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New access to *H*-phosphonates via metal-catalyzed phosphorus–oxygen bond formation

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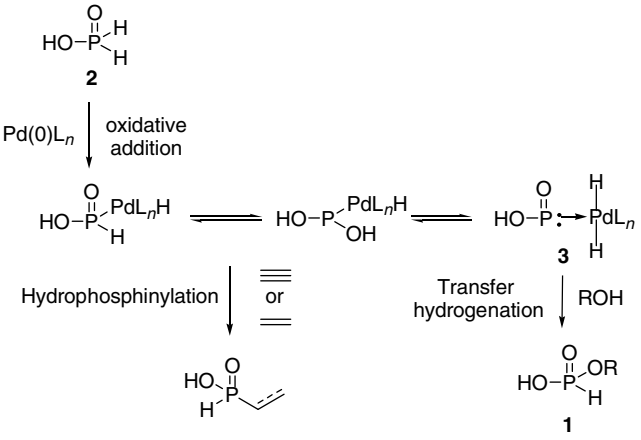
Abstract—A novel approach to *H*-phosphonates from hypophosphorous acid using a transfer hydrogenation process was developed. This method is atom-economical, environmentally friendly, catalytic, and efficient, leading easily to *H*-phosphonate monoesters or ammonium salt in moderate to good yields.

H-Phosphonate monoesters (**1**) are important synthetic intermediates in general phosphorus chemistry[1] but mostly in the synthesis of phosphates. Phosphate groups are present in numerous biological molecules such as nucleic acids, proteins, carbohydrates, lipids, coenzymes, and steroids. Therefore, in order to study biological pathways or for therapeutic applications, analogs of these compounds have been synthesized and phosphorylation reactions were developed. Among phosphorylating agents, phosphoric acid monoesters ($(RO)P(O)(OH)_2$), phosphoric acid diesters ($(HO)P(O)(OR)_2$), phosphorus pentoxide (P_2O_5), and phosphorus trichloride (PCl_3) are commonly used.[2] In the more recent literature, *H*-phosphonate monoesters have emerged as an interesting option to obtain phosphates in an atom-economical way. Several examples of phospholipid analogs,[3] carbohydrate analogs,[4] peptide analogs,[5] and nucleotide analogs[6] syntheses involved *H*-phosphonate monoesters intermediates.[7]

Current methods to access *H*-phosphonate monoesters (**1**) can be organized into two groups. The first uses P(III) phosphorus compounds such as PCl_3[8] or salicylchlorophosphite[9] in the presence of an alcohol and a base such as tetrazole or imidazole. The second group uses P(V) phosphorus compounds such as H_3PO_3[10] and diphenyl-*H*-phosphonate[11] in the presence of an alcohol, or the hydrolysis of *H*-phosphonate diesters.[12]

Our laboratory has been involved in the development of phosphorus–carbon bond formation using inexpensive and easily handled hypophosphorous acid (H_3PO_2) and its derivatives.[13] Based on the transfer hydrogenation mechanism,[14] we developed the hydrophosphinylation of alkenes and alkynes. We postulated that H_3PO_2 and its derivatives in the presence of a metal catalyst undergo an equilibrium (Scheme 1) between the P(V) form (**2**) and phosphinidene oxide complex (**3**) and we showed this equilibrium can be controlled by using different phosphine ligands. Based on this mechanism, we found a new atom-economical, efficient, and catalytic way to prepare *H*-phosphonate monoesters (**1**) by trapping phosphinidene oxide (**3**) with an alcohol.



Scheme 1. Hydrophosphinylation and transfer hydrogenation mechanisms.

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Table 1. Optimization of the catalytic oxidative phosphorylation of menthol[a]

Entry	H_3PO_2 (equiv)[b]	Catalyst		Solvent[c]	Yield[d] (%)
		Type	Amount (mol %)		
1	3.0	—	—	Toluene	0[e]
2a	1.5	Ni on Al_2O_3/SiO_2	5	Toluene/CH_3CN (1/1)	13
2b	1.5	Ni on Al_2O_3/SiO_2	5	Toluene	85
2c	1.3	Ni on Al_2O_3/SiO_2	5	Toluene	61
3a	1.5	Pd/C	5	Toluene/CH_3CN (1/1)	88
3b	1.5	Pd/C	5	Toluene	70
3c	1.5	Pd/C	5	CH_3CN	74
3d	1.5	Pd/C	5	DMF	49
4a	1.2	Pd/C	5	Toluene/CH_3CN (1/1)	77
4b	1.0	Pd/C	5	Toluene/CH_3CN (1/1)	62
4c	3.0	Pd/C	5	Toluene/CH_3CN (1/1)	80
5a	1.5	Pd/C	3	Toluene/CH_3CN (1/1)	80
5b	1.5	Pd/C	2	Toluene/CH_3CN (1/1)	76
5c	1.5	Pd/C	1	Toluene/CH_3CN (1/1)	63

[a] Unless otherwise noted, reactions were conducted with 1.0 equiv of menthol (0.32 M in solvent), 5 mol % catalyst under N_2 at 85 °C for 24 h.
[b] Commercial 50 wt % aqueous H_3PO_2 was concentrated in vacuo (0.5 mmHg) for 30 min at rt.
[c] Toluene and CH_3CN were freshly distilled over CaH_2, and DMF was stored over 4 Å sieves before use.
[d] *H*-Menthyl phosphonate was isolated by extraction of the acid form.
[e] Unreacted H_3PO_2 only.

Menthol was selected as test substrate to investigate the different parameters of the reaction: catalyst, solvent, temperature, and stoichiometry (Table 1).[15] *H*-Menthyl phosphonate was isolated by a basic–acidic extractive work-up to afford the acid form. First, and as expected, no product is formed in the absence of a catalyst (entry 1). Although the desired reaction takes place in all other cases, significant differences are observed. Since we were looking for an inexpensive catalytic P–O bond formation, Pd/C and Ni/Al_2O_3–SiO_2 were selected as catalysts. These catalysts proceed differently depending on the solvents (entries 2a–c vs 3a–d). Although the best

Table 2. Scope of the catalytic oxidative phosphorylation

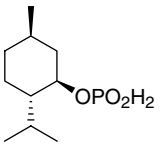
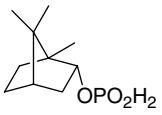
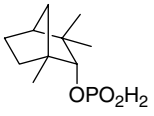
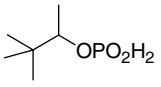
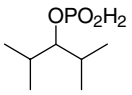
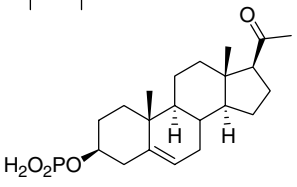
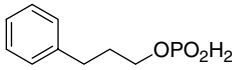
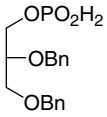
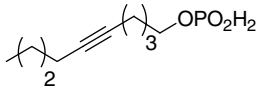
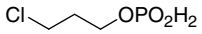
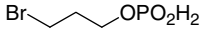
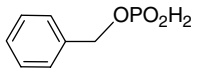
Entry[a]	Alcohol	*H*-Phosphonate	Isolated yield[b] (%)
1	(−)-Menthol		88
2	Borneol		70
3	(+)-Fenchyl Alcohol		97
4	3,3-Dimethyl-butan-2-ol		69
5	2,4-Dimethyl-pentan-3-ol		78
6	Pregnenolone		67

Table 2 (*continued*)

Entry[a]	Alcohol	*H*-Phosphonate	Isolated yield[b] (%)
7	3-Phenyl-propan-1-ol		67
8	Dibenzyl glycerol		68
9	Dec-5-yn-1-ol		80
10	3-Chloro-1-propanol		49[c]
11	3-Bromo-1-propanol		37[c]
12	Benzyl alcohol		56[c]

[a] See Supplementary data for detailed experimental procedures. Unless otherwise noted, reactions were conducted with 1.0 equiv of alcohol (0.32 M), 1.5 equiv of concentrated H_3PO_2 (prepared by evaporation of a commercial aqueous solution in vacuo (0.5 mmHg), for 30 min at rt) and 5 mol % Pd/C, in distilled toluene–CH_3CN (1:1, v/v), under nitrogen, at 85 °C for 24 h.
[b] Unless otherwise noted, the *H*-phosphonate is isolated by extraction as the acid form.
[c] *H*-Phosphonate was isolated by extraction and precipitation of the ammonium salt.

conditions are Pd/C in a toluene/CH_3CN mixture (1:1, v/v) (entry 3a), it should be noted that Ni/Al_2O_3–SiO_2 in toluene (entry 2b) leads to the product in comparable yield. Entries 3a and 4 show the influence of H_3PO_2 stoichiometry. In this process, residual water competes with the alcohol for **3** thereby transforming H_3PO_2 into H_3PO_3. Therefore, decreasing the amount of H_3PO_2 leads to lower yields (entries 4a and b vs entries 3a and 4c) and the optimum appears to be 1.5 equiv (entries 2b and 3a). As expected, catalyst loading controls the rate of the reaction. With Pd at 1 mol % loading in Pd/C, the reaction still proceeds in 63% yield after 24 h (entry 5c). On the other hand, reaction temperature is a critical parameter, and influences dramatically the speed of the reaction. Reactions performed at room temperature and at 40 °C, led to only 4% and 6% yields, respectively.

Reactivities of different H_3PO_2 salts (NH_3, $PhNH_2$, Et_3N, Na) were also tested but unsuccessfully (the sodium salt gave a 5% yield in CH_3CN or DMF). Dorfman and Aleshkova have studied the reaction of NaH_2PO_2 with methanol or butanol catalyzed by $PdCl_2$.[16] The alcohols were employed as solvents and no yields were reported.

After the establishment of the best conditions for menthol, we investigated the scope of the reaction (Table 2).[15] In most cases, the *H*-phosphonate monoester can be isolated in its acid form, in moderate to good yield by a basic–acidic extractive work-up (entries 1–9). In the case of more water-soluble products (entries 10–12), a simple extractive work-up followed by precipitation of the ammonium salt was necessary. Primary and secondary alcohols react well in this reaction (entries 7–12 and 1–6, respectively). But in spite of various efforts, the products derived from tertiary alcohols could not be isolated. As Cherbuliez et al. reported, it appears that these products are unstable in acidic conditions and elimination takes place.[17]

Hindered substrates give as good a yield as the unhindered alcohols (entries 3–5), thus supporting a highly reactive phosphinidene oxide intermediate. It should be noted that various functionalities, such as ketone (entry 6), alkene (entry 6), alkyne (entry 9), and halides (entries 10 and 11) are tolerated.

In conclusion, a simple and catalytic phosphorus–oxygen bond forming-reaction was developed based on the postulated transfer hydrogenation mechanism. Various primary and secondary alcohols, including hindered compounds, reacted satisfactorily. Hypophosphorous acid was shown to be a useful and inexpensive reagent to prepare various *H*-phosphonate monoesters via an oxidative phosphorylation which likely involves a highly reactive phosphinidene oxide intermediate. The method is atom-economical as it does not rely on protecting group strategies or on phosphorus(III) chlorides.

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Supplementary data

Representative experimental procedures and spectroscopic data. This material. Supplementary data associ-

ated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.057.

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15. *General procedure*: Aqueous hypophosphorous acid (50 wt %) was concentrated in vacuo (0.5 mmHg) for 30 min at rt. H_3PO_2 (1.5 equiv, 4.8 mmol), alcohol (1.0 equiv, 3.2 mmol), Pd/C (10 wt %, 5 mol % Pd, 0.16 mmol) in a mixture of distilled toluene–acetonitrile (10 mL, 1:1 v/v) were heated at 85 °C under a nitrogen atmosphere for 24 h. After cooling, the reaction was filtered through Celite® and concentrated in vacuo. The resulting oil was dissolved in ethyl acetate (25 mL) and washed with brine (10 mL, 3×). The organic layer was extracted with $NaHCO_3$ (0.5 M, 10 mL, 1×), then water (10 mL, 2×). The combined aqueous layers were acidified with 10% aqueous HCl until pH 1, and extracted with ethyl acetate (25 mL, 3×). The combined organic layers were washed with brine (5 mL, 1×), dried over $MgSO_4$, and concentration in vacuo to afford the acid form of *H*-phosphonate monoesters.
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