Chapter 3
The Use of MW in Organophosphorus Chemistry

György Keglevich, Erika Bálint and Nóra Zs. Kiss

Abstract The third chapter summarizes a special field, the application of the microwave (MW) technique in the synthesis of organophosphorus compounds. On the one hand, reactions are shown that are otherwise rather reluctant on traditional thermal heating. On the other hand, reactions are discussed, which, became more efficient (shorter reaction times and higher yields) on MW irradiation. Finally, the simplification of catalytic systems under MW conditions are surveyed.

Keywords Microwave · Organophosphorus chemistry · P-heterocycles · Direct esterification · Alkylating esterification · T3P® reagent · C-alkylation · Kabachnik–fields condensation · Arbuzov reaction · Hirao reaction

3.1 Introduction

The use of MW technique in general organic syntheses was spread revolutionarily in the last 35 years. As such, this novel approach was, of course, applied also in organophosphorus chemistry from the beginning (∼1980), however, the real break-through happened much later. Guenin was the first, who collected the examples of MW-assisted organophosphorus reactions into a review article [1] that was followed by a few others compiled mainly by the author of this chapter [2–7].

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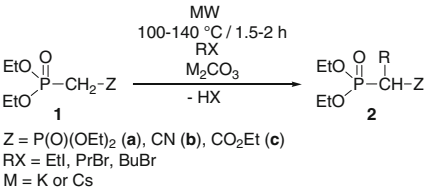
3.2 Alkylation of Active Methylene Containing Substrates

3.2.1 *Monoalkylation of P=O-Functionalized CH-Acidic Compounds*

It was found that simple active methylene containing compounds underwent C-alkylation by reaction with alkyl halides in the presence of K_2CO_3 under solvent-free MW conditions. The message of this discovery is that the phase transfer catalyst can be substituted by MW irradiation [8, 9]. This method was then extended to the alkylation of tetraethyl methylenebisphosphonate (**1a**), diethyl cyanomethylphosphonate (**1b**) and diethyl ethoxycarbonylmethylphosphonate (**1c**) using K_2CO_3 or Cs_2CO_3 as the base to give the corresponding monoalkylated products (**2a-c**) in variable yields (Scheme 3.1, Table 3.1) [10–12].

The phase transfer catalyzed and MW-assisted alkylations of active methylene containing substrates were summarized [13–15].



Scheme 3.1 MW-assisted substitution of active methylene containing compounds

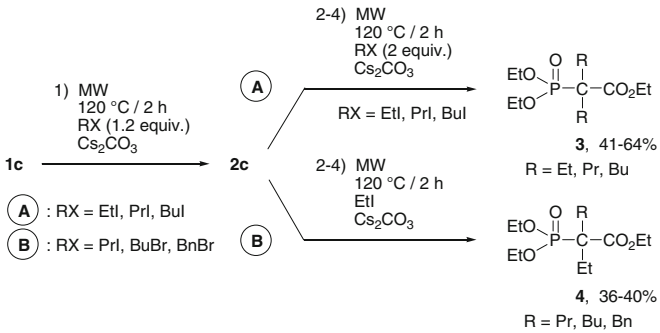
Table 3.1 Summary of the MW-assisted alkylation of CH-acidic compounds

Entry	Starting material	RX	M_2CO_3	Solvent	Mode of heating	T/p (° C/bar)	t (h)	Yield of **2**	Ref.
1	**1a**	EtI	Cs_2CO_3	–	MW	140/11	1.5	80	[10]
2	**1a**	^{n}PrBr	Cs_2CO_3	–	MW	120/6	4	57[a,b]	[10]
3	**1b**	^{n}PrBr	K_2CO_3	–	MW	100/2.5	2	64	[11]
4	**1b**	^{n}BuBr	K_2CO_3	–	MW	120/3	2	59	[11]
5	**1c**	EtI	Cs_2CO_3	–	MW	120	2	70	[12]
6	**1c**	^{n}PrBr	Cs_2CO_3	–	MW	120	2	71	[12]
7	**1c**	^{n}BuBr	Cs_2CO_3	–	MW	120	2	70	[12]

[a]Proportion in the mixture on the basis of GC
[b]The mixed esters with one or two PrO groups were also present in 33 % and 10 %, respectively

3.2.2 *Dialkylation of P=O-Functionalized CH-Acidic Compounds*

A multi-step variation of the above method led to dialkyl derivatives [16]. Reacting diethyl ethoxycarbonylmethylphosphonate (**1c**) with 1.2 equivalents of alkyl iodides in the presence of 1 equivalent of Cs_2CO_3 at 120 °C for 2 h, and repeating the treatment of the crude product using 2 equivalents of the same alkylating agent in the presence of 1.5 equivalents of Cs_2CO_3 for four times, the dialkylated products (**3**) were obtained in 41–64 % yields (Scheme 3.2/**A**). In a similar way, applying propyl iodide, butyl bromide, benzyl bromide in the first step, and ethyl iodide in the second, third and fourth steps, the mixed alkyl derivatives **4** were prepared in yields of 36–40 % (Scheme 3.2/**B**).



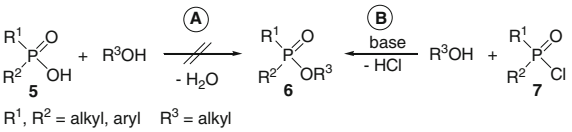
Scheme 3.2 Dialkylation of diethyl ethoxycarbonylmethylphosphonate

3.3 Esterification-Related Reactions

3.3.1 *Direct Esterification of Phosphinic Acids*

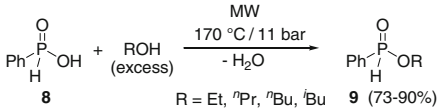
It is well-known that phosphinic acids (**5**) generally do not undergo direct esterification with alcohols to afford phosphinates (**6**) (Scheme 3.3/**A**). There are only a few examples for the direct esterification of phosphinic acids [17]. For this, the esters of phosphinic acids (**6**) are, in most cases, synthesized by the reaction of phosphinic chlorides (**7**) with alcohols in the presence of a base (Scheme 3.3/**B**) [18–20].

Scheme 3.3 Synthetic routes to alkyl phosphinates



The generally applied esterification method (Scheme 3.3/**B**) has the disadvantage of requiring the use of relatively expensive *P*-chlorides (**7**). Moreover, the hydrogen chloride formed as the by-product should be removed by a base, and this method is not atomic efficient.

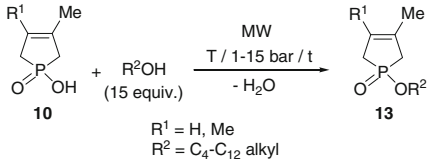
We have recently found that a series of phosphinic acids underwent direct esterification with longer chain alcohols on MW irradiation at around 170–220 °C [21]. The first example was the esterification of phenyl-*H*-phosphinic acid (**8**) at 170 °C to give the corresponding phosphinates (**9**) in yields of 73–90 % (Scheme 3.4).



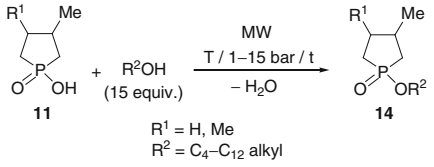
Scheme 3.4 Direct esterification of phenyl-*H*-phosphinic acid under MW conditions

This esterification was assumed to take place via the tervalent tautomer of the phenyl-*H*-phosphine acid, but no evidence was presented [22].

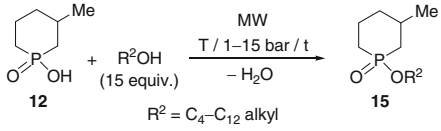
The MW-assisted esterification of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides (**10**), 1-hydroxy-phospholane oxides (**11**) and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxides (**12**) was carried out at 180–235 °C in the presence of *ca.* 15-fold excess of the alcohols to afford the corresponding alkyl phosphinates (**13–15**) in variable yields (Schemes 3.5, 3.6 and 3.7, Table 3.2) [23–26].



Scheme 3.5 MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxides

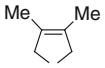
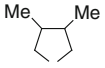


Scheme 3.6 MW-assisted direct esterification of 1-hydroxyphospholane 1-oxides



Scheme 3.7 MW-assisted direct esterification of a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine 1-oxide

Table 3.2 MW-assisted direct esterification of cyclic phosphinic acids (**10–12**)

Phosphinic acid	R^2	T (°C)	t (h)	Isomeric composition	Yield of **13–15** MW (%)	Entry
 **10** (R^1 = H)	^{n}Bu	200	2	–	58 (11)	1
	^{n}Pent	220	2.5	–	94	2
	^{i}Pent	235	3	–	74	3
	^{n}Oct	220	2	–	71	4
	^{i}Oct	220	2	–	76[a]	5
	^{n}Dodec	230	2	–	95	6
 **10** (R^1 = Me)	^{n}Pr	180	4	–	20	7
	^{n}Bu	220	3	–	60[b]	8
	^{i}Bu	200	2	–	30	9
	^{n}Pent	235	3	–	67	10
	^{i}Pent	235	4	–	57	11
	^{n}Oct	230	2	–	95	12
	^{i}Oct	220	2.5	–	82[c]	13
	^{n}Dodec	230	2	–	95	14
 **11** (R^1 = H)	^{n}Bu	230	3	~ 50–50	45	15
	^{n}Pent	235	3	~ 50–50	79	16
	^{i}Pent	235	4	~ 50–50	59	17
	^{n}Oct	230	4	~ 50–50	74	18
	^{i}Oct	220	3	~ 50–50	86	19
 **11** (R^1 = Me)	^{n}Bu	210	3	~ 60–20–20	54	20
	^{n}Pent	235	5	~ 70–15–15	60	21
	^{i}Pent	235	6	~ 64–19–17	56	22
	^{n}Oct	230	4	~ 60–20–20	70	23
	^{i}Oct	220	4	~ 66–19–15	50	24
 **12**	^{n}Bu	230	3	~ 69–31	45	25
	^{n}Oct	235	4	~ 66–34	62	26
	^{i}Oct	235	6	~ 69–31	54	27

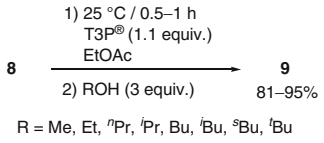
[a]In the thermal variation, the yield was 22 %
[b]In the thermal variation, the yield was 13 %
[c]In the thermal variation, the yield was 24 %

The method developed by us seems to be of more general value. It was also found that the esterification of phosphinic acids is thermoneutral and controlled kinetically. The reaction enthalpies were found to fall in the range of 0.1–4.0 kJ mol^{-1}, while the activation enthalpies were in the range of 102.0–161.0 kJ mol^{-1} [25, 27]. Interestingly, the analogous thioesterifications were reluctant and incomplete under MW conditions [28].

3.3.2 *Esterification in the Presence of the T3P® Reagent*

The phenyl-*H*-phosphinic acid (**8**) could be esterified with simple alcohols efficiently and under mild conditions in the presence of 1.1 equivalents of the T3P® reagent as the activating agent (Scheme 3.8) [29].

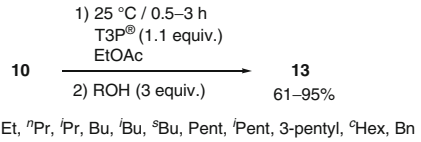
Scheme 3.8 T3P®-mediated esterification of phenyl-*H*-phosphinic acid



It was found that the use of only 0.66 equivalents of the T3P® reagent was also enough to reach yields of 78–91 % [29].

1-Hydroxy-3-phospholene 1-oxides (**10**) also underwent a similar T3P®-promoted direct esterification (Scheme 3.9) [29, 30].

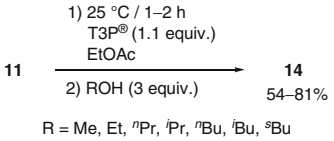
Scheme 3.9 T3P®-mediated esterification of 1-hydroxy-3-phospholene 1-oxides



However, the quantity of the T3P® reagent could be decreased to 0.66 equivalents only under MW conditions and working at 85 °C [29].

1-Hydroxyphospholane 1-oxides (**11**) were also converted to the corresponding phosphinates (**14**) in a similar way (Scheme 3.10) [29].

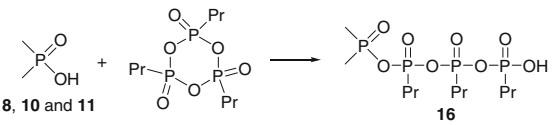
Scheme 3.10 T3P®-mediated esterification of 1-hydroxyphospholane 1-oxides



The use of only 0.66 equivalents of the T3P® reagent at 85 °C under MW conditions furnished the phosphinates (**14**) in somewhat lower (55–67 %) yields [29].

The role of the T3P® reagent is to activate the phosphinic acids (**8**, **10** and **11**) by converting them to the corresponding mixed anhydrides represented by general structure **16** (Scheme 3.11).

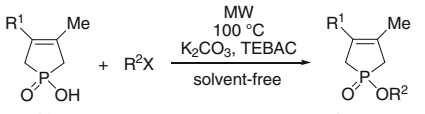
Scheme 3.11 Activation of phosphinic acids



3.3.3 *Alkylating Esterification of Phosphinic Acids*

Phosphinic esters may also be synthesized by alkylating esterification utilizing the MW and phase transfer catalytic (PTC) techniques. This is shown on the example of the alkylation of 1-hydroxy-3-phospholene oxides **10** (Scheme 3.12, Table 3.3) [24, 31]. During the alkylations, similarly to that of phenols, the combined application of MW irradiation and PTC was found to be synergistic [32, 33].

Scheme 3.12 Alkylating esterification of 1-hydroxy-3-phospholene 1-oxides



R^1 = H, Me
R^2X = EtI, ^{n}PrBr, ^{i}PrBr, ^{n}BuBr, BnBr

Table 3.3 Alkylating esterification of phospholene oxides under solvent-free MW conditions

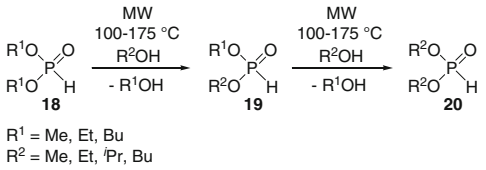
R^1	R^2X	TEBAC (%)	t (h)	Yield of **13** (%)
H	EtI	–	1	80
H	EtI	5	1	90
H	^{n}PrBr	–	1	73
H	^{n}PrBr	5	1	94
H	^{i}PrBr	–	1.5	42
H	^{i}PrBr	5	1	65
Me	EtI	–	1	83
Me	EtI	5	1	95
Me	^{n}PrBr	–	1	49
Me	^{n}PrBr	5	1	90
Me	^{i}PrBr	–	1.5	18
Me	^{i}PrBr	5	1	56

The O-alkylations could, of course, be extended to 1-hydroxyphospholane oxides and to a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxide [24].

The alkylation of thermally unstable cyclic phosphinic acids, such as a 1-hydroxy-3-phosphabicyclo[3.1.0]hexane 3-oxide and 1-hydroxy-1,2-dihydrophosphinine oxide was performed using K_2CO_3 in acetone at 63 °C [34].

3.3.4 Transesterification Reactions of Dialkyl Phosphites (H-Phosphonates)

It was found that dialkyl phosphites (**17**) underwent alcoholysis on exposing their alcoholic solutions to MW irradiation above 100 °C. In most cases, the three possible phosphites (**18**, **19** and **20**) were present in the mixture (Scheme 3.13, Table 3.4). The reaction could be controlled to give the dialkyl phosphite with two different alkyl groups (**19**) as the major component, or to provide the fully transesterified product (**20**) as an almost exclusive product. Comparative thermal experiments were also performed [35].



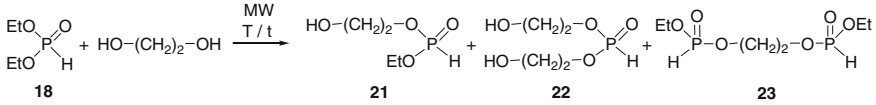
Scheme 3.13 Transesterification of dialkyl phosphites

Table 3.4 Results of the reactions of dialkyl phosphites with alcohols

R^1	R^2	Equivalents of R^2OH	T (°C)	t (min)	p (bar)	Composition (%)		
						18	**19**	**20**
Me	Et	5	100	120	3	29	**56**	15
Me	Et	50	125	60	6	2	37	61
Me	Et	50	175	40	15	0	4	**96**
Et	Me	50	125	60	8	48	**40**	12
Et	Me	50	150	60	15	1	19	**80**
Et	Me	50	175	40	19	0	21	79
Me	Bu	25	125	60	3	0	**40**	60
Me	Bu	50	150	90	6	0	0	**100**
Et	Bu	25	125	60	3	25	**54**	21
Et	Bu	50	175	40	9	0	2	**98**

As can be seen from Table 3.4, the outcome of alcoholysis depended on the nature of the reagents, the molar ratio of alcohol and substrate, the temperature and reaction time. Using the alcohol in a less excess and applying lower temperatures, the proportion of the mixed dialkyl phosphites (**19**) was 40–56 %. Increasing the proportion of the alcohols and elevating the temperature, the fully transesterified *H*-phosphonate (**20**) became the predominating component. The dialkyl phosphites with mixed alkyl groups are valuable building blocks.

The alcoholysis of diethyl phosphite with ethylene glycol may principally lead to mixed ester **21**, fully transesterified product **22** and bis(*H*-phosphonate) **23** (Scheme 3.14, Table 3.5). The composition of the mixture depended on the ratio of the starting materials and the temperature [36].



Scheme 3.14 MW-assisted alcoholysis of diethyl phosphite with ethylene glycol

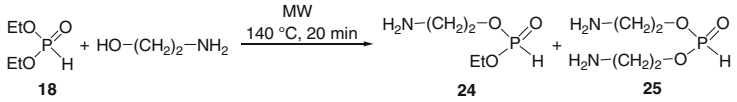
Table 3.5 MW-assisted alcoholysis of diethyl phosphite with ethylene glycol under different conditions

Entry	Molar ratio		T (°C)	t (h)	Conversion (%)	Product composition (%)		
	$(EtO)_2P(O)H$	$(HOCH_2)_2$				**21**	**22**	**23**
1	1	1	120	6	55	76	13	11
2	1	1	140	1[a]	67	**79**	11	9
3	1	4	140	1	64	59	41	0
4	1	8	140	1	39	41	**59**	0
5	2	1	140	3	59	75	0	**25**

[a]On a prolonged heating (3 h), a considerable amount of by-products were formed

The maximum proportion (79 %) of the mixed ester (**21**) was obtained at 140 °C using the reactants in a 1:1 ratio. The bis(hydroxyethyl) derivative (**22**) was formed in a relative proportion of 59 %, if the glycol was measured in an eight-fold quantity. The bis(phosphono) derivative (**23**) was present in 25 % at a $(EtO)_2P(O)H$–$(HOCH_2)_2$ molar ratio of 2:1.

In the MW-assisted reaction with diethyl phosphite, ethanolamine acted as an O–nucleophile. However, when ethanolamine was applied in only a 1–2 equivalents quantity, not alcoholysis, but mono- and diethylation of the ethanolamine took place. Using ethanolamine in a 4–10-fold quantity at 140 °C for 20 min, different ratios of the mixed phosphinate (**24**) and the fully transesterified product (**25**) were obtained (Scheme 3.15, Table 3.6) [36].



Scheme 3.15 MW-assisted alcoholysis of diethyl phosphite with ethanolamine

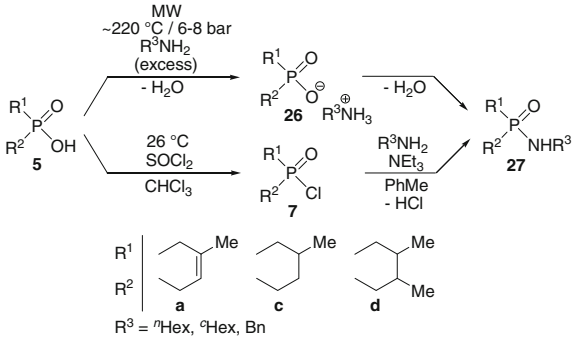
Table 3.6 MW-assisted alcoholysis of diethyl phosphite with ethanolamine at 140 °C for 20 min

Entry	Molar ratio		Conversion (%)	Product composition (%)	
	$(EtO)_2P(O)H$	$HO(CH_2)_2NH_2$		**24**	**25**
1	1	4	100	45	55
2	1	8	100	22	78
3	1	10	100	15	**85**

From the point of view of bis(aminoethyl)phosphite (**25**), the best experiment was, when ethanolamine was measured in a 10 equivalents quantity and the reaction was performed at 140 °C for 20 min.

3.4 Amidation of Phosphinic Acids

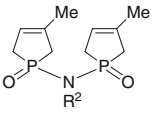
Phosphinic acids fail to undergo reaction with amines on heating. The usual synthesis of phosphinic amides (**27**) involves the reaction of phosphinic chlorides (**7**) with amines (Scheme 3.16). The direct amidations of phosphinic acids **5** attempted under MW irradiation remained incomplete with conversions of 30–33 % (Scheme 3.16) [37]. The ammonium salts of type **26** are intermediates in these amidations. The unreactivity even on MW is the consequence of the endothermicity of the direct amidations (ΔH^0 = 17.1–39.0 kJ mol^{-1}). It can be concluded that the amidation of phosphinic acids is controlled thermodynamically [25].



Scheme 3.16 Possible ways for the amidation of phosphinic acids

In the light of this fact, it is better to carry out the amidations under discussion via the traditional way, using phosphinic chlorides (**7**) as intermediates. However, it was observed that in the reaction of 1-chloro-3-methyl-3-phospholene oxide (**7a**)

with primary amines, bis(phosphinoyl)amine type side products (**28**) were also formed [38].

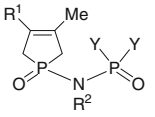


R^2 = ^{n}Hex, ^{c}Hex, Bu

28

Moreover, fine-tuning the molar ratio of the components and the addition technique, it was possible to obtain the bis(phosphinoyl)amine (**28**) as the exclusive product.

It was also possible to utilize this protocol in the synthesis of mixed derivatives represented by structure **29** [39].



R^1 = H, Me
R^2 = Bu, Bn
Y = Ph, EtO, PhO

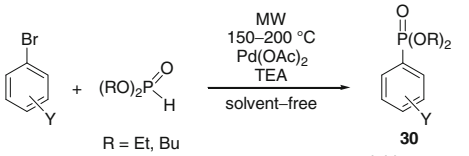
29

3.5 P–C Coupling Reactions

The Hirao-reaction comprising the P–C coupling of a vinyl halide/aryl halide/hetaryl halide and a >P(O)H species has become an important tool to synthesize phosphonates, phosphinates and phosphine oxides [40, 41]. This reaction model prompted many chemists to elaborate "green" variations.

It was interesting to find that there is no need to use the expensive $Pd(Ph_3P)_4$ catalyst in the coupling reaction of dialkyl phosphites with bromobenzene, as $Pd(OAc)_2$ also catalyses the Hirao reaction in the absence of any added P-ligand. A MW-assisted solvent-free accomplishment was the best choice [42, 43]. The arylphosphonates (**30**) were obtained in 69–93 % yields (Scheme 3.17).

Scheme 3.17 Pd-catalyzed coupling reaction of dialkyl phosphites and aryl bromides



R = Et, Bu

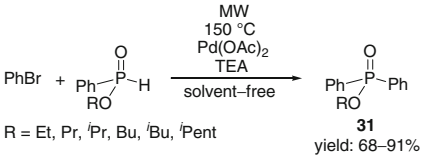
30

yield: 69–93%

Y = H, 4-MeO, 3-MeO, 4-^{t}Bu, 4-Pr, 4-Et, 4-Me, 3-Me, 4-F, 3-F, 4-Cl, 3-Cl, 4-CO_2Et, 3-CO_2Et, 4-COMe, 3-COMe

The use of alkyl phenyl-*H*-phosphinates in reaction with bromobenzene led to alkyl diphenylphosphinates (**31**) (Scheme 3.18).

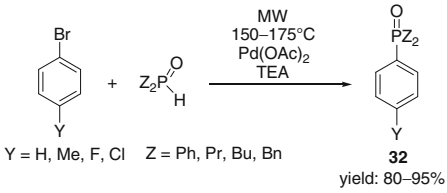
Scheme 3.18 Pd-catalyzed coupling reaction of alkyl phenyl-*H*-phosphinates and bromobenzene



Dibenzo[*c.e*][1,2]oxaphosphorine oxide was also utilized as a P-reagent.

Extending the reaction to secondary phosphine oxides, the products of the P–C coupling reaction are phosphine oxides (**32**) (Scheme 3.19).

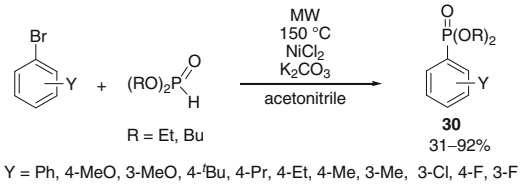
Scheme 3.19 Pd-catalyzed coupling reaction of secondary phosphine oxides and aryl bromides



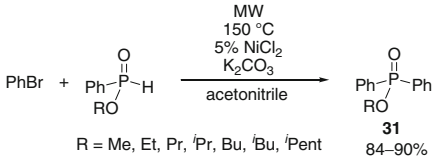
A P-ligand-free Pd-catalyzed method was also utilized in the reaction of 2-nitro-5-bromoanisole with diethyl phosphite using K_2CO_3 as the base and xylene as the solvent [44].

It was interesting to find that the MW-assisted P-ligand-free accomplishment worked also with $NiCl_2$ as the catalyst. In these variations, acetonitrile had to be used due to the heterogeneity of the reaction mixtures. The series of arylphosphonates (**30**), alkyldiphenylphosphinates (**31**) and diaryl-phenylphosphine oxides (**33**) were prepared as shown in Schemes 3.20, 3.21 and 3.22 [45].

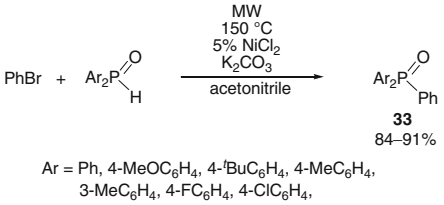
Scheme 3.20 Ni-catalyzed coupling reaction of alkyl phenyl-*H*-phosphinates and aryl bromides



Scheme 3.21 Ni-catalyzed coupling reaction of dialkyl phosphites and bromobenzene



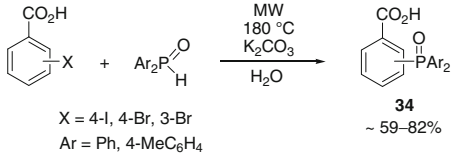
Scheme 3.22 Ni-catalyzed coupling reaction of secondary phosphine oxides and bromobenzene



The P-ligand-free approaches are environmentally-friendly as save costs and environmental burdens. Other MW-assisted variations of the Hirao-reaction were also described, but they applied P-ligands [46–49].

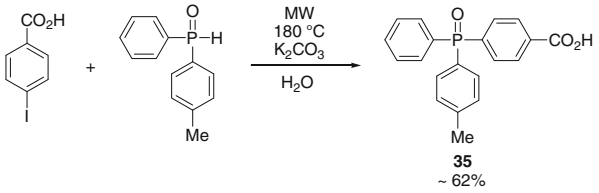
The P–C coupling of halobenzoic acids and diarylphosphine oxides was performed in the absence of any catalyst in the presence of K_2CO_3 in water under MW conditions (Scheme 3.23) [50].

Scheme 3.23 Catalyst-free coupling reaction of diarylphosphine oxides and halobenzoic acids



This protocol was then utilized for the synthesis of a mixed triarylphosphine oxide (**35**) (Scheme 3.24).

Scheme 3.24 Synthesis of trialkyl-substituted phosphine oxide with different aryl groups



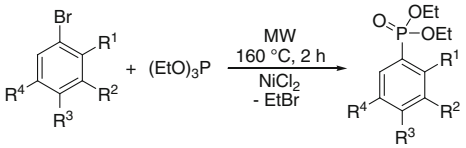
Till data, the P-ligand-free variation may be the most attractive protocol for the Hirao reaction. As a matter of fact, in the P-ligand-free cases, the trivalent tautomer form of the >P(O)H reagent may act as the ligand. The "green" accomplishments have been summarized [51, 52].

3.6 Arbuzov Reactions

Beside the Hirao-reaction, the Arbuzov-reaction is also a suitable method for the preparation of arylphosphonates [53]. However, special protocols are necessary to overcome the decreased reactivity of the aryl halides.

Arylphosphonates (**36**) are the products of the MW-assisted catalytic Arbuzov reaction of aryl bromides with triethyl phosphite. In the presence of a Ni salt catalyst, the phosphonates (**36**) could be prepared in yields of 67–86 % (Scheme 3.25) [54].

Scheme 3.25 MW-assisted Arbuzov reaction of aryl halides and triethyl phosphite



	R^1	R^2	R^3	R^4
a	H	H	H	H
b	CH_3	H	H	H
c	H	H	CH_3	H
d	H	H	cyclohexyl	H
e	H	H	OCF_3	H
f	H	H	CF_3	H
g	H	H	OCH_3	H
h	H	H	$C(O)CH_3$	H
i	F	H	H	H
j	H	F	H	H
k	H	H	F	H
l	F	H	H	F

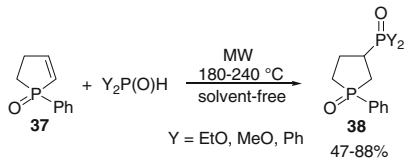
3.7 Phospha-Michael Additions

Simple phospha-Michael reactions, such as the addition of dialkyl phosphites or diphenylphosphine oxide to methyl vinyl ketone or cyclohexene-2-one were performed using NaOR/ROH (R = Me, Et), $NaOH/H_2O$ under PTC or 1,8-diazabicycloundec-7-ene (DBU). There was no need to apply MW irradiation [55]. Phospha-Michael reactions of methyl vinyl ketone with *P*-heterocyclic nucleophiles deriving from a dibenzo-1,2-oxaphosphorine oxide or 1,3,2-dioxaphosphorine oxide were carried out in the presence of DBU [56]. However, the addition of dialkyl phosphites, dibenzo-1,2-oxaphosphorine oxide and diphenylphosphine oxide to the electron-poor double-bond of a 1,2-dihydrophosphinine oxide required a greater activation, so that first the >P(O)H

species had to be converted to the corresponding anion by deprotonation with trimethylaluminum [57, 58]. In these reactions, MW irradiation was unable to enhance the addition of the >P(O)H species to the not too reactive CH=CH–P(O)< unsaturation of the reactants.

However, MW irradiation was useful in the addition of dialkyl phosphites and diphenylphosphine oxide to the double-bond of 1-phenyl-2-phospholene 1-oxide (**37**) (Scheme 3.26) [59]. In these cases, the adducts (**38**) were formed as 1:1 mixtures of two isomers.

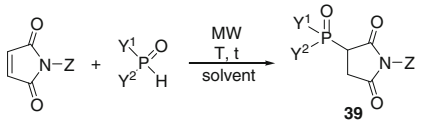
Scheme 3.26 Michael addition of >P(O)H species to 1-phenyl-2-phospholene 1-oxide



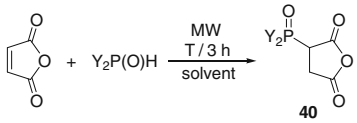
Using dialkyl phosphites pre-reacted with trimethylaluminum, the above additions took place more efficiently (in 89–93 % yields), and were selective leading to only one isomer.

MW addition promoted the addition of dialkyl phosphites, ethyl phenyl-*H*-phosphinate and diphenylphosphine oxide to the reactive unsaturation of *N*-phenyl and *N*-methylmaleimide, as well as maleic anhydride (Schemes 3.27 and 3.28) [60]. In most cases, the reactions were performed in the absence of any solvent. Products **39** and **40** were obtained, with one exception, in good yields.

Scheme 3.27 Michael addition of >P(O)H species to maleimide derivatives



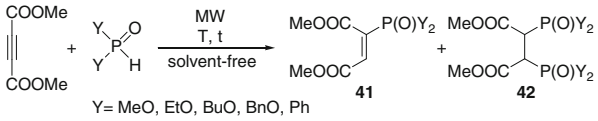
Z	Y^1	Y^2	T (°C)	t (h)	solvent	yield of **39** (%)
Ph	EtO	EtO	175	2.5	-	83
Ph	MeO	MeO	175	2.5	-	81
Me	EtO	EtO	175	3	-	95
Me	MeO	MeO	175	3	-	71
Ph	Ph	EtO	175	2.5	-	92
Me	Ph	EtO	175	3	-	80
Ph	Ph	Ph	120	3	MeCN	97
Me	Ph	Ph	120	3	MeCN	98



Y	T (°C)	solvent	yield of **40** (%)
EtO	120	-	49
Ph	175	MeCN	66

Scheme 3.28 Michael addition of > P(O)H species to maleic anhydride

Depending on the molar ratio of the reactants and the conditions (temperature and reaction time), the addition of dialkyl phosphites or diphenylphosphine oxide to the triple bond of dimethyl acetylenedicarboxylate resulted in the formation of a comparable mixture of the corresponding monoadduct (**41**) and bisadduct (**42**), or the bisadduct (**42**) as the predominating or exclusive product (Scheme 3.29, Table 3.7) [61].

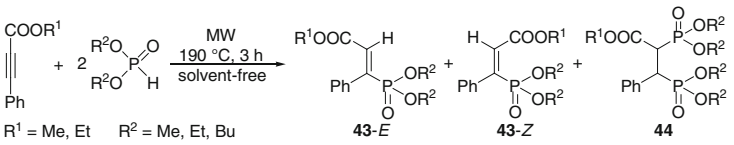


Scheme 3.29 MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to dimethyl acetylenedicarboxylate

Table 3.7 The MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to dimethyl acetylenedicarboxylate

Entry	Y	$\frac{n Y_2P(O)H}{n(MeO_2CC)_2}$	T (°C)	t (h)	Product composition (%)		Yield (%)
					41	**42**	
1	MeO	0.5	90 → 100	5.5	55	45	45 (**41** (Y = MeO))
2	MeO	2	100	3.5	5	95	90 (**42** (Y = MeO))
3	EtO	0.5	90 → 100	5.5	51	49	46 (**41** (Y = EtO))
4	EtO	2	100	3.5	7	93	87 (**42** (Y = EtO))
5	BuO	0.5	90 → 100	5.5	50	50	44 (**41** (Y = BuO))
6	BuO	2	100	3.5	6	94	90 (**42** (Y = BuO))
7	BnO	0.5	90 → 100	5.5	43	57	39 (**41** (Y = BnO))
8	BnO	2	100	3.5	0	100	96 (**42** (Y = BnO))
9	Ph	0.5	26	0.25	58	42	53 (**41** (Y = Ph))
10	Ph	2	80	0.75	4	96	94 (**42** (Y = Ph))

The similar reaction of alkyl phenylpropiolates and two equivalents of dialkyl phosphites at 190 °C afforded a mixture of *E* and *Z* alkyl 3-(dialkoxyphosphoryl)-3-phenylacrylates (**43**), and in a few cases some of the bisadducts (**44**). Within the phosphoryl-phenylacrylates (**43**) the *E* isomer predominated (Scheme 3.30, Table 3.8) [62].



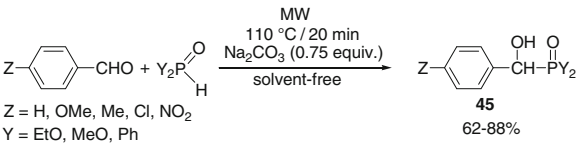
Scheme 3.30 MW-assisted addition of dialkyl phosphites to methyl- and ethyl phenylpropiolate

Table 3.8 The MW-assisted addition of dialkyl phosphites to alkyl phenylpropiolates

Entry	R^1	R^2	Product composition (%)			Yield (**43**-*E*) (%)
			Monoadduct (**43**)		Bisadduct (**44**)	
			E	*Z*		
1	Me	Me	73	13	14	60
2	Me	Et	90	10	0	84
3	Me	Bu	89	11	0	83
4	Et	Me	74	14	12	66
5	Et	Et	86	14	0	80
6	Et	Bu	85	15	0	72

3.8 The Addition of >P(O)H Species to Carbonyl-Compounds

α-Aryl-α-hydroxyphosponates and α-aryl-α-hydroxyphosphine oxides (**45**), potentially bioactive substrates, were synthesized in a catalytic and solvent-free MW-assisted reaction comprising the addition of >P(O)H species to aryl aldehydes (Scheme 3.31, Table 3.9) [63].



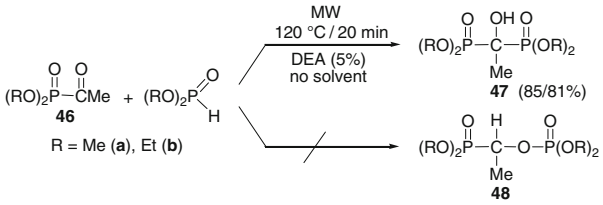
Scheme 3.31 MW-assisted synthesis of α-hydroxyphosphonates and α-hydroxyphosphine oxides

Table 3.9 Summary of the MW-assisted synthesis of α-hydroxyphosphonates and α-hydroxyphosphine oxides

Entry	Y	Z	Yield of **45** (%)
1	EtO	H	85
2	MeO	H	87
3	Ph	H	88
4	EtO	MeO	82
5	MeO	MeO	84
6	Ph	MeO	78
7	EtO	Me	87
8	MeO	Me	62
9	Ph	Me	80[a]
10	EtO	Cl	84
11	MeO	Cl	72
12	Ph	Cl	79[a]
13	EtO	NO_2	86[b]
14	MeO	NO_2	71
15	Ph	NO_2	80

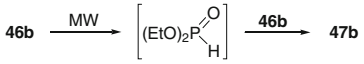
[a]110 °C, 0.5 h
[b]150 °C, 1 h

Dialkyl phosphites were also added to the carbonyl function of α-ketophosphonates (**46**) to result in the formation of dronate analogue α-hydroxybisphosphonates (**47**) in the presence of diethylamine and in the absence of any solvent. Under optimum conditions, the formation of the rearranged by-product **48** could be avoided (Scheme 3.32) [64, 65].



Scheme 3.32 MW-assisted reaction of α-ketophosphonates and dialkyl phosphites

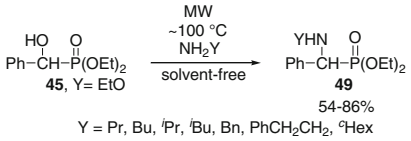
It was interesting to find that on MW irradiation, α-ketophosphonate **46b** was converted to α-hydroxybisphosphonate **47b**. Half of the starting material (**46b**) served as the precursor for diethyl phosphite which then reacted with the unchanged **46b** to afford bisphosphonate **27b** (Scheme 3.33) [65].



Scheme 3.33 Preparation of hydroxybisphosphonate **47b** directly from the α-ketophosphonate precursor

3.9 The Conversion of α-Hydroxyphosphonates to α-Aminophosphonates

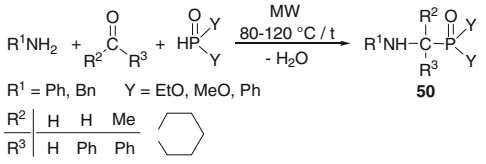
Surprisingly, α-hydroxyphosphonates **25** could be easily transformed to the corresponding α-aminophosphonates (**49**) by reaction with primary amines (Scheme 3.34) [66]. The substitution reaction was promoted by the neighbouring group effect of the adjacent P=O function.



Scheme 3.34 Preparation of α-aminophosphonates by substitution reaction of α-hydroxyphosphonates

3.10 The Kabachnik–Fields (Phospha-Mannich) Reaction

α-Aminophosphonates (**50**, Y = RO), the analogues of α-aminoacid esters, and α-aminophosphine oxides (**50**, Y = Ph) were synthesized by the solvent- and catalyst-free MW-assisted Kabachnik–Fields condensation of primary amines, aldehydes/ketones and >P(O)H reagents, such as dialkyl phosphites and diphenylphosphine oxide. Earlier preparations utilized special catalysts (e.g. $BiNO_3$ [67], phthalocyanine [68], and Lantanoid$(OTf)_3$ [69]), which mean cost and environmental burden. It was found that under MW conditions there is no need for any catalyst. Moreover, the condensation was performed in the absence of any solvent (Scheme 3.35, Table 3.10) [70]. In a few cases, the >P(O)H species was added to the preformed Schiff base ($R^1N{=}CR^2R^3$).



Scheme 3.35 MW-assisted Kabachnik–Fields condensations

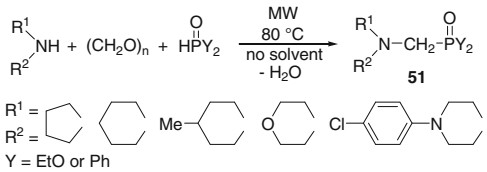
Table 3.10 Summary of the MW-assisted Kabachnik–Fields reactions

Entry	R^1	R^2	R^3	Y	T (°C)	t (min)	Yield of **50** (%)
1	Ph	H	H	EtO	80[a] 100[b]	15[a] 30[b]	91
2	Ph	H	H	MeO	80[a] 80[b]	15[a] 60[b]	80
3	Ph	H	H	Ph	80	30	94
4	Bn	H	H	EtO	100	30	81
5	Bn	H	H	Ph	80	30	88
6	Ph	H	Ph	EtO	100	30	93
7	Ph	H	Ph	MeO	100	30	86
8	Ph	H	Ph	Ph	80	30	87
9	Bn	H	Ph	EtO	100	20	83
10	Bn	H	Ph	MeO	100	20	87
11	Ph	Me	Ph	EtO	120	40	80
12	Bn	Me	Ph	EtO	120	30	84
13	Bn	Me	Ph	Ph	100[a] 120[b]	30[a] 30[b]	80
14	Ph			EtO	120	40	81
15	Bn			EtO	120	30	91
16	Bn			MeO	120	30	85
17	Bn			Ph	100[a] 120[b]	30[a] 30[b]	80

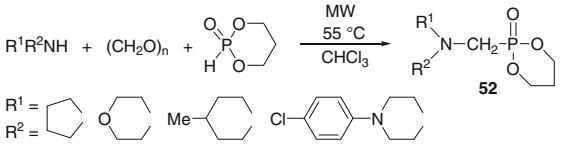
[a]Condensation of the oxo-component and the amine
[b]Addition of the >P(O)H species to the Schiff-base

MW-assisted phospha-Mannich condensations were also performed in an excess of diethyl phosphite. Due to the use of domestic MW ovens, the reaction temperatures were not reported [71, 72].

The use of heterocyclic amines pyrrolidine, piperidine derivatives, morpholine and piperazine derivatives or heterocyclic >P(O)H species (e.g. 1,3,2-dioxaphosphorine oxide) led to *N*-heterocyclic [73] and *P*-heterocyclic [74] α-aminophosphonates (**51**, Y = EtO and **52**) and α-aminophosphine oxides (**51**, Y = Ph) (Schemes 3.36 and 3.37).

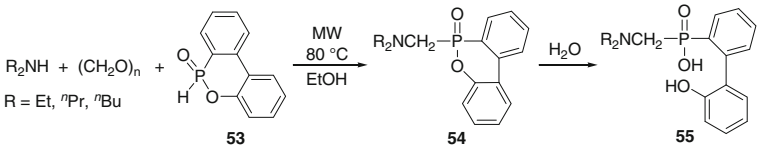


Scheme 3.36 Kabachnik–Fields reactions with *N*-heterocycles as the amine component



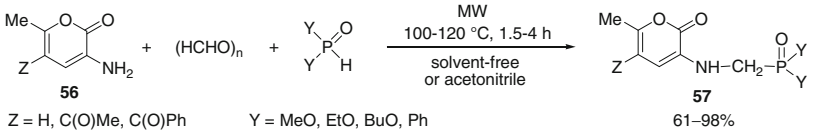
Scheme 3.37 Kabachnik–Fields reactions with 1,3,2-dioxaphosphorine oxide as the P-reactant

In the reaction of dialkylamines, paraformaldehyde and dibenzo[*c.e*][1,2]-oxaphosphorine oxide (**53**), the heterocyclic ring underwent ring opening by reaction with water formed in the condensation to result in end-product **55** (Scheme 3.38) [74].



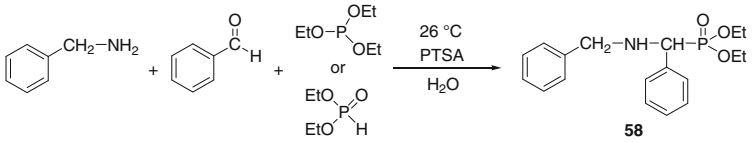
Scheme 3.38 Kabachnik–Fields reaction with a dibenzooxaphosphorine oxide as the P-reactant

Then 3-amino-6-methyl-2*H*-pyran-2-ones (**56**) were utilized in the Kabachnik–Fields reaction with formaldehyde and dialkyl phosphites or diphenylphosphine oxide (Scheme 3.39) [75].



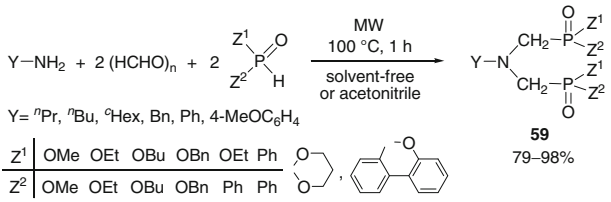
Scheme 3.39 The synthesis of phosphono- or phosphinoylmethylamino-2*H*-pyran-2-ones

Phospha-Mannich-condensations are also known to proceed with trialkyl phosphites in water as the solvent. In this respect, the reaction of benzylamine, benzaldehyde and triethyl phosphite was investigated in comparison with the variation using diethyl phosphite as the P-reagent. The first version was practically complete at room temperature, but the conversion with diethyl phosphite remained uncomplete (Scheme 3.40) [76]. This experience justifies again the MW-assisted and solvent-free accomplishment of the Kabachnik–Fields reactions utilizing dialkyl phosphites [70].



Scheme 3.40 Kabachnik–Fields condensation with triethyl phosphite or diethyl phosphite in water

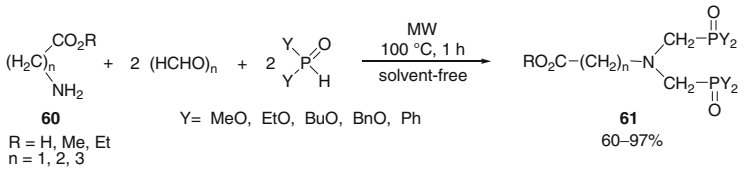
Primary amines are able to participate in bis(Kabachnik–Fields) condensations [77]. In such cases, alkyl or arylamines were reacted with two equivalents of the formaldehyde and the >P(O)H species to afford the bis($Z^1Z^2P(O)CH_2$)amines (**59**) (Scheme 3.41) [78–80]. Most of the reactions could be carried out without the use of any solvent, but for example the conversions with diphenylphosphine oxide had to be performed in acetonitrile due to the heterogeneity.



Scheme 3.41 The bis(Kabachnik–Fields) reaction

The bisphosphinoyl derivatives (**59**, $Z^1=Z^2=Ph$) were transformed after double-deoxygenation to bis(phosphines) that were useful in the synthesis of ring platinum complexes [79, 80].

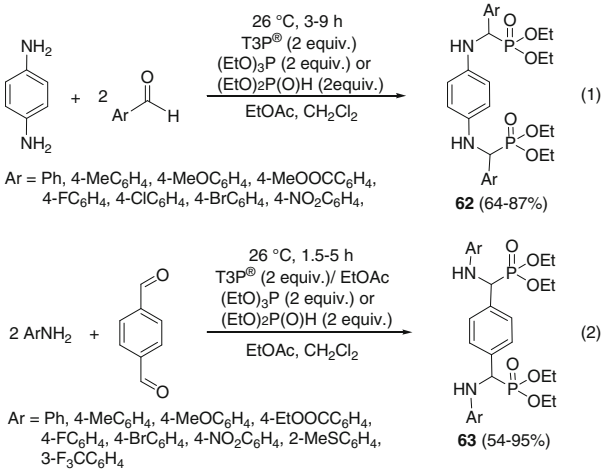
α-, β- and γ-amino acids (or esters) (**60**) were also utilized in the double Kabachnik–Fields condensation to furnish the bis(phosphono- or phosphinoyl) products (**61**) (Scheme 3.42) [81, 82].



Scheme 3.42 Bis(Kabachnik–Fields) reactions with amino acid derivatives

As further bis(Kabachnik–Fields) reactions, paraphenylene diamine was reacted with two equivalents of benzaldehyde derivatives and triethyl phosphite or diethyl phosphite (Scheme 3.43/(1)), or terephthalaldehyde was reacted with two

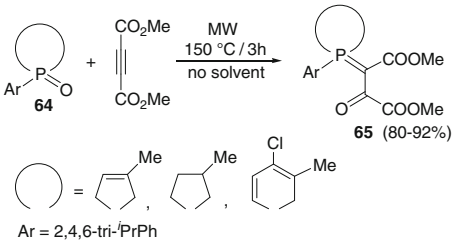
equivalents of arylamine and P-reagent (as above) (Scheme 3.43/(2)). The bis-products **62** and **63** were obtained in variable yields [83].



Scheme 3.43 Further variations of the bis(phospha-Mannich) reactions

3.11 Inverse Wittig-Type Reactions

The use of the MW technique was rather advantageous in the inverse Wittig-type reaction of 2,4,6-triisopropylphenyl-3-phospholene oxides, 2,4,6-triisopropylphenyl-phospholane oxides and 2,4,6-triisopropylphenyl-1,2-dihydrophosphinine oxides (all represented by formula **64**) and dimethyl acetylenedicarboxylate to furnish β-oxophosphoranes **65** (Scheme 3.44). Completion under thermal conditions required a *ca.* 2 week's heating at 150 °C, while on MW irradiation, the reactions were complete already after 3 h at the same temperature. No solvent had to be used in either case [84, 85].

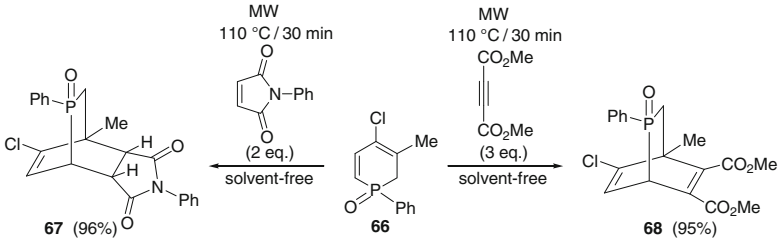


Scheme 3.44 The inverse Wittig-type reaction of P-aryl substituted cyclic phosphine oxides with dimethyl acetylenedicarboxylate

It should be noted that in case of the *P*-mesityl substituent (Ar = 2,4,6-Me_3Ph), the inverse Wittig-type reaction shown in Scheme 3.44 took place exclusively under MW irradiation.

3.12 Diels–Alder Cycloaddition Reactions

The reaction of 1-phenyl-1,2-dihydrophosphinine oxide **66** with dienophiles, such as *N*-phenylmaleimide and dimethyl acetylenedicarboxylate took place according to the [4+2] Diels–Alder protocol to provide the corresponding phosphabicyclo[2.2.2]octene oxide (**67**) or phosphabicyclo[2.2.2]octadiene oxide (**68**), respectively [86]. The MW technique was useful in shortening the reaction times [30 min (MW) versus 2 days (thermal heating) under solvent-free conditions] and in providing the cycloadducts (**67/68**) in almost quantitative yields (Scheme 3.45) [87].

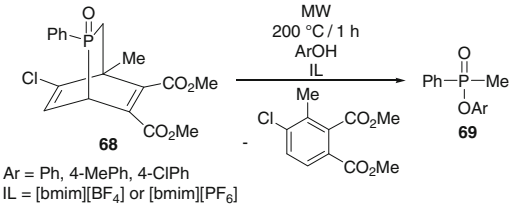


Scheme 3.45 Diels–Alder reactions of a 1,2-dihydrophosphinine oxide with different dienophiles

The absorption of MW irradiation was more efficient in the presence of onium salts, when a solvent was also used [88].

3.13 Fragmentation-Related Phosphorylations

The bridged *P*-heterocycles, such as phosphabicyclo[2.2.2]octadiene oxide **68** are useful in fragmentation-related phosphorylations [86]. On thermal influence or photochemical irradiation, the bridging methylenephosphine oxide [$PhP(O)(CH_2)$] unit of precursor **68** is ejected, and may phosphorylate a nucleophile e.g. a phenol added to the mixture prior to the fragmentation [89]. An alternative mechanism comprising a pentacoordinate intermediate was also proposed and proved [86]. It was found that the fragmentation-related phosphorylations are more efficient under MW conditions using ionic liquids as the solvent. The phosphorylated phenols (**69**) were obtained in somewhat better yields than in earlier experiments (Scheme 3.46) [90].



Scheme 3.46 Fragmentation-related phosphorylations utilizing phosphabicyclo[2.2.2]octadiene precursor

3.14 Conclusions

In summary, a number of organophosphorus reactions were performed under MW conditions. The transformations studied embraced esterifications, amidations, alcoholyses, cycloadditions, additions, substitutions and condensations. In most cases, the role of MW irradiation was to make the reactions faster, or to make them more efficient and selective. In a few instances, the reactions took place only under MW conditions. It also occurred that MW irradiation substituted for the catalyst, or simplified catalyst systems. The examples shown demonstrate the potential of MW irradiation in organophosphorus synthesis.

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