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Microwave-Assisted Functionalization of Phosphinic Acids: Amidations versus Esterifications

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ABSTRACT: *Both the reaction enthalpies and enthalpies of activation obtained by high-level quantum chemical calculations were against the direct amidation of phosphinic acids under traditional thermal conditions. However, the amidations, not expected to proceed on the basis of the endothermicity and the significantly high enthalpies of activation, did take place under microwave (MW) conditions in 30–36% conversions. As a comparison, the direct esterifications of phosphinic acids that are thermoneutral and have higher enthalpies of activation were quite efficient under MW conditions. The outcome of the MW-assisted amidation is the balance of two effects. The local overheating effect could overcome the barrier meant by the enthalpy of activation, but the endothermicity works against this. Comparison of the results of the syntheses and the energetics calculated for the esterification and amidation of phosphinic acids enabled us to draw more general conclusions on the scope and limitation of the use of MW irradiation in organic syntheses. The traditional amidation of phosphinic acids via the phosphinic chloride intermediate gave the products in much better yields.*

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INTRODUCTION

Phosphinic acids (**1**) are known to resist direct esterification and amidation. For this reason, the phosphinates (**3**) and phosphinic amides (**4**) are usually synthesized from the corresponding phosphinic chlorides (**2**) by reaction with alcohols and amines, respectively (Scheme 1) [1,2].

Although the above procedures are widespread in laboratories and in industry, they cannot be regarded as environmentally friendly ("green") due to the hydrochloric acid liberated that has to be removed by a base (or a second molecule of the amine). There is only one example for the direct esterification; in reaction with phenol, the dithio derivative of phenylphosphinic acid was converted to the corresponding phenylphosphinothioate [3].

Realizing the potential of the microwave (MW) technique, we attempted the direct esterification of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides, 1-hydroxyphospholane oxides, and a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxide. To our surprise, the esterifications took place in the range of 180–230°C in sealed tubes. The outcome depended on the nature of the alcohol used (Table 1) [4–6]. Obviously, the less volatile the

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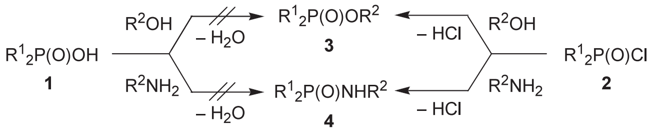


SCHEME 1

alcohol is, the higher the reaction temperature may be that can be attained considering the pressure limit of 25 bar of the MW equipment. Hence, the best results (70–95% yields) were obtained with *n*-octanol and *n*-dodecanol as the reaction components (Table 1, entries 2, 3, 5, 6, 8, and 10). Quantum chemical calculations suggested that the esterification of phosphinic acids is thermoneutral, and the enthalpy of activation for the rate-determining step is rather high (102–161 kJ mol^{-1}) [6]. This means that the phosphinic acids cannot be expected to undergo direct esterification under thermal conditions. The fact that the esterifications still did take place on MW irradiation shows the potential of this technique. The beneficial impact is the consequence of the so-called local overheating effect [7] that may, in most cases, reach 10–50°C or may be even higher. The extent of this effect is dependent on the dielectric constant of the medium. The specific role of MW will be discussed below, in the context of the reactions studied.

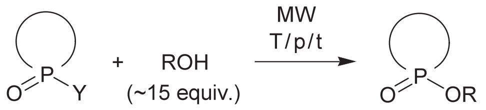
Encouraged by our previous results, we wished to study the MW-assisted direct amidation of phosphinic acids experimentally and theoretically. It was also our purpose to compare the MW-promoted esterifications and amidations.

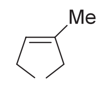
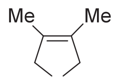
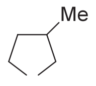
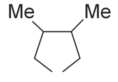
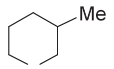
RESULTS AND DISCUSSION

Preparation of 1-Amino-3-phospholene 1-oxides and 1-Aminophospholane 1-oxides from the Corresponding Cyclic Phosphinic Acids

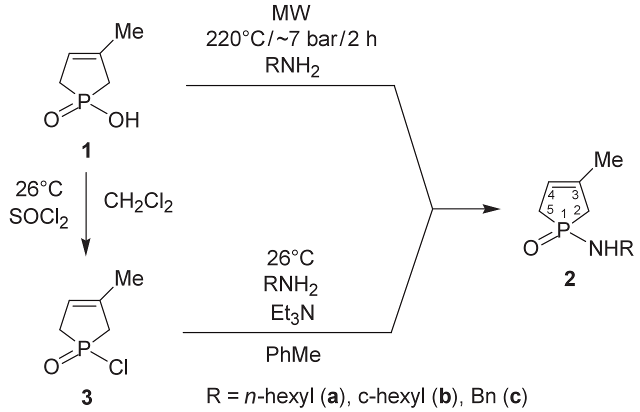
We decided to try the direct amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide **1** with *n*-hexylamine, *c*-hexylamine, and benzylamine that are not too volatile (with boiling points in the range of 132–185°C) and hence allowing the application of a reaction temperature of 220°C. Working in a sealed tube and using the amines in a

TABLE 1 Summary of the MW-Assisted Esterification of Phosphinic Acids [5, 6]



Entry		*R*	*T (°C)*	*p (bar)*[a]	*t (h)*	*Conversion (%)*	*Yield (%)*	*Ref.*
1	 Me	^{n}Bu	200	∼14	2	70 (11)[b]	58[c]	[5]
2		C_8H_{17}	220	1.2	2	100 (12)[b]	71	[6]
3		$C_{12}H_{25}$	230	0	2	100	95	[6]
4	 Me Me	^{n}Bu	220	∼14	3	75	60	[5]
5		C_8H_{17}	230	1.5	2	100	95	[6]
6		$C_{12}H_{25}$	230	0	2	100 (15)[b]	95	[6]
7	 Me	^{n}Bu	230	∼14	3	58	45[d]	[5]
8		C_8H_{17}	230	1.5	4	100	74[d]	[6]
9	 Me Me	^{n}Bu	210	∼14	3	65	54[e]	[5]
10		C_8H_{17}	230	1.5	4	100	70[e]	[6]
11	 Me	^{n}Bu	230	∼14	3	61	45[d]	[5]

[a] Overpressure.
[b] The result of comparative thermal experiment (in parentheses).
[c] 5% 1-hydroxy-3-methyl-2-phospholene 1-oxide was also formed as a by-product.
[d] As a mixture of two isomers.
[e] As a mixture of three isomers.

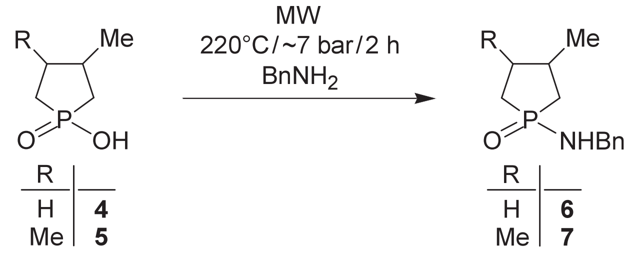


SCHEME 2

15-fold excess, the conversion of hydroxyphospholene oxide **1** to aminophospholene oxides **2a–c** was 30–36% after a 2-h reaction time (Scheme 2). Prolonged reaction times and the use of catalysts (e.g., $BF_3{\cdot}OEt_2$) did not promote higher conversions. Isolated yields of products **2a–c** were 25–29%. In comparative thermal experiments, not even traces of 1-amino-3-phospholene oxides (**2a–c**) were formed. Hence, despite the low conversions, the formation of phosphinic amides **2** under MW conditions is of principal importance, as it underlines the strength of MW irradiation. It is, however, noteworthy that the extent of the MW effect is by far lower in amidations than in esterifications. The energetics associated with the esterifications and amidations will be discussed below.

To achieve quantitative conversions, the traditional methodology had to be followed [8]. According to this, hydroxyphospholene oxide (**1**) was first converted to the corresponding phosphinic chloride (**3**), whose reaction with the amines provided aminophospholene oxides **2a–c** in ca. 81% yield after column chromatography (Scheme 2). Products **2a–c** were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectral data.

1-Hydroxy-3-methyl- and 1-hydroxy-3,4-dimethylphospholane 1-oxides **4** and **5** were also subjected to MW-assisted direct amidation with benzylamine at 220°C for 2 h. It was found that the expected amides **6** and **7** were formed in a conversion of ca. 31% (Scheme 3). Amides **6** and **7**, formed as two and three isomers, respectively, were obtained in low (ca. 23%) yields and were characterized by ^{31}P NMR, as well as high-resolution mass spectral data.



SCHEME 3

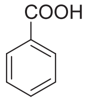
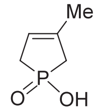
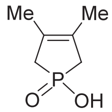
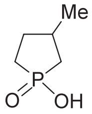
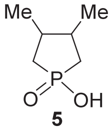
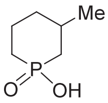
Thermodynamic and Kinetic Background of the Amidation of Phosphinic Acids as Compared to that of Benzoic Acid

B3LYP/6-31++G(d,p) calculations were carried out to evaluate the reaction enthalpy (ΔH^0) and free energy (ΔG^0) values, as well as the activation parameters (activation enthalpy [$\Delta H^\#$] and activation free energy [$\Delta G^\#$]) for the amidation of phosphinic acids with primary amines (benzylamine, *n*-hexylamine, *c*-hexylamine, and phenylethylamine) at 210°C in the gas phase (Table 2). For comparison purposes, the amidation of benzoic acid with primary amines was also calculated. The ca. 7 bar pressure may have only a slight impact on the energetics; for this, it was neglected in our case. The gas phase calculations mean a further simplification, but the results so obtained are informative for the solution phase as well. In overall, the energetics obtained in the gas phase at 210°C and 1 bar may provide an adequate basis to explain our preparative experiences.

For the amidation of benzoic acid, the ΔG^0 and ΔH^0 values fall in the range of –7.5 to –5.9 and –8.2 to –6.7 kJ mol^{-1}, respectively. The modest enthalpy gain justifies the amidations of benzoic acid studied. At the same time, for the amidation of phosphinic acids, such as phenylphosphinic acid, dimethylphosphinic acid, 1-hydroxy-3-phospholene 1-oxides, 1-hydroxyphospholane oxide, and a 1,2,3,4,5,6-hexahydrophosphinine 1-oxide with the amines mentioned above, the ΔG^0 and ΔH^0 values embrace the ranges 23.8–47.2 and 17.1–39.3 kJ mol^{-1}, respectively, suggesting that the amidation of phosphinic acids is unfavorable energetically due to the great extent of endothermicity.

In respect of the activation parameters calculated for the amidation of benzoic acid and for that of the phosphinic acids, the following can be said. For the amidation of benzoic acid, $\Delta G^\#$ values of 143.4–152.2 kJ mol^{-1} and $\Delta H^\#$ values of 52.1–64.0 kJ mol^{-1} were calculated, whereas for the amidation of phosphinic acids, significantly higher $\Delta G^\#$ and $\Delta H^\#$ values, 154.7–189.2 and 67.7–106.4 kJ mol^{-1},

TABLE 2 Energetics for the Amidation of Phosphinic Acids at 210°C Obtained by B3LYP/6-31++G(d,p) Calculations

			Reaction Energy and Enthalpy Parameters (kJ mol^{-1})		*Activation Energy and Enthalpy Parameters (kJ mol^{-1})*	
Entry	*Acid*	*Amine*	ΔG^0	ΔH^0	$\Delta G^\#$	$\Delta H^\#$
1		$BnNH_2$	–5.9	–6.7	149.1	59.2
2		$^nHexNH_2$	–7.5	–8.2	143.4	52.1
3		$BnCH_2NH_2$	–6.3	–7.9	152.2	64.0
4	PhP(O)(H)OH	$BnNH_2$	35.0	22.7	156.3	68.6
5		$^nHexNH_2$	31.9	27.0	154.7	67.7
6		$BnCH_2NH_2$	29.5	23.4	157.6	71.5
7	$Me_2P(O)OH$	$^nHexNH_2$	42.0	35.3	168.9	92.0
8		$BnCH_2NH_2$	42.5	38.0	174.1	92.8
9	 **1**	$BnNH_2$	47.2	39.3	168.5	86.1
10		$^nHexNH_2$	44.7	32.6	166.4	79.4
11		$^cHexNH_2$	37.2	34.3	187.4	99.6
12		$BnCH_2NH_2$	41.1	33.2	168.5	83.2
13		$BnNH_2$	46.4	33.9	169.9	88.5
14		$^nHexNH_2$	43.1	33.0	168.0	86.5
15		$^cHexNH_2$	43.1	34.7	179.4	106.4
16		$BnCH_2NH_2$	38.8	33.7	170.1	90.3
17	 **4**	$BnNH_2$	43.5	35.1	174.7	87.8
18		$^nHexNH_2$	43.1	33.9	175.1	85.7
19		$^cHexNH_2$	45.9	35.9	195.6	95.8
20		$BnCH_2NH_2$	43.1	35.0	179.7	89.9
21	 **5**	$BnNH_2$	43.1	35.1	176.4	87.8
22		$^nHexNH_2$	44.6	35.7	177.2	87.8
23		$BnCH_2NH_2$	43.1	35.1	181.4	91.5
24		$BnNH_2$	30.3	21.7	189.2	106.1
25		$^nHexNH_2$	23.8	17.1	188.5	104.2

respectively, were obtained (Table 2). The enthalpy profile for the amidation of benzoic acid and phenyl-*H*-phosphinic acid with *n*-hexylamine is shown in Fig. 1. On the basis of the data calculated, it can be said that neither the $\Delta H^\#$ values nor the endothermicity would allow the amidation of the phosphinic acids to take place under thermal conditions. However, under MW conditions, a conversion of ca. 33% could be obtained; ca. two-third parts of the starting phosphinic acid remained unchanged. The beneficial effect of MW allowing the reaction to take place in a modest conversion stems in the statistically occurring local overheating effect [7] that may help to overcome the barrier meant by the relatively high (68–106 kJ mol^{-1}) enthalpy of activation. At the same time, the endothermicity works against the positive effect of local overheating and, hence, the unfavorable thermodynamics prevents complete conversions.

A significant steric effect was recognized in the amidations with *c*-hexylamine. In these cases (Table 2, entries 11, 15, and 19), the $\Delta H^\#$ values were ca. 10–20 kJ mol^{-1} higher than for the amidations with *n*-hexylamine.

Our calculations showed that in the amidation of carboxylic acids and phosphinic acids, a four-center

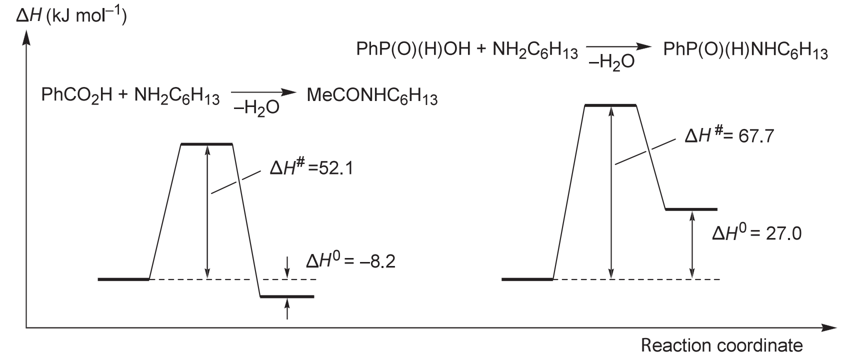
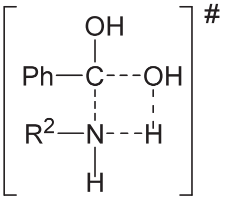
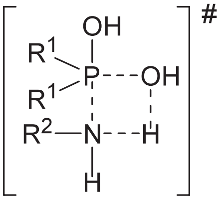


FIGURE 1 Enthalpy profile for the amidation of benzoic acid and phenyl-*H*-phosphinic acid with *n*-hexylamine.

transition state (TS) would be formed, shown as **8** and **9** in a general form.



8



9

The activation enthalpies must be the sum of the activation enthalpies of the H-atom transfer and the ring strain of the four-membered ring in the transition state. The situation is similar to that calculated for the direct esterification of carboxylic acids and phosphinic acids [6]. The TSs **8** and **9** are derived from the attack of the amine on the protonated form of benzoic acid and phosphinic acids. The protonated species are formed by autoprotonation. Calculations showed that the unprotonated acids did not undergo the reaction with amines. No stable adduct may be formed from the interaction of neutral reactants.

The TSs calculated for the reaction of benzoic acid with *n*-hexylamine and for the reactions of 1-hydroxy-3-methyl-3-phospholene 1-oxide **1** with *n*-hexylamine and *c*-hexylamine, as well as for the amidation of 1-hydroxy-3-methylphospholane 1-oxide **4** with benzylamine, are shown in Figs. 2–5, respectively, together with the geometries selected.

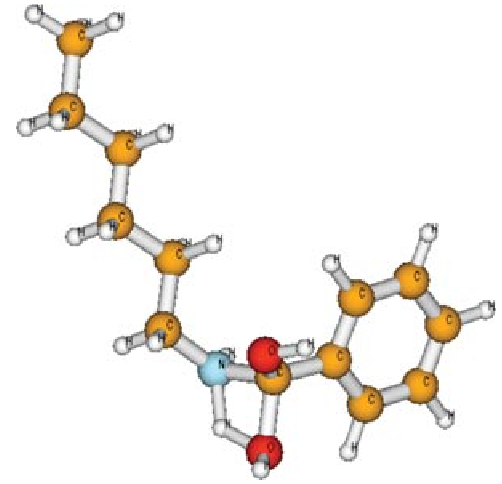


FIGURE 2 Perspective view for the TS of the amidation of benzoic acid with *n*-hexylamine obtained by the B3LYP/6-31++G(d,p) calculation in the gas phase. Selected geometries (bond distances, bond angles and torsion angles) are given in Å and deg. C–C(1) 1.502, C–NH 1.482, C–O(1)H 1.608, C–O(2)H 1.351, O(1)···H 1.154, NH···H 1.412, NH–C(2) 1.499, C–C(1)–O(1)H 108.85, C–C(1)–O(2)H 117.16, C–C(1)–NH 117.71, C(1)–O(1)···H 77.77, C(1)–NH–C(2) 120.61, NH–C(2)–C(3) 114.15, C–C(1)–NH–C(2) –125.89, C–C(1)–O(1)···H –124.27, C–C(1)–O(2)–H –23.98, C(1)–NH–C(2)–C(3) 77.86 C(1)–O(1)···H···NH 5.70.

In the TS for the reaction of benzoic acid with amines (**8**), the imaginary frequency is ca. i1400 cm^{-1} and the bond distances of N···H and O···H are ca. 1.41 and 1.16 Å, respectively (Table 3). The imaginary frequencies for the TS of the amidations of phosphinic acids (**9**) are ca. i1100–1300 cm^{-1}, whereas the bond distances of N···H and O···H are averagely 1.23 and 1.27 Å, respectively (Table 3). In TS **9**, the N···H distance is less elongated than in **8**. At the same time, the O···H distance in the TS **8** is shorter than in **9**. According to the bond lengths, the TS is somewhat looser for the amidation of phosphinic acid than it is for the amidation of benzoic acid. It is recalled that the distances for common N–H and O–H bonds are 1.03 and 0.99 Å, respectively.

For the amidation of benzoic acid, the reaction and activation entropy values (ΔS^0 and $\Delta S^{\#}$, respectively) fall in the range of –3.5 to –1.7 and –186.4 to –182.8 J mol^{-1} K^{-1}, respectively, whereas for the amidation of phosphinic acids, the ΔS^0 and $\Delta S^{\#}$ values were found to be –25.5 to –6.1 and –206.9 to –151.3 J mol^{-1} K^{-1}, respectively. On the basis of

FIGURE 3 Perspective view for the TS of the amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**) with *n*-hexylamine obtained by the B3LYP/6-31++G(d,p) calculation in the gas phase. Selected geometries (bond distances, bond angles, and torsion angles) are given in Å and deg. P–O(1) 2.058, P–O(2) 1.664, P–C(1) 1.831, P–C(2) 1.832, O(1) ···H 1.262, NH···H 1.232, P–NH 1.796, NH–C 1.509, C(1)–P–O(1)H 90.90, C(1)–P–O(2)H 102.46, C(1)–P–NH 125.44, C(2)–P–O(1)H 86.67, C(2)–P–O(2)H 102.45, C(2)–P–NH 127.06, HN–P–O(1)H 70.99, HN–P–O(2)H 91.10, HO(1)–P–O(2)H 161.81, P–O(1) ···H···NH −4.01, C(1)–P–O···H −125.17, C(2)–P–NH···H −72.53, C(1)–P–NH–C −43.92.

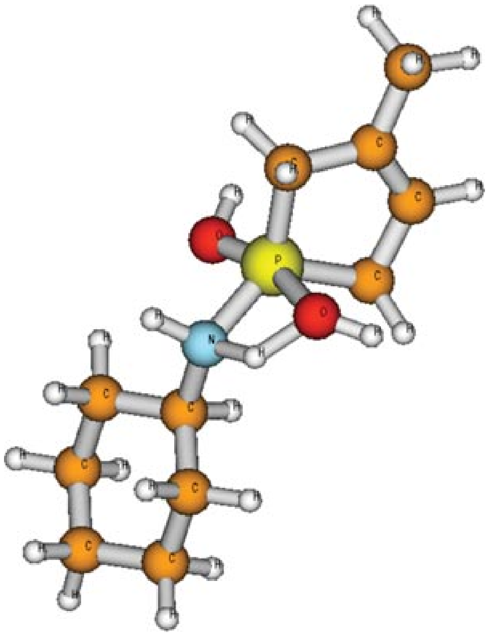


FIGURE 4 Perspective view for the TS of the amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**) with *c*-hexylamine obtained by the B3LYP/6-31++G(d,p) calculation in the gas phase. Selected geometries (bond distances, bond angles, and torsion angles) are given in Å and deg. P–C(1) 1.882, P–C(2) 1.841, P–O(1)H 1.995, P–O(2)H 1.616, P–NH 1.815, O(1) ···H 1.230, NH···H 1.265, C(1)–P–O(1)H 171.66, C(1)–P–O(2)H 101.12, C(1)–P–NH 100.06, C(2)–P–O(1)H 90.39, C(2)–P–O(2)H 118.75, C(2)–P–NH 118.52, HN–P–O(1)H 71.60, HN–P–O(2)H 116.63, HO(1)–P–O(2)H 83.20, P–O(1) ···H···H···NH −7.71, C(1)–P–O(1) ···H 3.86, C(2)–P–O(1) ···H −115.51, O(2)–P–O(1) ···H 125.57.

the transition state theory, these data mean that the preexponential factor is almost the same for the amidation of benzoic acid and for that of phosphinic acids. The rate constant can be calculated by the Eyring equation $\kappa \Gamma l^{\#}\ k_{\mathrm{B}}T/h\ e^{\Delta S\#/R}\ e^{-\Delta H\#/RT}$

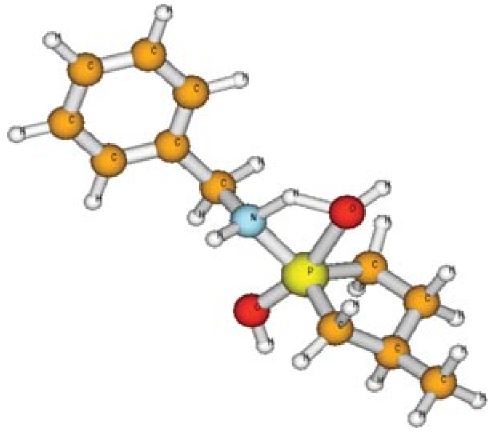


FIGURE 5 Perspective view for the TS of the amidation of 1-hydroxy-3,4-dimethylphospholane 1-oxide (**5**) with benzylamine obtained by the B3LYP/6-31++G(d,p) calculation in the gas phase. Selected geometries (bond distances, bond angles, and torsion angles) are given in Å and deg. P–C(1) 1.829, P–C(2) 1.839, P–O(1)H 2.091, P–O(2)H 1.660, P–NH 1.800, O(1) ···H 1.279, H···NH 1.219, NH–C) 1.519, C(1)–P–O(1)H 87.40, C(1)–P–O(2)H 103.43, C(1)–P–NH 123.90, C(2)–P–O(1)H 88.95, C(2)–P–O(2)H 103.40, C(2)–P–NH 128.08, HN–P–O(1)H 70.71, HN–P–O(2)H 90.70, HO(1)–P–O(2)H 161.40, O(1) ···H···O(2) 130.00, P–O(1) ···H···NH 1.67, C(1)–P–O(1) ···H −128.32, C(1)–P–NH–C −167.85.

with κ (transmission coefficient), Γ (quantum tunneling effect), and $l^{\#}$ reaction degeneracy) equal to 1 [9]. The rate constant for the reaction of benzoic acid with benzylamine) is ca. 100 times faster than it is for the similar amidation of 1-hydroxy-3,4-dimethylphospholane 1-oxide **5**.

In spite of the unfavorable energetics for the amidation of phoshinic acids, the reactions took place under the effect of MW irradiation, although only in incomplete conversions. This must be due to the effect of MW that promotes reactions with higher enthalpy of activation [6]. However, the complete conversions were prevented by the extent of endothermicity of the amidations.

Comparison of the Energetics of the Esterification and Amidation of Phosphinic Acids

It can be seen from Table 4, summarizing the experimental data and from Figure 6 showing the energetics for the comparative derivatization of 1-hydroxy-3-methyl-3-phospholene 1-oxide, that while the esterifications of the phosphinic acids are controlled kinetically, the amidations are governed mainly by thermodynamic factors. For comparison purposes, the energetics for the esterification and amidation of carboxylic acids are also shown in Table 4.

TABLE 3 Selected Bond Distances in the TS-s for the Amidation of Benzoic Acid and Phosphinic Acids Obtained by B3LYP/6-31++G(d,p) Calculations

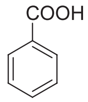
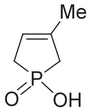
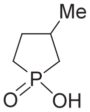
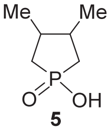
			Bond Distances (Å)			
Entry	*Acid*	*Amine*	*N···H (Å)*	*O···H (Å)*	*P(C) ···O (Å)*	*P(C) ···N (Å)*
1		$BnNH_2$	1.391	1.164	1.626	1.493
2		$^nHexNH_2$	1.412	1.154	1.608	1.482
3		$BnCH_2NH_2$	1.412	1.164	1.620	1.497
	Average		1.405	1.160		
4	 **1**	$BnNH_2$	1.234	1.261	2.064	1.796
5		$^nHexNH_2$	1.232	1.262	2.058	1.796
6		$^cHexNH_2$	1.265	1.230	1.995	1.815
7		$BnCH_2NH_2$	1.230	1.265	2.059	1.796
8	 **4**	$BnNH_2$	1.219	1.279	2.091	1.800
9		$^nHexNH_2$	1.218	1.279	2.081	1.799
10		$^cHexNH_2$	1.262	1.235	1.999	1.816
11		$BnCH_2NH_2$	1.219	1.278	2.078	1.799
12	 **5**	$BnNH_2$	1.219	1.279	2.091	1.800
13		$^nHexNH_2$	1.218	1.279	2.081	1.799
14		$BnCH_2NH_2$	1.218	1.280	2.080	1.800
	Average (for the amidations of phosphinic acids **1**, **4**, and **5**)		1.230	1.266		

TABLE 4 Summary for the Energetics of the Esterification/Amidation of Carboxylic Acids and Phosphinic Acids in Range (and as the Middle of the Range)

Esterifications [6]				*Amidations*			
ΔG^0	ΔH^0	$\Delta G^\#$	$\Delta H^\#$	ΔG^0	ΔH^0	$\Delta G^\#$	$\Delta H^\#$
$RCO_2H + R'OH \xrightarrow[-H_2O]{} RCO_2R'$				$RCO_2H + R'NH_2 \xrightarrow[-H_2O]{} RCONHR'$			
1–2 (1.5)	–4 to –5 (–4.5)	139–158 (148.5)	49–75 (62)	–7.5 to –6 (–7)	–8 to –7 (–7.5)	143–152 (148)	52–64 (58)
$>P(O)OH + R'OH \xrightarrow[-H_2O]{} >P(O)OR'$				$>P(O)OH + R'NH_2 \xrightarrow[-H_2O]{} >P(O)NHR'$			
6–16 (11)	0.1–4 (2.1)	184–243 (214)	102–161 (132)	24–47 (35.5)	17–39 (28)	155–189 (172)	68–106 (87)

All values are in kJ mol^{-1}.

One can conclude that the MW irradiation may be useful in overcoming relatively high enthalpies of activation, as in the case of the thermoneutral esterifications of phosphinic acids, but may be only of partial assistance if the reaction is significantly endothermic, as in the case of the amidation of phosphinic acids.

CONCLUSIONS

In summary, it was found that the thermally impossible amidation of phosphinic acids took place with a ca. 33% conversion on MW irradiation. B3LYP/6-31++G(d,p) calculations showed that, in contrast with the amidation of benzoic acid, that of the phosphinic acids is endothermic,

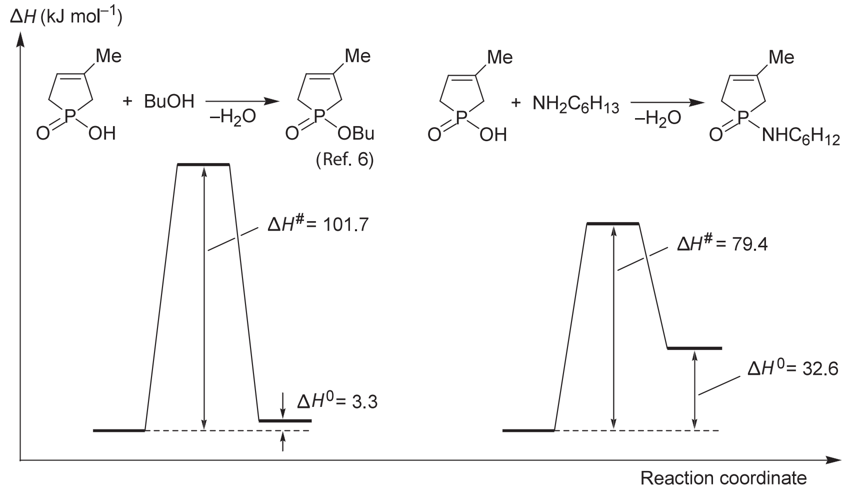


FIGURE 6 Enthalpy profile for the esterification and amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide **1** with butanol and hexylamine, respectively.

preventing direct amidation under traditional thermal conditions. The relatively high values (68–106 kJ mol^{-1}) of enthalpy of activation also preclude the direct amidation. The ca. 33% conversion achieved on MW irradiation still demonstrates the potential of the MW technique. The beneficial impact is the consequence of the local overheating effect that can overcome enthalpies of activation with higher values. It is recalled that the esterifications of phosphinic acids that are practically thermoneutral and have higher activation enthalpies (102–161 kJ mol^{-1}) could be performed efficiently under MW [6]. The above experiences suggest that the application of MW may be useful in reactions with higher $\Delta H^{\#}$ values. At the same time, endothermicity may prevent complete conversions. However, partial conversions may also be of a synthetic value due to the environmentally friendly accomplishment. Traditional syntheses of phosphinic derivatives involve expensive phosphinic chlorides as the starting materials and the formation of HCl as the by-product.

EXPERIMENTAL

General

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. The couplings are given in hertz. Mass spectrometry was performed on a ZAB-2SEQ instrument.

The amidations were carried out in a CEM Discover MW reactor (CEM Microwave Technology Ltd., Buckingham, UK) equipped with a stirrer and a pressure controller using 60–160 W irradiation.

General Procedure for the Amidation of 1-Hydroxy-3-methyl-3-phospholene 1-oxide (1) via the Phosphinic Chloride (3) Intermediate

To 1.50 g (11.4 mmol) of hydroxyphospholene oxide **1** in 5 mL of dry dichloromethane, 1 mL (13.8 mmol) of thionyl chloride was added and the mixture was stirred at 26°C for 24 h. Then the solvent was evaporated and the volatile residues were removed in high vacuum. 1.70 g (~100%) of 1-chloro-3-methyl-3-phospholene 1-oxide (**3**) so obtained was taken up in 3 mL of dry toluene, and the resulting solution was added dropwise to a mixture of 11.4 mmol of the primary amine (*n*-hexylamine: 1.5 mL, *c*-hexylamine: 1.4 mL, benzylamine: 1.3 mL) and 1.6 mL (11.4 mmol) of triethylamine in 3 mL of toluene at 60°C. The content of the flask was stirred at reflux for 2 h. Then, the amine hydrochloride salt was removed by filtration and the filtrate was evaporated. The crude product was purified by column chromatography (3% methanol in chloroform, silica gel) to afford phosphinic amide **2**.

*1-n-Hexylamino-3-methyl-3-phospholene 1-oxide (***2a***).* Yield: 82%; ^{31}P NMR ($CDCl_3$) δ: 63.1; ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3CH_2), 20.4 ($^3J = 12.1$, C_3–CH_3), 22.3 (CH_3CH_2), 26.2 (CH_2), 31.2 (CH_2), 31.8 ($^3J = 6.2$, CH_2), 31.9 ($^1J = 82.0$, C_5), 34.8 ($^1J = 85.5$, C_2), 40.4 (NCH_2), 120.5 ($^2J = 9.6$, C_4), 136.4 ($^2J = 15.2$, C_3); ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, $J = 6.2$, 3H, CH_3CH_2), 1.18–1.35 (m, 6H, 3×CH_2), 1.41–1.55 (m, 2H, CH_2), 1.76 (s, 3H, C_3–CH_3), 2.18–2.57 (m, total intensity 5H, 2×PCH_2, NH), 2.81–2.96 (m, 2H, NCH_2), 5.48 (d, $J = 33.4$, 1H, CH); $[M + H]^{+}_{\text{found}} = 216.1527$, $C_{11}H_{21}NOP$ requires 216.1517.

*1-c-Hexylamino-3-methyl-3-phospholene 1-oxide (***2b***).* Yield: 85%; ^{31}P NMR ($CDCl_3$) δ: 60.7; ^{13}C NMR

($CDCl_3$) δ: 20.5 ($^3J = 12.1$, C_3–CH_3), 24.9 ($C_{3'}$), 25.2 ($C_{4'}$), 33.1 ($^1J = 82.2$, C_5), 36.0 ($^1J = 85.7$, C_2), 36.1 ($^3J = 4.0$, $C_{2'}$), 49.9 ($C_{1'}$), 120.5 ($^2J = 9.7$, C_4), 136.4 ($^2J = 15.2$, C_3); ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, C_3–CH_3), overlapped by 1.02–2.00 (m, 5 × CH_2) total intensity 13H, 2.15–2.60 (m, 5H, NH, 2 × PCH_2), 2.94–3.14 (m, 1H, NH), 5.48 (d, $J = 37.1$, 1H, CH); $[M + H]^+_{found} = 214.1369$, $C_{11}H_{21}NOP$ requires 214.1361.

*1-Benzylamino-3-methyl-3-phospholene 1-oxide (**2c**)*. Yield: 76%; ^{31}P NMR ($CDCl_3$) δ: 63.5; ^{13}C NMR ($CDCl_3$) δ: 20.5 ($^3J = 12.1$, C_3–CH_3), 32.2 ($^1J = 81.8$, C_5), 35.0 ($^1J = 85.3$, C_2), 44.2 (NCH_2), 120.6 ($^2J = 9.8$, C_4), 127.3 ($C_{2'}$*, $C_{4'}$), 128.5 ($C_{3'}$)*, 136.6 ($^2J = 15.3$, C_3), 139.6 ($^3J = 5.8$, $C_{1'}$), * may be reversed; ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, 3H, C_3–CH_3), 2.18–2.62 (m, 4H, 2×PCH_2), 3.01–3.16 (m, 1H, NH), 4.08–4.20 (m, 2H, $NHCH_2$), 5.51 (d, $J = 33.6$, 1H, CH), 7.22–7.38 (m, 5H, Ar); $[M + H]^+_{found} = 222.1051$, $C_{12}H_{17}NOP$ requires 222.1048.

General Procedure for the MW-Assisted Amidation of 1-Hydroxy-3-methyl-3-phospholene 1-oxide **1** *and 1-Hydroxyphospholane 1-oxides* **4** *and* **5**

A mixture of 0.10 g of the phosphinic acid (**1**: 0.76 mmol, **4**: 0.75 mmol, **5**: 0.68 mmol) and 11.3 mmol of the primary amine (*n*-hexylamine: 1.5 mL, *c*-hexylamine: 1.3 mL, benzylamine: 1.2 mL) was measured in a sealed tube and irradiated in the MW reactor equipped with a pressure controller at 220°C for 2 h. (The pressure developed was in the range of ca. 7 bar) Then, the excess of amine was removed under reduced pressure and the residue was purified by flash chromatography. Amides **2a–c**, **6**, and **7** were formed in conversions of 30–36%, in purities of 95–97%.

Phosphinic Amide	Yield (%)	^{31}P NMR ($CDCl_3$) δ	$[M + H]^+_{found}$
2a	26	62.5	216.1522
2b	25	60.3	214.1368
2c	29	62.9	222.1053
6	24	66.1 (50%) and 66.2 (50%)	224.1209
7	22	59.0 (60%), 65.3 (30%), and 64.8 (10%)	238.1367

Theoretical Calculations

The structures for the reactants, products, and TSs were built up by PCMODEL [10]. The geometries of the molecules were optimized by the PM6 method implemented in MOPAC2009 [11]. The preoptimized structures were optimized by the B3LYP/6-31++G(d,p) method. The calculations were performed in the gas phase by Gaussian ‘03 [12]. The reactant and products had only positive frequencies in the normal coordinate analysis with the harmonic oscillator model. The transition states were found by the QST2 method. One and only one frequency was found to be imaginary. In the thermochemical calculations, the scale factor was 1.

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