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# 5-*H*-1,2-Oxaphosphole 2-oxides, key building blocks for diversity oriented chemical libraries

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ABSTRACT

A simple and effective preparation of 2-hydrogeno-5*H*-1,2-oxaphosphole 2-oxides **9a**–**b** has been developed involving direct cyclization of *H*-phosphinic allenes. *H*-1,2-Oxaphospholenes **9a**–**b** showed to be excellent building blocks for diversity oriented small chemical libraries. Then, reactivity of the cyclic *H*-phosphinates **9a**–**b** was investigated through Pd(0) catalyzed arylation, Pudovik and three-component Kabachnik–Fields reactions. 5*H*-1,2-Oxaphospholes are excellent heterocyclic platforms offering different opportunities to modulate the substituent directly bounded to the phosphorus atom.



## 1. Introduction

Among FDA-approved drugs, cytotoxic phosphorus heterocycles, such as cyclophosphamide, introduced on the market in the late 1950's in USA, is still currently used as anticancer agent.[1] Since this period, the interest for the development of phosphorus-heterocycles as source of innovation and original modes of action in pharmaceutical and agrochemical fields is far from being exhausted. For example, phosphorus-containing unsaturated five-membered heterocycles such as 3-phospholene 1-oxides **1** or **2** have been claimed for their bactericide, insecticide and pesticide properties.[2] Later, benzoxaphospholes **3** and **4** were reported to have herbicidal activities,[3] and Yudelevich et al. described both 1,2-oxaphospholenes **5** and **6** with fungistatic activities.[4] Brandi et al. also described a series of tetrahydrophospholo-[2,3-d]isoxazoles **7a**–**d** exhibiting weak to moderate herbicide activities, and good fungicide activities against *Botrytis cinerea* on apples for **7e** and *Plasmopara viticola* on vines for **8f**–**g** (Fig. 1).[5]

As part of our ongoing efforts in discovery and synthesis of new phosphorus heterocycles,[6] we herein report the preparation of 2-*H*-1,2-oxaphosphole-3-ene 2-oxides **9a**–**b** by direct cyclization of *H*-phosphinylallenes **10a**–**b**. In the second part, we explored *H*-oxaphospholene potential as key building blocks for the generation of chemical libraries playing with the wide reactivity of P–H function. Thus, oxaphosphole-3-enes **9a**–**b** were engaged in palladium catalyzed coupling reactions with aryl halides, Pudovik additions to aldehydes and the 3-component Kabachnik–Fields reaction with amines and aldehydes leading to P-substituted oxaphospholenes **11**–**16** (Fig. 1).

## 2. Results and discussion

Allenylphosphonates are stable molecules that can be readily obtained by intramolecular 1,3-rearrangement ($S_Ni'$) of 2-alkynyl phosphites,[7–11] themselves accessible either by reaction of alkyl-2-yn-1-ol derivatives with phosphorus trichloride (requiring a subsequent hydrolysis or methanolysis),[8] or by reactions with diethyl chlorophosphite[9,10] or triethyl phosphite.[11] On the other hand, trimethyl phosphite can also be used through an Arbuzov reaction ($S_N2'$) with propargyl halides to give allenylphosphonates.[12] A larger chemical diversity of allenylphosphonates was obtained by α-functionalization of the phosphonate group using palladium-catalyzed coupling reactions.[13,14]

Inspired by the preparation of allenylphosphonates, allenyl *H*-phosphinate derivatives were obtained by combination of hypophosphorous acid with propargyl alcohols.[4,14,15] The *H*-

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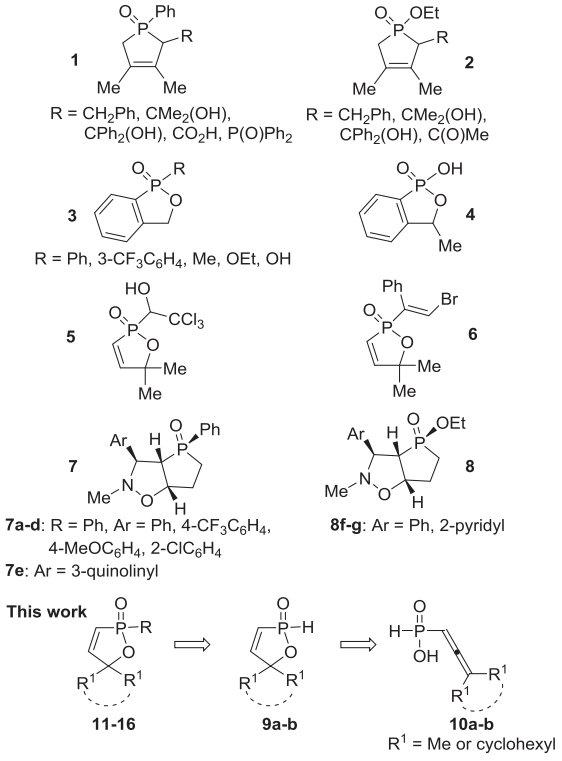
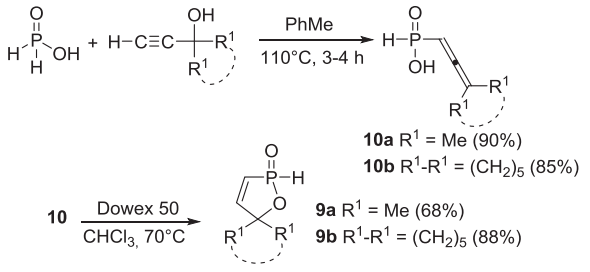



**Fig. 1.** Biologically active five-membered phosphorus heterocycles and this work.

allenylphosphinic acids **10a**–**b** were then prepared in high yields by this approach, i.e., by condensation/rearrangement of anhydrous hypophosphorous acid with propargyl alcohol in toluene under an inert atmosphere and removal of water (Scheme 1).[4]




**Scheme 1.** Synthesis of *H*-phosphinic allenes **10a**–**b** and oxaphospholenes **9a**–**b**.

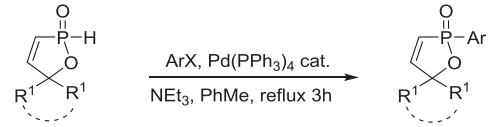
Various conditions are useful for the intramolecular cyclization of allenylphosphonates into 1,2-oxaphosphol-3-enes: using Brönsted acids,[8,16–18] Lewis acids,[19–22] halogens,[10,19,23–27] sulfuryl dichloride,[28,29] sulfenyl chlorides,[27,30–35] selenyl chlorides,[29,30,35] *N*,*N*-diethylphenylselenylamide with pyridine-$SO_3$ complex,[36] *m*-CPBA,[37] and Pd(II).[38] Here cyclization of allenylphosphinic acids **10a**–**b** has been accomplished by reaction in acidic conditions using a sulfonic acid resin, Dowex 50 as source of proton. 1,2-Oxaphospholenes **9a**–**b** were obtained in good yields after simple filtration of the resin and concentration to dryness (Scheme 1).

Consecutively to the synthesis of 1,2-oxaphospholenes **9a**–**b**, the introduction of chemical diversity at the phosphorus center has been accomplished through the reaction of the highly reactive P–H bond.

## 2.1. *P*-Arylation of *H*-1,2-oxaphospholenes 9a–b

Arylation takes place in the conditions usually described in the literature.[6c,39] *H*-1,2-Oxaphospholenes **9a**–**b** were reacted with various aryl halides in presence of catalytic amounts of tetrakis (triphenylphosphine)palladium (0) (5 mol%) and triethylamine in toluene at 80 °C in yields ranging from 41 to 72% (Table 1).

**Table 1**
Arylation of *H*-oxaphospholenes **9a**–**9b**




**9a** $R^1$ = Me
**9b** $R^1$-$R^1$ = $(CH_2)_5$
**11** $R^1$ = Me (56-72%)
**12** $R^1$-$R^1$ = $(CH_2)_5$ (41-55%)

| | X | Ar | Yield (%)[a] |
|---|---|---|---|
| **11** $R^1$=Me | | | |
| **11a** | I | $C_6H_5$ | 70 |
| **11b** | I | *p*-$CH_3O$-$C_6H_4$ | 72 |
| **11c** | I | *p*-Cl-$C_6H_4$ | 68 |
| **11d** | I | *p*-F-$C_6H_4$ | 60 |
| **11e** | Br | *p*-$CF_3$-$C_6H_4$ | 65 |
| **11f** | Br | 2-Pyridyl | 63 |
| **11g** | I | 2-Thienyl | 56 |
| **12** $R^1$–$R^1$=$(CH_2)_5$ | | | |
| **12a** | I | $C_6H_5$ | 45 |
| **12b** | I | *p*-Cl-$C_6H_4$ | 49 |
| **12c** | I | *p*-F-$C_6H_4$ | 51 |
| **12d** | I | *p*-$CF_3$-$C_6H_4$ | 55 |
| **12e** | Br | 2-Pyridyl | 41 |

[a] Yield after purification by column chromatography on silica gel.

For all the reactions, only one compound was observed with chemical shifts in $^{31}P$ NMR of the crude in the range of 40–50 ppm. These results established that the arylation only occurred on the phosphorus atom, and no product resulting from a competitive or a subsequent Heck or Tsuji–Trost reaction was observed.

## 2.2. Pudovik addition of *H*-1,2-oxaphospholenes 9a–b to aromatic aldehydes

Pudovik reaction is also an excellent opportunity to introduce substituents at the phosphorus center. Using potassium *tert*-butoxide for nucleophilic activation,[40] *H*-1,2-oxaphospholenes **9a**–**b** reacted smoothly with aromatic aldehydes, affording the α-hydroxy adducts **13a**–**d** and **14a**–**g** in yields ranging from 35 to 91% and diastereomeric excesses up to 62% (Table 2).

## 2.3. Three-component Kabachnik–Fields reaction of *H*-1,2-oxaphospholenes 9a–b

Following the previous results obtained for aldehydes, we investigated the 3-component Kabachnik–Fields reaction of *H*-1,2-oxaphospholenes **9a**–**b**,[41] using a methodology developed by Heydari et al., with activation by $LiClO_4$ in diethyl ether.[42] The rates and the yields of the reactions appeared to be similar in presence or not of $LiClO_4$, but the purification was much easier without this salt (see compound **15a**, Table 3).

Afterward, we performed the Kabachnik–Fields reaction without activation using **9b**. All the results are listed in Table 4. The reactions afforded the corresponding adducts in good yields (53–88%) with diastereoisomeric excesses ranging from 10 to 95% (Table 4).