New Feature of Friedel-Crafts Phosphonation of Anisoles: Unexpected *In Situ* Methylphosphorylation Reaction

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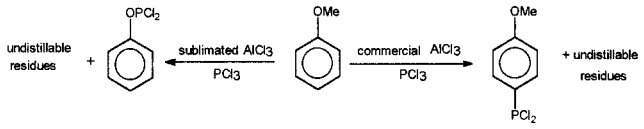
Received 8 February 1999

Abstract: Anisoles **1,** reacting with $AlCl_3$ and PCl_3 with appropriate reagent ratios, give, in good yields, the corresponding diaryl methylphosphonates **2** or the methylphoshinates **3b**,**c** and the methylphosphine oxides **4b**,**c**. This unexpected in situ methylphosphorylation explains the reported limited and conflicting results to obtain methoxy-substituted arylphosphonous dichloride with the same reagents. A suggested mechanism is also reported.

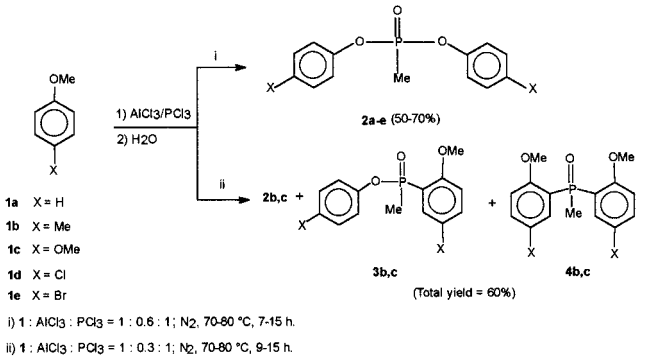
Key words: anisoles, Friedel-Crafts reactions, phosphorylation, phosphorus compounds, phosphorus trichloride

Since the last century, the Friedel-Crafts-type reaction[1] using PCl_3 and $AlCl_3$ has been of interest for the direct phosphonation of an aromatic ring. However, this reaction is very sensitive to the type of substituents present on the aromatic ring.[2] In particular, very limited success and conflicting results have been reported when the reaction is carried out with anisoles. For example, anisole,[3,4] upon treatment with PCl_3 and $AlCl_3$ gave complex reaction mixtures depending on the quality of $AlCl_3$ with poor yields of methoxy-substituted arylphosphonous dichloride or phenylphosphorodichloridite and large amounts of undistillable residues:



To increase the yield and the selectivity of this phosphonation reaction the use[4a] of $SnCl_4$ and very recently the use[4c] of $BiCl_3$ have been reported. In the past years we discovered[5] an unusual reaction of PCl_3 and $AlCl_3$ with thioanisoles which gave a new heterocyclic system (fused 1,2,3-benzothiadiphosphole) containing the P-PS_2 unit. Recently, the course of this unexpected diphosphonation reaction has been studied[6] and we have found that the reaction follows a complex multistep pathway which was a priori unpredictable and that the outcome of the reaction is very dependent on the ratio of the reagents and on the good quality of $AlCl_3$ (sublimated prior to use) which in this reaction is a true reagent and not a catalyst.

Then, we thought to study again the reaction of anisoles **1** with $AlCl_3$ and PCl_3, in order to find results which might explain the reported[3,4] formation of large amounts of undistillable residues. Several reactions were carried out with various molar proportions of reagents and different reaction conditions. The reaction of **1b** with an appropriate ratio of the reagents, afforded a mixture containing as major products the corresponding diaryl methylphosphoryl derivatives **2b**, **3b** and **4b** arising from an unexpected in situ methylphosphorylation (Scheme1).



Scheme 1

After several repeated attempts with small variations of reagent ratios and reaction conditions we could control the regiochemistry of this methylphosphorylation reaction in order to obtain mainly the diaryl methylphosphonates **2** (see Scheme 1). The best results were obtained with a **1:** $AlCl_3$: PCl_3 ratio of 1:0.6:1, at 70-80 °C in atmosphere of dry nitrogen and without solvent (Table 1). In the case of **1c** the reaction was complete in 7 h while in the other cases in about 10-15 h. A stoichiometric excess of PCl_3 was useful also to ease the stirring and the homogeneity of the reaction mixture. Compounds **2** have been fully characterised[7] by ^1H and ^{31}P NMR and spectral data of **2a**,**b**,**c**,**d** were in accord with existing literature data.[8] When the reaction was run with **1b**,**c** and a reagent ratio of 1:0.3:1, with the same sublimated $AlCl_3$, methylphosphinates **3b**,**c** and methyl phosphine oxides **4b**,**c**, respectively, were also formed as major products in a total yield of about 60% besides small amounts of the expected **2b**,**c** (Table 1). In contrast, when the reaction was run on **1a**,**d**,**e** the major product observed is always the corresponding methyl phosphonate **2a**,**d**,**e** but in lower yield**,** and no appreciable amount of the related ring substituted products **3** and **4** is detected.

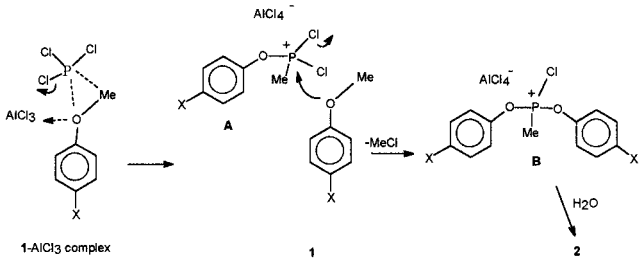
Table 1.

Anisole	Reagent ratio 1:0.6:1		Reagent ratio 1:0.3:1	
	Reaction time (h)	Products (yield%)	Reaction time (h)	Products (yield%)
1a	10	**2a** (70)	15	**2a** (30)
1b	12	**2b** (50) **3b** (5)	10	**2b** (5) **3b** (48) **4b** (13)
1c	7	**2c** (60) **3c** (4)	9	**2c** (8) **3c** (45) **4c** (15)
1d	13	**2d** (55)	15	**2d** (20)
1e	15	**2e** (50)	15	**2e** (20)

This could be due to the fact that the presence of the methyl or methoxy substituent activates the aromatic ring towards electrophilic substitution. The products **3b**,**c** and **4b**,**c** have been separated by flash chromatography on silica gel and have been fully characterised.[7]

The major issue was to determine whether products **3b** and **4b** are *ortho* or *meta* substituted with respect to the Me substituent. As reported in the literature,[4a] a methyl group *ortho* to a P atom should show a significant coupling. In our case no coupling was observed, in agreement with the structures we are reporting. NOE experiments obtained by irradiating the methyl group, further confirmed our assignment.

Probably, compounds **2**,**3**,**4** might be a part (or all) of the so-called undistillable residues reported previuosly.



Scheme 2

In order to obtain supporting evidences for a possible pathway of this unexpected methylphosphorylation, aliquots of a reaction mixture between **1c**, $AlCl_3$ and PCl_3 were analyzed by ^{31}P NMR spectroscopy. After severals minutes the ^{31}P NMR spectrum showed only the signal of PCl_3 (δ = 219.2 ppm).[9] After 3h we noted two prevalent strong signals at δ = 178 and 104 ppm as broad quartets. During the reaction no signal corresponding to $MePCl_2$ (δ = 192.1 ppm) or its complexes (δ = 131.9 and 97.5 ppm)[9] was observed indicating a possible concerted mechanism involving the migration of the methyl group on the phosphorus atom, as depicted in Scheme 2. At the end of the reaction we noted the prevalence of the second signal and after addition of water we noted the disappearance of the above two signals and the appearance of the signal of **2c**. Thus, the two signals might be assigned to intermediates **A** and **B** (Scheme 2), although more unequivocal data are necessary for their exact structural determination. However, their shifts are consistent with their ionic representation.[9] Evidence for the initial equilibrium:

1 + $AlCl_3$ ⇌ **1**-$AlCl_3$ complex

comes from the ^1H NMR spectrum of the $AlCl_3$-anisole $CDCl_3$ solution at 60 °C: the methoxy and aromatic protons are shifted selectively downfield, relative to anisole alone.

Diaryl methylphosphonates **2** are useful as both enzyme model substrates,[10] fungicides[11] and reactive intermediates.[12] The literature describes two basic routes for their preparation. One involves the condensation of methylphosphonic dichloride with the appropriately substituted phenol.[13] The second procedure consists of reacting a triarylphosphite with methyl iodide alone[14] or in methanolic solution[8] for 3 h at 200-250 °C. It should be noted that methylphosphonic dichloride is not readily available while in the second procedure the reaction temperature does not permit to obtain the corresponding *p*-halogen diaryl methylphosphonates in good yields. In our procedure, lower temperatures (70-80 °C) allow to obtain these halogen derivatives **2d**,**e** in good yields.

In conclusion, we have found that the reaction of anisoles **1** with $AlCl_3$ and PCl_3, with adequate reagents ratio, lead to the diaryl methylphosphonates **2a-e** or the methylphosphinates **3b**,**c** and the methylphosphine oxides **4b**,**c** in good yields. Formation of these compounds is due to a new unexpected in situ methylphosphorylation which could be useful for obtaining other new P-methyl substituted compounds and gives also an explanation about the limited success in the phosphonation of anisoles obtained so far with the same reagents.

Acknowledgement

Investigation supported by University of Bologna (funds for selected research topics A.A 1997-1999). Thanks are also due to Consiglio Nazionale delle Ricerche (CNR), Italy, for financial support.

References and Notes

(1) Michaelis, A. *Chem.Ber*., **1879**, *12*, 1009.
(2) Fild, M.; Schmutzler, R. In *Organic Phosphorus Compounds*, Vol.4, G. Kosolapoff and L.Maier Eds., Wiley-Interscience, 1972, p 79.
(3)(a) Michaelis, A. *Justus Liebigs Ann.Chem*., **1896**, *294*, 1. (b) Kunz, P. *Ber*., **1894**, *27*, 2559
(4) (a) Miles, J. A.; Beeny, M. T.; Ratts. K.W. *J.Org.Chem*., **1975**, *40*, 343. (b) Engel, R. In *Synthesis of Carbon-Phosphorus Bonds*, CRC Press, Inc. Boca Raton, Florida, 1988, chap.5 and 6. (c) Siméon, F.; Jaffrès, P.; Villemin, D. *Tetrahedron* **1998**, *54*, 10111.
(5) (a) Baccolini, G.; Mezzina, E.; Todesco, P.E.; Foresti, E. *J.Chem.Soc.,Chem.Commun*., **1988**, 304. (b) Baccolini, G.;

Mezzina, E.; Todesco, P.E. *J. Chem.Soc.,Perkin Trans.1*, 1988, 3281.
(6) Baccolini,G.; Beghelli, M.; Boga, C. *Heteroatom Chem.* **1997**, 551.
(7) **General procedure for preparation of 2a-e, 3b,c and 4b,c**
A solution of 0.1 mol of anisole **1**, 0.1 mol (8.7 mL) of phosphorus trichloride, and 0.06 mol of aluminum trichloride (sublimated prior to use) was refluxed (70-80 °C) and stirred under dry nitrogen for specified lenght of time (see Table 1). At the end, the reaction mixture appeared as a viscous oil, which was treated with a mixture of ice and dichloromethane; the organic layer was washed with a 5% aq. NaOH solution and two times with water. After removal of the solvent, compounds **2** were separated by distillation under reduced pressure or by flash chromatography in 50-70% yield.
In similar manner compounds **3b**,**c**, and **4b**,**c** were obtained using a **1b**,**c** : $AlCl_3$: PCl_3 ratio of 1:0.3:1.
Selected spectral data for new compounds **2e**, **3b**,**c** and **4b**,**c**
All gave satisfactory elemental analyses. Yields are not optimized. The ^{31}P signals are given in ppm downfield from 85% H_3PO_4.
2e as viscous oil, ^1H NMR(300MHz, $CDCl_3$): δ(ppm) 7.44(dd, 4H, *J* = 9.1, *J* = 0.7 Hz), 7.07(dd, 4H, *J* = 9.1, *J* = 1.4 Hz), 1.81 (d, 3H, *J* = 17.7 Hz); ^{31}P NMR(121.47 MHz, $CDCl_3$): δ(ppm) 25.3 (bq, *J* = 17.7 Hz), HRMS: Found, 403.8810, Calc. for $C_{13}H_{11}Br_2O_3P$, 403.8812.
3b as viscous oil, ^1H NMR(300MHz, $CDCl_3$): δ(ppm) 7. 75 (dd, 1H, *J* = 13.7, *J* = 2.4 Hz), 7.29(dd, 1H, *J* = 8.2, *J* = 2.4 Hz), 7.15 (bs, 4H), 6.81 (dd, 1H, *J* = 8.2 Hz, *J* = 7.2 Hz), 3.90 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 1.88 (d, 3H, *J* = 15.4 Hz); ^{31}P NMR(121.47 MHz, $CDCl_3$): δ(ppm) 40.8 (quintet of doublets, *J* = 15.4 Hz, *J* = 7.2 Hz); HRMS: Found, 290.1071, Calc. for $C_{16}H_{19}O_3P$, 290.1072.
3c as viscous oil,^1H NMR (300MHz, $CDCl_3$): δ(ppm) 7. 46 (dd, 1H, *J* = 14.4, *J* = 3.2 Hz), 7.05(dd, 1H, *J* = 9.1, *J* = 3.2 Hz), 7.01-6.8 (m, 4H), 6.72 (dd, 1H, *J* = 9.1 Hz, *J* = 6.8 Hz), 3.88 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 1.89 (d, 3H, *J* = 15.4 Hz); ^{31}P NMR(121.47 MHz, $CDCl_3$): δ(ppm) 40.9 (broad quintet, *J* = 15.4 Hz); HRMS: Found, 322.0967, Calc. for $C_{16}H_{19}O_5P$, 322.0970.
4b as greasy solid, ^1H NMR(300MHz, $CDCl_3$): δ(ppm) 7.44 (dd, 2H, *J* = 14.0 Hz, *J* = 3.7 Hz), 7.27 (m, 2H), 6.81 (dd, 2H, *J* = 8.4 Hz, *J* = 5.5 Hz), 3.70 (s, 6H), 2.28 (s, 6H), 2.10 (d, 3H, *J* = 14.6 Hz); ^{31}P NMR(121.47 MHz, $CDCl_3$): δ(ppm) 30.48 (m); HRMS: Found, 304.1222, Calc. for $C_{17}H_{21}O_3P$, 304.1228.
4c as greasy solid, ^1H NMR(300MHz, $CDCl_3$): δ(ppm) 7.23 (dd, 2H, *J* = 14.8 Hz, *J* = 2.8 Hz), 7.03 (dd, 2H, *J* = 8.9Hz, *J* = 2.8Hz), 6.81 (dd, 2H, *J* = 8.9 Hz, *J* = 7.4 Hz), 3.76 (s, 6H), 3.70 (s, 6H), 2.15 (d, 3H, *J* = 14.6 Hz); ^{31}P NMR(121.47 MHz, $CDCl_3$): δ(ppm) 30.30 (m); HRMS: Found, 336.1122, Calc. for $C_{17}H_{21}O_5P$, 336.1127.

(8) Honig, M.L.; Weil, E.D. *J.Org.Chem*., **1977**, *42*, 379.
(9) Symmes, C., Jr.; Quin, L.D. *J.Org.Chem*., **1978**, *43*, 1250.
(10) Brass, H. J.; Bender, M. L., *J Am. Chem. Soc*., **1973**, *95*, 5391.
(11) Roy, N.K.; Nidiry, E.S.; Vasu, K.; Bedi, S.; Lalljee, B.; Singh, B. *J.Agric.Food Chem*., **1996**, *44*, 3971.
(12) Coover Jr. H.W.; McConnell, L.R.; McCall, M.A. *Ind.Eng.Chem*. **1960**, *52*, 409.
(13) Hoskin, F.C. *Can. J. Chem*., **1957**, *35*, 581.
(a) Michaelis, A.; Kaehne, R. *Ber*., **1898**, *31*, 1048. (b) Behrman, E.J.; Biallas, M.J.; Brass, H.J.; O'Edwards, J.; Isaks, M. *J.Org.Chem.* **1970**, *35*, 3063.

Article Identifier:
1437-2096,E;1999,0,06,0822,0824,ftx,en;G06999ST.pdf