supports such as alumina, silica shows good thionating property with increase in yield. Use of polymer supported and *in situ* generated thionating reagent is another advance in this field.

The use of ionic liquids and solid supports to develop efficient and environmentally friendly 'GREEN' thionating reagent is still unexplored. Though there has been an extensive global development in this field, this area of chemistry is still in the infancy stage and therefore, both basic research and applied work in development of thionation methods for synthesis of organosulfur compounds is essential.

References

[1] E. Block. *Reactions of organosulfur compounds*, Academic Press, New York (1978).
[2] R.J. Cremlyn. *An introduction to organosulfur chemistry*, John Wiley and Son's, New York (1996).
[3] E. Block. *Angew. Chem. Int. Ed. Engl.*, **31**, 1135 (1992).
[4] A. Senning. *Sulfur Rep.*, **24**, 191 (2003).
[5] D. Brillon. *Sulfur Rep.*, **12**, 297 (1992).
[6] U. Schmidt, A. Luttringhaus, H. Trefzger. *Justus Liebigs Ann. Chem.*, **631**, 129 (1960).
[7] B.S. Pedersen, S. Scheibye, N.H. Nilsson, S.O. Lawesson. *Bull. Soc. Chem. Belg.*, **87**, 223 (1978).
[8] B.S. Pedersen, S.O. Lawesson. *Tetrahedron*, **35**, 2433 (1979).
[9] M.P. Cava, M.I. Levinson. *Tetrahedron*, **41**, 5061 (1985).
[10] A.W. Hofmann, S. Gabriel. *Chem. Ber*., **25**, 1578 (1892).
[11] R.N. Hurd. *Chem. Rev.*, **61**, 45 (1961).
[12] V. Polshettiwar. *Synlett*, 2245 (2004).
[13] A. Sudalai, S. Kanagasabapathy, B.C. Benicewicz. *Org. Lett.*, **2**, 3213 (2000).
[14] J. Romanski, G. Mloston. *Synthesis*, 1355 (2002).
[15] E.E. Artyukhova, L.D. Patsenker. *Ukrainskii Khimicheskii Zhurnal*, **70**, 42 (2004).
[16] S.S. Rao, K.S. Chowdary, A. Prashant, V.S.H. Krishnan. *Syn. Comm.*, **31**, 3469 (2001).
[17] E.M. Osika, W.G. Brouwer. *US Patent*: US 2005054860 A1 20050310 (2005).
[18] A. Yu. Egorova, V.A. Sedavkina, N.A. Morozova. *Chem. Heterocyclic Comp.*, **35**, 41 (1999).
[19] H.G. Schmarr, W. Eisenreich, K.H. Engel. *J. Agri. Food Chem*., **49**, 5923 (2001).
[20] E.U. Mughal, A. Hasan, L. Rasheed. *Heterocyclic Comm.*, **11**, 445 (2005).
[21] A. Corsaro, U. Chiacchio, G. Gumina, V. Pistara. *Sulfur Lett*., **19**, 235 (1996).
[22] F. Turksoy, J.D. Wallis, U. Tunca, T. Ozturk. *Tetrahedron*, **59**, 8107 (2003).
[23] M.G. Marei. *Phosphorus, Sulfur, Silicon Rel. Elem*., **81**, 101 (1993).
[24] H. Paulussen, H. Haitjema, A.R. Van, P. Mylle, P. Adriaensens, J. Gelan, D. Vanderzande. *Polymer*, **41**, 3121 (2000).
[25] W. Zhang, Y. Henry. *Synlett*, 1129 (2001).
[26] J.-D. Charrier, C. Landreau, D. Deniaud, F. Reliquet, A. Reliquet, J.C. Meslin. *Tetrahedron*, **57**, 4195 (2001).
[27] L.S. Boulos, I.T. Hennawy, M.H.N. Arsanious. *Heteroatom Chem.*, **5**, 30 (1994).
[28] M.G. Marei. *Afinidad*, **50**, 55 (1993).
[29] M.G. Marei, M.M. Mishrikey. *Phosphorus, Sulfur, Silicon Rel. Elem*., **73**, 229 (1992).
[30] I.H. Cho, M.Y. Chae, Y.H. Kim, K.J. Yeon, C.S. Lyu, J.H. Kim, S.H. Jung, S.W. Park, H.C. Ryu, J.Y. Noh, H.J. Park, J.E. Park, Y.M. Chung. *World Patent* : WO 2005051941 A1 20050609 (2005).
[31] A.G. Belyuga, V.S. Brovarets, B.S. Drach. *Russ. J. Gen. Chem*., **74**, 1418 (2004).
[32] P. Hradil, J. Hromas, J. Korner. *Czechoslovakia Patent*: CS 275533 B2 19920219 (1992).
[33] A.F. El-Farargy, M.G. Assy, M.M. Hassanien. *Pharmazie*, **48**, 109 (1993).
[34] T. Janosik, J. Bergman, B. Stensland, C. Stalhandske. *J. Chem. Soc., Perkin Transactions*, **1**, 330 (2002).
[35] H.S. Bhavana, B.J. Ghiya. *Ind. J. Heter. Chem.*, **2**, 133 (1992).
[36] D. Brillon, G. Sauve, Z. Boulos, B. Di Belleau. *World Patent* : WO 9101976 A1 19910221 (1991).
[37] C.E. McKenna, Z. Li *World Patent* : WO 2000066598 A1 20001109 (2000).
[38] V.I. Savran, V.V. Andronnikov. *Russian Patent* : RU 2245339 C2 20050127 (2005).
[39] V.A. Loskutov. *Russ. J. Org. Chem*., **36**, 528 (2000).
[40] W. Jiang, Q.L. Wang, Y.D. Ma, B.J. Zuo, L. Wang. *Chin. Chem. Lett*. **8**, 381 (1997).
[41] O.I. Kolodyazhnyi, S. Sheiko, I. Neda, R. Schmutzler. *Russ. J. Gen. Chem*., **68**, 1157 (1998).
[42] C. Holzner, O. Schlak, R. Grizan, J. Jezierski. *European Patent*: EP 723968 A2 19960731 (1996).
[43] E.J. Griffith, T.M. Ngo. *World Patent*: WO 9526357 A1 19951005 (1995).
[44] C. O-Yang, D.M. Rotstein, S.S. Labadie, K.A.M. Walker. *Synlett*, 655 (1995).
[45] M. Jesberger, T.P. Davis, L. Barner. *Synthesis*, 1929 (2003).

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[46] W. Przychodzen. *Eur. J. Org. Chem*., 2002 (2005).
[47] L. Valette, S. Poulain, X. Fernandez, L. Lizzani-Cuvelier. *J. Sulfur Chem.*, **26**, 155 (2005).
[48] L. Mendez, C.M.L. Delpiccolo, E.G. Mata. *Synlett*, 1563 (2005).
[49] A. Levai, J. Jeko. *J. Hetero. Chem*., **42**, 739 (2005).
[50] A.K. Mohanakrishnan, P. Amaladass. *Tetrahedron Lett*., **46**, 4225 (2005).
[51] T. Nishio, Y. Kodama, Y. Tsurumi. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **180**, 1449 (2005).
[52] Y. Kodama, M. Ori, T. Nishio. *Helvetica Chimica Acta*, **88**, 187 (2005).
[53] N.R. Mohamed, G.A. Elmegeed, H.A. Abd-ElMalek, M. Younis. Steroids, **70**, 131 (2005).
[54] N.R. Mohamed, G.A. Elmegeed, H.A. Abd-ElMalek, M. Younis. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **178**, 2003 (2003).
[55] M. Altamura, G. Balacco, A. Giolitti, A. Guidi, R. Patacchini, A.R. Renzetti, A. Triolo, C.A. Maggi. *Lett. Drug Desi. Disco*., **1**, 285 (2004).
[56] F. Peyrane, J.L. Fourrey, P. Clivio. *Chem. Comm*., 736 (2003).
[57] W. Przychodzen. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **179**, 1621 (2004).
[58] G. Mehta, V. Gagliardini, C. Schaefer, R. Gleiter. *Org. Lett*., **6**, 1617 (2004).
[59] S.K.D. Chowdhury, M. Sarkar, A. Chatterjee, K.K. Mahalanabis. *Ind. J. Chem. B*, **42**, 2563 (2003).
[60] Y. Ono, Y. Sugihara, A. Ishii, J. Nakayama. *J. Am. Chem. Soc*., **125**, 12114 (2003).
[61] D. Ach, V. Reboul, P. Metzner. *Eur. J. Org. Chem*., 3398 (2003).
[62] J.J. Filippi, X. Fernandez, L. Lizzani-Cuvelier, A.M. Loiseau. *Tetrahedron Lett*., **44**, 6647 (2003).
[63] M. Ben Mosbah, H. Chouaib, M. Kossentini, M. Salem. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **178**, 1433 (2003).
[64] S.J. Coats, J.S. Link, D.J. Hlasta. *Org. Lett*., **5**, 721 (2003).
[65] A. Ishii, R. Yamashita, M. Saito, J. Nakayama. *J. Org. Chem*., **68**, 1555 (2003).
[66] D. Brayton, F.E. Jacobsen, S.M. Cohen, P.J. Farmer. *Chem. Comm*., 206 (2006).
[67] A. Degl'Innocenti, A. Capperucci, G. Castagnoli, I. Malesci. *Synlett*, 1965 (2005).
[68] T.J. Curphey *World Patent* : WO 2002026909 A1 20020404 (2002).
[69] T.J. Curphey. *J. Org. Chem*., **67**, 6461 (2002).
[70] T.J. Curphey. *Tetrahedron Lett*., **43**, 371 (2002).
[71] T.J. Curphey. *Tetrahedron Lett*., **41**, 9963 (2000).
[72] V. Polshettiwar, M. Nivsarkar, D. Pardashani, M.P. Kaushik. *J. Chem. Res.*, 474 (2004).
[73] M. Nivsarkar, A.K. Gupta, M.P. Kaushik. *Tetrahedron Lett*., **45**, 6863 (2004).
[74] V. Polshettiwar, M.P. Kaushik. *Tetrahedron Lett*., **45**, 6255 (2004).
[75] V. Polshettiwar, M.P. Kaushik. *Tetrahedron Lett*., **47**, 2315 (2006).
[76] C. Bodea, I. Silberg. *Advances in Heterocyclic Chemistry*, Vol. 9, A.R. Katrizky, A.J. Boulton (Eds.), p. 321, Academic Press, London (1968).
[77] L.K. Landquist. *Comprehensive Heterocyclic Chemistry*, Vol. 4, P.G. Sammes (Ed.), p. 1102, Pergamon Press, Oxford (1978).
[78] G. Boyer, F. Chatel, J.P. Galy. *ARKIVOC*, **1**, 563 (2000).
[79] F. Chatel, S. Morel, G. Boyer, J.P. Galy. *Heterocycles*, **53**, 2535 (2000).
[80] S. Morel, F. Chatel, G. Boyer, J.P. Galy. *J. Chem. Res*., 4 (1998).
[81] G. Boyer, J.P. Galy, J. Barbe. *Heterocycles*, **41**, 487 (1995).
[82] P. Lopez-Alvarado, C. Avendano, J.C. Menendez. *Heterocycles*, **32**, 1003 (1991).
[83] P. Wipf, C. Jenny, H. Heimgartner. *Helvetica Chimica Acta*, **70**, 1001 (1987).
[84] S. Braverman, M. Cherkinsky, L. Kedrova. *Tetrahedron Lett*., **39**, 9259 (1998).
[85] S. Alibert, D. Crestia, F. Dujols, M. Mulliez. *Tetrahedron Lett*., **39**, 8841 (1998).
[86] Y. Hitotsuyanagi, Y. Matsumoto, S. Sasaki, J. Suzuki, K. Takeya, K. Yamaguchi, H. Itokawa. *J. Chem. Soc., Perkin Transactions*, **1**, 1749 (1996).
[87] A.C. Cano, R.A. Toscano, S. Bernes, O.G. Mellado, C. Alvarez-Toledano, H. Rudler. *J. Organometallic Chem*., **496**, 153 (1995).
[88] J. Nieschalk, E. Schaumann. *Liebigs Annalen*, 141 (1996).
[89] T. Strelow, J. Voss, R. Spohnholz, G. Adiwidjaja. *Chem. Ber*, **124**, 1397 (1991).
[90] F. Kazemi, A.R. Kiasat, S. Ebrahimi. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **176**, 135 (2001).
[91] A. Kiasat, F. Kazemi, M. Jardi. *Phosphorus, Sulfur, Silicon, Rel. Elem*., **179**, 1841 (2004).
[92] Z. Zong, Y. Peng, Z. Liu, S. Zhou, L. Wu, X. Wang, X. Wei, C.W. Lee. *Korean J. Chem. Eng.*, **20**, 235 (2003).
[93] C.T. Brain, A. Hallett, S.Y. Ko. *J. Org. Chem*., **62**, 3808 (1997).
[94] C.T. Brain, A. Hallett, S.Y. Ko. *Tetrahedron Lett.*, **39**, 127 (1998).
[95] A.H.M. Elwahy, G.S. Masaret. *J. Heterocyclic Chem.*, **41**, 711 (2004).
[96] M.M. Heravi, G. Rajabzadeh, M. Rahimizadeh, M. Bakavoli, M. Ghassemzadeh. *Synthetic Commun*., **31**, 2231 (2001).
[97] S.V. Ley, A.G. Leach, R.I. Storer. *J. Chem. Soc., Perkin Transactions*, **1**, 358 (2001).
[98] D. Brillon. *Synthetic Commun*., **20**, 3085 (1990).
[99] D. Brillon. *Synthetic Commun*., **22**, 1397 (1992).
[100] P. Ilankumaran, A.R. Ramesha, S. Chandrasekaran. *Tetrahedron Lett*., **36**, 8311 (1995).

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