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Synthesis of 2-(2-hydroxyaryl)alkenylphosphonium salts from phosphine oxides *via* ring-closing ring-opening approach and their antimicrobial evaluation

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ABSTRACT

A new two-step synthesis of phosphonium salts from phosphine oxides using Grignard reagents is reported. This approach involves a cyclization of *Z*-dialkyl-(diaryl)[2-(5-chloro-2-hydroxyphenyl)-2-phenylvinyl]phosphine oxides under the action of sulfinyl chloride with the formation of 2,2-dialkyl(diaryl)-6-chloro-4-phenyl-2*H*-1,2-benzoxaphosphinin-2-ium chlorides followed by ring opening under the action of organomagnesium compounds. The method was successfully applied to prepare a series of a new phosphonium salts bearing phenolic moiety with a wide range of substituents at phosphorus atom. Synthesized phosphonium salts shows high antibacterial and antifungal *in vitro* activity and low toxicity towards human red blood cell.

1. Introduction

Phosphonium salts are an extensively studied class of organophosphorus compounds. They have found application in asymmetric phase-transfer catalysis,[1–4] as organocatalyst[5] as well as ionic liquids.[6,7] The introduction of phosphonium functionality onto either natural or synthetic frameworks may lead to new pharmaceutically attractive compounds with antitumor[8–12] and antimicrobial activities.[13–15] Recently the structure, synthesis and practical application of polymeric materials containing a quaternary phosphonium moiety as antimicrobial agents have been observed.[16] In addition, some phosphonium salts are able to the reversible inhibition of cholinesterases[16,17] and possess a mitochondrion targeted antioxidant activity.[18–24]

The reactions of P(III) derivatives with alkyl halides or carbonyl compounds in the presence of hydrogen halide are commonly used for the obtaining of the phosphonium salts.[13,14] In such a reactions triphenyl- or tributylphosphines or rarely other trialkyl derivatives are usually applied. A few works on synthesis of phosphonium salts based on the reaction of tertiary phosphines with ortho-quinones[25,26] should also be noted. Recent advances of these synthetic approaches are widely reviewed.[13,14]

Earlier, we have shown by only one example that the reaction of 2-(5-chloro-2-hydroxyphenyl)-2-phenylvinyl diethylphosphine oxide with excess of bromine leads to the cyclic phosphonium salts.[27]

Here, we report a two-step synthesis of the functionally substituted phosphonium salts **9, 10** bearing a hydroxy-group in the position delta to phosphorus from quasiphosphonium salts **2**. This approach has been reported briefly earlier as the conference proceedings without any experimental details.[28]

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2. Results and discussion

Starting phosphine oxides **1** were obtained from 2,6-dichloro-4-phenylbenzo[*e*]-1,2-oxaphosphinine-2-oxide using a previously reported method.[29–32] The first stage of the proposed approach includes the cyclization of the corresponding phosphine oxides **1** using sulfinyl chloride under mild conditions (CH_2Cl_2, r.t.) to form quasiphosphonium salts **2** with quantitative yield under the conditions which were similar to those reported earlier (Scheme 1).[33]

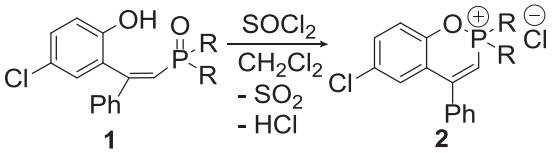
In a related work, in 1978, an electrophilic cyclization of allenylphosphine oxides **3** and products of their transformation - phosphine oxide **5** to cyclic phosphonium salts **4** by bubbling of gaseous HCl was reported.[34] Under those reaction conditions, phosphine oxide **5** was transformed to quasiphosphonium species **4** even in water solution at pH ≤ 1 (Scheme 2).

Similar results were obtained when allenylphosphine oxides **3** were halogenated and transformed to the halogen containing cyclic quasiphosphonium salts **6**.[35]

In contrast to reported data,[34] a trace amount of water leads to the hydrolysis of quasiphosphonium salts **2** back to phosphine oxides **1.** We attempted to use gaseous HCl for the cyclization of phosphine oxides **1** as described earlier (Scheme 3).[34] According to ^{31}P NMR data the reaction mixture contained equal amounts of phosphine oxides adduct with hydrogen chloride **A** (δ_P 60–70 ppm)[36–38] and quasiphosphonium salts **2** (δ_P 85–95 ppm). The **1**: **2** ratio was unchanged even in the presence of a large excess of HCl. It points out to the reaction reversibility and ability of quasiphosphonium salts **2** to hydrolyze under these conditions.

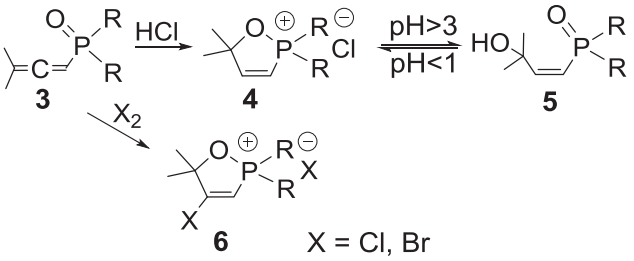
Quasiphosphonium salts **2** contain a phosphorus atom, which is ready available for nucleophilic attack. We assumed that the reaction of the cyclic salts **2** with such nucleophiles as organomagnesium compounds could result in a new P–C bond formation and give quaternary phosphonium salts (Scheme 4). The reactions were carried out in THF under inert atmosphere. To a stirred solution of quasiphosphonium salts **2** a freshly prepared Grignard reagent was added *via* cannula. The reaction occurs with a slight exothermic effect and color change from light brown to dark red.

In the ^{31}P NMR spectrum registered *immediately* after the addition of Grignard reagent to compound **2** only one signal was observed (δ_P −58 ppm) which may belong to the P(V) intermediate **7**. This signal disappeared after 30 min and the ^{31}P NMR spectrum contained the signal related to the phosphonium species **8** (δ_P ~ 12–20 ppm). After hydrolysis with aqueous hydrochloric acid, the reaction mixture becomes yellow and only the signal of compounds **9, 10** (δ_P ~ 12–20 ppm) was observed in ^{31}P NMR spectrum ($CDCl_3$). It is likely that, magnesium halide reacts with intermediate **7** as Lewis acid with ring opening to give magnesium salt **8**. After hydrolysis with aqueous hydrochloric acid, magnesium salts **8** transformed to phosphonium compounds **9, 10**. Herewith, chemical shifts of the signals in ^{31}P NMR spectra of compounds **8** and **9, 10** are not significantly differred. In all cases, phosphonium salts **9, 10** were obtained with high yields.

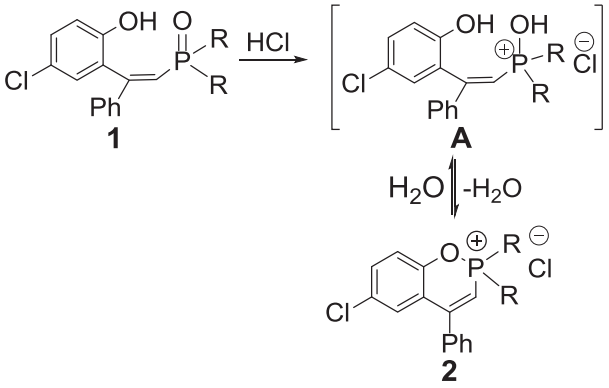


2a R = CH_3, **2b** R = C_2H_5, **2c** R = C_3H_7,
2d R = C_4H_9, **2e** R = C_5H_{11}, **2f** R = C_6H_{13},
2g R = Ph

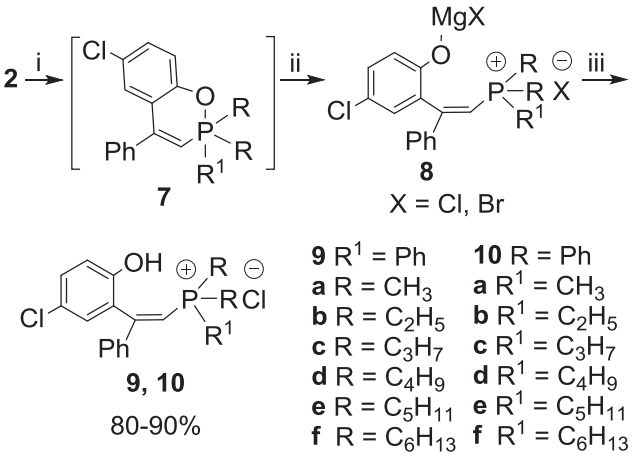
Scheme 1. Synthesis of quasiphosphonium salts **2**.



Scheme 2. Electrophilic cyclization of allenylphosphine oxides **3**.



Scheme 3. Reversibility of the reaction of phosphine oxide **1** with HCl.



Scheme 4. Synthesis of phosphonium salts **9, 10**.

The isolation of compounds **7** directly from reaction mixture was difficult due to its instability in reaction condition (magnesium salts, Grignard reagent excess), therefore, we attempted to obtain the supposed phosphorane **7** by the treatment of phosphonium salt with a base. It was turned out that the addition of ammonium hydroxide to the suspension of salt **9a** in benzene resulted in dissolving of phosphonium salt and the formation of phosphorane **7a** which smoothly reacts with hydrochloric acid to form back the phosphonium salt **9a** (Scheme 5). A cyclization of phosphonium salts **9, 10** to phosphorane **7** followed by the ring opening under the action of acid is a convenient method for counter ion replacement.

The structure of all new compounds was established using