

Synthesis of perhaloaromatic diethyl methylphosphonates containing α -electron-withdrawing group

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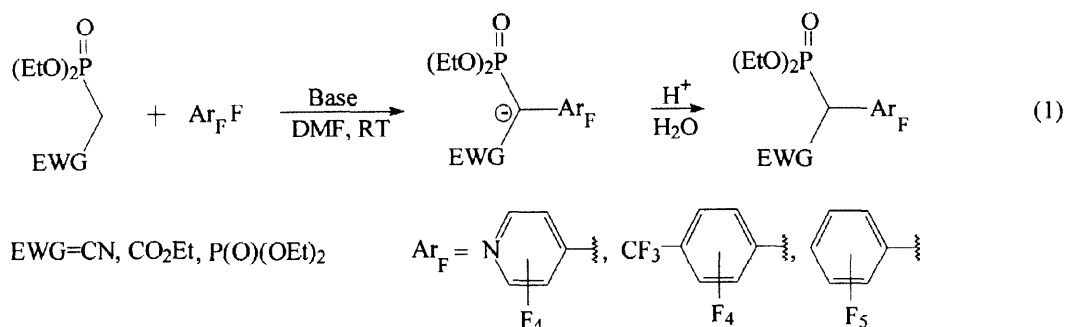
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Abstract: The synthesis of new perhaloaryl(hetaryl)substituted methylphosphonates using nucleophilic aromatic substitution is described. Transformations of synthesized phosphonates into perhaloaryl(hetaryl)substituted methanes are presented.

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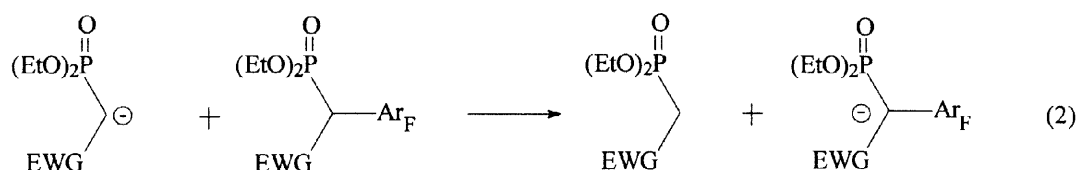
Perhaloaryl and hetaryl diethyl methylphosphonates $\text{Ar}_{\text{F(Cl)}}\text{CH}(\text{EWG})\text{P}(\text{O})(\text{OEt})_2$ (Ar =aryl or hetaryl, $\text{EWG}=\text{CN}$, CO_2Et , $\text{P}(\text{O})(\text{OEt})_2$) are of interest due to their potential biological activity¹ and utility as versatile intermediate reagents for organic synthesis. These compounds can be transformed to mono-, bis- and tris[perhaloaryl(hetaryl)]methanes and can be used in Wittig-Horner reaction to provide perhaloaryl(hetaryl)substituted olefins.

We have found that these compounds can be obtained by the reaction of nucleophilic aromatic substitution of perhaloarenes, such as pentafluoropyridine, octafluorotoluene, hexafluorobenzene and 3,4,5,6-tetrachloro-2-cyano-pyridine, with carbanions of diethyl methylphosphonates $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{EWG}$ bearing electron-withdrawing substituent in α -position (Table 1)²⁻⁴. The reaction is carried out in solid/liquid system using 2-3 equiv. CsF or NaH (entries 1,4,6,7,10,13) as a base or using 3 equiv. K_2CO_3 in the presence of $\text{Et}_3\text{BnN}^+\text{Cl}^-$ (TEBA) as a phase transfer agent (entries 2,3,8,9) resulting in high yields of products (^{31}P NMR).

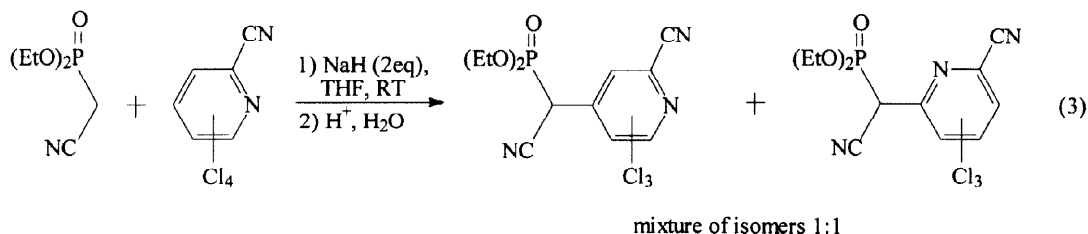


The rate of the reaction and the yield depend on the acidity of CH-acids and the nature of Ar_F ⁵. In the reaction with pentafluoropyridine under the same conditions the rate is decreased in the following sequence $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CN} > (\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et} > [(\text{EtO})_2\text{P}(\text{O})]_2\text{CH}_2$.

Since the final product is more acidic than starting CH-acid one can expect that transmetallation process prevents the reaction and decreases yields of final compounds. In the reactions of fluoroarenes nucleophilic substitution leads to elimination of fluoride ion which acts as a base. However in the case of C_6F_6 , which is less active in nucleophilic substitution, the reaction provides only 52% yield (entry 10). This fact can be explained by transmetallation reaction and the decrease of reactivity of the carbanion towards C_6F_6 after the elimination of HF.

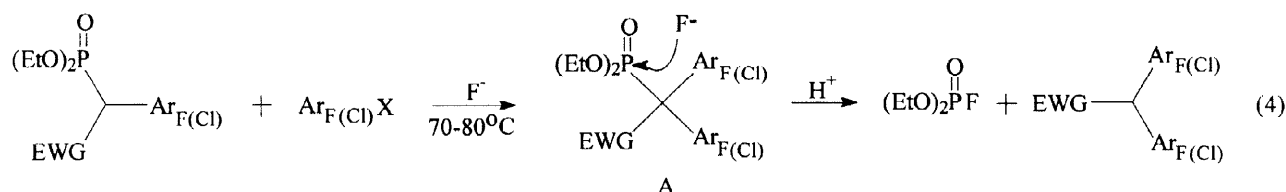


In the case of tetraethyl methylenediphosphonate (less acidic CH-acid) the use of 2 mol of NaH decreases the influence of transmetallation process and provides high yield of final compounds (entries 6,7). The same is true for the reaction of $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CN}$ with tetrachloro- α -cyanopyridine, which is less active in nucleophilic substitution. The yield of final compound is only 50% for CsF or K_2CO_3 as a base (entries 11,12). The use of 2 mol NaH increases the yield up to 89% (entry 13)⁶.




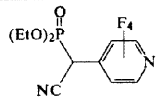

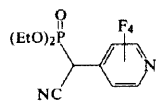

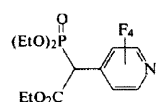

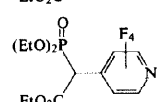

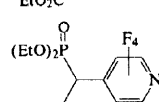

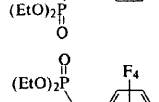

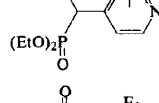
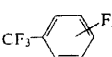
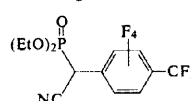
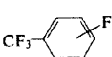
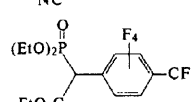

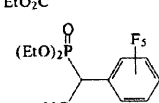



The reaction of starting phosphonates with 2 equivalents of perhaloarene $\text{Ar}_{\text{F}(\text{Cl})}\text{X}$ on heating ($70\text{--}80^\circ\text{C}$) leads to the formation of bis(perhaloarene)acetonitrile or ethyl bis(perhaloarene)acetate⁷ and diethyl fluorophosphate (δ_P -10.3 ppm, J_PF 970 Hz).

We suppose that this result may be explained by the following reaction



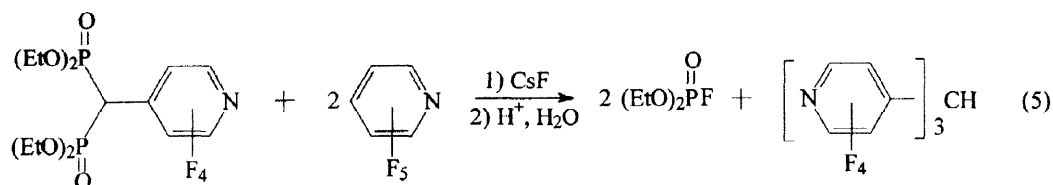
X=F,Cl

Table 1. Nucleophilic aromatic substitution reactions in polyhaloarenes by diethyl methylphosphonates containing electron-withdrawing group

Entry	EWG in starting phosphonate	Polyhaloarene	Conditions ^a	Product ⁸	Yield(%)	
					anion of product	product (isolated yield)
1	CN		CsF, 3 h		91	66
2	CN		K ₂ CO ₃ /TEBA ^b , 4 h		90	52
3	CO ₂ Et		K ₂ CO ₃ /TEBA ^b , 12 h		100	85
4	CO ₂ Et		CsF, 28 h		77	-
5	P(O)(OEt) ₂		K ₂ CO ₃ /TEBA ^b , 8 h		3	-
6	P(O)(OEt) ₂		NaH (2eq), 10 min		76	61
7	P(O)(OEt) ₂		NaH (2eq), 18-c-6 (2eq), 10 min		90	74
8	CN		K ₂ CO ₃ /TEBA ^b , 11 h		97	72
9	CO ₂ Et		K ₂ CO ₃ /TEBA ^b , 35 h		78	60
10	CN		CsF, 20 h		52	-
11	CN		K ₂ CO ₃ /TEBA ^b , 11 h	mixture of two isomers (see eq.3)	45	-
12	CN		CsF, 6 h	mixture of two isomers (see eq.3)	50	-
13	CN		2eq NaH, 30 min	mixture of two isomers (see eq.3)	89	70

^aSolvent: entries 1-12 - DMF, entry 13 - THF. ^bTEBA (5% mol based on starting phosphonate).

In the reaction of $(\text{Py}_F)\text{CH}[\text{P}(\text{O})(\text{OEt})_2]_2$ with 2 eq of pentafluoropyridine in the presence of CsF we obtained tris(2,3,5,6-tetrafluoro-4-pyridyl)methane⁹.



We suggested that diarylated (EWG=CN, CO₂Et) and triarylated (EWG=P(O)(OEt)₂) products were formed in the course of thermal degradation of unstable (due to sterical reason) compound (A). The reaction (4) proceeds faster with phosphonate containing CN-group. It may be explained by both steric and electronic factors.

The cleavage of C-P bond under the action of base (nucleophile) in the product formed may proceed also with monoarylated methylphosphonates giving monoarylated CH-acids $\text{Ar}_{\text{F}(\text{CN})}\text{CH}_2\text{EWG}$. We have shown the formation of $\text{Py}_F\text{CH}_2\text{CN}$ (55% after isolation by column chromatography) by water treatment of the reaction mixture which contained carbanion $(\text{Py}_F)(\text{CN})\text{C}(\text{Cs})[\text{P}(\text{O})(\text{OEt})_2]$ and excess of CsF. This reaction may be the reason of decrease in the yields of isolated products in comparison with the yields determined by ³¹P NMR (Table 1).

Acknowledgement. We are grateful to INTAS (Grant N 93-1482-ext) for financial support.

References and Notes

1. *The Role of Phosphonates in Living Systems*; Hilderbrand, R.L., Ed.; CRC Press: Boca Raton, FL, 1983.
2. Similar reactions of perfluoroarenes with anions of strong CH-acids, for example diethyl malonate, malononitrile or ethyl cyanoacetate, proceed smoothly at 20°C using NaH, LiH, K₂CO₃, CsF or KF as a base: Artamkina, G.A.; Kovalenko S.V.; Beletskaya I.P.; Reutov O.A. *Uspekhi Khim.* **1990**, 59, 1288-1337.
3. The products were isolated by vacuum distillation (entries 1-3,6,8,9) or by column chromatography (silica gel, ethyl acetate : petroleum ether = 1:1) (entry 7), and in the case of entry 13 the residue was washed by ether after removing the solvent. All new compounds have been fully characterized.
4. Typical experimental procedure: A mixture of ethyl α-(diethylphosphono)acetate (1.12 g, 5.0 mmol), pentafluoropyridine (1.27 g, 7.5 mmol), K₂CO₃ (2.07 g, 15 mmol) and TEBA (0.06 g, 0.25 mmol) in 8.5 ml DMF was stirred at 20°C under argon for 12 h. The reaction mixture was separated from solid, treated by cool saturated solution of KCl, neutralised with HCl and extracted with ether. The combined extracts were dried (MgSO₄) and evaporated. The residue was distilled in vacuum to give 1.63 g (87%) of ethyl 2-(diethylphosphono)-2-(2,3,5,6-tetrafluoro-4-pyridyl)acetate as a colourless oil. bp 132°C (0.5 mm), n_D²⁰ 1.4488.
5. Activity of perfluoroarenes in reactions of nucleophilic aromatic substitution is decreased in the sequence $\text{Py}_F > \text{CF}_3\text{C}_6\text{F}_5 > \text{C}_6\text{F}_6$. For example, in the reaction with MeONa in MeOH k₂, l/(mol²·c), Py_F 0.142, $\text{CF}_3\text{C}_6\text{F}_5$ 1.37·10⁻³, C_6F_6 2·10⁻⁵: Rodionov P.P.; Furin G.G. *Izv. SO Akad. Nauk.* **1990**, 3-26.
6. Spectroscopic data for mixture of two isomers (eq 3): ³¹P-NMR (Et₂O) δ +9.9; ¹H-NMR (400MHz, CDCl₃) δ 1.36 (t, 6H, J=7.1 Hz, CH₃), 1.39 (t, 6H, J=7.0 Hz, CH₃), 4.29 (m, 8H, CH₂), 5.22 (d, 1H, J_{HP}=28.5 Hz, CH), 5.30 (d, 1H, J_{HP}=28.1 Hz, CH); ¹³C-NMR (CDCl₃) δ 20.11 (CH₃), 37.97 (J_{CP}=137.8 Hz, CH), 38.29 (J_{CP}=135.5 Hz, CH), 69.11 (CH₂), 69.72 (CH₂), 114.56, 114.66, 116.87, 116.98 (CN), 138.56, 139.81, 142.28 (Ar).
7. Yield of ethyl 2,2-bis(2,3,5,6-tetrafluoro-4-pyridyl)acetate 82% (column chromatography, silica gel, ethyl acetate : petroleum ether = 1:3). Spectroscopic analyses of the obtained product were in good agreement with the reported data: Artamkina G.A.; Beletskaya I.P. *Zh. Org. Khim.* **1995**, 31, 1044-1047.
8. ¹H NMR data for α-CH (CDCl₃ or C₆D₆): δ 4.53-4.71, J_{HP} 25.2-26.6 Hz.
9. Yield 79% (purification by ether washing): mp 212°C; ¹H-NMR (400MHz, acetone-d₆) δ 6.79 (s, 1H). Anal. calcd. for C₁₆H₁₂N₃: C, 41.47; H, 0.22. Found: C, 41.61; H, 0.22.