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Microwave-assisted direct esterification of a cyclic phosphinic acid with phenols

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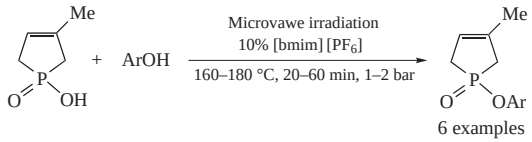
The direct esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide with substituted phenols under microwave irradiation in the presence of 10% of [bmim][PF_6] affords the corresponding aryl phosphinates in 52–64% yields.

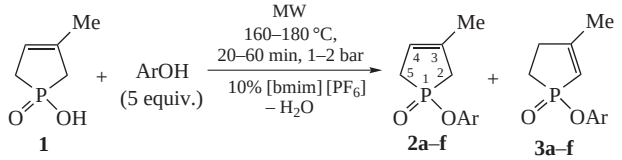


Since phosphinic acids do not undergo direct esterification, alkyl phosphinates are usually prepared by the reaction of phosphinic chlorides with alcohols.[1,2] This method suffers of a few drawbacks: it involves the use of acid chlorides, bases and solvents, and the esterification is not atomic efficient.[3–6] A better method may be the microwave (MW)-assisted direct esterification of phosphinic acids and alcohols used in a 15-fold excess.[7,8]

Aryl phosphinates may be synthesized by the traditional method outlined above.[3–6] An alternative Atherton–Todd reaction of secondary phosphine oxides with phenols[9] is disadvantageous as requires CCl_4 as the reagent and solvent. The arylation of phosphinic acids was also performed by reaction with diaryliodonium triflates,[10] or by reaction with phenols using copper as the catalyst,[11] or *N*,*N'*-carbonyldiimidazole,[12] or uranium-based salts[13] as the coupling agents. Our earlier attempts to prepare aryl phosphinates by direct MW-assisted esterification of phosphinic acids with phenols was unsuccessful, as the expected products were formed in only < 3%.[14]

According to a new trend, ionic liquids (ILs) are used as additives or catalysts to promote reactions.[15] Task-specific ILs, such as a peptide tagged to 1-methylimidazolium hexafluorophosphate and the same imidazolium scaffold bearing an aminoalkylamide substituent were efficient catalysts in asymmetric aldol reactions and Michael additions, respectively.[16,17] We have found that ILs can greatly enhance the MW-assisted direct esterifications.[18] This observation offered us a new chance to attempt the MW-assisted direct esterification of phosphinic acids with phenols.

In the first step, we tested a series of ILs (as potential additives) in the MW-assisted esterification of 1-hydroxy-3-phospholene 1-oxide **1** with phenol used in a five-fold excess (Scheme 1, Table 1).



a Ar = Ph, **d** Ar = 4-MeC_6H_4
b Ar = 4-$MeOC_6H_4$ **e** Ar = 4-ClC_6H_4
c Ar = 4-$Bu^tC_6H_4$ **f** Ar = 4-BrC_6H_4

Scheme 1

Table 1 The effect of different ILs on the MW-assisted esterification of 1-hydroxy-3-phospholene 1-oxide **1** with phenol.

Entry	IL (10%)	Conversion of **1** (%)	Entry	IL (10%)	Conversion of **1** (%)
1	–	< 3[14]	5	[emim][HSO_4]	72
2	[emim][OAc]	32	6	[emim][$EtOSO_3$]	74
3	[bmim][Cl]	51	7	[bmim][PF_6]	100
4	[bmim][BF_4]	54	8	[bmim][PF_6]	0[a]

[a] Comparative thermal experiment in a bomb tube.

As can be seen, the esterification that did not occur even under MW conditions,[14] proceeded in the presence of ILs (Table 1, entries 1–7). While, in accordance with our previous experience,[18] all ILs tested exerted some kind of positive effect, the use of [bmim][PF_6] was the most beneficial (entry 7). In the comparative thermal experiment, no phosphinate **2a** was formed (entry 8).

Then, to synthesize new aryloxy-3-phospholene oxides **2a–f**, we applied 10% of [bmim][PF_6] under MW irradiation with different phenols (see Scheme 1).† Along with the expected products **2**, 2-phospholene isomers **3** were also formed as by-products (see Scheme 1, Table 2). The major phosphinates **2a–f**

Table 2 Direct MW-assisted esterification of 1-hydroxy-3-phospholene 1-oxide **1** with phenols in the presence of 10% of [bmim][PF_6] as an additive.

Entry	Ar	*T*/°C	*t*/min	Conversion (%)	Ratio of **2**:**3** isomers[a]	Yield of **2**[b] (%)
1	Ph	160	20	100	87:13	59 (**2a**)
2	4-$MeOC_6H_4$	180	30	> 95	83:17	64 (**2b**)
3	4-$Bu^tC_6H_4$	180	35	100	90:10	52 (**2c**)
4	4-MeC_6H_4	160	60	100	89:11	52 (**2d**)
5	4-MeC_6H_4	180	30	100	63:37	– (**2d**)
6	4-ClC_6H_4	160	30	100	100:0	62 (**2e**)
7	4-BrC_6H_4	160	30	100	85:15	57 (**2f**)

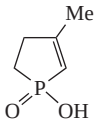
[a] Based on relative ^{31}P NMR intensities. [b] After column chromatography.

† *General procedure for the preparation of compounds* **2**. A mixture of phosphinic acid (0.76 mmol), phenol (3.8 mmol) and [bmim][PF_6] (0.08 mmol, 15.6 μl) was irradiated in a CEM Discover microwave reactor equipped with a stirrer and a pressure controller under 50–150 W irradiation at temperatures and for times given in Table 2 (the pressure developed

were isolated in 52–64% yields after column chromatography. At higher temperatures (180 *vs.* 160 °C), the extent of the isomerization was higher (Table 2, entries 4 and 5).

Thus, six new 1-aryloxy-3-methyl-3-phospholene oxides **2a–f** were obtained.

The esterification of 1-hydroxy-3-methyl-2-phospholene oxide **4** at 160 °C (30 min) afforded the corresponding phosphinate **3a** in 80% yield.



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was in the range of 1–2 bar). The excess of phenol was removed by extraction with a 22% NaOH solution. The crude products were purified by column chromatography (silica gel, 3% MeOH in CH_2Cl_2) to afford phosphinates **2a–f** as oils in a purity of ⩾ 98% according to GC.

3-Methyl-1-phenoxy-3-phospholene 1-oxide **2a**. ^{1}H NMR ($CDCl_3$) δ: 1.83 (s, 3H, C^3*Me*), 2.46–2.74 (m, 4H, 2PCH$_2$), 5.58 (d, 1H, C^{4}H, ^3J 36.9 Hz), 7.12–7.39 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.8 (d, C^3*Me*, ^3J 13.2 Hz), 30.7 (d, C^5, ^1J 88.2 Hz), 33.4 (d, C^2, ^1J 92.3 Hz), 120.3 (d, C^4, ^2J 11.1 Hz), 120.4 (d, C$^{2'}$, ^3J 4.8 Hz), 124.8 (C$^{4'}$), 129.9 (C$^{3'}$), 136.4 (d, C^3, ^2J 17.4 Hz), 150.9 (d, C$^{1'}$, ^2J 8.8 Hz). ^{31}P NMR ($CDCl_3$) δ: 74.1.

1-(4-Methoxyphenoxy)-3-methyl-3-phospholene 1-oxide **2b**. ^{1}H NMR ($CDCl_3$) δ: 1.83 (s, 3H, C^3*Me*), 2.42–2.70 (m, 4H, 2PCH$_2$), 3.79 (s, 3H, OMe), 5.58 (d, 1H, C^{4}H, ^3J 35.7 Hz), 6.81–7.18 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.8 (d, C^3*Me*, ^3J 13.1 Hz), 30.5 (d, C^5, ^1J 88.2 Hz), 33.2 (d, C^2, ^1J 92.4 Hz), 55.6 (OMe), 114.8 (d, C$^{3'}$, ^4J 0.4 Hz), 120.3 (d, C^4, ^2J 11.2 Hz), 121.3 (d, C$^{2'}$, ^3J 4.4 Hz), 136.4 (d, C^3, ^2J 17.4 Hz), 144.4 (d, C$^{1'}$, ^2J 9.0 Hz), 156.7 (d, C$^{4'}$, ^5J 0.9 Hz). ^{31}P NMR ($CDCl_3$) δ: 74.3.

*1-(4-*tert*-Butylphenoxy)-3-methyl-3-phospholene 1-oxide* **2c**. ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 9H, 3Me), 1.83 (s, 3H, C^3*Me*), 2.43–2.71 (m, 4H, 2PCH$_2$), 5.57 (d, 1H, C^{4}H, ^3J 36.9 Hz), 7.08–7.36 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.8 (d, C^3*Me*, ^3J 13.1 Hz), 30.7 (d, C^5, ^1J 88.3 Hz), 31.4 (3Me), 33.4 (d, C^2, ^1J 92.4 Hz), 34.3 (*C*Me$_3$), 119.8 (d, C$^{2'}$, ^3J 4.5 Hz), 120.4 (d, C^4, ^2J 11.3 Hz), 126.7 (C$^{3'}$), 136.4 (d, C^3, ^2J 17.4 Hz), 147.7 (C$^{4'}$), 148.5 (d, C$^{1'}$, ^2J 9.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 73.8.

3-Methyl-1-(4-methylphenoxy)-3-phospholene 1-oxide **2d**. ^{1}H NMR ($CDCl_3$) δ: 1.83 (s, 3H, C^3*Me*), 2.32 (s, 3H, Me), 2.43–2.69 (m, 4H, 2PCH$_2$), 5.57 (d, 1H, C^{4}H, ^3J 36.9 Hz), 7.06–7.16 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.70 (Me), 20.74 (d, C^3*Me*, ^3J 13.1 Hz), 30.6 (d, C^5, ^1J 88.3 Hz), 33.3 (d, C^2, ^1J 92.4 Hz), 120.1 (d, C$^{2'}$, ^3J 4.6 Hz), 120.3 (d, C^4, ^2J 11.2 Hz), 130.3 (C$^{3'}$), 134.4 (d, C$^{4'}$, ^5J 0.9 Hz), 136.4 (d, C^3, ^2J 17.4 Hz), 148.7 (d, C$^{1'}$, ^2J 9.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 74.0.

1-(4-Chlorophenoxy)-3-methyl-3-phospholene 1-oxide **2e**. ^{1}H NMR ($CDCl_3$) δ: 1.84 (s, 3H, C^3*Me*), 2.48–2.68 (m, 4H, 2PCH$_2$), 5.57 (d, 1H, C^{4}H, ^3J 37.2 Hz), 7.14–7.33 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.7 (d, C^3*Me*, ^3J 13.2 Hz), 30.6 (d, C^5, ^1J 87.7 Hz), 33.3 (d, C^2, ^1J 92.0 Hz), 120.2 (d, C^4, ^2J 11.2 Hz), 121.7 (d, C$^{2'}$, ^3J 4.7 Hz), 129.9 (C$^{3'}$), 130.1 (C$^{4'}$), 136.4 (d, C^3, ^2J 17.4 Hz), 149.4 (d, C$^{1'}$, ^2J 8.9 Hz). ^{31}P NMR ($CDCl_3$) δ: 73.1.

1-(4-Bromophenoxy)-3-methyl-3-phospholene 1-oxide **2f**. ^{1}H NMR ($CDCl_3$) δ: 1.83 (s, 3H, C^3*Me*), 2.46–2.66 (m, 4H, 2PCH$_2$), 5.58 (d, 1H, C^{4}H, ^3J 37.3 Hz), 7.06–7.50 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.7 (d, C^3*Me*, ^3J 13.2 Hz), 30.6 (d, C^5, ^1J 87.8 Hz), 33.3 (d, C^2, ^1J 92.0 Hz), 117.8 (d, C$^{4'}$, ^5J 1.2 Hz), 120.3 (d, C^4, ^2J 11.3 Hz), 122.1 (d, C$^{2'}$, ^3J 4.8 Hz), 132.8 (C$^{3'}$), 136.4 (d, C^3, ^2J 17.4 Hz), 150.0 (d, C$^{1'}$, ^2J 8.8 Hz). ^{31}P NMR ($CDCl_3$) δ: 75.1.

δ_P ($CDCl_3$) for the minor isomers **3b–f** are 75.2, 74.5, 74.2, 73.2, 75.7, respectively.

In summary, a new method comprising the MW-assisted [bmim][PF_6]-catalyzed direct esterification of cyclic phosphine oxide with phenols has been developed. We believe that the method is of more general value.

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3-Methyl-1-phenoxy-2-phospholene 1-oxide **3a**. ^{1}H NMR ($CDCl_3$) δ: 2.00 (s, C^3*Me*) overlapped by 2.02–2.30 (m, CH_2) total intensity 5H, 2.40–2.70 (m, 2H, CH_2), 5.94 (d, 1H, C^{2}H, ^2J 23.9 Hz), 7.10–7.38 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.4 (d, C^3*Me*, ^3J 20.4 Hz), 21.8 (d, C^5, ^1J 93.0 Hz), 30.4 (d, C^4, ^2J 13.1 Hz), 116.7 (d, C^2, ^1J 129.0 Hz), 119.5 (d, C$^{2'}$, ^3J 4.5 Hz), 123.5 (d, C$^{4'}$, ^5J 1.2 Hz), 128.7 (C$^{3'}$), 150.2 (d, C$^{1'}$, ^2J 8.6 Hz), 163.6 (d, C^3, ^2J 34.3 Hz). ^{31}P NMR ($CDCl_3$) δ: 74.2.