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ORGANOTHIOPHOSPHORUS REAGENTS IN ORGANIC SYNTHESIS

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CONTENTS

Organophosphorus compounds are widely used in organic synthesis.[1] The use of phosphorus ylides—Wittig reagents—for the synthesis of unsaturated systems is well known.[1,2] Various derivatives of pentacoordinated phosphorus have served as valuable initial substances in the molecular design of bioorganic structures.[3,4] One can hardly overestimate the importance of phosphine,[5] phosphoryl,[6] and phosphacyclane[7] metal complexes in the development of the chemistry of organometallic compounds and metal-complex catalysis. Great progress has been made in the application of combined reagents—tertiary phosphine, di- or polyfunctional organic compounds—for the functionalization of organic substrates.[8,9]

Inorganic phosphorus compounds have found an extensive application in synthetic organic chemistry for the purposes of halogenation, thionation and in other preparative problems.[10,11] The most frequently used thionating agent, mainly for carbonyl-containing substrates, is phosphorus pentasulfide, P_4S_{10}.[12]

In recent years a new area of intensive development has appeared in the application of organophosphorus compounds in organic synthesis. This involves the use of organothiophosphorus reagents which not only introduce a sulfur atom into organic substances but also permit other synthetic operations. As a rule, such processes are characterized by a high regio- and, sometimes, also stereoselectivity, and almost in all cases by exceptional efficiency: the yields of required products are usually from satisfactory to quantitative.

In the present review an attempt has for the first time been made at summarizing and systematizing the methods of using in organic synthesis the new thionating and functionalizing reagents: (i) derivatives of phosphorus thio- and dithioacids, (ii) triphenylphosphine–thiocyanogen (TPPT) combined reagent and (iii) *p*-methoxyphenylthiophosphine sulfide dimer (Lawesson's reagent—LR).

The driving force of many of these reactions involving organothiophosphorus reagents is the formation of stronger P=O and P—O bonds instead of labile P=S and P—S bonds.[13] An important contribution to the reaction energetics is made by the transformation of intermediate 4-membered heterocycles or intermediate phosphorane structures into more stable 6-membered cyclic or acyclic

phosphoryl (thiophosphoryl) products. On the whole, the possibility of these reactions taking place is based on the relative ease with which the phosphorus atom coordination number can change in its organic compounds, P(IV) → P(V) → P(IV).[14,15]

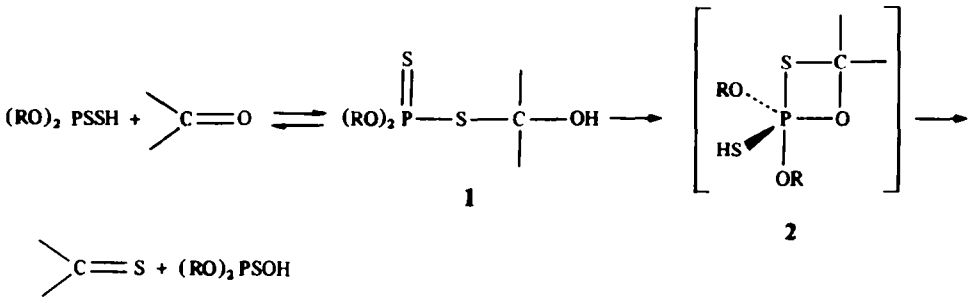
The ways of using organothiophosphorus reagents for the synthesis of organic compounds with the help of thionation, functionalization, heterocyclization and cross-linking methods is now described. We also thought it necessary to examine some new trends in the application of methods for the thiophosphorylation of organic substrates, as no reviews on the subject are available in literature.

1. PHOSPHORUS THIOACIDS AND THEIR DERIVATIVES

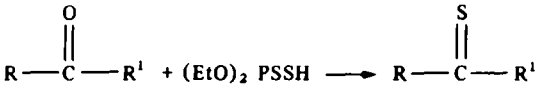
1.1. O,S-*Interchange reactions*

Derivatives of phosphorus thioacids (among which a special place is occupied by dithioacids) are widely used in chemical practice to obtain various thiocarbonyl compounds.

Having a pronounced acid function (pK_a = 2–4) and considerable nucleophilic properties, phosphorus dithioacids are easily and, in most cases, reversibly attached to the carbonyl group of aldehydes and ketones.[16,17] The dithiophosphates (**1**) which are formed are converted via the intermediate **2** into C=S compounds and thiophosphoric acid (O,S-interchange reaction).

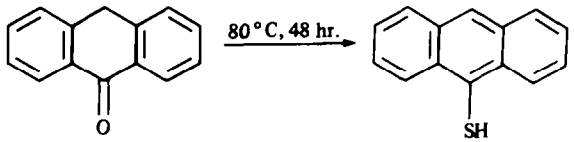


This O,S-interchange reaction using phosphorus dithioacids was successfully used to synthesise 4,4'-dimethoxythiobenzophenone (**3a**), cyclohexanethione (**3b**), thiobenzaldehyde (**3c**), anthracene thiol (**3d**) from the corresponding carbonyl reagents.[18]



3a-d

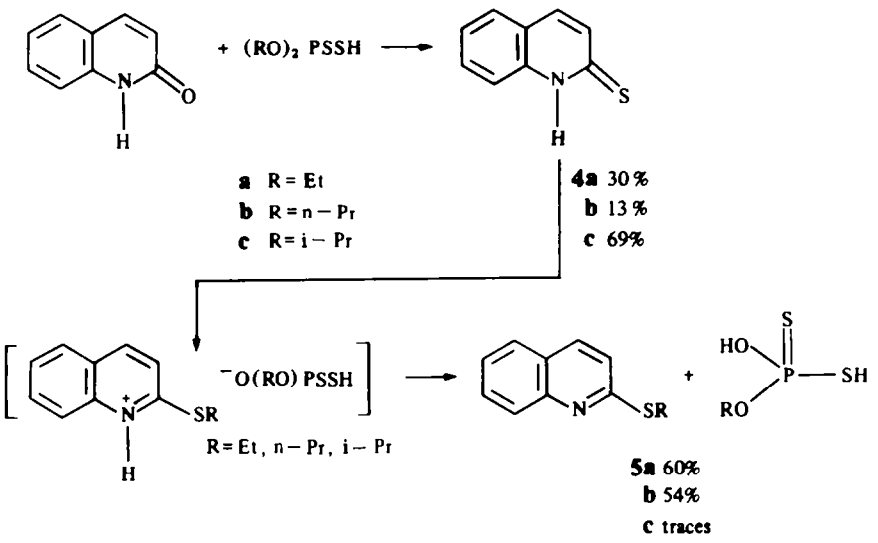
a R = R¹ = *p* – $MeOC_6H_4$, t = 80°C, time 50 hr, yield (**3**) 66%; **b** R + R¹ = –$(CH_2)_5$–, 80–85°C, 50 hr, 60% (dimer); **c** R = H, R¹ = Ph, 80 °C, 24 hr, 100% (dimer); **d**



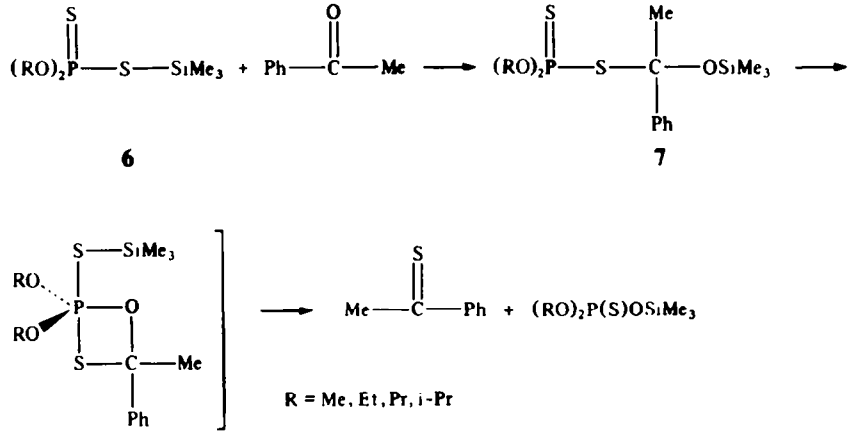
, 100%.

Carbostyril is converted in accordance with this scheme into thiocarbostril (**4**), which is then partly transformed into 2-alkylthioquinoline (**5**) as a result of the nucleophilic attack of thione sulfur on the α-carbon of the dithioacid alkoxy group.[19] Alkylating activity of dithiophosphates decreases with increase in the volume of the R radical at the phosphorus atom. This reaction is completely suppressed in the case of diphenyl dithiophosphoric acid.

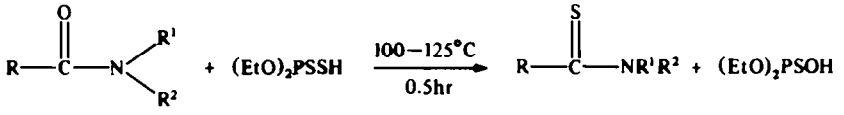
S-Trimethylsilyl esters of phosphorus dithioacids are also effective thionating agents towards ketones. A strong oxygenophilicity of the silicon atom (the difference in Si—O and Si—S bond energies is ~34 kcal/mol),[20] together with a high nucleophilicity of the  triad, promotes the easy addition of silyldithiophosphates (**6**) to the C=O bond of aldehydes and ketones with the formation of the kinetically controlled products—α-trimethylsilyloxyorganyl dithiophosphates (**7**). At an elevated



temperature the products decompose into a thiocarbonyl compound and O-trimethylsilyl thiophosphate. This method is especially effective for the synthesis of aromatic thiocarbonyl compounds. For instance, the interaction of O,O-dimethyl-S-trimethylsilyl dithiophosphate with acetophenone at 60–70° results in a quantitative formation of thioacetophenone and O,O-dimethyl-O-trimethylsilyl thiophosphate.[21]



Under the action of phosphorus dithioacids, C=S groups are easily substituted for C=O in amides of carboxylic acids.[22] The highest yield of thioamides (8) is reached in the reaction with secondary and tertiary amides.

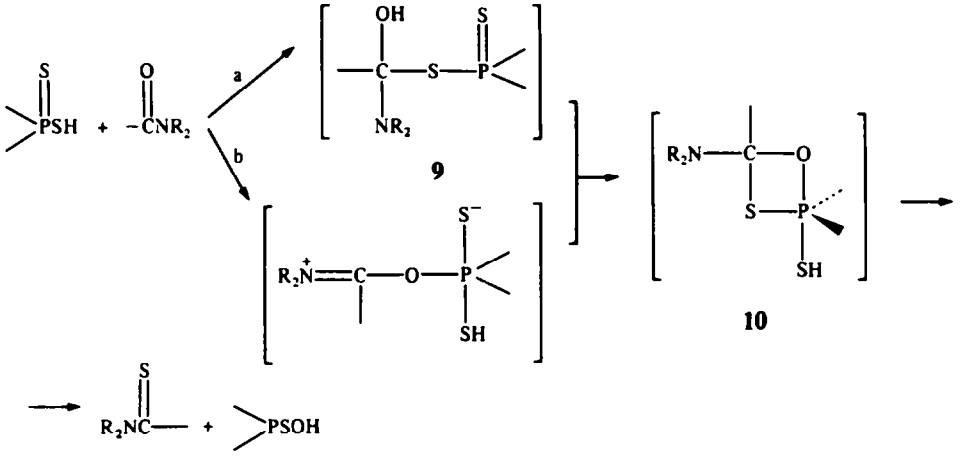


8a-o

a R = Ph, $R^1 = R^2$ = H, yield 22%, **b** R = R^1 = Ph, R^2 = H, 67%; **c** R = Ph, $R^1 = R^2$ = Me, 96%; **d** R = Ph, $R^1 + R^2 = -(CH_2)_4-$, 47%; **e** R = *o* − MeC_6H_4, R^2 = Me, 45%; **f** R = *m* − Me_6H_4, $R^1 = R^2$ = Me, 47%; **g** R = *p* − MeC_6H_4, $R^1 = R^2$ = Me, 50%; **h** R = *o* − $NO_2C_6H_4$, $R^1 = R^2$ = Me, 62%; **i** R = *p* − $NO_2C_6H_4$, $R^1 = R^2$ = Me, 73%; **j** R = *o* − ClC_6H_4, $R^1 = R^2$ = Me, 64%; **k** R = CH_2Ph, R^1 = H, R^2 = Ph, 24%; **l** R = $R^1 = CH_2Ph$, R^2 = H, 89%; **m** R = R^1 = H, R^2 = Ph, 28%; **n** R = $R^1 = R^2$ = Me, 46%; **o** R = t − Bu, $R^1 = R^2$ = Me, 45%.

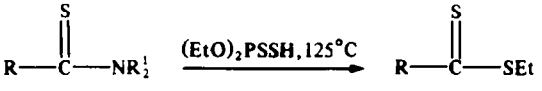
It is believed[22] that the reaction proceeds via the product of dithioacid addition to the carbonyl group of the amide 9 (pathway a), as in the case of the reaction with aldehydes and ketones.[18] In this

system a second possibility is that the carbonyl oxygen first attacks the dithioacid phosphorus atom (pathway b), because thionophosphates which do not contain an SH function [$P(S)Cl_3$, $(Me_2N)_2P(S)Cl$] also convert amides into the corresponding thiono-derivatives.[23]



Reaction pathways a and b both include the formation of the intermediate **10** with the pentacoordinated phosphorus atom.

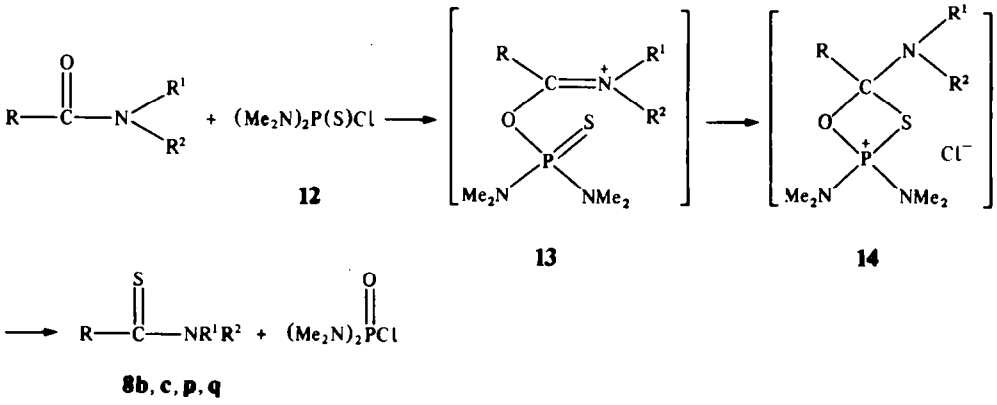
If the reaction mixture of dithiophosphoric acid and the amide is kept for a long time at elevated temperatures then the product of O,S-interchange reaction—the thioamide—is partially converted into the corresponding alkyldithiocarboxylate (**11**).[22]



11a-c

11a R = Ph, R^1 = Me, reaction time 4 hr, yield 65%; **b** R = *p*-MeC_6H_4, R^1 = Me, 1.5 hr, 60%; **c** R = R^1 = Me, 0.5 hr, 41%.

Comparative analysis of the thionating reactivity in the reaction with amides has shown[23] that in the series of thiophosphates: $(Me_2N)_3P(S)$, $(Me_2N)_2P(S)Cl$, $Me_2NP(S)Cl_2$, $P(S)Cl_3$, the highest yield of thioamides is achieved in the case of N,N,N′,N′-tetramethyldiamidochlorothiophosphate (**12**). Hexamethyltriamidothiophosphate does not produce thioamides even at 200° in accordance with the proposed mechanism.



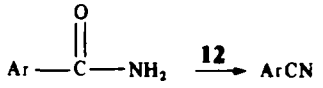
8b, c, p, q

8b yield 75%; **c** 90%; **p** R = H, R^1 = R^2 = Me, 69%; **q** R = R^1 = Me, R^2 = Ph, 55%.

The nucleophilic and the electrophilic properties of the thiophosphate P=S group play an important part in the process. The reaction starts with nucleophilic attack of carbonyl oxygen upon

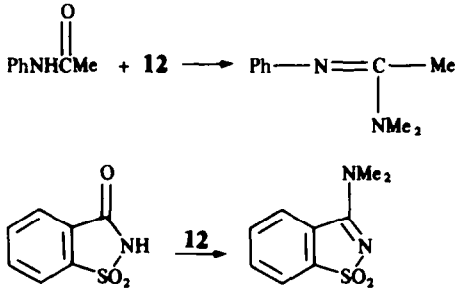
the phosphorus centre, and a cyclic intermediate (**14**) is then formed as a result of a nucleophilic interaction of the thionosulfur with C_{sp^2} in structure **13**. Combined action of both these factors, whose optimum relationship is apparently achieved in **12**, determines the ease of thioamide **8** formation.

It is of interest to note that variation of the nature of substituents in amides changes sharply the character of the products of their interaction with organothiophosphorus reagents (**12**). Reactions with most of the secondary and tertiary amides (**11a–d**) leads to the formation of the corresponding thiono-derivatives (**8**). Primary amides produce nitriles (**15**) in quantitative yield.[23] In a number of cases

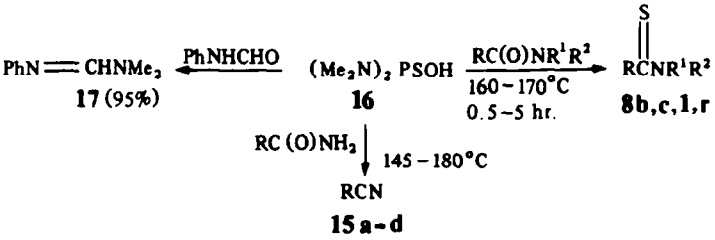


15

(acetanilide, formanilide, saccharin) the reaction products are amidines or amidine salts.

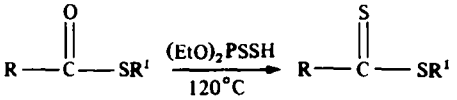


The thionating action of N,N,N'N'-tetramethylthiophosphoric diamide (**16**) is in many respects similar to the chemical behaviour of chlorothiophosphate (**12**). With the help of reagent **16** one can easily convert amides into thioamides (**8**), amidines (**17**) or nitriles of the corresponding carboxylic acids (**15**).[22]



8b yield 92%; **c** 97%; **l** 96%; **r** R = Me, $R^1 + R^2 = -(CH_2)_2O(CH_2)_2-$, 86%.
15a R = Ph, yield 87%; **b** R = *p* – $MeOC_6H_4$, 78%; **c** *o* – HOC_6H_4, 76%;
d R = *p* – C_5H_4N, 72%.

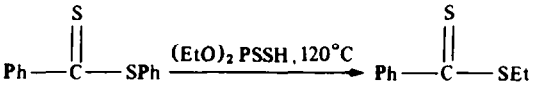
Substitution of a thiocarbonyl for a carbonyl group can be achieved in good yield (60–95%) by heating thiol carboxylates with O,O-diethyldithiophosphoric acid.[24]



11a, **18a–f**

11a yield 92%.
18a R = Ph, R^1 = Me, yield 79%; **b** R = Ph, R^1 = CH_2Ph, 81%;
c R = R^1 = Ph, 59%; **d** R = Me, R^1 = CH_2Ph, 66%;
e R = Me, R^1 = Ph, 85%; **f** R = nPr, R^1 = Et, 95%

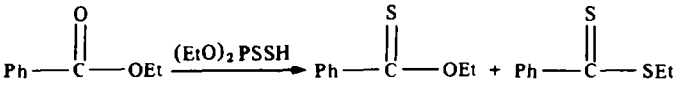
The reaction-time should not be too long, however, because the dithiocarboxylates formed are transformed into different dithiocarboxylates.



18c **11a**

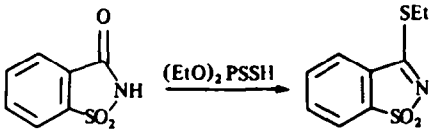
11a Reaction time, yield: 8 hr, 8%; 10 hr, 67%; 12 hr, 86%

A mixture of thio- (**19**) and dithiobenzoates (**11a**) has been obtained in the reaction with ethyl benzoate.[24]



19 (45%) **11a** (11%)

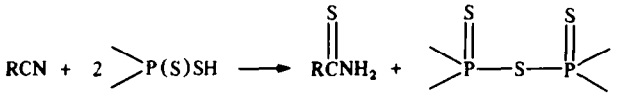
The alkylating activity of dithiophosphoric acids is observed in the reaction with potential hydroxy-heterocycles. For instance, O,O-diethyldithiophosphoric acid converts saccharin (**20**) into 3-ethyl-thiobenzoylthiazole-S-dioxide (**21**).



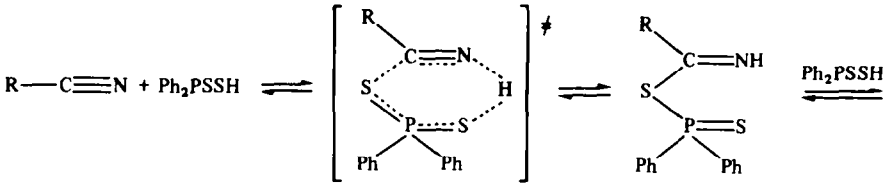
20 **21**

1.2. *Reactions with compounds containing multiple carbon–nitrogen bonds*

A convenient method of obtaining thioamides and related compounds is to use reactions of phosphorus dithioacids with nitriles. These reactions proceed under mild conditions, they require no catalyst and give a quantitative formation of thioamides.[25–31]



Kinetic investigation of the mechanism of reaction between diphenyldithiophosphinic acid and aryl nitriles has shown[32] that, similarly to the great majority of processes with the participation of phosphorus dithioacids (e.g. addition to acrylonitrile[33,34]), the first stage of the reaction consists of the addition of the dithiophosphinic acid along the C≡N bond. This yields the imidoyldithiophosphinates (**22**) which are powerful phosphorylating compounds and they react further with the dithiophosphinic acids, yielding the corresponding thioamides.



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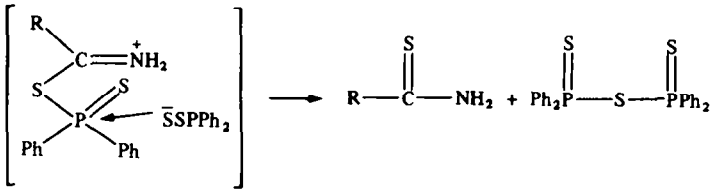
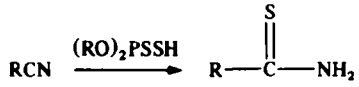


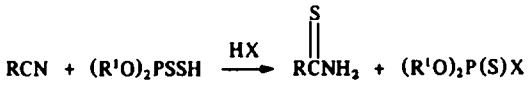
This offers an opportunity of synthesising various functional thioamides (**23**) containing carbonyl and phosphono-groups,[25] halogen atoms[25,30] and other substituents.[31]



23

23 R = **a** $EtOOCCH_2$; **b** $(EtO)_2P(O)$; **c** $ClCH_2$; **d** Cl_3C; **e** $PhCH_2$; **f** Et; **g** Ph; **h** $o-ClC_6H_4$; **i** $p-ClC_6H_4$; **j** $p-NO_2C_6H_4$; **k** $p-CH_3OC_6H_4$, **l** $NH_2C(S)(CH_2)_4$

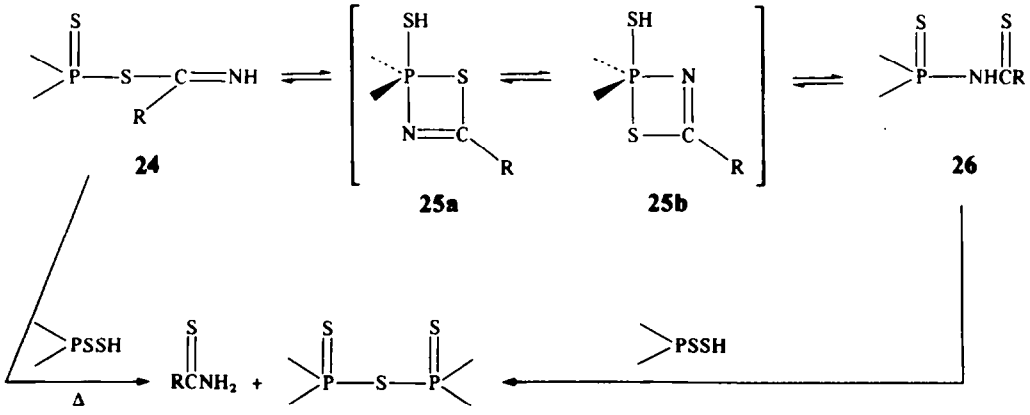
In the presence of water[26] or hydrogen chloride[35,36] the reaction products, along with thioamides (**23**), are monothiophosphoric acid or chlorothiophosphate, respectively.



23

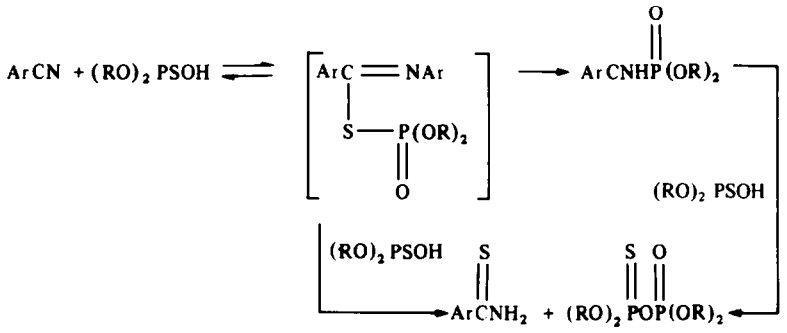
23 X = OH; R = Me, Ph; R^1 = Et, n-Pr, i-Pr; yield 85 – 100%. X = Cl; R^1 = Et; **a** yield 54%; **c** 80%; **d** 80%; **e** 82%; **g** 90%; **m** R = Me, 84%; **n** $R = MeOCH_2$, 29%; **o** R = 2,6 – $FClC_6H_3$, 42%; **p** R = 2,6 – $ClIC_6H_3$, 71%; **q** R = 2,4 – $Cl_2C_6H_3$, 73%; **r** R = 2,6 – Cl(PhS) C_6H_3, 20%.

Stabilization of imidoyldithiophosphates (**24**) can also be accomplished by means of S → N migration of the thiophosphoryl group with the formation of thiophosphorylated thioamides (**25**).[27,28,30] This rearrangement seems to proceed via intermediates of the phosphorane type (**25a,b**) and is actually realized for dithiophosphate and -phosphonate systems only. The latter fact is due to the necessity for substituents at the phosphorus atom to be apically orientated in the course of the permutational isomerization of the trigonal-bipyramidal structure with pentacoordinated phosphorus.[37,38]

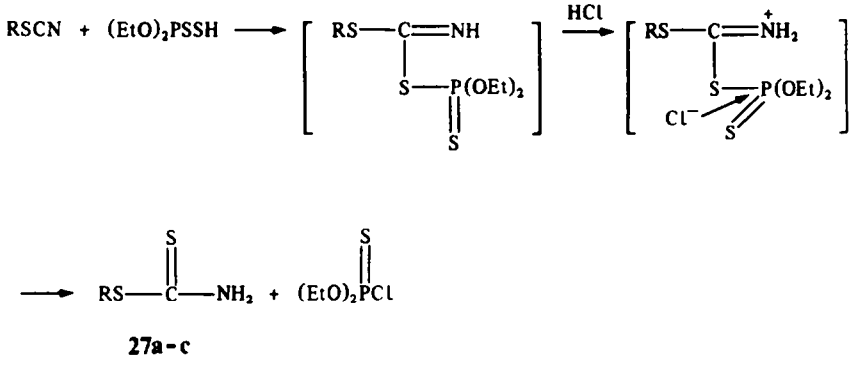


At an elevated temperature, the amidothiophosphate (**26**) is capable of reacting with more dithiophosphinic acid producing thioamide and trithiopyrophosphate. Conducting the reaction under mild conditions makes it possible to direct the reaction of dithiophosphoric acids towards the predominant formation of amidothiophosphates (**26**). At elevated temperatures, the use of an excess of dithiophosphinic acids, yields the thioamide and trithiopyrophosphate (-phosphinate).

It should be noted that phosphorus monothioacids react with nitriles in accordance with the same scheme as the one for dithiophosphates. Their reactivity, however, is much lower than that of the dithioacids.[38]



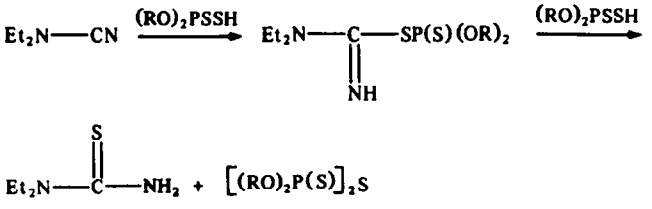
This method for the synthesis of thioamide compounds has also been successfully applied to obtain dithiocarbamates from thiocyanates. The reaction of phosphorus dithioacids with thiocyanates goes along several parallel routes and leads to the formation, together with dithiocarbamates, of isothiocyanatothiophosphates and N-thiophosphonodithiocarbamates.[30,39] In the presence of hydrogen chloride, however, it becomes possible to synthesise dithiocarbamates (**27a–c**) in high yield.[36]



27a–c

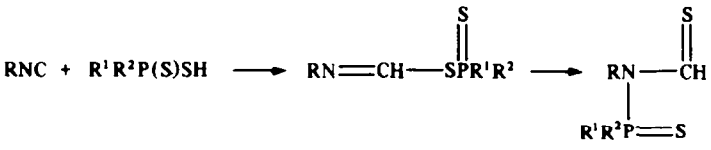
27 a R = Et, yield 91%; **b** R = Ph, 94%; **c** R = $PhCH_2$, 90%.

The action of an excess of dithiophosphoric acid upon N,N-diethyl cyanamide produced N,N-diethylthiourea .[40]



Unsubstituted cyanamide reacts with phosphorus dithioacids, forming a complex mixture of products.[41] Synthetic possibilities of using the reactions of phosphorus dithioacids with nitriles are thus mainly based upon the high phosphorylating activity of the intermediate adducts—the imidoyl-dithiophosphates. The P—S bond in the intermediate is cleaved as a result of the action of an external nucleophile (initial dithioacid, water, HCl), or following the mechanism of intramolecular substitution. The chemical consequences of the 1,3 S → N migration of the thiophosphoryl group are not yet sufficiently well studied. However, this process does appear to us to be very promising for preparative production of N-substituted thioamide systems.

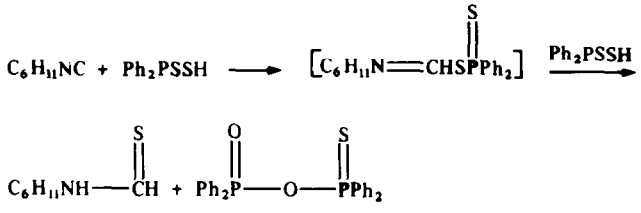
The dithiophosphate–amidothiophosphate rearrangement of the products of α-addition of phosphorus dithioacids to isonitriles (**28**) yields N-phosphorylated thioformamides (**29a–d**).[42,43]



28a-e **29a-d**

a R = 2,6 – $Et_2C_6H_3$; $R^1 = R^2$ = MeO; **b** R = 2,6 – $Et_2C_6H_3$, $R^1 = R^2$ = EtO;
c R = 2,6 – $Me_2C_6H_3$; $R^1 = R^2$ = MeO; **d** R = 2,6 – $Et_2C_6H_3$, R^1 = Me, R^2 = EtO;
e R = 2,6 – $Et_2C_6H_3$; $R^1 = R^2$ = Ph.

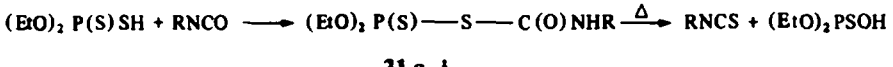
Participation of diphenyldithiophosphinic acid in the reaction stops the process at the stage of **28e** addition. In the case of monothiophosphinates the adduct is not isomerized but it phosphorylates the thioacid yielding the N-thioformamide (**30**).[44]



30

Another example illustrating the possibilities of using the derivatives of phosphorus dithioacids in organic synthesis are the reactions of acid dithiophosphates or their S-trimethylsilyl esters with isocyanates.

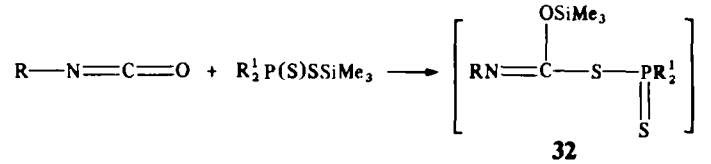
It is well known that dithioacids add to the C=N bond of alkyl- and arylisocyanates yielding S-thiophosphono-thiocarbamates (**31**) which at a temperature above 40° decompose into isothiocyanate and monothiophosphoric aicd.[45,46]



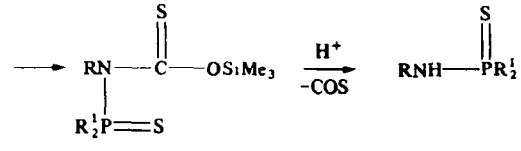
31 a-j

31a R = Et, yield 57%; **b** R = i – Pr, 68% **c** R = n – Bu, 73%; **d** R = $OCN(CH_2)_6$; **e** R = Ph, 69%;
f R = *m* – MeC_6H_4, 61%; **g** R = *o* – ClC_6H_4, 44%; **h** R = *p* – ClC_6H_4, 54%; **i** R = 3,4 – $Cl_2C_6H_3$, 73%; **j** R = *m* – $NO_2C_6H_4$, 48%.

In contrast with dithioacids, the interaction of S-trimethylsilyldithiophosphates with isocyanates proceeds with predominant participation of the C=O bond of heterocumulene. The intermediate **32** is stabilized by the migration of the thiophosphoryl group from the thiol sulfur atom to nitrogen.[47] The O-trimethylsilyl esters of N-thiophosphorylated thiocarbamic acid (**33**), are formed in quantitative yield. They are stable under normal conditions but in aqueous or alcohol media they split off COS yielding amidothiophosphates (**34**):



32



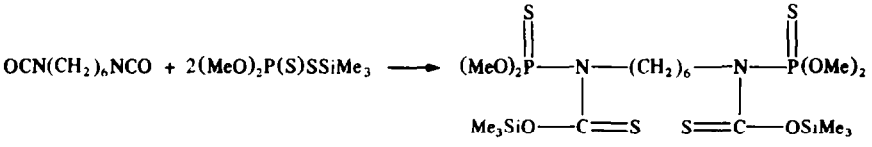
33a-e **34a-e**

a R = Me, R^1 = MeO; **b** R = Me, R^1 = EtO; **c** R = Me, R^1 = i – PrO;
d R = Me, R^1 = MeO(Me); **e** R = Et, R^1 = MeO

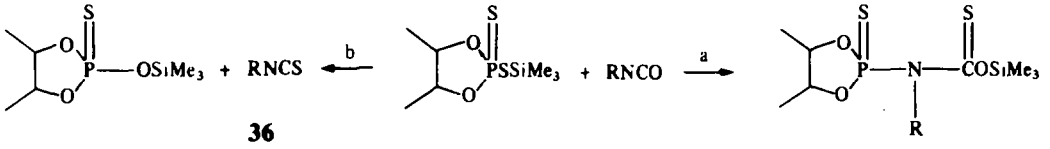
By prolonged heating of the reaction mixture in a closed reactor isocyanates are converted into isothiocyanates.[47]

$$RNCO \xrightarrow[80-90^{\circ}C]{R^1_2P(S)SSiMe_3} RNCS + R^1_2P(S)OSiMe_3$$

Depending on the ratio of reagents, one or both isocyanate groups can take part in the reaction of silyldithiophosphates with hexamethylene diisocyanate.



Inclusion of the phosphorus atom of silyldithiophosphates in a 5-membered heterocycle not only speeds up the S → N migration of the thiophosphoryl fragment (pathway a), but also promotes the O,S-interchange reaction with the formation of the stable products: the isothiocyanate (**36**) and O-trimethylsilylthiophosphate (pathway b).



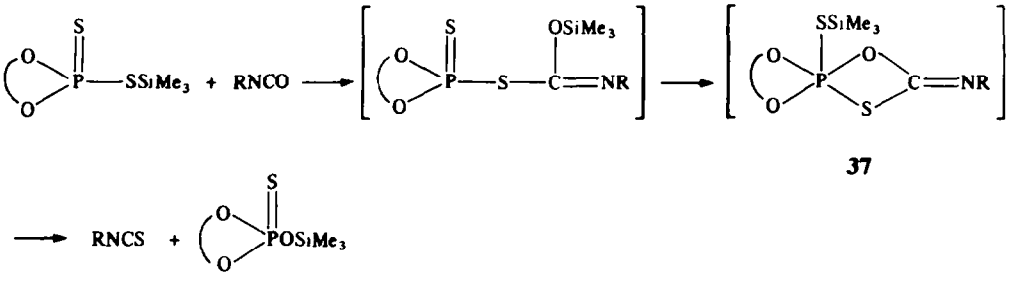
36

35

R: **a** Me; **b** Et; **c** i-Pr.

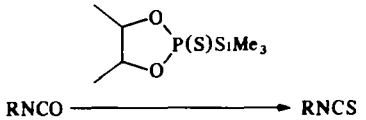
The ratio of the rates of the competing pathways (a : b) depends to a great extent upon the size of radical R at the nitrogen atom. In the case of methylisocyanate, the kinetically controlled product is thiophosphorylated thiocarbamide (**35a**), which, on standing or heating, is transformed into methylisothiocyanate (**36a**). An increase in the size of the nitrogen atom of the heterocumulene as in isopropylisocyanate, hinders the S → N migration of the dioxathiophospholane group and as a result only route (b) is observed with the formation of the isothiocyanate **36c**.

A marked reduction of the O,S-interchange activation barrier in the reactions of cyclic dithiophosphates is, in our opinion, caused by a low energy of formation of spirocyclic phosphorane intermediates (**37**).[14,37,48,49]



37

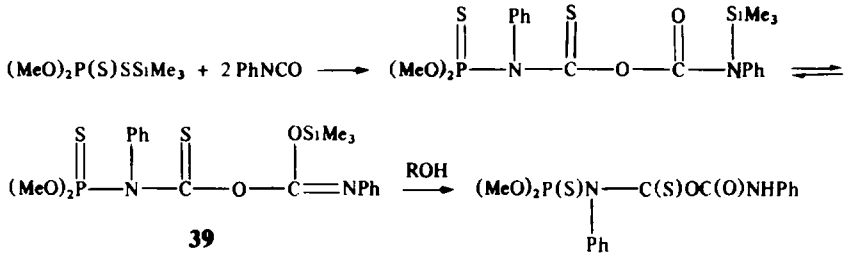
Introduction of 1,2-dioxyalkylene(-arylene) substituent on the phosphorus atom is thus an effective method of raising the thionating activity of dithiophosphates. This approach has been successfully applied to synthesise aryl- and acylisothiocyanates (**36d–g**), from the corresponding isocyanates[47,50] under mild reaction conditions and a very high yield of reaction products (95–100%).



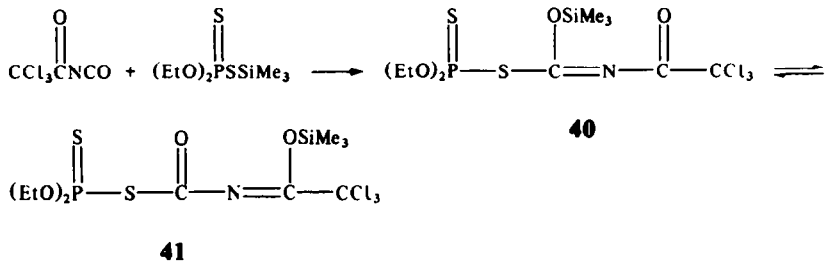
36d-g

R: **d** Ph; **e** $Cl_3CC(O)$; **f** PhC(O); **g** $(EtO)_2P(O)$

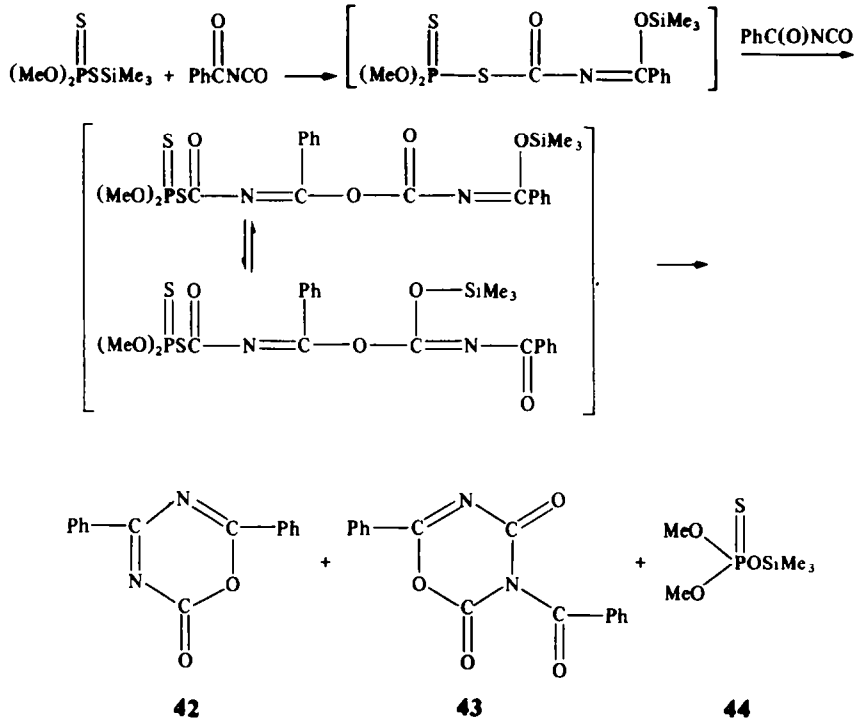
For comparison, O,O-dimethyl-S-trimethylsilyldithiophosphate reacts with phenyl isocyanate, forming a mixture of adducts of 2:1 composition (**38**, **39**).



Interaction with trichloroacetylisocyanate leads to an equilibrium mixture of the products of addition along the isocyanate (**40**) and the carbonyl (**41**) groups of the heterocumulene molecule.

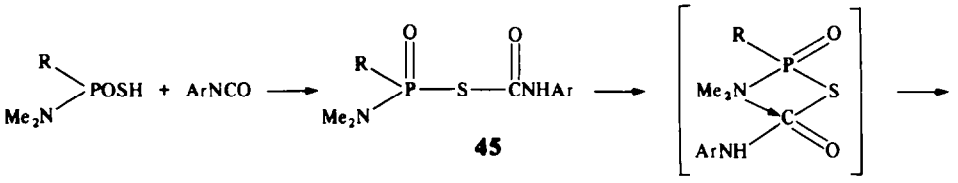


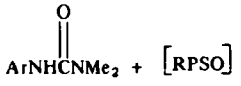
The reaction with benzoyl isocyanate proceeds in a much more complex way and is accompanied by the formation of 2,4-diphenyl-6-oxo-1,3,5-oxadiazine (**42**), benzoylisocyanate dimer (**43**) and O-methyl-O-trimethylsilyl-S-methyldithiophosphate (**44**).[47]



It is believed that the use of cyclic derivatives of phosphorus dithioacids as thionating agents will also prove effective in reactions with other carbonyl-containing compounds such as aldehydes, ketones, carboxylates and carboxamides, in which intermediates of the phosphorane type are formed.

It is of interest to note that, if there is a dimethylaminogroup at the thioacid phosphorus atom, the stabilization of adducts with aryl isocyanates is accomplished by the splitting of the thiophosphinyl carbamate (**45**) C—S bond.[51] The yield of N,N-dimethyl-N'-arylureas (**46**) is 75%.



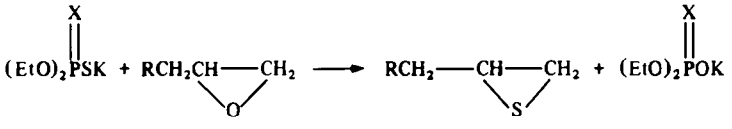


46

R = EtO, Me_2N; Ar = **a** Ph; **b** *p*-ClC_6H_4; **c** 3,4-$Cl_2C_6H_3$.

1.3. *Other synthetic uses of phosphorus thioacid derivatives*

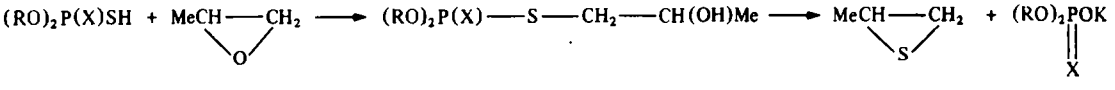
Oxiranes are usually converted into thiiranes by alkali metal thiocyanates and thiourea.[52] Derivatives of phosphorus thio- and dithioacids are also good reagents for this transformation. Thus, on heating (60–70°) equimolar quantities of an epoxy-compound with thioacid salts in water, thiiranes (**47a, b**) and 2,3-thioepoxypropylphosphonate (**47c**) have been obtained in satisfactory yields (40–55%).[53]



47a–c

X = O, S; **a** R = H, **b** R = Ph, **c** R = $(EtO)_2P(O)$

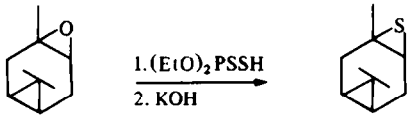
The synthesis of thiiranes can also be achieved with thiophosphoric acids. At the first stage the product is formed of the acid addition to the epoxide—S-2-hydroxyorganylthio(dithio)phosphate (**48**), whose treatment with a base (Na_2CO_3, $NaHCO_3$, KOH, Et_3N) results in a corresponding thiirane (**47a**; yield 80–100%).[54–56]



48 **47a**

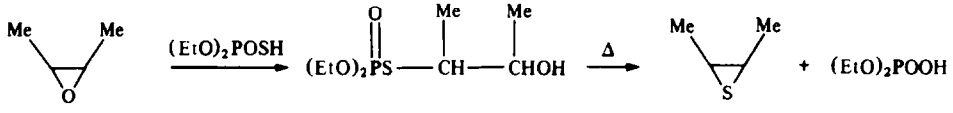
X = O, S

This method was successfully applied to obtain thiiranes of Δ^3-carene (**49**).[57]

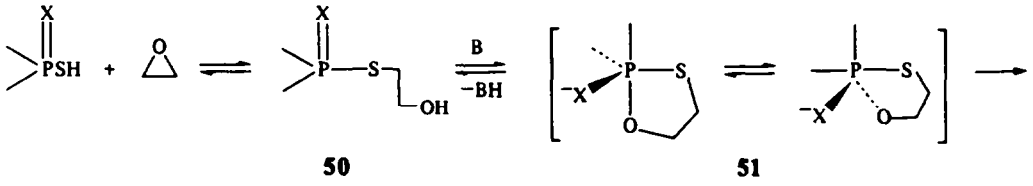


49 (73%)

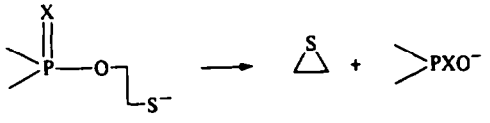
Some 2-oxyalkylthiophosphates can be thermally transformed yielding thiiranes.[58]



Based on a detailed analysis of the factors influencing the activity of phosphorus thioacids, the following reaction scheme has been proposed.[56]



50 **51**

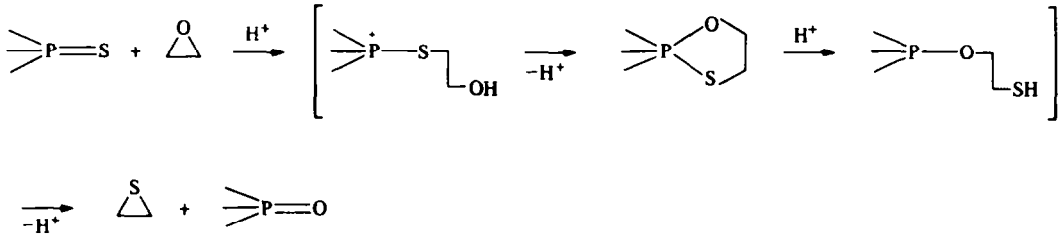


52

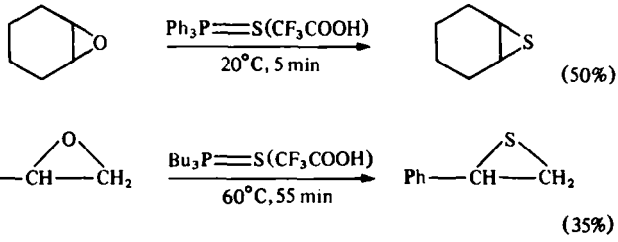
X = O, S

A necessary condition for this process is the phosphoryl (thiophosphoryl) group 1,4-S → O migration. This was confirmed by independent experiments on the isomerization of S-2-oxyalkylthiophosphates (**50**) into 2-mercapto-derivatives (**52**).[59–61] The speed of this rearrangement, including the formation of the intermediate phosphorane structure (**51**), sharply increases in the case of cyclic thiophosphates.[62] Addition of a base facilitates the nucleophilic attack of the oxygen atom on the phosphoryl centre and promotes the fragmentation of the isomeric phosphate (**52**) with the generation of the thiirane.

The mechanism of the thionarion action of phosphine sulfides upon oxiranes in the presence of trifluoroacetic acid[63] is in many respects similar to the process examined above. The reaction is

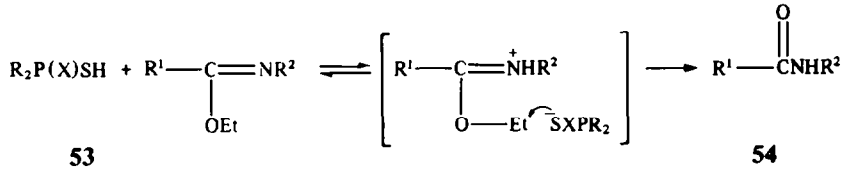


conducted at room temperature or slight heating. The yeild of thiiranes is 50–60%.



The pronounced dealkylating and reducing properties of phosphorus thioacids and their derivatives are of synthetic utility. The interaction of acid thio- and dithiophosphates with imino-esters (**53**) yields the corresponding carboxamides (**54**).[64–66]

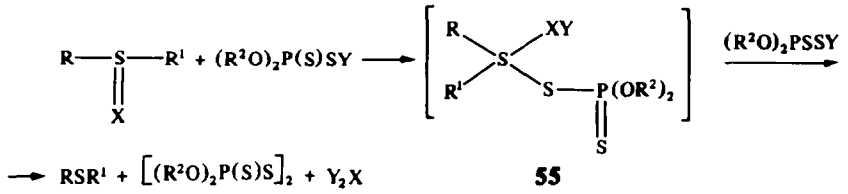
Reactions of dithioacids and S-trimethylsilyldithiophosphates with sulfoxides[67,68] and sulfinylimines[69] seem to start with the formation of addition products along the S=X bond (**55**). Under



53 54

X = S;	R = i–PrO,	R^1 = Ph,	R^2 = C(O)Me,	yield 96%
	R = i–PrO,	R^1 = H,	R^2 = Ph	70%
	R = MeO,	R^1 = Ph,	R^2 = H	90%
	R = Ph,	R^1 = Ph,	R^2 = H	90%
	R = n–PrO,	R^1 = Ph,	R^2 = H	92%
	R = i–PrO,	R^1 = Ph,	R^2 = H	92%
X = O;	R = EtO,	R^1 = Ph,	R^2 = H	51%
	R = n–PrO,	R^1 = Ph,	R^2 = H	53%
	R = i–PrO,	R^1 = Ph,	R^2 = H	54%

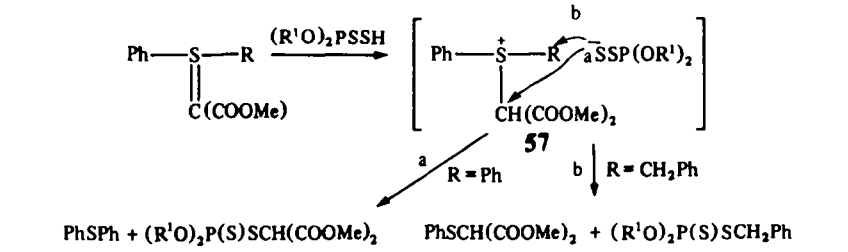
the action of the second molecule of dithiophosphate the adduct decomposes with a quantitative generation of the sulfide (**56**).



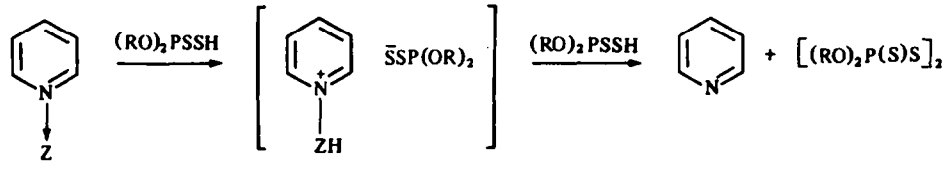
55

56 X = O, Y = H; R = R^1 = Me, R^2 = Et
R = Ph, R^1 = Me, R^2 = i–Pr
R = Ph, R^1 = R^2 = Et
R = Ph, R^1 = $PhCH_2$, R^2 = Et
R = R^1 = Ph, R^2 = Et
X = O, Y = $SiMe_3$; R = R^1 = R^2 = Me
X = NTs, Y = H; R = R^1 = Me, R^2 = Et
R = Ph, R^1 = Me, R^2 = Et
R = R^1 = Ph, R^2 = Et.

In the reaction of dithiophosphoric acids with sulfur ylides, the intermediate is the sulfonium salt (**57**). The course of its subsequent transformations is determined by the direction of dithiophosphoryl anion nucleophilic attack and this depends on the nature of substituents at the sulfur atom.[69]

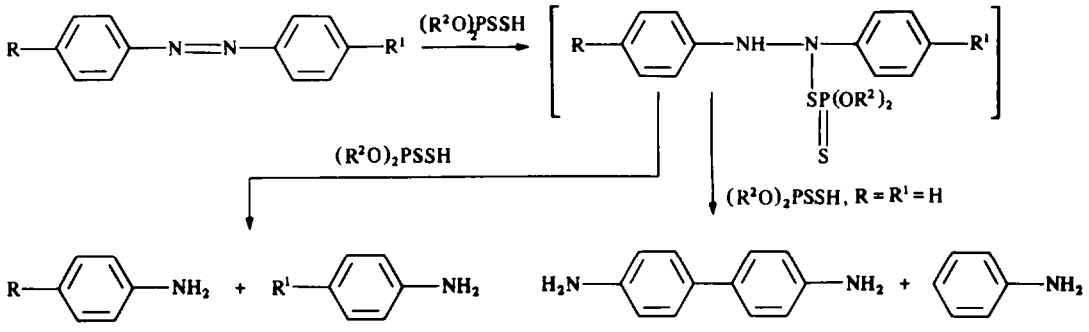


Pyridine N-oxide and N-iminopyridinium betaines are reduced by dithiophosphoric acid to the corresponding pyridines.[67]



Z = O, $NC_6H_4NO_2$–*o*, NC(O)Ph

Dithiophosphoric acid is one of the few organic reagents which reduces azobenzene. The interaction of unsubstituted azobenzene with an excess of dithioacid yields benzidine (**58**) and aniline.[70] Substituted azobenzenes form a mixture of anilines.



58

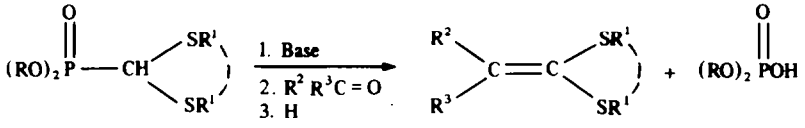
S-Alkyl thiophosphates can be used for the synthesis of mercapto-derivatives. The P—S bond in phosphorus- and sulfur-containing compounds is easily split by fluoride anion ($[Bu_4N]F \cdot 3\,H_2O$, CsF) in aprotic solvents (CH_2Cl_2, $CHCl_3$, THF). This process makes it possible to regenerate the SH group after protection by $Ph_2P(O)$ or $Ph_2P(S)$ groups by reaction with diphenylphosphino-(thiophosphino)cyanides. S-Phosphorylation of thiols by phosphorus cyanides proceeds selectively even in the presence of NH_2 groups in the reactant.[71]

$$Ph_2P(X)CN + HSCH_2CH_2NH_2 \xrightarrow[-HCN]{} Ph_2P(X)SCH_2CH_2NH_2$$

$$\xrightarrow{[Bu_4N]F\cdot 3H_2O} HSCH_2CH_2NH_2 + Ph_2P(X)F$$

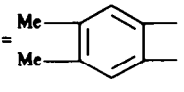
X = O, S.

Extending the Horner–Wittig reaction to sulfur-containing phosphonates provides an easy synthesis of ketene S,S- (**60a–q**) and O,S-acetals (**62a–c**).[72] Various formylphosphinate S,S- and O,S-thioacetals (**59**) can be used for reaction with aliphatic, aromatic and carbocyclic aldehydes and ketones.

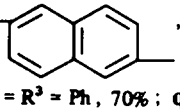


59 **60 a-q**

60 a R = R¹ = Me, R² = R³ = H, yield 96%; **b** R = R¹ = R³ = Me, R² = H, 92%; **c** R = R¹ = R² = R³ = Me, 80% **d** R = R¹ = Me, R² + R³ = $-(CH_2)_4-$, 82%; **e** R = R¹ = Me, R² + R³ = $-(CH_2)_5-$, 80%; **f** R = R¹ = Me, R² = H, R³ = Ph, 82%; **g** R = Et, R¹ + R¹ = $-(CH_2)_3-$, R² = H, R³ = Ph, 92%; **h** R = Et, R¹ + R¹ = $-CH_2SCH_2-$, R² = H, R³ = Ph, 80%; **i** R = Et, R¹ + R¹ =

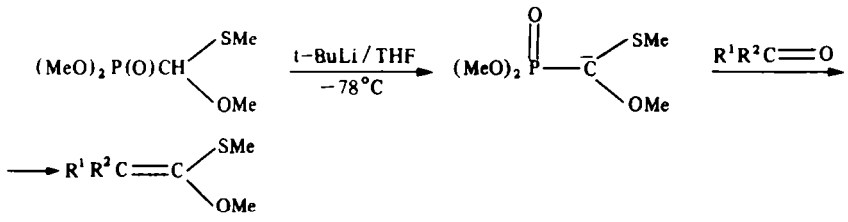


, R² = H, R³ = Ph, 75%; **j** R = R¹ = Et, R² = H, R³ = *p* – BrC_6H_4, 90%; **k** R = R¹ = R² = Me, R³ = Ph, 81%; **l** R = Et, R¹ + R¹ = $-(CH_2)_3-$, R² = Me, R³ = Ph, 86%; **m** R = R¹ = R² = Me, R³ = *p* – $iBuC_6H_4$, 80%; **n** R = R¹ = R² = Me, R³ =



, 78% **o** R = R¹ = Me, R² = R³ = Ph, 78%; **p** R = Et, R¹ + R¹ = $-(CH_2)_3-$, R² = R³ = Ph, 70%; **q** R = Et, R¹ + R¹ = $-CH_2SCH_2-$, R² = R³ = Ph, 72%.

In the reaction of formylphosphonate O,S-thioacetal (**61**) with carbonyl compounds a mixture of isomeric *E*- and *Z*-ketene-O,S-thioacetals (**62a–c**) is formed.



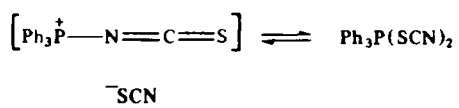
E– and *Z*– **62 a–c**

62 a $R^1 = H$, $R^2 = n-Pr$, yield 82%; **b** $R^1 = H$, $R^2 = Ph$, 80%; **c** $R^1 = R^2 = Me$, 79%.

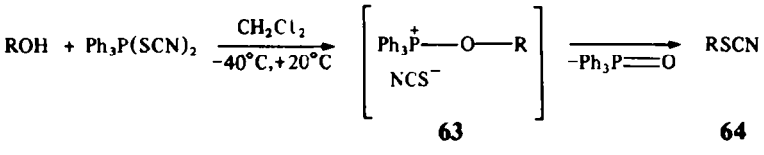
This section demonstrates that derivatives of phosphorus thioacids, especially dithiophosphates, are convenient thionating reagents. Considerable acidity and the pronounced nucleophilic properties of dithiophosphates promotes their chemical reactivity with numerous types of organic systems. This, in combination with a low strength of the P—S bond as compared to P—O or P—N, facilitates an easy migration of the phosphorus residue under the action of external or internal nucleophilic centres. Alkylating, reducing and dealkylating properties of phosphorus thio- and dithioacid derivatives also expands even further the range of their application in preparative organic chemistry.

2. COMBINED REAGENT—TRIPHENYLPHOSPHINE–THIOCYANOGEN

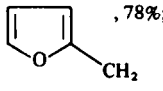
Preparative organic chemistry has been recently reinforced with a new reagent—triphenylphosphine–thiocyanogen.



Triphenylphosphine–thiocyanogen interacts vigorously with alcohols, forming the corresponding alkyl thiocyanates and/or isothiocyanates.[73,74] The process involves the replacement of the NCS fragment at the phosphorus atom being substituted by an alkoxy group, followed by nucleophilic attack of thiocyanate anion on the α-carbon of the alkyl radical in the phosphonium intermediate (**63**). If primary alcohols take part in the reaction, only thiocyanates (**64**) are formed.

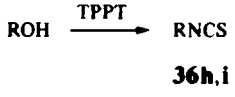


63 **64**

64 R, yield; **a** Me, 75%; **b** Et, 80%; **c** n – Pr, 84%; **d** i – Pr, 95%; **e** $PhCH_2$, 80%; **f** $p-ClC_6H_4CH_2$, 99%; **g** $p-MeOC_6H_4CH_2$, 95%; **h**  , 78%;

i $E-PhCH{=}CHCH_2$, 65%; **j** $PhCH_2CH_2$, 48%; **k** $n-C_5H_{11}$, 80%; **l** $n-C_{12}H_{25}$, 60%.

In the case of tertiary alcohols, isocyanates (36 hr, **i**) have been isolated.



36h,i

h $R = PhMe_2C$; **i** Me_3C

Reactions with secondary alcohols and sterically loaded primary carbynols result in a mixture of thiocyanates (**64m, n, o**) and isothiocyanates (**36j, k, l**).

$$ROH \xrightarrow{TPPT} RSCN + RNCS$$

64m, n, o 36j, k, l

R = cyclo−C_5H_9	m 62%	j 4%
cyclo−C_8H_{15}	n 53%	k 2%
t−$BuCH_2$	o 51%	l 34%

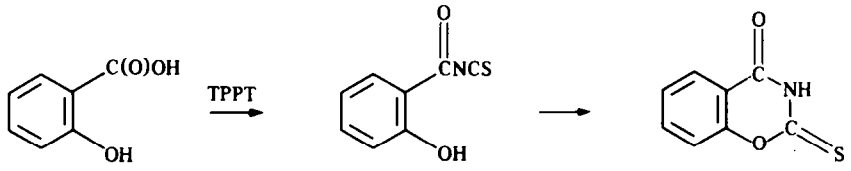
It is believed that the formation of isothiocyanates may be associated with either the isomerization of initially formed thiocyanate structures,[73] or the ambidentate nature of the SCN anion.[74]

Interaction of carboxylic and phosphoric acids with triphenylphosphine–thiocyanogen proceeds by a similar scheme.[74,75]

$$AcOH + Ph_3P(SCN)_2 \longrightarrow [Ac{-}O{-}\overset{+}{P}Ph_3\ \ \overset{-}{N}CS] \xrightarrow[-Ph_3P{=}O]{} AcNCS$$

Ac = MeC(O), $(EtO)_2P(O)$, $(EtO)_2P(S)$

When salicylic acid is used, the intermediate acylisothiocyanate (**65**) is intramolecularly cyclized yielding 2-thioxo-3,4-dihydro-2H-1,3-benzoxazine-4-one (**66**).[75]



65 **66**

The reaction of triphenylphosphine–thiocyanogen with secondary amines involves nucleophilic addition of the amine to the NCS group of the reagent with the formation of the phosphonium intermediate (**67**) which, in the presence of water generates 1,1-disubstituted thioureas (**68**).[76,77]

$$R{-}NH{-}R^1 + [Ph_3\overset{+}{P}{-}N{=}C{=}S] \xrightarrow[-40°C,+20°C]{CH_2Cl_2} [Ph_3\overset{+}{P}{-}NH{-}\overset{S}{\overset{\|}{C}}{-}NRR^1]\ {}^-SCN$$

67

$$\xrightarrow{H_2O} H_2N{-}\overset{S}{\overset{\|}{C}}{-}NRR^1$$

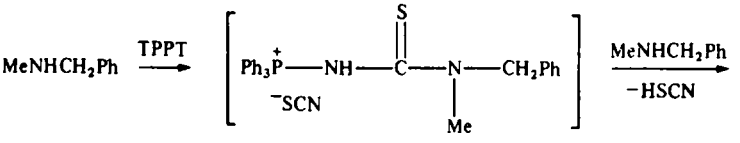
68a-g

68a R = Me, R^1 = Ph, yield 80%; **b** R = Et, R^1 = Ph, 50%; **c** R = Me, R^1 = $PhCH_2$, 65%;
d R + R^1 = $-(CH_2)_5-$, 70%; **e** R + R^1 = $-(CH_2)_4-$, 77%; **f** R = R^1 = Et, 70%;
g R = Me, R^1 = cyclo − C_6H_{11}, 70%.

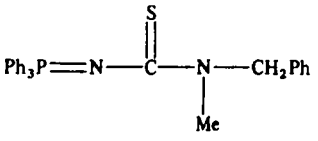
Intermediate formation of the phosphonium salt (**67**) was confirmed by the formation of the corresponding phosphine imine (**69**) by the reaction of triphenylphosphine–thiocyanogen with two equivalents of methylbenzylamine.

Under the action of carboxylic acids, the thiocarbamoylaminophosphonium intermediates (**67**) decompose with the formation of amides (**70**) and/or acylthioureas (**71**).[72] Competition between the pathways (a and b) depends on the structure of the amine and the acid. With an increase in the size of substituents at the nitrogen atom and the carbonyl group the rate of pathway b increases because pathway b is less sensitive to steric factors than pathway a (Scheme 1).

The presence of a carbonyl group in the initial amine makes it possible to synthesise heterocyclic systems with the help of triphenylphosphine–thiocyanogen. For instance, the reaction of

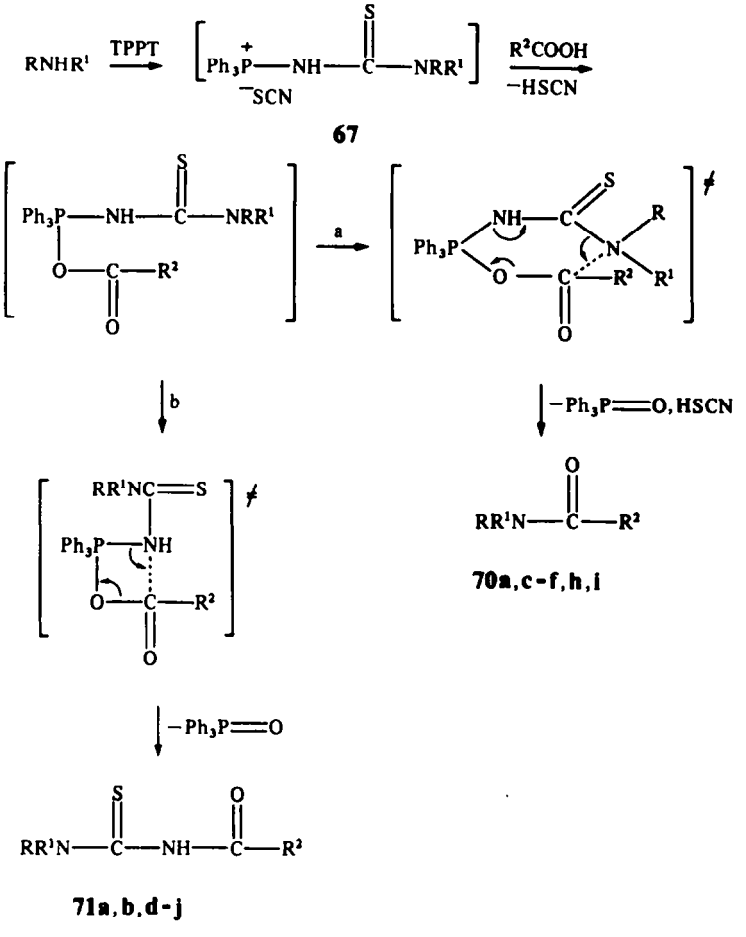


67c



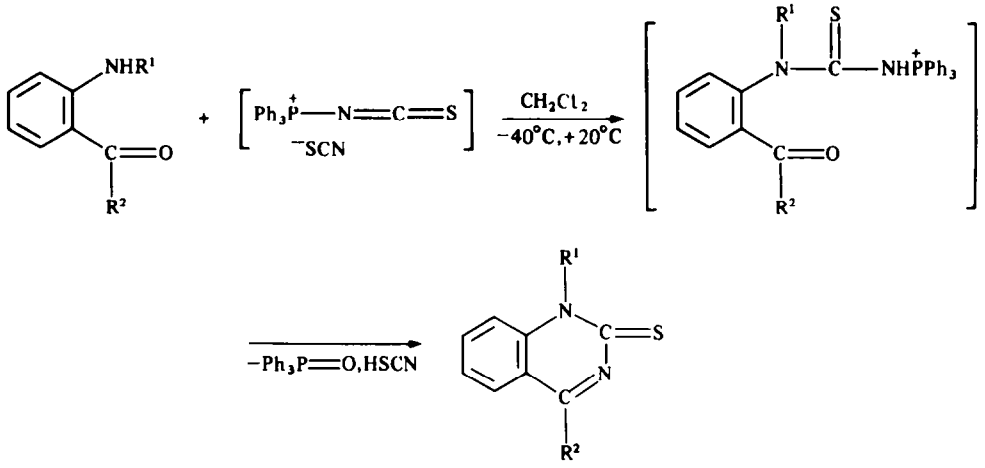
69

triphenylphosphine–thiocyanogen with 2-acylanilines (72) produces the pharmacologically important 2-thioxo-1,2-dihydroquinazolines (73)[77,78] (Scheme 2).



a R = R^2 = $PhCH_2$, R^1 = Me, yield **70** 19%, yield **71** 28%; **b** R = Ph, R^1 = Me, R^2 = cyclo – C_6H_{11}, –, 31%; **c** R = Ph, R^1 = H, R^2 = Me, 72%, –; **d** R = Ph, R^1 = H, R^2 = n – C_5H_{11}, 45%, 13%; **e** R = Ph, R^1 = H, R^2 = $PhCH_2$ 62%, 21%; **f** R = Ph, R^1 = H, R^2 = cyclo – C_6H_{11}, 16%; 45%; **g** R = R^2 = Ph, R^1 = H, –, 42%; **h** R = Ph, R^1 = Et, R^2 = $PhCH_2$, 8%, 89%; **i** R = Ph, R^1 = Et, R^2 = $PhCH_2$, –, 83%; **j** R = Ph, R^1 = i – Bu, R^2 = $PhCH_2$, –, 75%.

Scheme 1.

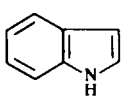
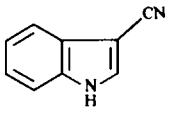
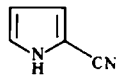
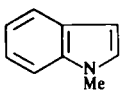
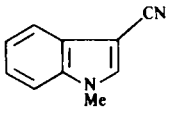
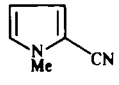
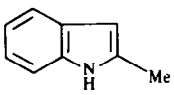
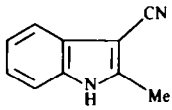
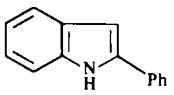
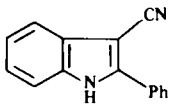
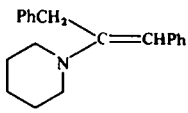
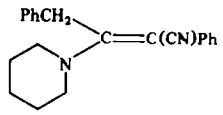
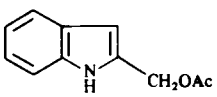
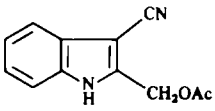
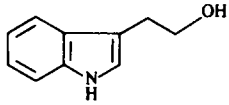
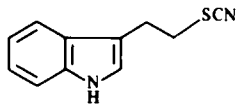
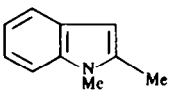
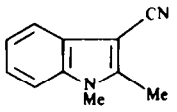
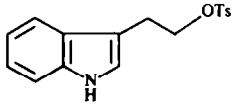
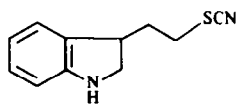
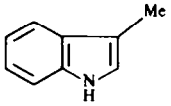
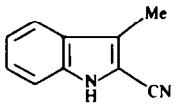


73a–f

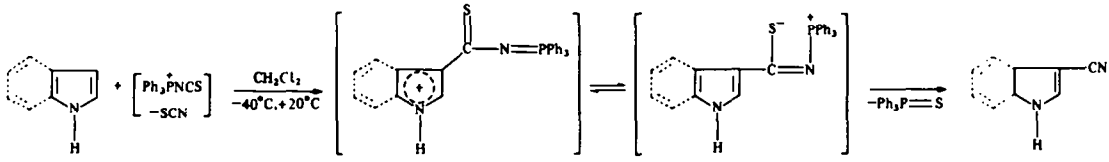
73a R = R^1 = H, R^2 = Ph, yield 88%; **b** R = Cl, R^1 = H, R^2 = Ph, 87%; **c** R = H, R^1 = Et, R^2 = Ph, 78%; **d** R = H, R^1 = i–Pr, R^2 = Ph, 70%; **e** R = Cl, R^1 = i–Pr, R^2 = Ph, 64%; **f** R = R^1 = H, R^2 = Me, 62%.

Scheme 2.

Table 1. Reactions of triphenylphosphine–thiocyanogen with indoles, pyrroles and enamines[79]

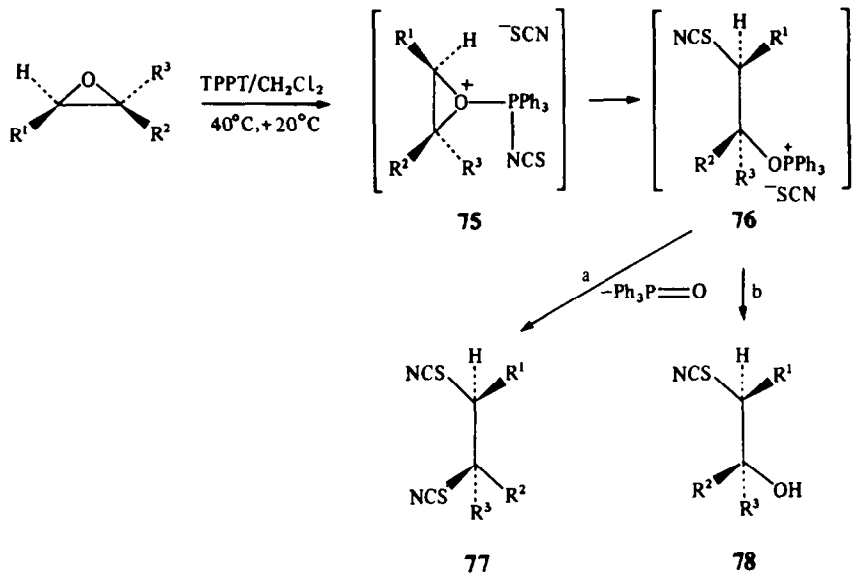
Initial compound	Product	Yield (%)	Initial compound	Product	Yield (%)
		93			50
		64			61
		99			
		88			61
		66			43
		70			32
		85			

A different chemical action is observed in the reaction of triphenylphosphine–thiocyanogen with indoles, pyrroles and enamines. Nucleophilic attack of the unsaturated partner upon the isothiocyanate group, followed by the elimination of triphenylphosphine sulfide, results in the formation of the corresponding nitriles (**74**).[79] The cyanation of indoles proceeds regioselectively in position 3 of the heterocyclic system when there is no substituent at C-3.



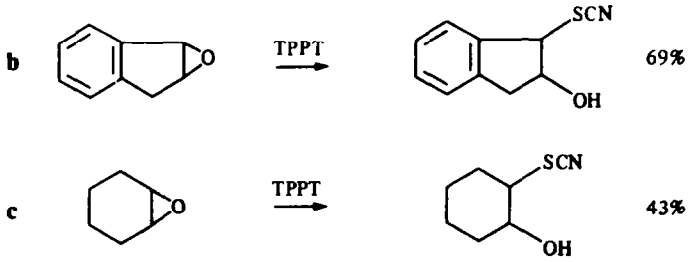
74

Triphenylphosphine–thiocyanogen easily converts epoxides into 1,2-dithiocyanates (**77**) or 1,2-thiocyanatohydrins (**78**).[80] The reaction starts with the coordination of the oxirane oxygen atom with the phosphonium centre and the formation of the intermediate (**75**) the nucleophilic opening of whose epoxide ring, under the action of thiocyanate anion, produces the quasiphosphonium salt (**76**). The direction of subsequent stabilization of the intermediate **76** and, therefore, the nature of the products formed depend upon the structure of the initial oxirane. In the case of monosubstituted and 1,2-disubstituted epoxides, the NCS anion attacks the α-carbon atom of the quasiphosphonium salt (**76**) with the elimination of $Ph_3P{=}O$ and the formation of 1,2-dithiocyanates (pathway a). If steric conditions hinder this process, the intermediate **76** is hydrolyzed and this leads to 1,2-thiocyanohydrins (**78**) (pathway b).

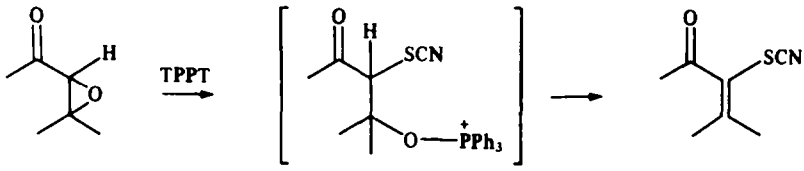


77a R^1 = Ph, R^2 = R^3 = H, yield 50%; **b** R^1 = Ph, R^2 = H, R^3 = Me, 21%;
c R^1 = Ph, R^2 = Me, R^3 = H, 32%; **d** R^1 = R^3 = Ph, R^2 = H, 34%;

78a R^1 = H, R^2 = Ph, R^3 = Me, yield 42%.



When α,β-epoxyketones are used, the α-carbon atom becomes the centre of nucleophilic attack in the intermediate **79**. The reaction results in the formation of α-thiocyanatovinylketones (**80**),[80,81] which are convenient synthons for organic synthesis.

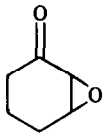
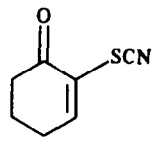
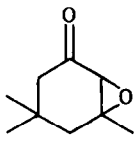
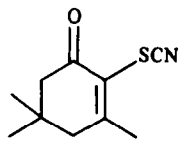
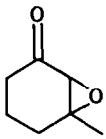
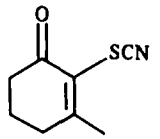
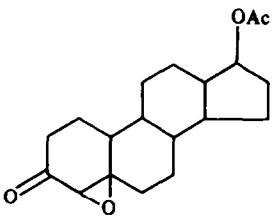
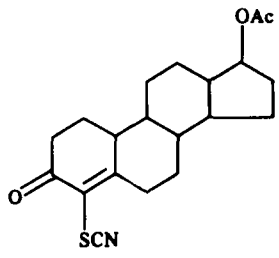
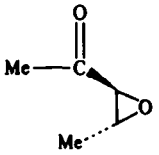
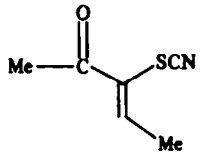


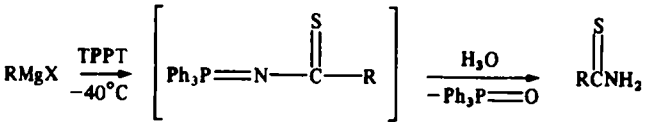
79 **80**

Organomagnesium compounds react with triphenylphosphine–thiocyanogen with the predominant formation of thioamides (**81**).[82] This method of synthesising thioamides involves mild conditions and high efficiency.

Thus, the presence of two electrophilic centres in triphenylphosphine–thiocyanogen (the phosphorus atom and the carbon of the isothiocyanate group), combined with an easy P(IV) ⇌ P(V)

Table 2. Reactions of triphenylphosphine–thiocyanogen with epoxyketones[67]

Epoxyketone	Product (**80**)	Yield (%)
		92
		71
		73
		38
		57



81a–i

81a R = $PhCH_2$, X = Cl, yield 58%; **b** R = Et, X = Br, 42%,

c R = n-Pr, X = Cl, 53%; **d** R = i-Pr, X = Br, 61%;

e R = n-Bu, X = Br, 66%; **f** R = i-Bu, X = Cl, 89%;

g R = n-C_6H_{13}, X = Cl, 60%; **i** R = n-C_8H_{17}, X = Cl, 62%

transition

$$[Ph_3\overset{+}{P}-N=C=S]\bar{S}CN \rightleftharpoons [Ph_3P=N-\overset{+}{C}=S]\bar{S}CN,$$

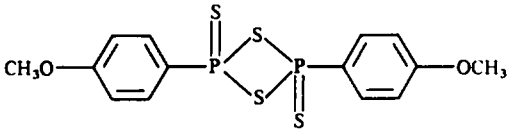
makes it possible to obtain different types of organic compounds.

In the reactions with alcohols, acids and epoxides, where the nucleophilic attack on the phosphorus atom takes place followed by NCS substitution, triphenylphosphine–thiocyanogen acts as a thiocyanating (isothiocyanating) agent. When the nucleophile becomes attached to the isocyanate group as with amines, Grignard reagents, indoles, pyrroles and enamines, then triphenylphosphine–thiocyanogen functions as a thiocarbamoylating and cyanating reagent.

A wide spectrum of its synthetic possibilities, simplicity of obtaining it, and its high reactivity make triphenylphosphine–thiocyanogen a powerful reagent.

3. LAWESSON'S REAGENT (LR)

Among the most effective thionating reagents known at present is the dimeric anhydride of methoxyphenyldithiophosphinic acid—2,4-bis-(*p*-methoxypheny)-1,2,3,4-dithiadiphosphetane-2,4-disulfide, known in literature as Lawesson's reagent.



LR, developed and introduced into the practice of chemical synthesis by Lawesson and co-workers in 1978, has been widely used to synthesise thioketones, thioamides, esters of thio- and dithiocarboxylic acids, thiopeptides, sulfur-containing heterocycles, thioxocyclanes, various phosphacyclanes and macrocyclic thioesters, which are often inaccessible by other methods.

Reactions of anhydrides of alkyl(aryl)dithiophosphonic acids—alkyl(aryl)thionophosphine sulfides—with different nucleophilic reagents, with or without a mobile hydrogen atom, are used to synthesise alkyl(aryl)dithiophosphonic acids, their salts and other derivatives.[83,84] Thionophosphine sulfides themselves were mainly obtained in the reaction of alkyl(aryl)dichlorophosphine sulfides with hydrogen sulfide at elevated temperatures.[85]

The attractiveness of LR is associated with its ready availability, simplicity and convenience of use, high yields of sulfur-containing reaction products, and comparative ease of isolating them from reaction mixtures.

Two simple methods have been developed to obtain LR: the reaction of anisole with P_4S_{10} (150°, 6 hr, yield 71%)[86] and reaction of anisole with red phosphorus and elemental sulfur[87] (150–155°, 5.5 hr, yield 76%). LR is a commercial product.[88]

The following processes are associated with the chemical reactions of LR:

(i) substituting sulfur for oxygen in oxygen-containing functional groups (a variant of the O,S-interchange reaction);

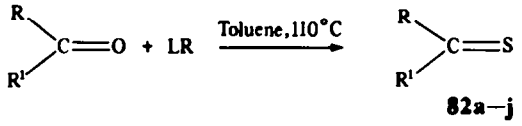
(ii) opening the LR dithiadiphosphetane ring under the action of the substrate functional groups with the formation of *p*-methoxyphenyldithiophosphonic acid derivatives which subsequently participate in various intra- and intermolecular transformations;

(iii) reactions of monomeric *p*-methoxyphenylphosphine disulfide cycloaddition to substrate's multiple bonds;

(iv) insertion of monomeric *p*-methoxyphenylphosphine sulfide into the substrate's labile bonds.

3.1. *Reactions with carbonyl compounds*

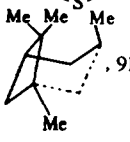
3.1.1. *Ketones.* Under the action of LR, ketones are easily converted into thioketones (**82**) by heating a mixture of reagents at 110° in anhydrous toluene in a current of nitrogen.[86]



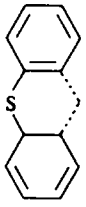
82a–j

82a R = R¹ = Ph, yield 98%; **b** R = Ph, R¹ = *p*–MeC$_6$H$_4$, 95%; **c** R = Ph, R¹ = *p*–BrC$_6$H$_4$, 98%,

d R = Ph, R¹ = *m*–NO$_2$C$_6$H$_4$, 96%; **e** R = Ph, R¹ =  , 97%; **f** R = R¹ = *p*–Me$_2$NC$_6$H$_4$, 92%;

g R = Ph, R¹ =  , 32%; **h** R + R¹ = 

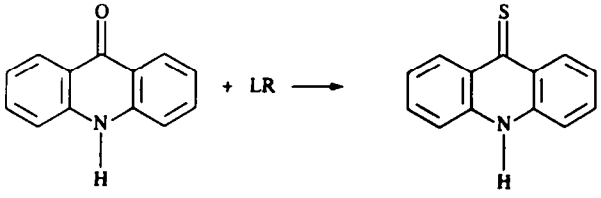
, 91%; **i** R = R¹ =  , 83%;

j R + R¹ = 

, 95%

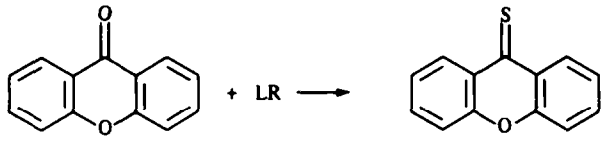
In most cases, thioketones are the only reaction products, even if there are other functional groups in the substrate molecule. It should be noted that practically all the Michler's ketone is also converted into Michler's thioketone (**82f**), in spite of the fact that tertiary amines usually form betaines with thiophosphine sulfides.[83] The dimethylamino-group in Michler's ketone does not seem to be affected in the reaction with LR because of the delocalization of the nitrogen atom unshared electron pair, or for steric reasons.[86] The method of obtaining Michler's thioketone with the help of LR is much more convenient than the previous method of thionation of Michler's ketone in liquid HF.[89]

The ease of ketone thionation with LR depends on the solvent. For instance, 9-acridanone is converted into 9-acridanthione (**83**) within 1 hr at 80° in benzene and dimethoxyethane to the extent of 72 and 70%, respectively; in toluene within 0.5 hr at 110° (69%) and in hexamethylphosphorus triamide (HMPA) within 3 hr at 140° (70%).[90] Note that 9-acridanone was also converted into **83** with the help of P_4S_{10} in HMPA[91] and with elemental sulfur.[90] The yield of **83** in the latter case is, however, much lower.



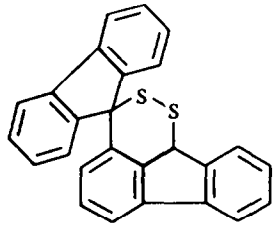
83

Other cyclic ketones are also easily converted into corresponding thioketones with the help of LR. Xanthone is quantitatively converted into thioxanthone (**84**) at 80°.[92] Fluorenone, in the reaction with



84

LR at 80°, initially forms thiofluorenone, which, however, is gradually converted into thiofluorenone dimer (**85**) (yield 55%) and 9,9'-bis-9H-fluorenylidene (**86**) (5%).[92] In a special experiment it was



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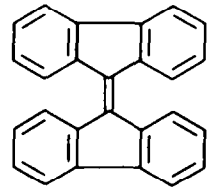
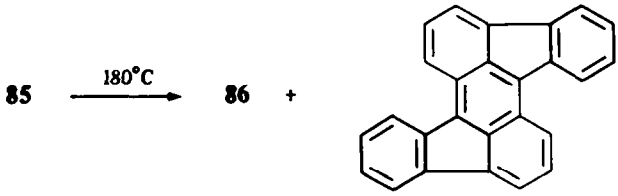


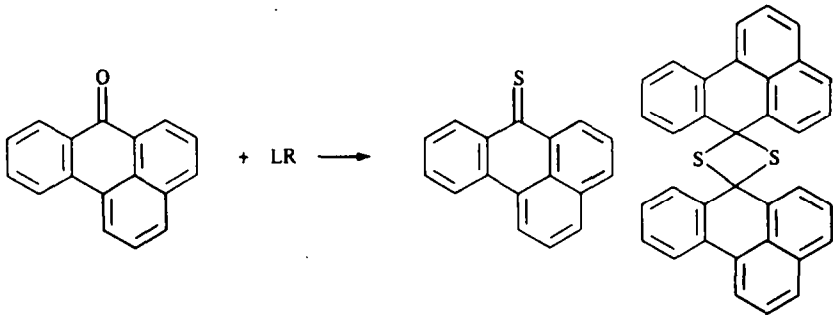
86

shown[92] that, when heated to 180°, fluorenone dimer forms a mixture of **86** and rubicene (**87**).



87

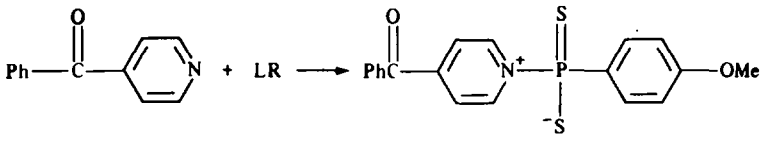
It was believed that benzanthrone thionation, passing through a stage of thiobenzanthrone (**88a**), also leads to its dimer (**88b**). Later, however, on the strength of ^{13}C-NMR spectra analysis it was established[92] that the product of benzanthrone thionation is actually a monomeric thioketone (**88a**). The broadening of all the proton lines in its PMR spectrum at low temperatures is caused not by dimerization but by a certain association of **88a** molecules.



88a **88b**

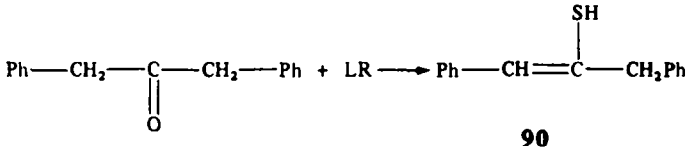
As already mentioned, thionation of ketones with the help of LR does not in all cases result in the formation of thioketones. Sometimes the reaction does not proceed at all, or sulfur-containing products other than thioketones are formed. For instance, while 3-benzoylpyridine is easily converted into 3-thiobenzoylpyridine (**82**), 2- and 4-benzoylpyridines do not form thioketones in their reaction

with LR. In these cases, LR was shown to react with the pyridine ring at 20°, leading to the organophosphorus betaine (**89**).[92]



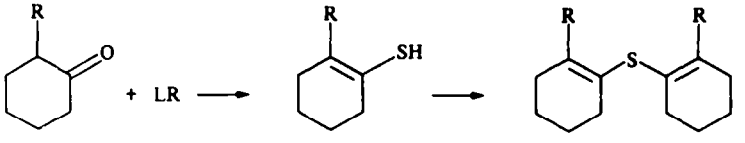
89

In the reaction of LR with dibenzyl ketone, the enethiol (**90**) is obtained (46% yield).[86]



90

Enethiolization of the formed thioketones occurs rather frequently in the reactions of ketones with LR. Cyclic enethiols (**91a** and **91b**), obtained as a result of the interaction of LR with methyl- and phenylcyclohexanone, respectively (80°, 3 hr), are converted into the unsaturated sulfides (**92**).[92]

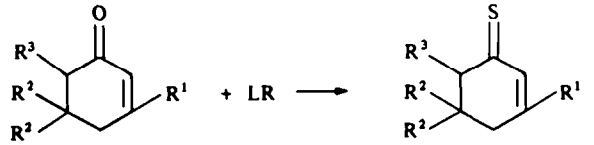


91 **92**

a R = Me
b R = Ph

Sterically hindered ketones—2,2,5,5-tetramethylcyclopentanone and di-tert-butyl ketone—are not thionated by LR. In other cases, such as the reaction with simple ketones—octanone and diisopropyl ketone—thionation proceeds but the isolation of the thioketones is impossible.[92]

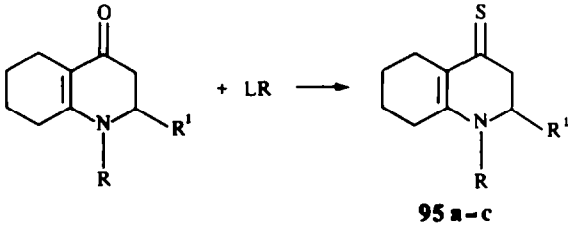
The synthetic result of the reaction of LR with α,β-unsaturated ketones is determined by their structure. Cyclic α,β-unsaturated ketones (**93**) are smoothly thionated yielding thioketones (**94**) at 60° within 4 hr but only **94c** is stable.[92]



93 a–c **94 a–c**

94a R^1 = Me, R^2 = R^3 = H, yield 86%; **b** R^1 = Me, R^2 = H, R^3 = i – Pr, 25%; **c** R^1 = SPh, R^2 = Me, R^3 = H, 81%.

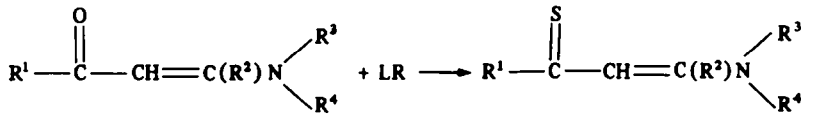
Cyclic enaminones form the corresponding thioketones (**95**) in the reaction with LR during 1 hr at room temperature.[93]



95 a–c

95a R = Ph, R^1 = H, yield 95%; **b** R = Ph, R^1 = Me, 88%; **c** R = *p* – ClC_6H_4, R^1 = H, 70%.

Acyclic α,β-unsaturated ketones interact readily with LR. The composition of the reaction products is in this case determined by a number of factors: reaction temperature, ratio between reagents, nature of chosen solvent, and the nature of substituents. Enamines (**96**) are converted into enaminothiones (**97**) (yield 20–92%) at room temperature in benzene solution.[93,94]

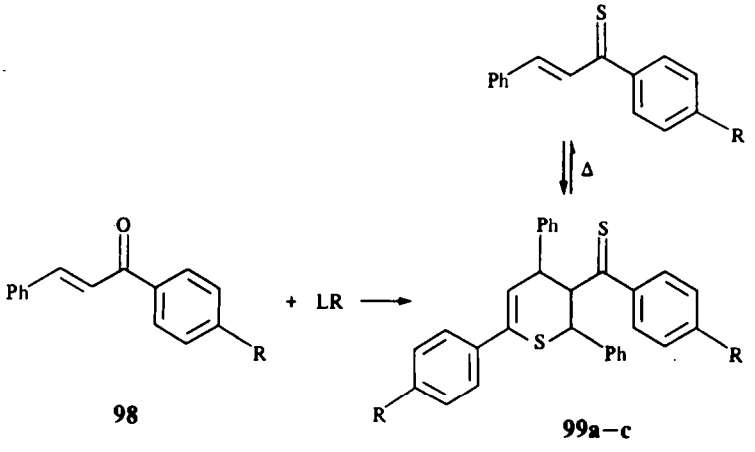


96 **97a–h**

97a R^1 = Me, R^2 = Me, R^3 = R^4 = H, yield 20%; **b** R^1 = R^2 = Me, R^3 = Ph, R^4 = H, 63%; **c** R^1 = Ph, R^2 = H, R^3 + R^4 = $-(CH_2)_4-$, 92%[93], 87%[94] **d** R^1 = *p*-$CH_3OC_6H_4$, R^2 = H, R^3 + R^4 = $-(CH_2)_4-$, 90%; **e** R^1 = *p*-BrC_6H_4, R^2 = H, R^3 + R^4 = $-(CH_2)_4-$, 92%; **f** R^1 = Ph, R^2 = H, R^3 + R^4 = $-(CH_2)_5-$, 58%[93], 87%[94]; **g** R^1 = *p*-$CH_3OC_6H_4$, R^2 = H, R^3 + R^4 = $-(CH_2)_5-$, 81%; **h** R^1 = *p*-BrC_6H_4, R^2 = H, R^3 + R^4 = $-(CH_2)_5-$, 87%.

Especially high yields of enaminothiones (**97c–h**) are characteristic for the thionation of aromatic compounds.[94]

The reaction of chalcones (**98**) with LR in boiling benzene produces a dimer (**99**).[95] When this

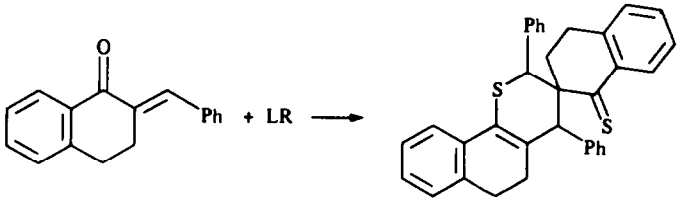


98 **99a–c**

99a R = H, yield 20%; **b** R = *p*-CH_3O, 16%; **c** R = *p*-Cl, 27%

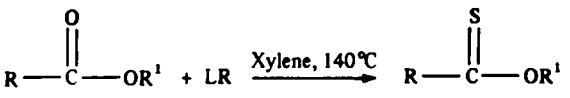
reaction is conducted in acetonitrile at room temperature[92] or when a mixture of chalcone with a twofold amount of LR is boiled in *p*-xylene,[95] heterocyclic phosphorus-containing adducts of 1:1 composition (Section 3.3) are formed.

Thione dimer **101** is also obtained by thionation of 2-phenylmethylene-1-tetralone (**100**) with LR at 80° in benzene. In boiling xylene, cyclic derivatives of dithiophosphoric acid (Section 3.3) have been isolated.[95]



100 **101**

3.1.2. *Esters of carboxylic and thiocarboxylic acids.* Aliphatic and aromatic esters of carboxylic acids react smoothly with LR in anhydrous xylene at 140°, forming the corresponding O-

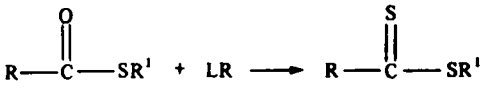


102 a–h

102a R = n – C_6H_{13}, R^1 = Et, reaction time 25 hr, yield 91%; **b** R = C_6H_{13}, R^1 = CH_2Ph, 15 hr, 90%; **c** R = Ph, R^1 = Me, 24 hr, 87%; **d** R = Ph, R^1 = Et, 25 hr, 98%; **e** R = Ph, R^1 = i – Pr, 25 hr, 93%; **f** R = Ph, R^1 = CH_2Ph, 30 hr, 88%; **g** R = 1 – $C_{10}H_7$, R^1 = Et; 24 hr, 70%; **h** R = 2 – $C_{10}H_7$, R^1 = Et, 24 hr, 92%.

alkyl(aryl)thioacylates (**102**) in high yield.[96] Thionation of the esters of carboxylic acids requires the use of a 20% LR excess, because the comparatively low reactivity of acylates in this reaction necessitates a prolonged (15–30 hr) reaction time during which part of LR is consumed by side reactions.[96]

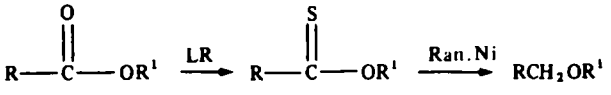
Under milder conditions (boiling toluene, 10 hr) LR thionates the S-esters of thiocarboxylic acids.[96] Dithiocarboxylates (**18b–g**) are formed with a yield approaching quantitative.



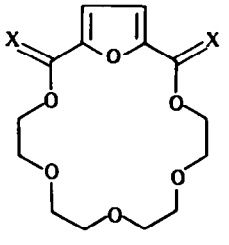
18 b–g

18b reaction time 10 hr, yield 99%; **c** 15 hr, 90%; **d** 10 hr, 99%; **e** 10 hr, 90%; **f** 10 hr, 97%; **g** R = Ph, R^1 = t – Bu, 25 hr, 97%.

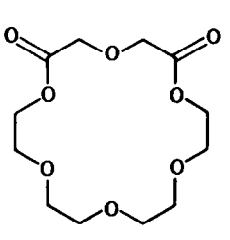
The use of LR provides a simple method for the conversion of the esters into ethers.[97] O-Esters of thiocarboxylic acids, resulting from thionating alkylcarboxylates with the help of LR, are then reduced with Raney nickel to ethers at a low temperature (– 10 to – 30°) (yield 60–70%).



This synthetic technique has also been applied to convert the crown-ester (**103a**) into furano-18-crown-6 (**103c**).[97] The thioacylate **103b**, which is formed as an intermediate, is the first representative of crowns containing a thioacylate function. It can also serve as a good complexing agent or as an



103a–c



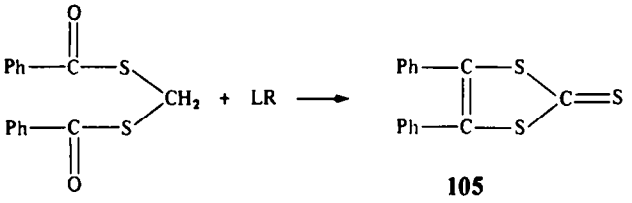
104

103a X = O, **b** X = S **c** X = H_2

intermediate to obtain other crown-esters. The crown-ester **104** is not thionated with LR in these conditions.

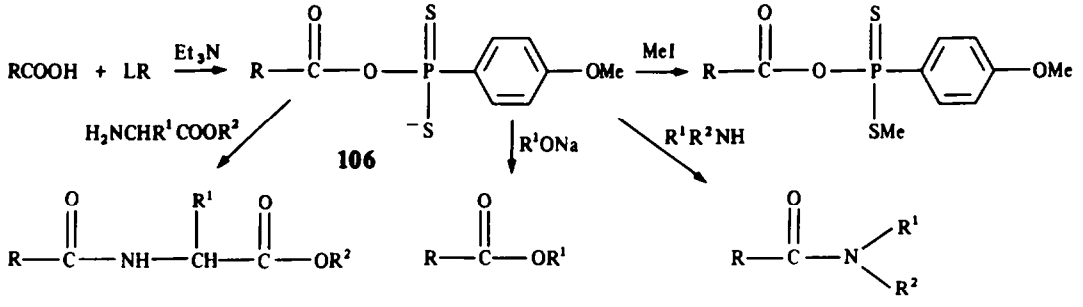
When certain acylates interact with LR, the products which are formed are not those of a simple O,S-interchange process but those resulting from subsequent reactions. For instance, in the interaction

of LR with thiobenzoic acid S,S'-methylene ester 4,5-diphenyl-1,3-dithiol-2-thion (**105**) was unexpectedly obtained.[96]

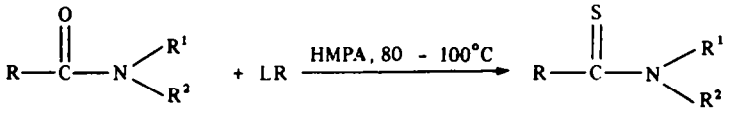


105

The carboxylic acids themselves, as most of the compounds with a mobile hydrogen atom,[83,84] open the LR dithiadiphosphetane ring with the formation of mixed carboxylic-dithiophosphonic acid anhydrides (**106**).[100,101] The mixed anhydrides (**106**) can serve as intermediates for the synthesis of peptides, esters and amides of carboxylic acids and S-alkyldithiophosphonates. LR in this case is playing the role of a cross-linking reagent.



3.1.3. *Amides of carboxylic acids.* Primary, secondary and tertiary carboxamides are converted by LR into thiocarbonyl compounds even more readily than esters of carboxylic acids.[102] Wide variation of substituents in the amine part of the acylamides does not alter the course of the O,S-interchange reaction. The introduction of even such highly reactive functions as nitro, halogen and amino groups does not complicate the thionation process. The yield of thiocarboxamides (**8, 23, 107**), when the reactions are conducted in HMPA at 80–100°, is almost quantitative.



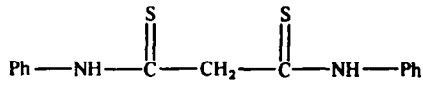
8,23,107

8a reaction time 1 hr, yield 92%; **b** 8 hr, 99%; **f** 1 hr, 99%; **g** 2 hr, 99%; **h** 5 hr, 99%; **m** 1 hr, 85%; **p** 3 hr, 98%; **q** 3 hr, 98%; **r** 2 hr, 98%. **23m** 4 hr, 88%. **107a** R = H, R^1 = Me, R^2 = Ph, 2 hr, 96%; **b** R = Me, R^1 = H, R^2 = CH(Me) Et, 3 hr, 98%; **c** R = Me, $R^1 + R^2 = -(CH_2)_4-$, 2 hr, 96%; **d** R = Me, R^1 = H, R^2 = Ph, 6 hr, 98%; **e** R = Me, R^1 = $CHPh_2$, 2 hr, 100%, **f** R = Me, R^1 = H, R^2 = *p* – ClC_6H_4, 2 hr, 98%; **g** R = Me, R^1 = H, R^2 = *o* – ClC_6H_4, 2 hr, 99%; **h** R = Me, R^1 = H, R^2 = *p* – $MeOC_6H_4$, 3 hr, 98%; **i** R = Me, R^1 = H, R^2 = *o* – $MeOC_6H_4$, 3 hr, 98%; **j** R = Me, R^1 = H, R^2 = *m* – $NO_2C_6H_4$, 3 hr, 99%; **k** R = Et, R^1 = H, R^2 = CH_2Ph, 3 hr, 98%; **l** R = CH_2Ph, R^1 = H, R^2 = Ph, 4 hr, 99%; **m** R = Ph_2CH, R^1 = R^2 = Me, 7 hr, 100%; **n** R = 4 – C_5H_4N, R^1 = R^2 = H, 15 hr, 87%.

It has been noted[102] that conversion into nitriles is not observed with primary amides. In the case of 3-pyridyl ketone, the 3-pyridine carboxylic acid amide is almost completely converted into the corresponding thiocarbonyl compound (**107n**). It is difficult to make a detailed comparison between the reactivity of ketones and carboxamides in the course of thionation with the help of LR, as these reactions were conducted under different conditions (temperature, solvent, duration).[82,102]

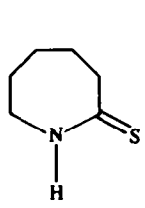
In the series of acyclic amides one can note that the time required for the completion of the O,S-interchange process increases with the introduction of large substituents in the acyl part of the molecule: for **8m** (R = H)—1 hr, for **107d** (R = Me)—6 hr, for **8b** (R = Ph)—8 hr. The effect of the electronic nature of substituents, both in the acyl and the amine parts of the substrate, cannot be rationalized distinctly.

Bifunctional amides, e.g. N,N'-diphenylmalonamide, are converted into the corresponding bisthioamide (**108**) with both carbonyl groups being involved in the process. No sign of the formation of tautomeric forms were noted in this case.[102]



108

Cyclic amides (**109** and **110**) are very easily formed within 1 hr with yields of 82 and 91%, respectively, when LR acts on the corresponding cyclic carboxamides in HMPA at 80–100°.



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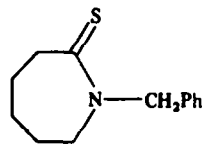
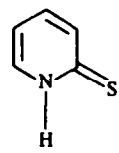


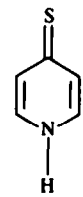
110

As already noted, the interaction of O,O-diethyldithiophosphoric acid with saccharin, 2-pyridones and 4-pyridones results in the formation of S-alkyl thioheterocycles (**21**). The reaction of the same compounds with LR during 4–5 hr leads to thiocarbonyl products (**111–113**) directly.[86,102]

111 (100%)

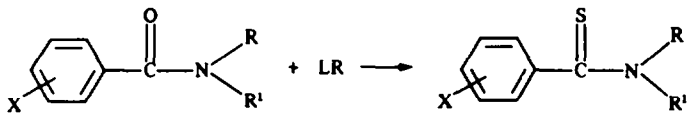


112 (63%)



113 (81%)

It is noteworthy that the O,S-interchange reaction products are also obtained from N-aroyl amines containing functional groups (OH, NH_2) in the phenyl ring that are capable of opening the dithiadiphosphetane cycle using LR in HMPA solution.[102] The yield of thioamides (**114**) in this case is somewhat lower.

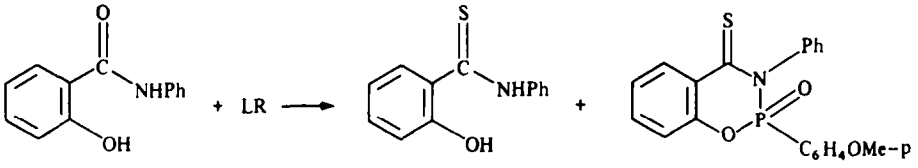


114a–e

114a X = *o* – OH, R = R¹ = H, reaction time 1 hr, yield 70%;
b X = *o* – OH, R = H, R¹ = Ph, 3 hr, 51%; **c** X = *o* – OH, R = R¹ = Me, 2 hr, 66%; **d** X = *p* – OH, R = R¹ = Me, 2 hr, 75%; **e** X = *p* – NH_2, R = R¹ = H, 3 hr, 30%.

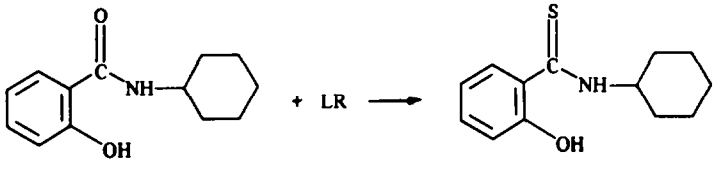
HMPA forms complexes with the aryl proton-donating substituents and this protects these groups in hydroxy- and amino-aromatic compounds.[102]

However, salicyl anilide in its reaction with LR forms, along with thionation products (**115**; 51%), a small amount (21%) of the phosphorus-containing heterocycle **116**.[102]

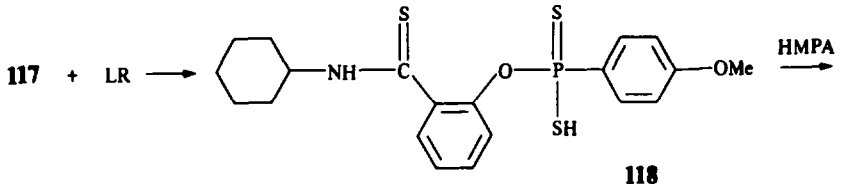


115 (51%) **116** (21%)

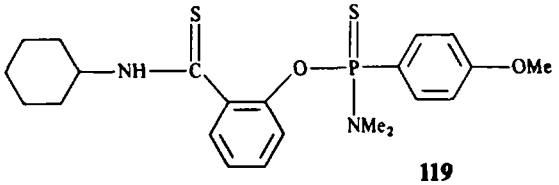
LR thionates cyclohexylsalicyl amide in HMPA with the formation of a phosphorus-containing by-product. The primary product in this case is thioamide **117** which yields the intermediate dithiophosphonic acid (**118**) which with the solvent (HMPA) is finally converted into thiophosphonic acid dimethylamide (**119**).[103]



117



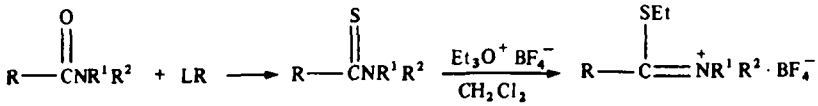
118



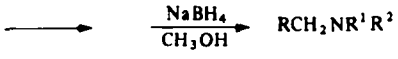
119

The use of LR reactions with carboxylic acid amides offers new possibilities of synthesising some other types of organonitrogen compounds besides thioxamides.

The selective reduction of amides to amines involves the conversion of amides into thioxamides (yield 70–90%), alkylating the latter to mercaptomethyleniminium salts (**120**), followed by reducing them to amines (**121**) with sodium borohydride. The overall yield of amines is 70–100%.[104]

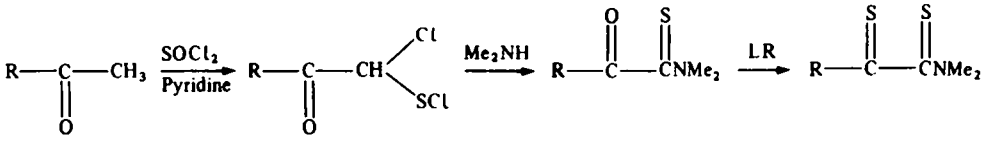


120



121

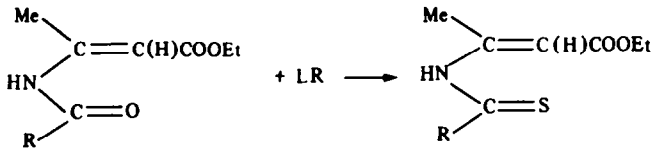
LR was used to obtain new thioxo-thioamides (**124**)—representatives of an almost unexplored class of compounds—in accordance with the following scheme.



122 **123** **124**

Successive interaction with thionyl chloride in pyridine and dimethyl amine converts ketones into α-oxothioamides (**123**) via the unstable sulfenyl chlorides (**122**). Thionation of **123** in toluene produces the final product (**124**; 50%).[105]

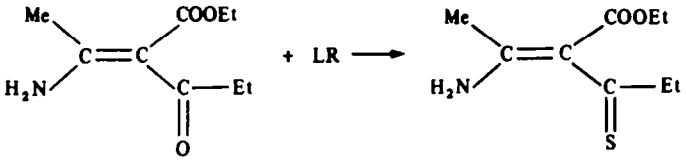
Thionation reactions with LR have been studied for the molecules of enamines with different carbonyl-containing groups in α- and β-positions. When *Z*- and *E*-isomers of 2-acylamino-2-butenoates (**125**) are heated with LR in xylene, then only the amide group is thionated, and not the carbethoxyl group, giving the thioamides (**126a–c**) plus cyclization products (see Section 3.2).[106]



125a–d **126a–c**

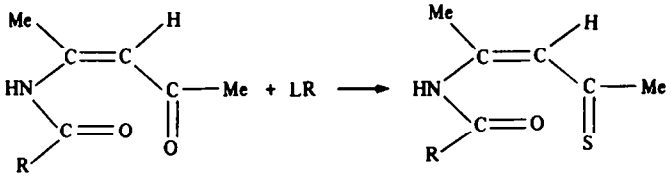
126a R = Me, yield 16%; **b** R = i – Pr, 29%; **c** R = Ph, 11%; **d** R = t – Bu, 0%.

The keto-group in the molecule of enaminone (**127**) is selectively thionated even at room temperature in dimethoxyethane solution.[106] The yield of thioxoenamine (**128**) is 65%.



127 **128**

4-Acylaminopent-3-ene-2-ones (**129**) in mild conditions in dimethoxyethane solution are also readily converted by LR into enaminothiones (**130**; yield 30–90%).[107]

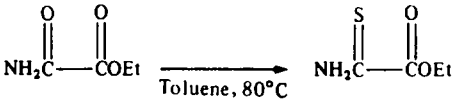


129a–d **130a–d**

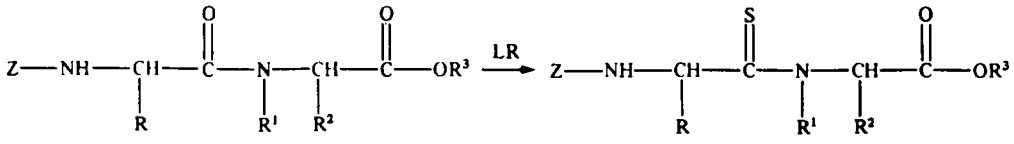
130a R = Me, yield 30%; **b** R = i – Pr, 90%; **c** R = t – Bu, 70%; **d** R = Ph, 60%.

At higher temperatures the yield of **130** decreases, because the carboxamide function is also thionated.

Ethyl oxamate is selectively transformed into ethylaminothioxoacetate (yield 87%) as a result of heating with LR at 80° for 1 hr.[108]



Differences in the reactivity of carbonyl-containing functions have made it possible to insert selectively a thiocarbonyl group into peptide molecules. At 80° only the oxamide group reacts with LR, and the urethan or the ester groups do not (these are thionated by LR at 110° and 140°, respectively). Carboxamide groups in N-Z-protected dipeptides were selectively thionated giving the thioxopeptide esters (**131**) with LR in benzene (yield 78–98%).[109]



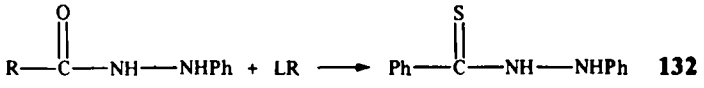
131a–f

131 Z = $PhCH_2OC(O)$; **a** $R = R^1 = R^2 = H$, $R^3 = Et$; **b** $R = R^1 = R^2 = H$, $R^3 = CH_2Ph$;
c $R = R^1 = H$, $R^2 = Me$, $R^3 = CH_2Ph$; **d** $R = R^1 = H$, $R^2 = CH_2C(O)OCH_2Ph$, $R^3 = CH_2Ph$;
e $R = H$, $R^1 + R^2 = -(CH_2)_3-$, $R^3 = CH_2Ph$; **f** $R = Me$, $R^1 = R^2 = H$, $R^3 = CH_2Ph$.

3.1.4. *Hydrazides of carboxylic acids.* Various methods have been examined to obtain hydrazides of thiocarboxylic acids. These include the reaction of dithiocarboxylic acids and their esters, as well as of sodium dithioformate and N-thiobenzoyl imidazoles, with hydrazines.[110] In some cases, thiohydrazides were synthesised by thionating the corresponding oxohydrazides with the help of P_4S_{10}.[110] All these methods were, however, associated with either a poor yield of the required products or the formation of a mixture of reaction products.

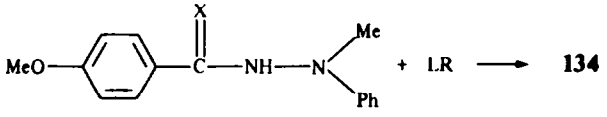
The interaction of carboxylic acids hydrazides with LR is, in principle, capable of leading to thiohydrazides. It is only in a few cases, however, that the reaction stops at the stage of the thiohydrazide.

Benzoic acid phenyl hydrazide produces the corresponding thiocarbonyl compound **132** (yield 24%) on heating a mixture of the reagents in benzene.[111] Along with **132**, phosphorus-containing heterocycles are obtained in this case. Phenyl hydrazides of other carboxylic acids are cyclized in the

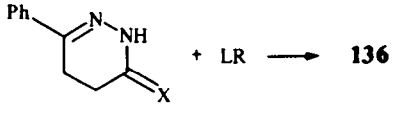


132

reaction with LR to form the corresponding thiazaphospholes (Section 3.3). In this reaction acyl hydrazides which are incapable of forming heterocycles such as 4-methoxy-N′-methyl-N′-phenylbenzohydrazide (**133**) and the heterocyclic hydrazide (**135**) are thionated to thioxo-compounds (quantitative yield).

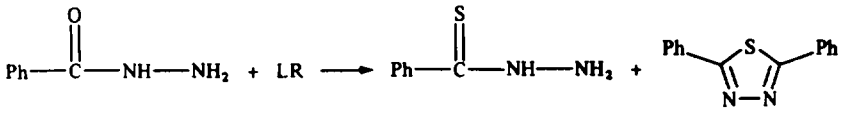


133 X = O
134 X = S

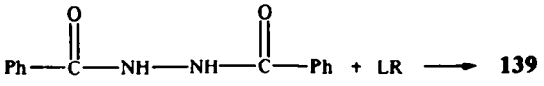


135 X = O
136 X = S

Thiobenzoic acid hydrazide has been isolated (yield 20%) in the reaction of benzoylhydrazine (**137**) with LR. Thionation is accompanied by the production of small amounts (9%) of 2,5-diphenyl-1,3,4-thiadiazole (**139**). The formation of **139** is assumed to be associated with intermediate N-benzoylation



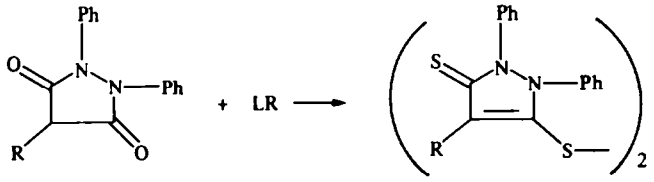
137 **138** **139**



140

or thiobenzoylation of **137** or **138**. This is confirmed by the conversion of 1,2-dibenzoylhydrazine (**140**), into **139** by LR. Cyclization of this kind was also observed in the reaction of **140** with P_4S_{10}.[112,113]

The compounds formed in the reaction of 3,5-pyrazolidinediones with LR (80–110°, 4 hr) are not the corresponding 3,5-pyrazolidinedithiones, but 3-pyrazoline-5-thione disulfides (**141**).[108]

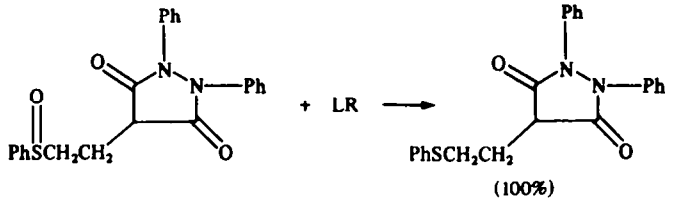


141

141a R = Me, yield 85%; **b** R = Bu, 89%; **c** R = Ph, 78%

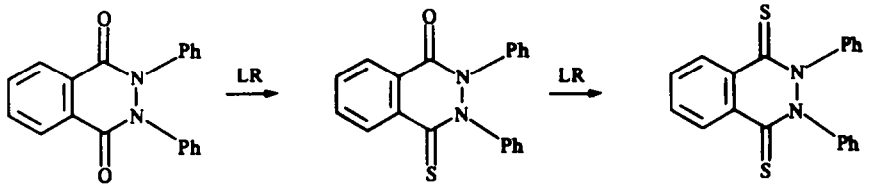
d R = CH_2CH_2SPh, 74%

Unsubstituted in the C-4 position (R = H) or benzal-substituted (R = PhCH=) 1,2-diphenyl-3,5-pyrazolidinediones react with LR but do not yield identifiable products. If the C-4 substituent contains a sulfoxide group then the sulfoxide is reduced (Section 3.4).



(100%)

1,4-Phthalazinedione (**142**) can be thionated in a step-wise manner. The reaction conducted at 80° with the molar ratio of **142**: LR = 2:1 produced 1-phthalazine-4-thion (**143**; yield 85%). With a molar ratio of **142**: LR = 1:1 then the reaction product is 1,4-phthalazinedithione (**144**; yield 91%).[108]

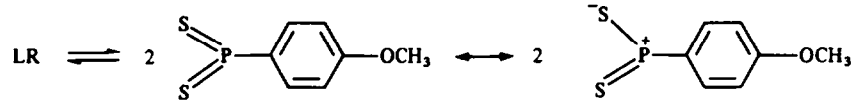


142 **143** **144**

Although there is no information in literature on the mechanism of LR thionation, the available experimental data leads to the following proposal.

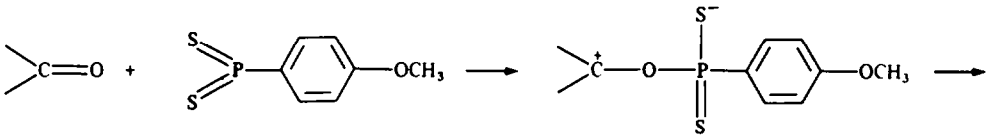
The most characteristic feature of thiophosphinyl sulfides is their high reactivity towards nucleophiles. Proton-donating reagents in this case convert LR and its analogues into derivatives of dithiophosphonic acids. Neutral nucleophiles and LR form betaines.[83,84]

In reactions with carbonyl compounds LR is assumed to act in its monomeric dithiometaphosphonate form LR'[92,95] with a contribution from the resonance structures LR".[92]

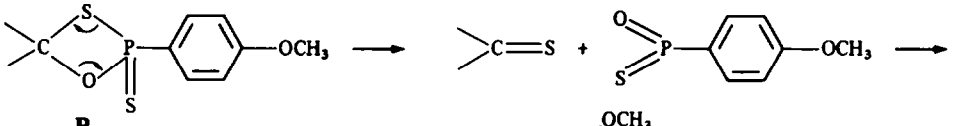


LR' LR"

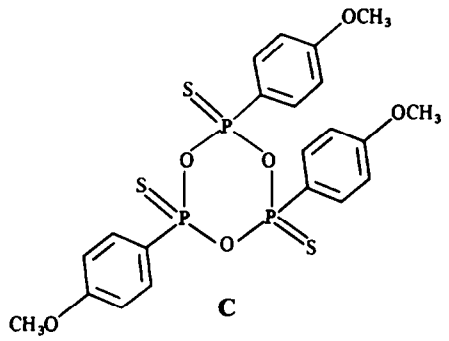
In the LR' ↔ LR" form the phosphorus atom is electrophilic as are other derivatives of tricoordinated pentavalent phosphorus.[114–116] Consequently, it is this atom which is attacked by the electron-donating substrate. This results in the formation of the intermediate **A**, which then, via the thioketal cyclic structure **B**, decomposes into a thiocarbonyl compound and the product **C**.



A



B



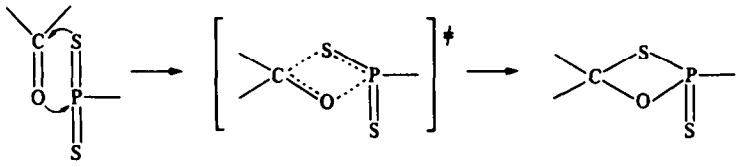
C

This scheme is similar to that proposed for the O,S-interchange reactions of phosphorus dithioacids. In both cases, at intermediate stages of thionation, the phosphorus atom coordination number increases, in dithiophosphates from 4 to 5 and in thionophosphine sulfides from 3 to 5. Two important factors determine the ability of phosphorus dithio-derivatives to enter easily into O,S-interchange processes (i) the kinetic factor involving the relative ease of the phosphorus atom changing its coordination number, and (ii) the thermodynamic factor involving the formation of a stronger P=O (130 kcal/mol) bond instead of a P=S (90 kcal/mol) bond.[13]

This thionation mechanism with the participation of LR can be confirmed by the increasing activity of carbonyl compounds in their reactions with LR, coinciding with the growth of carbonyl oxygen nucleophilicity. In some cases, a trimer of *p*-methoxyphenylmetathiophosphonate **C** has been isolated from a mixture of products of the interaction between carbonyl compounds and LR.[102,117,118]

It should be noted that the scheme of nucleophilic attack upon the electron-deficient phosphorus atom by oxygen can also be suggested for thionation by the thionophosphine sulfide dimer. This is made even more probable by the inclusion of the phosphorus atom in strained 4- and 5-membered rings which raises substantially the effective positive charge upon it.[14,15]

Another variant of the mechanism for the thionating action of phosphorus dithioacid derivatives which can explain the low sensitivity of reaction rate towards the nature of substituents is the proposal of simultaneous electron density transfer between the carbonyl group and the P=S group with the formation of the cyclic intermediate **B** via the transition state **D**. This would reduce the electronic effect



D **B**

of substituents bonded to the phosphorus and the carboxylic oxygen atoms. The occurrence of [2+4] and [2+3] cycloaddition of LR with various unsaturated systems (Section 3.3) serve as evidence supporting such a mechanism.

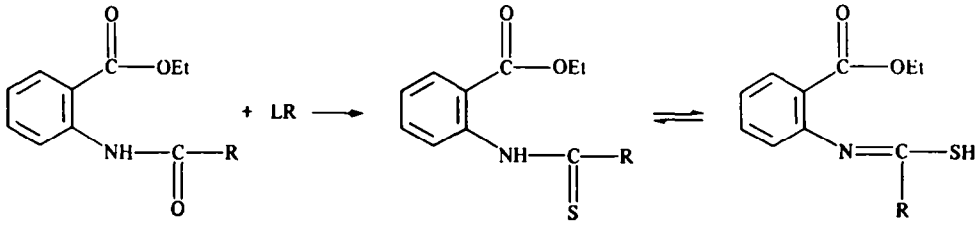
On this basis it can be assumed that all 1,2,3,4-dithiadiphosphetanes will function as thionating agents irrespective of the nature of organic groups attached to the phosphorus atom. The convenience of using LR is mainly associated with the ease of obtaining it, although it is not excluded that the *p*-methoxyphenyl group proves to be optimal, from the point of view of the most favourable electronic situation on the thiophosphoryl reaction centre, in the course of the O,S-interchange process.

3.2. *Synthesis of sulfur-containing heterocyclic compounds*

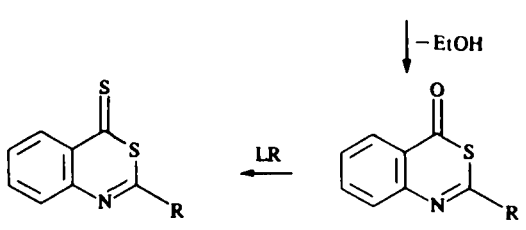
Examples of the formation of sulfur-containing cyclic compounds in O,S-interchange reactions between oxocyclanes and LR, or by intramolecular transformations of the thionation products of carbonyl substrates by triphenylphosphine–thiocyanogen have already been given.

If LR thionation produces compounds where the thiocarbonyl group is adjacent to the atom (N,C) carrying a sufficiently mobile hydrogen, conditions for enethiolization are created. Enethiolization often accompanies the formation of thiocarbonyl compounds with the insertion of a sulfur atom into the organic molecule by different methods.[119,120] The equilibrium of thiocarbonyl compound–enethiol tautomers may be completely shifted towards the latter when there is a strong enough electron-acceptor group at the thiocarbonyl carbon.[121]

If the thiocarbonyl product capable of enethiolization contains a functional group with which the enethiol sulfhydryl group can interact then sulfur-containing heterocycles may be formed. Thus, ethyl-2-acylaminobenzoates (**145**) react with LR in benzene at 80°, forming a mixture of ethyl-2-thioacylbenzoates (**146**), 2-substituted 3,1-benzoathiazine-4-ones (**148**) and 2-substituted 3,1-benzothiazine-4-thiones (**149**).[122]



145a-f **146a-f** **147**



149a-f **148a-f**

Table 3. Products of LR thionation of **145** (benzene, 80°)[122]

R	Reaction time (hr)	Yield (%)		
		146	**148**	**149**
a H	1	98	—	—
b Me	5	62	8	16
c Et	5	47	7	45
d i-Pr	5	44	8	32
e t-Bu	72	2	—	96
f Ph	10	67	—	30

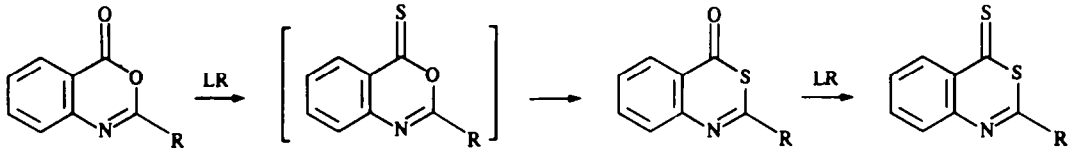
Thionation of **145** proceeds selectively, involving the amide but not the ester groups and this results in the formation of thioamides (**146**). These thioamides (**146**) can yield imidothiols (**147**), which can undergo intramolecular cyclization to 3,1-benzothiazine-4-ones (**148**) which enter into the O,S-interchange reaction with the excess of LR, yielding the dithio-derivatives (**149**).

2-Formamidobenzoate (**145a**) yields the thioamide (**146a**; quantitative yield). An increase in the volume of substituents at the amide carbon atom leads to a decrease in the activity of amides at the thionation stage in the **145b–f** series and requires an increasing period of time for O,S-interchange. The processes of ring-closure and dithionation in this case have enough time to be completed. The tert-butyl analogue (**145e**), within the period of time required for thionation, is almost fully converted into the dithio-derivative (**149e**).

A similar effect is attained with an increase in the temperature of the reaction between 2-acylaminobenzoates (**145**) and LR. When thionation is conducted in xylene (140°) the reaction products are mainly 2-*R*-3,1-benzothiazine-4-thiones (**149**; yield 82–89%; in the case of **145a** the yield is small—20%).

Ethanol, generated in the course of the reaction, in some cases complicates the process by interacting with LR giving small amounts of phosphorus-containing by-products.[122]

The step-wise course of the thionation process was demonstrated in a model reaction of 2-substituted 3,1-benzoxazine-4-ones (**150**) with LR.



150a R = Me, **b** R = Ph **148b,f** **149b,f**

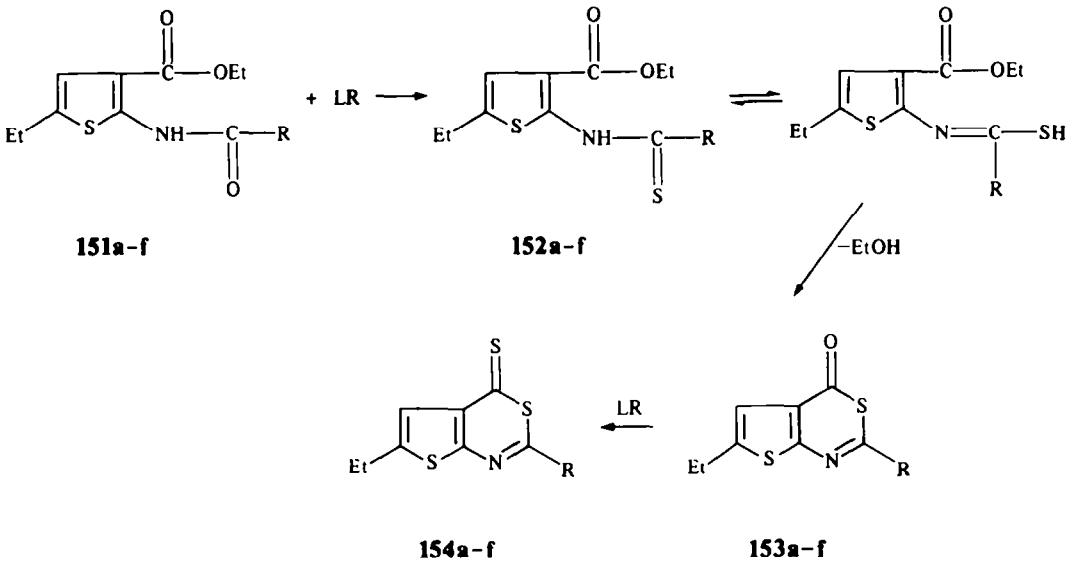
2-*R*-3,1-benzoxazine-4-thiones, formed at the first stage of **150** thionation, are unstable and are easily isomerized into thiacyclanes (**148b, f**) which can be isolated and separately converted into thioxoderivatives (**149b, f**) by reaction with LR.

Ring-closure was also observed to be taking place in the thionation of ethyl-2-acylamino-5-ethyl-3-thiophene carboxylates (**151**) with LR.[123] When the reaction is conducted in benzene at 80° ethyl-2-thiocycloamino-5-ethyl-3-thiophene carboxylates (**152**) are formed (yield 78–86%).

At an elevated temperature (140°) in xylene, the result depends upon the reaction time. After 12 hr a mixture of 2-thioacylamino-5-ethyl-3-thiophene carboxylates (**152**) and 6-ethylthieno[2,3-d] [1,3]-thiazine-4-thiones (**154**) is formed. After 24 hr the processes of ring-closure and thionation are fully completed, and **154a–f** are formed as the only reaction products (yield 64–84%).

The validity of this reaction scheme is confirmed by isolation of all the intermediate substances. Thioamides (**152**), by heating in xylene in the presence of bases, are cyclized to form 6-ethylthieno[2,3-d][1,3]thiazine-4-ones (**153**), which are easily converted into the final products (**154**) by reaction with LR.

The selectivity of LR thionation makes it possible to separate all the stages of the formation of thiacyclanes (**149** and **154**).[122,123] This disproves the previously made assumption[35] that both

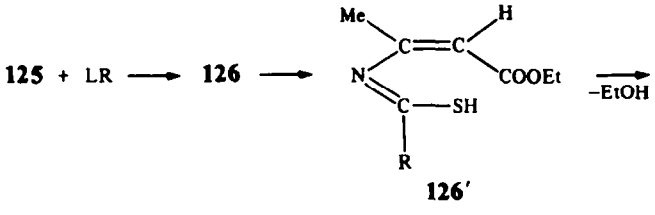


151a-f **152a-f** **154a-f** **153a-f**

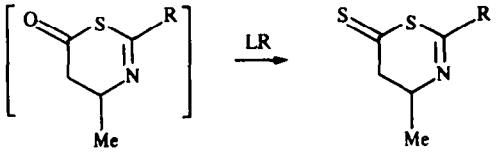
151-154a R = H; **b** R = Me; **c** R = Et; **d** R = i – Pr; **e** R = t – Bu; **f** R = Ph.

carbonyl-containing groups—the amide and the ester ones—are thionated before the ring-closure stage. On the other hand, the scheme for the formation of thioxothiacyclanes (**149** and **154**) proposed by Lawesson and his co-workers is in agreement with the previously proposed[124,125] schemes for thionation and heterocyclization produced by other thionation reagents.

Enethiolization is the cause of the appearance of the sulfur-containing heterocycles—2-*R*-1,3-thiazine-4-thiones (**156**) by the reaction of LR with substituted enamines (**125**) in xylene at 140°.[106,107]



126'

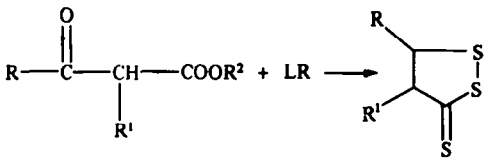


155 **156a-d**

156a R = Me, yield 55%; **b** R = i – Pr, 58%; **c** R = t – Bu, 50%; **d** R = Ph, 46%.

Cyclization of enethiols (**126'**) leads to unstable cyclic 2-*R*-1,3-thiazine-4-ones (**155**) which under the reaction conditions yield **156**.

Carbonyl compounds with an active methylene group, as already shown for dibenzyl ketone (see Section 3.1.1), easily form enethiols in the reaction with LR (e.g. **90**). Good conditions for enethiolization followed by cyclization are created with the thionation of β-ketocarboxylic acids esters. Unsubstituted and 2-monosubstituted 3-oxoacylates smoothly react with LR in toluene at 110° and a ratio of oxoester : LR = 1 : 2, producing 3H-1,2-dithiol-3-thiones (**157**).



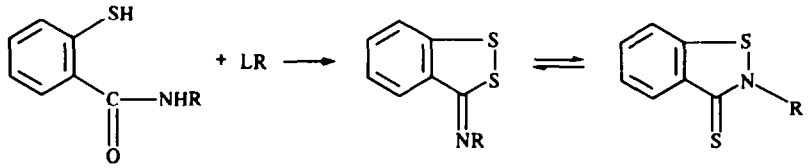
157a–i

157a R = Me, R^1 = H, yield 90%; **b** R = Me, R^1 = i – Pr, 87%;
c R + R^1 = $-(CH_2)_4-$, 90%; **d** R = Ph, R^1 = H, 95%;
e R = *p* – MeC_6H_4, R^1 = H, 96%; **f** R = *p* – FC_6H_4, R^1 = H, 90%;
g R = *p* – ClC_6H_4, R^1 = H, 91%; **h** R = *p* – BrC_6H_4, R^1 = H, 92%;
i R = *m* – $MeOC_6H_4$, R^1 = H, 90%.

The mechanism for **157** formation has not been established. However, the most probable course is an initial thionation of the keto-group, followed by enethiolization and cyclization. It is noteworthy that, if the reaction is conducted in the presence of elemental sulfur then the yields of **157** become almost quantitative. It should also be noted that thionation of 3-oxoesters by means of P_4S_{10} leads to **157** with a yield of 20%, and the presence of sulfur raises the yield to 40%.[127] The necessity of enethiolization in the course of 3-oxoacylates conversion into **157** is confirmed by the fact that these are not formed in the 2,2-disubstituted 3-oxoester–LR–sulfur system.[126]

Various sulfur-containing heterocycles have been obtained from N-substituted amides and hydrazides of 2-mercaptobenzoic acid by their reaction with LR in benzene at 80° or in HMPA at 100°.[128]

Interaction of N-substituted 2-mercaptobenzamides (**158**) or their disulfides (**159a–c**) with LR produces as the main reaction product a mixture of 3H-benzodithiol-3-imines (**160a–c**) and 1,2-benzoisothiasol-3(2H)-thiones (**161a–c**).

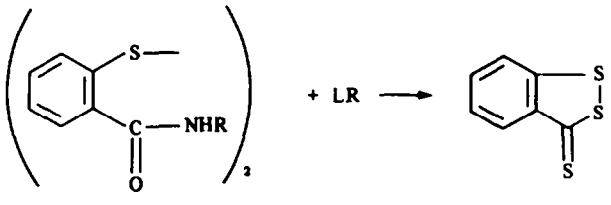


158a–e **160a–e** **161a–c**

160, 161a R = C_6H_{13}, reaction time 4 hr, total yield 62%; **b** R = cyclo – C_6H_{11}, 3.5 hr, 52%;
c R = CH_2Ph, 1.5 hr, 45%; **d** R = Ph, 9 hr, yield (**160**) 54%; **e** R = 2,5 – $Me_2C_6H_3$, 15 hr, 19%.

The isomerization **160** ⇌ **161** is known as the Dimroth rearrangement.[129] No equilibrium is observed for **160d, e** and only cyclic imides are formed.

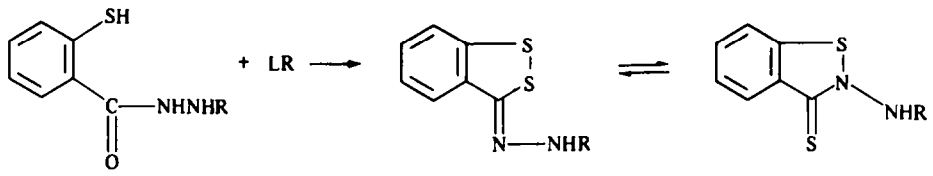
Nitrogen-containing heterocycles turn out to be unobtainable in those cases when there is no mobile hydrogen at the nitrogen atom in **158**. N,N′-Disubstituted 2-mercaptobenzamides and their



159 **162**

disulfides interact with LR with the formation of 3H-benzodithiol-4-thione (**162**). Evidently, the same thionation processes are responsible for **162** formation as those which lead to dithiolthione (**157**) in the reactions of 3-oxoesters with LR.

Dimroth rearrangements are also involved in the reactions of unsubstituted hydrazide of 2-

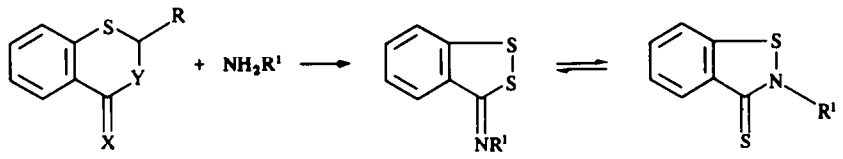


163a,b **164a,b** **165a**

164, 165a R = H, reaction time 18 hr, yield (total) 5%; **b** R = Ph, 1 hr, yield (**164**) 50%.

mercaptobenzoic acid (**163a**), or its disulfide, with LR.[128] The N-phenyl hydrazide of mercaptobenzoic acid produces only the imide (**164b**).

Heterocycles (**160, 161, 164, 165**) were also obtained in an independent way by the reaction of cyclanes (**166**) with secondary amines.[128]



166 X,Y = O,S

160, 161, 164, 165

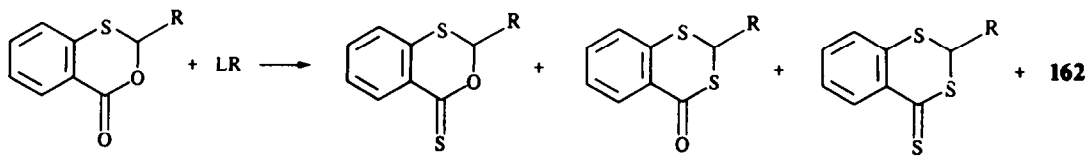
$R^1 = CH_2Ph, NHPh, OH$

Sulfur-containing heterocycles are formed in the reactions of bifunctional derivatives of aliphatic and aromatic carboxylic acids in accord with a common scheme. The first step involves thionation of the carbonyl functional group which is the most reactive with respect to LR. This is followed by enethiolization of thioxo-intermediates and, finally, the intramolecular interaction of the enethiol mercapto-group with the second functional group of the substrate gives heterocycles.

The mechanism of cyclization of oxo-compounds thionation products is not established with sufficient clarity in all cases. When heterocycles are formed in the reaction of LR with 3-oxoesters, 2-acylaminobenzoates, 2-acylaminothiophene carboxylates, the ring-closure proceeds by way of intramolecular cyclization after enethiolization. The trithio-derivatives (**157, 162**) are evidently produced subsequent to the formation of some other intermediates which are produced by "additional" thionation by LR and/or elemental sulfur. The same should be said about the formation of imino- and thioxycyclanes (**160, 161, 164, 165**) from 2-mercaptobenzoic acid amides and hydrazides.

The use of LR made it possible for Lawesson to develop a combination of original and sufficiently simple methods to obtain various oxygen-, sulfur- and nitrogen-containing heterocycles, based on the cyclization of thioxo-compounds produced by O,S-interchange.

However, the use of LR provides synthetic routes to a number of new heterocyclic systems. 3,1-Benzoxathiane-4-ones (**166**), formed in the reaction of aldehydes with 2-mercaptobenzoic acid, are converted by boiling with LR in benzene and toluene into sulfur-containing heterocycles (**167–169, 162**).[128]



166 **167** **168** **169**

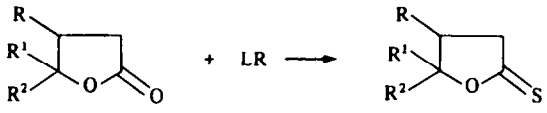
166–169a R = H, **b** $R = CCl_3$, **c** R = Ph, **d** $R = o-NO_2C_6H_4$.

In each case one or more of these heterocycles was isolated: reaction of **166a** with LR produced **167a**

(yield 68%); **166b** forms **167b** (yield 28%). With the interaction of oxathiane (**166c**) with LR, 2-phenyl-1,3-benzodithiane-4-thione (**169c**; 39%) and trithioheterocycle (**162**; 19%) were isolated; 2-*o*-nitrophenyl-substituted heterocycle (**166d**) is converted by LR into **162** (yield 33%).

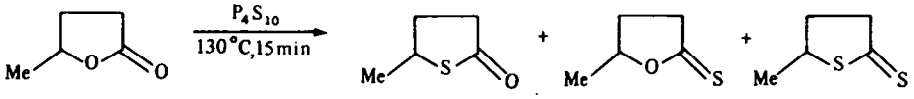
In all these reactions **166** is evidently thionated to thionocyclanes (**167**) which are isomerized to thiol isomers (**168**) which then interact further with LR to form the thionated heterocycles (**169**). Heterocycle **162** has also been obtained (yield 75–98%) in the reactions of LR with 2-mercaptobenzoic acid and its diethyl ester.[128]

Simple lactones (**170**) are converted by LR into thiolactones (**171**), when the reagents are heated in toluene at 110° or xylene at 120–125°.[130] In contrast thionation of lactones with P_4S_{10},[131] leads to a



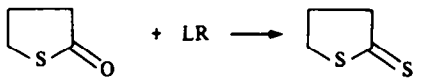
170 a–d **171 a–d**

171a R = R^1 R^2 = H, reaction time 5 hr, temperature 120°C, yield 98%; **b** R = CN, R^1 = R^2 = Me, 6 hr, 120°C, 90%; **c** R = Pr, R^1 = R^2 = Me, 8 hr, 125°C, 66%; **d** R = R^2 = H, R^1 = Me, 3 hr, 110°C, 97%.



172 **173** **174**

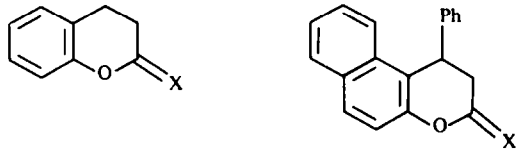
mixture of thiolo- (**172**), thiono- (**173**) and dithiolactones (**174**). Thiololactone (**175**) is converted under these conditions into dithiolactone (**176**) quantitatively.



175 **176**

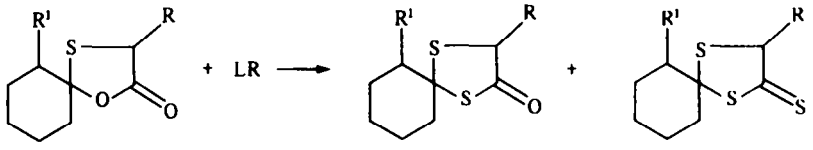
Noteworthy are the much milder conditions for the thionation of lactones by LR in comparison with carboxylic esters. A high reactivity of cyclic oxo-compounds seems to be associated with more favourable steric conditions for O,S-interchange processes.[130]

Aromatic lactones—2H-1-benzopyran-2-one (**177**) and 3,4-dihydro-4-phenyl-2H-naphtho[1,2-b]pyran-2-one (**178**) are converted into the corresponding thiono-analogues (**179** and **180**): the first when heated with LR in toluene at 110° for 2 hr (yield 99%) and the second in xylene at 140° for 11 hr (yield 87%).



177 X = O **178** X = O
179 X = S **180** X = S

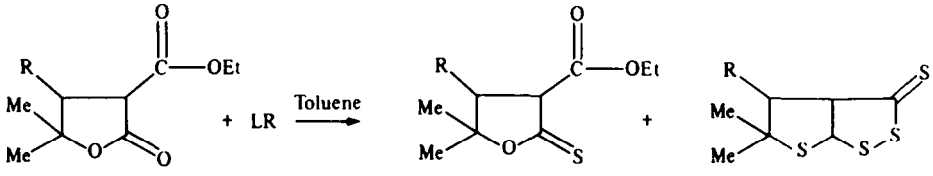
In the reaction of spirocyclic lactones (**181**) with LR (xylene, 120°, 3–7 hr) a mixture of thiolo- (**182**) and dithiolactones (**183**) is formed. The reaction seems to proceed according to the scheme of the O,S-interchange process with thionolactones being formed first. However, thionolactones are under these



181a R = R¹ = H **182a** yield 28% **183a** 58%
b R = Me, R¹ = H **b** 33% **b** 0%
c R = H, R¹ = Me **c** 12% **c** 40%

reaction conditions: they are easily rearranged into thiololactones (**182**), which are then converted into dithiolactones (**183**) by an excess of LR.

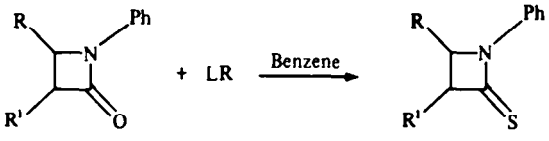
The difference between the reactivity of lactones and esters is shown in the thionation reactions of tetrahydro-2-oxo-3-furancarboxylic acid ethyl ester (**184**). At 110° in toluene the *endo*-, and not the *exo*-cyclic oxo-group, is thionated and this leads to the 2-thionolactone (**185**), and 4,5-dihydrothieno[2,3-c]1,1-dithiole-3-thione (**186**) is generated as a side-product.[130] The optimum conditions to obtain **185a**



184a R = Pr **185a,b** **186a,b**
b R = Ph

(yield 31%) and **185b** (27%) are: heating **184a, b** in toluene at 110° for 6–8 hr; the yields of **186a** and **186b** are 19 and 7%, respectively. An increase in reaction time increases the yield of **186**. Cyclization of thioxo-compounds to **186** with "additional" thionation of the substrate is similar to that resulting in the formation of dithiacyclanes (**157, 162**). Note that in the tetrathiobicycles (**186**), the original lactone ring contains a sulfur atom, which is evidently associated with thion–thiole isomerization of **185**.

Lactams are thionated by LR under even milder conditions than lactones.[118] β-Thionolactams (**188**) were obtained with a high yield by heating the corresponding lactams (**187**) with LR in benzene at 80° for 2 hr.



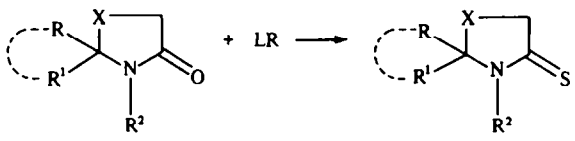
187 **188a-c**

188a R = Ph, R¹ = H, yield 87%; **b** R = Ph, R¹ = Me, 90%;
c R = PhCH=CH, R¹ = Me, 90%.

Thionation of **187** by LR proceeds nonstereospecifically. In **187** the ratio of *syn–anti* forms is 8 : 20, whereas in the products **188** the *anti*-isomer content is reduced to 10%.

Five-membered lactams (**189**) are thionated by LR to thionolactams (**190**) in high yield and rather rapidly (0.5–1 hr). However, N-vinyl-2-pyrrolidine thione (**190b**) was obtained in a yield of 24%, possibly, because polymerization of this unsaturated reagent occurred during the course of the reaction.[118]

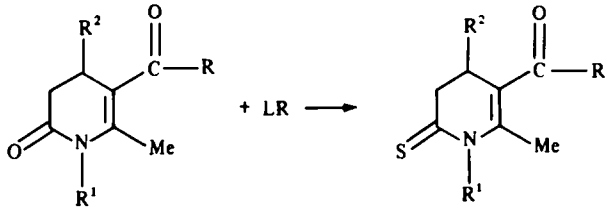
The synthetic result of the thionation reaction of 6-membered cyclic lactams (**191**) is strongly dependent on the nature of substituents R at the exocyclic carbonyl carbon and at the N- and C-4 atoms



189a-f **190a-f**

190a $R = R^1 = R^2 = H$, $X = CH_2$, reaction time 0.5 hr, yield 75%;
b $R = R^1 = H$, $R^2 = CH{=}CH_2$, $X = CH_2$ 0.5 hr, 24%;
c $R + R^1 = -(CH_2)_3-$, $R^2 = Ph$, $X = S$, 1 hr, 95%; **d** $R + R^1 = -(CH_2)_3-$, $R^2 = o-MeOC_6H_4$, $X = S$, 1 hr, 90%; **e** $R = R^1 = -(CH_2)_3-$, $R^2 = p-MeOC_6H_4$, $X = S$, 1 hr, 90%; **f** $R + R^1 = -(CH_2)_3-$, $R^2 = p\text{-}ClC_6H_4$, $X = S$, 1 hr, 99%.

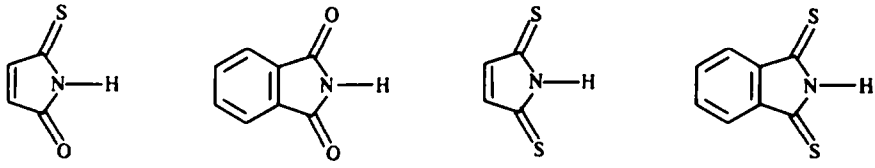
of the ring.[118] If the 3-substituent in the ring is an ester group (R = OAlkyl) a rapid and effective thionation to 6-thioxolactams (**192a–d**) occurs; the ester group in the reaction conditions (boiling in benzene) is not involved. 3-Ketosubstituted lactams (**191e, f**, R = Me) form a smaller amount of thioxolactam (**192e**) or do not form it at all (**192f**).



191a-f **192a-f**

192a R = OEt, $R^1 = R^2 = H$, reaction time 15 min, yield 88%;
b R = OEt, $R^1 = Me$, $R^2 = H$, 45 min, 75%; **c** R = OEt, $R^1 = H$, $R^2 = Me$, 20 min, 70%; **d** R = OBu-t, $R^1 = R^2 = H$, 15 min, 93%; **e** R = Me, $R^1 = R^2 = H$, 15 min, 40%;
f $R = R^1 = Me$, $R^2 = H$, 30 min, traces.

Mono- and dithioxoimides have been obtained from imides of maleic and phthalic acids. In this case, the ratio of initial reagents affects the composition of thionation products. When the reaction is conducted in the imide : LR = 1 : 0.5 system the yields of monothioxoimides (**193** and **194**) amount to 70 and 37%, and of dithio-derivatives (**195** and **196**) to 19 and 25%, respectively.



193 **194** **195** **196**

With an increase of the molar fraction of LR in the reaction mixture to 1 : 1 the yields of dithioimides increase: phthalimide produces 90% of dithiophthalimide and only traces of monothiophthalimide. Succinimide is converted into dithioimide to the extent of 70% and into the monothioxo-derivative (**193**) in 30% yield.[118]

3.3. *Synthesis of phosphorus- and sulfur-containing heterocycles*

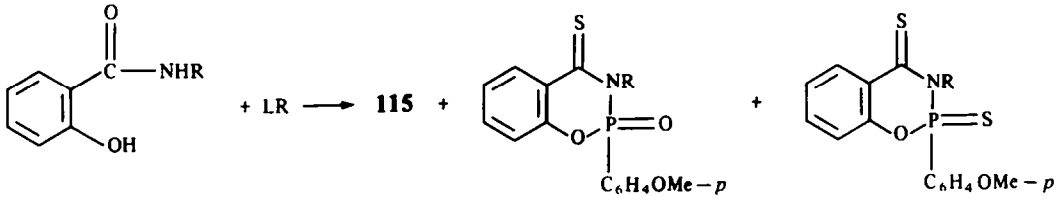
The formation of phospha- and thiaphosphacyclanes by LR involves (i) the opening of the LR dithiadiphosphetane ring under the action of proton-donating functional groups of the substrates; (ii)

the cycloaddition reactions of dithiometaphosphonate LR′ with unsaturated partners and (iii) the reactions of LR′ insertion into the labile bonds of organic cyclic carbonyl compounds.

In the first case the reaction starts with the formation of *p*-methoxyphenyldithiophosphonic acid derivatives as a result of the reaction with bifunctional reagents. One of the functions contains a mobile hydrogen which reacts with P—S forming a P—SH group and the second, located in the substrate in a position suitable for cyclization, reacts with the thiol group.

An extensive series of heterocycles containing phosphorus, nitrogen and sulfur has been obtained based on salicyclic acid derivatives. We have already noted (see Section 3.1.3) that thionation of secondary salicylamides by LR in HMPA results not only in the formation of the thioamide (**115**) but also the 2-oxo-oxazaphosphorinane (**116**).[102]

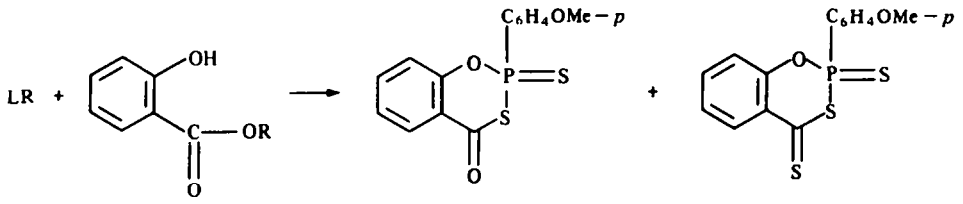
If this reaction is conducted not in HMPA which can protect the 2-oxy and the secondary amide groups, but in toluene, thus promoting the interaction of LR with salicylamide proton-donating groups, the heterocycles obtained will have 2-oxo- and 2-thioxoazaphosphorinane structures.[102]



116 **197**

a R = Ph, reaction time 10 hr, temperature 100°C, yield **115** 51%, **116** 21%, **197** 8%; **b** R = 2,5 – $Me_2C_6H_3$, 6 hr, 110°C, **116** 14%, **197** 24%; **c** R = $PhCH_2$, 11 hr, 110°C, **116** 13%, **197** 23%; **d** R = n – C_6H_{13}, 4 hr, 110°C, **116** 18%, **197** 5%; **e** R = cyclo-C_6H_{11}, only **115** (36%) was obtained.

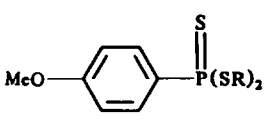
Salicylic acid (**198a**), heated with LR in toluene at 110° for 2–3 hr, forms two heterocycles: 2-(*p*-methoxyphenyl)-4H-1,3,2-benzoxathiaphosphorin-4-on-2-sulfide (**199**; yield 72%) and its thioxo-analogue (**200**; yield 10%).[132] Ethyl (**198b**) and phenyl (**199c**) esters of 2-hydroxybenzoic acid form the



198 **199** **200**

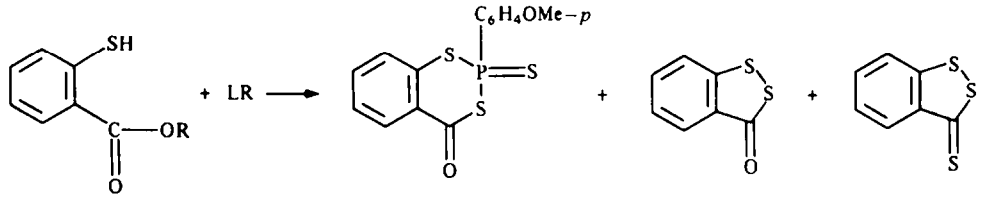
a R = H, **b** R = Et, **c** R = Ph

trithionated heterocycle (**200**; 40% yield from **198b**) and (81% yield from **198c**). The higher reaction temperature (xylene, 140°) in the last examples causes the thionation of the intermediate (**199**) yielding **200**. Diethyl-*p*-methoxyphenyltrithiophosphonate was isolated (yield 7%) as a side-product in the reaction of ethyl salicylate. Its formation is probably associated with the reaction between LR and ethanol generated during the cyclization.[132]



201a R = Et, **b** R = Me

2-(*p*-Methoxyphenyl)-4H-1,3,2-benzodithiaphosphorin-4-on-2-sulfide (**203**), along with the dithiacyclanes (**204** and **162**) are formed in the reaction of 2-mercaptobenzoic acid (**202a**) with LR in toluene at 110° with the ratio of reagents 1 : 1.



202a R = H
b R = Et

203a yield 32%
b 33%

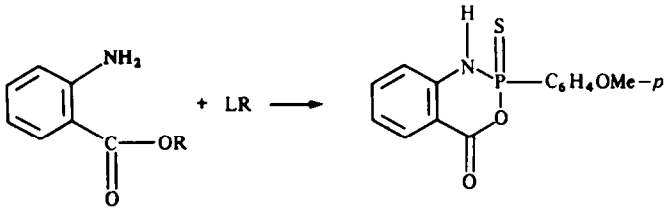
204 15%

162a 52%
b 80%

An increase in the LR ratio of reagents (1 : 2) in these conditions does not change the yield of **203**. The amount of **162** increases, and **204** is not detectable.

Ethyl 2-mercaptobenzoate (**202b**) requires harsher conditions (xylene, 140°, 2 hr) for its reaction with LR. Compound **162** is obtained in high yield, along with **203** (33%) and **201b** (10%).

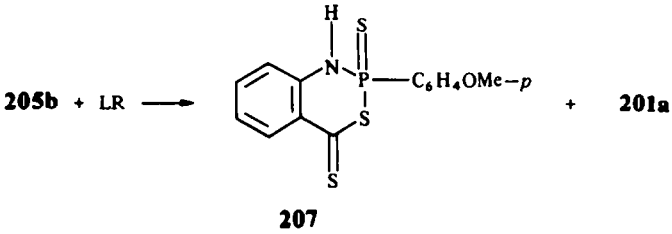
2-Aminobenzoic acid (**205a**) reacts with LR in benzene (60°) without entering into O,S-interchange; 1,2-dihydro-2-(*p*-methoxyphenyl)-4H-1,3,2-benzoxaphosphorin-4-one (**206**) is formed (50% yield).



205a R = H
b R = Me

206

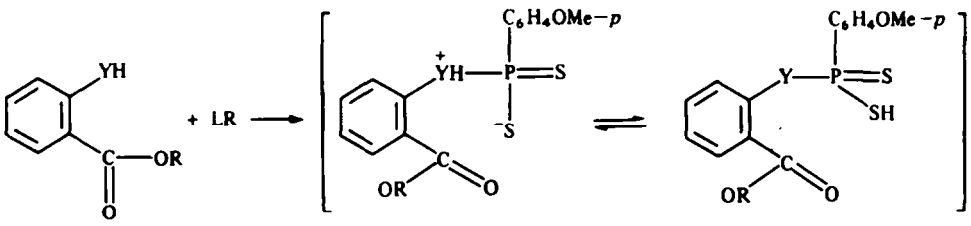
However, methyl 2-aminobenzoate (**205b**), reacting with LR in xylene at 140°, produces the fully thiilated heterocycle (**207**; yield 10%), along with trithiophosphonate (**201a**; yield 31%).



207

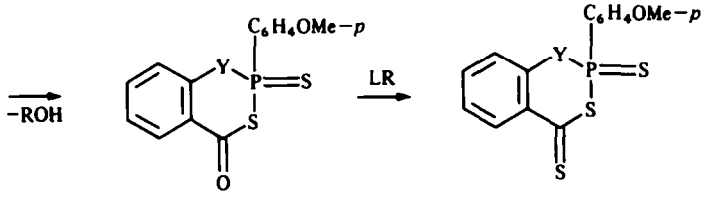
The mechanism of **199**, **200**, **203**, **206**, **207** heterocycle formation from **205b**,[132] evidently includes the nucleophilic attack by the 2-functional group of salicylates upon the monomeric LR′ phosphorus atom (or the LR 1,3,2,4-dithiadiphosphetane fragment) with the formation of the inner salt (**208**) or dithiophosphonic acid (**209**). This is followed by intramolecular cyclization with the participation of thiophosphoryl anion (in **208**) or sulfhydryl group (in **209**), leading to 6-oxophosphorinanes (**199** or **203**). Depending upon the reactivity of substrates with respect to LR and the reaction conditions, the reaction stops at the stage of oxo-derivatives (**199** and **203**) for 2-substituted salicylic acids or develops further to 2,6-dithioxocyclanes (**200** and **206**) for 2-substituted O-organosalicylates.

2-Aminobenzoic acid, probably, reacts with LR in the zwitterionic form **205a′**, and nucleophilic



198a-c (Y = O)
202a,b (Y = S)
205a (Y = NH)

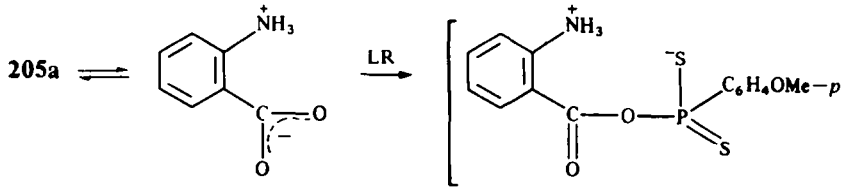
208 **209**



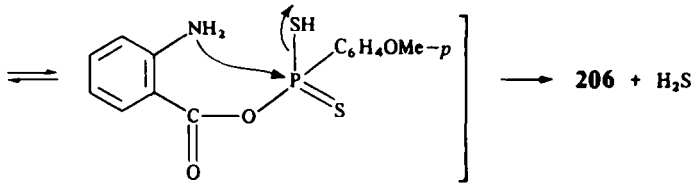
199 (Y = O)
203 (Y = S)

200 (Y = O)
207 (Y = NH)

interaction of the carboxylate anion with the phosphorus atom of LR, followed by intramolecular amination leads to the phosphorinane (**206**) with the release of H_2S.[132] In this reaction the intra-



205a'

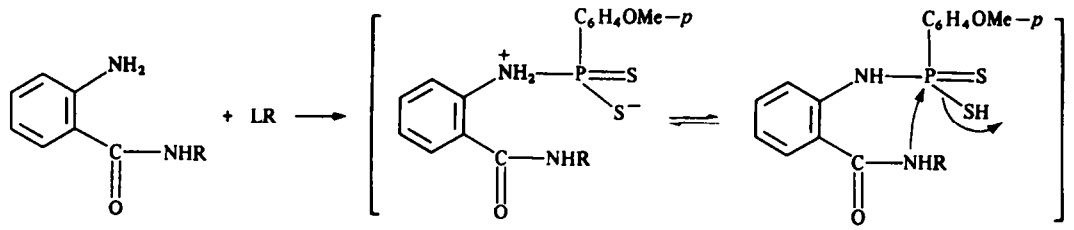


molecular basic catalysis of the nucleophilic addition of the carboxylate anion to the P=S fragment of LR inhibits the O,S-interchange.

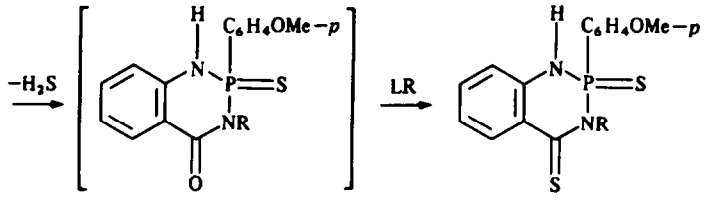
Initial formation of betaine structures is also possible in the reaction of 2-aminobenzamides (**210**) with LR which lead to 2,3-dihydro-2-(*p*-methoxyphenyl)-1,3,2,-benzodiazaphosphorin-4-(1H)-thion-2-sulfides (**211**).

Substituting the sulfur atom at the thiophosphoryl centre of LR with nucleophilic amines yields *p*-methoxyphenylthiophosphonic acid diamines (**213**). In mild conditions ammonium salts (**212**) are formed which are then transformed at higher temperature into diamides (**213**).[133]

Cyclization with the incorporation of a dithiophosphinyl group into the ring occurs in the reaction of LR with some 1,2-bifunctional aliphatic compounds.



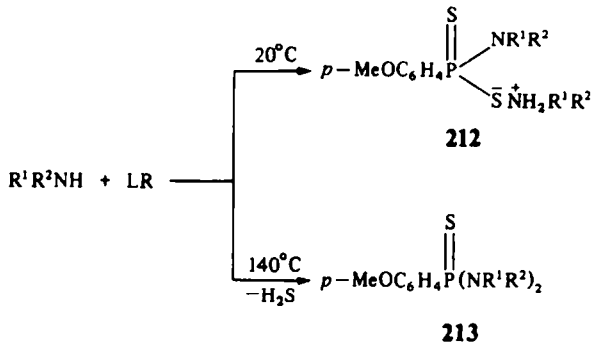
210a R = H
b R = cyclo – C_6H_{11}



211

211a R = H, benzene, reaction time 24 hr, temperature 20°C, yield 24%.
b R = cyclo – C_6H_{11}, toluene, 6 hr, 110°C, 20%.

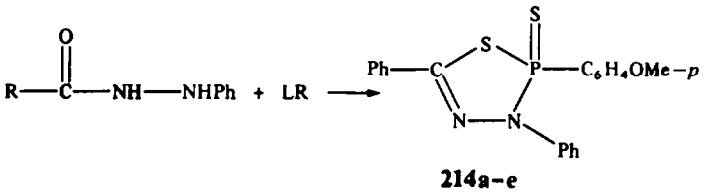
N′-Phenylhydrazides of carboxylic acids and LR in boiling benzene yield 2,3-dihydro-1,3,4,2-thiadiazaphospholes (**214**).[111] In the case of R = Ph, along with **214e**, N′-phenylhydrazide of



212

213

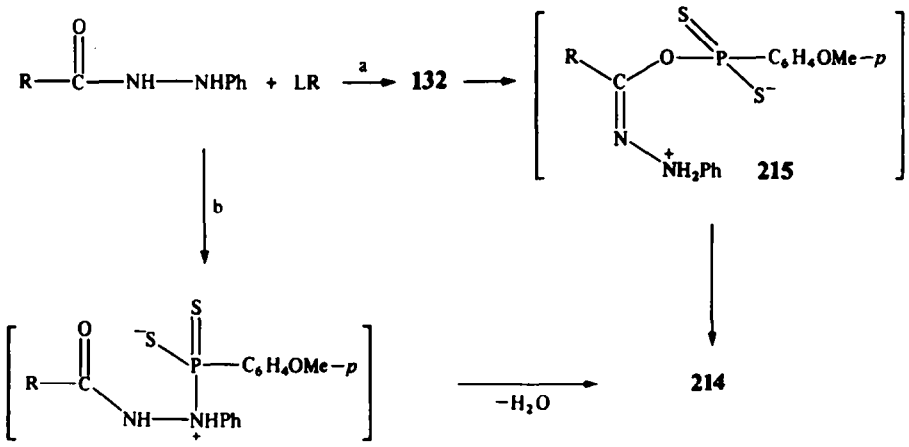
thiobenzoic acid (yield 24%) has been obtained.



214a–e

214a R = H, reaction temperature 25°C, reaction time 12 hr, yield, 36%;
b R = Me, 80°C, 10 hr, 97%; **c** R = i – Pr, 80°C, 12 hr, 65%;
d R = t – Bu, 80°C, 8 hr, 100%; **e** R = Ph, 80°C, 1.5 hr, 40 %.

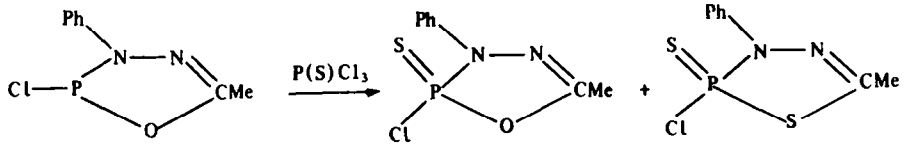
Two pathways of the formation of phospholes (**214**) are possible.[111] According to one of them (pathway a), thionation products—thiohydrazides of the **132** type—which then attacks the LR thiophosphoryl centre producing the betaine (**215**), which is then cyclized with the release of H_2S.



216

The second pathway (b) involves initial attack by the N-aryl nitrogen atom upon the P=S fragment of LR, giving the betaine (**216**). Subsequent conversion of **216** into diazaphospholes (**214**) proceeds in several stages, one of which could involve the nucleophilic addition of the thiolate anion to the carbonyl carbon. Ring-formation resulting in **214** is accompanied by the dehydrogenation of the intermediates.

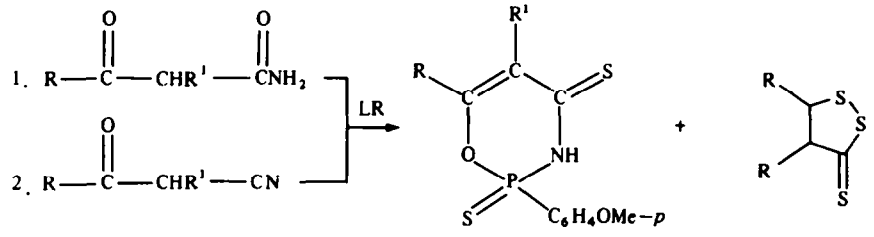
Thiadiazaphospholes (**219**) were also obtained by the thionation of phospholes (**217**), containing a trivalent phosphorus atom by $P(S)Cl_3$.[134]



217 **218** **219**

When this reaction is conducted for 20 hr at 140–180° the yields of **218** and **219** amount to 16 and 68%, respectively; under more vigorous conditions (150–170°, 25 hr) **219** was obtained (yield 96%).

Amides (reaction 1) and nitriles (reaction 2) of β-ketocarboxylic acids form in reactions with LR 6-membered organophosphorus heterocycles —4H-1,3,2-oxazaphosphorins (**220**),[126] with trithiocyclane (**157**; yield 2–17%). The reaction is conducted at 110° in toluene for 1 hr. Carbonyl substrates are

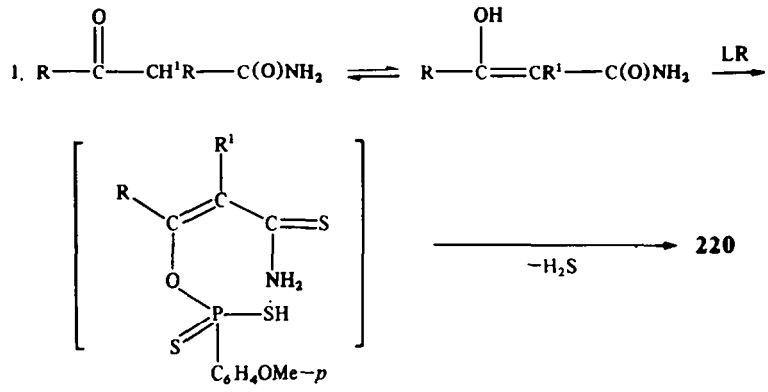


220 **157**
2–17%

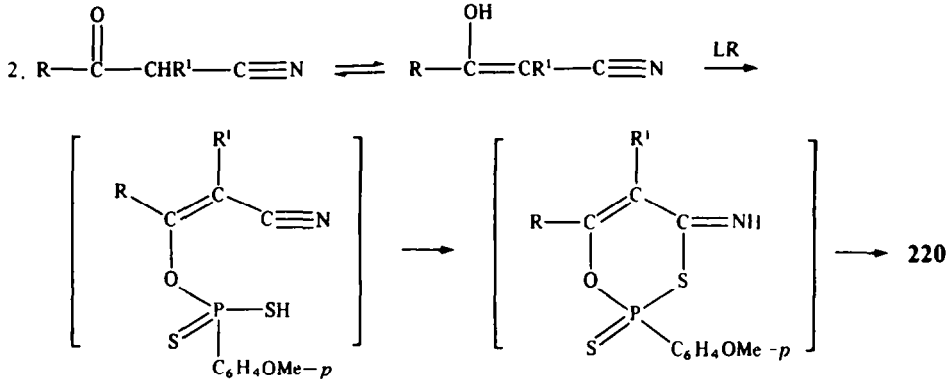
220 reaction 1 **a** R = Ph, R^1 = H, yield 94%; **b** R = $PhCH_2$, R^1 = Ph, 85%;
c R + R^1 = $-(CH_2)_4-$, 76%; reaction 2 **a** 86%; **d** R = Me, R = Ph, 72%.

assumed[126] to participate in this reaction in the enol form, yielding *p*-methoxyphenyldithiophosphonic acids (**221** and **222**) as intermediates. After that the reaction proceeds in different ways: intramolecular dehydrothionation in the case of amides and intramolecular addition of the SH

group to the C≡N bond in the case of nitriles.



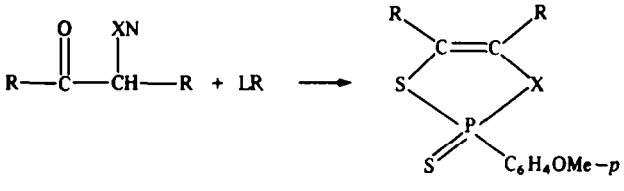
221 **220**



222 **223** **220**

Imidoyl derivatives (**223**) presumably rearrange into 4-thioxycyclanes (**220**) by a mechanism related to the isomerization of imidoyldithiophosphates into thioxoamidophosphates found in the reaction of phosphorus dithioacids with nitriles (see Section 1.2).

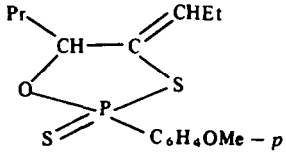
α-Hydroxy- and α-aminoketones (**224**) react with LR, forming oxathiaphospholes (**225a, b**) and thiazaphospholes (**225c**), respectively.



224 **225a-c**

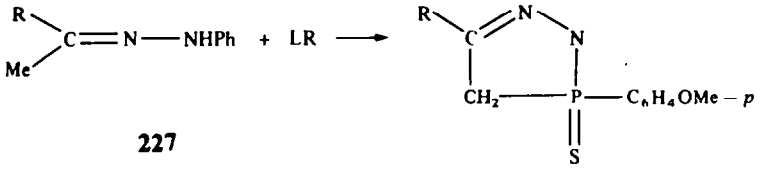
225a R = Ph, X = O, temperature 80°C, reaction time 12 hr, yield 30%; **b** R = Pr, X = O, 80°C, 1.5 hr, 10%; **c** R = Ph, X = NPh, 110°C, 35%, 12 hr.

5-Hydroxy-2-octanone (butyroin, **224b**) yields **225b** as the main product with **266** (yield 20%).



226

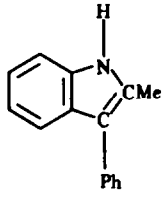
Hydrazones of acyclic and cyclic ketones and LR yield Δ^5-diazaphospholenes. The reaction of phenyl hydrazones of acyclic ketones (**227**) with LR in benzene at 50–80° give Δ^5-1,3,2-diazaphospholenes (**228**) in high yield.[135]



227 **228**

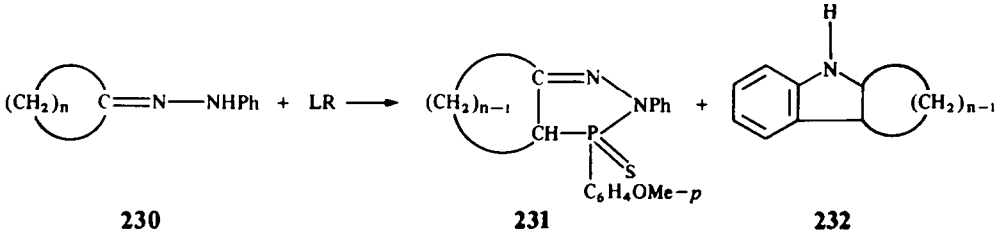
228a R = Me, reaction time 3 hr, yield 58%; **b** R = Et, 2.25 hr 83%; **c** R = Pr, 2.5 hr, 85%; **d** R = i – Pr, 4 hr, 70%; **e** R = t – Bu, 1.5 hr, 70%; **f** R = Ph, 6 hr, 69%; **g** R = CH_2Ph, 4 hr, 64%.

Methylbenzylketone phenylhydrazone (**227g**) is converted in these reactions not only into the phosphorus heterocycle (**228g**) but also into 2-methyl-3-phenyl-indole (**229**).



229

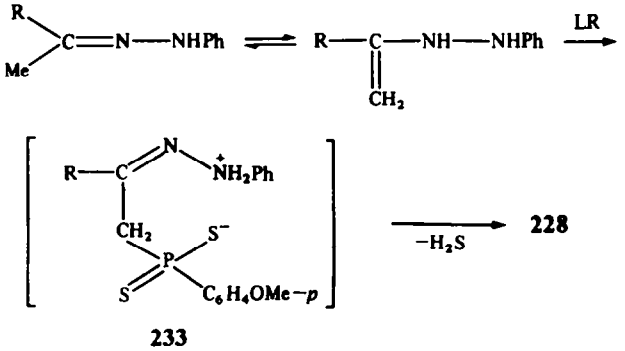
High yields of indoles (**232a** and **232b**) are characteristic of the reactions of LR with phenyl hydrazones of cyclic ketones including cyclopentanone (**230a**) and cyclohexanone (**230b**). Bicyclic organophosphorus diazaphospholes (**231a, b**) have also been obtained in these reactions. The cyclization of hydrazones to indoles is assumed[135] to proceed in accordance with Fischer's scheme of indole synthesis catalyzed by LR.



230 **231** **232**

231a n = 4, yield 21%; **b** n = 5, 40%.
232a n = 4, yield 13%; **b** n = 5, 50%.

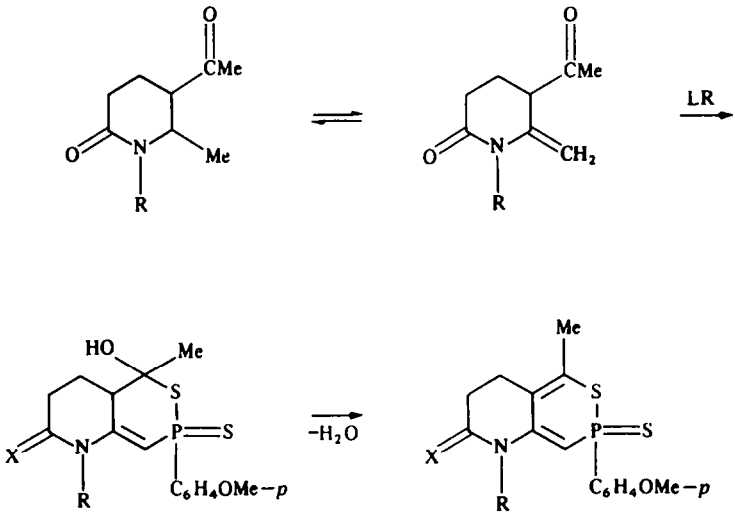
The authors[135] consider that the formation of phosphacyclanes results from the participation in these reactions of the enehydrazine forms of hydrazones, in which the terminal carbon atom becomes attached to the phosphorus centre of LR (or LR').



233

The intermediate **233** leads to the products (**228**). Hydrazones of aldehydes do not form phosphorus-containing rings in reactions with LR. Dibenzylketone phenylhydrazone reacts with LR yielding only 2-benzyl-3-phenyl indole.

C-Nucleophilic attack is also likely in the transformation of 6-membered 3-acetyl lactones (**191e** and **191f**) into heterocyclic dithiophosphonates (**234**) which accompanies the formation of the thiolactones (**192**).[118]

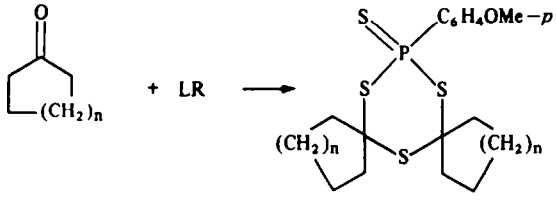


234 **235a-d**

235a X = O, R = H, yield 7%; **b** X = O, R = Me, 25%; **c** X = S, R = H, 15%; **d** X = S, R = Me, 10%.

A ring-formation process consisting of several stages leads to the compounds **234** and then yield the compounds **235**.[118]

It was assumed[92] that the interaction of cyclopentanone and cyclohexanone with LR will proceed along the O,S-interchange pathway, leading to thioketones or their trimers. Unexpectedly, however, trithiaphosphorinanes (**236**) were obtained in these reactions (benzene, 80°) (yield 50–60%).

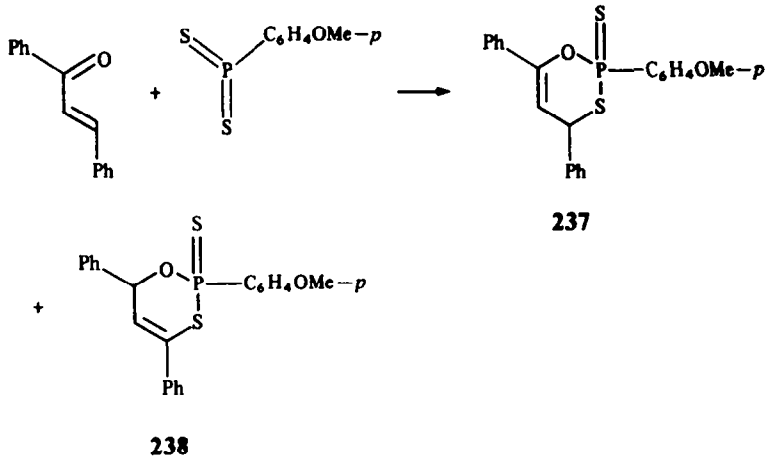


236a n = 1
236b n = 2

The authors[92] do not show the scheme of dithiaphosphacyclanes formation, believing it to be rather complicated, but do not exclude the participation of monomeric LR forms (LR', LR'', etc.)

The capability of LR' monomer to enter into the cycloaddition reactions was widely utilized for the synthesis of 4- and 6-membered heterocycles containing a phosphorus atom.[2] We should note here several later examples of phosphacyclanes formation resulting from LR' cycloaddition.

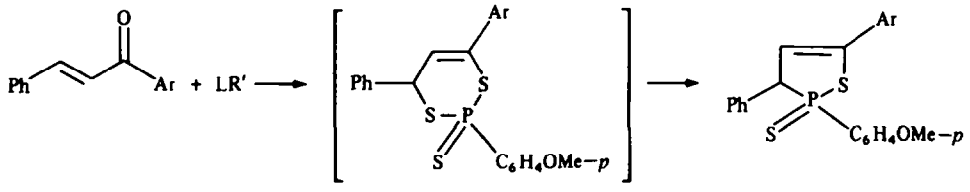
The reaction of chalcone with LR' at room temperature[92] in acetonitrile leads to an adduct comprising a mixture of isomers (**237** and **238**; yield 82%).



237

238

Under more vigorous conditions (boiling in xylene, 0.5 hr) chalcone and a two-fold excess of LR form an unstable adduct (**239**) which then passes into thiaphospholenes (**240a–c**).[95]

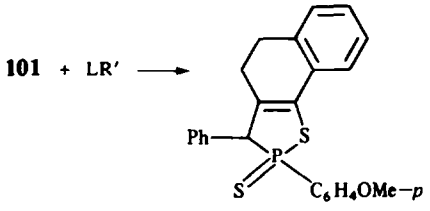


239 **240a–c**

240a Ar = Ph, yield 56%; **b** Ar = *p* – $MeOC_6H_4$, 56%; **c** Ar = *p* – ClC_6H_4, 21%.

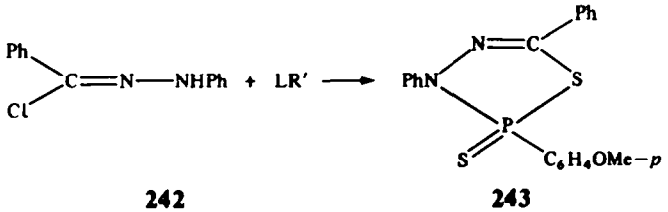
The treatment of thiochalconate dimer (**99a**) with LR was also shown to lead to **240a** (yield 36%).

In a similar way the dimer (**101**) is converted into a condensed heterocycle of thiaphospholene, structure **241** (yield 31%).



241

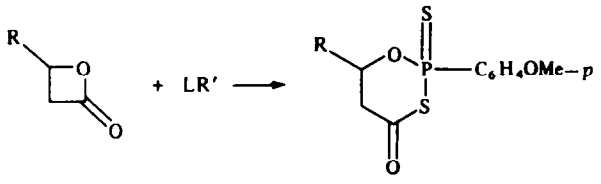
The [2+3] cycloaddition with the formation of 1,3,4,2-thiadiazaphospholene-2-thiones (**243**) occurs when LR (as well as other thionophosphine sulfides) interacts with benzophenylhydrazonyl chloride (**242**) in benzene for 20 hr.[136]



242 **243**

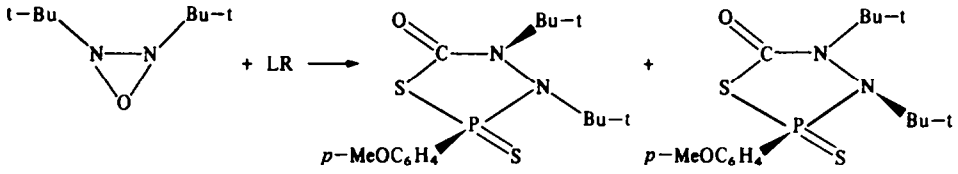
Strained 3- and 4-membered rings, containing labile bonds, can react with monomeric LR', forming adducts of the phosphacyclane structure. In this case the size of the ring increases with the thiophosphorus fragment which is incorporated.

β-Propiolactone and its 3-methyl analogue (**244a, b**) and LR in boiling toluene, lead to the products of LR' insertion—2(*p*-methoxyphenyl)-1,3,2-oxathiophosphorin-4-on-2-sulfide (**245**).[137]



244 **245a** R = H (yield 60%)
b R = Me (53%)

The carbonyl group in **224** or **245** is not thionated. Heating LR with di-tert-butyloxadiaziridine (**246**) yields an adduct of 1 : 1 composition which is comprising a mixture of diastereoisomeric 3,4-bis(tert-butyl)-2-(*p*-methoxyphenyl)-1,3,4,2-thiadiazaphospholidine-5-on-2-sulfides (**247a** and **247b**; overall yield 27%).[138]



246 **247a** **247b**

Prolonged heating at 70° in toluene converts the low-melting isomer (**247b**) into a more stable isomer (**247a**).

The ring is, probably, also expanding during the course of phosphorus exchange in the cyclophosphazene ring (**248**) under the action of LR. In an ambident N—P=N system of the phosphazohydride (**248**), there is a possibility of the phosphorus, as well as the nitrogen, atom nucleophilically attacking the LR thiophosphoryl phosphorus. In pathway a the P—Me fragment is thionated giving the product (**249**). In pathway b the sequence of conversions leads to the insertion of an anisylthiophosphoryl group into the phosphazene ring with the formation of *p*-anisylcyclophosphazene (**250**).

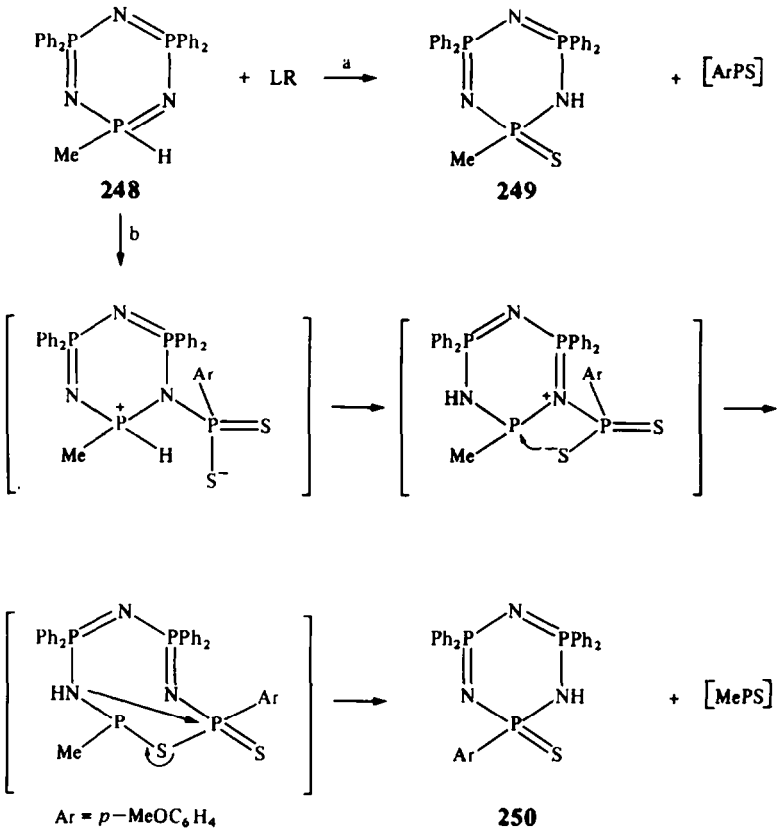
3.4. *Reactions with compounds containing element–oxygen bonds*

At the first stage of these reactions, compounds with an element–sulfur fragment are formed. Then depending on the nature of the element, they can constitute the final products of reaction with LR. Alternatively, various intramolecular or intermolecular transformations can occur.

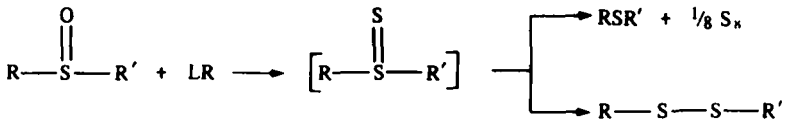
Reactions of LR with sulfoxides are accomplished very easily (5 min at 30–35°)[140] and lead to dialkyl sulfides and dialkyl disulfides. The process is regarded, by analogy with thionation by means of P_4S_{10},[141–143] as starting with the thionation of the substrate, followed by its dethionation. As in the case of reactions with P_4S_{10},[141] the $S{=}O \leftrightarrow S^+{-}O^-$ group attacks the LR phosphorus or P_4S_{10} nucleophilically.

The yield of products is quantitative in the LR reaction and in the thionation by P_4S_{10} in CS_2 at 0°.

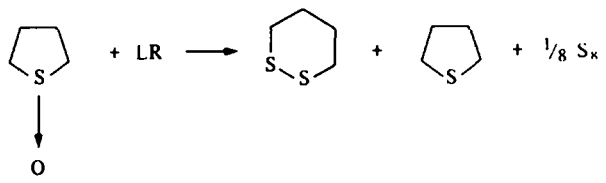
It is possible that the disulfide is formed as a result of the rearrangement of intermediate **251**.[143] In the reaction of LR with tetrahydrothiophenylsulfoxide (**252**), the formation of disulfide product—1,2-dithiane (**253**)—is accompanied by the expansion of the ring. Tetrahydrothiophene is also formed upon the reduction of **252** with LR. This presumably involves an intermediate of the **251** type.



Compounds containing a semipolar N → O bond : C- and N-nitroso-compounds, nitrones and N-oxides, are also thionated by LR. The fate of intermediates with a thionitroso-structure is then determined by the nature of the substrate.[144,145]



251

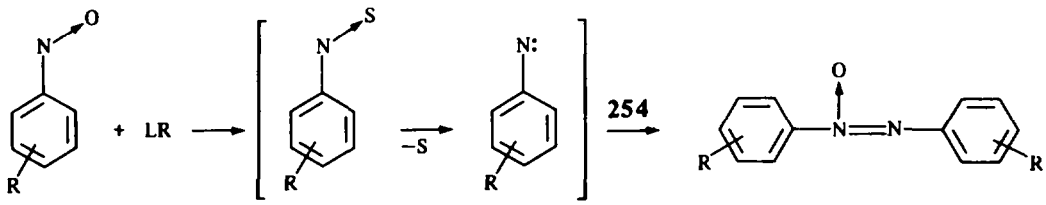


252 253

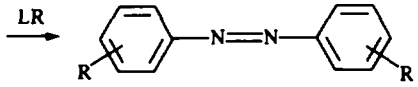
Nitrosobenzenes (**254a–e**) interact with LR under mild conditions, yielding azobenzenes (**256a–e**). In one case (**254a**) azoxybenzene (**255a**) was isolated (yield 80%).

The reaction of **255a** with LR results in the formation of **256a**. When the reaction of N,N-dimethyl-*p*-nitrosoaniline (**254c**) with LR is conducted under very mild conditions (methylene chloride–benzene, 0°), then the crystalline *p*-dimethylamino-N-thiosulfinylaniline (**257**) was obtained.[144]

The formation of thionitrosyl intermediates in the reactions of nitroso-compounds with LR can be inferred from the results of the thionation of benzofurazan-1-oxide (**258**). The product of this reaction—

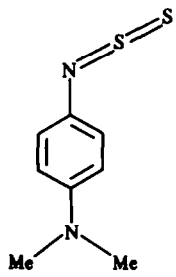


254a-e 255



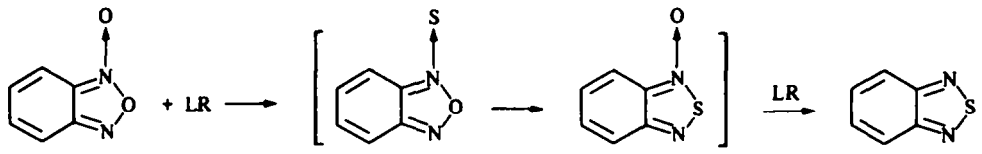
256a-e

256a R = H, yield 93%; **b** R = 2 – Me, reaction temperature 60°C, reaction time 4 hr, yield 20%; **c** R = 4 – NMe_2, 25°C, 2 hr, 30%; **d** R = 4 – NEt_2, 25°C, 15 min, 18%; **e** R = 4 – Me, 60°C, 1 hr, 62%.



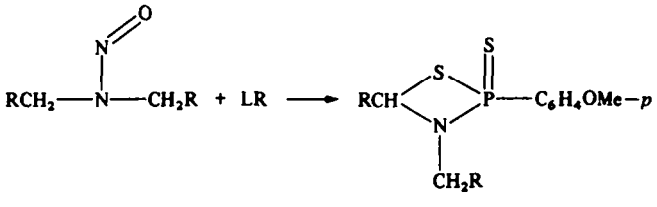
257

2,1,3-benzothiadiazole (**261**) is, most probably, formed via the unstable compound **259**, which, after the **259** → **260** rearrangement, is deoxidized by another LR molecule.[144]



258 259 260 261

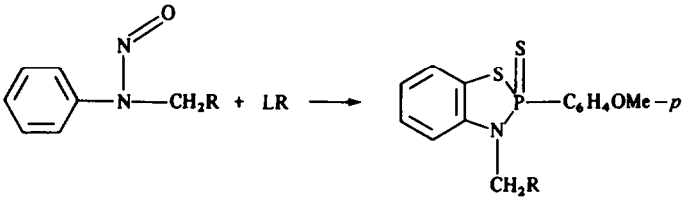
The course of the reactions of N-nitroso-compounds with LR is primarily determined by the nature of groups bonded with the nitrogen atom. Aliphatic N-nitrosoamines (**262**), when heated with LR at 80° (**262a**) and 100° (**262b**), form 1,3,2-thiazaphosphetanes (**259a, b**).



262 263

263a R = H, reaction time 24 hr, yield 74%; **b** R = Pr, 15 hr, 36%.

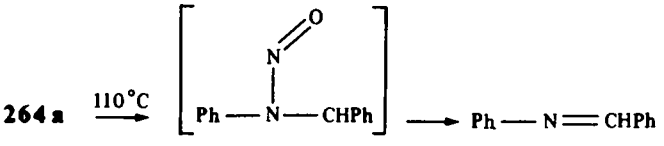
Aromatic N-nitroso-compounds (**264**) need a higher temperature: 110° for **254a** and 120° for **264b**. In both cases the interaction with LR results in phosphorus heterocycles—1,3,2-thiazaphospholes (**265a,b**).[144,145]



264 **265**

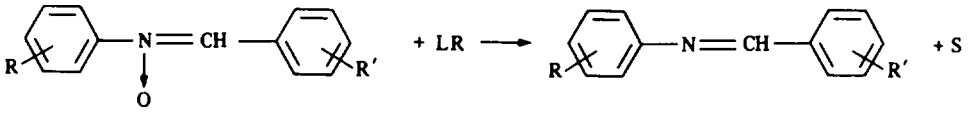
265a R = Ph, reaction time 48 hr, yield 74%; **b** R = Pr, 15 hr, 40%.

These interesting processes of ring-formation with the LR monomer participation obviously involve HNO-elimination and the formation of benzal-aniline (**266**) as an intermediate. In this connection **264a** on heating, either with the addition or in the absence of potassium t-butoxide, yields **266**.



266

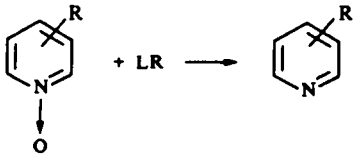
Nitrones (**267**) and pyridine N-oxides (**269**) are deoxygenated by LR, as well as by other derivatives of phosphorus dithioacids (see Section 1).



267 **268 a-e**

268a R = R' = H, yield 61%; **b** R = 4 – Cl, R = H, 64%; **c** R = H, R' = 2 – OH, 47%;
d R = H, R' = 3 – OH, 39%; **e** R = 4 – MeO, R' = H, 57%.

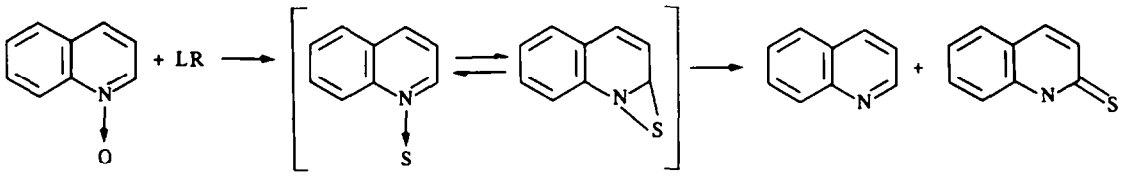
It is noteworthy that under the mild conditions of deoxygenation, the hydroxyl groups on aromatic rings (**267c, d**) are not affected, although it is not excluded that low yields of anils (**268c, d**) are associated with the side-reaction of LR with phenolic residues. Pyridines (**270**) are formed from N-oxides (**269**) with high yields.



269 **270**

270a R = 2 – Me, yield 65%;
b R = 2,4,6 – triphenyl, 90%;
c R = 4 – MeO, 80%.

A thionitroso-intermediate seems to be formed during the reaction of quinoline N-oxide (**271**) with LR. At 25° within 4 hr this reaction yields quinoline (**273**; 80%) and quinoline-2-thione (**274**; 20%). This result is assumed[144] to involve the participation of the intermediate compounds (**272**).



271 **272** **273** **274**

LR has been recently shown to offer opportunities for synthesising thiophosphoryl compounds from phosphoryl ones.[146] As in the series of carbonyl substrates, the ease of O,S-interchange in P=O systems increases with an increase in the nucleophilicity of phosphoryl oxygen: phosphinates (**275**) > phosphonates (**277**) > phosphates (**279**).

$$Ph_2P(O)R + LR \longrightarrow Ph_2P(S)R$$

275 **276**

276 a R = Me, reaction time 1 hr, yield 80%; **b** R = Cl, 1 hr, 84%; **c** R = NHBu, 1 hr, 81%; **d** R = NEt_2, 2 hr, 83%; **e** R = $OC_6H_4NO_2$-*p*, 1 hr, 66%.

$$RP(O)R^1R^2 + LR \longrightarrow RP(S)R^1R^2$$

277 **278**

278 a R = Me, $R^1 = R^2$ = OPh, yield 81%; **b** R = Ph, $R^1 = R^2$ = OBu, 60%; **c** R = Et, $R^1 = R^2$ = OEt, 83%; **d** R = Ph, R^1 = OPh, R^2 = NHBu, 77%; **e** R = Ph, $R^1 = R^2$ = NHBu, 70%.

$$R_2P(O)R^1 + LR \longrightarrow R_2P(S)R^1$$

279 **280**

280 a $R = R^1$ = OEt, yield 61%; **b** R = OPh, R^1 = NHBu, 75%.

It should be noted that previously the thionating organophosphorus reagents were only used to convert triphenylphosphine oxide into the corresponding sulfide.[18,147] P=O → P=S conversion has been performed by using P_4S_{10} to thionate phosphinates,[148] thiol phosphonates[149,150] and phosphine oxides.[150]

The history of the use of organothiophosphorus reagents in preparative organic chemistry is short. However, impressive progress has already been made and we are convinced that the potential of the application of these reagents in synthesis will continue to be developed and many novel reactions await discovery.

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