Synthesis of Phosphinic Acid Derivatives; Traditional Versus up-to-Date Synthetic Procedures

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Abstract

Synthetic methods for the preparation of phosphinic derivatives (esters and amides) are summarized. The basic method is, when phosphinic chlorides are reacted with alcohols or amines. These reactions take place under mild conditions, but utilize expensive chlorides, need a solvent, and a base has to be added to remove the HCl formed. On conventional heating, the phosphinic acids resist undergoing derivatizations by nucleophiles. However, on microwave (MW) irradiation, the phosphinic acids could be esterified by alcohols. The direct esterification does not require an extra solvent, it is atomic efficient, but needs a relatively higher temperature. The similar amidations were reluctant. Phosphinic acids may also be esterified by alkylation that may be promoted by combined phase transfer catalysis and MW irradiation. It is also possible to convert the phosphinic acids by different reagents (*e.g.* by the T3P® reactant) to a more reactive intermediate that is ready to react with alcohols or amines. Other methods, such as preparation by the Arbuzov reaction or by fragmentation-related phosphorylation are also discussed.

Introduction

Phosphinic derivatives (acids, chlorides, esters, amides etc.) are important building blocks (starting materials and intermediates) in synthetic organic chemistry [1]. They are produced on an industrial scale, and utilized in the synthesis of fine chemicals, plant protecting agents and medicines. Until now, there has been no comprehensive review on the synthesis of phosphinic derivatives. For this we undertook to compile this review including also our quite experiences. The discussion has been grouped around two major point of views: traditional syntheses and green chemical aspects.

Traditional Methods for the Synthesis of Phosphinate

irect Esterification

It is known, that phosphinic acids cannot be esterified by alcohols (Scheme 1).
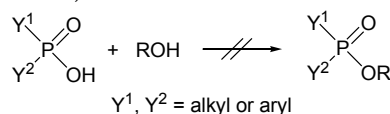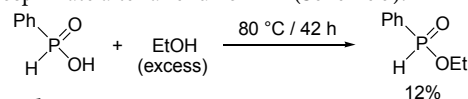
Scheme 1

Only a few examples are known for direct esterification. Nifant'ev reported the direct esterification of hypophosphorous acid in the presence of acidic catalysts under azeotropic water removal in benzene or toluene (Scheme 2) [2,3].
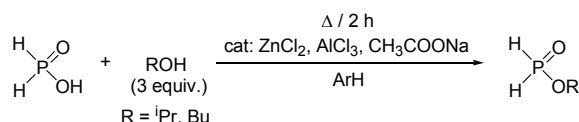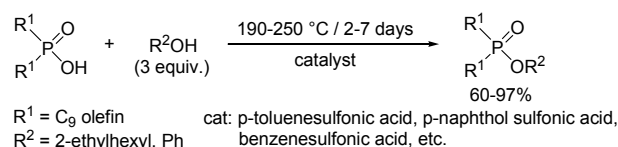
Scheme 2

Cherbuliez substantiated that the direct esterification of tetracoordinated P-acids with at least one P-H bond is only possible via the tautomeric tri coordinated form [4]. The direct esterification of orthophosphoric acid with ethanol yielded 2.5% of the monoethyl ester after 22 days, at the same time, the esterification of phenyl-*H*-phosphinic acid with an excess of ethanol gave 12% of the ethyl phenyl phosphinate after a reflux of 42h (Scheme 3).

Scheme 3

One patent reports the esterification of dialkylphosphinic acids in the presence of different catalysts under quite extreme conditions and prolonged reaction times (Scheme 4) [5].

R^1 = C_9 olefin　　cat: p-toluenesulfonic acid, p-naphthol sulfonic acid,
R^2 = 2-ethylhexyl, Ph　　benzenesulfonic acid, etc.

Scheme 4

In another patent, authors claimed that two phosphinates were synthesized from the corresponding phosphinic acids by reaction with 2 equiv. of allyl or crotyl alcohol in the presence of p-toluenesulfonic acid in aromatics with water removal. However, there was no evidence for the formation of the esters [6].

It is remarkable, that no other example for the direct esterifications of phosphinic acids have been reported. However, diphenylphosphinothioates were prepared by the direct esterification of diphenylphosphinodithioic acid with certain alcohols and phenols in the absence of a catalyst [7].The reaction required long reaction times.

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Esterification of Phosphinic Chlorides with Alcohols

The usual synthesis of phosphinic esters involves the reaction of phosphinic chlorides with alcohols (Scheme 5) [1,8-10], It is drawback that this method applies chlorides and an aromatic solvent, the acylation is not atomic efficient and environmentally problematic due to the formation of hydrochloric acid.
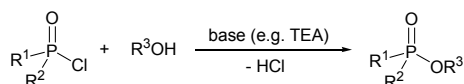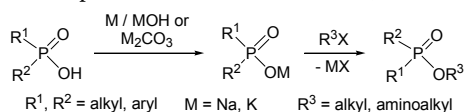
Scheme 5

In most cases a tertiary amine [11], an alcoholate [12] or a phenolate is used in a polar solvent [13]. Despite the disadvantages, this method is widely used due to its general applicability.

A few examples were described for the esterification of chloro-phospholene oxides by alcohols in the presence of NEt_3 or NaOMe as the base in different solvents. The preparative details can be seen (Table 1). The yields were variable (27-85%) [14-18].

Alkylating Esterification of Phosphinic Acids

Phosphinates may also be obtained by O-alkylation [7-9]. In the first step, the acid is transformed into the corresponding sodium or potassium salt that is then reacted with an alkyl halide. However, only a few examples were described (Scheme 6) [19, 20].
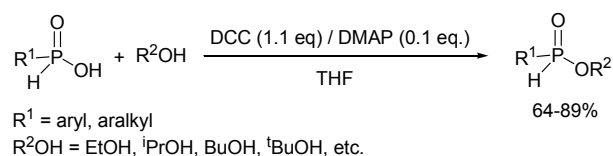
Scheme 6

Under phase transfer catalytic (PTC) conditions, the acids may be transformed directly to the corresponding phosphinates. It is also possible to use an alkali salt as the starting material [21].

The addition of unsaturated compounds, such as terminal acetylenes to phosphinic acids may also lead to phosphinates [22].

A few laboratory methods utilize diazomethane or diazoalkanes for the esterification of phosphinic acids [23-29]. The first alkyl di *H*-phosphinates was also prepared by this approach [30].

Esterification of Phosphinic Acids using Activating Agents

Since the nucleophilic substitution on the phosphorus atom of phosphinic acids by alcohols does not take place, the acid should be transformed to a more active species. Such procedure is when the phosphinic acid is reacted by a carbodiimide. Karanewsky reported the esterification of phosphinic acids in the presence of dicyclohexylcarbodiimide (DCC), 10% of *N, N*-dimethylaminopyridine (DMAP) and a slight excess of alcohol in THF to give the corresponding phosphinates in good yields (Scheme 7) [31-33].

R^1 = aryl, aralkyl
R^2OH = EtOH, ^{i}PrOH, BuOH, ^{t}BuOH, etc.

Scheme 7

Mixed anhydrides of $Y^1 Y^2 P (O)O-C(O)OR$ type can be formed easily that undergo CO_2 elimination to provide the $Y^1 Y^2 P(O)OR$ phosphinate [34].
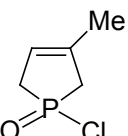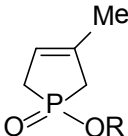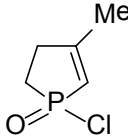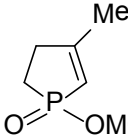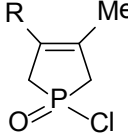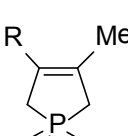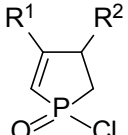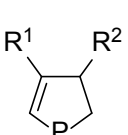
Phosphinic chloride	Conditions			Yield [%]^{ref}	Product
	Reagents	Solvent	R		
	MeOH/NEt_3 ^{neo}PentOH/NEt_3 EtOH/NEt_3	Et_2O PhH CH_2Cl_2	Me ^{neo}Pent Et	64[14] 85[15] 47[16]	
	MeOH/NEt_3	Et_2O	Me	62[14]	
 R=H, Me	NaOMe	PhMe	Me	80–81[17]	
 R^1, R^2=H, Me	ROH/NEt_3	CH_2Cl_2	C_1-C_{12} alkyl	27–72[16]	

Table 1: Esterification of chloro-phospholene oxides

Esterification of Phosphinic Acids by Orthocarbonyl Compounds

Alkyl hypophosphinates ($H_2P(O)OR$) that are starting materials in the synthesis of alkyl- and aryl phosphinates, are prepared through the alkaline hydrolysis of P_4 in an industrial scale, [35] however, a few alternative methods were also described for their preparation. Fitch reported the reactions of hypophosphorous acid with compounds having an orthocarbonyl function, such as orthoesters (n=0), orthocarboxylates (*e.g.* orthoformates/orthoacetates) (n=1), ketals and acetals (n=2) [36] . Schwabacher studied the reaction of anhydrous hypophosphorus acid and trimethylorthoformate, that is a specific but not a clean method for the preparation of methyl phosphinate [37]. The reaction of ketals and acetals required higher temperatures and resulted in the formation of 1-hydroxyphosphinates [36]. A Japanese research group has carried out the synthesis of phosphinic esters with trialkyl orthocarboxylates, such as trialkyl orthoacetates in ionic liquid applying lower reaction temperatures and shorter reaction times [38].

Esterification of Phosphinic Acids by Orthosilicates

Montchamp has studied the esterification of *H*-phosphinic acids or their salts using orthosilicates or alkoxysilanes in detail [39,40]. The same group prepared stable hypophosphite esters by the reaction of hypophosphorus acid salts with aminoalkoxysilanes [40].

Esterification of phosphinic acids by trialkyl phosphites

Trialkyl phosphites may also be effective esterifying agents, however, this method is of limited use (Scheme 8) [41,42].

Scheme 8

Michaelis-arbuzov Reaction of Phosphonous Diesters

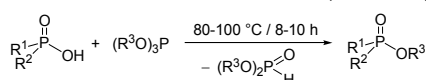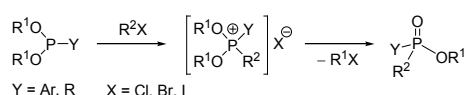The Michaelis–Arbuzov reaction of aryl or alkylphosphonous diesters with alkyl halides affords phosphinates (Scheme 9) [9,43].
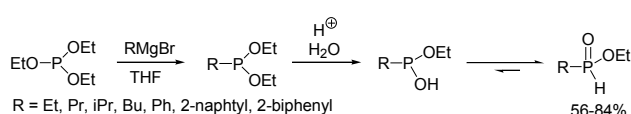

Scheme 9

Primary alkyl halides react faster than secondary, while tertiary alkyl halides usually fail to enter in the Arbuzov reaction. The reaction of aryl halides of decreased reactivity may be promoted by Ni salts (at higher temperatures) [44,45]. Vinyl halides may react in the presence of Cu (I) bromide [46].

Reaction of Trialkyl Phosphites with Grignard Reagents followed by Hydrolysis

H-Phosphinates were synthesized by the reaction of triethyl phosphite with one equiv. of Grignard reagent followed by hydrolysis (Scheme 10) [47-49].
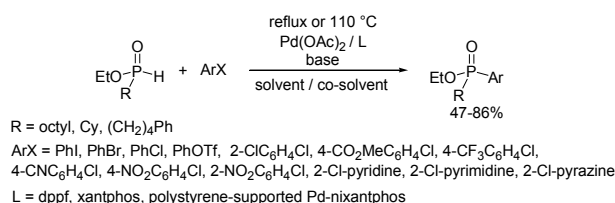

R = Et, Pr, iPr, Bu, Ph, 2-naphtyl, 2-biphenyl

Scheme 10

P-C Bond formation from *H*-Phosphinates or Hypophosphinate

The Hirao reaction has been applied widely to form P-C bond in the coupling of aryl halides or other derivatives with >P(O)H reagents, mainly dialkyl phosphites in the presence of a complex catalyst [50]. In a modification, alkyl-*H*-phosphinic acids were coupled with aryl halides to give phosphinates (Scheme 11) [51].

R = octyl, Cy, $(CH_2)_4Ph$
ArX = PhI, PhBr, PhCl, PhOTf, $2\text{-}ClC_6H_4Cl$, $4\text{-}CO_2MeC_6H_4Cl$, $4\text{-}CF_3C_6H_4Cl$, $4\text{-}CNC_6H_4Cl$, $4\text{-}NO_2C_6H_4Cl$, $2\text{-}NO_2C_6H_4Cl$, 2-Cl-pyridine, 2-Cl-pyrimidine, 2-Cl-pyrazine
L = dppf, xantphos, polystyrene-supported Pd-nixantphos

Scheme 11

Zhao obtained the same type of P-C coupled products using CuI /proline catalysts [52], but Ni salts can also be applied as catalysts [53] .Mont champ and co-workers synthesized a variety of dialkylphosphinates by different organometallic reagents in the phosphorylation of alkyl and alkenyl derivatives [54].

Dialkylphosphinates were obtained via the Pd-catalyzed hydrophosphinylation of olefins [55]. Several applications were described for the combination of the above mentioned methods. Sterically hindered unsymmetrical diarylphosphinates were synthesized starting from hypophosphorous acid and applying an esterification step by orthoacetate that was followed by a palladium-catalyzed P-C bond formation step [56]. Another example is a one-pot process including an esterification step by aminoalkoxysilanes followed by a P-C coupling step giving rise to phenyl-*H*-phosphinates [57].

Formation of Cyclic Phosphinates from Phosphonium Salts

Cyclic phosphinates may be obtained by the alcoholysis of the McCormack cycloadducts of 1, 3-dienes with phosphorus trihalides (Scheme 12) [16,58,59].

R^1 = H, Me, Ph
R^2 = H, Me
X = Cl, Br

R^3 = Me, Et, Bu, Hex, Dodec
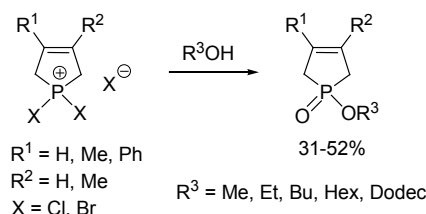
Scheme 12

The original procedure involving the alcoholysis of the cycloadduct (X = Br) was modified by the senior author of this chapter applying an excess of the alcohol as the solvent, and solid sodium carbonate, as the base resulting in the alkoxy-3-phospholene 1-oxides in better (57-68%) yields [60,61].

Instead of PX_3, the cycloaddition reaction was also performed using other reactants, such as $ROPX_2$ or $ArOPX_2$ to give corresponding phosphinates after hydrolysis [62-64].

Formation of Cyclic Phosphinates by Ring Closure

Bis-Grignard reagents may be used in the synthesis of phospholane oxide derivatives. An example is the ring closure of the bis (Grignard reagent) obtained from 2,5-dibromopentane and magnesium by $EtOP(O)Cl_2$ that resulted in the formation of 1-ethoxy-2,5-dimethylphospholane 1-oxide [65].

A 1-butoxy-hexahydrophosphinine-oxide was also synthesized involving the Michaelis–Arbuzov reaction of 1,5-dibromopentane and

tri-*n*-butylphosphite in the first step followed by cyclization through a Grignard-intermediate to provide eventually n-butoxy-1,2,3,4,5,6-hexahydrophosphinine oxide (Scheme 13) [66].
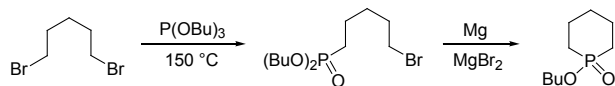
Scheme 13

The same phosphinate was also obtained by an intramolecular alkylation [54]. A recent review summarizes the possible syntheses of heterocycles with phosphinate function including phosphole, phosphindole-, oxaphosphole-, phosphorine- and other derivatives, mainly from acyclic phosphinate precursors [67].

Alcoholysis of Phosphinic Derivatives

Reaction of phosphinates with alcohols is also a known procedure that is accomplished by heating of the given esters with higher boiling point alcohols for a longer period of time [68]. Although several examples can be found for the "transesterification" of phosphinates by alcohols, it can be said that these reactions, in most cases, lead only to incomplete conversions [37,39,40,69].

Amides can also be converted to esters by alcoholysis [70,71]. The alcoholysis of anhydrides affords phosphinates and phosphinic acids (Scheme 14) [72,73].

Y = ar$_{yl}$

Scheme 14

Fragmentation-Related Phosphorylation of Strained *P*-heterocycles

H-Phosphinates may be synthesized by the UV light-mediated fragmentation of a suitable precursor in the presence of an alcohol that is "phosphorylated". The precursor is ideally a bridged *P*-heterocycle [74-81], such as a 7-phosphanorbornene derivative (Scheme 15).

Y = ar$_{yl}$

Scheme 15

However, 5- or 6-membered *P*-heterocycles, such as phospholene oxides, could also be used [82,83]. The reactive phosphinidenes could also be generated thermally from strained cyclic phosphine oxides, such as phosphanorbornenes [84].
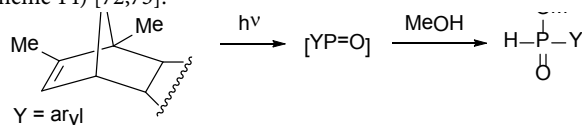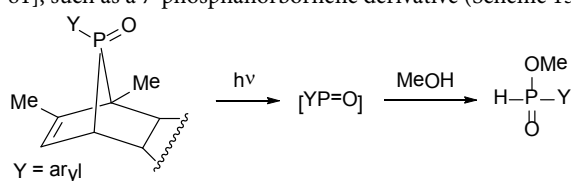
According to another protocol, phosphabicyclo[2.2.2]octadiene- or -octene derivatives served as the precursors of methylenephosphine oxides giving the phosphinates by phosphorylation of the alcohols or phenols. The fragmentation was achieved photo chemically or thermally (Scheme 16) [85-92].
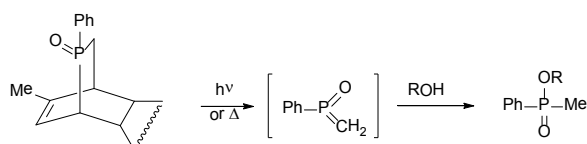
Scheme 16

Phosphinates by the Atherton–Todd Reaction

The reaction of secondary phosphine oxides with alcohols under the conditions of the Atherton-Todd reaction may give phosphinates (Scheme 17) [93] .

R^1 = alkyl, alkoxy, aryl
R^2 = aryl
R^3 Me, Et, ^{i}Pr, Ph, p-MeOC$_6$H$_4$

88-92%
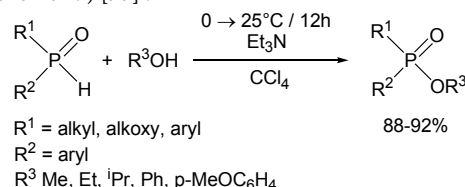
Scheme 17

Phosphinates by Rearrangement Reactions

Interestingly, the treatment of diaryl ethyl phosphates with lithium diisopropylamide led to the corresponding ethyl diarylphosphinates by a double rearrangement after hydrolysis [94]. On the other hand 3-aryl-3-phospha-1,5-hexadienes may furnish phosphinates via a phospha-Cope rearrangement. The reaction of the intermediate so formed with an alcohol gives phosphinates [95].

Treatment of diaryl ethyl phosphates with lithium diisopropylamide (LDA) in tetrahydrofuran yields ethyl bis-(2-hydroxyary1) phosphinates via the intramolecular double migration of the phosphorus moiety [94].

Traditional Methods for the Synthesis of Phosphinic Amides

Reaction of Phosphinic Chlorides with Amines

The most general method for the preparation of phosphinic amides is the reaction of phosphinic chlorides with primary or secondary amines. In these cases, the hydrochloric acid formed can be removed by a second equivalent of the amine (Scheme 18) [1,8-10,13,96].

R^2, R^2 = alkyl, aryl

49-95%

| R^3 | alkyl | Ph | H | |
| R^4 | alkyl | H | H | |
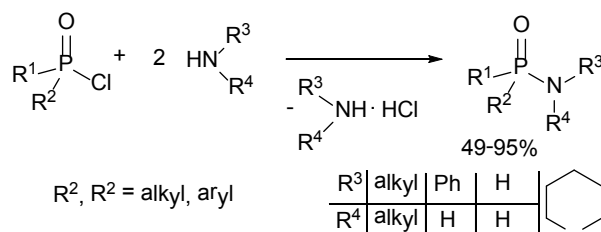
Scheme 18

A series of 1-amino-3-phospholene 1-oxides was synthesized in a similar way, using the secondary amines in a two-fold quantity (Scheme 19) [97,98].

R^1 = H, Me   R^2 = Me, Et
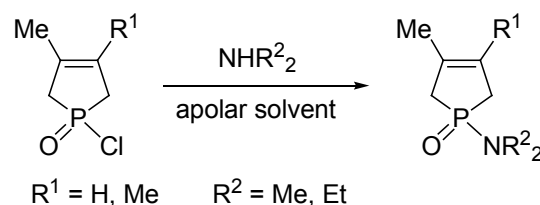
Scheme 19

In rare cases, the corresponding bromide was used instead of the phosphinic chloride [99]. The reaction of primary amines with

1-chloro-3-phospholene 1-oxides prepared from the corresponding hydroxy-phospholene 1-oxides was studied by the authors this chapter [100]. It was found, that depending on the molar ratio of the reactants and on the order of mixing, the reaction afforded either 1-amino-phospholene 1-oxides (**A**), or their *N*-phosphinoyl derivatives (**B**) (Scheme 20). Thus, the product composition could be fine-tuned.
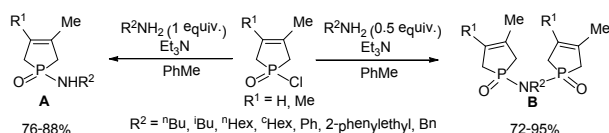
Scheme 20

Moreover, it was also possible to convert the 1-amino-phospholene 1-oxides (**A**) to the corresponding bisproducts (**B**) by reaction with another 3-phospholene-1-chloride. On this basis, mixed "phosphimides" could be synthesized from the 1-amino-phospholene 1-oxides by reaction with different P-chlorides (Scheme 21) [101].
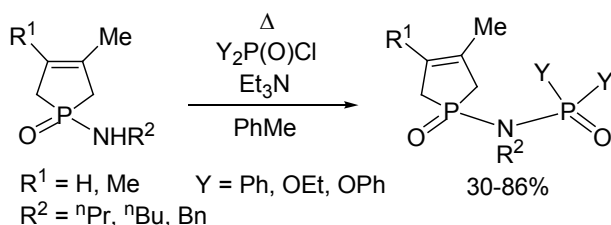
Scheme 21

A 3-ethoxy-phosphabicyclo[3.1.0]hexane 3-oxide was converted to the corresponding phosphinic amide in two steps via the P-chloride (Scheme 22) [102].
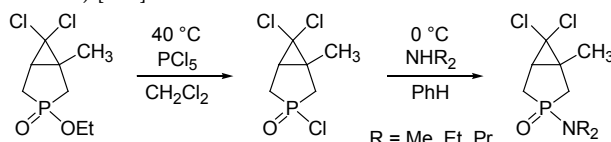
Scheme 22

Miscellaneous Methods

Analogously to phosphinates, phosphinic amides may also be synthesized by the Atherton-Todd reaction using secondary phosphine oxides and amines as the nucleophiles [93,103].

Oxidation of alkyl or arylphosphinous amides [104], or cyclic P-compounds, such as aminophospholanes [105] also leads to phosphinic amides. Organophosphorus borane complexes may also be subjected to oxidation [106].

The reaction of 1-hydroxy-3-methyl-3-phospholene 1-oxide with tris(*N*,*N*-dialkylamino)phosphines afforded the corresponding amino-phospholene oxide via three steps. The key intermediates were the corresponding salt and an anhydride that underwent a transamination reaction to afford amino-phospholene oxides in good yields (Scheme 23) [98].

Scheme 23

On irradiation at 254 nm, the 2-phosphabicyclo[2.2.2]octene derivatives were readily fragmented to methylenephosphine oxides that phosphorylated the amines added to the reaction mixture prior to the irradiation. In this way, the UV-light mediated fragmentation-related phosphorylation yielded phosphinic amides (Scheme 24) [107].
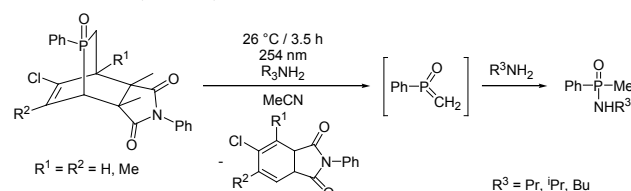
Scheme 24

Green Methods for the Synthesis of Phosphinates and Phosphinic Amides
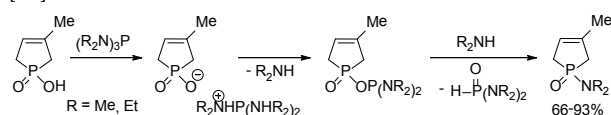
Green Methods for Phosphinates

It was shown in subchapter 2.2. that the traditional synthesis of phosphinates by the reaction of phosphinic chlorides and alcohols is not green due to the need of solvent and base, and the reaction is not atomic efficient as a consequence of the formation of HCl. It would be a "greener" procedure to start from the corresponding phosphinic acid. The formation of H_2O as the by-product would mean a better atomic efficiency. The microwave (MW) and the phase catalytic techniques offer good possibilities to perform environmentally-friendly transformations.

Microwave-Assisted Direct Esterification of Cyclic Phosphinic Acids

Direct Esterification of 1-Hydroxy-3-Phospholene 1-Oxides

With Butyl Alcohol: It was shown in subchapter 2.1. that the phosphinic acids usually do not undergo direct esterification. This is well exemplified by the fact that 1-hydroxy-3-methyl- and -3,4-dimethyl-3-phospholene oxides cannot be esterified with butyl alcohol on heating. However, we found, that on MW irradiation at 22°C/8 bar, applying the alcohol in a 15-fold excess, the corresponding phosphinates were obtained in 44/58% conversion (Scheme 25/**A**). Comparative thermal experiments under similar conditions (220°C/8 bar) provided the butyl esters in only low conversions (Scheme 25/**B**) [108].
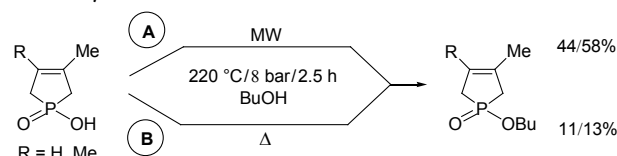
Scheme 25

Both the MW and the comparative thermal experiments were accomplished in sealed reaction vessels. Regarding the MW-assisted reactions, the distribution of the temperature may be regarded macroscopically isotherm in the bulk of the mixture. However, in nano-segments there is a statistically occurring local overheating effect that is very efficient in promoting faster and more quantitative reactions.

With longer carbon atom chain alcohols: Later on we found that it is more advantageous to use longer carbon atom chain, and hence less volatile alcohols as the reagents. In these cases, even a higher reaction temperature (up to 235°C) may be applied and the overpressure developed is only 1-1.5 bar. Carrying out the esterifications of

1-hydroxy-3-methyl- and -3,4-dimethyl-3-pholene oxides with n-pentyl alcohol, i-pentyl alcohol, n-octyl alcohol, i-octyl alcohol and dodecyl alcohol, the cyclic phosphinates were obtained in yields of 57-95%, after almost quantitative conversions (Scheme 26) [109-111].

Direct Esterification of 1-Hydroxy-3-Methyl- and -3,4-Dimethylphospholane 1-Oxides: Then the esterifications were extended to 1-hydroxy-3-methylphospholane 1-oxides. Applying the above used conditions, the 1-alkoxyphospholane oxides were obtained in yields of 59-86% (Scheme 27). The products were formed as a *ca.* 1:1 mixture of two diastereomers. The 3,4-dimethyl analogue consisting of a 2:1 mixture of isomers was esterified under similar conditions to furnish the cyclic phosphinates as a mixture of three isomers (a racemate and two optically inactive diastereomers). In these cases, the isolated yields fall in the range of 50-72% (Scheme 28)

Direct Esterification of 1-Hydroxy-3-Methyl-1,2,3,4,5,6-Hexahydrophosphinine 1-Oxide: Finally, 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine oxide was subjected to MW-assisted direct esterification. In this instance, the *ca.* 2:1 mixture of the cyclic phosphinate isomers were obtained in 62/54% yields (Scheme 29)

In respect of the cyclic phosphinic acids, the following order of reactivity was observed:

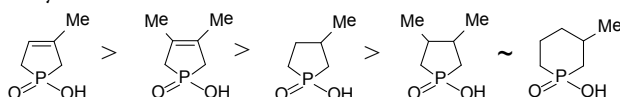In respect of the reagents used, the MW-assisted direct esterification of phosphinic acids may be regarded green. However, the need for a reaction temperature of *ca.* 200°C may mean a disadvantage. If a professional MW reactor is available, the assurance of the relatively higher reaction temperature is not a problem.

Energetics of the Direct Esterification: The energetics of the esterification of phosphinic acids was evaluated by B3LYP/6-31++G (d,p) calculations in comparison with that of acetic acid. In these cases a single alcohol molecule was assumed [112]. It was found that the formation of methyl acetate goes with an enthalpy of activation of 75 kJ mol^{-1} and the reaction is slightly exothermic (Figure 1/**a**). At the same time, the esterification of 1-hydroxy-3-methyl-3-pholene oxide with butyl alcohol has a higher activation barrier of 102 kJ mol^{-1}
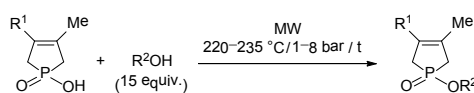
R^1	R^2	T (°C)	t (h)	Conversion (%)	Yield (%)
H	^{n}Pent	220	2.5	100	94
H	^{i}Pent	235	3	100	74
H	^{n}Oct	220	2	100	71
H	^{i}Oct	220	2	100	76
H	Dodecil	230	2	100	95
Me	^{n}Pent	235	3	90	67
Me	^{i}Pent	235	4	80	57
Me	^{n}Oct	230	2	100	95
Me	^{i}Oct	220	2.5	100	82
Me	Dodecil	230	2	100	95

Scheme 26: MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxides
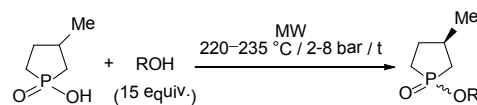
R	T (°C)	t (h)	Isomeric composition (%)	Yield (%)
^{n}Pent	235	3	1:1	79
^{i}Pent	235	4	1:1	59
^{n}Oct	230	4	1:1	72
^{i}Oct	220	3	1:1	86

Scheme 27: MW-assisted direct esterification of 1-hydroxy-3-methylphospholane 1-oxides
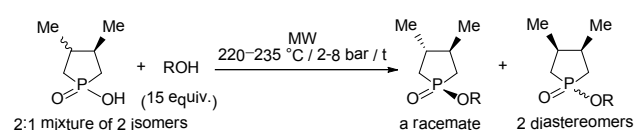
R	T (°C)	t (h)	Isomeric composition (%)	Yield (%)
^{n}Pent	235	5	70-15- 15	60
^{i}Pent	235	6	64 -19 - 17	56
^{n}Oct	230	4	~70 - 15 - 15	72
^{i}Oct	220	4	66 -19- 15	50

Scheme 28: MW-assisted direct esterification of 1-hydroxy-3,4-dimethylphospholane 1-oxides
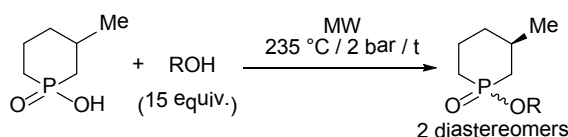
R	t (h)	Isomeric composition (%)	Yield (%)
^{n}Oct	4	66- 34	62
^{i}Oct	6	69 - 31	54

Scheme 29: MW-assisted direct esterification of 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine 1-oxide

and the transformation is slightly endothermic, let say thermoneutral (Figure 1/**b**). It is a noteworthy finding that both direct esterifications under discussion involve a 4-membered ring transition state (TS) formed from the protonated acid in a one elementary step process (Figure 2/a,b). Analogous TSs was also assumed for other type of reactions, such as for trans esterifications and hydrolytic processes [113]. It is important to stress that these results were obtained for gas phase reactions. It is obvious that the direct esterification of phosphinic acids is prevented on conventional heating by the relatively high values for the enthalpy of activation. However, the beneficial effect of the statistically occurring local overheatings may promote to overcome the energy barrier.

Possible Mechanisms for the Formation of Esters by the Reaction of Phosphinic Esters with Alcohols: Basically, the reaction of phosphinic acids and alcohols may take place by the phosphorylation of the alcohol, or by the alkylation of the phosphinic acid (Scheme 30). The classical "acylation" route is represented by protocol "A", while the novel sequence including the above-mentioned 4-center TS is shown by protocol "B". The esterification by the alkylation of the phosphinic

Figure 1: Enthalpy profile for the esterification of acetic acid and 1-hydroxy-3-methyl-3-phospholene 1-oxide

Figure 2: TSs for the esterification of acetic acid with methanol and 1-hydroxy-3-methyl-3-phospholene oxide with butanol
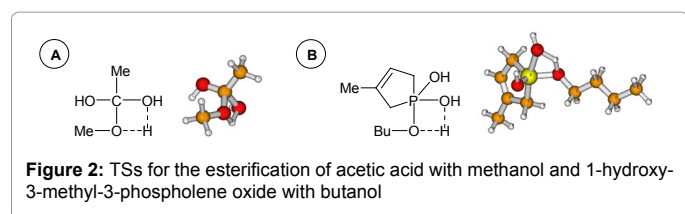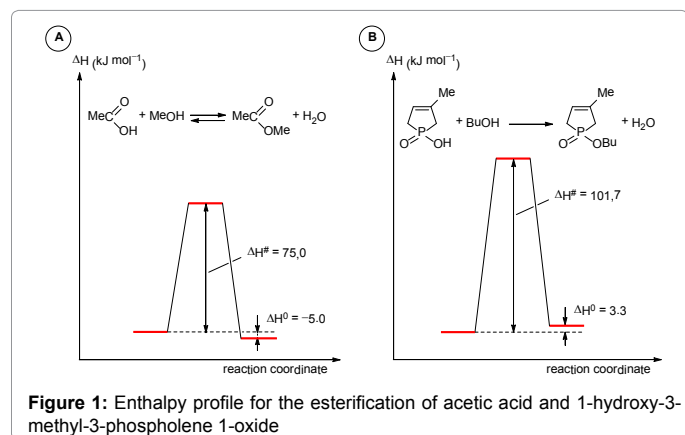
acid follows the scheme marked by "C". It is important that in all cases the phosphinic acid serves as a protonating agent. It is clear that in our case mechanism "B" may be operative.
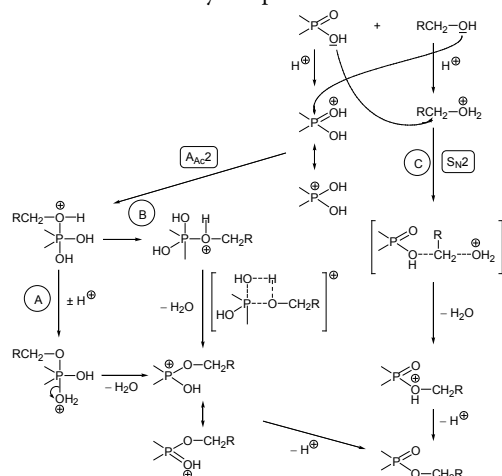
Scheme 30

Mechanism of the Esterification of 1-Hydroxy-3-Methyl-3-Phospholene oxide with Butanol using the Explicit-Implicit Solvent Model: A more reliable explicit-implicit solvent model was constructed by the consideration of a few solvent molecules and an additional phosphinic acid as a proton donor in the starting state as illustrated in Scheme 27 [112]. The two Bu OH (solvent) molecules form an important hydrogen bond net in the associate. The esterification starts with the nucleophilic attack of the oxygen of BuOH on the P=O group of the reactant, resulting in a rather unstable (131.1 kJ mol⁻¹) first intermediate state, via high energy TS1 (134.6 kJ mol⁻¹). Then, the following low energy multistep transformation involves proton transfers through the two butanol molecules. In the final step, the phosphinic acid catalyst helps the departure of the OH group form the P atom of the second intermediate by protonation via a high energy

TS2 (133.5 kJ mol⁻¹). The activation enthalpies of the last steps are somewhat lower, than those for the first TS1, therefore the reaction rate is controlled by the first nucleophilic attack of BuOH. The overall process is entropically driven by the elimination of water, but the non-beneficial enthalpy could not be compensated by that. In the light of the activation enthalpies computed, the nominal temperature of 180-235°C and even the local overheatings caused by the MW irradiation could be essential to overcome the high activation Gibbs free energy. It can be concluded that MW may promote thermoneutral reactions with relatively high enthalpies of activation.
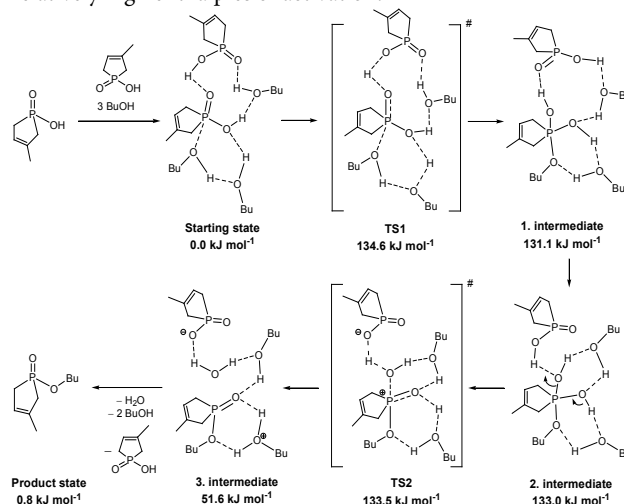
Scheme 31

Esterification of 1-Hydroxy-3-Methyl-3-Phospholene-1-Oxide with a Thioalcohol: It was not so surprising that the MW-assisted direct esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide with thiobutanol resulted in the formation of the thiobutoxy-3-phospholene oxide (Scheme 32) [114].The conversion was, however, only 51%, consequently, the isolated yield of the monothiophosphinate was only 38%. The experimental fact, that no 1-butoxy-3-phospholene oxide was formed confirmed the "acylation" mechanism. The question emerged what the reason may be that this reaction was so reluctant, even under MW irradiation. The energetics of the reaction under discussion was evaluated by quantum chemical calculations. We learned that as compared to the esterification with butanol, the enthalpy of activation was significantly higher (145 kJ mol⁻¹) and what is more, the reaction turned endothermic (Figure 3/**a** and **b**). This explains why the esterification with thiobutanol remained incomplete. Endothermicity is against the beneficial effect of the local overheatings. The 4-membered TS established for this reaction is shown in (Figure 4).
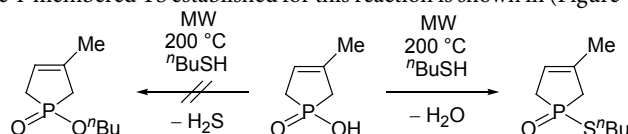
Scheme 32

According to a more sophisticated computational study carried out with the explicit-implicit solvent model an even higher TS (230.5 kJ mol⁻¹), was found and the endothermicity was (ΔH = 47.9 kJ mol⁻¹) by this method. This reaction route starts with the protonated hydroxyphospholene oxide getting the proton from another molecule

Figure 3: Enthalpy profile for the esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide with thiobutanol and butanol

Figure 4: TS for the esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide with thio butanol

R	T (°C)	t (min)	Conversion (%)	Yield (%)
Et	160	60	100	80
^nPr	160	60	100	73
^iPr	180	120	100	48
^nBu	180	30	100	90
^nBu	160	60	100	85
^iBu	160	60	100	75
^nPen	190	30	100	89
^iPen	190	30	100	87
^nOct	180	30	100	84
^iOct	180	30	100	75

Scheme 34: MW-assisted esterification of phenyl-*H*-phosphinic acid with alcohols[108]

of the phosphinic acid. It is noteworthy that although the species protonated on the P=O group is *ca.* 104.4 kJ mol^{-1} more stable than that protonated on the OH unit, it is still the latter form that reacts, although it is present only in a small quantity. This species is attacked by a thiobutanol molecule to form protonated thioester via a relatively high activation barrier (230.5 kJ mol^{-1}) belonging to the corresponding TS. Deprotonation of the final intermediate affords the thiophosphinate (Scheme 33). The incompleteness of the reaction is explained rather by its high endothermicity, than its high overall activation barrier.
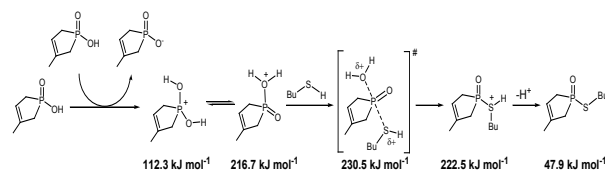
Scheme 33

Direct Esterification of Phenylphosphinic Acids: Phenyl-*H*-phosphinic acids underwent direct esterification with alcohols relatively easily under MW conditions (Scheme 34). Except one case, the alkyl phenyl-*H*-phosphinates were obtained in yields of 73-90% [115].

The sterically hindered diphenylphosphinic acid was also esterified, but these reactions required somewhat more forcing conditions and the yields were lower (Scheme 35).
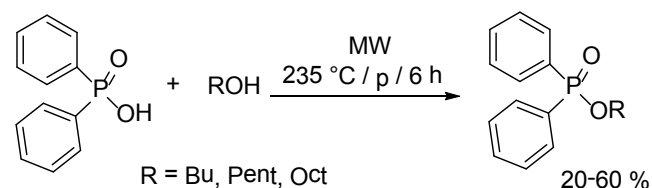
Scheme 35

Direct Esterification of Phenylphosphonic Derivatives: The phenyl-*H*-phosphinates prepared according to (Scheme 34). were oxidized to
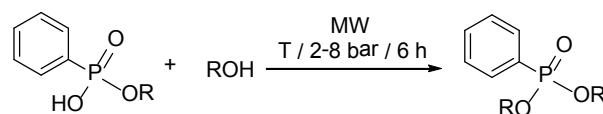
R	T (°C)	Conversion (%)	Yield (%)
^nBu	220	31	25
^nPent	220	40	35
^nPent	235	57	51
^iPent	235	50	43
^nOct	235	72	62
^iOct	235	51	45

Scheme 37: MW-assisted esterification of diphenylphosphonic acid-esters with alcohols

R^1	R^2X	TEBAC	Mode of heating	Yield of ester (%)
H	EtI	5%	MW	90
H	^nPrBr	5%	MW	94
H	^iPrBr	5%	MW	65
H	^nBuBr	–	MW	69
H	^nBuBr	5%	MW	96
H	^nBuBr	–	Δ	64
H	^nBuBr	5%	Δ	89
Me	EtI	5%	MW	95
Me	^nPrBr	5%	MW	90
Me	^iPrBr	5%	MW	56
H	BnBr	–	MW	92
H	BnBr	5%	MW	94
H	BnBr	–	Δ	85
H	BnBr	5%	Δ	87

Scheme 38: Alkylating esterification of 1-hydroxy-3-methyl- and -3,4-dimethyl-3-phospholene oxides
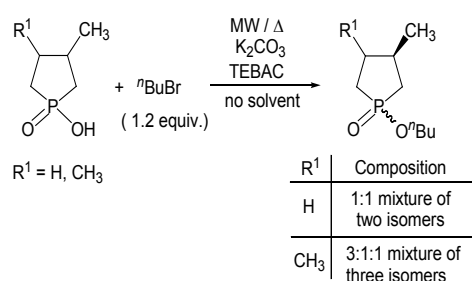
R^1	TEBAC	Mode of heating	T (°C)	t (h)	Yield
H	–	MW	100	2	77
H	5%	MW	100	1.5	95
H	–	MW	120	2	95
H	5%	MW	120	1	94
H	–	Δ	100	2	22
H	5%	Δ	100	2	80
CH₃	–	MW	100	2	46
CH₃	5%	MW	100	1.5	98
CH₃	–	MW	120	2	93
CH₃	5%	MW	120	1	94
CH₃	–	Δ	100	2	16
CH₃	5%	Δ	100	2	75

Scheme 39: Alkylating esterification of 1-hydroxy-3-methyl- and -3,4-dimethyl-phospholane oxides

the corresponding phosphonic ester-acidderivatives(Scheme 36) [115].
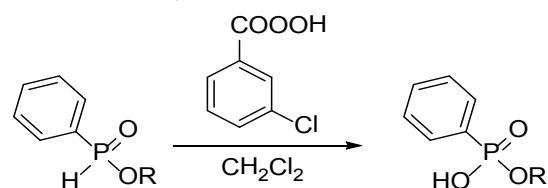
Scheme 36

The phosphonic acid-ester derivatives could also be esterified by alcohols under MW conditions to furnish dialkyl phenylphosphonates in variable yields 35-62%, (Scheme 37). This is the first case for the MW-assisted direct esterification of phosphonic acid derivatives.

Alkylating Esterification of Cyclic Phosphinic Acids

Alkylation Esterification of 1-Hydroxy-3-Phospholene 1-Oxides: The senior author of this chapter, together with others studied the alkylating esterification of cyclic phosphinic acids under phase transfer catalytic (PTC) and solvent-free microwave (MW) conditions using alkyl halides in the presence of potassium carbonate [109,116].

Carrying out the alkylation of 1-hydroxy-3-methyl- and -3,4-dimethyl-3-pholene oxides with alkyl halides of normal reactivity, such as ethyl iodide, n-propyl bromide and butyl bromide, the simultaneous use of the phase transfer catalyst (triethylbenzylammonium chloride [TEBAC]) and MW was beneficial (Scheme 38). The alkylations carried out on conventional heating led to somewhat lower yields as compared to the MW variations. The alkylation with the sterically hindered i-propyl bromide was not so efficient. It was found, that in case of benzyl bromide that is of increased reactivity the phase transfer catalyst could be omitted, thus a solvent- and catalyst-free method was developed.

Alkylating Esterification of Hydroxy-phospholane Oxide: Similar trends were experienced in the phase transfer catalyzed (PTC) and MW-assisted alkylating esterification of 1-hydroxy-3-methyl- and -3,4-dimethylpholene oxides (Scheme 39). The esterifications with n-butyl bromide could be enhanced by the addition of TEBAC as the catalyst at 100°C. However, at 120°C there was no need for the catalyst. Similarly to the direct esterifications, the monomethyl cyclic phosphinates were obtained as a mixture of two isomers, while the dimethyl derivatives as a mixture of three isomers.

Alkylating Esterification of 1-Hydroxy 1,2,3,4,5,6-Hexahydro-phosphinine Oxide

Finally, the 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine oxide was also the subject of O-alkylation by n-butyl bromide under PTC and MW conditions. The experiences were quite similar with the exception that the addition of the phase transfer catalyst was also useful at 120°C (Scheme 40).

It was shown recently that the alkylating esterification of phenyl-*H*-phosphinic acid with alkyl halides takes place using triethylamine in a homogeneous medium (Scheme 37) [117].

RX = EtI, nPrBr, ^iPrBr, ^nBuBr, ^iBuBr, ^iPentBr

Scheme 41

TEBAC	Mode of heating	T (°C)	t (h)	Yield
–	MW	100	3	64
5%	MW	100	1	73
–	Δ	100	1	41
5%	Δ	100	1	66
–	MW	120	1	70
5%	MW	120	1	81

Scheme 40: Alkylating esterification of 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine oxide

ROH	t (h)	Yield (%)
MeOH	0.5	80
EtOH	0.5	77
PrOH	0.5	80
^{i}PrOH	3	76
BuOH	0.5	82
^{i}BuOH	0.5	86
^{s}BuOH	3	88
PentOH	0.5	94
^{i}PentOH	0.5	91
3-pentyl alcohol	3	79
^{c}HexylOH	2	89
BnOH	0.5	95
2-phenylethanol	0.5	90
2-(1-naphthyl)ethanol	0.5	93
menthol	3	95

Scheme 42: T3P®-mediated esterification of 1 hydroxy-3-methyl-3-phospholene 1-oxide

R	Yield (%)
Et	85
^{n}Pr	91
^{i}Pr	68
^{n}Bu	87
^{i}Bu	76
^{i}Pent	92

Scheme 45: P-C coupling reaction of alkyl phenyl-*H*-phosphinate

Phosphinates by T3P®-Mediated Esterification: The propylphosphonic anhydride (T3P®) reagent is also a powerful coupling (dehydrating/condensing) agent applied in a wide range of reactions [118]. The senior author of this article together with co-workers reported the fast and efficient esterification of cyclic phosphinic acids with a series of alcohols at 25°C, in the presence of 1.1 equivalent of the T3P® reagent (Scheme 42). [119].

The T3P®-promoted protocol could be applied well also for the esterification of 1-hydroxy-3,4-dimethyl-3-phospholene oxide, 1-hydroxy-3-methylphospholane oxide and 1-hydroxy-3,4-dimethylphospholane oxide. The corresponding phosphinates were obtained in 70-81% yields, and, where it was appropriate, as a mixture of diastereomers (Schemes 42-44).

81%

Scheme 43

70%
1:1 mixture of two isomers

Scheme 44

75%
3:1:1 mixture of three isomers

Scheme 45

The role of the T3P® reagent is to form a reactive anhydride intermediate from the cyclic phosphinic acid, which may then undergo reaction with the alcohol already at room temperature.

The by-product HOP(O)(Pr)OP(O)(Pr)OP(O)(Pr)OH formed can be removed by extraction with water. It is a challenging question if the other units of the T3P® reagent can also be utilized or not. We have got encouraging preliminary results in finding that with reactive phosphinic acids it might be enough to apply 0.66 equivalents of the T3P® reagent.

Phosphinates by P-Ligand-free P-C Coupling: An environmentally friendly approach for the synthesis of arylphosphinates by the Hirao reaction of phenyl-*H*-phosphinate with bromobenzene involves the use of P-ligand-free Pd(OAc)$_2$ catalyst under solvent-free MW conditions as this was observed by the senior author of this chapter together with

a co-worker (Scheme 46). [117,120].

Green Methods for Phosphinic Amides

Amidation of Cyclic Phosphinic Acids: After the esterifications, the 1-hydroxy-3-methyl-3-pholene oxides were also subjected to amidation with primary amines at 220°C/~7 bar under MW conditions (Scheme 46/A). After average conversions of 33%, the yields were around 27%. Hence, in these cases, it is better to prepare the 1-alkylamino-3-methyl-3-pholene oxides via the conventional method involving the corresponding 1-chloro-pholene oxide as the intermediate (Scheme 46/B).

Amidation of the monomethyl- and dimethyl-hydroxyphospholanes with benzylamine under similar MW-assisted conditions gave the phosphinic amides in low yields (23%) (Scheme 47).
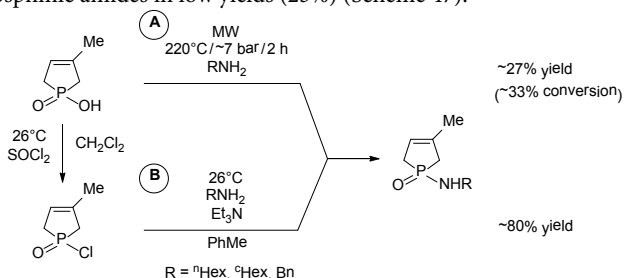
Scheme 47
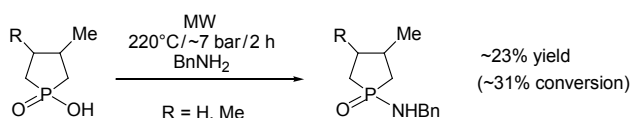
Scheme 48

Theoretical calculations on the amidation of acetic acid and 1-hydroxy-3-methyl-3-pholene oxide suggested that the amidation of acetic acid is slightly exothermic, while that of the cyclic phosphinic acid is significantly endothermic (-8.2 vs. 32.6 kJ mol^{-1}). The enthalpies of activation are not too high (-52.1 vs. 79.4 kJ mol^{-1}) [121]. The energetics of the direct amidations discussed in comparison are shown in (Figure 5), while the TS for the amidation of 1-hydroxy-3-methyl-3-pholene oxide with hexylamine can be seen in (Figure 6). Endothermicity works against the beneficial effect of MW irradiation. Theoretical calculations at the B3LYP/6-31G(d,p) level of theory utilizing the solvent model [112] showed that the amidation of 1-hydroxy-3-methyl-3-pholene oxide by hexylamine, analogously to the thioesterification, also exhibits a rather endothermic enthalpy profile (35.2 kJ mol^{-1}), which means an unfavourable course for the reaction. According to a detailed study [112] the mechanism starts with a proton exchange pre-equilibrium between hexylamine and cyclic phosphinic acid. The resulting phosphinic acid anion is, however, inactive toward the amine nucleophile, consequently, the series of elemental steps starts from the neutral form of the phosphinic acid that is attacked by the hexylamine. In the quantum mechanical model shown in (Figure 7), a protonated hexylamine molecule (HexNH$_3^+$) acts as an acid catalyst, while an additional HexNH$_2$ molecule behaves as base catalyst in the course of the reaction. After a few steps, the reaction sequence ends up by the elimination of a molecule of water to afford the amide as the final product. The enthalpy of activation corrected by the energy gain of the protolytic equilibrium is moderate (114.1 kJ mol^{-1}) as compared to that of the esterification and thioesterification.
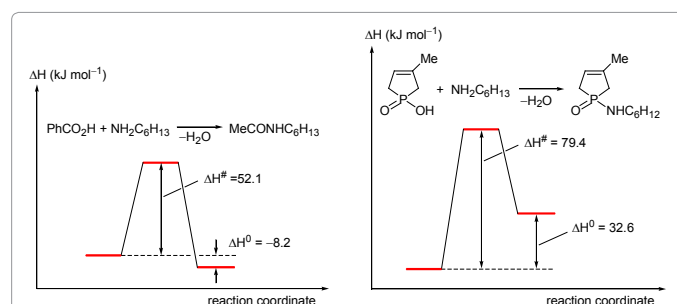

Figure 5: Comparative direct amidation of benzoic acid and 1-hydroxy-3-methyl-3-pholene oxide
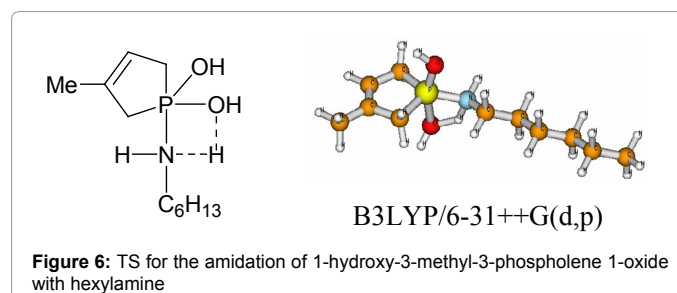
Figure 6: TS for the amidation of 1-hydroxy-3-methyl-3-pholene 1-oxide with hexylamine
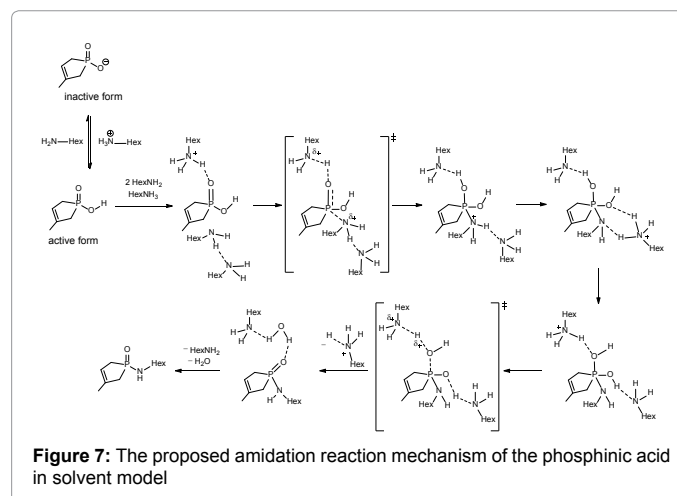
Figure 7: The proposed amidation reaction mechanism of the phosphinic acid in solvent model

The results show undoubtedly that the amidation under discussion is controlled by the endothermic pattern and the kinetic energy gap. It can be concluded that the reluctance of the amidation of the phosphinic acids, in the case under discussion 1-hydroxy-3-pholene oxide, is explained by the endothermicity. MW may promote only exothermic or thermoneutral transformations.

Conclusions

The possible synthetic methods for phosphinic derivatives have been summarized. On the one hand, the traditional methods starting form phosphinic chlorides or phosphinic acids via activation (*e.g.* by the T3P□ reagent) to give phosphinates and phosphinic amides mean a good choice for the preparation. These common methods are completed well by more special reactions, such as the Arbuzov reaction, Hirao reaction, alcoholysis, fragmentation-related phosphorylation and other approaches, like intramolecular cyclization and the alcoholysis of phosphonium salts. On the other hand, there are "greener" variations

utilizing MW irradiation and/or the phase transfer catalytic technique. Such transformation is the synthesis of phosphinates from the corresponding phosphinic acids by MW-assisted direct esterification, or by MW- and phase transfer catalysis promoted alkylation. The latter reaction can be performed under solvent-free conditions.

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