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Alkylating Esterification of 1-Hydroxy-3-phospholene Oxides under Solventless MW Conditions

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ABSTRACT: *1-Alkoxy-3-phospholene 1-oxides were synthesized by the alkylating esterification of the corresponding 1-hydroxy derivatives under phase transfer catalytic, microwave, and solventless conditions using alkyl halides as the reactants and potassium carbonate as the base. In the case of alkylating agents of increased reactivity, there was no need for the use of phase transfer catalyst. Regarding the phosphinic acids, the 3-methyl-3-phospholene oxides were more reactive than the 3,4-dimethyl derivatives. Applying cesium carbonate, isomerization of the 3-phospholene oxide to the 2-phospholene also took place.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:211–214, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20596

INTRODUCTION

The most widespread method for the synthesis of phosphinic esters involves the reaction of phosphinic chlorides with alcohols [1,2]. The phosphinic chlorides may be prepared from the corresponding phosphinic acids by reaction with inorganic chlorides. The method is also applicable for the synthesis of cyclic phosphinates, such as 1-alkoxyphospholene 1-oxides (**3**) involving the hydroxyphospholene oxide (**2**) as the starting material and the chlorophospholene oxide (**4**) as the intermediate (Scheme 1) [3,4]. The alkoxyphospholene oxides (**3**) can also be obtained directly by the alcoholysis of the phospholium salts (**1**) [5–7] available from the McCormack cycloaddition of a variety of dienes with phosphorus tribromide. According to a recent method developed by the Keglevich group, the hydroxyphospholene oxides can be directly esterified by alcohols under solventless MW conditions [8]. These conversions were not, however, too efficient.

It was of interest to establish whether the alkylating esterification of the cyclic phosphinic acids may be a suitable approach under MW and phase transfer catalytic conditions for the preparation of 1-alkoxyphospholene oxides.

RESULTS AND DISCUSSION

The first model compound was 3-methyl-1-hydroxy-3-phospholene oxide **5**. The MW-promoted alkylations were carried out in solid–liquid phase in the presence of 1 equiv of potassium carbonate, in the absence of any solvent at 100°C, in a sealed tube using ethyl iodide, *n*-propyl bromide, isopropyl bromide, *n*-butyl bromide, and benzyl bromide as the alkylating agent (Scheme 2). In the first round, phase transfer catalyst was not added. After an irradiation time of 1 h, the ethyl (**6a**), *n*-propyl (**6b**), *n*-butyl

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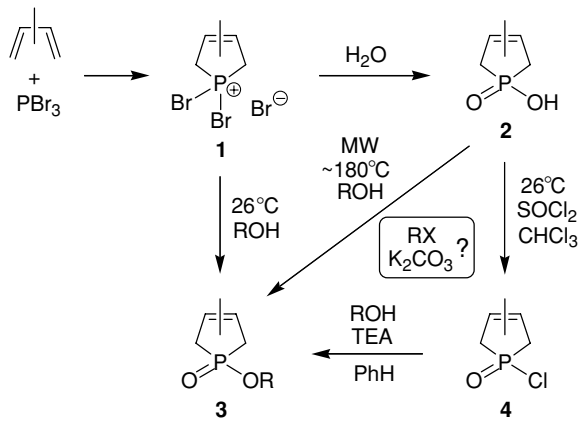
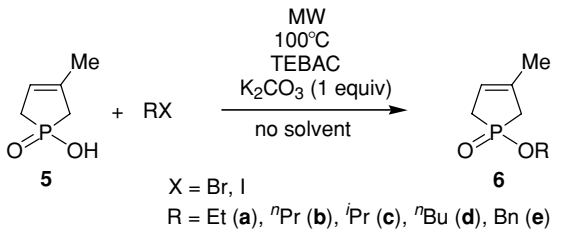


SCHEME 1



SCHEME 2

(**6d**), and benzyl (**6e**) esters were obtained in 80, 73, 69, and 92% yield, respectively, after flash column chromatography (Table 1, entries 1, 3, 7, and 9). Repeating the alkylations in the presence of 5% of triethylbenzylammonium chloride (TEBAC), all reactions went to completion and the yields were, in the above order, 90, 94, 96, and 94%, respectively (Table 1, entries 2, 4, 8, and 10). It can be seen that with the exception of the case using benzyl bromide, the yields were significantly higher in the presence of 5% of TEBAC. In other words, the alkylations with reagents of normal reactivity may be promoted by the use of the phase transfer catalyst, TEBAC. The esterification with isopropyl bromide was quite reluctant: after a 1.5-h heating at 100°C, the yield of **6c** was only 42%, while in the presence of TEBAC **6c** was isolated in 65% yield after an irradiation of 1 h (Table 1, entries 5 and 6, respectively).

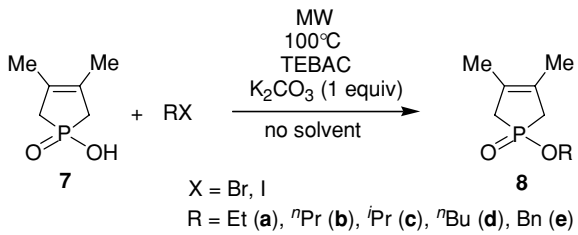
For the purpose of comparison, some of the above reactions were also carried out under thermal conditions. In the reaction of hydroxyphospholene oxide **5** with *n*-butyl bromide and benzyl bromide, esters **6d** and **6e** were obtained after 1 h in 64 and 85%, respectively (Table 1, entries 11 and 13). Repeating the experiments in the presence of 5% of TEBAC, both alkylations were essentially completed as the isolated yields were 89 and 87%, respectively (Table 1, entries 12 and 14). The MW-promoted esterifications were more efficient than the thermal variations, resulting in improved yields (5–7%) (Table 1, entries 7 vs. 11, 8 vs. 12, 9 vs. 13, and 10 vs. 14).

The second model compound was 3,4-dimethyl-1-hydroxy-3-phospholene oxide **7**. The MW-assisted alkylations were carried out as described for monomethyl derivative **5** (Scheme 3). Running the

TABLE 1 Esterification of 1-Hydroxy-3-methyl-3-phospholene 1-Oxide (**5**) by Alkylation at 100°C in the presence of K_2CO_3

RX	*TEBAC*	*Mode of Heating*	*Irradiating/heating Time (h)*	*Yield of **6** (%)*[a]	*Entry*
EtI	–	MW	1[b]	80	1
EtI	5%	MW	1[b,c]	90	2
^{n}PrBr	–	MW	1[b]	73	3
^{n}PrBr	5%	MW	1[b,c]	94	4
^{i}PrBr	–	MW	1.5[d]	42	5
^{i}PrBr	5%	MW	1[b]	65	6
^{n}BuBr	–	MW	1[b]	69	7
^{n}BuBr	5%	MW	1[b,c]	96	8
BnBr	–	MW	1[b,c]	92	9
BnBr	5%	MW	1[b,c]	94	10
^{n}BuBr	–	Δ[e]	1[b]	64	11
^{n}BuBr	5%	Δ[e]	1[b,c]	89	12
BnBr	–	Δ[e]	1[b,c]	85	13
BnBr	5%	Δ[e]	1[b,c]	87	14

[a]Obtained after flash column chromatography.
[b]Irradiating/heating time.
[c]Reaction time.
[d]Incomplete conversion even after longer reaction time.
[e]Thermal heating.



SCHEME 3

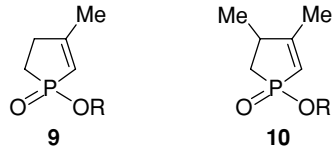
reactions with ethyl iodide, *n*-propyl bromide, *n*-butyl bromide, and benzyl bromide at 100°C in the presence of potassium carbonate and in the absence of TEBAC for 1 h, the corresponding alkyl esters (**7a,b,d,e**) were obtained in 83, 49, 40, and 84% yield, respectively (Table 2, entries 1, 3, 7, and 9). The presence of 5% of TEBAC resulted in almost complete reactions represented by 95, 90, 90, and 85% yields, respectively (Table 2, entries 2, 4, 8, and 10). One can see that in the case of alkylating agents that are of normal reactivity, the yields became again significantly higher. The effect of phase transfer catalyst was also evident when isopropyl bromide was the alkylating agent (Table 2, entries 5 and 6). Applying *n*-butyl bromide and benzyl bromide under thermal conditions, the yields were 35 and 75%, respectively (Table 2, entries 11 and 13). In the presence of TEBAC, the yields increased to 86 and 80%, respectively (Table 2, entries 12 and 14). The MW-assisted reactions were 5–9% more efficient than the thermal reactions (Table 2, entries 7 vs. 11, 8 vs. 12, 9 vs. 13, and 10 vs. 14).

Comparing the results with those obtained for monomethyl derivatives **5**, it can be seen that the use of TEBAC is more efficient for the alkylation of the dimethyl derivative **7**. Using *n*-propyl bromide, the increase in yield was 21 and 41% in respect of phospholene oxides **5** and **7**, respectively (Table 1, entries 3 and 4; Table 2, entries 3 and 4). In case of *n*-butyl bromide, the increases are 27 and 55%, respectively (Table 1, entries 7 and 8; Table 2, entries 7 and 8).

In most cases, three parallel experiments were carried out. The deviation was ±1.5–2%.

Studying the effect of temperature, it was found that using *n*-butyl bromide at 80°C, the alkylation of hydroxyphospholene oxide **5** was reluctant. At the same time, at 120°C there was no need for catalyst as after 1 h; the conversion was quantitative.

It was observed that a small amount (≤2%) of the isomerized product, 1-alkoxy-2-phospholene 1-oxide **9** or **10**, was also formed under MW conditions at 100°C. Using Cs_2CO_3 instead of K_2CO_3, the relative proportion of **9** and **10** increased to 7–24%.



In conclusion, an environment friendly method was developed for the alkylating esterification of 1-hydroxy-3-phospholene oxides comprising solventless, phase transfer catalytic, and MW conditions.

TABLE 2 Esterification of 1-Hydroxy-3,4-dimethyl-3-phospholene 1-Oxide (**7**) by Alkylation at 100°C in the presence of K_2CO_3

RX	*TEBAC*	*Mode of Heating*	*Irradiating/Heating Time (h)*	*Yield of **8** (%)*[a]	*Entry*
EtI	–	MW	1[b]	83	1
EtI	5%	MW	1[b,c]	95	2
^{n}PrBr	–	MW	1[b]	49	3
^{n}PrBr	5%	MW	1[b,c]	90	4
^{i}PrBr	–	MW	1.5[d]	18	5
^{i}PrBr	5%	MW	1[b]	56	6
^{n}BuBr	–	MW	1[b]	40	7
^{n}BuBr	5%	MW	1[b,c]	90	8
BnBr	–	MW	1[b,c]	84	9
BnBr	5%	MW	1[b,c]	85	10
^{n}BuBr	–	Δ[e]	1[b]	35	11
^{n}BuBr	5%	Δ[e]	1[b,c]	86	12
BnBr	–	Δ[e]	1[b]	75	13
BnBr	5%	Δ[e]	1[b,c]	80	14

[a]Obtained after flash column chromatography.
[b]Irradiating/heating time.
[c]Reaction time.
[d]Incomplete conversion even after longer reaction time.
[e]Thermal heating.

TABLE 3 ^{31}P NMR Chemical Shifts for 1-Alkoxy-3-phospholene-1-oxides **6a–e** and **8a–e**

	6a	***6b***	***6c***	***6d***	***6e***	***8a***	***8b***	***8c***	***8d***	***8e***
$\delta_P^{measured}$ ($CDCl_3$)	74.7	74.5	73.2	74.7	76.0	68.3	68.5	66.8	68.6	69.9
$\delta_P^{literature}$	67.0	–	–	74.6	76.1	68.4	68.5	–	68.4	70.7
Reference	[9]	[6]	[6]	[8]	[10]	[11]	[8]	[7]	[8]	[12]

EXPERIMENTAL

General

The alkylations were carried out in a CEM Discover microwave reactor equipped with a pressure controller using 30–40 W irradiation.

GC was carried out on an HP5890 series 2 GC-FID chromatograph, using a 15 m × 0.18 mm Restek, Rtx-5 column with a film layer of 0.20 μm. The temperature of the column was initially held at 40°C for 1 min, followed by programming at 25°C/min up to 300°C, and a final period at 300°C (isothermal) for 10 min. The temperature of the injector was 290°C, and of the FID detector was 300°C. The carrier gas was H_2.

GC-MS was carried out on an Agilent 6890 N-GC-5973 N-MSD chromatograph, using a 30 m × 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 μm. The initial temperature of column was 45°C for 1 min, followed by programming at 10°C/min up to 310°C and a final period at 310°C (isothermal) for 17 min. The temperature of the injector was 250°C. The carrier gas was He, and the operation mode was splitless.

General Procedure for Solid–Liquid Phase Esterification of 3-Hydroxy-3-phospholene-oxide Derivatives under Solventless and MW Conditions

A mixture of 0.76 mmol of 3-hydroxy-3-phospholene oxide (0.10 g of 1-hydroxy-3-methyl-3-phospholene oxide **5** or 0.11 g of 1-hydroxy-3,4-dimethyl-3-phospholene oxide **7**), 0.10 g (0.76 mmol) of K_2CO_3, 0.91 mmol of alkyl halide (0.10 mL of ethyl iodide, 0.08 mL of 1-bromopropane, 0.09 mL of 2-bromopropane, 0.10 mL of 1-bromobutane, or 0.11 mL benzyl bromide), and where it was applied, 10 mg (0.038 mmol) of TEBAC in a closed vial was irradiated in a CEM Discover (300 W) microwave reactor at 10–20 W for the appropriate time. (The pressure developed was in the range of 2–3 bar.)

The reaction mixture was taken up in 50 mL of ethyl acetate, and the suspension was filtered. Evaporation of the volatile components provided the crude product that was passed through a thin (ca. 3 cm) layer of silica gel using 3% MeOH in CH_2Cl_2 as the eluant to give an oil analyzed by GC-MS or GC.

As a comparison, similar reactions were carried out with conventional heating. The work-up was similar to that described above for the microwave reactions.

^{31}P NMR characterization of cyclic phosphinic esters **6** and **8** can be found in Table 3.

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