Coordination Chemistry Reviews, 137 (1994) 525–559

Practical aspects of the chemistry of metaphosphates and other transient dioxophosphoranes

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(Received 6 May 1994; accepted 2 June 1994)

CONTENTS

ABSTRACT

Practical laboratory procedures now exist for the generation of organic derivatives of metaphosphoric acid ($HO–PO_2$), as well as for dioxophosphoranes ($R–PO_2$). These methods are evaluated in this review. Although these substances are highly reactive and have but a fleeting existence, they can nevertheless be employed as reactants in synthetic phosphorus chemistry. The various applications that have been demonstrated in the literature are also discussed in this review.

1. INTRODUCTION

Dioxophosphoranes (three-coordinate phosphoryl derivatives **1**) have been mentioned in the literature for many years as transient species or reaction intermedi-

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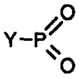
0010-8545/94/$26.00

SSDI 0010-8545(94)03011-E

ates. A signal event in this area was the proposal in 1955 [1,2] that the anion of metaphosphoric acid (**1**, Y = OH) had an involvement in biological phosphorylation.



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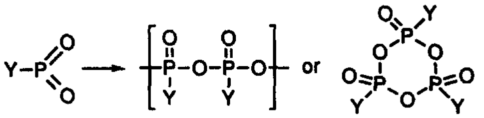
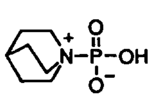
Serious effort then commenced to generate and characterize metaphosphoric acid and derivatives. While many other types of low-coordination phosphorus species have been successfully synthesized in recent years, metaphosphates and other dioxophosphoranes have remained elusive, and there appears to be only one compound bearing structure **1** [3,4] that can be directly observed, if not isolated in the conventional sense, by measurement of some physical parameter; the IR spectrum of chlorodioxophosphorane (**1**, Y = Cl) preserved in an argon matrix was recently recorded [4], as was the photoelectron spectrum of a gaseous sample at 450 K [5] (the IR spectrum of sodium metaphosphate, $NaPO_3$, has been recorded in an argon matrix [6]).

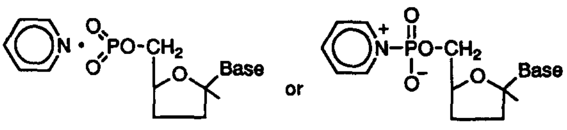
The difficulty associated with experimental work on dioxophosphoranes arises not from thermal instability of the species, but from the very powerful electrophilic character at phosphorus; when generated in solution the species instantly undergoes self-reaction to form cyclic or linear polymeric species with P—O—P bonds (reaction 1). Many low-coordination phosphorus compounds have been stabilized by complexation with metals, but there is no record of this approach having been successfully applied to dioxophosphoranes. However, the high electrophilicity of the species does allow a different approach to effect stabilization; both the metaphosphate ion [7] and a complex metaphosphoric acid ester [8] appear to give Lewis salts with a tertiary amine; these complexes **2** and **3** were formed when the dioxophosphorane was generated in the presence of the amine, and were detected by ^{31}P NMR spectroscopy. The ^{31}P chemical shifts are consistent with four-coordinate structure at phosphorus and are in the region where phosphoramidates absorb (generally 0 to +10 [9a]). The ^{31}P NMR shift of a free metaphosphate is of course unknown, but a much more downfield shift, common to other forms of 3-coordinate-λ^5 phosphorus



(1)

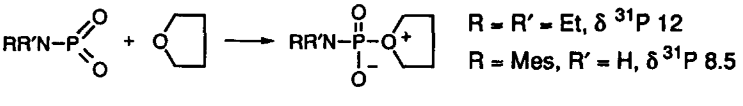


2, $\delta\ ^{31}P$ 10.2 [7]



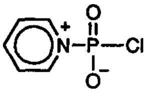
3, $\delta\ ^{31}P$ -5.1 [8]

[9b], can be expected. In support of this prediction, advances in computational techniques and instruments have recently allowed the first calculation of the shift for metaphosphoric acid (in the gaseous state) and provided a value of δ 53 [10]. Also, aminodioxophosphoranes have been generated at low temperature in the presence of tetrahydrofuran [11]; they are stabilized by these conditions, although retaining high reactivity to nucleophiles, and judging from their ^{31}P NMR shifts, which are also in the four-coordinate region, they appear to be in the form of Lewis salts with THF (reaction 2).

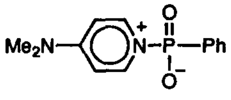


(2)

Betaines (**4** [12–14] and **5** [14]), which can be likened to Lewis salts **2** and **3** from other dioxophosphoranes, have been generated by indirect methods (vide infra) that do not involve trapping of a dioxophosphorane. Nevertheless, these betaines can be viewed as stabilized forms of dioxophosphoranes; in the case of **4**, chlorodioxophosphorane has been released on thermolysis. In spite of this paucity of information about the free forms of the dioxophosphoranes, the concept of their having a real but fleeting existence is now well accepted, as is made obvious in some prominent reviews of the accumulated evidence on this subject [15–17].



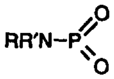
4 (δ ^{31}P −8.6^{14})



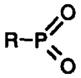
5 (δ ^{31}P 9.2^{14})

Even having to deal with the dioxophosphoranes as transient species, research in recent years has been directed at the development of practical laboratory methods for their generation and characterization, as well as for their utilization as highly reactive phosphorylating agents towards substrates included in the media of their generation. The picture has emerged of a species so reactive that it exhibits little selectivity when it has options for attack at different sites of a substrate, or for attack at different nucleophiles in the solution [18]. This high reactivity can be moderated, and selectivity increased, by using solvents with lone pairs that can act as bases to the electrophilic phosphorus center and form adducts such as those discussed above.

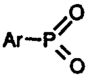
In the view of the author, it is now appropriate to consider the practical side of dioxophosphorane chemistry, and to make the argument, in this review, that there now exist reasonable approaches for their generation, effected under a variety of conditions, and that some of the phosphorylations that can be performed with them are unique and of synthetic value. The discussion is limited to neutral molecules having the dioxophosphorane moiety, thus excluding the extensive work on metaphosphate ions. The specific structural types to be considered are listed below, along



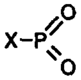
(RR′N = Me$_2$N, Et$_2$N, MesNH, 1-adamantyl NH, *t*-BuNH)



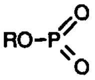
(R = Me)



(Ar = Ph)



(X = Cl)



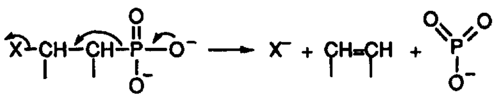
(R = Me, Et, *i*-Pr, (S)sec.-butyl, (+)-menthyl, neopentyl, 1-adamantyl)

with a summary of all of the derivatives that have been generated by the various methods to be discussed in this review as well as in other papers. A further limitation is that only those methods considered by the author to have practical value are discussed; other methods can be found in other reviews [15–17]. There has also been increasing recognition of these three-coordinate species as leaving groups that figure in reaction mechanism explanations [17].

2. PRACTICAL GENERATIVE TECHNIQUES IN SOLUTION

2.1. *Fragmentation of alkyl β-haloalkylphosphonates*

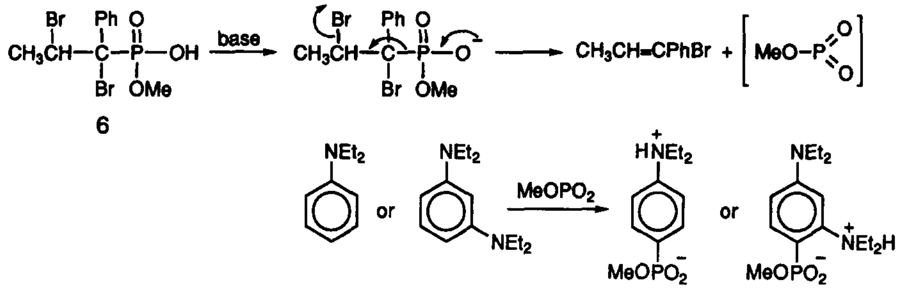
One of the earliest methods for the generation of the metaphosphate ion was the fragmentation of β-haloalkylphosphonate dianions [19], some of which fragment virtually on generation. This reaction was discovered by Conant [19], and later recognized by Swan [20] to proceed through elimination of metaphosphate ion (reaction 3). It has become known as the Conant–Swan reaction, and has been



$$X{-}CH{-}CH{-}\overset{O}{\overset{\|}{P}}(O^-){-}O^- \longrightarrow X^- + CH{=}CH + PO_2(O^-) \qquad (3)$$

adequately reviewed [15]. In 1978, this reaction was successfully extended to the generation of methyl metaphosphate in a non-aqueous solution [21]. This was accomplished by heating samples of methyl hydrogen *erythro-* or *threo*-1-phenyl-1,2-dibromopropylphosphonate (**6**) at 70°C for 6–10 h in acetonitrile. Present also were aromatic tertiary amines, which served both to generate the anion required for the fragmentation and as a trap (through electrophilic substitution, see Section 4) for the released methyl metaphosphate (reaction 4).

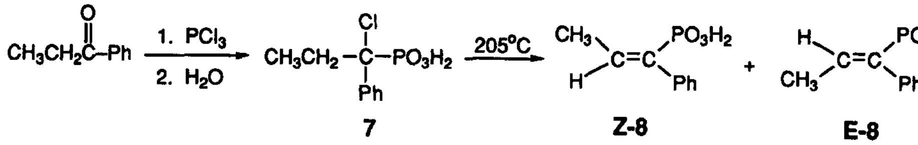
Crude kinetics measurements showed that the elimination reactions were first



(4)

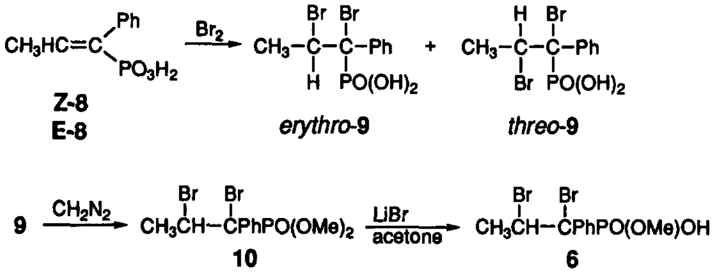
order, with half-lives of 31 min (*erythro*) and 22 min (*threo*), in a medium consisting of a tertiary aromatic amine and acetonitrile (1 : 1) with a trace of water. These reactions were about 1000 times slower than were the eliminations of the metaphosphate ion from the dianion of the corresponding phosphonic acid. Various other media were used in later studies [18], which introduced 2,2,6,6-tetramethylpiperidine as the base for generating the anion of **6**. These reactions were subsequently employed by a different group [22] which generated methyl metaphosphate from the *erythro* dibromide with diisopropylethylamine in acetonitrile. Different trapping reactions were used in these later studies, as is discussed in Section 4.

Several steps were required to synthesize the methyl hydrogen phosphonate **6**. The first phosphorus-containing intermediate, 1-phenyl-1-chloropropylphosphonic acid (**7**), was synthesized (20% yield) from propiophenone by the procedure of Kenyon and Westheimer [23] (based on an early procedure of Conant [19a] for the reaction with acetophenone). Acid **7** on strong heating lost HCl to give the propenylphosphonic acid isomers **Z-8** and **E-8** (reaction 5) [23,24]. These acids (**E-8** in pure form, **Z-8** impure) were converted to the dibromides (**9**, *threo*- from **Z-8**; *erythro* from **E-8**), and then to the dimethyl esters (reaction 6). The cleavage of one methoxy group was accomplished with LiBr, thus giving the half-ester **6** required for metaphosphate generation.



(5)

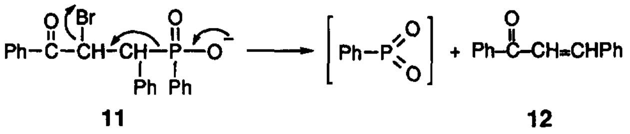
While phosphonate **6** functions as a useful source of methyl metaphosphate in an inert solvent, the method is more of historical than practical importance. Its value is diminished by the numerous steps required for synthesis of the precursor. Furthermore, some of the yields are modest (e.g. **7**→**8**, 20%; *threo*-**10**→**6**, 25% [21]; *erythro*-**10**→**6**, 61% [21]). Simpler haloalkylphosphonates are not as readily fragmented; in the most recent report on the Conant–Swan reaction [25], it was shown that the triethylamine salt of *beta*-chloroethylphosphonic acid (of great value as a plant growth regulator) was stable for 4 days in chloroform, acetonitrile, or methanol,



(6)

and did not function as a phosphorylating agent in the way that the more highly substituted phosphonate from **9** did. This was true also of the *beta*-bromoethyl derivative. As will be seen, some of the recently introduced methods for metaphosphate generation depend on more easily obtained starting materials, and require shorter reaction periods. Nevertheless, the monoalkyl *β*-haloalkylphosphonate fragmentation holds a major position in the development of dioxophosphorane chemistry.

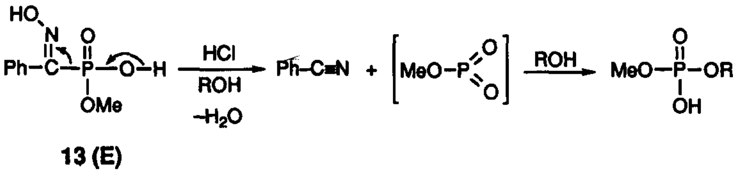
There is no record of the method ever being used to generate alkyl metaphosphates other than methyl, but there is no reason to think the process would be limited in this regard. The early literature [19b] does contain an indication that the fragmentation could be used to generate phenyldioxophosphorane; the phosphinate anion **11** was found to fragment spontaneously to give alkene **12**, perhaps owing to elimination of the dioxophosphorane (7).



(7)

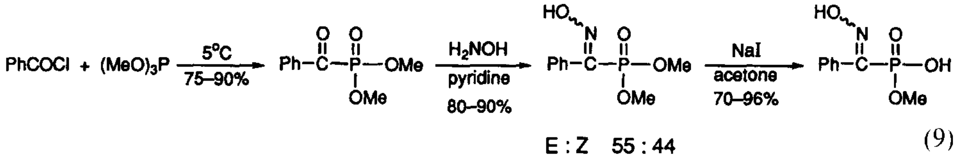
2.2. *Fragmentation of alkyl α-oximinobenzylphosphonates*

Another type of phosphonate, with an α-oximino function (**13**), also undergoes ready cleavage of the C–P bond and is a practical source of alkyl metaphosphates. As first introduced, the method required the action of anhydrous HCl on an alcohol solution of the α-oximinobenzylphosphonate [26,27] to effect the fragmentation; this resulted in the formation of dialkyl phosphates from the second-stage reaction of



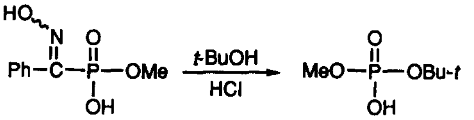
(8)

the metaphosphate with the alcohol (reaction 8). The process is conducted at room temperature. The synthesis [27] of the phosphonate used to generate methyl metaphosphate is outlined in reaction 9 where it is seen that the process requires only three steps from readily available starting materials, and proceeds in 42%–78% overall yield (exact yields for the methyl esters were not recorded). Other O-alkyl substituents (Me, *n*-Bu) have also been present in this reaction series.



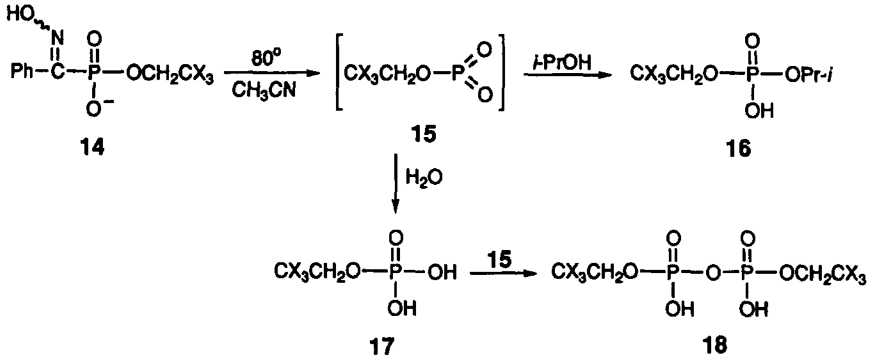
(9)

Mechanistic studies of the fragmentation [28] indicated that the HCl acted through protonation of the hydroxy group on nitrogen allowing facile cleavage of the N–O bond, and that the *E*-isomer (**13**), and not the *Z*-isomer, was the species fragmenting to the metaphosphate. The *Z*-isomer, however, was converted to the *E*-isomer, and thus virtually all phosphorus was released as the metaphosphate. A later development was the replacement of alcohol as solvent by the inert toluene; this allowed the use of the generated metaphosphate as a phosphorylating agent towards a small amount of an alcohol when present in the solution [29]. Both methyl and ethyl metaphosphates were generated by this method, and trapped by alcohols in the medium. It is especially to be noted that *tert*-butyl alcohol, when used as solvent, was phosphorylated by this method (reaction 10) [28]; it is accepted that it is quite difficult to phosphorylate this alcohol by conventional means, and thus it functions as an indicator for the presence of a phosphorylating agent of uncommon strength (i.e. a metaphosphate).



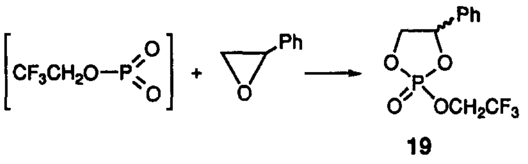
(10)

The presence of halogen atoms on the β-carbon of the alkyl group in the *E*-isomeric form of the oximinobenzylphosphonate makes it possible to conduct the fragmentation with the sodium salts (**14**), obviating the need for the highly acidic conditions required for simple alkyl esters whose salts do not undergo fragmentation (reaction 11). By this approach, two new trihaloethyl metaphosphates [30] (**15**, X = Cl or F) and a hexafluoropropyl metaphosphate [31] [$(CF_3)_2CHOPO_2$] were generated. The fragmentations could be effected especially well in acetonitrile at 80°C (14 h). In the absence of a trapping agent, the product was the anhydride (**18**), presumably formed from attack of the metaphosphate on the monoalkyl phosphate (**17**) that would arise from some hydrolysis of the metaphosphate. In the presence of a few equivalents of isopropyl alcohol, all of the metaphosphate was trapped as



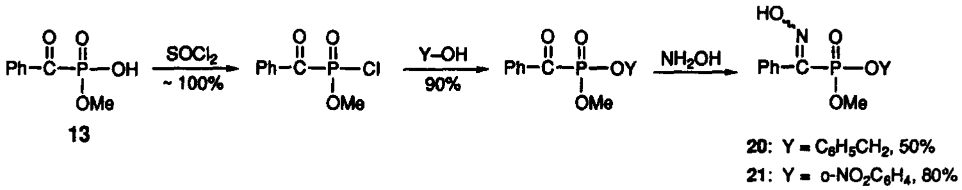
(11)

the dialkyl phosphate (**16**). Curiously, the fragmentation could not be effected in pure water or methanol, but occurred readily in pure ethanol or isopropyl alcohol [31]. Apparently stabilization of the reactant by hydrogen bonding is less effective in the more hindered alcohols. When the fragmentation was conducted in a 1:1 mixture of ethanol and isopropyl alcohol, the metaphosphate reacted at the same rate with each; this lack of selectivity is, of course, indicative of the presence of the highly reactive metaphosphate, as noted in earlier studies [18]. Also providing convincing proof of the intermediacy of the metaphosphate was the formation of 1,3,2-dioxaphospholanes (**19**) when the fragmentation was conducted in the presence of styrene oxide (reaction 12). This reaction had been employed previously [32] when metaphosphates were generated by a different process, and is discussed in Section 4.



(12)

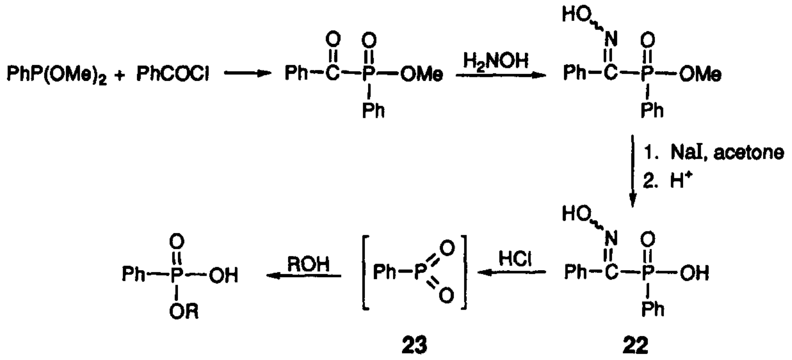
The fragmentation of the oximinophosphonates is virtually quantitative, and the overall method has considerable value as a source of metaphosphates. However, a possible drawback, depending on the character of the substrate to receive the metaphosphate, is the high acidity of the medium required to generate the simple alkyl derivatives. This has recently been completely circumvented by the introduction of a photochemical method for the cleavage of the oximinophosphonate [33]. This method requires the presence of a photo-cleavable O-substituent on phosphorus, and benzyl and *o*-nitrobenzyl were found to serve in this capacity. The synthesis of such species is shown in reaction 13. The photolyses were performed at room temperature in dioxane solution, employing a 450 W medium-pressure Hanovia lamp supplying UV light with a maximum at 254 nm. When a few equivalents of ethanol were present, all phosphorus appeared in the form of the dialkyl phosphate. In the



(13)

absence of alcohol, typical ^{31}P NMR spectra for a polymeric form of methyl metaphosphate (complex signals centered at δ-10 for terminal and −21 for internal or cyclic phosphate groups) resulted. This method therefore has considerable potential for performing phosphorylations at room temperature, without the presence of harmful acidic or basic reagents. The substrate to be used must, of course, be stable to the radiation.

An extension of the above process to the production of phenyldioxophosphorane (phenyl metaphosphonic anhydride, $Ph–PO_2$) has also been accomplished [34]. The precursor is the phosphinic acid **22**, whose synthesis is shown in reaction 14. When **22** was treated with HCl, the dioxophosphorane **23** was released, which reacted with an alcohol if present in the medium. The fact that *t*-BuOH was phosphorylated

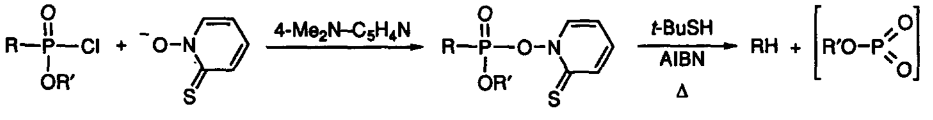


(14)

under these conditions attests to the reality of **23** as an intermediate. This approach to phenyldioxophosphorane may prove to be of practical value, since there are few methods that could be used to generate this substance on a preparative scale. The drawback again is the requirement for high acidity, but if this can be tolerated the method can be of synthetic value.

2.3. *Fragmentation of phosphonyl radicals*

This method [35] resulted from studies (cited in ref. 35) on the biological degradation of phosphonates, where it was shown that cleavage of the C–P bond can proceed through a phosphonyl radical intermediate (R–P(O)(OR)(O·). Presumably phosphorus is eliminated as a metaphosphate. To approach this type of intermediate in a non-biological system, a compound with a P–O–N bond (**24**) was synthesized and refluxed in benzene with AIBN as radical initiator, along with one of *tert*-butylmercaptan, tributyltin hydride or carbon tetrachloride as chain propagator/radical quencher (reaction 15) [35]. The most compelling case for the intermediacy of a metaphosphate came from the result of including *tert*-butyl alcohol in the medium as a trapping agent when phosphonate **25** was fragmented (reaction 16).



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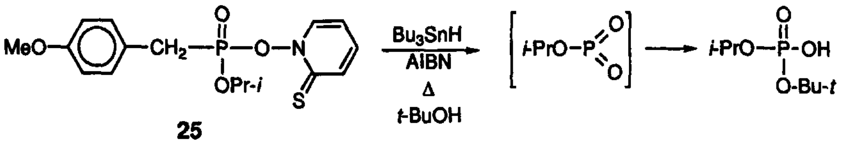

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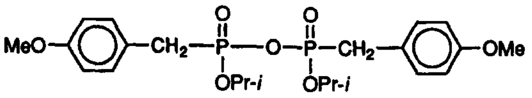
(16)

The subsequent isolation of isopropyl *tert*-butyl phosphate was indicative of the intermediacy of isopropyl metaphosphate (which was in fact the first case of generation of this substance). The amount isolated corresponded to 38% trapping efficiency of the metaphosphate. A complication from a preparative standpoint is that much of the phosphorus appeared in the form of the pyrophosphate **26**. Nevertheless, the method holds promise of development into a practical source of metaphosphates, provided the requisite phosphonate (**24**) can be synthesized in a straightforward and efficient way.



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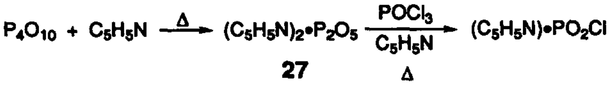
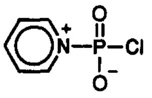
2.4. *Lewis salts of chlorodioxophosphorane*

A number of years ago, the discovery was made [13] that a compound having the composition of a pyridine adduct with Cl–PO$_2$ resulted from the series of reactions 17. The structure is probably represented as a four-coordinate phosphorus betaine (**28**). The yield is excellent; the first product **27** is formed in 96% yield, and



$$P_4O_{10} + C_5H_5N \xrightarrow{\Delta} \underset{\mathbf{27}}{(C_5H_5N)_2\cdot P_2O_5} \xrightarrow[C_5H_5N \atop \Delta]{POCl_3} (C_5H_5N)\cdot PO_2Cl \qquad (17)$$



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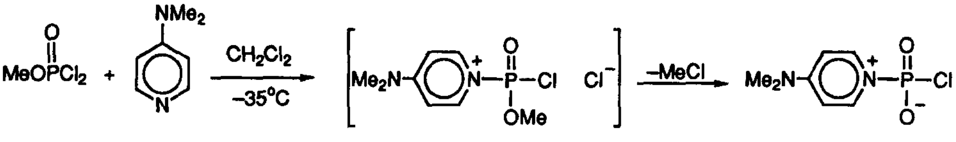
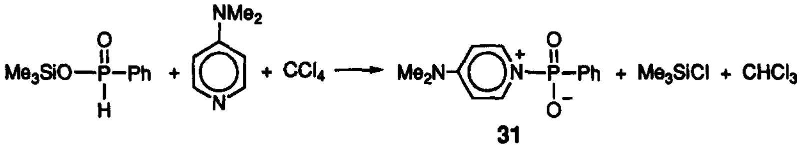
from 20 g of this Lewis salt in the reaction with 100 g of $POCl_3$ there was obtained 27 g of the adduct **28** as needle crystals. In the present context, the most significant use found for this adduct is its service as a generator of the free molecular species $Cl{-}PO_2$ in the gas phase. This was accomplished [5] by heating **28** at 450 K (pressure not specified) in a short-path pyrolysis unit. That the free species $ClPO_2$ was formed was proved by photoelectron spectral measurements of the gas. The gas stream is therefore a potentially valuable source of PO_2Cl for preparative purposes, but at the time of writing no experiments along this line have been reported. Attempts have been made [36] to use the Lewis adduct **28** in direct reactions with alcohols (including the bulky 1-adamantanol) or amines with the hope of forming the Lewis salt of alkoxy or amino dioxophosphoranes by displacement of chlorine, but only oligomeric or polymeric phosphoric derivatives resulted. This does not necessarily point to a failure to achieve the desired dioxophosphoranes; these species are of such high reactivity, even when stabilized as Lewis salts [7,8,11], that they may have been formed but under the conditions used proceeded to give the usual condensation reactions. While beyond the scope of this review, the pyridine complex of the corresponding dithiono derivative ($ClPS_2$) does give useful reaction chemistry and has, for example, been used as a source of diazadiphosphetidine derivatives [36,37].

Another laboratory reported later that the same type of betaine was formed when 4-dimethylaminopyridine (or pyridine) was allowed to react with methyl phosphorodichloridate (reaction 18) [37,38]. Presumably the pyridine nitrogen displaces



(18)

chlorine from the phosphorodichloridate to give a salt (**29**), which then loses MeCl to give the betaine **30**. The yield of **30**, a crystalline solid, was 95% [38]. The ^{31}P NMR shift was δ-8.6, which seems appropriate for the four-coordinate structure. ^{1}H and ^{13}C NMR spectra also support this structure [39]. Other tertiary amines were found to form similar complexes [39,40]. In the same study [37], a complex having a phenyldioxophosphorane unit coordinated with pyridine nitrogen was prepared by the reaction 19. The complex **31** could be of considerable interest. It was isolated in 63% yield as a solid that could be recrystallized from $MeNO_2$ and had $\delta^{31}P$ 9.2.



31

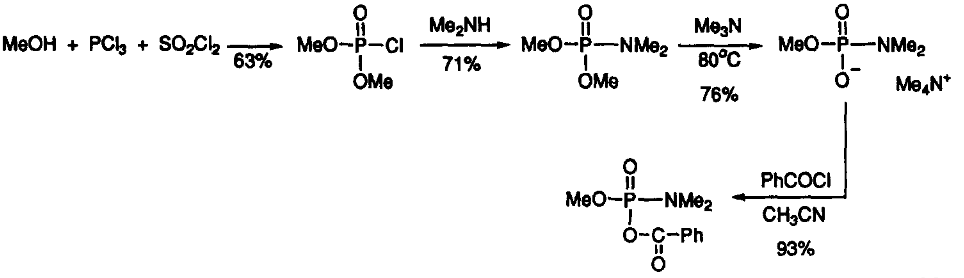
(19)

No other data have as yet been published that support structure **31**, however, and the mechanism of its formation is unknown.

Since betaines such as **28** or **30**, and **31** are stable crystalline solids, prepared in high yield from simple compounds, they could become quite valuable as precursors of dioxophosphoranes. Especially intriguing is the complex **31** based on phenyldioxophosphorane; as noted, the chemistry of this substance appears not to have been investigated as yet, but **31** could achieve considerable importance if it can function to release the reactive dioxophosphorane.

2.5. Thermal fragmentation of mixed phosphoric–carboxylic anhydrides

Symes and Modro have reported [41] a method for metaphosphate generation that could have considerable practical value. The method depends on the unimolecular fragmentation of anhydrides formed by reacting carboxylic acid chlorides with the anion of O-alkyl N-substituted phosphoramidic acids. The complete reaction sequence for the preparation of a typical anhydride is shown in reaction 20. The anhydride (**32**) fragments with the migration of the amino group from phosphorus to the carbonyl center. This reaction occurs at 50°C in acetonitrile, and is complete in 60 h. The reaction followed first-order kinetics, and proceeded through a transition state with little charge separation, as in **33**. To show that methyl metaphosphate was formed, a trapping experiment with *N*-methylaniline in acetonitrile was performed (reaction 21). This agent had been used by previous workers [42] and the expected product from attack on nitrogen (phosphoramidic acid salt **34**) was obtained, as verified by its proton NMR spectrum. As will be noted in Section 4, aromatic substitution can also occur in the reaction of metaphosphates with anilines, but this is suppressed by certain donor solvents, among them acetonitrile, and was not noted



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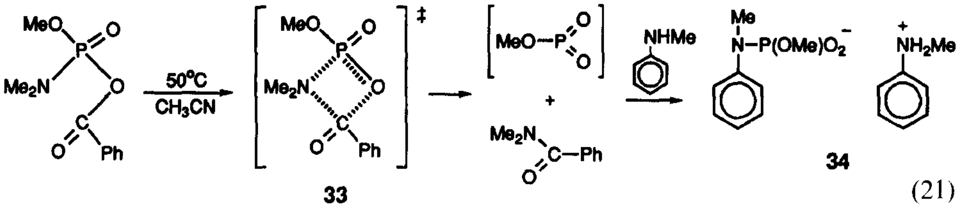
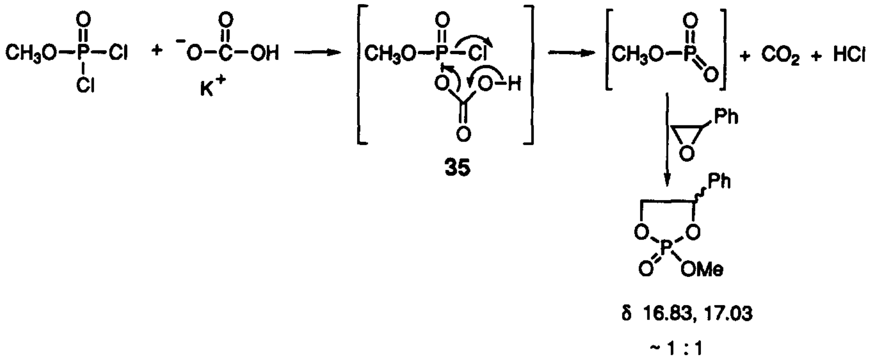


(21)

here. No other examples of the trapping of the metaphosphate intermediate from the mixed anhydride precursor were reported, but the simplicity of the method certainly makes it attractive for further development in this direction.

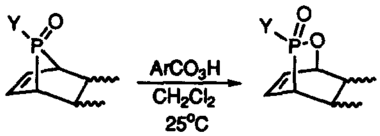
A preliminary report [43] has described the formation of a quite different type of mixed carboxylic-phosphoric anhydride that has great potential as a practical source of metaphosphates. As shown in reaction 22, it was proposed that an unstable anhydride (**35**) is formed from a carbonate and a phosphorus chloride, which then fragments to a metaphosphate. These workers also employed an epoxide as a trapping agent to form a 1,3,2-dioxaphospholane (cis, trans), as first reported by Bodalski and Quin [32]. No experimental details have yet been published, but they are awaited with interest, since the preparation of the precursor is based on such simple starting materials.



(22)

2.6. Fragmentation of derivatives with the 2,3-oxaphosphabicyclo[2.2.2]octene framework

The 2,3-oxaphosphabicyclo[2.2.2]octene ring system is formed in high yield when peracids or *tert*-butyl hydroperoxide perform an insertion of oxygen into a ring C—P bond of 7-phosphanorbornenes (reaction 23) [44].



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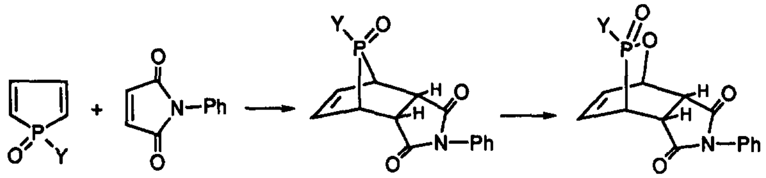
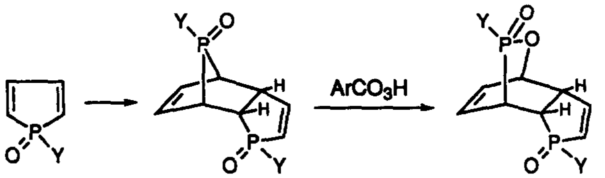


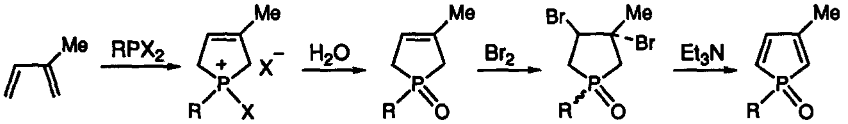
(24)

The O-insertion reaction takes precedence over epoxidation of the double bond, and generally gives a crystalline product with retained configuration at phosphorus. The most commonly used type of 7-phosphanorbornene derivative is that formed by Diels–Alder reactions of phosphole oxides with *N*-phenylmaleimide [45,46], which is peculiarly useful in this reaction and leads to the formation of only one of the possible stereoisomers (*syn*-Y, *endo*-fusion) (reaction 24). Phosphole oxides rapidly form dimers if they are not generated in the presence of a trapping agent [44]; these dimers also contain the 7-phosphanorbornene system, and are useful participants in the O-insertion reaction 25 [44]. The phosphole oxide may have as



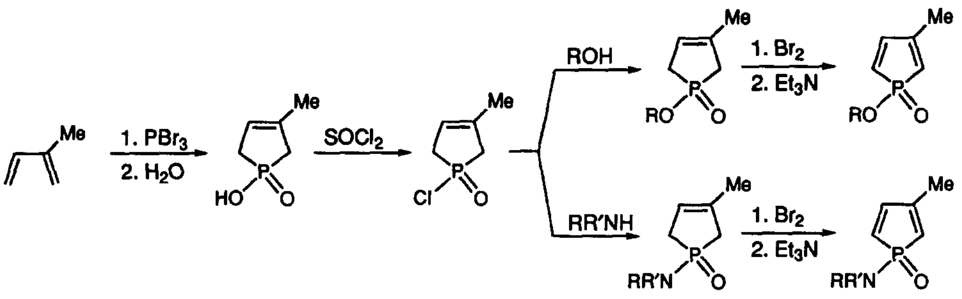
(25)

P-substituent an alkoxy [45,47], a monosubstituted or disubstituted amino group [48], or a carbon substituent (methyl [45] or phenyl [45,49]). Some reactions used to synthesize the phosphole oxides are summarized in reactions 26 and 27. In common to all is the use of the McCormack cycloaddition for the construction of the five-membered ring (3-phospholene). However, in none of these cases is the phosphole oxide stable; unless the dienophile is present in the generation step, the phosphole oxide rapidly forms a dimer.

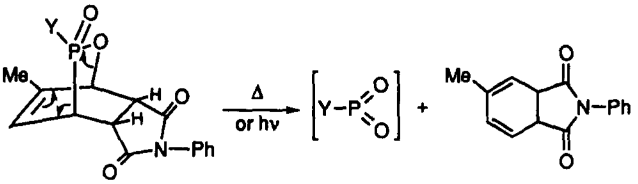


(26)

The 2,3-oxaphosphabicyclo[2.2.2]octene ring system can be fragmented either thermally or photochemically, with the release of the bridging P–O unit as a dioxophosphorane (reaction 28). A number of solvents have been used for the thermal fragmentation, including toluene, chloroform, chlorobenzene, and dimethyl



(27)



(28)

sulfoxide. A commonly used procedure employs toluene as solvent, with a reaction temperature of 110°C. Usually the reaction for an ester takes about 4–6 h; that with a carbon substituent is faster, while that with an amino substituent is slower. The reaction gives clean first-order kinetics, with activation parameters consistent with a retrocycloaddition mechanism [50]. The expelled phosphorus fragment gives the usual polyphosphate product, easily recognized by the characteristic ^{31}P NMR signals clustered in the general regions of $\delta - 10$ and -20. With a trapping agent in the reaction mixture, virtually all of the phosphorus can be diverted away from these self-condensation reactions, and because of this the fragmentation has value as a source of dioxophosphoranes for phosphorylation purposes. In addition to $MePO_2$ and $PhPO_2$, the dioxophosphoranes that have been generated by this approach are summarized below:

Esters $EtOPO_2$, $Me_3CCH_2OPO_2$, (S)-$EtMeCHOPO_2$, 1-adamantyl

Amides Et_2NPO_2, mesityl NH-PO_2, 1-adamantyl NH-PO_2,$PhNHPO_2$, *t*-BuNH-PO_2

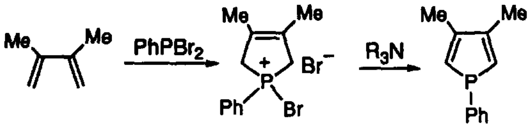
Numerous types of substances have been phosphorylated by these dioxophosphoranes, including alcohols, amines, ethylene diamine, and various solid surfaces containing OH groups. In addition, epoxides react to give cyclic phosphates, and *N*-methylpyrrole undergoes C-substitution. Details on these reactions are presented in Section 4.

As depicted in reactions 26 and 27, there are several steps involving isolation of products in the formation of the bicyclic precursors of metaphosphoric esters and amides. These include the phosphinic acid and its chloride, the ester or amide, the

7-phosphanorbornene adduct with *N*-phenylmaleimide, and finally the O-insertion product. The yield in each step is generally around 50%–80%, while the fragmentations of the O-insertion product seem to proceed in yields exceeding 90%. From the practical standpoint, the synthesis of the dioxophosphorane precursor would seem to require an undesirable number of steps. However, the simplicity of the actual step of generation of the dioxophosphorane is a compensating valuable feature of the process; no additional reagents are necessary, and the solvent requirements are broad and allow the phosphorylation of a number of substrate types.

An additional advantage of the ring fragmentation process is that it may be conducted at or below room temperature when effected by the use of UV light. Conventional apparatus using a medium-pressure mercury lamp delivering UV radiation with a maximum at 254 nm is employed. Again the efficiency of the fragmentation is high and a number of solvents are useful (acetonitrile, 1,2-dichloroethane, THF, dioxane). Obviously, however, the substrate placed in the medium to be phosphorylated must be photochemically stable; usually alcohols have been used in this process. Some dioxophosphoranes that have been generated by this method include the following: $PhPO_2$ [49], EtO-PO_2 [51], Me_3CCH_2O-PO_2 [47], 1-adamantyl-O-PO_2 [47], Me_2N-PO_2 [51], Et_2N-PO_2 [48], MesNH-PO_2 [48], *t*-BuNH-PO_2 [48].

A special feature of phosphole chemistry allows a precursor of phenyldioxophosphorane to be synthesized with considerable ease, making the fragmentation method preferred for generating this species. 3,4-Dimethyl-1-phenylphosphole (**36**) can be synthesized in over 80% yield (overall) by the McCormack cycloaddition reaction of 2,3-dimethylbutadiene and phenylphosphonous dibromide, followed by the Mathey dehydrobromination with a base such as DBU or 2-methylpyridine [52] (reaction 29). The phosphole can then be subjected, in one flask, to sequential reactions culminating in the synthesis of the desired precursor **39** in 84% overall yield. The conditions consist of mixing the phosphole with *N*-phenylmaleimide (NPM) and a three-fold excess of *m*-chloroperbenzoic acid in $CHCl_3$. The peracid first oxidizes the phosphole to the phosphole oxide (**37**); this undergoes rapid Diels–Alder reaction with the maleimide, and the resulting 7-phosphanorbornene derivative (**38**) undergoes the O-insertion reaction with the remaining peracid (reaction 30). Phenyldioxophosphorane has been generated from the precursor **39** by heating for only 15 min in toluene at 110°C; with alcohols present, the dioxophosphorane is trapped in high yield as the mono-alkyl phenylphosphonate (**40**) (reaction 31).



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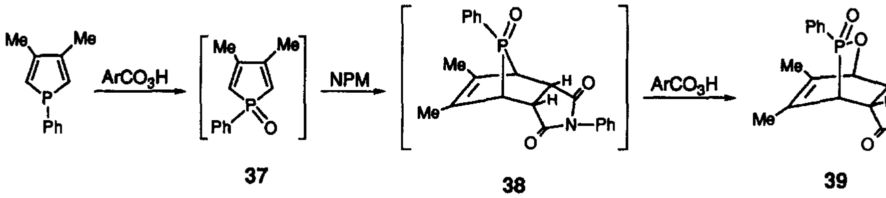
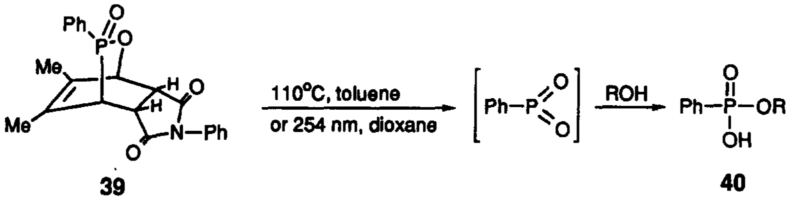
(29)



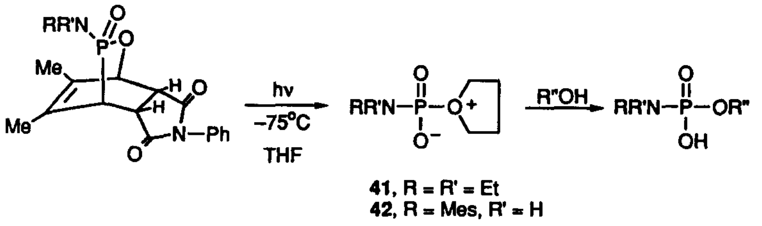
(30)

Precursor **39** has also been photolyzed at room temperature, again with virtually quantitative release of the dioxophosphorane.



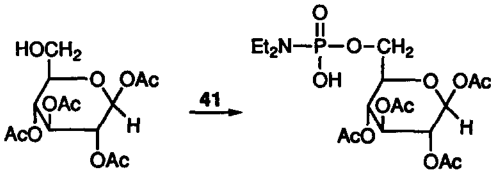
(31)

A valuable feature of the photochemical ring fragmentation as applied to P-amide derivatives of the oxaphospha bicyclic system is that the process can be performed in such a way that the released aminodioxophosphorane can be preserved in the solution for a secondary reaction with substrate. This has been accomplished [11,46,48] by performing the photolysis at −75°C to retard the polymerization process, so rapid at room temperature. The choice of solvent is important in this process also; THF, which is one of the few solvents having a sufficiently low freezing point yet exhibiting good solubility for the precursor, is preferred, since it has the ability to form a (presumed) Lewis salt with the dioxophosphorane that is stable at −75°C (reaction 32). The Lewis salt may be detected in the solution by ^{31}P NMR



(32)

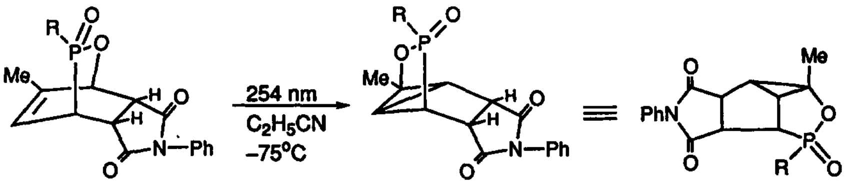
spectroscopy; signals appeared at δ 12 for the *N*,*N*-diethylamino derivative (**41**) and at δ 8.5 for the mesitylamino derivative (**42**). In both cases, the signals disappeared immediately on addition at −75°C of an alcohol reactant, or on warming the solution to room temperature, which caused formation of the usual polyphosphate signals. The significance of these observations from a practical standpoint is that substrates can be phosphorylated at −75°C simply on addition to the photolysis product, and thus need not be subjected to the photochemical or thermal conditions used to effect the ring fragmentation. A case in point is provided [46] by a glucose derivative as the substrate; addition to the −75°C solution of the *N*,*N*-diethylamino dioxophosphorane–THF complex resulted in formation at that temperature of the phosphoramidate **43** (reaction 33)



43

(33)

The low temperature photolysis takes a different course when applied to P-alkoxy or P-phenyl derivatives of the bicyclic ring system, and cannot be used to prepare solutions functioning as donors of dioxophosphoranes. With these P-substituents, a rearrangement of the bicyclic framework takes place; a stable

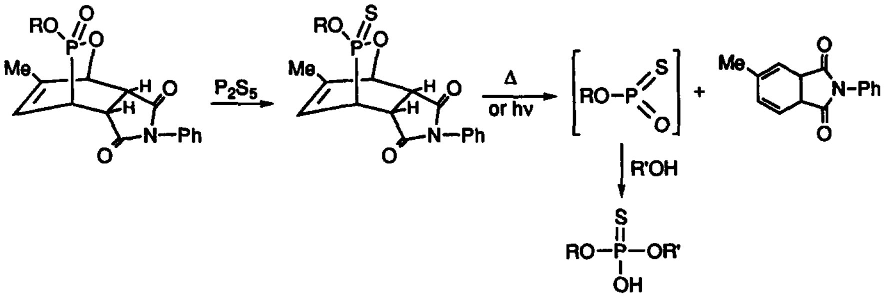


44

(34)

isomeric structure (**44**) is formed (reaction 34) that does not undergo fragmentation by either thermal or photochemical treatment [53].

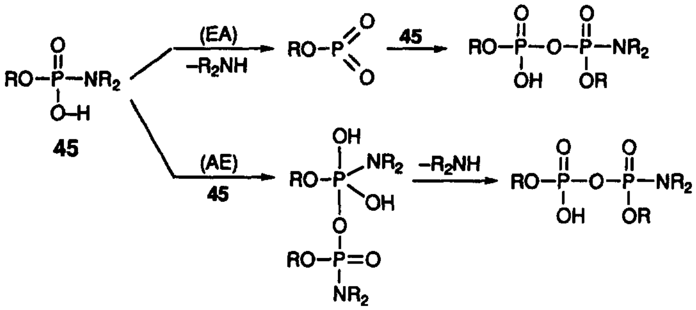
The ring fragmentation method has another valuable aspect; it can be used to generate oxothiophosphoranes, (Y–P(S)O) and indeed it is the only source known at this time for this species [54]. Sulfur is introduced by reacting the bicyclic phosphonate with P_2S_5, which specifically replaces phosphoryl oxygen by sulfur (reaction 35). Fragmentation of the sulfide has been accomplished by both the thermal and photochemical methods. The released fragment is not stable but is easily trapped by an alcohol.



(35)

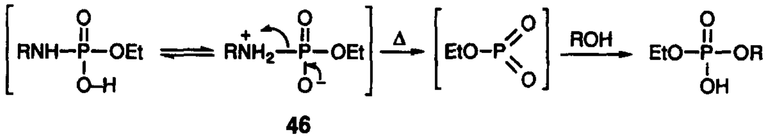
2.7. *Thermal fragmentation of O-alkyl N-substituted phosphoramidic acids*

It has been known for many years that phosphoramidic acids lose their amino group on being heated, and it has been suspected that this could result in the generation of a metaphosphate as a transient intermediate [55]. The products usually observed were pyrophosphate derivatives, which could be explained as arising from attack of the released metaphosphate on unreacted starting phosphoramidic acid. However, the pyrophosphates could also be formed in a bimolecular reaction of the phosphoramidic acids (reaction 36). Early attempts to distinguish between these pathways (elimination–addition (EA) and addition–elimination (AE), respectively) were not definitive.



(36)

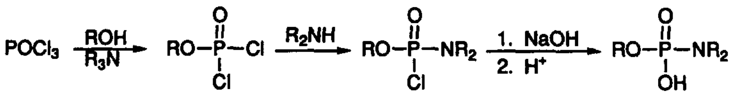
It has now been found [56,57] that the mechanism of phosphoramidic acid fragmentation is strongly influenced by the nature of the substituent on nitrogen. When this is a large bulky group, the bimolecular (AE) process, which involves a crowded five-coordinate intermediate from the addition step, is retarded and the fragmentation follows the EA mechanism as clearly indicated by the observation of clean first-order kinetics. The fragmentation occurs with the dipolar form (**46**) of the phosphoramidic acid (reaction 37) [57]. Consistent with the notion of a metaphosphate intermediate, alcohols included in the reaction medium are phosphorylated in an overall first-order process. Two N-substituents found to give clean first-order kinetics were mesityl and 1-adamantyl; both precursors have been used as generators of metaphosphates on heating at 70–80°C in solvents such as toluene, CH_3CN or DMSO.



(37)

R = Mesityl or 1-Adamantyl

These compounds are easily synthesized (reaction 38) in only three steps from the readily available phosphorus oxychloride; each step proceeds generally in

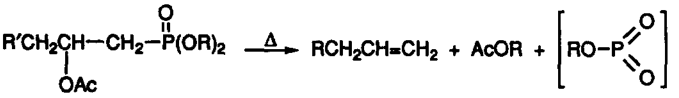


$$POCl_3 \xrightarrow[R_3N]{ROH} RO-\underset{Cl}{\overset{O}{\overset{\|}{P}}}-Cl \xrightarrow{R_2NH} RO-\underset{Cl}{\overset{O}{\overset{\|}{P}}}-NR_2 \xrightarrow[2.\ H^+]{1.\ NaOH} RO-\underset{OH}{\overset{O}{\overset{\|}{P}}}-NR_2 \qquad (38)$$

70%–80% yield, and thus these phosphoramidic acids may be the most accessible of the numerous compounds known to function as metaphosphate generators. They are not, however, very stable and are best generated from the sodium salt with an ion-exchange resin immediately before use. With an anilino or *N*,*N*-diethylamino group, the fragmentations were slower and exhibited mixed first and second-order kinetics. Nevertheless, these compounds in certain applications (vide infra) appear to function effectively as donors of metaphosphates.

2.8. *Fragmentation of alkyl 2-acyloxyalkylphosphonates*

A recent report [58] has described the generation of alkyl metaphosphates by the thermal fragmentation of alkylphosphonates bearing acyl or sulfonyl groups at the 2-position) (reaction 39). No details were given for the synthesis of the required



$$R'CH_2\underset{OAc}{CH}-CH_2-\overset{O}{\overset{\|}{P}}(OR)_2 \xrightarrow{\Delta} RCH_2CH{=}CH_2 + AcOR + \left[RO-P\begin{smallmatrix}{\nearrow}O\\{\searrow}O\end{smallmatrix}\right] \qquad (39)$$

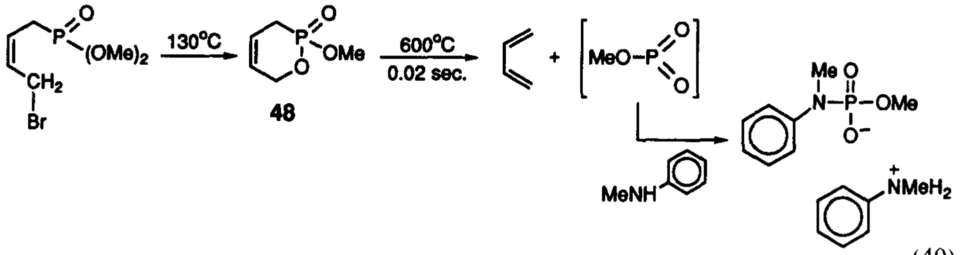
47

phosphonates **47** so it is difficult at this time to evaluate the process in terms of practicality. Furthermore, little information has been provided on the ability of the process to generate alkyl metaphosphates as free transient species available for other purposes; it is simply stated that "metaphosphates were identified in the aqueous phase as monoalkyl phosphates" by comparing properties with known compounds, but no intentional trapping of the presumed metaphosphate intermediate was performed. The reaction seems to require a high temperature (178–213°C in sulfolane, which permits a reaction rate over twice that of another aprotic, polar solvent, diglyme). Both methyl and ethyl metaphosphate are said to have been generated by this new method.

3. GENERATION OF DIOXOPHOSPHORANES IN THE GAS PHASE

The first examples [42,59] of the generation of dioxophosphoranes by pyrolysis of precursors in the gas phase were of great importance in the development of knowledge about these three-coordinate species, but in their present form are of low practical preparative value. Methyl metaphosphate was generated for the first time [42] by flash vacuum pyrolysis of an unsaturated 1,2-oxaphosphorinane (**48**), but the synthesis of this precursor is a low-yield process (not reported, but less than

25%). Condensation of the gaseous products gave largely polymeric products, but it was possible to intercept some (3%–5%) of the metaphosphate in a reaction with aromatic amines placed in the condensation trap (reaction 40). This reaction is described in Section 4.



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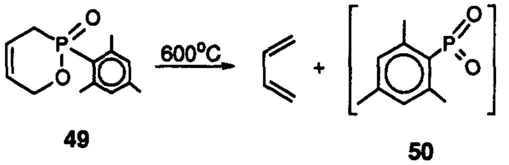
Mesityldioxophosphorane (**50**) was generated [60] by a similar reaction from **49** (reaction 41), as well as during the course of Diels–Alder reactions applied to



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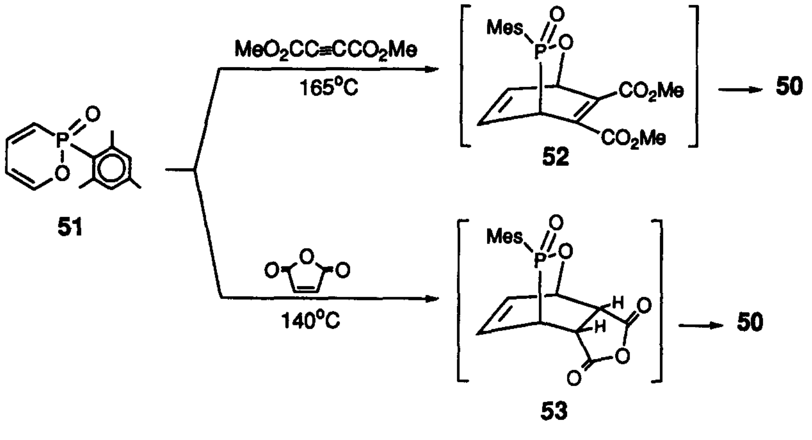
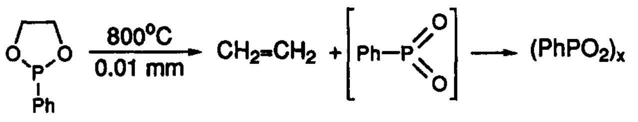


(42)

diene **51** (reaction 42). The Diels–Alder adducts **52** and **53** could not be observed under the experimental conditions. Adducts similar to **53**, obtained by the O-insertion process [46], were later shown elsewhere [45] to fragment in solution at even lower temperatures. Trapping experiments with methanol or *N*-methylaniline were reported to be only partly successful, and no products were isolated. The intermediacy of **50** was deduced from the nature of the polymeric products.

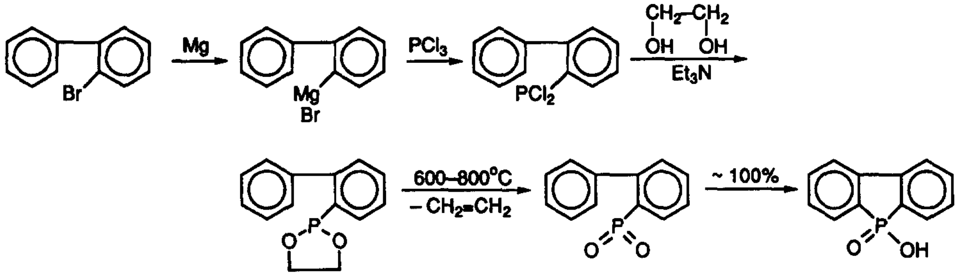
A gas-phase reaction of considerably more practical importance is based on the elimination of ethylene from the readily obtained 1,3,2-dioxaphospholanes [61]. When performed on the 1-phenyl derivative **54**, a self-condensation product of phenyldioxophosphorane (reaction 43) was detected by ^{31}P NMR (a six-line signal



54

(43)

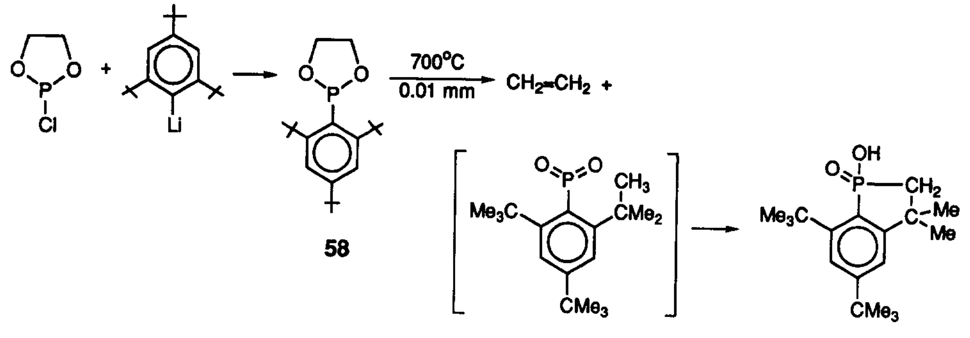
at $\delta + 3.2$ to -1.1 was reported; a singlet at δ 11.8 has been observed by other workers [49] for a condensation product, but the composition may differ). This product was formed in almost quantitative yield, but it was not possible to intercept the presumed intermediate phosphorane with trapping agents under the conditions used. Nevertheless, derivatives of the 1,3,2-dioxaphospholane system were synthesized that had features allowing intramolecular trapping of the dioxophosphorane, and because of the novelty of some of the resulting products, the process is judged as having practical value. In the first example [62], the 2-biphenyl derivative **55**, synthesized as shown in reaction 44, was pyrolyzed and gave a nearly quantitative yield of the product (**57**) resulting from electrophilic attack of the dioxophosphorane moiety in **56** on the adjacent phenyl group.



55 **56** **57**

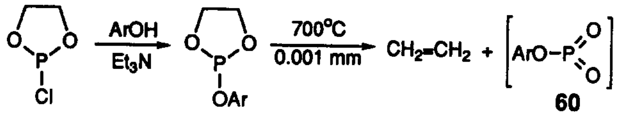
(44)

In the second example, the substituent on phosphorus was the 2,4,6-tri-*tert*-butylphenyl group; a C–H bond of a methyl group was the site of the intramolecular trapping, and the product was a novel dihydrophosphindole **59** formed in quantitative yield. The synthesis of the precursor **58** was accomplished as shown in reaction 45. The process was later adapted [63] to the formation of metaphosphates (reaction 46). In every case, however, the released aryl metaphosphates (**60**) proceeded under the experimental conditions to undergo insertion of phosphorus into a CH bond, thus giving new cyclic phosphonates. These products would be difficult to obtain by other procedures, as would the corresponding phosphonic acids that were formed on hydrolysis. The cyclic phosphonates, prepared at 600–800°C, are shown in Scheme I.



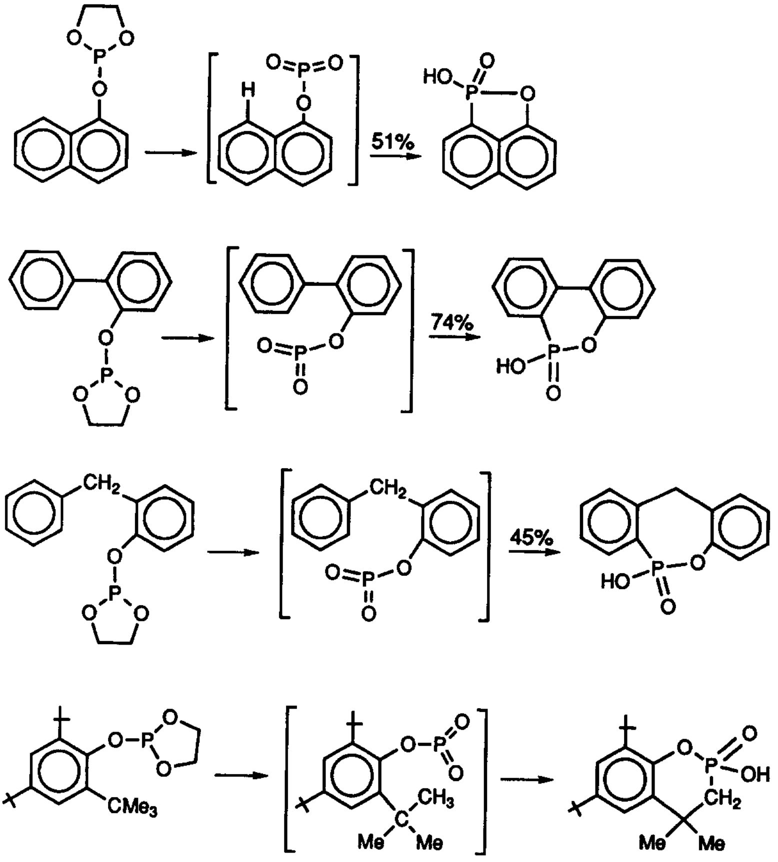
58

59 (45)



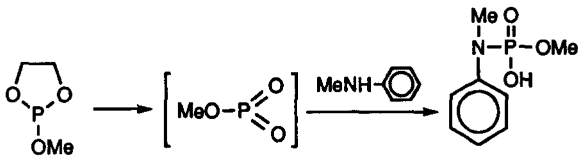
60

(46)



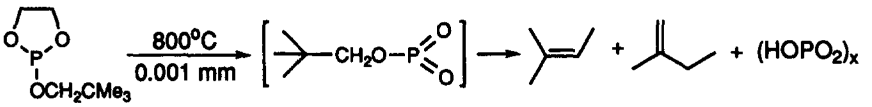
Scheme I.

Trapping reactions for the aryl metaphosphate were not successful, but evidence supporting the intermediacy of a metaphosphate was obtained from the pyrolysis of 2-methoxy-1,3,2-dioxaphospholane (reaction 47). In this case, the methyl metaphosphate produced was trapped with *N*-methylaniline [43], giving the same phosphoramidate observed by Clapp and Westheimer.



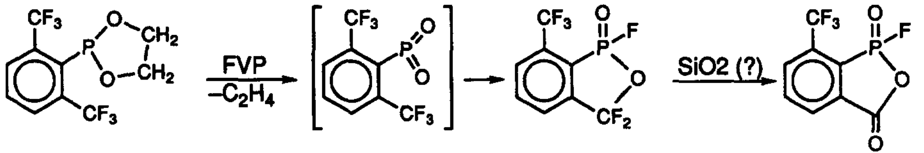
(47)

The FVP approach was also used to generate neopentyl metaphosphate, but under the conditions required this substance underwent elimination of metaphosphoric acid with the formation of butenes (reaction 48) [64]. When generated in solution by the fragmentation of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system [47], neopentyl metaphosphate is stable and detectable by trapping reactions.



(48)

Other workers [65] have replaced the *ortho*-alkyl substituents by trifluoromethyl groups in an effort to block the further reaction of the dioxophosphorane when generated by the FVP method. Compound **61** was pyrolyzed at 440°C to give a solid product in 80% yield. The product was a 9:1 mixture of two compounds; the major component had the novel structure **63**, which was explained by the reaction sequence 49.



61 **62** **63** (49)

None of the intramolecular products described in this section could have been anticipated from the solution chemistry known for metaphosphates. It might be expected that other novel intramolecular reactions of dioxophosphoranes in the gas phase will be encountered in the future, adding another dimension to practical aspects of dioxophosphorane chemistry.

4. REACTIONS OF DIOXOPHOSPHORANES WITH NUCLEOPHILIC COMPOUNDS

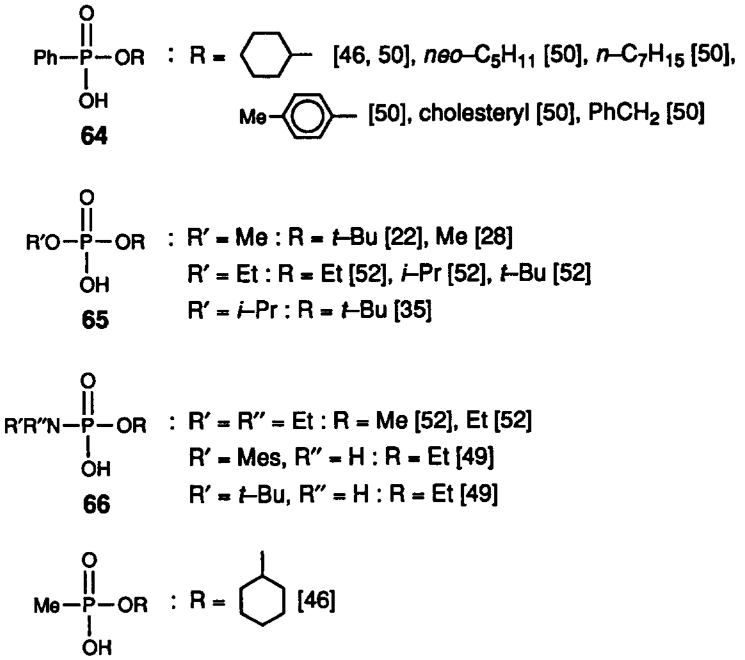
In this section the known reactions of dioxophosphoranes are summarized. Some are of interest primarily for trapping purposes, used to prove the existence of the transient species. Others are capable of producing novel phosphorylated compounds that would be difficult to obtain by more conventional methods. It is this group of reactions that will give practicality to dioxophosphoranes as laboratory reagents, although much remains to be done to develop these methods. In many cases, a reaction has been performed with a dioxophosphorane generated by only one of the various available methods, not necessarily the best one for that particular product. When viewed in the present way, one can see that there are many reactions now known for dioxophosphoranes, and the discovery of more can be anticipated. In every case known so far, the phosphorus atom acts as an electrophilic center, attacking nucleophiles with displaceable hydrogen, adding to oxygen atoms, or performing electrophilic substitution at electron-rich carbon.

4.1. Alcohols and silanols

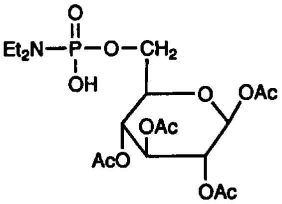
By far the most commonly used trapping agent to detect dioxophosphoranes is an alcohol, which adds to a phosphoryl group. From an alkyl- or aryldioxophosphorane is formed a phosphonate half ester (**64**); metaphosphates form phosphodiesters (**65**), while metaphosphoramides form *O,N,N*-substituted phosphoramidic acids (**66**). A summary of the products isolated and identified from these reactions is provided as Scheme II. In addition to their use as trapping agents, there can be valuable preparative aspects to these reactions. Thus, the phosphodiesters resulting from metaphosphates can have two different alkyl groups present, which is not always easy to achieve by other methods. This is particularly true if one alkyl group has tertiary structure. To illustrate, in the work of Avila and Frost [35] (Section 2.3) *tert*-butyl isopropyl phosphate was prepared for the first time, when isopropyl metaphosphate was generated in the presence of *tert*-butyl alcohol. As noted in Section 2.7, a glucose derivative was phosphorylated at −75°C, giving a new phosphoramidate **43** of a structure that would be difficult to make by other methods [46].

The half esters of phenylphosphonic acid that result from the trapping of phenyl dioxophosphorane have a structure that can also be difficult to generate in some cases. Of special note was the use [66] of cholesterol as the alcohol when the 2,3-oxaphosphabicyclo[2.2.2]octene **39** was the precursor (reaction 50) [49]. This followed an earlier example of Ramirez who had shown that metaphosphate anion gave phosphates with cholesterol and other sterols [67].

The OH group of a silanol has also been phosphorylated with a metaphosphate [68]. *tert*-Butyldimethyl silanol was used instead of an alcohol as a trapping agent in the thermal fragmentation of the bicyclic ester **67** (reaction 51). However, under the reaction conditions used, a secondary reaction occurred between the mono silyl



Scheme II.



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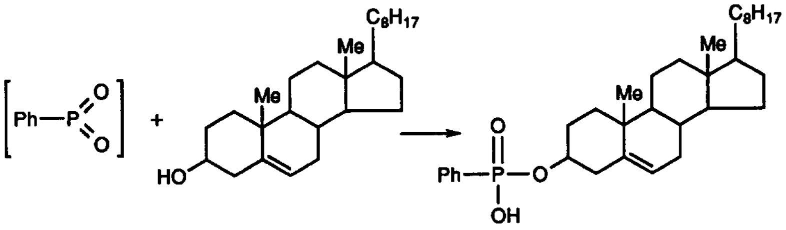
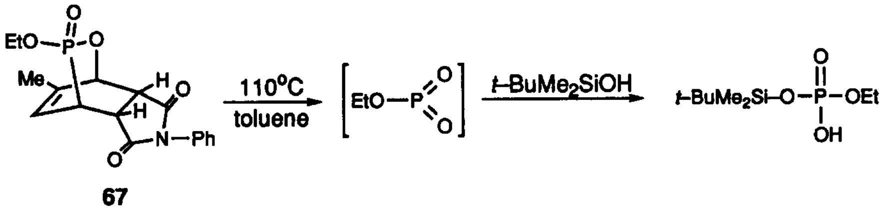
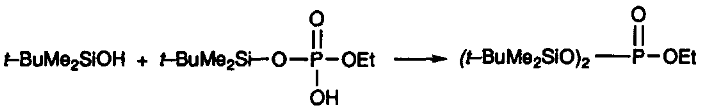


(50)



(51)

phosphate and the silanol to give a disilyl phosphate (reaction 52). This reaction

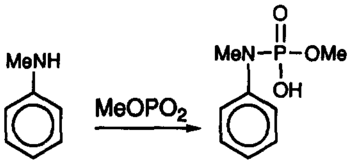


$$t\text{-BuMe}_2\text{SiOH} + t\text{-BuMe}_2\text{Si–O–}\overset{\text{O}}{\overset{\|}{\underset{\text{OH}}{\underset{|}{\text{P}}}}}\text{–OEt} \longrightarrow (t\text{-BuMe}_2\text{SiO})_2\text{–}\overset{\text{O}}{\overset{\|}{\text{P}}}\text{–OEt} \qquad (52)$$

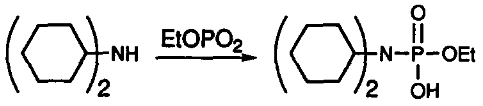
type is being further developed and may have considerable broadness. The reaction with a silanol will be seen in Section 4.6 to occur also with silanol groups on the surface of silica gel and zeolites.

4.2. *With amino groups*

Amines can also function as trapping agents for dioxophosphoranes and the known reactions are 53 and 54. The reaction with methylaniline deserves special



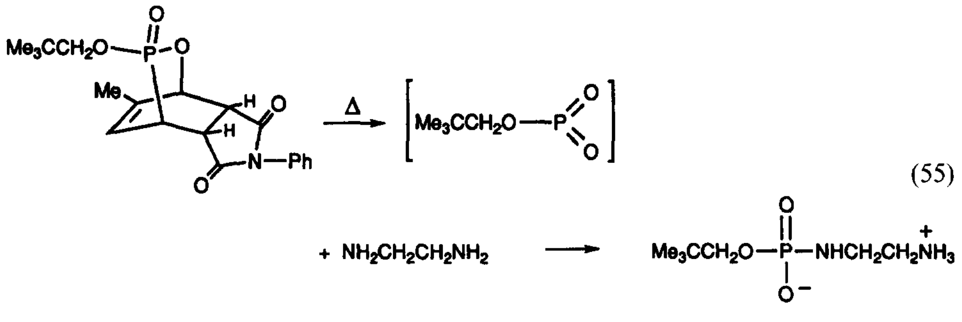
Ref. 42, 43 (53)



Ref. 46 (54)

comment. Dioxophosphoranes are of such high electrophilicity that they can perform substitution of hydrogen on activated benzene rings [21,42,59]. In the case of methylaniline, attack can occur either at nitrogen or at the *o,p* carbons. The reaction in a solvent such as chloroform is quite non-selective and leads to a mixture of products. However, in a solvent that is a lone pair donor capable of coordinating with the metaphosphate, the electrophilicity is reduced, and selectivity is increased. In this case attack on carbon predominates [18].

An advantage of the dioxophosphorane approach to phosphorylate amines is that a mixed O-alkyl N-substituted phosphoramidic acid results; while simple compounds with this structure are known, compounds with more complicated amine substituents are quite rare, and the route through a metaphosphate may deserve consideration in these cases. Another special advantage of phosphorylation by a dioxophosphorane is found with ethylenediamine [66] (and presumably with other diamines). Here the attack can occur on only one of the two amino groups. The phosphoramidic acid moiety first formed at one amino site reacts with the other amino group to form a dipolar salt; this salt can then precipitate from a non-polar reaction medium. This approach, where the dioxophosphorane was generated by the ring fragmentation method of Section 2.7, provided the novel salt **68** in 86% yield (reaction 55) [67].

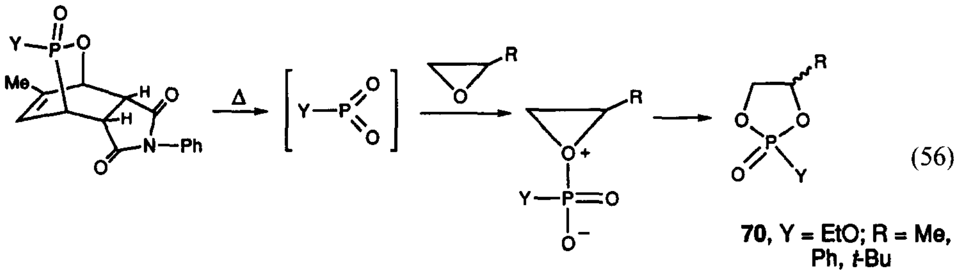


(55)

68

4.3. *With epoxides*

Ethyl metaphosphate generated by the ring fragmentation method of Section 2.7 attacks the oxygen of epoxides, presumably forming a Lewis salt **69** (reaction 56) [32]. This product undergoes a rearrangement, by a complex pathway not completely unraveled, to form five-membered cyclic phosphates (1,3,2-dioxaphospholanes, **70**). *N*,*N*-Diethylamino dioxophosphorane acts in the same way, forming cyclic phosphoramidates (**71**). These reactions are of interest in confirming the powerful Lewis acid character of dioxophosphoranes, a property seen in the suspected formation of adducts with tertiary amines [7,8,37] and with tetrahydrofuran [11]. Epoxides are advantageous as traps because they are not reactive to the common four-coordinate phosphorus groups used as precursors of dioxophosphoranes; alcohols and amines as traps have the possibility of being involved in preliminary formation of five-coordinate adducts with the precursors that then decompose to the same products as would be formed by addition to a three-coordinate transient intermediate phosphorane, thus giving uncertainty to the meaning of the observed reaction product. The ^{31}P NMR signals from the 1,3,2-dioxaphospholane ring system are in a unique, easily detected region (δ 15–20).

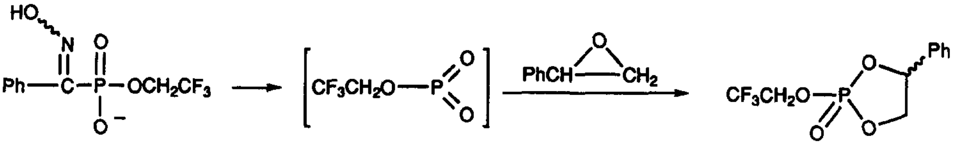


(56)

69

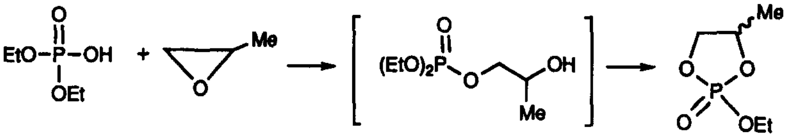
70, Y = EtO; R = Me, Ph, *t*-Bu
71, Y = Et$_2$N; R = Me

Epoxide trapping has already proved of value in other studies. It was noted in Section 2.4 that the epoxide trapping reaction was very recently employed to show the intermediacy of methyl metaphosphate in the decomposition of a (presumed) mixed phosphoric–carbonic anhydride [43]. The more conventional traps with OH or NH groups would not be useful in this reaction, since they would react either with the phosphorochloridate or with the mixed anhydride. Another application of the epoxide trapping techniques was described by Breuer [31] in his studies of the fragmentation of haloalkyl oximinophosphinates (reaction 57) (Section 2.2). As in the work of Bodalski and Quin [32], the dioxaphospholane was obtained as a mixture of cis and trans isomers.



(57)

Epoxides will probably not be useful as traps in a process where an acidic compound is used as the dioxophosphorane precursor, such as the phosphoramidic acids. It can be expected that ring opening of the epoxide would occur with an acidic OH group, as noted by Bodalski and Quin [32] with diethylphosphoric acid (reaction 58).



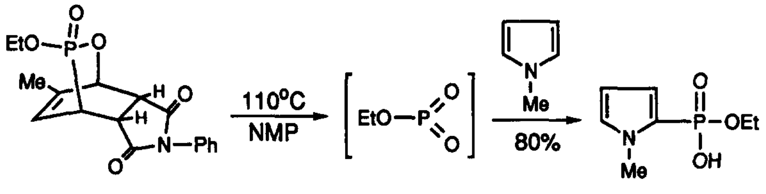
(58)

4.4. *With electron-rich carbon in anilines and N-methylpyrrole*

That three-coordinate phosphoryl species could function as electrophilic substitution agents was first observed in the work on the generation of methyl metaphosphate in the gas phase [42] and later in solution by the Conant–Swan method [21]. *N*,*N*-Dimethylaniline was found to undergo phosphonation at the ortho and para positions. Yields varied from 5% to 30% in the solution method, depending on the solvent. This was a dramatic discovery in metaphosphate chemistry, pointing so clearly to the power of the phosphorus center as an electrophile. It was later shown that the phosphonation also occurred when ethyl metaphosphate was generated [45] in solution by the ring fragmentation method (Section 2.7).

The electron-rich pyrrole ring was also found to be sensitive to phosphonation by ethyl metaphosphate [45]; when the metaphosphate was generated by the ring fragmentation approach in *N*-methylpyrrole (NMP) as solvent, the new

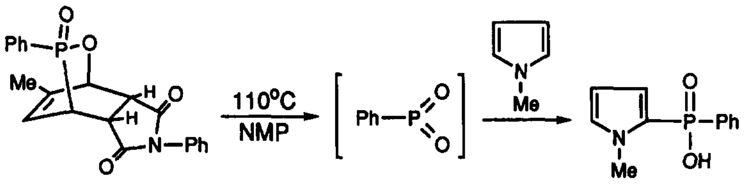
2-pyrrylphosphonic acid derivative **72** was formed in 80% yield (reaction 59).



72

(59)

Similarly, phenyl dioxophosphorane generated from the bicyclic compound **73** in *N*-methylpyrrole attacked the 2-position to form phosphinic acid derivative **74** (reaction 60), also a new substance. This reaction failed with thiophene [66], which is well known to be less reactive to electrophiles than is the pyrrole ring. The reaction with *N*-methylpyrrole is of value in uniquely confirming the existence of a dioxophosphorane intermediate, since no preliminary reaction is likely to occur with the precursor compound that would confuse the interpretation of the trapping result. With further development, it is possible that some synthetic value can be found in this process for preparing specialized pyrroles.

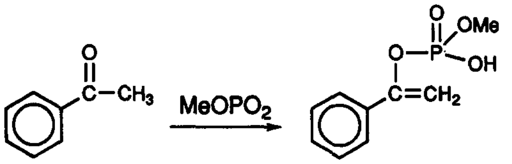


73 **74**

(60)

4.5. With carbonyl compounds

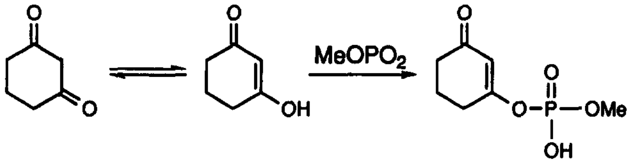
Enol phosphates result from the reaction of methyl metaphosphate with ketones. This reaction was observed [18] in the Westheimer laboratory when methyl metaphosphate was generated from methyl hydrogen erythro-1,2-dibromo-1-phenylpropylphosphonate in the presence of acetophenone (reaction 61). The anion was formed from the phosphonate with 2,2,6,6-tetramethylpiperidine; no solvent was used, and the reaction required 1 day at 70°C for completion. Analysis of the product



75

(61)

by ^{31}P NMR showed that 90% of the phosphorus was in the form of the enol phosphate **75**, and 10% as methyl phosphate (a hydrolysis product of the metaphosphate). The enol phosphate could be isolated by chromatography. The authors considered the carbonyl oxygen of the ketonic form as the site of attack by the metaphosphate; the enolic form is present in only a very small (about 0.035%) amount, and because of the lack of selectivity shown by the metaphosphate in other reactions, it was not considered likely that this was the reactive form. Ramirez et al. [22], however, made observations suggesting that in reactions with the metaphosphate ion it was the enolic form that reacted (reaction 62). These authors also



76

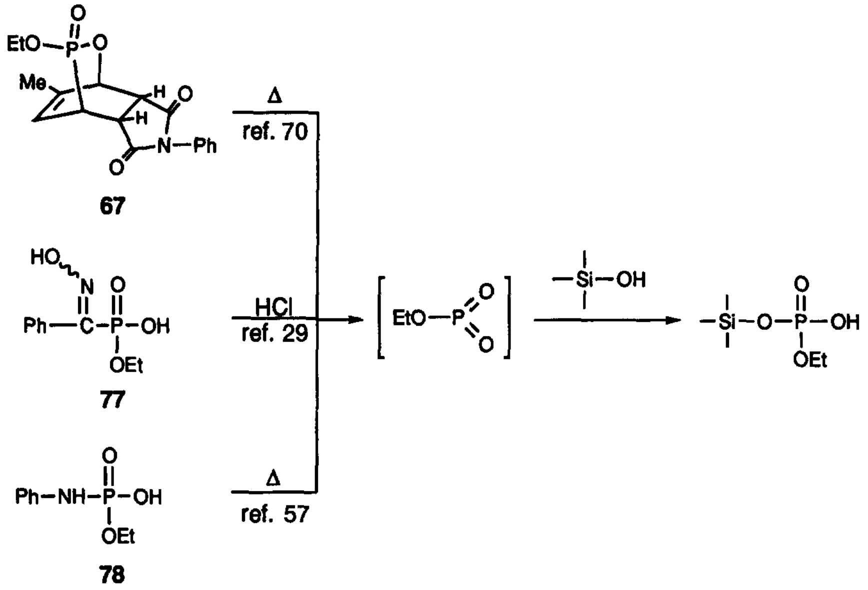
(62)

employed methyl metaphosphate, generated from the same precursor but in CD_3CN as solvent and with diisopropylethylamine as base. The reaction required 17 h at 70°C; the sodium salt of the mono enol phosphate **76** was isolated in 90% yield from the starting dibromophosphonate. This is an excellent example of a preparative use for a metaphosphate.

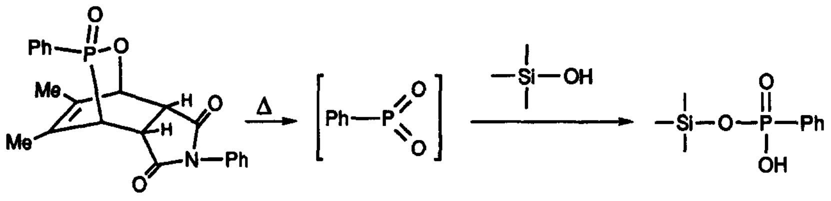
4.6. *With hydroxy groups on the surface of solids*

Dioxophosphoranes are such powerful phosphorylating agents that they are capable of reacting with the OH groups on the surface of certain solids [69]. Such reactions are carried out simply by generating the dioxophosphorane in one of the usual ways; an inert solvent is employed, and the solid is kept in suspension by stirring. The reaction of ethyl metaphosphate with silica gel is typical, and provides a product with the ethyl phosphate group directly bonded to the surface. Three different methods have been used to generate the metaphosphate (reaction 63); all gave the same product with silica as evidenced by the ^{31}P NMR spectrum of the recovered solid, which had δ -9 to -10 as obtained with the cross polarization-magic angle spinning (CP MAS) technique. Analysis of the solid for phosphorus indicated that some 50%–75% of the OH groups had been phosphorylated. The Si–OH groups in certain zeolites (silicoaluminates) were just as readily phosphorylated; both the bicyclic precursor (**67**) and the phosphoramidic acid **78** were useful for this purpose [57]. Alumina has also been phosphorylated by **67** [70].

In addition to the metaphosphates, phenyl dioxophosphorane serves as a reactant with silica gel (reaction 64). These reactions with solids are of interest for two reasons. In the first place, the solids function as highly effective trapping agents, and are therefore of value in detecting the intermediacy of low-coordination [71]

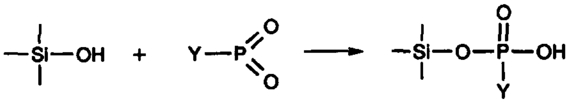


(63)



(64)

transient electrophilic agents. Positive indications of the presence and type of phosphorus bonded to the surface is easily provided by CP MAS ^{31}P NMR spectroscopy. In addition, the phosphorylated solids themselves may have practical value. Thus, it has already been demonstrated that an HPLC grade of silica gel after phosphorylation with ethyl metaphosphate has improved characteristics in the separation of certain mixtures, notably of aromatic amines and of petroleum distillates. It is likely that the loss of the SiOH groups and creation of the more acidic POH groups plays a role in the change in adsorption characteristics. It is an essential feature of the use of dioxophosphoranes of all types for surface phosphorylation that the OH group is created on phosphorus (reaction 65); there appears to be at present no other method that can give the same phosphorus functionality on the surface with the ease that the use of dioxophosphoranes provides.



(65)

A new possibility now being explored is that silica gel phosphorylated with metaphosphates bearing optically active groups may be of value in the separation of racemic mixtures. For this purpose, (+)-menthyl metaphosphate has been generated by the phosphoramidic acid fragmentation method and reacted with silica gel [70]. The solid is at present being evaluated. Zeolites are some of the most important commercial catalysts; the easy way with which the surface can be modified by the use of dioxophosphoranes certainly suggests that exploration of catalytic properties of the phosphorylated zeolites be performed.

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