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Esterification of five-membered cyclic phosphinic acids under mild conditions using propylphosphonic anhydride (T3P®)

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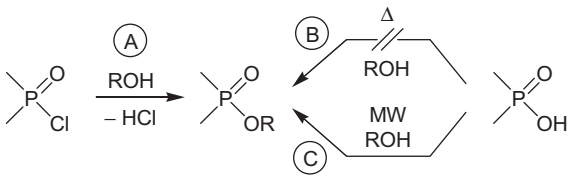
ABSTRACT

1-Hydroxy-phospholene 1-oxides (**1** and **3**) and 1-hydroxy-phospholane oxides (**5** and **7**) undergo fast and efficient esterification with a series of alcohols, at room temperature, in the presence of 1.1 equiv of propylphosphonic anhydride (T3P®).

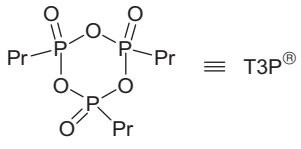
Phosphinates are usually synthesized by the reaction of phosphinic chlorides with alcohols (Scheme 1A).[1] This method works well, but it utilizes rather expensive chlorides and cannot be regarded as being environmentally friendly due to the formation of hydrochloric acid. It is well-known that phosphinic acids do not undergo direct esterification with alcohols on conventional heating (Scheme 1B). However, under microwave irradiation, direct esterification of phosphinic acids does take place (Scheme 1C).[2] Although these esterifications are 'green' from the point of view of the starting materials, the reaction temperature of ca. 200 °C is a disadvantage.

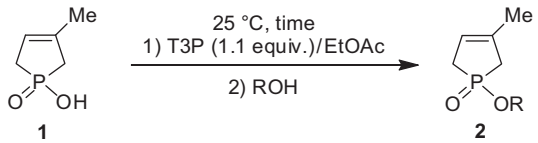
There are alternative possibilities for the esterification of phosphinic acids. Such reactions require specialized reagents, such as orthoesters,[3a] chloroformates,[3b,c] and orthosilicates.[3d] Direct esterification of phosphinic acids has not been reported, but phenylphosphinodithioates were prepared by heating PhP(S)(SH)H with primary alcohols.[3e]

The propylphosphonic anhydride (T3P®) reagent is a powerful coupling (dehydrating/condensing) agent applied in a wide range of reactions,[4] including peptide syntheses,[5] polyamidations,[6] amidations,[7] and esterifications,[8] as examples of only acylation reactions among the great variety of the reactions studied.



Scheme 1. Synthetic routes to phosphinates utilizing alcohols.





1 2

R= Me (**a**), Et (**b**), Pr (**c**), ^{i}Pr (**d**), Bu (**e**), ^{i}Bu (**f**), ^{s}Bu (**g**), Pent (**h**), ^{i}Pent (**i**), 3-pentyl (**j**), ^{c}Hexyl (**k**), Bn (**l**), 2-phenylethyl (**m**), 2-(1-naphthyl)ethyl (**n**), menthyl (**o**)

Scheme 2. Esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**) in the presence of T3P®.

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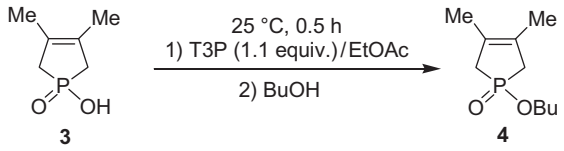
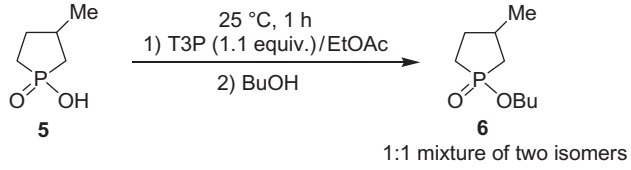
Table 1
Esterification of 2-hydroxy-3-methyl-3-phospholene 1-oxide (**1**)

Entry	ROH	Time (h)	Yield (%)	^{31}P NMR (121.5 MHz, $CDCl_3$)	δ_P^{Lit}	$[M+H]^+_{found}$	$[M+H]^+_{requires}$
1	MeOH	0.5	80 (**2a**)	76.8	77.0[11a]	147.0575	147.0575
2	EtOH	0.5	77 (**2b**)	74.7	74.7[11b]	161.0730	161.0731
3	PrOH	0.5	80 (**2c**)	72.5	74.5[11b]	175.0888	175.0888
4	^{i}PrOH	3	76 (**2d**)	73.0	73.2[11b]	175.0888	175.0888
5	BuOH	0.5	82 (**2e**)	74.7	74.6[2a]	189.1045	189.1044
6	^{i}BuOH	0.5	86 (**2f**)[11c]	74.6	–	189.1045	189.1044
7	^{s}BuOH	3	88 (**2g**)	73.23 (50%) 73.24 (50%)			
8	PentOH	0.5	94 (**2h**)	74.8	75.4[2d]	203.1200	203.1201
9	^{i}PentOH	0.5	91 (**2i**)	74.7	74.7[2d]	203.1201	203.1201
10	3-Pentyl alcohol	3	79 (**2j**)	73.6	—	203.1201	203.1201
11	^{c}HexylOH	2	89 (**2k**)	73.1	—	215.1201	215.1201
12	BnOH	0.5	95 (**2l**)	75.9	76.0[11b]	223.0889	223.0888
13	2-Phenylethanol	0.5	90 (**2m**)[11c]	75.5	—	237.1044	237.1044
14	2-(1-Naphthyl)ethanol	0.5	93 (**2n**)	75.7	—	287.1201	287.1201
15	Menthol	3	95 (**2o**)	73.32 (50%) 73.36 (50%)	73.28 (50%) 73.33 (50%)[11d]	271.1828	271.1827



3 **4**

Scheme 3. Esterification of 1-hydroxy-3,4-dimethyl-3-phospholene 1-oxide (**3**) in the presence of T3P®.



5 **6**
1:1 mixture of two isomers

Scheme 4. Esterification of 1-hydroxy-3-methyl-phospholane 1-oxide (**5**) in the presence of T3P®.

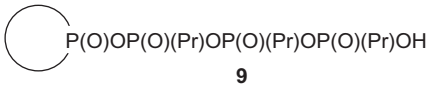
We herein describe the esterification of cyclic phosphinic acids with alcohols in the presence of the T3P® reagent.

Initially, the model compound, 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**),[9] was reacted with 1.1 equiv of T3P® in ethyl acetate at 25 °C for 10 min. Next, 1.5–3 equiv of an alcohol was added and the mixture was stirred further. With simple alcohols, such as methanol, ethanol, propanol, butanol, *i*-butanol, pentanol, *i*-pentanol, benzyl alcohol, 2-phenylethanol, and 2-(1-naphthyl)ethanol, the esterification was complete after 30 min, while the use of sterically hindered alcohols (*i*-propanol, *sec*-butanol, 3-pentyl alcohol, cyclohexanol, and menthol) required longer reaction times, typically three hours. With *tert*-butanol there was no reaction at all. The corresponding phosphinates **2a–o** where obtained in yields of 76–95% after flash column chromatography (Scheme 2, Table 1).[10] Phosphinates **2g** and **2o** were obtained as 1:1 mixtures of two isomers.

The T3P® promoted esterification was then extended to 1-hydroxy-3,4-dimethyl-3-phospholene 1-oxide (**3**),[9] and 1-hydroxy-3-methyl- and 1-hydroxy-3,4-dimethyl-phospholane 1-oxides (**5** and **7**)[2b] with butanol as the alcohol component. Carrying out the esterifications as described for the **1**→**2** transformation, phosphinates **4**, **6**, and **8** were obtained in yields of 81%, 70%, and 75%, respectively (Schemes 3–5). 1-Butoxy-3-methyl-phospholane 1-oxide (**6**) was obtained as a mixture of two isomers (on the basis of GC–MS), while the dimethyl analogue **8** was isolated as a mixture of three isomers. The isomers **8A**, **8B$_1$**, and **8B$_2$** were identified on the basis of our earlier study.[2b] The major isomer (**8A**) was separated by column chromatography in a yield of 42%.

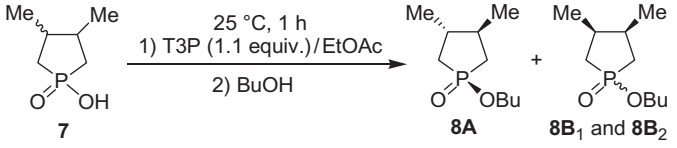
The known phosphinates (**2a–e**, **2h**, **2i**, **2l**, **2o**, **4**, **6,** and **8**) were identified by ^{31}P NMR spectroscopy and HRMS (Tables 1 and 2), while the new products (**2f**, **2g**, **2j**, **2k**, **2m,** and **2n**) were also characterized by ^{13}C and ^{1}H NMR spectroscopy.

The role of the T3P® reagent is to form a reactive anhydride type intermediate (**9**) from the phosphinic acid, which may then undergo reaction with the alcohol at room temperature. The by-product HOP(O)(Pr)OP(O)(Pr)OP(O)(Pr)OH formed was removed by extraction from the organic phase with water.



9

The T3P®-mediated reaction of phosphinic acids with alcohols is obviously of more general value.



7 **8A** **8B$_1$** and **8B$_2$**
3:2 mixture of two isomers
3:1:1 mixture of three isomers

Scheme 5. Esterification of 1-hydroxy-3,4-dimethyl-phospholane 1-oxide (**7**) in the presence of T3P®.

Table 2
Selected spectral data for phosphinates **4**, **6,** and **8**

Product	^{31}P NMR (121.5 MHz, $CDCl_3$)	δ_P^{2b}	$[M+H]^+_{found}$	$[M+H]^+_{requires}$
4	68.5	68.6	203.1203	203.1201
6	79.4 (broad)	79.40 (50%) 79.38 (50%)	191.1204	191.1201
8A	72.4 (92%)	72.5 (60%)	205.1350	205.1357
8B$_1$	78.3 (7%)	78.4 (20%)		
8B$_2$	79.9 (5%)	79.0 (20%)		

In summary, a mild and efficient esterification of a series of five-membered cyclic phosphinic acids was elaborated utilizing the T3P® reagent.

Acknowledgment

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10. *General procedure for the esterification of phosphinic acids in the presence of T3P®*: a mixture of 0.76 mmol of phosphinic acid (1-hydroxy-3-methyl-3-phospholene 1-oxide: 0.10 g, 1-hydroxy-3,4-dimethyl-3-phospholene 1-oxide: 0.11 g, 1-hydroxy-3-methyl-phospholane 1-oxide: 0.10 g, 1-hydroxy-3,4-dimethyl-phospholane 1-oxide: 0.11 g) and 0.55 mL (50 wt %, 0.84 mmol) of T3P® in EtOAc was stirred for 10 min. To the resulting mixture was added 2.3 mmol (or, in the case of non-volatile reagents, 1.1 mmol) of the alcohol [methanol: 0.09 mL, ethanol: 0.13 mL, propanol: 0.17 mL, isopropanol: 0.18 mL, butanol: 0.21 mL, isobutanol: 0.21 mL, *sec*-butanol: 0.21 mL, pentanol: 0.25 mL, isopentanol: 0.25 mL, 3-pentyl alcohol: 0.25 mL, cyclohexanol: 0.12 mL, benzyl alcohol: 0.12 mL, 2-phenylethanol: 0.14 mL, 2-(1-naphthyl)ethanol: 0.20 g or (1*R*,2*S*,5*R*)-(−)-menthol: 0.18 g] and the contents of the flask were stirred at 25 °C for the appropriate amount of time. The excess T3P reagent was hydrolyzed with 7 mL of 10% $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated to provide a crude residue that was passed through a thin (ca. 3–4 cm) layer of silica gel using 3% MeOH in CH_2Cl_2 as the eluent to give the products (**2a–p**, and **4**, **6,** and **8**) in ⩾99% purity, as oils.

*1-Isobutoxy-3-methyl-3-phospholene 1-oxide (**2f**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8 (2 × $CHCH_3$), 20.9 (d, J = 12.9, C3–CH_3), 29.3 (d, J = 6.2, OCH_2CH), 30.8 (d, J = 88.3, C2), 33.5 (d, J = 92.3, C5), 70.8 (d, J = 7.0, OCH_2), 120.4 (d, J = 10.8, C3), 136.4 (d, J = 16.9, C4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 6H, J = 6.7, $CHCH_3$), 1.80 (s, 3H, C3–CH_3), 1.86–2.03 (m, 1H, OCH_2CH), 2.28–2.55 (m, 4H, 2 × PCH_2), 3.79 (t, 2H, J = 6.7, OCH_2), 5.53 (d, 1H, J = 35.9, C4–H).

*1-(1-Methylpropoxy)-3-methyl-3-phospholene 1-oxide (**2g**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.5 (CH_2CH_3), 20.6 (d, J = 12.9, C3–CH_3), 21.6 ($OCHCH_3$), 30.6 (d, J = 5.0, $OCHCH_2$), 31.3 (d, J = 88.6, C2, isomer **A**), 31.7 (d, J = 88.6, C2, isomer **B**), 34.0 (d, J = 92.5, C5, isomer **A**), 34.4 (d, J = 92.5, C5, isomer **B**), 74.3 (d, J = 6.9, OCH), 120.1 (d, J = 11.1, C3, isomer **A**), 120.3 (d, J = 11.0, C3, isomer **B**), 136.1 (d, J = 16.9, C4, isomer **A**), 136.2 (d, J = 16.8, C4, isomer **B**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.4, CH_2CH_3), 1.27 (d, 3H, J = 6.2, $OCHCH_3$), 1.42–1.71 (m, 2H, $OCHCH_2$), 1.73 (s, 3H, C3–CH_3), 2.15–2.50 (m, 4H, 2 × PCH_2), 4.32–4.53 (m, 1H, OCH), 5.46 (d, 1H, J = 35.8, C4–H).

*1-(1-Ethylpropoxy)-3-methyl-3-phospholene 1-oxide (**2j**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.5 (CH_2CH_3), 20.9 (d, J = 12.9, C3–CH_3), 28.0 (d, J = 3.6, $OCHCH_2$), 31.8 (d, J = 88.8, C2), 34.5 (d, J = 92.6, C5), 79.4 (d, J = 7.4, OCH), 120.5 (d, J = 10.9, C3), 136.4 (d, J = 16.9, C4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 6H, J = 7.4, CH_2CH_3), 1.51–1.71 (m, 4H, 2 × $OCHCH_2$), 1.80 (s, 3H, C3–CH_3), 2.28–2.59 (m, 4H, 2 × PCH_2), 4.25–4.41 (m, 1H, OCH), 5.53 (d, 1H, J = 35.7, C4–H).

*1-Cyclohexyloxy-3-methyl-3-phospholene 1-oxide (**2k**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6 (d, J = 13.0, C3–CH_3), 23.6 (C3′), 24.9 (C4′), 31.6 (d, J = 88.5, C2), 33.79 and 33.83 (d, J = 2.9, C2′), 34.3 (d, J = 92.5, C5), 74.6 (d, J = 6.8, C1′), 120.2 (d, J = 11.0, C3), 136.1 (d, J = 16.9, C4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01–1.94 (m, 13H, C3–CH_3, 5 × CH_2), 2.18–2.52 (m, 4H, 2 × PCH_2), 4.20–4.40 (m, 1H, C1′–H), 5.44 (1H, J = 35.9, C4–H).

*1-(2-Phenylethoxy)-3-methyl-3-phospholene 1-oxide (**2m**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (d, J = 12.9, C3–CH_3), 30.8 (d, J = 88.1, C2), 33.4 (d, J = 91.8, C5), 37.2 (d, J = 5.8, OCH_2CH_2), 65.4 (d, J = 6.8, OCH_2), 120.3 (d, J = 10.9, C3), 126.7 (C4′), 128.6 (C2′), 129.1 (C3′), 136.3 (d, J = 17.0, C4), 137.5 (C1′); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 3H, C3–CH_3), 2.00–2.60 (m, 4H, 2 × PCH_2), 2.99 (t, 2H, J = 6.6, OCH_2CH_2), 4.12–4.33 (m, 2H, OCH_2), 5.46 (1H, J = 36.0, C4–H), 7.12–7.40 (m, 5H, ArH).

*1-[2-(1-Naphthyl)ethoxy]-3-methyl-3-phospholene 1-oxide (**2n**):* ^{31}P NMR and HRMS: Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (d, J = 12.9, C3–CH_3), 30.8 (d, J = 87.9, C2), 33.5 (d, J = 91.9, C5), 34.4 (d, J = 5.6, OCH_2CH_2), 65.0 (d, J = 6.8, OCH_2), 120.3 (d, J = 10.9, C3), 123.7 (C2′)[a], 125.6 (C3′)[a], 125.8 (C1′)[a], 126.3 (C4′)[a], 127.3 (C9′)[a], 127.6 (C8′)[b], 128.9 (C10′)[b], 132.1 (C7′)[b], 133.5 (C6′)[b], 134.0 (C5′)[b], 136.3 (d, J = 16.9, C4),[a,b] may be reversed; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3H, C3–CH_3), 2.01–2.45 (m, 4H, 2 × PCH_2), 3.47 (t, 2H, J = 7.0, OCH_2CH_2), 4.35 (q, 2H, J = 7.2, OCH_2), 5.37 (1H, J = 35.4, C4–H), 7.26–7.56 (m, 4H, ArH), 7.74 (d, 1H, J = 7.6, C5′–H)[c], 7.84 (d, 1H, J = 7.7, C4′–H)[c]; 8.04 (d, 1H, J = 8.1, C8′–H)[c], [c]may be reversed.

Spectral data for the additional products (**4**, **6** and **8**) are listed in Table 2.

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