Pergamon

Tetrahedron Letters, Vol. 37, No. 4, pp. 425-428, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02209-0

Improved Preparation of Phosphinate Esters for Palladium-Catalyzed Cross-Coupling

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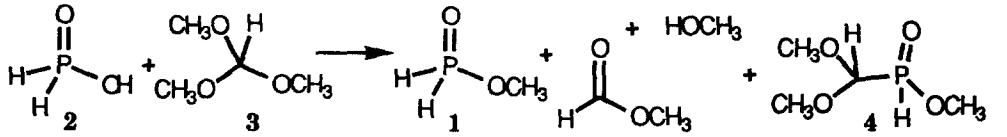
Abstract: *The reaction between phosphinic acid and trimethyl orthoformate to yield methyl phosphinate shows a pronounced solvent dependence. Conditions are defined to improve ester purity. t-Butyl phosphinate is also prepared cleanly, and its palladium-catalyzed reaction with aryl iodide is reported.*

Methyl phosphinate **1** is easily formed from anhydrous phosphinic acid (hypophosphorus acid, **2**) on treatment with trimethylorthoformate.[2] Several side products are observed in the reaction, the major one derived from dimethoxymethylation at phosphorus.[3] Ethyl phosphinate free of these impurities is available by treatment of anhydrous sodium hypophosphite in dichloromethane with triethyloxonium tetrafluoroborate.[4] Although hydrolytically labile, the ester is reasonably stable in solution; the pure substance deteriorates thermally. Other esters of phosphinic acid have been obtained by transesterification from the methyl ester,[5] or by other methods.[6]

Here we report studies on the optimization of the reaction between phosphinic acid **2** and trimethylorthoformate **3** to avoid dimethoxymethylation at phosphorus. We also demonstrate clean preparation of t-butyl phosphinate **5** by transesterification. We have shown that palladium-catalyzed cross-coupling of methyl phosphinate with aryl iodides yields methyl arylphosphinates.[7-9] Similar reactions of t-butyl phosphinate to form t-butyl arylphosphinates are effective only if t-butyl phosphinate is free of methyl phosphinate.

Side product **4** is presumably formed by attack of dimethoxymethyl cation on the phosphorus (III) tautomer of **1** or **2**. A polar solvent will encourage the undesirable formation of free cation from the initially formed ion pairs whose collapse leads ultimately to desired product **1**. Consequently we investigated the effects of cosolvents on the reaction, rather than using **3** as solvent as before. ^{31}P NMR was used to follow the reactions.



2 **3** **1** **4**

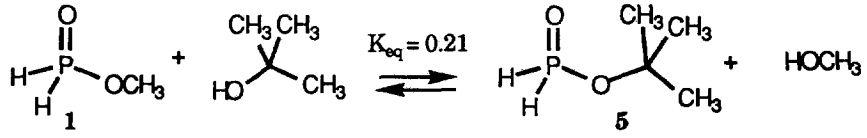
When the esterification is carried out in **3** without added solvent, **84% 1** is apparent at δ 19.3 ppm downfield of external standard 85% H_3PO_4. Impurity **4** (15%) is observed at

δ 30.2 and unreacted **2** (0.6%) at δ 8.7. Dilution of a mixture of **2** and **3** with an equal volume of cosolvent yielded a solution about 1M in **2** and 3-5M in **3**. The yield of **4** formed was dependent on solvent: CH_3CN, 23%; no cosolvent, 15%; CH_2Cl_2, 7%; $CHCl_3$, 4%; THF, 3.3±0.6%; 1:1 THF/toluene, 0.6±0.5%; toluene, 1.9±1.3%. As the solvent polarity decreases, so does contamination with **4**. In the case of toluene, a two-phase reaction mixture is observed at early reaction times, and **4** is probably formed in the more polar phase. Reactions run at RT are only slightly less selective, nonetheless the reactions are begun on an ice bath. We have found that methyl phosphinate prepared in THF/toluene in this way gives consistently good results in palladium-catalyzed cross-couplings.[7-9]

In 1:1 THF/toluene, the ^{31}P resonance for unreacted phosphinic acid **2** gradually shifts from about δ 11 to about δ 8 over the course of the reaction as the concentration and solvent composition change. Other signals also shift substantially, however identification of ^{31}P resonances in this solvent is straightforward with proton coupled spectra:[3] **4** (δ 30.1, dqd, J = 560, 11.7, 8.0 Hz), **2** (δ 8.7, t, J = 564Hz), **1** (δ 18.5, tq, J = 567, 12.9 Hz). Some impurities observed previously are not seen under our reaction conditions.[3]

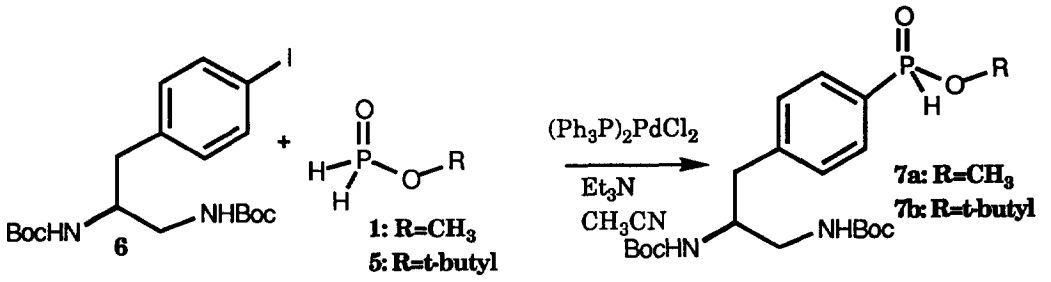
Solutions of methyl phosphinate in toluene/THF/trimethylorthoformate can be kept at room temperature with relatively little decomposition. After 1 week, ^{31}P NMR shows that the major component is still methyl phosphinate **1** (58%) with traces of phosphinic acid **2** (3%) and substantial amounts of methyl dimethoxymethylphosphinate **4** (9%). A significant amount of dimethyl phosphonate ($HPO(OCH_3)_2$), an impurity sometimes observed by Gallagher *et al.* [3] has now formed (δ 11.9, d sept, J=699, 11.8 Hz, 30%), though we are not sure whether it is formed by disproportionation or air oxidation. We do not observe this side product in the first several hours of reaction, so recommend preparation of the ester just prior to its reaction.

We have also prepared the t-butyl ester **5** by transesterification of **1** with t-butanol,[5] simply by carrying out the preparation of **1** in t-butanol as solvent. Interestingly, t-butanol is a superior solvent for the reaction of **2** with **3** to form **1** and **5** without contamination by **4** or related materials. Repeated addition of t-butanol, and evaporation under reduced pressure, leads to a mixture, predominantly **5**, but containing some **1**. This mixture, however, is unsuitable for cross-coupling reactions with aryl iodides. Reaction of a 7:1 molar ratio of **5**:**1** in CH_3CN with aryl iodide **6** [(S)-N,N'-di-Boc-1,2 diamino-3-(4-iodophenyl)-propane] and triethylamine under catalysis by $(Ph_3P)_2PdCl_2$, gave a roughly 1:1 mixture of methyl arylphosphinate **7a** and t-butyl arylphosphinate **7b**. Methyl phosphinate **1** appears to react sufficiently faster than t-butyl phosphinate **5** that **1** is consumed before significant reaction of **5** takes place. Therefore **5** free of **1** is needed for practical use.



We have used excess orthoformate in solution with phosphinate ester to consume adventitious water. Clearly, that is not ideal in the preparation of the t-butyl ester since phosphinic acid, formed by reaction of ester with water (or by elimination of isobutylene from the t-butyl ester), would react with orthoformate to give the methyl ester, in this case an undesired contaminant. Consequently, during ester exchange triethylamine is added to prevent orthoformate reaction, and volatiles are removed in vacuo. Repeated dissolution of

the residue in t-butanol to drive the transesterification further toward the t-butyl ester, and removal of volatiles in vacuo, leads to a crude t-butyl phosphinate that is almost completely free of methyl ester. Dissolution in toluene and filtration through basic alumina removes traces of phosphinic acid to provide a solution of t-butyl phosphinate **5** suitable for further reaction.



Coupling of **5** to **6** is effective, though slower than coupling of **1**. This is acceptable because **5** is substantially more stable than **1**. If methyl phosphinate in ethyl acetate solution is washed with aqueous $NaHCO_3$, the ester is completely hydrolyzed. In contrast, if a solution of t-butyl ester **5** is similarly treated, it remains largely intact, though the wet solution will slowly hydrolyze on standing. Consequently alumina, rather than aqueous extraction, is preferred for removal of traces of acid. t-Butyl ester **5** is also thermally more robust than is methyl ester **1**. Palladium catalyzed reactions using about a 3-fold excess of **1** show no remaining **1** after 77°C reflux for 100 min. In contrast, 13% of **5** remains in similar reactions, even after heating at 80-90°C for 100 min to complete reaction of aryl iodide, followed by filtration through silica gel.

Use of the t-butyl ester in place of the methyl ester allows facile cleavage under acidic conditions. Another advantage of the more hindered ester is its greater stability toward mildly basic conditions, simplifying the purification of the t-butyl monoarylphosphinate. Several of the t-butyl arylphosphinates we have prepared have been solids at RT, while the corresponding methyl arylphosphinates were oils.

In summary, practical and convenient procedures have been defined for the preparation of methyl phosphinate largely free of side products, and its transformation to other useful species. t-Butyl phosphinate has been shown to be readily preparable in useful form, and to have very desirable reactivity. These procedures increase the flexibility and reliability of synthetic routes using phosphinate esters.

Methyl phosphinate **1**:
To a solution of anhydrous phosphinic acid **2** (143 mg, 2.17 mmol) in dry THF (500 μL) and toluene (500 μL) stirred at 5°C under N_2 was added trimethyl orthoformate (970μL, 8.69 mmol). After 1 hr at 5°C, the mixture was allowed to warm to RT, and stirred for 2 hr. ^{31}P NMR of reaction mixture vs external H_3PO_4: δ 17.9, 96.3% (product **1**); δ 29.8, 0.9% (impurity **4**); δ 8.2, 2.8% (unreacted **2**). ^1H NMR ($CDCl_3$): δ 7.19 (d, J=562.1 Hz, 2H); δ 3.89 (d, J=12.7 Hz, 3H).

t-Butyl Phosphinate **5**:
Anhydrous phosphinic acid (415 mg, 6.3 mmol) in t-BuOH (3 mL, 31.8 mmol) was treated under N_2 at RT with trimethyl orthoformate (2.7 mL, 24 mmol). After 3 hr, ^{31}P NMR of

reaction mixture diluted into $CDCl_3$ shows a 1.1:1 mixture of $H_2PO_2CH_3$: $H_2PO_2C(CH_3)_3$, with no significant side products. Triethylamine (0.4 mL) was added to prevent further reaction of trimethylorthoformate, and volatiles were removed in vacuo. Two cycles of addition of t-butanol (3.4 mL), and removal by 10 min of evacuation after 90 min reaction, were followed by dissolution in toluene (2.00 mL) and triethylamine (0.20 mL), filtration through a 5 x 0.4 cm column of basic alumina, and rinsing of the column with toluene (1.0 mL) gave a solution of **5** free of **1**, **2** and **3**. The concentration was determined by ^1H NMR integration of a sample dissolved in $CDCl_3$ with 1,3,5-trimethoxybenzene added as an integration standard. Yield 3.0 mL of 0.82 M **5** (37%).
^{31}P NMR ($CDCl_3$) δ4.03; ^1H NMR ($CDCl_3$) δ7.10 (d, J=559.7 Hz, 2H), δ1.47 (s, 9H).

(S)-N,N'-di-Boc-1,2 diamino-3-(4-t-butoxyphosphinylphenyl)-propane **7b**:
A suspension of aryl iodide **6** (190.4 mg, 0.400 mmol) and $(Ph_3P)_2PdCl_2$ (14 mg, 0.020 mmol) in CH_3CN (1.0 mL) and triethylamine (31 μL, 0.22 mmol) was treated with t-butyl phosphinate **5** (0.82 mmol, added as 1.00 mL of a 0.82 M toluene solution also 0.58M in Et_3N). The reaction mixture was sealed under N_2, and heated in a 90° oil bath for 100 min. After solvent removal by rotary evaporation, product was isolated by flash chromatography (19:1 EtOAc/Et_3N) as a white solid MP = 56-60°C, yield 142 mg, 75%.
^1H NMR($CDCl_3$): 7.72 (d, J=551 Hz, 1H), 7.69 (dd, J=13.8 , 7.8 Hz 2H), 7.33 (dd, J=8.0, 3.1 Hz, 2H), 4.95 (broad, 1H) 4.87 (broad, 1H), 3.88 (broad m, 1H), 3.18 (broad m, 2H), 2.81 (broad m, 2H), 1.57 (s, 9H), 1.44 (s, 9H), 1.39 (s, 9H). ^{31}P NMR($CDCl_3$): Diastereomers 15.66 and 15.70 (dt, J=552.4 Hz, 12.3 Hz). ^{13}C ($CDCl_3$) 156.7, 155.9, 142.8, 131.7(d, J=11.9 Hz), 129.6 (d, J=139.3 Hz), 129.6 (d, J=14.3 Hz), 83.1, 83.1, 79.7, 79.5, 52.6, 43.7, 39.2, 30.4 (d, J=4.5 Hz), 28.3. Anal. Calcd for $C_{23}H_{39}N_2O_6P$: C, 58.71; H, 8.35; N, 5.95. Found: C, 57.93; H, 8.73; N, 6.06.

Support for this research by a grant from the NIH is gratefully acknowleged.

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(2) Fitch, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 61-64.
(3) Gallagher, M. J.; Honegger, H. *Tetrahedron Lett.* **1977**, *34*, 2987-2990.
(4) Pinnick, H. W.; Reynolds, M. A. *Synth. Commun.* **1979**, *9*, 535-538.
(5) Gallagher, M. J.; Honegger, H. *J. Chem. Soc., Chem. Commun.* **1978**, 54-55.
(6) Stawinski, J.; Thelin, M.; Westman, E.; Zain, R. *J. Org. Chem.* **1990**, *55*, 3503-3506.
(7) Lei, H.; Stoakes, M.; Schwabacher, A. W. *Synthesis* **1992**, 1255-1260.
(8) Lei, H.; Stoakes, M. S.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206-4210.
(9) Schwabacher, A. W.; Zhang, S.; Davy, W. *J. Am. Chem. Soc.* **1993**, *115*, 6995-6996.

(*Received in USA* 9 *August* 1995; *accepted* 14 *November* 1995)