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A Direct Catalytic Synthesis of Sodium Diarylphosphinates and Their Corresponding Acids from Sodium Phosphate

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Abstract: In this contribution we present the direct conversion of sodium phosphinate \((\text{NaH}_2\text{PO}_2\cdot\text{H}_2\text{O})\) to symmetrical sodium diarylpiphosphinates and their corresponding acids by using palladium catalysis. This route eliminates the need for chlorinated precursors, such as \(\text{PCl}_3\) and intermediate alkyl- or ammonium-phosphinates.

Introduction

Organophosphinic acids \(\text{R}_2\text{P(O)OH}\) \((\text{R} = \text{hydrocarbyl group})\) and their esters and salts are relevant compounds in many fields: from flame retardants to solar cells and from ligands for catalysis to pharmaceutical applications and metal extraction.[1,2] They are interesting intermediates in the synthesis of other P-derivatives such as phosphines through reduction and/or functionalization.[3]

Current processes for the industrial production of organophosphinic acids and derivatives involve the use of phosphorus trichloride \((\text{PCl}_3)\) as starting material. Its availability is often taken for granted, but it should be realized that its production is energy-intensive and requires the use of chlorine gas, which carries inherent risks. Furthermore, arylation or alkylation is accomplished by using Grignard-, Michaelis–Arbuzov- or Michaelis–Becker-type coupling. These couplings start from \(\text{N,N-dialkylphosphoramido dichlorides} \ (\text{R}_2\text{NPCl}_2)\) or \(\text{N,N-dialkylphosphoronic dichlorides} \ (\text{R}_2\text{NP(O)Cl}_2)\) or alternatively involve the reaction of arylchloroazanium fluoroborates with \(\text{PCl}_3\) in the presence of a catalyst \((\text{CuBr})\).[4] These methods generally give suboptimal yields, often lead to mixtures, and also generate significant amounts of waste salts.

In an attempt to develop a more efficient and environmentally friendly[5] synthetic pathway for diarylphosphinic acids, we considered the direct arylation of sodium phosphinate [also known as sodium hypophosphate, \(\text{NaH}_2\text{PO}_2\cdot\text{H}_2\text{O}\) (1)]. By starting from this raw material, the use of chlorine gas can be eliminated, which potentially improves overall atom efficiency and reduces the risks associated with the process. Sodium phosphinate and its monohydrate are odorless, air- and water-stable solids, produced industrially at a multiton scale through basic hydrolysis of white phosphorus \((\text{P}_4)\) and mainly used in platerless plating.[2] They are registered under REACH as non-hazardous compounds.[6] In synthesis, sodium phosphinate has been applied as a reducing agent[7] and for the hydrophosphination of alkenes and terminal alkynes.[8]

Results and Discussion

Inspired by previous work on diarylphosphinate synthesis,[9,10] we investigated the direct diarylation of sodium phosphinate 1 to sodium diarylphosphinates 2 (Scheme 1, bottom route). Diarylphosphates 2 have been prepared from 1 before, but only indirectly through the corresponding esters or ammonium salts 1′, which require at least two additional steps to generate diarylphosphinic acids 3 (top route). Direct diarylation of 1 has only been mentioned so far as a side reaction in the monoarylation of \(\text{H}_2\text{H-phosphinates}\).[11]

Scheme 1. Synthesis of diarylphosphinic acids through arylation of \(\text{H}_2\text{H-phosphinates} \) esters or ammonium salts (1′)[9,10] and directly from \(\text{NaH}_2\text{PO}_2\cdot\text{H}_2\text{O}\) (1; this work).

To explore the feasibility of converting 1 \([\delta(31\text{P}) = 2.2 \text{ ppm}\) in toluene/methanol \((1:1))\] directly into 3, we chose \(\text{Pd(OAc)}_2\) or \(\text{Pd}_2(dba)_3\) (dibenzylideneacetone) combined with the large-bite-angle bidentate phosphine ligands dppf \([1,1′-\text{bis}(\text{diphenylphosphino})\text{ferrocene}]\), dppp \([1,3\text{-bis}(\text{diphenylphosphino})\text{propene}]\), and xantphos \([4,5\text{-bis}(\text{diphenylphosphino})-9,9\text{-dimethylxanthene}]\) as catalysts to promote rapid reductive elimination during the \(\text{P–C}\) coupling reaction. Initially, with iodobenzene as substrate \((\text{Pd loading}: 4.0 \text{ mol-%})\), we only observed low yields of sodium diphenylphosphinate 2a \([2–7 \% \text{ by in situ NMR spectroscopy}; \delta(31\text{P}) = 20.6 \text{ ppm}]\) in toluene/methanol \((1:1))\).[12]
Monohydrate 1 performed better than water-free sodium phosphinate (Scheme 2).[13] Analysis of the crude reaction mixture by $^{31}$P NMR spectroscopy indicated that significant amounts of unreacted 1 were present along with small amounts of sodium monophenylphosphinate $[\delta(^{31}P) = 15.0$ ppm in toluene/methanol (1:1)].[14]

Scheme 2. Direct diarylation of $\text{NaH}_2\text{PO}_2\cdot\text{H}_2\text{O}$ (1) with PhI.

We then continued our studies by using bromobenzene as substrate, NEt$_2$P$_2$ as the base, and Pd(OAc)$_2$/dppe or Pd(OAc)$_2$/dppp as catalysts, which gave much higher conversions (Table 1, entries 1–3). The choice of solvent [toluene/DME (dimethoxyethane) or DMF (dimethylformamide)] is crucial, as there was little or no conversion in protic solvents (methanol, acetic acid, water; not shown). More interestingly, the catalyst derived from the low-valent Pd precursor Pd$_2$(dba)$_3$/xantphos gave even higher conversions (Table 1, entries 5–7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Solvent</th>
<th>31P NMR yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>dppe</td>
<td>toluene/DME (9:1)</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>dppp</td>
<td>toluene/DME (9:1)</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>dppp</td>
<td>DMF</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>xantphos</td>
<td>DMF</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Pd$_2$(dba)$_3$</td>
<td>xantphos</td>
<td>DMF</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$(dba)$_3$</td>
<td>xantphos</td>
<td>DMF</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>Pd$_2$(dba)$_3$</td>
<td>xantphos</td>
<td>toluene</td>
<td>90 (100)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: NaH$_2$PO$_2$·H$_2$O (1.0 mmol) in solvent (5 mL); entries 1–4: PhBr (2 equiv.), Pd(OAc)$_2$ (4.0 mol-%), NEt$_2$P$_2$ (2.3 equiv.); entries 5–7: PhBr (2.5 equiv.), Pd$_2$(dba)$_3$ (2.0 mol-%), xantphos (4.4 mol-%); NEt$_2$P$_2$ (3.5 equiv.).

Following these in situ studies, we used the set of conditions with reduced Pd concentration (2.0 mol-%) for preparative work (Table 1, entry 7). To isolate diphenylphosphinic acid 3a in pure form and to extend the scope of the reaction,[15] a simple purification protocol was devised. This involved evaporation of the volatiles after the reaction, dissolving the residue in diethyl ether, extracting the ether solution with aqueous sodium hydroxide followed by acidification, and back extraction into dichloromethane. Evaporation of the solvent afforded disubstituted phosphinic acids 3a–j (see Table 2 and the Supporting Information for more details).

This method afforded 3a$^{[16]}$ ($\delta(^{31}P)$ = 23.4 ppm in D$_2$JDMSO (dimethyl sulfoxide)) in 86 % isolated yield. Good yields (75–83 %) were also obtained when using the substrates 4-bromo-toluene (3b$^{[17]}$), 5-bromo-1,3-xylene (3c$^{[18]}$), 4-bromobiphenyl (2d, new compound), 4-bromofluorobenzene (3g$^{[19]}$), and even 4-bromonitrobenzene (3j$^{[20]}$). A reduction in the yield (41–66 %)
was observed for the deactivated 3- and 4-bromoanisoles (3e[21] and 3f[22]) and for bromoarenes containing groups sensitive to reduction and/or aldol condensation [ethyl 4-bromo-
benzoate (3i[23]) and/or 4-bromoacetophenone (3h, new compound), respectively]. In all cases the mass balance was completed by un consumed starting material. The reaction can be run in air with only a 15% drop in yield (3a).

Our new method outperforms the known procedures for making these phosphinic acids, certainly when considering the fact that the reaction times were not optimized (to allow better comparison between different substrates).

With the exception of poorly soluble 2d, the reaction products were isolated as the acids [Ar$_2$P(O)O]OH, all of which are stable towards air and moisture. They were obtained as white [Ar$_2$P(O)O]Na is faster than the first aryl introduction on (salts [Ar$_2$P(O)O]Na from the inexpensive, hazard-free sodium K. Lammertsma for his generous support.

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**Keywords:** Phosphinates · Homogeneous catalysis · Cross-coupling · Palladium · Sustainable chemistry · Industrial chemistry

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[14] Lower yields of aryliodides vs. arylbromides have been observed previ- ously in the context of P-C coupling[110].

[15] The influence of different bases was briefly studied: potassium carbonate gave only modest improvements. A quick test to achieve a catalytic Ullmann coupling[110] gave no conversion.

[16] For comparison, the reported total yield for compound 3a, starting from PCl$_3$ appears to be at best 49–52% (76% in B. Quangxing, C. Jiangan, F. Riqing (Huangshi Lifuda Medicine Chemical Co. Ltd.), CN105001258A, 2014) in three steps: diphenylphosphinic acid from chlorodiphenylphos-
Communication

Phosphine in 90–96% yield, chlorodiphenylphosphine from \(N, N\)-diisopropylphosphoramid dichloride and phenyl Grignard in 80% yield, \(N, N\)-diisopropylphosphoramid dichloride from \(PCl_3\) in 68% yield and the yield of phenyl Grignard from bromobenzene assumed to be quantitative. The reported yield of \(3a\) through P–C coupling is 85%. Chlorotoluene also afforded \(3b\) in 10% yield; for comparison, the best reported yield for compound \(3b\) is 75% through Grignard reaction (G. M. Kosolapoff, *J. Am. Chem. Soc.* 1949, 71, 369–370).


For comparison, the best reported yield for compound \(3g\) is 7% (by-product of monoarylation) through the reaction of diazonium fluoroborate with \(PCl_3\) and catalyst (CuBr). (R. W. Bost, L. D. Quin, A. Roe, *J. Org. Chem.* 1953, 18, 362–366).

For comparison, the best reported yield for compound \(3j\) is 14% through the reaction of diazonium fluoroborate with \(PCl_3\) and catalyst (CuBr) (G. O. Doak, L. D. Freedman, *J. Am. Chem. Soc.* 1951, 73, 5656–5657).

For comparison, the reported yield for compound \(3e\) through P–C coupling is 89%.


For comparison, the best reported yield for compound \(3i\) is 16% through the reaction of diazonium fluoroborate with \(PCl_3\) and catalyst (CuBr), followed by oxidation (L. D. Freedman, G. O. Doak, *J. Org. Chem.* 1959, 24, 638–641).

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