Tetrahedron Vol. 41, No. 22, pp. 5061 to 5087, 1985
Printed in Great Britain.

0040-4020/85 $5.00 + .00
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 192

THIONATION REACTIONS OF LAWESSON'S REAGENTS

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(*Received in USA* 15 *October* 1984)

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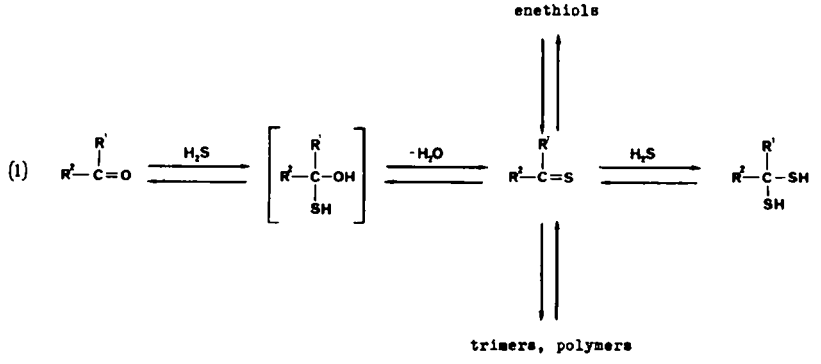
1. INTRODUCTION

The chemical conversion of carbonyl to thiocarbonyl compounds has been an area of interest to synthetic organic chemists for over a century. The use of phosphorus pentasulfide as a reagent for effecting this transformation has been the subject of continued investigation since it was first reported in 1869 by Henry,[1] and by Wislicenus.[2] The usual procedure, which involves boiling toluene, xylene or pyridine as solvent, normally requires a large excess of reagent and long reaction times, and results in quite variable yields.[3–6] A recent investigation has shown that the reaction of carbonyl compounds with phosphorus pentasulfide can be carried out advantageously at 30° in polar solvents such as acetonitrile, tetrahydrofuran, or diglyme, and in the presence of a base catalyst.[7a,b]

Attempts to synthesize thioketones or thioaldehydes by reaction of the corresponding carbonyl compounds with hydrogen sulfide, usually in the presence of an acid catalyst, have been made since the end of the last century, but until recently with only limited success. Very often the products obtained were not the expected thiocarbonyl compounds, but rather their cyclic trimers, the corresponding gem-dithiols, or simply polymeric materials.[3–6,8]



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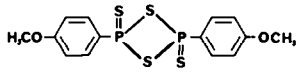
Recent work has extended the utility of this reaction, which is critically dependent on temperature, reaction time, solvent, and substrate. Thus, a large number of aliphatic, unsaturated and aromatic thioketones have been obtained by this method, the reactions being performed in ethanol at -80 to $-55°$.[9,10]

In the search for new, useful and general thionation reagents, O,O-diethyldithiophosphonic acid,[11] boron sulfide,[12] silicon disulfide,[13] and elemental sulfur in HMPA[14] have found application as alternatives to P_2S_5. Most recently, investigations of the chemistry of 2,4-bis(*p*-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide **1** indicate that it is a superior reagent for the conversion of a wide variety of carbonyl to thiocarbonyl compounds.



1

The first detailed report on the synthesis of arylthionophosphine sulfides such as **1a–f** dates back to 1956, when Lecher *et al.* described the reaction of phosphorus pentasulfide with a number of aromatic substrates at elevated temperatures.[15] The crystalline products, isolated in varying yields, were assigned the dithiadiphosphetane structure based upon analyses and molecular weight determinations (Table 1).[15,16]

Subsequent reports of new aryl analogs have appeared only sporadically,[17,18] and the chemistry of these compounds received no further attention except in the patent literature as lubricating oil additives.[19,20]

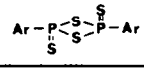
In 1967, Hoffman and Schumacher reported in a brief communication that the action of **1** in acetonitrile effected the conversion of benzophenone to thiobenzophenone in modest yield.[21] The potential of this reagent remained unexplored until 1978 when Lawesson and co-workers initiated a systematic study of the use of this compound, now popularly referred to as Lawesson's reagent.

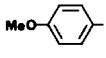
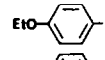
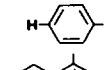
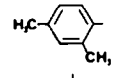
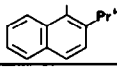
The first advantage of Lawesson's reagent is that it is prepared easily and safely by the reaction of phosphorus pentasulfide with refluxing anisole.[15,22a] The second is that it reacts in nearly equimolar proportions with a wide range of carbonyl compounds to give, in most cases, almost quantitative yields of easily purified products.

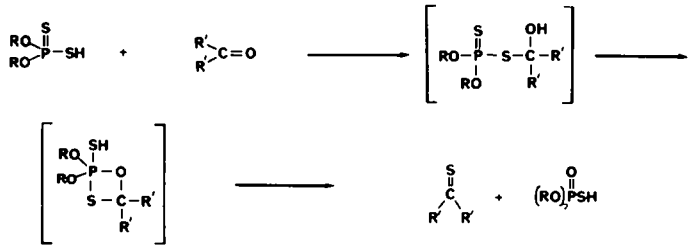
2. PREPARATION OF 1[22a]

Anisole and P_4S_{10} in the molar ratio of 10:1 were agitated and heated to reflux. Moisture was strictly excluded. The reaction mixture was maintained at 155° for 6 hr, during which time all of the solid dissolved, accompanied by considerable evolution of hydrogen sulfide. On cooling, the bulk of the

Table 1. Aryl thionophosphine sulfides from aromatic compounds and phosphorus pentasulfide



Product number	Ar	Yield (%)	mp °C	Reference
1a		80	228	15
1b		68	219-24	15
1c		65	203-15	15
1d		42	-	15
1e		48	-	15
1f		10	-	15



Scheme 1.

thionophosphine sulfide crystallized. The precipitate was filtered off, washed with 50:50 methylene chloride/ether, and dried *in vacuo* at room temperature; yield: 80%; m.p. 228–229.5°.

As noted first by Lecher *et al.*,[15] and later by Lawesson *et al.*,[14] reagent **1** is not stable indefinitely in solution at temperatures over 110°, but slowly undergoes polymerization or other changes. It follows that during its preparation heating should not be continued after H_2S evolution has ceased.

As can be seen from the results tabulated in the following sections, Lawesson's reagent ("LR") is rapidly displacing previously used thionation reagents, both because of its convenience and the excellent results which it usually gives.

3. MECHANISM OF THE THIONATION REACTION

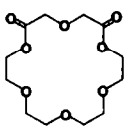
There has been little speculation as to the mechanism of the reaction of Lawesson's reagent with carbonyl compounds. Scheeren and co-workers, and recently Panda and co-workers have suggested that the reactions of phosphorus pentasulfide actually involve a highly polar intermediate, and have successfully correlated reactivity in thionation reactions to solvent polarity.[7]

In the reaction of the related O,O-dialkyldithiophosphoric acids with ketones and aldehydes, Oae formulated a pentacoordinated phosphorus intermediate, as in the Wittig reaction, resulting from the addition of the mercapto function to the carbonyl group (Scheme 1).[11]

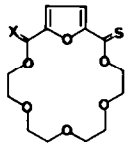
This mechanism might be logically extended to the reaction of **1** since it has been demonstrated that a P—SH group is not necessary in order to produce thiocarboxamides from carboxamides. For example, it has been shown that thiophosphoryl trichloride and N,N,N'N'-tetramethyldiamidothiophosphoryl chloride react with carboxamides to give thiocarboxamides in high yield.[23]

However, the alternate possibility of an initial attack by the carbonyl oxygen on phosphorus must also be considered in these reactions. It seems likely that a highly reactive dithiophosphine ylide, rather than Lawesson's reagent itself, may be the active thionating agent (Scheme 2). Based on ^{31}P spectroscopy of **1** in solution, Lawesson has suggested that such a dipolar species may be present in low concentration.[25] As shown in Scheme 2, two possible mechanisms may be envisioned, both involving Wittig-type intermediates.[26]

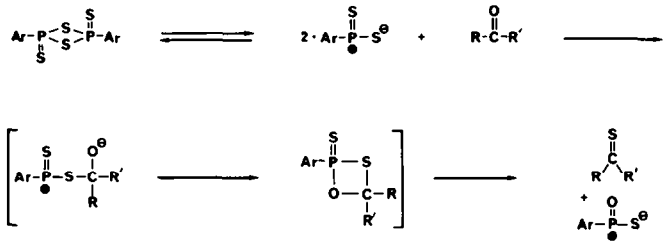
In corroboration of the latter proposal, Baxter and Bradshaw have reported that compounds with electron-withdrawing substituents conjugated with an ester carbonyl (cf. methyl *p*-nitrobenzoate, methyl picolinate) failed to react with **1**, while conjugated electron-donating groups increased the rate of the reaction (cf. methyl *p*-methoxybenzoate, methyl furoate).[27] Furthermore, esters containing an ether functionality were found to be difficult substrates to thionate (cf. diethyl diglycolate, *β*-methoxyethyl benzoate).[27] This was attributed to competition between the carbonyl oxygen and the more basic ether oxygen for the electrophilic phosphorus. In concurrence with this observation, it was noted that the simple crown ether-diester **2** failed to undergo thionation. The more reactive furano crown ether-diester **3** was, however, thionated in good yield (83%) to give dithiono crown ether-diester **4**, as a yellow solid.[27]



2

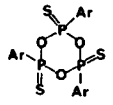


3 x=O
4 x=S



Scheme 2.

Lawesson's investigation of reaction stoichiometry has revealed that, in facile reactions proceeding at low temperature (i.e. little loss of **1** through decomposition), a ratio of 0.5 : 1 reagent/reactant yields near quantitative thionation with attendant formation of trimer **5**, isolated as a white crystalline powder of low solubility.[28] This would appear to lend credibility to the proposed betaine mechanism.[29]

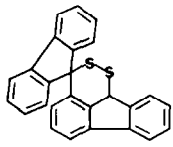


5

4. REACTIONS OF KETONES

Aromatic and aliphatic ketones react smoothly with LR in anhydrous benzene or toluene at reflux to give, in most cases, the corresponding thioketones. From Table 2 it is seen that the yields are usually quite high and that substituents like Br, NO_2, and $N(CH_3)_2$ do not lead to side products (Table 2, entries 3, 4 and 6).[22a] In the case of Michler's ketone, no reaction was observed at the dimethylamino group, probably because of delocalization of the lone pair electrons of the nitrogen atoms (Table 2, entry 6).[22a] This method for the preparation of the thione analog of Michler's ketone is much more convenient than the earlier hazardous procedure: thiolysis of the carbonyl in anhydrous HF.[30]

Lawesson's reagent is, in most cases, the reagent of choice when preparing pyranthiones from pyranones. Xanthone (Table 2, entry 14) yields xanthione quantitatively upon treatment with LR at 80°. Benzanthrone (Table 2, entry 15), which was earlier incorrectly reported to dimerize on thionation, is converted in 90% yield to monomeric thiobenzanthrone.[22,31] The reaction of fluorenone (Table 2, entry 16) with LR at 80° leads to the formation of the highly labile thiofluorenone, which reacts further on standing to give a 55% yield of the yellow thiofluorenone dimer **6**, the structure of which was determined by X-ray diffraction methods.[31]

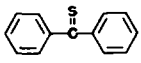
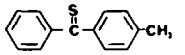
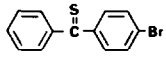
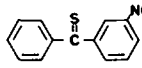
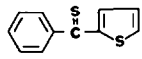
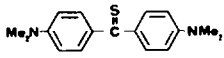
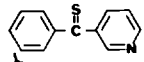
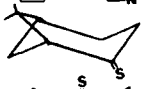
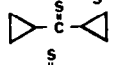
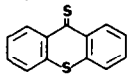
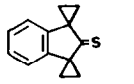
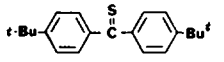
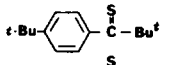
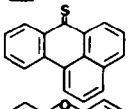
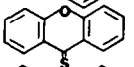
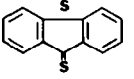


6

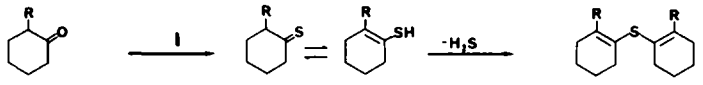
The lower stabilization of the thiocarbonyl group as compared with the carbonyl group is characteristically reflected in the more pronounced tendency of thiocarbonyl compounds to undergo tautomeric change. Thus, even simple aliphatic thioketones, in which the necessary α-hydrogen atom does not belong to a methyl group, in reality exist as mixtures of tautomeric thioketone and enethiol forms, these being separable by glpc.[15] Not surprising then is the reaction of **1** with dibenzyl ketone which yields the corresponding enethiol as a colorless oil. The ^{13}C-NMR shift for the enethiol carbon was observed at δ 175.7, comparing favorably with reported values, and sufficiently upfield from the typical thiocarbonyl shift range of δ 210–240.[22a]

2-Methylcyclohexanone and 2-phenylcyclohexanone (**7a, b**) react with LR at 80° within 3 hr to form the enethiols (**8a, b**) of the corresponding ketones. On standing for several days the sulfides **9a** and **b** are

Table 2. Thioketones from ketones and Lawesson's reagent, 1

Entry	Thioketone	Yield(%)	mp °C	Reference
1		98	53	22
2		95	--	22
3		98	--	22
4		96	--	22
5		97	--	22
6		92	202	22
7		32	--	22
8		91	142	22
9		83	--	22
10		95	168	22
11		85	--	32
12		22	--	32
13		30	--	32
14		90	132	31
15		94	157	31
16		71	75	31

formed, presumably by attack of the enethiol on a thioketone tautomer followed by loss of hydrogen sulfide.[31]

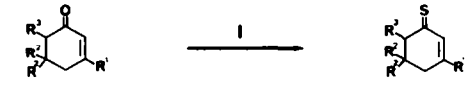


7a R=Me
b R=Ph

8 a,b

9 a,b

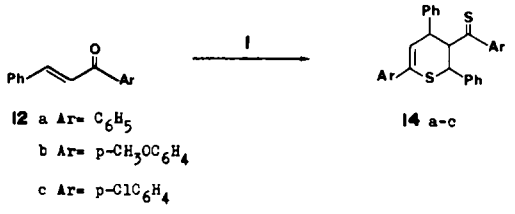
The 2-cycloalkenethiones, **11a–c**, were obtained in good yields from the corresponding ketones and LR, but only the vinylogous dithioester **11c** was stable upon standing in the cold.[31] In contrast, acyclic α,β-unsaturated ketones such as 1,3-diphenyl-2-propen-1-one (chalcone) (**12a–c**) and 2-



10	R^1	R^2	R^3
a	Me	H	H
b	Me	H	Pr^i
c	SPh	Me	H

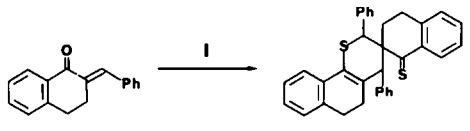
11 a-c

phenylmethylene-1-tetralone (**13**) gave on reaction with **1** the corresponding thione dimers **14a–c** and **15**.[33]



12 a Ar= C_6H_5
b Ar= p-$CH_3OC_6H_4$
c Ar= p-ClC_6H_4

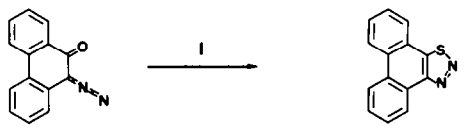
14 a-c



13 **15**

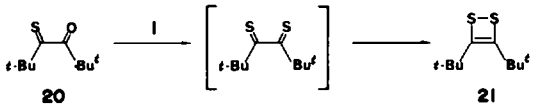
Lawesson's reagent has been found to react with the cyclic *cis*-diazoketones **16** and **17** yielding the 1,2,3-thiadiazoles **18** and **19**, presumably via cyclization of an unstable 1,2-thiodiazoketone intermediate. Conformationally unrestricted diazoketones did not give thiadiazoles with **1**, but rather gave complex unresolved mixtures.[34]

16 **18**



17 **19**

While dithione systems are exceedingly rare and have usually been prepared by indirect means, Kope and Voss have reported the use of **1** in the synthesis of 3,4-di-t-butyl-1,2-dithiete (**21**), the valence isomer of a 1,2-dithione. This was prepared by the simple reaction of the 2,2,5,5-tetramethyl-4-thioxohexan-3-one (**20**) with **1** in refluxing toluene, resulting in a 45% yield of **21**.[35]



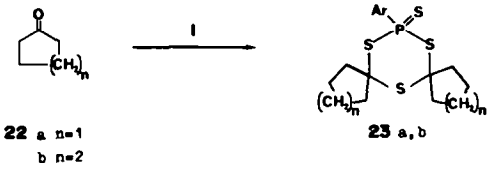
20 **21**

5. REACTIONS OF KETONES RESULTING IN P—S INCORPORATION

As mentioned previously, the mechanism of thionation proposed for Lawesson's reagent involves, at some point, attack of nucleophilic oxygen on phosphorus. In fact, the entire family of substituted dithiadiphosphetane disulfides $(RP(S)S)_2$ readily undergo nucleophilic attack on phosphorus by Grignard reagents,[36–40] amines,[41–43] alkoxides,[23,44] and hydrazones[45,46] to yield dithiophosphinic acids, phosphonamidodithioates, dithiophosphonates, and diazaphospholines, respectively. In light of this reactivity, it is not unreasonable to expect the incorporation of a thiophosphine ylide to be a competing side reaction in the conversion of carbonyls.

For example, cyclohexanone and cyclopentanone (**22a, b**) react with LR at 80° in toluene to give the heretofore unknown 1,3,5,2-trithiaphosphorins **23a** and **b** in 50–60% yield. The formation of these products is assumed to involve thionation of **22a** and **b** to the corresponding cycloalkanethiones which

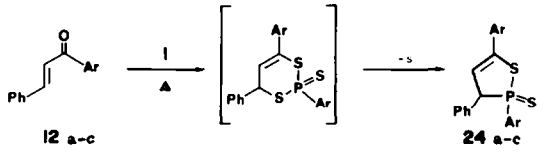
are known to trimerize within a few hours. However, no trimer could be isolated from these reactions.[31]



22 a n=1
b n=2

23 a, b

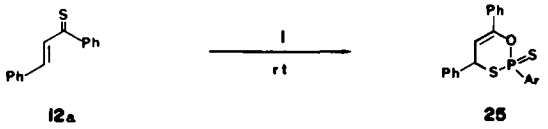
Kametani *et al.* reported that the treatment of substituted chalcones **12a–c** with excess of **1** at 140° in xylene led, presumably through the thioketone followed by loss of sulfur, to phosphorus heterocycles **24a–c**.[33] Simultaneously, Lawesson and co-workers described the isolation of a product **25** which they describe as the 1,4-adduct of **1** to chalcone **12a** at ambient temperature in acetonitrile.[31]



12 a-c

24 a-c

Finally, α-hydroxy and α-amino ketones were found to react with **1** to give 5-membered phosphorus heterocycles (see Section 14).[31]



12a

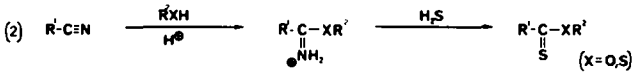
25

6. REACTIONS OF ESTERS AND LACTONES

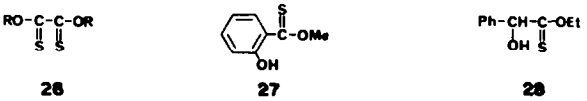
The synthesis of thiono and dithio esters and lactones has been of growing interest over the past few years due to their altered reactivity in relation to their oxygen analogs.[47]

Historically, thiono and dithio esters and lactones have been prepared using phosphorus pentasulfide as discussed earlier. This method is applicable to the preparation of both aliphatic and aromatic thiono and dithio esters, but these reactions generally require high temperatures and result in low yields due to significant side reactions.[7a,48]

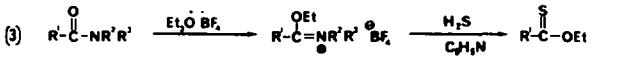
However, the most important method of preparing thiono and dithio esters depends upon the reactivity of imino esters and imino thiolo esters towards hydrogen sulfide (eqn (2)).[49] This method has been used with some success for the preparation of simple aliphatic and aromatic thiono and dithio esters,[49] dithionoxalic esters **26**,[50] thio analogs of malonic esters,[51] and certain α-hydroxy thiono esters **27** and **28**.[52] A variation of this method is based on the use of an N,N-disubstituted amide (eqn (3)) as the starting material, this being converted into a thiono ester by successive reactions with triethyloxonium tetrafluoroborate and hydrogen sulfide.[53] While Lawesson's reagent may not supplant this important method, it is a strong complement in the arsenal of synthetic methodologies and provides many clear advantages over phosphorus pentasulfide.



(2) (X=O,S)

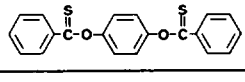


26 27 28



(3)

Table 3. Thionesters from esters and Lawesson's reagent, 1

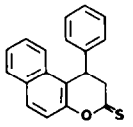
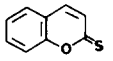
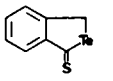
Entry	Thioneater	Yield (%)	mp °C (bp/mmHg)	Reference
1		91	80-85/12	22
2		90	63-5/0.4	22
3		87	110-12/10	22
4		98	112-16/10	22
5		93	105-10/15	22
6		88	115-20/1	22
7		70	41	22
8		92	65/10	22
9		42	167	22b

As demonstrated in Tables 3 and 4, Lawesson's reagent effects the facile conversion of simple aliphatic and aromatic O- and S-substituted esters and lactones to the corresponding thiones in nearly quantitative yields.[14] In addition, α,β-unsaturated O-alkyl esters are converted in moderate yield to the thiocarbonyl compounds (Table 4, entries 7–10).[54]

Table 4. Dithioesters from thiolesters and Lawesson's reagent, 1

Entry	Dithioester	Yield (%)	mp °C (bp/mmHg)	Reference
1		90	64/0.5	54
2		99	83/0.4	22
3		97	74/10	22
4		90	61	22
5		99	160/0.5	22
6		97	104/0.5	22
7		46	60/10	54a
8		72	140/12	"
9		40	68-70	"
10		39	24	"
11		67	174	22b

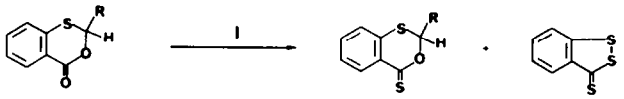
Table 5. Thiolactones from lactones and Lawesson's reagent, 1

Entry	Thiolactone	Yield (%)	mp °C	Reference
1		87	165	55
2		99	45	55
3		69	97	56
4		34	69	56a

For the thionation of lactones (Tables 5 and 6) and thiolesters, 0.6 mol of **1** was sufficient for the total conversion of 1 mol of substrate, but the thionation of normal esters required a molar ratio of at least 1.2 : 1. The reason for the use of an excess of **1** is that the reaction time is quite long (approx. 25 hr), giving rise to consumption of **1** in side reactions (conversion to polymers).

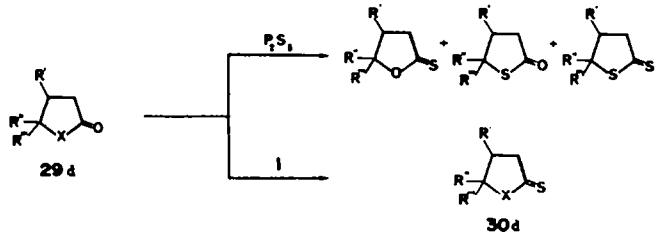
Lawesson's reagent has proven particularly useful for the thionation of lactones, demonstrating its selectivity over phosphorus pentasulfide in the quantitative transformation of dihydro-2(3H)-furanone (**29a**) to the respective thione (Scheme 3).[55]

Similarly, some 3,1-benzoxathian-4-ones **31a** and **b**, were converted to the corresponding 4-thiones **32a** and **b**, where the reaction with phosphorus pentasulfide led in all cases to lower yields and attendant formation of by-product **33** (see Section 13).[57]



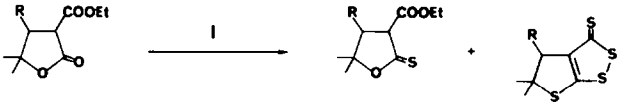
As a consequence of the lower reaction temperature needed for lactones compared to esters, treatment of tetrahydro-2-oxo-3-furancarboxylic acid ethyl ester (**34**) with **1** resulted in the corresponding 2-thione (**35**) in high yield, with only small quantities of by-product **36** (see Section 13).[55]

Table 6. Five-membered thiolactones from lactones and Lawesson's reagent, 1 (Scheme 3)



Scheme 3.

	X	R'	R''	R'''	Yield(%)	Reference
30						
a	O	H	H	H	98	55
b	O	CH	CH_3	CH_3	90	"
c	O	C_3H_7	CH_3	CH_3	66	"
d	O	H	CH_3	H	97	"
e	S	H	H	H	100	"

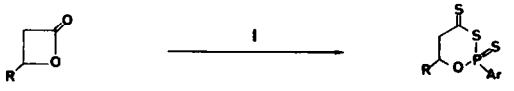


34 a R= C_3H_7
b R= CH_2Ph

35 a, b **36** a, b

7. COMPLEX REACTIONS OF LABILE LACTONES

Certain highly reactive substrates undergo apparent ring opening reactions when subjected to **1**. For instance, Lawesson observed that the strained α-propiolactones **37a** and **b**, on reaction with **1** in toluene at 80° were transformed to the 1,2,3-oxathiaphosphorinan-4-one-2-sulfides **38a** and **b** in high yields.[59] An analogous conversion of a strained lactam was first reported by L'Abbe *et al.* (see Section 10).[58]



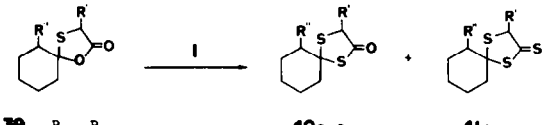
37 a R= H
b R= CH_3

38 a, b

The 6-membered ring products appear to arise from acyl–oxygen fission, perhaps induced by attack of the nucleophilic thiophosphine ylide sulfur. These products remain stable at elevated temperatures and do not expel **1** in ring contractive reactions.

By means of a different ring fission reaction, certain labile thionolactones are converted to thiololactones. The first example of such a rearrangement was identified by Prey and Kondler in the thermally induced transformation of 2-thiophthalide to 1-thiophthalide.[60]

When the 1-oxa-4-thiaspiro[4,5]decan-2-ones, **39a–c**, were reacted with **1**, 1,4-dithiaspiro[4,5]decan-2-ones, **40a–c** and -2-thiones, **41a–c**, were isolated in low to moderate yields.[55]

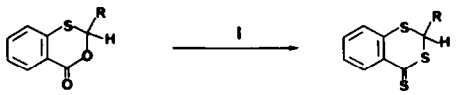


39	R	R
a	H	H
b	CH_3	H
c	H	CH_3

40a-c **41**a-c

In contrast to the reactions previously mentioned, it was not possible to isolate any thionolactone, implying quantitative rearrangement to the thiololactone, a portion of which was subsequently transformed into the dithiolactone. Treatment of **40** with **1** yielded **41** as the only product.[55] This rearrangement reaction may involve formation of a charge separated or diradical species in the course of carbon–oxygen bond fission. Such a mechanism would explain the facility of this rearrangement in systems capable of stabilizing the incipient radical or carbocation.

The 3,1-benzoxathian-4-ones **42a** and **b** react with **1** to give the ring thiolated thiones **43a** and **b**.[57]



42 a R= Ph
b R= p-NO_2-Ph

43 a, b

This type of rearrangement explains, in part, the formation of **36** as a side product in the reaction of **34** with **1**. The thionolactone undergoes a ring-opening, ring-closure O—S-exchange, and subsequent thionation of the lactone carbonyl and ester carbonyl, eventually leads to **36** (see also Section 13).[55]

8. REACTIONS OF AMIDES

In contrast to many other types of thiocarbonyl compounds, thioamides and thiolactams are generally very stable materials. They are, however, labile to the extent that they undergo a variety of reactions and have, because of the diversity of their chemical properties, found wide application in technology, agriculture, medicine, and not least of all, in synthetic practice. The properties and chemistry of thioamides have been reviewed frequently.[61–64]

Introduced as early as 1878 by Hoffman, the thionation of amides by phosphorus pentasulfide has been the most utilized method for preparing thioamides.[61–64] This is a direct reflection of the relatively high thermal stability of these systems, since the thionation conditions are rather drastic.

In many cases an acceptable yield of thioamide depends on specified reaction conditions, the nature of the solvent often constituting a crucial factor. For instance, in the synthesis of simple N-unsubstituted thioamides by phosphorus pentasulfide thionation of the corresponding amides, special care is required in order to avoid considerable decomposition of the thioamides into nitriles and H_2S.[61–63] Additionally, even though this thionation method has proven its applicability to the synthesis of a variety of heterocyclic compounds containing the thioamide moiety, other functional groups in such molecules often suffer adverse side reactions.

In this regard, Lawesson's reagent proves again to be a superior agent for the smooth, selective transformation of aromatic, aliphatic and unsaturated amides, enaminones, and lactams to their corresponding thio-analogs. Tables 7 and 8 demonstrate that variously substituted thioamides have been prepared in high yield with **1**. Nitro substituents are not attacked by LR, and neither dealkylation of ethers nor transformation of primary amides into nitriles is observed.

Some hydroxy- and aminobenzamides were reacted with **1** in HMPA giving moderate to low yields of the corresponding thioamides (Table 8).[28] The potential problem in these reactions is that phenols and anilines are known to react with **1** to give products with new P—O and P—N bonds, respectively (see Section 14). These reactions are apparently suppressed when using HMPA as solvent since HMPA is known to form complexes with hydroxyaromatics and anilines. Lawesson suggests that HMPA acts as a protecting agent for hydroxy and amino groups in these reactions.[28]

Table 7. Thiocarboxamides from amides and Lawesson's reagent, **1**

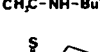
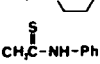
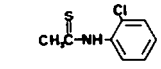
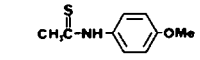
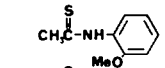
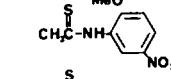
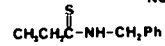
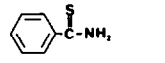
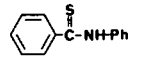
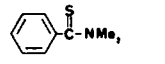
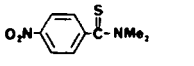
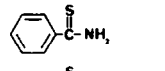
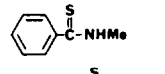
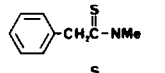
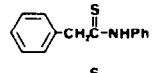
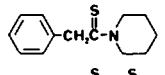
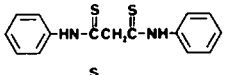
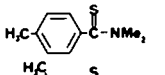
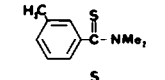
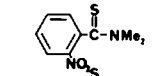
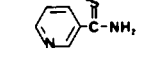
Entry	Thiocarboxamide	Yield (%)	mp °C bp/mmHg	Reference
1		98	95-7/10	28
2		85	139	"
3		96	96-8/0.3	"
4		88	111	"
5		98	98-100/.9	"
6		96	66	"
7		98	90	"
8		98	76	"
9		99	62	"
10		99	131-3	"
11		98	144	"

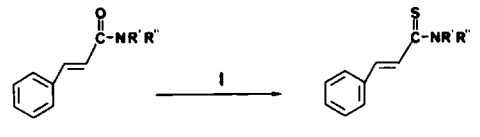
Table 7 (*Contd.*)

Entry	Thiocarboxamides	Yield(%)	mp °C	Reference
12		99	62	28
13		98	116	"
14		98	50	"
15		99	98	"
16		98	46	"
17		92	118	"
18		99	100	"
19		89	--	66
20		90	--	"
21		63	--	"
22		98	--	"
23		99	133-4	28
24		99	87	"
25		75	--	"
26		94	152	"
27		99	52	"
28		99	64	"
29		99	160	"
30		87	191	"

Thioformamides are readily prepared by means of Lawesson's reagent, obviating the time-honored reaction of thioformates with amines.[11,61]

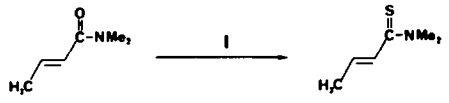
3-Phenyl-2-propenamides **44a–d** react with **1** in benzene at 60° to give the corresponding thioamides **45a–d** in high yields.[54] N,N-Diethyl-2-butenamide (**44c**) reacts exothermically with **1** in 0.5 hr giving the thiocarbonyl product in quantitative yield.[54] In contrast, 2-propenamide and several 2-butenamides react with **1** in HMPA to give phosphorus heterocycles (see Section 14).[54]

Utilizing this new found methodology, Lawesson and co-workers prepared and cataloged the ^{13}C-NMR spectra of nearly 50 tertiary thioamides of formic, acetic, trifluoroacetic, propionic and butyric acids (Table 9). With the aid of extensive double resonance and shift reagent experiments, the chemical shifts were completely assigned and the data compared with that from the analogous amides in order to establish a linear mathematical relationship between the ^{13}C-NMR chemical shifts for the thiocarbonyl of thioamides and the carbonyl of the corresponding amides.[65]



44	R'	R''
a	H	H
b	H	Ph
c	Et	Et
d	Me	p-Me-Ph

46 a-d



9. ENAMINETHIONES

Vinylogous thiocarboxamides (enaminothiones) are important intermediates in the synthesis of various heterocyclic compounds such as thiopyrans[67–69] and thiophenes.[70] However, a simple method for their preparation in good yields and on a large scale has not hitherto been available.[71] Because of the vinylogous effect, enaminones show great similarities to carboxamides and lactams. Several groups have reported the successful reactions of cyclic and non-cyclic 1°, 2° and 3° enaminones with Lawesson's reagent to give enaminothiones in high yields (Table 10). The conversions were best carried out at room temperature in DME or benzene, conditions which minimized product loss

Table 8. Hydroxy-substituted thiobenzamides from hydroxybenzamides and Lawesson's reagent, 1

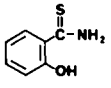
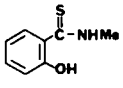
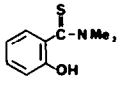
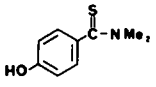
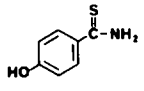
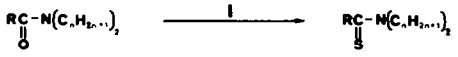
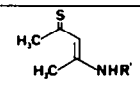
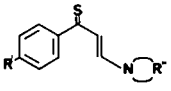
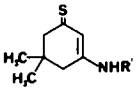
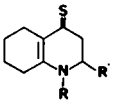
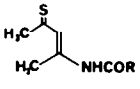
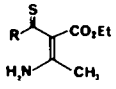
Entry	Thiobenzamide	Yield (%)	mp °C bp/mmHg	Reference
1		70	118	28
2		51	112	"
3		66	135/0.9	"
4		75	163-5	"
5		30	178	"

Table 9. Thioamides from amides and Lawesson's reagent, 1 (physical data not provided)



	R	n
a	H	1-4
b	CH_3	1-4,6,12
c	Et	1-4,6,12
d	Pr^n	1-4,6,12
e	F_3C	1-4,6

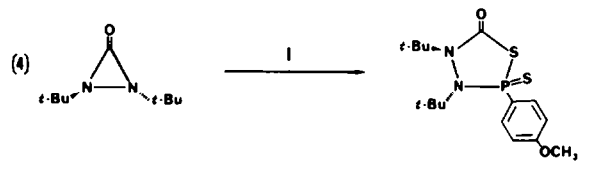
Table 10. Enaminethiones from enaminones and Lawesson's reagent, 1

Enaminethione	R'	R''	Yield (%)	mp °C bp/mmHg	Reference
					
	H	-	74	101-2/0.7	71
	Ph	-	42	45	"
	CH_2Ph	-	60	63	"
	m-tolyl	-	54	48	"
	p-Cl-Ph	-	20	72	"
					
	H	$-(CH_2)_4-$	92	146	70
	OCH_3	"	90	163	73
	Br	"	92	170	73
	H	$-(CH_2)_5-$	87	128	70
	OCH_3	"	81	173	73
	Br	"	87	173	73
					
	Ph	-	58	175	71
	p-Cl-Ph	-	80	170	"
	p-MeO-Ph	-	69	155-6	"
	CH_3	-	64	115	"
					
	Ph	H	95	-	70
	Ph	Me	88	-	"
	p-Cl-Ph	H	70	-	"
					
	Me	-	30	oil	68
	Pr^i	-	90	-	"
	Bu^t	-	70	-	"
	Ph	-	60	70	"
					
	Me	-	65	-	44

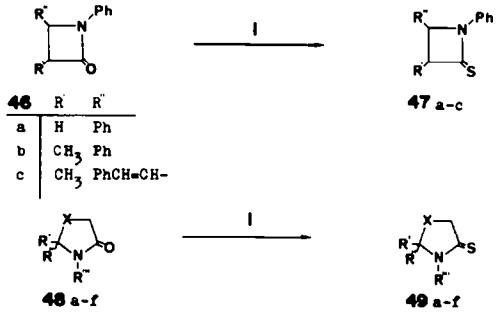
through polymerization.[70,71] Such mild conditions have allowed for selective, high yield thionation of N-acyl enaminones (vinylogous imides) to the N-acyl enaminothiones. At elevated temperatures, the yields of products decreased, yet no thionation of the carboxamide function occurred.[72] The ^{13}C-NMR spectra showed C=S resonances at δ 223–225 and C=O at δ 167–178, clearly indicating that thionation had taken place at the keto group, and that the molecule exists in solution as the enethione.[72]

10. THIOLACTAMS

As previously noted, L'Abbe reported that N,N'-disubstituted aziridinone on reaction with 1 in toluene at 80° was converted to the 1,3,4,2-thiadiazaphosphilidin-5-one-2-sulfide (eqn (4)).[58]



In contrast to the reaction of β-lactones previously detailed, substituted β-lactams **46a–c** react with **1** to yield solely the β-thiolactams **47a–c**.[74] The 5-membered lactams **48a–f**, reacted with **1** to give the corresponding thiolactams, **49a–f**.[74] N-Vinyl-2-pyrrolidinethione (**49b**) was isolated in only 24% yield, however, probably due to polymerization. This compound has been synthesized in 60% yield using



46	R'	R''
a	H	Ph
b	CH_3	Ph
c	CH_3	PhCH=CH-

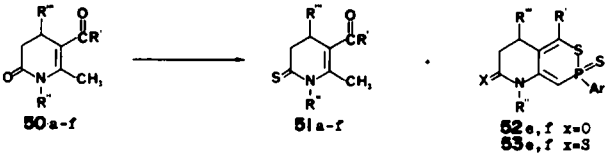
47 a-c

48 a-f

49 a-f

Entry	R'	R''	R'''	X
49a	H	H	H	$-CH_2-$
b	H	H	$-CH\ CH_2$	$-CH_2-$
c	$-(CH_2)_5-$		C_6H_5	-
d	$-(CH_2)_5-$		o-$CH_3OC_6H_4$	S
e	$-(CH_2)_5-$		p-$CH_3OC_6H_4$	S
f	$-(CH_2)_5-$		p-Cl-C_6H_4	S

phosphorus pentasulfide.[74] Some 6-membered lactams, **50a–f**, containing additional carbonyl functionality reacted with **1** in refluxing benzene. When the 3-substituent was an alkoxycarbonyl group, the only products were the thiolactams, **51a–d**. When R = CH_3 (an N-acyl enamine), some quite unexpected thiophosphine heterocycles were isolated (see Section 14).[74]



50 a-f

51 a-f

52 e,f x=O
53 e,f x=S

Entry	R'	R''	R'''
a	OC_2H_5	H	H
b	OC_2H_5	CH_3	H
c	OC_2H_5	H	CH_3
d	O-tBu	H	H
e	CH_3	H	H
f	CH_3	CH_3	H

Shridhar *et al.* reported the successful conversion of 1,4-benzothiazines and 1,4-benzoxazin-3-ones (Table 11) with **1** into the 3-thiones, making particular note of the ease of isolation in comparison to preparations involving phosphorus pentasulfide.[76] Lawesson reported the thionation of 2- and 4-pyridones, the latter of which may be viewed as a dienaminone (Table 12, entries 4 and 5).[28]

Monothio derivatives of cyclic imides have been synthesized with phosphorus pentasulfide and their chemistry has been investigated. In the case of N-unsubstituted compounds only low yields have been obtained. When succinimide and phthalimide were reacted with **1** (molar ratio 1 : 1), in refluxing toluene, the dithioimides were formed in 70–90% yield and less than 30% of the monothioimide could be isolated. The structures of the monothioimides were investigated by ^{13}C-NMR, ^{1}H-NMR, and IR which indicate, surprisingly, that in solution these compounds exist exclusively in the keto form

Table 11. Thiolactams from lactams and Lawesson's reagent, 1

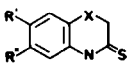
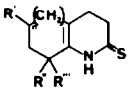
Entry	Thiolactam					Yield	mp °C	Reference
								
			R'	R''	X			
1			H	H	S	99	128	76
2			H	Cl	S	94	206	"
3			H	H	O	92	119	"
4			Cl	H	O	90	195	"
5			H	OCH_3	S	92	162	"
6			H	CH_3	S	93	187	"
								
		n	R'	R''	R'''			
7		1	H	H	H	65	140	75
8		1	Me	H	H	50	112	"
9		1	H	nPr	H	82	--	"
10		0	H	H	H	60	140	"
11		0	Me	Me	Me	69	135	"

Table 12. Thiolactams from lactams and Lawesson's reagent, 1

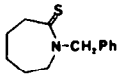
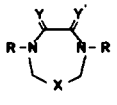
Entry	Thiolactam	Yield (%)	mp °C	Reference
1		82	106	28
2		91	76	"
3		100	181	"
4		63	125-7	"
5		81	180	"

Table 13. Mono- and dithiooxamides from oxamides and Lawesson's reagent, 1



Entry	R	X	Y	Y'
1	Bnz	$-CH_2-$	O	S
2	i-Pr	$-CH_2-$	O	S
3	i-Pr	$-CH_2-$	S	S
4	Bnz	$-CH_2-$	S	S
5	Bnz	$-CMe_2-$	S	S
6	Me	$-CH_2-$	S	S
7	Me	--	S	S
8	H	--	S	S

(no —N=C—XH or —N=C—YH present).

X = O, S
Y = S, S

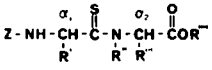
As previously mentioned, α-dithione systems are relatively rare and are not usually produced by obvious routes. Several N,N'-disubstituted 5-, 6-, and 7-membered cyclic oxamides were readily converted to either the mono or dithio analogs in high yields (80–100%) depending upon the quantity of the reagent used (Table 13).[77]

11. ENDOTHIODIPEPTIDE DIESTERS

As previously pointed out, the hierarchy of reactivity of various functionalities with LR allows for selective transformations based upon reaction temperature; lactones and lactams react at 80°, ketones and urethanes at 110°, and acyclic esters react at 130°. This graduated reactivity has proven particularly advantageous for the preparation of thioamides from amides in the presence of urethane or ester functions, combinations found in amino acids and peptides. Lawesson described the conversion of N-benzyloxycarbonyldipeptide esters with **1** in anhydrous benzene at 80° to the N-benzyloxycarbonylendothiodipeptide esters (Table 14), in high yields, and with retention of configuration at chiral centres α_1 and α_2.[78]

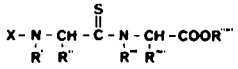
As it is known that **1** reacts with nucleophiles such as amines, alcohols, phenols and thiols, peptides containing such functionalization in their chains require adequate protection. Such a family of N—Z and N—Boc dipeptide benzyl and t-butyl esters with appropriate side chain protection were efficiently converted to the corresponding endothiodipeptides (Table 15).[79]

Table 14. N-Benzyloxycarbonylendothiodipeptide esters from the corresponding dipeptides and Lawesson's reagent, **1**



Entry	R'	R''	R'''	R''''	N-Z-dipeptide ester	N-Z-dithiodipeptide ester	Yield (%)	mp °C	Ref
1	H	H	H	Et	Z-Gly-Gly-OEt	Z-Glyt-Gly-OEt	78	82-84	79
2	H	H	H	Bnz	Z-Gly-Gly-OBnz	Z-Glyt-Gly-OBnz	93	112-14	"
3	H	H	Me	Bnz	Z-Gly-Ala-OBnz	Z-Glyt-Ala-OBnz	97	--	"
4	H	H	CH_2COBz	Bnz	Z-Gly-Asp-OBnz OBnz	Z-Glyt-Asp-OBnz OBnz	98	66-8	"
5	H	$-(CH_2)_3-$		Bnz	Z-Gly-Pro-OBnz	Z-Glyt-Pro-OBnz	91	--	"
6	Me	H	H	Bnz	Z-Ala-Gly-OBnz	Z-Alat-Gly-OBnz	95	--	"

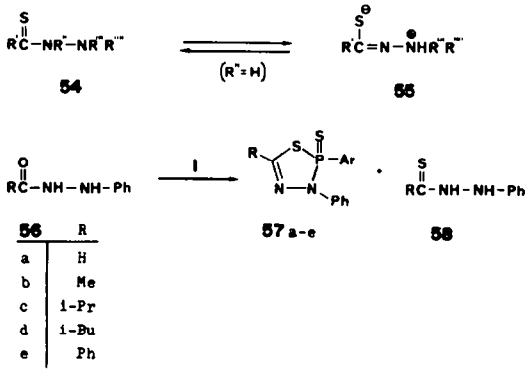
Table 15. N—Z and N—Boc endothiodipeptide esters from the corresponding dipeptides and Lawesson's reagent, **1**



	X	R'	R''	R'''	R''''	-OR'''''	Yield (%)	mp °C	Reference
a	Boc	H	H	H	H	-OBnz	93	114-16	79
b	Boc	H	$-CH_2-OBnz$	H	H	"	99	oil	"
c	Boc	H	$-CH_2-\phi-OBnz$	H	H	"	73	123-4	"
d	Boc	H	$-(CH_2)_2-S-CH_3$	H	H	"	99	oil	"
e	Boc	H	$-CH_2-S-Bnz$	H	H	"	98	oil	"
f	Boc	H		H	H	"	39	oil	"
g	Z	H		H	H	"	67	56-7	"
h	Boc	H	$-(CH_2)_4-NH-Boc$	H	H	"	75	66-9	"
i	Z	H	$-CH_2-\phi$	$-(CH_2)_3-$		$-OBu^t$	69	oil	"
j	Z	$-(CH_2)_3-$		H	Bnz	$-OBu^t$	91	95-6	"

12. REACTIONS OF HYDRAZIDES

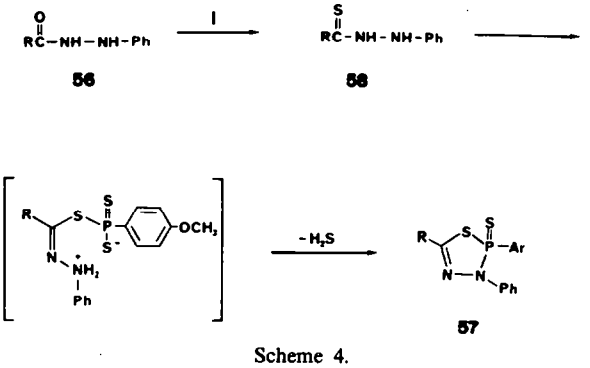
Thiohydrazides are compounds of the general structure **54**. Various methods for the preparation of thiohydrazides are known, e.g. the reactions of dithioacids,[80] dithioesters,[81] or sodium dithioformate with hydrazines[82,83] and reactions of N-thiobenzoyl imidazoles with hydrazines.[84] The preparation of thiohydrazides from hydrazides and phosphorus pentasulfide has been reported in a few cases,[85,86] but the yields are poor (see also a review on thiohydrazides).[87] A particular property of the thiohydrazides (**54**; R^2 = H) is that these compounds may exist alternatively in an isolable tautomeric zwitterionic form **55**, the two forms, (**55**; R^2 = H) and **54**, being interconvertible.[47] Not surprisingly, many hydrazides react with LR to form a dipolar thiohydrazide, which reacts immediately with the thiophosphine ylide to yield a 2,3-dihydro-1,3,4,2-thiadiazaphosphole.[89]



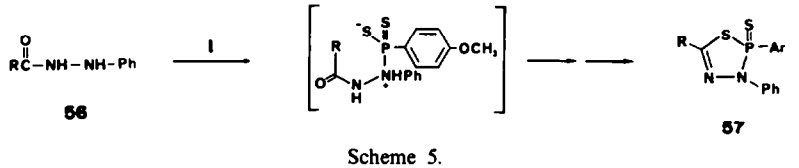
Concerning the mechanism for the formation of the 5-membered heterocyclic ring, different possibilities exist: as a thiohydrazide has in one case been isolated as a component of the product mixture, and since treatment of thiohydrazide **58e** with **1** gave **57** quantitatively, the reaction path in Scheme 4 has been suggested. It is possible that the thiohydrazide reacts through the thiol form as has been proposed recently.[89]

The last step is plausible in view of the fact that salts of the type R—P(S)(NHR')S^- $^+NH_3R$ lose H_2S upon heating to 140° yielding the corresponding diamides.[90] An alternative mechanism (Scheme 5) involves attack of the nucleophilic nitrogen of **56** on **1** giving the zwiterionic intermediate. Subsequent ring closure and elimination of water gives **57**.[88]

4-Methoxy-N'-methyl-N'-phenylbenzohydrazide (**59**), which is unable to give a phosphorus

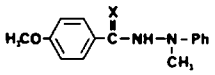


Scheme 4.

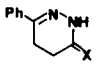


Scheme 5.

heterocycle, was reacted with **1** to give **60** in a quantitative yield, and similarly **61** was then transformed into **62**.[88]

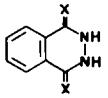


59 x=O
60 x=S



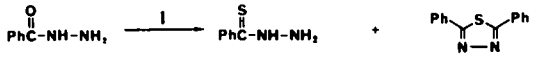
61 x=O
62 x=S

2,3-Dihydrophthalazinedione (phthalhydrazide, **63**) was subjected to reaction with **1** which led to isolation of 2,3-dihydrophthalazinedithione (**64**) in high yield.[91]



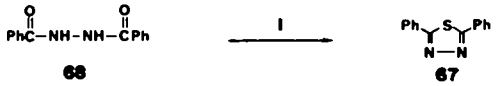
63 x=O
64 x=S

The reaction between **65** and **1** gave **66** in 20% yield as well as 2,5-diphenyl-1,3,4-thiadiazole (**67**) in 9% yield.[88]



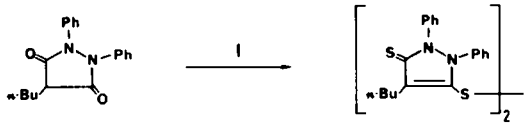
65 **66** **67**

The formation of **67** from **65** would imply an acylation or thioacylation on the nitrogen of **65** or **66**: Lawesson noted that 1,2-dibenzoylhydrazine (**68**) gave **67** on reaction with either phosphorus pentasulfide or **1**.[88]



68 **67**

When 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone) (**69**) was allowed to react with **1** at 80° for 3 hr, 3,3-dithiobis(4-butyl-1,2-diphenyl-5-thioxo-3-pyrazoline) (**70**) was isolated in 85% yield; the structure of this disulfide was confirmed by X-ray crystallography.[88]



69 **70**

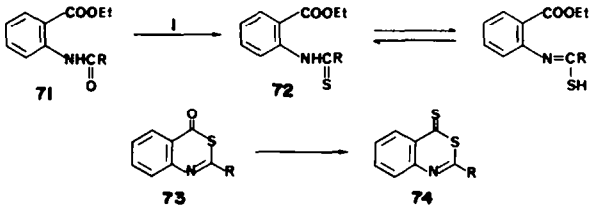
While Lawesson's reagent does not offer a direct route to acyclic thiohydrazides, it provides an advantageous method for preparing 2,3-dihydro-1,3,4,2-thiadiazaphospholes. This novel group of heterocycles has been little explored and is relatively inaccessible by other routes.

The usefulness of Lawesson's reagent as compared to phosphorus pentasulfide has been clearly established in the preceding text in regard to the simple conversion of the carbonyl to the thiocarbonyl moiety. Further, the established hierarchy of reactive functionalities has allowed for selective conversions in multifunctional molecules (i.e. peptides).[78,79] There exist, however, a few subgroups of multifunctional molecules which undergo ring-closure reactions in the course of thionation with **1**, yielding either sulfur or phosphorus–sulfur heterocycles with varying degrees of efficiency. It is appropriate to categorize these new families of noteworthy reactions as they represent convenient routes to several hitherto unavailable types of heterocycles.

13. REACTIONS YIELDING SULFUR HETEROCYCLES

Ethyl 2-(acylamino)benzoates **71a–f** react with **1** in anhydrous benzene at 80° giving a mixture of ethyl 2-thioacylaminobenzoates, **72**, 2-substituted 3,1-benzothiazin-4-ones, **73**, and 2-substituted 3,1-

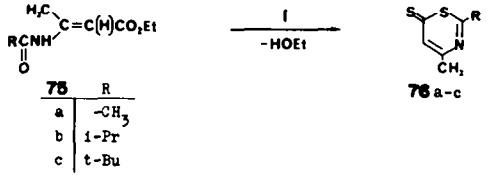
Table 16. 3,1-Benzothiazine-4-thiones from 2-(axylamino)benzoates and Lawesson's reagent, 1



Scheme 6.

Entry	R	Yield (%)	mp °C	Ref.
a	H	20	113	92
b	Me	82	97	"
c	Et	95	64	"
d	Pr^i	99	91	"
e	Bu^t	93	79	"
f	Ph	90	126	"

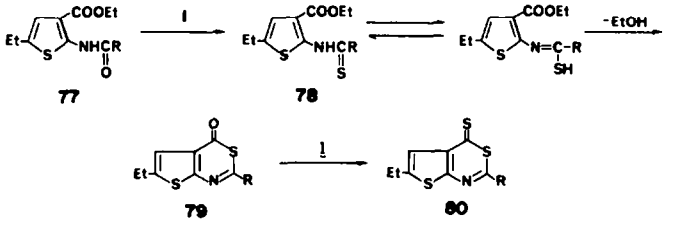
benzothiazine-4-thiones **74** (Scheme 6).[92] However, at elevated temperatures (140°) in xylene the reaction gives the 3,1-benzothiazine-4-thiones as the sole product (Table 16).[92] It has been suggested that the initially produced imidothiol form of **72** undergoes a ring-closure reaction giving **73**, which is subsequently transformed by **1** into **74**.[92] This mechanism is in accord with one proposed by Kerzer[93] and Jepson *et al.*,[94] and accounts for all products isolated. Walter and Bode, on the other hand have suggested that both the amide and ester functions are thionated before ring closure occurs.[95]



75	R
a	$-CH_3$
b	i-Pr
c	t-Bu

Similarly, the acyclic ethyl 3-(acylamino)-2-butenoates **75a–c** on reaction with **1** gave the 2-substituted 4-methyl-1,3-thiazine-6-thiones **76a–c**.[72]

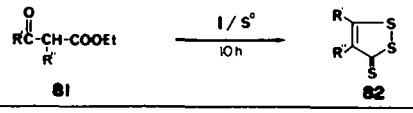
Table 17. Thiazine-4-ones from 2-acylamino-3-thiophenecarboxylates and Lawesson's reagent, 1



Scheme 7.

Entry	R	Yield (%)	mp °C	Ref.
a	H	64	63	96
b	Me	84	81.5	"
c	Et	88	46	"
d	Pr^i	89	44	"
e	Bu^t	76	131	"
f	Ph	71	112.5	"

Table 18. 1,2-Dithiole-3-thiones from 3-oxoesters and Lawesson's reagent, 1



81 82

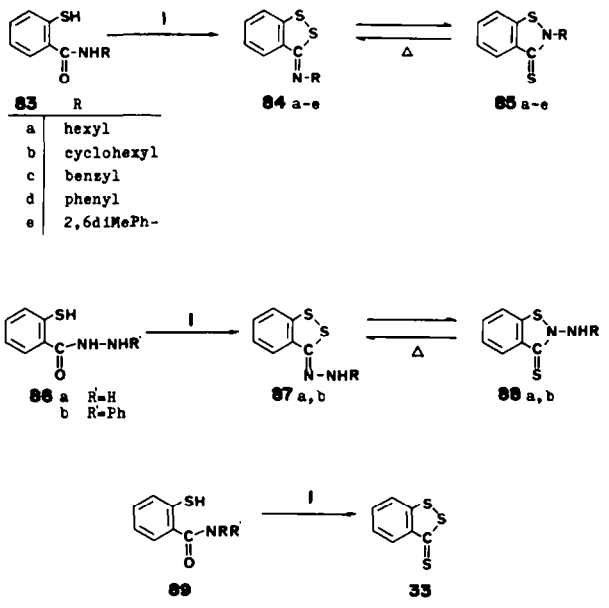
Entry	R'	R''	Yield (%)	mp °C	Ref.
a	$-CH_3$	H	90	33	97
b	$-CH_3$	Pr^i	87	38	"
c	$-CH_2-CH_2-CH_2-CH_2-$		90	102	"
d		H	95	126	"
e		H	96	119	"
f		H	90	116	"
g		H	91	136	"
h		H	92	129	"
i		H	90	114	"

Lawesson also reported that the reaction of **1** with ethyl 2-(acylamino)-5-ethyl-3-thiophenecarboxylates, **77a–f**, led to the formation of a new ring system, 6-ethylthieno(2,3-d)(1,3)thiazine-4-thiones (Table 17). Selective thionation of the amide functionality was accomplished under mild conditions, and the resultant 2-thioacylamino-5-ethyl-3-thiophenecarboxylates, **78a–f**, were transformed in refluxing xylene in the presence of base to the corresponding thiazine-4-ones (Scheme 7).[96]

Furthermore, **79a–f** were easily transformed into **80a–f** by reaction with **1**.[96] Walter and Bode suggest that both the amide and ester functions are thionated prior to ring closure.[95] The preceding body of work substantiates that amides are much more readily thionated than esters.

In a most unusual reaction, unsubstituted and 3-mono-substituted 3-oxo-esters **81a–i** (Table 18) and N-substituted 3-oxo-amides (Table 20), reacted smoothly with **1** in anhydrous toluene at 110° producing the corresponding 3H-1,2-dithiole-3-thione, **82**. Initial studies were conducted using 2 mol of **1** per mol of 3-oxo-ester, and the corresponding heterocycles were isolated in yields of 65–70%.[97] Attempts to optimize the yields of **82** by using a large excess of **1** resulted in a negligible improvement. However, Lawesson and co-workers found that addition of elemental sulfur to the reaction of **81a–i** with **1** resulted in formation of the corresponding dithiole-3-thiones in nearly quantitative yields. By isolating excess sulfur, they established that 1 mol of sulfur was consumed per mol of 3-oxo-ester.[97] Later, Lawesson reported the preparation of 3H-1,2-benzodithiole-3-thione (**33**) by the reaction of **1** with 2-mercaptobenzoic acid, ethyl 2-mercaptobenzoate, 2,2-dithiobisbenzoic acid, or diethyl 2,2-dithiobisbenzoate in varying yields from 78–98% *without* addition of elemental sulfur.[98] This would seem to indicate that LR or the cyclic by-product may be acting as a source of S^0. Further evidence of this is provided by the reaction detailed in Section 6 in which 4,5-dihydrothieno-(2,3-c)-1,2-dithiole-3-thione (**36**) was isolated as a by-product from the thionation of oxo-ester **34**.[55]

A third type of ring forming reaction appears to involve oxidative ring closure to give a pair of isomeric products related through a Dimroth rearrangement. Specifically, 2-mercaptobenzamides **83a–c**, 2-mercaptobenzohydrazides **86a, b** and their respective disulfides reacted with **1** in benzene or HMPA to give new and unexpected routes to 3H-1,2-benzodithiol-3-imines **84** and **85** and the related heterocycles **87** and **88**.[98] The amides and hydrazides are apparently converted to the thioamides and thiohydrazides, respectively, which then undergo tautomerization to the imine thiol and oxidative ring closure to the 1,2-dithiol-3-imines **84** and **87**, followed by a Dimroth rearrangement to the 1,2-benzoisothiazole-3-thiones, **85** and **88**.[98] Understandably, the N,N-disubstituted 2-mercaptobenzamides, incapable of iminethiol tautomerization, gave on reaction with **1** only the 3H-1,2-benzodithiole-3-thione (**33**).[98]

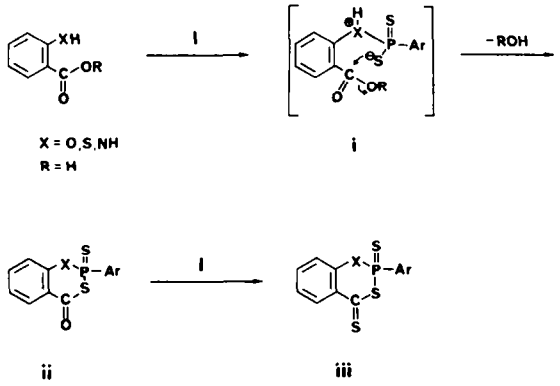


14. PHOSPHORUS–SULFUR HETEROCYCLES

In bifunctional systems in which the substituents are located 1,2 or 1,3 to each other, the opportunity exists for ring-closure reactions involving **1** to give 5- and 6-membered rings. Lawesson first observed such side reactions in the attempt to thionate 2-hydroxy- and 2-aminobenzamides,[14] and expanded the scope of this reaction to include 2-substituted benzoic acids and their derivatives (Table 19).[99] The variety of O-, N-, and S-phosphorus heterocycles implies a diversity of mechanistic pathways. However, the following schemes have been proposed.[99]

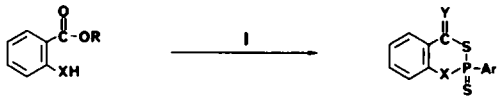
Nucleophilic attack by the heteroatom on **1** would give **i** (Scheme 8), followed by ring closure and expulsion of the alcohol (ROH) to give **ii**. Subsequent thionation produces **iii**. When R = H (Y = O or S) the same mechanism as above is suggested, but with anthranilic acid (Scheme 9) it is assumed that the carboxylate of the betaine **iv** attacks **1** on phosphorus giving salt **v**, which at elevated temperatures loses H_2S to give **vi**. The reaction of 2-aminobenzamide, in contrast, probably involves initial attack on phosphorus by the more nucleophilic amine nitrogen, followed again by loss of H_2S to give the 1,3,2-benzodiazaphosphorine-4(1H)-thione-2-sulfides (Scheme 10).[99]

Thionations of benzamides and salicylamides, as mentioned previously, proceed with a minimum of ring-closure reactions in HMPA, usually giving yields of uncyclized thioamides in excess of 30%.[28] For example, N-cyclohexylsalicylamide reacted with **1** in HMPA above 120° to give the thioamide as the main product, with none of the cyclized phosphorine. Instead, a phosphorus containing product **90**

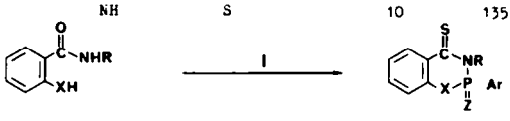


Scheme 8.

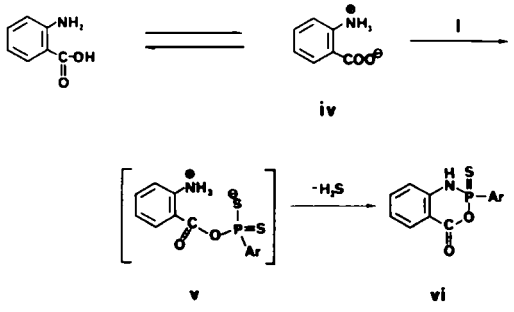
Table 19. 1,3,2-Benzophosphoranes from 2-substituted benzoic acids, esters, and amides and Lawesson's reagent, 1



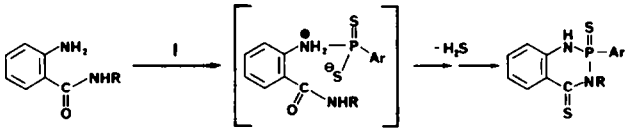
Reactant		Product			
R	X	Y	Yield (%)	mp°C	Ref.
H	O	O	72	98	105
H	O	S	10	102	"
H	S	O	52	94	"
H	S	S	32	130	"
Et	O	O	40	oil	"
Et	O	S	7	oil	"
Et	S	O	70	oil	"
Et	S	S	30	oil	"
Ph	O	O	81	oil	"
Me	NH	S	10	135	"



Reactant		Product			
R	X	Z	Yield (%)	mp°C	Ref.
H	NH	S	24	95	105
	NH	S	20	110	"
Ph	O	S	21	149	106
Ph	O	O	8	173	"
	O	S	14	142	"
"	O	O	23	oil	"
Benzyl	O	S	13	88	"
Benzyl	O	O	23	oil	"

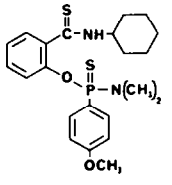


Scheme 9.



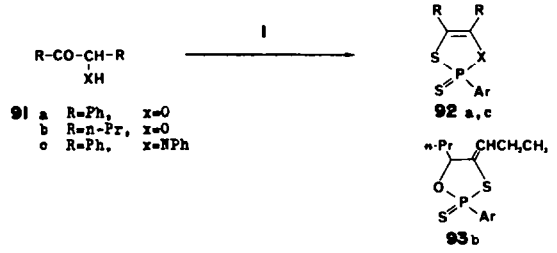
Scheme 10.

containing an N,N-dimethylamino group (presumably from decomposition of HMPA) was obtained in low yield.[100]



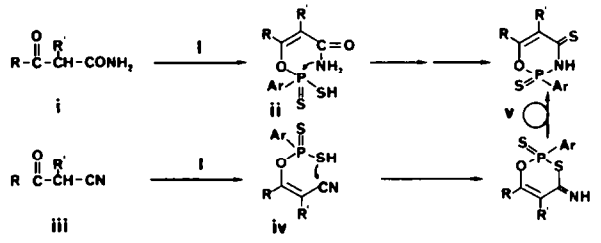
90

In the course of studying some vicinally substituted ketones, Lawesson found that α-hydroxy and α-aminoketones **91a–c** reacted with LR resulting in the formation of oxathiaphospholes **92a** and **b** and thiazaphosphole **92c**, respectively.[31] The yields were low (10–35%), and in the case of 5-hydroxy-4-octanone (butyroin), the main product was **93**.[31]

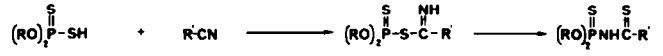


In contrast to N-substituted 3-oxoamides, which afford 1,2-dithiole-3-thiones (Section 7), Lawesson reported that primary 3-oxoamides and some 3-oxonitriles reacted with **1** to yield cyclic 4-H-1,3,2-oxazaphosphorins in high yields (Table 20).[97]

Regarding the mechanisms, Lawesson suggested that the enol-form of the substrates with **1** give thiophosphoric acid intermediates **ii** and **iv** in the first step. A subsequent P—SH addition to the nitrile, followed by a rearrangement yields the final product **v**.[97] The reaction between nitriles and O,O-



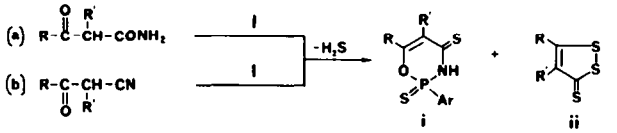
dialkylthiophosphoric acids, involving an analogous rearrangement, has recently been reported.[97]



The formation of **v** from 3-oxocarboxylic amides and **1** can also be accounted for in a similar way, the thiophosphoric acid intermediate **iv** undergoing cyclization by attack of the nucleophilic amide nitrogen and subsequent loss of H_2S.

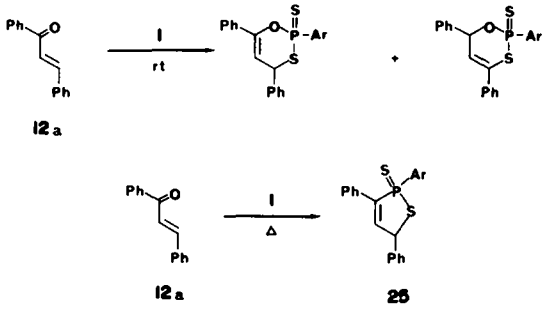
A few α,β-unsaturated carbonyl compounds are known to undergo ring closure with **1** by means of a 1,4-addition reaction of the thiophosphine ylide. In view of the high polarity of the thiophosphine

Table 20. 1,3,2-Oxazaphosphorins from 3-oxo-amides and 3-oxonitriles and Lawessson's reagent, 1

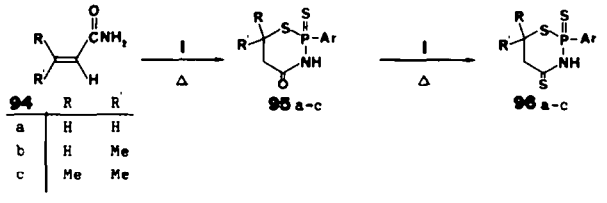


Reactant	R	R'	Yield i (%)	Yield ii (%)	mp(i)°C	Ref.
a	Ph	H	94	3	50-60	97
a	Ph-CH_2-	Ph	85	2	167	"
a	CH_2-(CH_2)$_2$-CH_2		76	17	155	"
b	Ph	H	86	-	56-60	"
b	CH_3	Ph	72	-	181	"

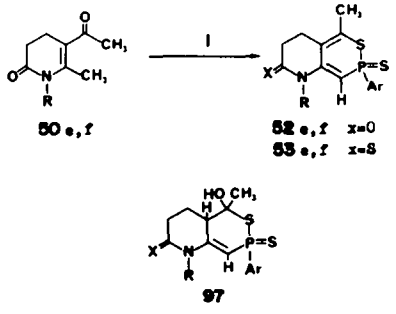
betaine, this reaction might be initiated by a Michael addition of nucleophilic sulfur to the double bond. Lawesson observed that the reaction of chalcone (**12a**) with **1** in acetonitrile resulted in the isomeric 1,3,2-oxathiaphosphorin-2-sulfides.[31] The reaction of chalcone (**12a**) and **1** in refluxing xylene, according to Kametani *et al.*, resulted in the thiophospholene-2-sulfide (**25**) (Section 5).[33]



A similar 1,4-addition was observed in the reaction of 2-propenamide, 2-butenamide, and 3-methyl-2-butenamide with **1** in HMPA leading to the 1,3,2-thiazaphosphorin-4-ones, **95a–c**.[54] No clarification has been made as to whether this reaction involves 1,4-addition to the conjugated imine-ol tautomer, or stepwise addition by initial attack of nucleophilic sulfur, or nitrogen. At higher temperatures the 4-ones, **95a–c**, were converted to the 4-thiones, **96a–c**.



A most unusual reaction of the ketolactams **50e, f** was noted by Lawesson *et al.* during attempts to selectively thionate this multifunctional system.[74] The phosphorus heterocycles **52** and **53** were isolated in low yield as the only products. Mass spectra of compounds **52** and **53** recorded immediately



after isolation detailed the presence of fragments of mass M + 18, corresponding to structure **97** which would presumably undergo loss of water to give products **52** and **53**. As it is known that nucleophiles attack **1** at the phosphorus atom, it has been suggested that **50e** and **f** react with **1** through their enamines.[74]

REFERENCES

[1] L. Henry, *Ann. Chem. Pharm.* **152**, 148 (1869).
[2] J. Wislicenus, *Z. Chem.* 324 (1869).
[3] E. Campaigne, *Chem. Rev.* **1**, 39 (1946).
[4] A. Schobel and A. Wagner, *Methoden der Organische Chemie* (Edited by E. Muller), Vol. IX, p. 699. Huben-Weyl (1955).
[5] E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. 3, Chap. 2. Chem. Pub., New York (1960).
[6] E. Campaigne, *The Chemistry of the Carbonyl Group* (Edited by S. Patai), Chap. 17. Interscience, New York (1966).
[7a] J. W. Scheeren, P. H. J. Ooms and R. J. F. Nivard, *Synthesis* 149 (1973); [b] B. Dash, E. K. Dora and C. S. Panda, *Heterocycles* **19** (11), 2093 (1982).
[8] R. Mayer, J. Morgenstern and J. Fabian, *Angew. Chem.* **76**, 157 (1964).
[9] D. Paquer and J. Vialle, *Bull. Soc. Chim. Fr.* 3595 (1969).
[10] S. Bleisch and R. Mayer, *Chem. Ber.* **100**, 93 (1967).
[11] S. Oae, A. Nakanishi and N. Tsujimoto, *Chem. Ind.* 575 (1972).
[12] F. M. Dean, J. Goodchild and A. W. Hill, *J. Chem. Soc.* (*C*) 2192 (1969).
[13] F. M. Dean, J. Goodchild and A. W. Hill, *Ibid.* 12 (1969).
[14] S.-O. Lawesson, J. Perregaard, S. Scheibye, H. J. Meyer and I. Thomsen, *Bull. Soc. Chim. Belg.* **86**, 679 (1977).
[15] H. Z. Lecher, R. A. Greenwood, K. C. Whitehouse and T. H. Chao, *J. Am. Chem. Soc.* **78**, 5018 (1956).
[16] P. Fay and H. P. Lankelma, *J. Am. Chem. Soc.* **74**, 4933 (1952).
[17] R. E. Dunmar and E. Fluck, *Phosphorus Sulfur* **5**(1), 13 (1974).
[18] H. Keck and W. Kuchen, *Phosphorus Sulfur* **4**(2), 173 (1978).
[19] C. G. Pritzger, *Nat. Petroleum News* **37R**, 1001 (1945).
[20] J. S. Staral and F. W. Koch (Lubrizol Corp.), Ger. Offen. 2, 606,083, Sept. (1976).
[21] H. Hoffman and G. Schumacher, *Tetrahedron Lett.* **31**, 2963 (1967).
[22a] B. S. Pedersen, S. Scheibye, N. H. Nilsson and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 223 (1978); [b] M. P. Cava and M. I. Levinson, unpublished results.
[23] J. Perregaard, B. S. Pedersen and S.-O. Lawesson, *Acta Chem. Scand.* **B31**, 460 (1977)
[24] G. Martin and M. Martin, *Bull. Soc. Chim. Fr.* 1637 (1963).
[25] J. Navech, J. P. Majoral and R. Kraemer, *Tetrahedron Lett.* **24**, 5885 (1983).
[26] J. Perregaard, I. Thomsen and S.-O. Lawesson, *Bull Soc. Chim. Belg.* **86**, 321 (1977).
[27] S. L. Baxter and J. S. Bradshaw, *J. Org. Chem.* **46**, 831 (1981).
[28] S. Scheibye, B. S. Pedersen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 229 (1978).
[29] E. Fluck and H. Binder, *Z. Anorg. Allg. Chem.* **354**, 113 (1967).
[30] R. A. Elofson, L. A. Baker, F. F. Gadallah and R. A. Sikstrom, *J. Org. Chem.* **29**, 1355 (1964).
[31] S. Scheibye, R. Shabana, S.-O. Lawesson and C. Roemming, *Tetrahedron* **38**(7), 993 (1982).
[32] C. P. Klages and J. Voss, *Chem. Ber.* **113**(6), 2255 (1980).
[33] S. Kametani, H. Ohmura, H. Tanaka and S. Motoki, *Chem. Lett.* 793 (1982).
[34] M. I. Levinson and M. P. Cava, *Heterocycles* **19**, 241 (1981).
[35] B. Kope and J. Voss, *J. Chem. Res.* (*S*) 314 (1982).
[36] W. Kuchen, J. Delvanthal and H. Keck, *Chem. Ber.* **107**(9), 2938 (1974).
[37] W. Kuchen and H. Keck, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **31B**(4), 437 (1976).
[38] K. Diemert and W. Kuchen, *Phosphorus Sulfur* **3**(2), 131 (1977).
[39] K. Diemert, P. Haas and W. Kuchen, *Chem. Ber.* **111**(2), 629 (1978).
[40] W. Kuchen, R. Uppenkamp and K. Diemert, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**(10), 1398 (1979).
[41] N. Schindler (Henkel und Cie, G.m.b.H.), Ger. Offen. 2, 133, 329, 25 Jan. (1973).
[42] W. Zeiss, A. Henjes, R. Lux, M. Schwartz and K. Hess, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**(9), 1334 (1979).
[43] K. Clausen, A. A. El-Barbary and S.-O. Lawesson, *Tetrahedron* **37**(5), 1019 (1981).
[44] R. Shabana, J. B. Rasmussen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **90**, 75 (1981).
[45] W. Zeiss and A. Schmidpeter, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**(7), 1042 (1979).
[46] A. A. El-Barbary and S.-O. Lawesson, *Tetrahedron* **37**(15), 2647 (1981).
[47] F. Duus, *Comprehensive Organic Chemistry* (Edited by D. H. R. Barton and W. D. Ollis), Chap. 11, p. 423. Pergamon Press, Oxford (1979).
[48] C. Trebaul and J. Teste, *Bull. Soc. Chim. Fr.* 2272 (1970).
[49] M. J. Janssen, *The Chemistry of Carboxylic Acids and Esters* (Edited by S. Patai), Chap. 15. Interscience, New York (1969).
[50] K. Hartke and F. Meisner, *Chem. Ber.* **107**, 3121 (1974).
[51] S. Scheithauer and R. Mayer, *Chem. Ber.* **100**, 1413 (1967).
[52] P. Vinkler, K. Thimm and J. Voss, *Annalen* 2083 (1976).
[53] M. Mori, Y. Ban and T. Oishi, *Int. J. Sulfur Chem.* (*A*) **2**, 79 (1972).
[54a] B. S. Pedersen, S. Scheibye, K. Clausen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**, 293 (1978); [b] S. Scheibye, S.-O. Lawesson and C. Romming, *Acta Chem. Scand.* **B35**, 239 (1981).
[55] S. Scheibye, J. Kristensen and S.-O. Lawesson, *Tetrahedron* **35**, 1339 (1979).
[56a] L. Engman and M. P. Cava, *J. Org. Chem.* **46**(21), 4194 (1981); [b] S. Ayral-Kaloustian and W. C. Agosta, *J. Org. Chem.* **47**, 284 (1982).
[57] S. Scheibye and S.-O. Lawesson, *Tetrahedron* **36**, 3309 (1980).
[58] G. L'Abbe, J. Flemal, J. P. Declercq, G. Germain and M. Van Meerssche, *Bull. Soc. Chim. Belg.* **88**(9), 737 (1979).
[59] R. Shabana, J. Rasmussen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **90**(1), 103 (1981).
[60] V. Prey and P. Kondler, *Monatsch.* **89**(4–5), 509 (1958).

[61] R. N. Hurd and G. DeLaMater, *Chem. Rev.* **61**, 45 (1961).
[62] W. Walter and K.-D. Bode, *Angew. Chem.* **78**, 517 (1966).
[63] K. A. Petrov and L. N. Andreev, *Russ. Chem. Rev.* **38**, 21 (1969).
[64] W. Walter and J. Voss, *The Chemistry of the Amide Group* (Edited by J. Zabicky), p. 383. Interscience, London (1970).
[65] H. Fritz, P. Hug, S.-O. Lawesson, E. Logemann, B. S. Pedersen, H. Sauter, S. Scheibye and T. Winkler, *Bull. Soc. Chim. Belg.* **87**(7), 525 (1978).
[66] S. Raucher and P. Kein, *Tetrahedron Lett.* **21**, 4061 (1980).
[67] J.-P. Pradere and H. Quiniou, *Ann. Chem. Ital.* **63**, 563 (1973).
[68] J.-P. Pradere, Y. T. N'Guessan and H. Quiniou, *Tetrahedron* **31**, 3059 (1975).
[69] J.-P. Pradere, Y. T. N'Guessan and H. Quiniou, *Ibid.* **31**, 2679 (1975).
[70] S.-O. Lawesson, R. Shabana, J. B. Rasmussen and S. O. Olesen, *Tetrahedron* **36**, 3047 (1980).
[71] W. Walter and T. Proll, *Synthesis* **12**, 941 (1979).
[72] R. Shabana, J. B. Rasmussen and S.-O. Lawesson, *Tetrahedron* **37**, 1819 (1981).
[73] J. B. Rasmussen, R. Shabana and S.-O. Lawesson, *Tetrahedron* **37**, 197 (1981).
[74] R. Shabana, S. Scheibye, K. Clausen, S. O. Olesen and S.-O. Lawesson, *Nouv. J. Chim.* **4**(1), 47 (1980).
[75] A. A. El-Barbary, S. Carlsson and S.-O. Lawesson, *Tetrahedron* **38**(3), 405 (1982).
[76] D. R. Shridhar, C. V. Reddy Sastry, L. C. Vishwakarma and G. K. A. S. S. Narayan, *Org. Prep. Proceed. Int.* **12**(3–4), 203 (1980).
[77] R. Isaksson, T. Liljefors and J. Sandstroem, *J. Chem. Res.* (S) **2**, 43 (1981).
[78] K. Clausen, M. Thorsen and S.-O. Lawesson, *Tetrahedron* **37**(21), 3635 (1981).
[79] K. Clausen, M. Thorsen and S.-O. Lawesson, *Chemica Scripta* **20**(1–2), 1418 (1982).
[80] K. A. Jensen and C. Jensen, *Acta Chem. Scand.* **6**, 957 (1952).
[81] B. Holmberg, *Ark. Kemi. Mineral. Geol. A.* **17**(23), 10 (1944).
[82] W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.* 3389 (1950).
[83] T. Sato and M. Ohta, *Bull. Soc. Chem. Japan* **27**, 624 (1954).
[84] W. Walter and M. Radke, *Justus Liebigs Annln Chem.* **739**, 201 (1970).
[85] E. Profft, F. Schneider and H. Beyer, *J. Prakt. Chem.* **2**, 147 (1955).
[86] K. A. Jensen and C. Pedersen, *Acta Chem. Scand.* **15**, 1097 (1961).
[87] W. Walter and K. J. Reubke, *The Chemistry of Amides* (Edited by J. Zabicky), p. 477. Interscience, London (1970).
[88] A. A. El-Barbary, S. Scheibye, S.-O. Lawesson and H. Fritz, *Acta Chem. Scand.* **B34**, 597 (1980).
[89] N. D. Heindel, G. Freidrich and M. C. Tsai, *J. Het. Chem.* **17**, 191 (1980)
[90] K. Clausen, A. A. El-Barbary and S.-O. Lawesson, *Tetrahedron* **35**(5), 101 (1981).
[91] M. I. Levinson, M. V. Lakshmikantham and M. P. Cava, unpublished results.
[92] K. Clausen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **88**(5), 305 (1979).
[93] F. Kerzer, *Chem. Ind.* 1333 (1961).
[94] J. B. Jepson, A. Lawson and V. D. Lawton, *J. Chem. Soc.* 1791 (1955).
[95] W. Walter and K.-D. Bode, *Angew. Chem.* **78**, 522 (1966).
[96] K. Clausen and S.-O. Lawesson, *Nouv. J. Chem.* **4**(1), 43 (1980).
[97] B. S. Pedersen and S.-O. Lawesson, *Tetrahedron* **35**(20), 2433 (1979).
[98] A. A. El-Barbary, K. Clausen and S.-O. Lawesson, *Tetrahedron* **36**, 3309 (1980).
[99] A. A. El-Barbary and S.-O. Lawesson, *Tetrahedron* **37**, 2641 (1981).
[100] S. Scheibye, B. S. Pedersen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **87**(4), 299 (1978).