Pergamon

Tetrahedron Letters 42 (2001) 6121–6124

TETRAHEDRON
LETTERS

One-pot synthesis of unsymmetrical aryl methylphosphinates by insertion of dichlorophosphines into the O–Me bond of anisoles

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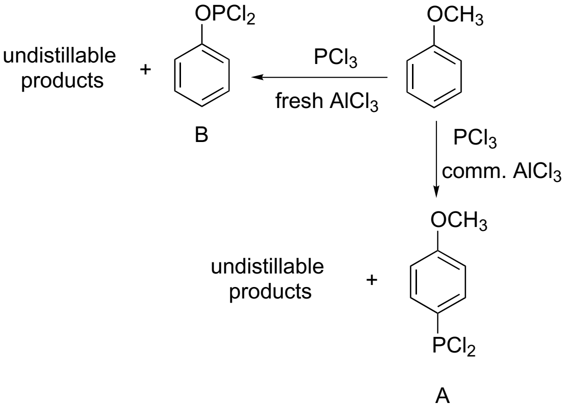
Received 21 June 2001; accepted 4 July 2001

Abstract—This letter describes a new one-pot method for the synthesis of unsymmetrical aryl methylphoshinates by insertion of phosphorus moiety into the O–Me bond of anisoles. These products are very difficult to obtain with other reported methods requiring several steps. © 2001 Elsevier Science Ltd. All rights reserved.

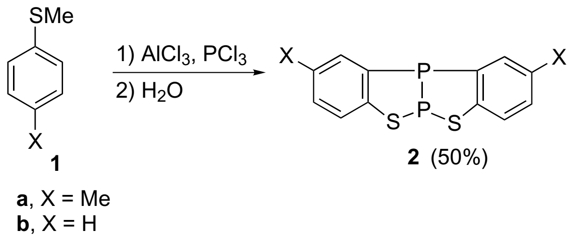
Since the last century, the Friedel–Crafts type reaction using PCl_3 and $AlCl_3$ has been an excellent method for the direct attachment of a phosphorus atom to an aromatic ring to give aryldichlorophosphines or diarylchlorophosphines. However, this reaction is very sensitive to the type of substituents present on the aromatic ring[1,2] and often the literature gives conflicting results.[3,4] In particular, it is reported[4a] that anisole, upon treatment with phosphorus trichloride and aluminum chloride, afforded *p*-anisylphosphonous dichloride (A) but in very poor yields and with large amounts of undistillable residues while in some cases it gave phenyl dichlorophosphite (B) but always in poor yields. In addition, it is reported[4a,b] that this phosphonation reaction fails completely when thioanisoles are used (Scheme 1).

In contrast to these reported results, in the past years, we discovered[5] that the reaction of PCl_3 and $AlCl_3$ with thioanisoles **1** gave, unexpectedly, the new fused-bicyclic system[6] **2** (fused 1,2,3-benzothiadiphosphole) in good yields (see Scheme 2).

Recently, analyzing the above reported[4] data on anisoles and our results[5] on thioanisoles we decided to reinvestigate the reaction of anisoles with the couple PCl_3/$AlCl_3$, in order to verify whether the reported[3,4] large amounts of undistillable residues and the conflictuality of the reported results might be due to the formation of heterocyclic compounds related to **2** or of other unexpected products. In fact, we found that varying the reagent ratios and the reaction conditions we have been able to obtain, as prevalent product (30–40% yield), the benzooxadiphosphole systems **4** and **5** (Scheme 3) using a ratio of **3a**:$AlCl_3$:PCl_3 of 1:0.6:7



Scheme 1.



Scheme 2.

Keywords: phosphorylations; insertions; Lewis acids.

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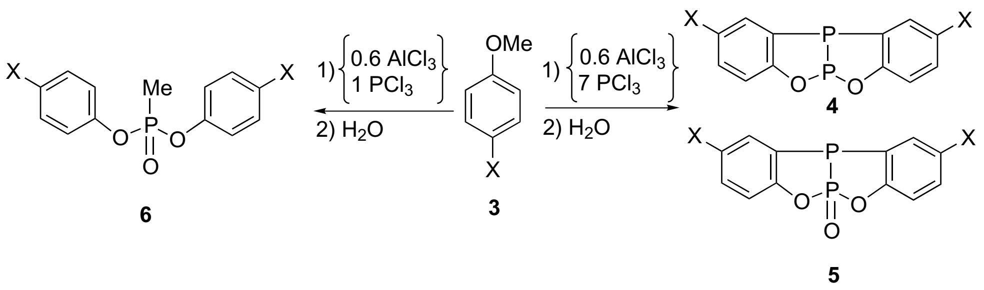
PII: S0040-4039(01)01197-2

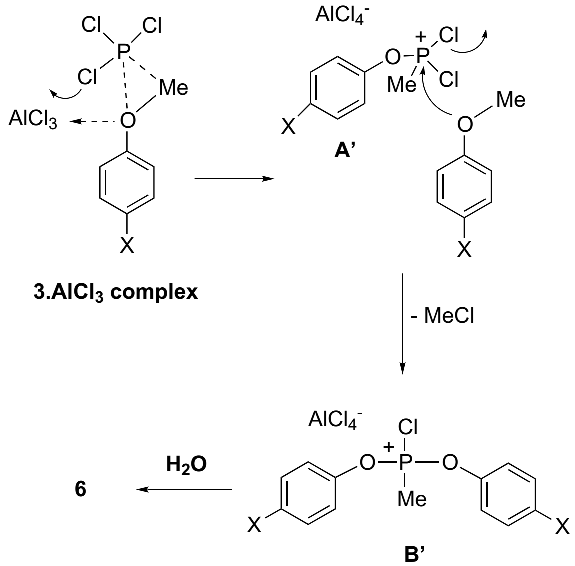


Scheme 3.

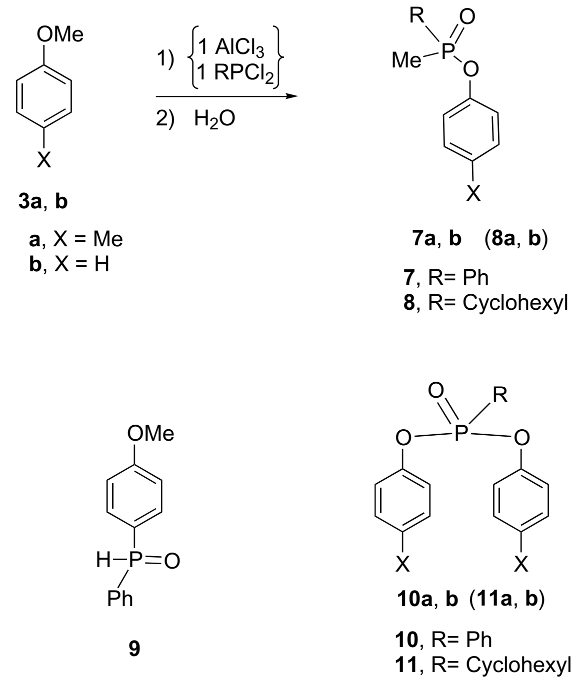
and refluxing for about 20–25 h without solvent. After several studies to understand the structure of the other by-products, we found[7,8] that, when the reaction is carried out in appropriate reaction conditions, an unexpected 'insertion' of the phosphorus moiety into the O–Me bond of anisole **3** occurs, to give compound **6** as the major product (Scheme 3). The best selective formation of **6** (50–70% yield) was obtained with anisole **3**: $AlCl_3$:PCl_3 ratio of 1:0.6:1, at 70–80°C for 7–10 h in an atmosphere of dry nitrogen and without solvent.

A suggested mechanism, depicted in Scheme 4, for this phosphorus insertion reaction was also reported.[7] The insertion of the P moiety is explained by the attack of a molecule of PCl_3 on the anisole–$AlCl_3$ complex and subsequent migration of the methyl group on the same P atom giving the intermediate **A′**. Subsequent nucleophilic attack of free anisole on phosphonium salt **A′** gives **B′** which, after quenching with water, gives phosphonate **6**.

Now, analyzing the above results, we decided to investigate the reaction of anisoles **3** with the couple $RPCl_2$/$AlCl_3$, in order to verify whether the insertion of the P moiety into the O–Me bond of anisole may occur also with dichlorophosphines $RPCl_2$. In this manner it should be possible to obtain in a one-pot procedure racemic methylphosphinates such as **7** or **8** (see Scheme 5), which are very difficult to obtain with simple procedures. In fact, it should be noted that the aryl methylphenylphosphinates **7** are known but their synthesis[9] requires complex procedures involving several steps, as described in Scheme 6, while compounds **8** are still unknown.

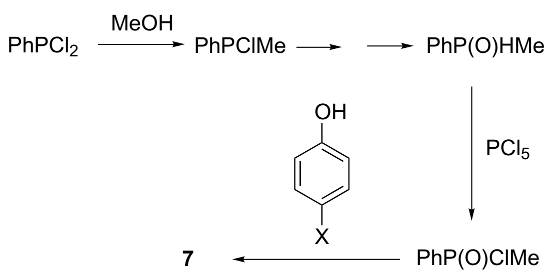


Scheme 4.



Scheme 5.

When we used $RPCl_2$ with R = cyclohexyl, the reaction led to the formation of the corresponding aryl cyclohexylmethylphoshinates **(8a,b)** in good yields. When we used $PhPCl_2$ we obtained a good formation of **7a** (50%) but small amounts of **7b** (20%). In this case the formation



Scheme 6.

of phosphinoxide **9** (40%) is preferred due to the competitive attack on the para position of anisole. The best selective formation of **7** or **8** was obtained with anisole **3a**:$AlCl_3$:$RPCl_2$ ratio of 1:1:1, at room temperature for 30–35 h or at 60°C for 4–6 h in an atmosphere of dry nitrogen and without solvent. Compounds **10** or **11** were obtained in small amounts as by-products. When we used a ratio of anisole **3**:$AlCl_3$:$RPCl_2$ of 2:1:1, we obtained a good formation of diarylphosphonate **10** or **11** (45–60%). In all cases, the structures were assigned by comprehensive spectral data.[10]

In conclusion we have found that insertion of the phosphorus moiety into the O–Me bond of anisoles can occur also with $RPCl_2$. In this manner the reaction permits to obtain in a one-pot reaction at room temperature racemic methylphosphonates which are very difficult to obtain with other reported methods.

Acknowledgements

Investigation supported by University of Bologna (funds for selected research topics A.A. 1999–2001), Ministero dell' Università e della Ricerca Scientifica e Tecnologica (MURST, Roma), Consiglio Nazionale delle Ricerche (CNR, Roma).

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10. *Typical procedure*: *p*-Methylanisole (**3b**) (0.007 mol), $AlCl_3$ (1.2 g, 0.009 mol), and dichlorophenylphosphine (0.007 mol) were placed in a dried apparatus, filled with dry nitrogen. The mixture was stirred at room temperature and the reaction was monitored both by TLC and GC–MS analyses. After about 30–35 h the reaction mixture was diluted with 25 mL of dichloromethane, then it was quickly treated with water and extracted. The organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed. A quick flash chromatography of the residue gave compounds **7a** in 50% yield.

4-Methylphenyl methyl(phenyl)phosphinate (7a): mp 65–67°C (lit.[9] 66–67°C), $R_f = 0.20$ (light petroleum:ethyl acetate = 1:1), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.90–7.80 (m, 2H), 7.60–7.40 (m, 3H), 7.05–6.95 (m, 4H), 2.26 (s, 3H, *p*-CH_3), 1.84 (d, 3H, $^2J_{P-H} = 14.4$ Hz, PCH_3); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 148.5 (d, 1C, $J = 9.0$ Hz), 134.2 (s, 1C), 132.5 (d, 1C, $J = 2.3$ Hz), 131.3 (d, 2C, $J = 10.6$ Hz), 130.1 (s, 2C), 128.6 (d, 2C, $J = 13.0$ Hz), 120.4 (d, 2C, $J = 4.5$ Hz), 115.6 (d, 1C, $J = 75.7$ Hz), 20.7 (s, 1C), 16.0 (d, 1C, $J = 102.2$ Hz); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 41.8 (m); MS (70 eV, EI): m/z (%): 246 (M^+, 52), 245 (M^+–1, 100), 139 (67), 91 (20), 77 (49), 41 (3); HRMS: calcd for $C_{14}H_{15}O_2P$: 246.0810. Found: 246.0808; calcd C, 68.29; H, 6.14; found C, 68.32, H, 6.12.

4-Methylphenyl cyclohexyl(methyl)phosphinate (8a): 60% yield as greasy solid, $R_f = 0.13$ (light petroleum:ethyl acetate = 6:4), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.15–7.05 (m, 4H), 2.31 (s, 3H, *p*-CH_3), 2.14–2.00 (m, 2H), 1.92–1.78 (m, 3H), 1.78–1.68 (m, 1H), 1.47 (d, 3H, $^2J_{P-H} = 13.0$ Hz, PCH_3), 1.50–1.20 (m, 5H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 148.6 (d, 1C, $J = 9.1$ Hz), 134.0 (s, 1C), 130.1 (s, 2C), 120.2 (d, 2C, $J = 3.8$ Hz), 38.5 (d, 1C, $J = 96.2$ Hz), 26.0 (d, 2C, $J = 14.9$ Hz), 25.7 (s, 1C), 25.4 (dd, 2C, $J = 8.0$ Hz, $J = 2.9$ Hz), 20.6 (s, 1C), 10.7 (d, 1C, $J = 87.3$ Hz); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 57.3 (m); MS (70 eV, EI): m/z (%): 252 (M^+, 91), 197 (M^+– 55, 99), 170 (84), 155 (100), 108 (35), 91 (46); HRMS: calcd for $C_{14}H_{21}O_2P$: 252.1279. Found: 252.1275; calcd C, 66.65; H, 8.39; found C, 66.60; H, 8.37.

Phenyl cyclohexyl(methyl)phosphinate (8b): greasy solid, 40% yield, $R_f = 0.20$ (light petroleum:ethyl acetate = 1:1), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.38–7.25 (m, 2H), 7.24–7.10 (m, 3H), 2.15–2.00 (m, 2H), 1.95–1.80 (m, 2H), 1.80–1.70 (m, 1H), 1.49 (d, 3H, $^2J_{P-H} = 13.0$ Hz, PCH_3), 1.60–1.10 (m, 6H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 151.0 (d, 1C, $J = 9.1$ Hz), 129.7 (s, 2C), 124.5 (s, 1C), 120.6 (d, 2C, $J = 4.1$ Hz), 38.6 (d, 1C, $J = 96.3$ Hz), 26.1 (d, 2C, $J = 14.9$ Hz), 25.7 (d, 1C, $J = 1.2$ Hz), 25.5 (dd, 2C, $J = 7.2$ Hz, $J = 3.0$ Hz), 10.9 (d, 1C, $J = 87.2$ Hz); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 58.1 (m); MS (70 eV, EI): m/z (%): 238 (M^+, 66), 183 (M^+–55, 100), 141 (82), 94 (37), 77 (74), 41 (69); HRMS: calcd for $C_{13}H_{19}O_2P$: 238.1123. Found: 238.1120; calcd C, 65.53; H, 8.04; found C, 65.50; H, 8.07.

(4-Methoxyphenyl)phenylphosphine oxide (9): mp 68–70°C, lit. [11]69–70°C, ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 1H, $^1J_{P-H} = 481$ Hz), 7.80–6.90 (m, 9H), 3.85 (s, 3H, OCH_3), ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 21.7 (dm, $^1J_{P-H} = 481$ Hz); MS (70 eV, EI): m/z (%): 232 (M^+, 100), 231 (M^+–1, 92), 155 (13), 154 (14), 139 (7), 108 (45), 92 (10), 77 (29); HRMS: calcd for $C_{13}H_{13}O_2P$: 232.0653. Found: 232.0656; calcd C, 67.24; H, 5.64; found C, 67.20; H, 5.67.

Bis(4-methylphenyl) phenylphosphonate (10a): greasy solid, 60% yield, $R_f = 0.80$ (light petroleum:ethyl acetate = 1:1), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00–7.88 (m, 2H, arom.), 7.65–7.55 (m, 1H, arom.), 7.55–7.45 (m, 2H, arom.), 7.15–7.05 (m, 8H, arom.), 2.29 (s, 6H, CH_3); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 148.1 (d, $J = 7.7$ Hz), 134.6 (s), 133.1 (d, $J = 3.1$ Hz), 132.3 (d, $J = 10$ Hz), 130.1 (s), 128.6 (d, $J = 15.6$ Hz), 126.9 (d, $J = 192.2$ Hz), 120.3 (d, $J = 4.6$ Hz), 20.7 (s); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 12.16 (t, $J_{PH} = 13.5$ Hz, P); MS (70 eV, EI): *m/z* (%): 338 (M^+, 96), 337 (M^+–1, 100), 231 (44), 198 (24), 108 (17), 91 (80), 65 (47); HRMS: calcd for $C_{20}H_{19}O_3P$: 338.1072. Found: 338.1074; calcd: C, 71.00; H, 5.66; found C, 71.05; H, 5.64.

Bis(4-methylphenyl) cyclohexylphosphonate (11a): greasy solid, 55% yield, $R_f = 0.73$ (light petroleum:ethyl acetate = 6:4), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.20–6.95 (m, 8H), 2.27 (s, 6H, CH_3), 2.25–2.00 (m, 3H), 2.00–1.80 (m, 2H), 1.80–1.70 (m, 1H), 1.70–1.45 (m, 2H), 1.40–1.15 (m, 3H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 148.3 (d, 2C, $J = 9.5$ Hz), 134.3 (s, 2C), 130.0 (s, 4C), 120.1 (d, 4C, $J = 4.1$ Hz), 35.9 (d, 1C, $J = 141.5$ Hz), 25.9 (d, 2C, $J = 17.1$ Hz), 25.64 (d, 2C, $J = 6.6$ Hz), 25.60 (d, 1C, $J = 1.8$ Hz), 20.6 (s, 2C); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 26.7 (m); MS (70 eV, EI): *m/z* (%): 344 (M^+, 71), 289 (M^+–55, 26), 155 (20), 108 (100), 91 (21), 55 (42), 41 (31); HRMS: calcd for $C_{20}H_{25}O_3P$: 344.1541. Found: 344.1539; calcd C, 69.75; H, 7.32; found C, 69.70; H, 7.30.

Diphenyl cyclohexylphosphonate (11b): 50% yield, mp: 62–63°C, lit.[12] 62°C, $R_f = 0.81$ (light petroleum:ethyl acetate = 1:1), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.20 (m, 4H), 7.20–7.05 (m, 6H), 2.30–2.00 (m, 3H), 1.95–1.80 (m, 2H), 1.80–1.45 (m, 3H), 1.45–1.20 (m, 3H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm): 150.5 (d, 2C, $J = 9.7$ Hz), 129.6 (s, 2C), 124.9 (d, 4C, $J = 1.1$ Hz), 120.5 (d, 4C, $J = 4.3$ Hz), 36.0 (d, 1C, $J = 141.5$ Hz), 25.9 (d, 2C, $J = 17.1$ Hz), 25.74 (d, 2C, $J = 4.9$ Hz), 25.62 (d, 1C, $J = 1.6$ Hz); ^{31}P NMR (120.75 MHz, $CDCl_3$) δ (ppm): 27.0 (m); MS (70 eV, EI): *m/z* (%): 316 (M^+, 78), 261 (M^+–55, 31), 140 (22), 94 (100), 55 (50), 41 (40); HRMS: calcd for $C_{18}H_{21}O_3P$: 316.1228. Found: 316.1224; calcd C, 68.34; H, 6.69; found: C, 68.30; H, 6.67.

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