Revisited Synthesis of Aryl-H-phosphinates

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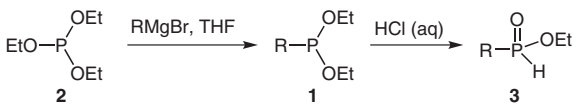
Received 19 April 2011; revised 20 May 2011

Abstract: A systematic study of the reaction conditions for the preparation of pure aryl-H-phosphinate esters, originally developed by Sander and optimized by Petneházy, is reported. The influence of the reaction concentration has been investigated for the formation of phosphonite intermediates via direct addition of triethyl phosphite to the appropriate Grignard reagent. Subsequent hydrolysis of the phosphonites under acidic conditions gives various aryl-H-phosphinates in high yields and purities.

Key words: phosphonites, phosphinates, aryl-H-phosphinates, triethyl phosphite, hydrolysis, Grignard reagent

Aryl-H-phosphinate esters are versatile building blocks for the preparation of heterocycles of biological interest.[1] Several strategies have been developed for the syntheses of these structures, including alcoholysis of aryl bischlorophosphines[2] (themselves accessible from bis(diethylamino)chlorophosphine[2a] or trichlorophosphine[2b,c] precursors), nucleophilic substitution of chlorophosphites using organolithium reagents,[3] and by palladium-catalyzed arylations of H-phosphinate esters,[4] hypophosphorous acid[5] or hypophosphorous acid anilinium salt.[6] Each method exhibited several advantages together with some major disadvantages. These drawbacks included the necessity for careful handling of trichlorophosphine, the use of expensive starting materials [$(Et_2N)_2PCl$, $(EtO)_2PCl$ and the palladium catalyst], and purification by column chromatography. Petneházy et al.[7] optimized the strategy originally developed by Sander[8] which enabled them to prepare H-phosphinate esters from relatively cheap starting materials and the easy-to-handle reagent, triethyl phosphite. Their procedure furnished efficiently and preferentially pure alkyl-H-phosphinates after distillation (Scheme 1). However, among the aryl derivatives shown in Scheme 1, only that with a phenyl group was described by Petneházy. Later, Wolf and co-workers reported two other aryl derivatives via the same strategy, but no information concerning the purity of the products was provided.[9]

Herein, we report the preparation of a series of aryl H-phosphinates by revisiting Petneházy's procedure. The original reaction took place through two consecutive steps; firstly an aryl (or alkyl) phosphonite intermediate **1** was generated by nucleophilic substitution of one of the ethoxide groups of triethyl phosphite (**2**) using a Grignard reagent. The former was transformed into aryl-H-phosphinate **3** by hydrolysis under aqueous acidic conditions. Applying the initial Petneházy conditions (addition of a solution of phenylmagnesium bromide to a tetrahydrofuran solution of triethyl phosphite), we observed that the corresponding phosphonite (δ_P = 154.0 ppm, DMSO-d_6 probe) was generated in 90–91% yield along with two other minor products, namely ethyl diphenylphosphinite (δ_P = 109.8 ppm , 6–7%) and triphenylphosphine (δ_P = –6.3 ppm , ~2%). Unreacted starting material was found to be present in an amount less than 1%. A reaction involving direct addition of triethyl phosphite to the Grignard reagent was attempted, but a less satisfactory result in terms of phosphonite formation (86% yield) was achieved. Moreover, side-products were obtained, including ethyl diphenylphosphinite (9%) and triphenylphosphine (4%), together with unreacted triethyl phosphite (~1%). The phosphonites obtained via these two approaches were subjected to direct hydrolysis under acidic conditions, followed by workup, to afford only 63–74% of the desired phenyl-H-phosphinate along with three other compounds, namely diphenylphosphine oxide (δ_P = 18.4 ppm , 14–18%), phenylphosphinic acid (δ_P = 16.6 ppm , 4–5%) and triphenylphosphine (δ_P = –6.7 ppm , 8–14%). Separation of the mixture gave pure phenyl-H-phosphinate in a low 22% yield. In order to improve the procedure and facilitate purification of the aryl-H-phosphinates, optimizations of the phosphonite formation and the subsequent hydrolysis step were undertaken.



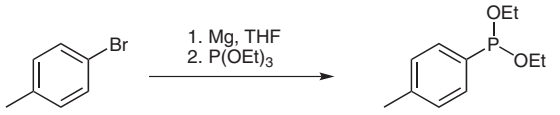
Scheme 1 Preparation of alkyl- and aryl-H-phosphinates using Petneházy's strategy

Firstly, the addition of triethyl phosphite to the Grignard reagent, (4-methylphenyl)magnesium bromide, was studied by varying several parameters; these included the reaction time, temperature, solvent, concentration and the

SYNTHESIS 2011, No. 15, pp 2490–2494
Advanced online publication: 14.07.2011
DOI: 10.1055/s-0030-1260109; Art ID: Z41611SS

ratio of Grignard reagent and triethyl phosphite (Table 1). For this study, solid 4-bromotoluene was preferred over bromobenzene. Using initial conditions of temperature (50 °C), time (three hours) and a final concentration of 1.5 M, phosphonite **1** (R = 4-MeC_6H_4) was formed in 90% yield (Table 1, entry 1). Using a final concentration of 0.8 M and temperature of 50 °C or 70 °C, no significant enhancement in the yield of the phosphonite was evident (Table 1, entries 2–5). In addition, it was found that applying a smaller or larger excess of the Grignard reactant (Table 1, entries 6 and 7) led to a lower yield of the phosphonite. Very low yields of the phosphonite were observed when the reagents were heated at reflux temperature in diethyl ether, toluene and 2-methyltetrahydrofuran (Table 1, entries 8–10). By contrast, a beneficial dilution effect was apparent in tetrahydrofuran (Table 1, entry 11). Indeed, phosphonite formation was maximized when the final mixture concentration was 0.2 M, affording an almost quantitative yield of ethyl 4-(methyl)phenylphosphinite (96%), along with ethyl bis[4-(methyl)phenyl]phosphinite (2%) and only 2% of unreacted starting material. A possible reason for this result might be due to modification of the Schlenk equilibrium toward the reactive monomeric Grignard reagent in dilute conditions, thereby reducing the formation of by-products.

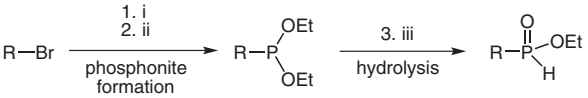
Table 1 Optimization of the Conditions for the Formation of Phosphonite Intermediate **1** (R = 4-MeC_6H_4)



Entry	Time (h)	Temp (°C)	Ratio[a]	Solvent	Final concn (M)[b]	Yield (%)[c]
1	3	50	1.5:1	THF	1.5	90
2	3	50	1.5:1	THF	0.8	87
3	5	50	1.5:1	THF	0.8	92
4	3	70	1.5:1	THF	0.8	91
5	5	70	1.5:1	THF	0.8	88
6	5	70	1.2:1	THF	0.8	79
7	5	70	1.7:1	THF	0.8	75
8	5	35	1.5:1	Et_2O	0.8	41
9	5	110	1.5:1	toluene	0.8	10
10	5	80	1.5:1	2-MeTHF[d]	0.8	45
11	5	70	1.5:1	THF	0.2	96

[a] Molar ratio of Grignard reagent to $P(OEt)_3$.
[b] Final concentration with respect to $P(OEt)_3$ (± 0.03 M).
[c] Yield estimated from the ^{31}P NMR (DMSO-d_6) spectrum of the crude product mixture.
[d] 2-MeTHF = 2-methyltetrahydrofuran.

Table 2 Preparation of Aryl-H-phosphinates **3**[a]



Entry	R	Phosphonite yield (%)[b]	Aryl H-phosphinate yield (%)[c]	Purity (%)[d]
1	Ph	96	63[e]	98
2	4-MeC_6H_4	96	60[e]	99
3	3-MeC_6H_4	93	63[e]	99
4	2-MeC_6H_4	88[f]	–[g]	–[g]
5	4-MeOC_6H_4	90	53[e]	99
6	3-MeOC_6H_4	98	50[e]	99
7	4-FC_6H_4[h]	94[i]	53[e]	98
8	3-FC_6H_4[h]	96[i]	56[e]	99
9	3-F_3CC_6H_4[h]	82[i]	39[e]	96
10	4-PhC_6H_4	93	49[j]	97
11	4-PhOC_6H_4	89	51[k]	97

[a] Reaction conditions: (i) RBr (1.5 equiv), THF, Mg (1.5 equiv), reflux, 1 h; (ii) $P(OEt)_3$ (1 equiv), THF, reflux, 5 h; (iii) HCl (1.0 M) until pH 2, r.t.
[b] Yield of the phosphonite calculated by ^{31}P NMR spectroscopy.
[c] Yield of isolated product based on $P(OEt)_3$.
[d] Purity determined by ^{31}P NMR spectroscopy.
[e] After distillation under high vacuum.
[f] Reaction took place over 20 h at reflux temperature.
[g] The product was not isolated.
[h] The fluorine-containing Grignard reagent was prepared from R–Br (1.75 equiv) and Mg (1.75 equiv).
[i] Reaction took place over 15 h at reflux temperature.
[j] After trituration with *n*-pentane and *n*-heptane.
[k] After trituration with *n*-pentane.

Secondly, we were interested in optimizing the phosphonite hydrolysis step to give the corresponding aryl H-phosphinate **3** using a minimum quantity of acid and water. Thus, it was first necessary to remove the basic magnesium salts present in the reaction mixture. This was achieved by evaporation of the solvent, treatment of the resulting oily residue with *n*-heptane and filtration over Clarcel® under a nitrogen atmosphere. After evaporation of the solvent, the residue was dissolved in tetrahydrofuran and hydrolysis was initiated by addition of an aqueous solution of hydrochloric acid (1.0 M). In general, a stoichiometric quantity of water was sufficient to transform, cleanly and quantitatively, phosphonite **1** (R = 4-MeC_6H_4) into aryl-H-phosphinate **3** (R = 4-MeC_6H_4). The measured pH of the reaction mixture was approximately 2 (if a pH value of 2 was not reached, an additional quantity of hydrochloric acid was added). Using these conditions, only traces of the corresponding arylphosphinic acid were detected.

A series of aryl-H-phosphinates was prepared and the results are summarized in Table 2. In general, conversion into the intermediate phosphonite was excellent when the starting aryl bromide contained electron-donating or electron-withdrawing substituents, with the yields ranging from 90–98% (Table 2, entries 1–3, 5–8 and 10). An exception was the sterically hindered *ortho*-tolyl derivative which required a prolonged reaction time of 20 hours to reach a maximum 88% yield (Table 2, entry 4). A similar situation was encountered with the 4-trifluoromethylphenyl derivative which gave an 82% yield of the phosphonite (Table 2, entry 9). The subsequent hydrolysis of each phosphonite occurred without any problem and yielded the corresponding aryl-H-phosphinate **3** contaminated with only small amounts of side-products. However, the 4-trifluoromethylphenyl derivative gave by-products in excess of 30%. After workup, the oily residue was purified either by distillation under very high vacuum for the most volatile H-phosphinates (Table 2, entries 1–9) or by trituration with *n*-pentane and *n*-heptane for heavier compounds (Table 2, entries 10 and 11). The aryl-H-phosphinates **3** were obtained in purities of 96% or greater.

In summary, we have described an optimized strategy for the efficient large-scale laboratory preparation of a range of aryl-H-phosphinates **3** in high purity.

All reactions were carried out under anhyd N_2 in flame-dried glassware. Liquid aryl bromides and triethyl phosphite were purified by distillation. THF was dried according to the standard procedure and stored under an N_2 atm. Commercial Mg turnings were dried overnight at 100 °C in an oven. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer in DMSO-d_6 as the solvent, operating at frequencies of 400.13 MHz (^{1}H), 100.62 MHz (^{13}C) and 161.97 MHz (^{31}P). The ^{31}P NMR spectra are decoupled. All studies carried out during processing were performed using a DMSO-d_6 probe introduced into the NMR tube. HRMS were measured on a Micromass Q-TOF instrument (ES+ ion mode).

Ethyl Arylphosphinates; General Procedure

A soln of aryl bromide [0.15 mol (0.175 mol for fluorinated aryl bromides)] in THF (225 mL) was added dropwise to Mg turnings [0.15 mol, 3.6 g (0.175 mol for fluorinated aryl bromides)] over a period of 1 h. The reaction mixture was stirred vigorously and heated at reflux temperature for 1 h. A soln of $P(OEt)_3$ (0.10 mol, 17.3 mL) in THF (280 mL) was then added rapidly over 5–10 min and the mixture heated at reflux temperature for 5 h. The solvent was evaporated under vacuum after which Clarcel® [10 g (15 g for fluorinated aryl bromides)] and *n*-heptane (100 mL) were added to the residue under an N_2 atm. The resulting gum was filtered and washed with *n*-heptane. After removal of the solvent under vacuum, the resulting colorless oil was dissolved in THF (280 mL) at r.t. Next, an aq soln of HCl (1.8 mL, 1.0 M) was added, or sufficient to attain a mixture of pH 2. The mixture was stirred for 20 min, dried over anhyd Na_2SO_4 and filtered. The solvent was evaporated and the oily residue was purified by distillation or by trituration to afford the pure aryl-H-phosphinate.

Ethyl Phenylphosphinate (Table 2, Entry 1)[1,7,10]

The product was prepared starting from bromobenzene (23.6 g) and was purified by distillation.

Colorless oil; yield: 10.8 g (63%); bp 75 °C (0.1 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.80–7.72 (m, 2 H), 7.72–7.65 (m, 1 H), 7.65–7.55 (m, 2 H), 7.57 (d, $^1J_{HP}$ = 565.7 Hz, 1 H), 4.16–3.99 (m, 2 H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 133.02 (d, $^4J_{PC}$ = 2.9 Hz), 130.45 (d, $^2J_{PC}$ = 11.7 Hz), 130.38 (d, $^1J_{PC}$ = 129.5 Hz), 128.84 (d, $^3J_{PC}$ = 13.2 Hz), 61.82 (d, $^2J_{PC}$ = 5.9 Hz), 16.18 (d, $^3J_{PC}$ = 6.2 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.63 (s).

HRMS (Q-TOF MS ES+): *m*/*z* [M + H]$^+$ calcd for $C_8H_{12}O_2P$: 171.0575; found: 171.0577.

Ethyl (4-Methylphenyl)phosphinate (Table 2, Entry 2)[1,11]

The product was prepared starting from 4-bromotoluene (25.9 g) and was purified by distillation.

Colorless oil; yield: 11.1 g (60%); bp 80 °C (0.03 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.63 (dd, $^3J_{HP}$ = 13.6 Hz, $^3J_{HH}$ = 7.9 Hz, 2 H), 7.52 (d, $^1J_{HP}$ = 563.1 Hz, 1 H), 7.39 (dd, $^3J_{HH}$ = 7.9 Hz, $^4J_{HP}$ = 3.0 Hz, 2 H), 4.13–3.97 (m, 2 H), 2.38 (s, 3 H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 143.25 (d, $^4J_{PC}$ = 2.9 Hz), 130.52 (d, $^2J_{PC}$ = 12.4 Hz), 129.41 (d, $^3J_{PC}$ = 13.9 Hz), 127.20 (d, $^1J_{PC}$ = 131.7 Hz), 61.62 (d, $^2J_{PC}$ = 5.9 Hz), 21.18 (d, $^5J_{PC}$ = 1.5 Hz), 16.18 (d, $^3J_{PC}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.78 (s).

HRMS (Q-TOF MS ES+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}O_2P$: 185.0731; found: 185.0734.

Ethyl (3-Methylphenyl)phosphinate (Table 2, Entry 3)[1]

The product was prepared starting from 3-bromotoluene (26.0 g) and was purified by distillation.

Colorless oil; yield: 11.8 g (63%); bp 80 °C (0.03 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.60–7.40 (m, 4 H), 7.53 (d, $^1J_{HP}$ = 563.6 Hz, 1 H), 4.16–3.98 (m, 2 H), 2.38 (s, 3 H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 138.33 (d, $^3J_{CP}$ = 13.9 Hz), 133.65 (d, $^4J_{CP}$ = 2.9 Hz), 130.68 (d, $^2J_{CP}$ = 12.4 Hz), 130.29 (d, $^1J_{CP}$ = 128.8 Hz), 128.76 (d, $^3J_{CP}$ = 13.9 Hz), 127.52 (d, $^2J_{CP}$ = 12.4 Hz), 61.76 (d, $^2J_{CP}$ = 6.6 Hz), 20.78 (s), 16.18 (d, $^3J_{CP}$ = 5.9 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.90 (s).

HRMS (Q-TOF MS ES+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}O_2P$: 185.0731; found: 185.0733.

Ethyl (4-Methoxyphenyl)phosphinate (Table 2, Entry 5)[1,11,12]

The product was prepared starting from 4-methoxybromobenzene (28.3 g) and was purified by distillation.

Colorless oil; yield: 10.6 g (53%); bp 110 °C (0.08 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.72–7.62 (m, 2 H), 7.51 (d, $^1J_{HP}$ = 562.3 Hz, 1 H), 7.16–7.08 (m, 2 H), 4.12–3.96 (m, 2 H), 3.83 (s, 3 H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 162.82 (d, $^4J_{CP}$ = 2.9 Hz), 132.60 (d, $^2J_{CP}$ = 13.2 Hz), 121.49 (d, $^1J_{CP}$ = 136.1 Hz), 114.39 (d, $^3J_{CP}$ = 14.6 Hz), 61.46 (d, $^2J_{CP}$ = 6.6 Hz), 55.39 (s), 16.19 (d, $^3J_{CP}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.41 (s).

HRMS (Q-TOF MS ES+): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}O_3P$: 201.0681; found: 201.0678.

Ethyl (3-Methoxyphenyl)phosphinate (Table 2, Entry 6)[1]

The product was prepared starting from 3-methoxybromobenzene (28.1 g) and was purified by distillation.

Colorless oil; yield: 8.7 g (50%); bp 80 °C (0.1 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.54–7.47 (m, 1 H), 7.54 (d, $^1J_{HP}$ = 567.9 Hz, 1 H), 7.31 (ddt, $^3J_{HP}$ = 13.4 Hz, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.3 Hz, 1 H), 7.26 (ddd, $^3J_{HP}$ = 15.7 Hz, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.3 Hz, 1 H), 7.23 (ddd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.3 Hz, 1 H), 4.14–3.98 (m, 2 H), 3.82 (s, 3 H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 159.73 (d, $^3J_{CP}$ = 16.8 Hz), 132.26 (d, $^1J_{CP}$ = 128.8 Hz), 130.80 (d, $^3J_{CP}$ = 16.1 Hz), 122.89 (d, $^2J_{CP}$ = 11.7 Hz), 119.40 (d, $^4J_{CP}$ = 2.9 Hz), 115.57 (d, $^2J_{CP}$ = 13.2 Hz), 62.30 (d, $^2J_{CP}$ = 5.9 Hz), 55.81 (s), 16.64 (d, $^3J_{CP}$ = 5.9 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.54 (s).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_9H_{14}O_3P$: 201.0681; found: 201.0683.

Ethyl (4-Fluorophenyl)phosphinate (Table 2, Entry 7)[1,13]

The product was prepared starting from 4-fluorobromobenzene (30.6 g) and was purified by distillation.

Colorless oil; yield: 9.7 g (53%); bp 72 °C (0.15 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.88–7.76 (m, 2 H), 7.58 (d, $^1J_{HP}$ = 571.9 Hz, 1 H), 7.48–7.40 (m, 2 H), 4.18–3.98 (m, 2 H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 164.90 (dd, $^4J_{CP}$ = 2.9 Hz, $^1J_{CF}$ = 251.0 Hz), 133.59 (dd, $^2J_{CP}$ = 9.5 Hz, $^3J_{CF}$ = 13.9 Hz), 126.78 (dd, $^1J_{CP}$ = 132.1 Hz, $^4J_{CF}$ = 2.9 Hz), 116.17 (dd, $^2J_{CF}$ = 21.2 Hz, $^3J_{CP}$ = 14.6 Hz), 61.92 (d, $^2J_{CP}$ = 5.9 Hz), 16.17 (d, $^3J_{CP}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 23.24 (s).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_8H_{11}FO_2P$: 189.0481; found: 189.0476.

Ethyl (3-Fluorophenyl)phosphinate (Table 2, Entry 8)[1]

The product was prepared starting from 3-fluorobromobenzene (30.6 g) and was purified by distillation

Colorless oil; yield: 10.6 g (56%); bp 64 °C (0.1 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.70–7.50 (m, 4 H), 7.59 (d, $^1J_{HP}$ = 577.8 Hz, 1 H), 4.18–4.00 (m, 2 H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 161.90 (dd, $^1J_{CF}$ = 247.4 Hz, $^3J_{CP}$ = 19.0 Hz), 133.07 (dd, $^1J_{CP}$ = 128.1 Hz, $^3J_{CF}$ = 5.8 Hz), 131.49 (dd, $^3J_{CF}$ = 15.4 Hz, $^3J_{CP}$ = 7.3 Hz), 126.72 (dd, $^2J_{CP}$ = 11.7 Hz, $^4J_{CF}$ = 3.7 Hz), 120.16 (dd, $^4J_{CP}$ = 2.9 Hz, $^2J_{CF}$ = 21.2 Hz), 117.08 (dd, $^2J_{CF}$ = 22.0 Hz, $^2J_{CP}$ = 13.2 Hz), 62.16 (d, $^2J_{CP}$ = 6.6 Hz), 16.16 (d, $^3J_{CP}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 22.68 (d, $^4J_{PF}$ = 7.9 Hz).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_8H_{11}FO_2P$: 189.0481; found: 189.0477.

Ethyl [3-(Trifluoromethyl)phenyl]phosphinate (Table 2, Entry 9)

The product was prepared starting from 3-(trifluoromethyl)bromobenzene (39.4 g) and was purified by distillation.

Colorless oil; yield: 9.4 g (39%); bp 69 °C (0.1 mmHg).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 8.15–8.00 (m, 3 H), 7.90–7.80 (m, 1 H), 7.67 (d, $^1J_{HP}$ = 582.8 Hz, 1 H), 4.22–3.98 (m, 2 H), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 134.70 (d, $^2J_{CP}$ = 11.7 Hz), 132.03 (d, $^1J_{CP}$ = 128.1 Hz), 130.17 (d, $^3J_{CP}$ = 13.2 Hz), 129.62 (pent, $^3J_{CF}$ and $^4J_{PC}$ = 3.3 Hz), 127.11 (dq, $^3J_{CF}$ = 3.7 Hz, $^2J_{CP}$ = 13.2 Hz), 122.99 (q, $^1J_{CF}$ = 272.3 Hz), 62.37 (d, $^2J_{CP}$ = 6.6 Hz), 16.14 (d, $^3J_{CP}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 21.84 (s).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_9H_{11}F_3O_2P$: 239.0449; found: 239.0446.

Ethyl [1,1′-Biphenyl]-4-ylphosphinate (Table 2, Entry 10)[1]

The general procedure described above was applied starting from 4-bromo-1,1′-biphenyl (35.0 g), but after hydrolysis, the title product was purified via a modified process. The oily residue was dissolved in Et_2O (300 mL) and washed with aq $NaHCO_3$ soln (4 × 30 mL, 10%) and H_2O (30 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The resulting solid was triturated with *n*-pentane (3 × 30 mL) and *n*-heptane (2 × 30 mL) at 50 °C, and then dried under vacuum.

White solid; yield: 12.2 g (49%); mp 36–38 °C.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.92–7.78 (m, 4 H), 7.78–7.70 (m, 2 H), 7.61 (d, $^1J_{PH}$ = 567.1 Hz, 1 H), 7.56–7.48 (m, 2 H), 7.47–7.44 (m, 1 H), 4.18–4.02 (m, 2 H), 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 144.50 (d, $^4J_{CP}$ = 2.9 Hz), 138.88 (d, $^5J_{CP}$ = 1.5 Hz), 131.20 (d, $^2J_{CP}$ = 12.4 Hz), 130.31 (d, $^1J_{CP}$ = 117.1 Hz), 129.09 (s), 128.41 (s), 127.14 (s), 127.07 (d, $^3J_{CP}$ = 13.9 Hz), 62.36 (d, $^2J_{CP}$ = 6.6 Hz), 16.73 (d, $^3J_{CP}$ = 5.9 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 24.40 (s).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_{14}H_{16}O_2P$: 247.0888; found: 247.0888.

Ethyl (4-Phenoxyphenyl)phosphinate (Table 2, Entry 11)

The general procedure described above was applied starting from 1-bromo-4-phenoxybenzene (37.4 g). Purification was achieved by treatment of the residue with *n*-pentane (6 × 30 mL) at reflux temperature. The solid obtained was dried under vacuum.

White solid; yield: 13.4 g (51%); mp 31–33 °C.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 7.80–7.68 (m, 2 H), 7.54 (d, $^1J_{PH}$ = 566.1 Hz, 1 H), 7.52–7.40 (m, 2 H), 7.30–7.22 (m, 1 H), 7.18–7.08 (m, 4 H), 4.15–4.08 (m, 2 H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3 H).

^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 166.34 (d, $^4J_{CP}$ = 2.9 Hz), 160.12 (s), 138.26 (d, $^2J_{CP}$ = 13.2 Hz), 135.59 (s), 130.04 (s), 128.70 (d, one transition is missing), 125.25 (s), 122.86 (d, $^3J_{CP}$ = 14.6 Hz), 66.95 (d, $^2J_{CP}$ = 5.9 Hz), 21.45 (d, $^3J_{CP}$ = 6.6 Hz).

^{31}P NMR (161.97 MHz, DMSO-d_6): δ = 23.90 (s).

HRMS (Q-TOF MS ES+): *m/z* [M + H]$^+$ calcd for $C_{14}H_{16}O_3P$: 263.0837; found: 263.0823.

Acknowledgment

Sylvain Bianchi, Eric Gayon and Zofia Dziuganowska are gratefully acknowledged for their practical work.

References

(1) (a) Pirat, J.-L.; Virieux, D.; Clarion, L.; Volle, J.-N.; Bakalara, N.; Mersel, M.; Montbrun, J.; Cristau, H.-J. PCT WO 2009004096, **2009**; *Chem. Abstr.* **2009**, *150*, 98586. (b) Volle, J.-N.; Filippini, D.; Krawczyk, B.; Kaloyanov, N.; Van der Lee, A.; Maurice, T.; Pirat, J.-L.; Virieux, D. *Org. Biomol. Chem.* **2010**, *8*, 1438.

(2) (a) van der Knapp, Th. A.; Klebach, T. h. C.; Lourens, R.; Vos, M.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1983**, *105*, 4026. (b) Yoshifuji, M.; Hirano, M.; Toyota, K. *Tetrahedron Lett.* **1993**, *34*, 1043. (c) Wang, F.; Schwabacher, A. *Tetrahedron Lett.* **1999**, *40*, 7641.

(3) Yoshifuji, M.; Nakazawa, M.; Sato, T.; Toyota, K. *Tetrahedron* **2000**, *56*, 43.

(4) (a) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255. (b) Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206. (c) Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425. (d) Schwabacher, A. W.; Stefanescu, A. D.; Rehman, A. *J. Org. Chem.* **1999**, *64*, 1784.
(5) Schuman, M.; Lopez, X.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299.
(6) (a) Deprèle, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *643-644*, 154. (b) Bravo-Altamirano, K.; Huang, Z.; Montchamp, J.-L. *Tetrahedron* **2005**, *61*, 6315.
(7) Petneházy, I.; Jászay, Z. M.; Szabó, A.; Everaert, K. *Synth. Commun.* **2003**, *33*, 1665.
(8) Sander, M. *Chem. Ber.* **1960**, *93*, 1220.
(9) Xu, H.; Ekoue-Kovi, K.; Wolf, C. *J. Org. Chem.* **2008**, *73*, 7638.
(10) Kiss, N. Z.; Keglevich, G.; Ludanyi, K.; Drahos, L. *Synth. Commun.* **2009**, *39*, 2392.
(11) Vinogradov, L. I.; Zimin, M. G.; Samitov, Y. Y.; Pudovik, A. N. *Zh. Obshch. Khim.* **1972**, *42*, 1724.
(12) Dahn, H.; Van Toan, V.; Ung-Truong, M.-N. *Magn. Reson. Chem.* **1992**, *30*, 1089.
(13) Parsy, C. C.; Alexandre, F.-R.; Surleraux, D.; Derock, M.; Leroy, F. US 2009/0202480, **2009**; *Chem. Abstr.* **2009**, *151*, 267307.