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Facile Synthesis of Phosphorus-containing Heterocycles

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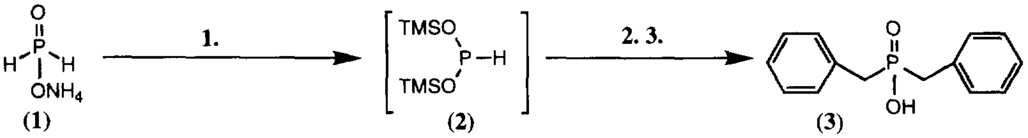
Abstract: *2-Hydroxyisophosphindoline-2-oxide 4 and the previously unreported 2-hydroxy-2,3-dihydrophosphaphenalene-2-oxide 5 have been prepared in a one-pot reaction under mild conditions.* Copyright © 1996 Elsevier Science Ltd

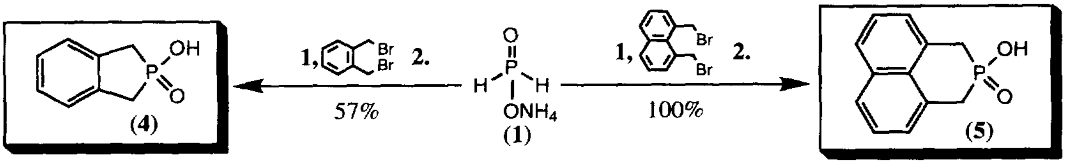
The use of silylphosphorus reagents for the construction of phosphorus-carbon bonds has greatly expanded the range of phosphorus-containing molecules which are synthetically accessible, in particular phosphonic and phosphinic acids.[1,2] In this context, for the preparation of substituted phosphinic acids we previously reported the addition of bis(trimethylsilyl)phosphonite (BTSP) **2** to α,β-unsaturated esters using triethylamine as the base.[3] Recently we found that dibenzylphosphinic acid **3** could be prepared in high purity but relatively low yield (44%) under these conditions using benzyl bromide as the electrophile. However, under these conditions triethylamine benzylation was found to be a significant problem, causing a reduction in yield. It was subsequently found that the use of the more sterically hindered *N,N*-diisopropylethylamine (Hunigs Base) significantly improved the yield, in line with our previous finding in analogous reactions.[4] In another change to the previously reported conditions it was found more convenient to use ammonium phosphinate rather than triethylammonium phosphinate as the precursor to BTSP. Hence in this new methodology for the synthesis of phosphinic acids, BTSP **2** was generated *in situ* by addition of an excess of Hunigs Base and trimethlysilyl chloride to ammonium phosphinate **1**,[5] (Scheme 1). Dibenzylphosphinic acid **3** was subsequently prepared in 83% yield by the addition of benzyl bromide to the solution of BTSP followed by hydrolytic work-up.



Conditions: **1**. $Pr^i_2NEt/TMSCl$, CH_2Cl_2, 0°C; **2**. BnBr, rt; **3**. H_3O^+

Scheme 1. Synthesis of dibenzylphosphinic acid

Our attention then turned to the potential of this reaction for the synthesis of phosphorus-containing heterocycles. We reasoned that under the reaction conditions described above, if *α,α'*-dibromo-*o*-xylene were to be used as the electrophile the intermediate functionalized benzylphosphonite ester might, in the presence of an excess of base, undergo a second intramolecular alkylation resulting in formation of a five membered phosphorus-containing ring. This was found to be the case, and 2-hydroxyisophosphindoline-2-oxide **4** was isolated in 57% yield (Scheme 2). This one-pot synthesis represents a considerably shorter and more efficient method for the preparation of **4** than the previously reported six step synthesis from 4-cyclohexen-*cis*-1,2-dicarboxylic acid, which gave an overall yield of 28%.[6]



Conditions: 1. $Pr^i_2NEt/TMSCl$, CH_2Cl_2, rt; 2. H_3O^+

Scheme 2. Synthesis of phosphorus-containing heterocycles

In a further extension of this methodology, 1,8-bis(bromomethyl)naphthalene was used as the electrophile under the same reaction conditions. After work-up and purification 2-hydroxy-2,3-dihydrophosphaphenalene-2-oxide **5** was isolated in quantitative yield, (Scheme 2). Phosphaphenalene **5** represents the first example of a previously unreported class of phosphinic acid-containing heterocycle.

In conclusion we report the development of a synthetic procedure for the preparation of the phosphorus-containing heterocycles **4** and **5** using silylphosphorus reagents. Work is under way to establish the generality of this methodology for the preparation of substituted and heterocyclic derivatives of **4** and **5**. Since completion of this work an isolated report detailing the synthesis of **4** using BTSP has appeared.[7] This methodology is described as straightforward and mild however it uses a considerably less convenient method for generation of BTSP, and is performed at 163 °C in refluxing mesitylene. In comparison the procedure described in this letter is far more straightforward and is considerably milder.

Typical Experimental Procedure: *Synthesis of 2-Hydroxy-2,3-dihydrophosphaphenalene-2-oxide 5.*
To a solution of ammonium phosphinate (0.26 g, 3.13 mmol) in dichloromethane (20 ml) was added *N,N*-diisopropylethylamine (1.44 g, 11.2 mmol) and trimethlysilyl chloride (1.20 g, 11.1 mmol) at 0 °C under argon. The solution was stirred at room temperature for 2 h and 1,8-bis(bromomethyl)naphthalene (1.08 g, 3.43 mmol) in dichloromethane (20 ml) was added. After 20 h the reaction was filtered and the filtrate washed with hydrochloric acid (2M, 2 x 15 ml) and water (10 ml) and dried over magnesium sulphate. Removal of the solvent *in vacuo* yielded a solid which was washed with hexane to give **5** (747 mg, 100%) (Found: (M^+) 218.0497. $C_{12}H_{11}O_2P$ requires M, 218.0497); ^1H NMR (250 MHz, CD_3OD) δ 3.37-3.44 (4H, d, $J_{P\text{-}H}$ 17.8 Hz, P-CH_2-), 7.18-7.89 (6H, m, Ar); ^{31}P NMR (101 MHz, CD_3OD) δ 39.5.

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