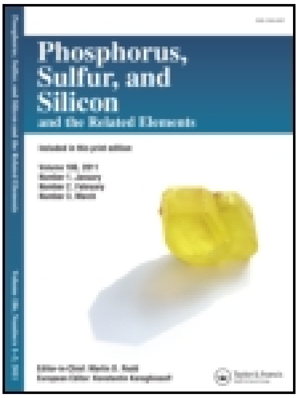

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DIRECT ESTIRIFICATION AND AMIDATION OF PHOSPHINIC ACIDS UNDER MICROWAVE CONDITIONS

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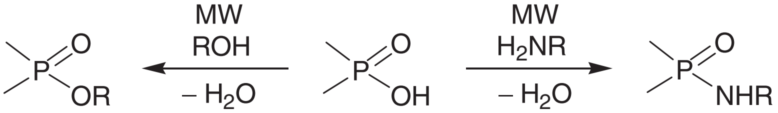
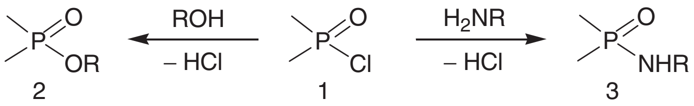
GRAPHICAL ABSTRACT



Abstract *Phosphinic acids may be efficiently esterified in microwave-assisted reactions with alcohols. Especially alcohols with longer alkyl chain are suitable reagents for direct esterifications. At the same time, the direct amidation cannot be complete under such conditions. Hence, the tradional amidations via the phosphinic chloride intermediates have to be applied. The values of activation enthalpies and reaction enthalpies obtained by quantum chemical calculations justified the experimental observations. Microwave has a potential in overcoming relatively high activation enthalpies.*

Keywords Phosphinic derivatives; esterification; amidation; microwave; quantum chemical calculations

The usual way for the preparation of phosphinic esters (**2**) and amides (**3**) involves the reaction of phosphinic chlorides (**1**) with alcohols and amines, respectively.[1]



However, it is a disadvantage that the phosphinic chlorides are relatively expensive, the reactions are not atomic efficient and hydrochloric acid is formed as the by-product. It is known that phosphinic acids (**4**) do not undergo direct esterification and amidation.

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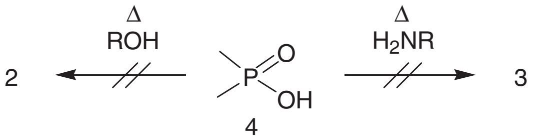
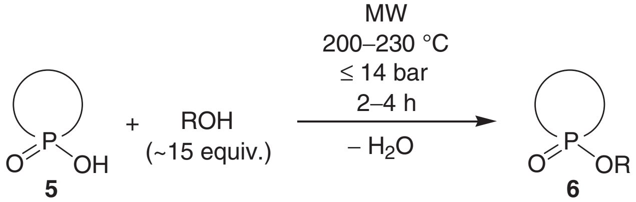
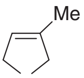
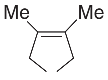
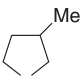
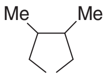
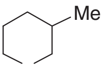


It was a challenge for us to attempt the direct derivatization of phosphinic acids under microwave (MW) conditions. Recent studies showed the potential of MW in organophosphorus chemistry. MW irradiation was successfully applied in *C*-alkylations, additions, cycloadditions and condensations.[2–4] Cyclic phosphinic acids (**5**), such as 1-hydroxy-3-phospholene oxides, 1-hydroxyphospholane oxides and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxides were irradiated in the presence of ca. 15 equivalents of alcohols at 200–230°C in sealed tubes. The over-pressure developed depended on the volatility of the alcohols used and falls in the range of 0–14 bar. The phosphinates (**6**), with one exception, were obtained in yields of 45–95% (Table 1).[5–7]

Using longer chain alcohols and applying ca. 210°C, the esterifications were quantitative. Comparative thermal experiments showed reluctancy of the direct esterifications; in the best case a conversion of 11% was achieved.

Table 1 Direct esterification of cyclic phosphinic acids



	R	Yield of **6** (%)	Ref.
 (**a**)	^{n}Bu	58	7
	C_8H_{17}	71	8
	$C_{12}H_{25}$	95	8
 (**b**)	^{n}Bu	60	7
	^{i}Bu	30	7
	C_8H_{17}	95	8
	$C_{12}H_{25}$	95	8
 (**c**)	^{n}Bu	45	7
	C_8H_{17}	74	8
 (**d**)	^{n}Bu	54	7
	C_8H_{17}	70	8
 (**e**)	^{n}Bu	45	7

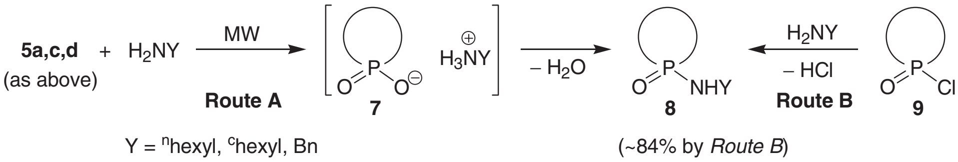
Alkylating esterification of the phosphinic acids (**5**) by alkyl halides was a good alternative to prepare the phosphinates (**6**). These reactions were performed under phase transfer catalytic (PTC) conditions in the presence of K_2CO_3 without any solvent (Scheme 1).[6,8] In particular the reactions with alkyl halides of normal reactivity were enhanced by the use of MW.

$$\mathbf{5} + \mathrm{RX} \xrightarrow[\substack{\mathrm{K_2CO_3} \\ \text{no solvent}}]{\substack{\text{MW} \\ 100\text{–}120\ ^\circ\text{C} \\ \text{PTC}}} \underset{(73\text{–}98\%)}{\mathbf{6}}$$

$\mathrm{RX} = \mathrm{EtI}, {}^{n}\mathrm{PrBr}, {}^{n}\mathrm{BuBr}, \mathrm{BnBr}$

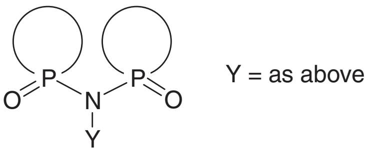
Scheme 1

Regarding the direct amidations of phosphinic acids **5a,c,d** our results were more modest. Under MW conditions the phosphinic amides (**8**) were formed only in conversions of ca. 30% (Scheme 2/Route A). Obvious intermediates of these amidations are the corresponding ammonium salts (**7**) formed from the phosphinic acid (**5**) and the amine. For the synthesis of phosphinic amides **8** the traditional method remains which applies phosphinic chlorides **9** as the starting material (Scheme 2/Route B).



Scheme 2

However, it was observed that the reaction of phosphinic chlorides **9** with primary amines was accompanied by the formation of bis(phosphinic) derivatives **10**. Moreover, the reaction could be directed so that the bis(phosphinic) amide **10** was the predominant product.[9]



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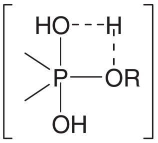
The question arises how it is possible that while the direct esterification of phosphinic acids **5** is quite efficient under MW conditions, the amidations can only be performed in low conversions. This experience is the consequence of the thermodynamics of the reactions. B3LYP/6–31++G(d,p) calculations suggested that while the direct esterifications are thermoneutral, as shown by the reaction enthalpies, the direct amidations are by ca. 30–40 kJ/mol endothermic.

The mechanism of the esterifications and amidations was also investigated by B3LYP/6–31++ G(d,p) calculations. It was found that both the esterifications and the amidations take place *via* four-center transition states like **11** and **12**. The activation enthalpy leading to them is rather high (ca. 70–160 kJ/mol for the esterifications and ca. 60–90 kJ/mol for the amidations).



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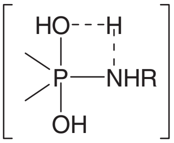

12

It may be concluded that the esterifications are kinetically controlled and the high barrier can be overcome by the beneficial effect of MW.

Further evidences have been collected and show that the esterifications are indeed phosphorylations (acylations) and do not involve alkylations taking place via the S_N2 or S_N1 mechanism or *via* the formation of olefins from the alcohols under the circumstances of the reaction.

In summary, MW irradiation promotes highly the direct esterification of phosphinic acids, while the analogous amidations are enhanced only moderately by MW. The practice and theory are in full agreement.

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