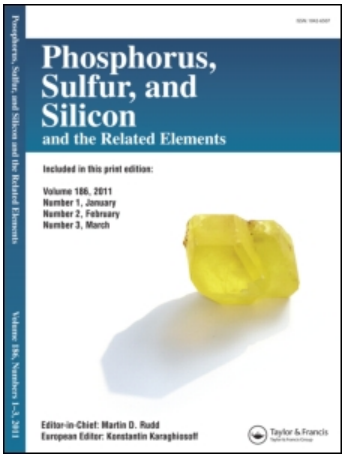

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Friedel-Crafts Reaction of Dimethyl 2-Oxopropylphosphonate and Diethyl 2,2-Diethoxyethylphosphonate With Electron-Rich Arenes

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Friedel-Crafts Reaction of Dimethyl 2-Oxopropylphosphonate and Diethyl 2,2-Diethoxyethylphosphonate With Electron-Rich Arenes

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Dimethyl 2-oxopropylphosphonate and diethyl 2,2-diethoxyethylphosphonate react with electron-rich arenes such as phenol, anisole, 1,3-dimethoxybenzene, and 1-methylpyrrole in the presence of trifluoromethanesulfonic acid to afford β,β-diarylphosphonates in moderate to good yield. The minor products observed in some cases are β-aryl-α,β-unsaturated phosphonates.

Keywords β-Ketophosphonate; Friedel-Crafts reaction; trifluoromethanesulfonic acid

The chemistry of β-ketophosphonates has been thoroughly studied and it has been found that these compounds are versatile starting materials in the syntheses of a variety of products.[1] However, surprisingly little is known about the reactivity of β-ketophosphonates under strongly acidic conditions, i.e., when extensive protonation of both functional groups of these compounds takes place.

We have recently reported[2] that β-ketophosphonates and β,β-dialkoxyethylphosphonates (masked 2-formylphosphonates) react with ferrocene in the presence of trifluoromethanesulfonic or methanesulfonic acid to afford (*E*)-β-ferrocenyl-α,β-unsaturated phosphonates in good yields and excellent stereoselectivity (Scheme 1).

It is now well established that ferrocene behaves in many reactions as an electron-rich arene,[3] reacting even with relatively weak electrophiles, e.g., with CO_2 activated by $AlCl_3$[4,5] or protonated aldehydes and ketones[6,7] in Friedel-Crafts type reactions. The reactions shown in Scheme 1 undoubtedly involve protonated β-ketophosphonates or β,β-dialkoxyethylphosphonates acting as electrophilic reagents, although

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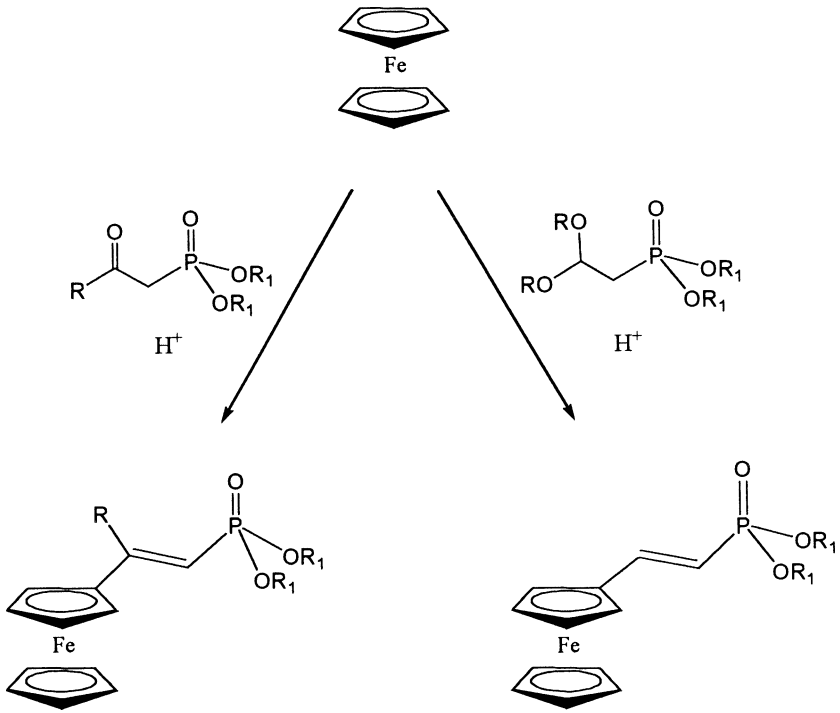


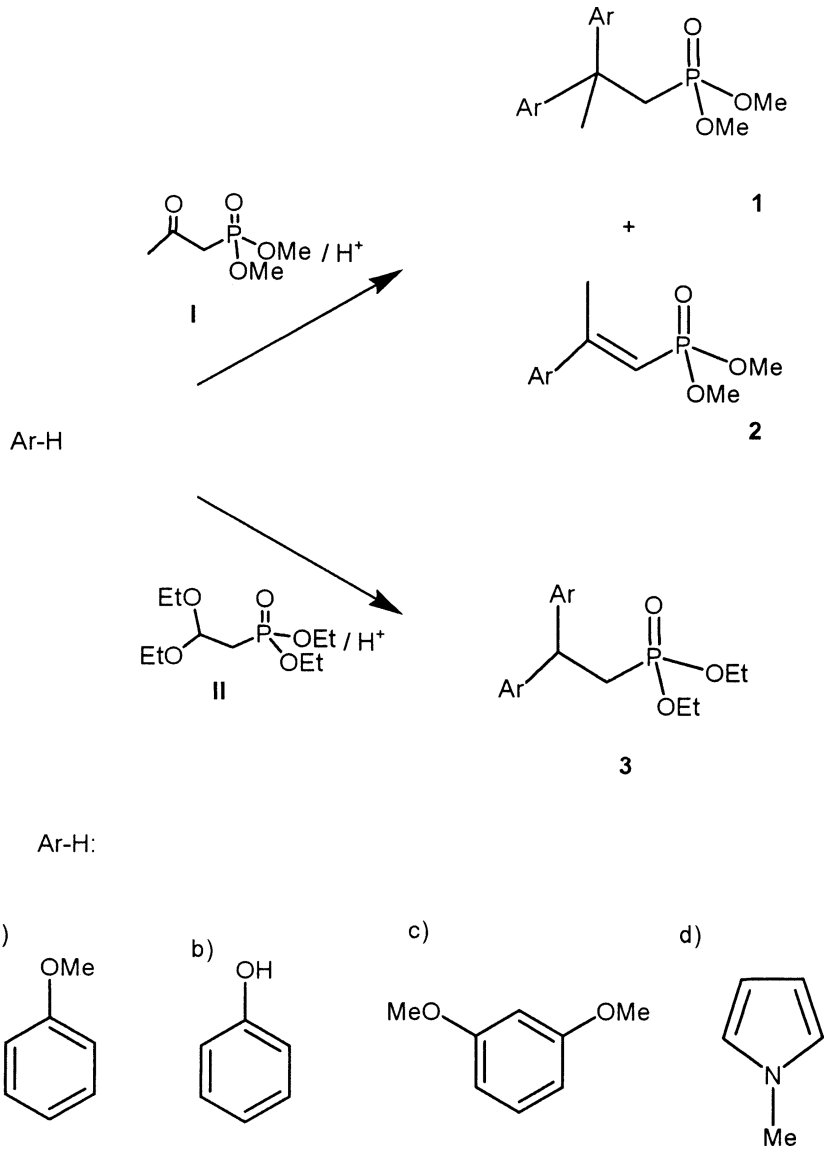
SCHEME 1

the exact structure of such species remains unknown. We therefore wondered whether the reaction represented in Scheme 1 would also take place with organic electron-rich arenes or heteroarenes, such as phenols and their alkyl ethers, or pyrroles. Synthesis of aryl- and heteroaryl alkenyl phosphonates is of obvious synthetic interest because these compounds can be used as starting materials in further syntheses.[8–12]

Herein we report that dimethyl 2-oxopropylphosphonate (**I**) and diethyl 2,2-diethoxyethylphosphonate (**II**) react in an acidic medium with phenol, anisole, 1,3-dimethoxybenzene, and 1-methylpyrrole in a different manner than they react with ferrocene, the main products of these reactions being β, β-diarylphosphonates (Scheme 2).

RESULTS AND DISCUSSION

Reactions of **I** and **II** with arenes, shown in Scheme 2, were carried out in dichloromethane containing trifluoromethanesulfonic acid at r.t. at various molar ratios of reactants (Table I). In the case of anisole at the molar ratio of anisole to **I** equals 1:1.1, according to ^{1}H and ^{31}P NMR,



SCHEME 2

a 3:1 mixture of the diarylated phosphonate **1a** and the unsaturated phosphonate **2a** was formed in a 64% yield. At the molar ratio anisole to **I** of 2.2:1, the formation **2a** totally was suppressed and compound **1a** was obtained in a 51% yield. The further increase of this ratio to 4:1 brought

TABLE I Reaction of Electron-Rich Arenes with Dimethyl 2-oxopropylphosphonate (I) and Diethyl 2,2-Diethoxyethylphosphonate (II) in an Acidic Medium[a]

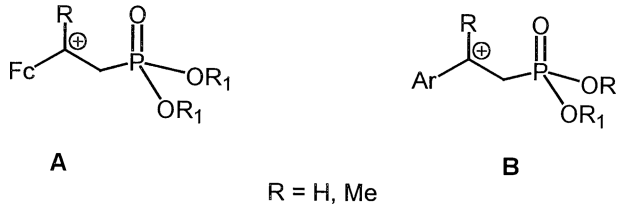
Arene (mmol)	Phosphonate (mmol)	Product(s)	Yield (%)
Anisole (1)	**I** (1.1)	**1a** + **2a** (3:1)[b,c]	64
Anisole (2.2)	**I** (1)	**1a**	51[c]
Anisole (4)	**I** (1)	**1a**	41[c]
Anisole (2.2)[d]	**I** (1)	**1a**	26[e]
Phenol (4)	**I** (1)	**1b**	38
1,3-dimethoxy-benzene (4)	**I** (1)	**1c**[e] + **2c**(2:1)[b]	42[b]
1,2-dimethoxy-benzene (2.2)	**I** (1)	NR	
1,4-dimethoxy-benzene (2.2)	**I** (1)	NR	
1-methylpyrrole (2)	**I** (1)	**1d**[f]	78
Anisole (4)	**II** (1)	**3a**	75
1,3-dimethoxy benzene (4)	**II** (1)	**3c**[e]	48

[a]Reactions carried out in dichloromethane (5 ml) and TfOH (4 mmole) at r.t. for 2 h.
[b]Ratio of products was determined by ^{1}H and ^{31}P-NMR analysis.
[c]**1a** was mainly (95%) 4,4′-isomer containing 5% of the 2.4′-isomer.
[d]Reaction carried out in neat methanesulfonic acid (5 ml).
[e]Pure (>98%) 4,4′-isomer.
[f]Mixture of 2,2′- and 2,3′-isomers (3:1).

a slight decrease of this yield. Similarly, the reaction of anisole with **II** (arene to phosphonate molar ratio 4:1) gave the diarylated phosphonate **3a** in a 75% yield (no traces of unsaturated phosphonate were detected by NMR). However, in this case, according to ^{1}H and ^{31}P NMR, a mixture of 4,4′-, 2,4′-, and 2,2′-regioisomers in approximately a 2:1:0.05 ratio was obtained. Phenol reacts with **I** similarly as anisole and phosphonylated bisphenol **1b** was isolated in a 38% yield (only a 4,4′-isomer was formed). Among dimethoxybenzenes only the 1,3-isomer reacts with **I** and **II** yielding a ~2:1 mixture of **1c** and **2c** in the former and **3c** (only a 4,4′-isomer) in the latter case. In the reaction of **I** with 1-methylpyrrole compound, **1d** (according to ^{1}H NMR a 3:1 mixture of 2,2′- and 2.3′-isomers) was isolated in a 78% yield.

These results show that electron-rich organic aromatic compounds such as anisole, phenol, 1,3-dimethoxybenzene, or 1-methylpyrrole react with dimethyl 2-oxopropylphosphonate and diethyl 2,2-diethoxyethylphosphonate under an acidic condition in a different manner than ferrocene, showing a tendency to form diarylated products. This difference can be attributed to a higher stability of the ferrocenyl carbenium ions **A** that should be formed in the reaction mixture in comparison to their organic arene counterparts **B** (obviously, in a strongly acidic medium the phosphonate group also can undergo

protonation, bringing about additional activation of the carbenium ion, similarly observed for ketophosphonium salts).[13] The species **A** are not reactive towards ferrocene or electron-rich arenes (as checked in an attempt of reaction of unsaturated phosphonate FcC(Me)=CH-P(O)$(OEt)_2$ with anisole and triflic acid resulting only in recovery of the starting phosphonate). Consequently, during the workup they undergo deprotonation yielding β-ferrocenyl-α,β-unsaturated phosphonates. In contrast, cations **B** are able to attack electron-rich arenes, resulting in the formation of β,β-diarylphosphonates (Scheme 3).



SCHEME 3

A bigger tendency of **I** to form vinyl phosphonates also is worth noting. It may be explained by the lower electrophilicity of **B** when R = Me in comparison to R = H.

Reactions of arenes with carbonyl compounds or acetals in acidic media frequently lead to gem-diarylated compounds.[14,15] However, to the best of our knowledge there has been no example of such a reaction with a carbonyl compounds bearing the phosphonate group. β,β-diarylphosphonates synthesized in this work are potential reagents for Horner-Wadsworth-Emmons reactions introducing, e.g., a 2,2-bis(p-hydroxyphenyl)ethyl moiety, displaying antiestrogenic properties[16–18] to organic or organometallic compounds.

EXPERIMENTAL

Solvents were dried using standard procedures. All reagents are commercially available and were used as received. Chromatographic separations were carried out on Silicagel 60 (Merck, 230–400 mesh ASTM). NMR spectra were recorded in a Varian Gemini 200BB (200 MHz for ^{1}H) and Bruker DRX500 (500 MHz for ^{1}H) spectrometers They were referenced to internal TMS (^{1}H and ^{13}C) or external 85% H_3PO_4(^{31}P) references. Mass spectra were recorded using a Finnigan MAT 95 spectrometer.

General Procedure

To a solution of phosphonate **I** or **II** (1 mmole) and arene (1–4 mmole, see Table I) in dichloromethane (5 mL), trifluoromethanesulfonic acid (600 mg, 4 mmole) was added and the reaction mixture was stirred at r.t. for 2 h. After quenching with water and extraction with dichloromethane, the products were separated by flash chromatography (SiO_2, dichloromethane-ether 1:1 or dichloromethane-methanol 9:1). All pure compounds were fully characterized by spectroscopic data.

Spectral Data of Selected Compounds

1a ^{1}H NMR ($CDCl_3$): 1.88 (s, 3H, Me); 2.67 (d, J = 19.5 Hz, 2H, CH_2); 3.35 (d, J = 11.0 Hz, 6H, $PO(OMe)_2$); 3.77 (s, 6H, OMe); 6.80 (d, J = 9.0 Hz, 4H, Ar); 7.12 (d, J = 9,0 Hz, 4H, Ar); ^{13}C NMR ($CDCl_3$): 29.10; 38.21 (d, J = 140.9 Hz); 42.87; 51.80 (d, J = 6.4 Hz); 55.22; 113.21; 128.01; 141.13 (d, J = 11.7 Hz); 157.59; ^{31}P NMR ($CDCl_3$): 32.65; HRMS (EI): Found: 364.14327 calculated for $C_{19}H_{25}O_5P$ 364.14396. **1b**: ^{1}H NMR (acetone-d_6): 1.84 (s, 3H, Me); 2.66 (d, J = 19.2Hz, 2H, CH_2); 3.33 (d, J = 10.9Hz, 6H, $PO(OMe)_2$); 6.72 (d, J = 8.5 Hz, 4H, Ar); 7.06 (d, J = 8.8 Hz, 4H, Ar); 8.25 (s, 2H, OH); ^{13}C NMR (acetone-d_6): 37.70 (d, J = 140.0 Hz); 42.76; 49.11; 51.43 (d, J = 6.5 Hz); 114.68; 128.25; 140.31 (d, J = 11.8 Hz); 155.63; ^{31}P NMR (acetone-d_6): 28.17; HRMS (EI): Found: 336.11250 calculated for $C_{17}H_{21}O_5P$: 336.11266. **1d** (2,2′-isomer): 1.81 (s, Me); 2.52 (d, J = 17.9 Hz, 2H, CH_2); 3.43 (d, J = 10.9 Hz, 6H $PO(OMe)_2$); 3.57 (s, 6H, 2 × Me); 6,04 (s, 2H, pyrrole); 6.42 (s, 2H, pyrrole); 6.49 (s, 2H, pyrrole); ^{13}C NMR ($CDCl_3$): 28.27; 34.96; 36,01; 40.10 (d, J = 135.4 Hz); 51.45 (d, J = 6.4 Hz); 106.96; 118.25; 121.14; 133.66 (d, J = 12.2 Hz); ^{31}P NMR ($CDCl_3$): 32.09; HRMS(EI): Found: 310.14385 calculated for $C_{15}H_{23}N_2O_3P$: 310.14463. **3c**:^{1}H NMR ($CDCl_3$): 1.14 (t, J = 7.1 Hz, 6H, OCH_2CH_3); 2.58 (dd, J = 17.9 Hz, J = 7.6, 2H, CH_2); 3.76 (s, 12H, OMe); 3.79–3.91 (m, 4H, CH_2); 4.87 (dt, J = 11.6 Hz, H = 7.5 Hz, 1H, CH); 6.37–6.43 (m, 4H, Ar); 7.13 (d, J = 9.1 Hz 2H, Ar)^{13}C NMR ($CDCl_3$): 16.21 (d, J = 6.2 Hz); 29.65; 29.73 (d, J = 136.6 Hz); 33.25 (d, J = 2.3 Hz); 55.30 (d, J = 6.3 Hz); 61.06 (d, J = 6.4 Hz); 98.70; 103.66; 124.20 (d, J = 10.5 Hz); 129.52; 158.04; 159.26; ^{31}P NMR ($CDCl_3$): 30.81; HRMS (EI): Found: 438.18219 calculated for $C_{22}H_{31}O_7P$ 438.18074.

REFERENCES

[1] P. Savignac and B. Iorga, *Modern Phosphonate Chemistry* (CRC Press, Boca Raton, FL, 2003), Chapt. 7, pp. 360–374.

[2] D. Plażuk, A. Rybarczyk-Pirek, and J. Zakrzewski, *J. Organomet. Chem*., **689,** 1165 (2004).
[3] N. J. Long, *Metallocenes* (Blackwell Science, Oxford, 1998) Chapt. 4.1, pp. 123–129.
[4] T. Ito, N. Sugahara, and Y. Takini, *J. Chem. Soc. Jpn*., **353,** (1976).
[5] V. Guerchais, E. Roman, and D. Astruc, *Organometallics*, **5,** 2505 (1986).
[6] B. Misterkiewicz, *J. Organomet. Chem*., **224,** 43 (1982).
[7] B. Misterkiewicz, R. Dabard, and H. Patin, *Tetrahedron*, **41,** 1685 (1985).
[8] A. A. A. Quantar and M. Srebnik, *J. Org. Chem*., **66,** 6650 (2001).
[9] A. A. Thomas and K. B. Sharpless, *J. Org. Chem*., **64,** 8379 (1999).
[10] J. M. Gil and D. Y. Oh, *J. Org. Chem*., **64,** 2950 (1999).
[11] K. Afarinkia, H. M. Binch, and C. Modi, *Tetrahedron Lett*., **39,** 7419 (1999).
[12] H.-J. Cristau, X. Y. Mbianda, Y. Beziat, and M.-B. Gasc, *J. Organomet. Chem.*, **529,** 301 (1997).
[13] Y. Zhang, S. L. Aguirre, and D. A. Klumpp, *Tetrahedron Lett*., **43,** 6837 (2002).
[14] M. B. Smith and J. March, *March's Advanced Organic Chemistry* (Wiley, New York, 2001), Chapt. 11–22, pp. 719–720.
[15] D. A. Klumpp, G. V. Sanchez, Jr., S. L.Aguirre, Y. Zhang, and S. de Leon, *J. Org. Chem*., **67,** 5028 (2002).
[16] J. B. Matthews, K. Twomey, and T. R. Zacharewski, *Chem. Res. Toxicol.*, **14,** 149 (2001).
[17] A. Rivas, M. Lacroix, F. Olea-Serrano, I. Laïos, G. Leclercq, and N. Olea, *J. Steroid Biochem. Mol. Biol.*, **82,** 45 (2002).
[18] R. D. Bindal, J. T. Golab, and J. Katzenellenbogen, *J. Am. Chem. Soc.*, **112,** 7861 (1990).