Pergamon

Tetrahedron Letters 40 (1999) 8099–8101

TETRAHEDRON LETTERS

First synthesis of α-fluorinated cyclopropylphosphonates using magnesium electrochemical activation

Sophie Goumain, Philippe Jubault, Christian Feasson * and Jean-Charles Quirion

Laboratoire d'Hétérochimie Organique de l'IRCOF, Université de Rouen-INSAR, Place Emile Blondel, BP 08, F-76131 Mont-Saint-Aignan, France

Received 5 July 1999; accepted 5 September 1999

Abstract

The synthesis of α-fluorinated cyclopropylphosphonates is efficiently achieved for the first time by electroreduction of diisopropyl dibromofluoromethylphosphonate in the presence of Michael acceptors in a one-compartment cell equipped with a magnesium sacrificial anode.

Keywords: organic electrochemical reactions; cyclopropanes; fluorine; fluorine compounds; phosphorus compounds.

Cyclopropane derivatives play an important role in bioorganic[1] and synthetic chemistry.[2] Furthermore, cyclopropyl amino acids function as conformationally constrained amino acid analogues[3] and provide mechanistic probes to determine reaction pathways.[4] Moreover, some phosphonic acids exhibit important biological properties because of their similarity to phosphates.[5] The carbon–phosphorus bond in phosphonates, unlike the carbon–oxygen one in phosphates, is not susceptible to the hydrolytic action of phosphatases, thereby imparting them higher stability under physiological conditions. In their pioneering work, Blackburn et al. established that the α-fluorination of phosphonates is a successful strategy for the design of phosphonate analogues of phosphate esters.[6]

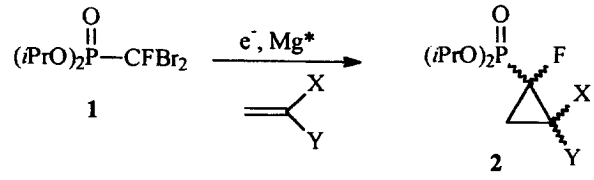
The combination of these two patterns (fluorine and phosphonate) directly linked on the same carbon of a cyclopropane moiety might lead to valuable products with potential biological properties. We therefore became interested in the synthesis of α-fluorinated cyclopropylphosphonates **2** from the readily available[7] diisopropyl dibromofluoromethylphosphonate **1** (Scheme 1). To our knowledge, no example of such compounds has been thus far described.

1. Results and discussion

Electroreductions[8] of **1**, in a DMF medium, between a carbon-felt cathode and a sacrificial magnesium anode in a one-compartment cell at ambient temperature, performed in the presence of two equivalents of

* Corresponding author. E-mail: cfeasson@ircof.insa-rouen.fr

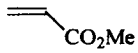
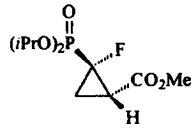
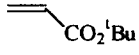
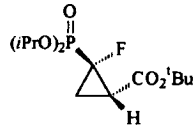
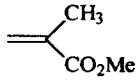
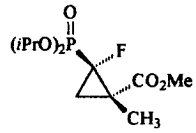
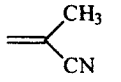
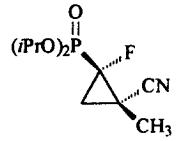
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01698-6



Scheme 1.

Michael acceptor, afforded α-fluorinated cyclopropylphosphonates **2** in moderate to good isolated yields (Table 1). In most cases (entries a, b, d), the electrochemical cyclopropanation occurred well, within 2 h 10 min. With the magnesium anode, the previously described activation phenomenon[9–12] again occurred with beneficial consequences. For example, the quantity of electricity consumed was decreased because of a lowering of the electrolysis duration [in this case 2 h 10 min instead of 3 h 10 min (6 mmol of **1**) for the theoretical bielectronic electrochemical reduction of **1**]. The main problem encountered during the purification process was partial decomposition of these compounds during bulb-to-bulb distillation.

Table 1
Electrosynthesis of α-fluorinated cyclopropylphosphonates **2**

Entry	Alkene	Yield (%)[a] [evaluated yield (%)[b]]	de (%)[c]	Major Diastereoisomer[d]	δ ^{19}F ($CDCl_3$) in ppm[e] [$^2J_{FP}$ in Hz]
a.		43 [60]	70		- 215.9 [70.6]
b.		49 [60]	80		- 216.5 [70.6]
c.		11 [50]	34		- 204.1 [73.8]
d.		58 [90]	10		- 208.4 [73.4]

[a]Yield of isolated, purified product.
[b]Determined by ^{19}F NMR spectroscopy on the reaction mixture at the end of the electrolysis, using 3-fluoropyridine as internal standard. The major by-products detected are diisopropyl bromofluoromethylphosphonate [^{31}P NMR ($CDCl_3$), δ=6.8 (d, $^2J_{PF}$=74.8)] and phosphates.
[c]Diastereomeric excess, determined by CPG analysis, on the crude product.
[d]Only one enantiomer of each diastereomer is represented.
[e]^{19}F NMR data for the major diastereomer. Compound **2** appeared as a doublet in ^{19}F {^{1}H}NMR. In each case, the minor diastereomer appeared upfield at −189.9 (**2a**), −188.7 (**2b**), −202.5 (**2c**) and −193.3 (**2d**) ppm, respectively.

The relative configuration of substituted α-fluorinated cyclopropylphosphonates **2** was elucidated by measuring the 3-bond fluorine–carbon coupling constants. In the case of methacrylonitrile (Table 1, entry d), the nitrile carbon atom of the major isomer appeared as a doublet in the ^{13}C NMR spectrum ($^3J_{CF}$=6.8 Hz, characteristic of a *cis*-relationship between this carbon and the fluorine atom) while the minor isomer gave a singlet. We confirmed that this constant was due to a 3-bond fluorine–carbon coupling by carrying out the ^{19}F-decoupled-^{13}C spectrum, in this experiment the nitrile carbon atom of each diastereomer appeared as a singlet. The absence of a $^3J_{CP}$ coupling constant was not surprising as it has been previously shown[11,13] that the presence of an electronegative atom in the α position of the phosphorus (here, the fluorine atom) is expected to decrease the magnitude of $^3J_{CP}$. Furthermore, it was observed in each case that the ^{19}F chemical shift observed for the *trans*-diastereomer (δ=–204.1 to –216.5 ppm) was downfield compared to the chemical shift observed for the *cis*-diastereomer (δ=–188.7 to –202.5 ppm). The same results were obtained in the case of **2a**. That is to say, $^3J_{CF}$ (*cis*)=3 Hz for the major diastereomer and $^3J_{CF}$ (*trans*)=0 Hz for the minor one. The above criterion (upfield, downfield ^{19}F chemical shift) has been used for determining the relative configuration of all α-fluorinated cyclopropylphosphonates **2** which possessed the same configuration.

In conclusion, we describe, for the first time, the synthesis of α-fluorinated cyclopropylphosphonates with moderate to good yields using magnesium electrochemical activation. Synthetic transformations of such compounds are under study within our laboratory (in particular, to access α-fluorinated β-amino and α-fluorinated γ-amino cyclopropylphosphonates) and will be reported in due course.

References

1. Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511–542.
2. (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (b) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20–32.
3. Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 54–65.
4. (a) He, M.; Dowd, P. *J. Am. Chem. Soc.* **1996**, *118*, 711. (b) Mattalia, J.-M.; Chanon, M.; Stirling, C. J. M. *J. Org. Chem.* **1996**, *61*, 1153–1154.
5. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
6. (a) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913–917. (b) Blackburn, G. M.; Parrat, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1425–1430.
7. Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329–332.
8. Electrosynthesis of diisopropyl 1-fluoro-2-methyl-2-cyanocyclopropyl-1-phosphonate **2d**: In a one-compartment cell, equipped with a carbon felt cathode (S=16 cm^2) and a magnesium anode, a solution of diisopropyl dibromofluoromethylphosphonate **1** (2.1 g, 6 mmol) and methacrylonitrile (12 mmol) in DMF (35 mL) containing Et_4NBr (0.02 mol L^{-1}) was introduced. A 100 mA constant current was applied. The electrolysis was continued until **1** was completely consumed (monitored by ^{31}P NMR spectroscopy). The reaction mixture was poured into THF (80 mL), then acidified with 1N HCl (100 mL) and extracted with ether (3×50 mL). The combined organic layers were washed with 1N HCl (2×50 mL) and dried. The solvents were evaporated in vacuo to give **2d**. Further purification by bulb-to-bulb distillation led to the pure diisopropyl cyclopropylphosphonate **2d**, obtained as a mixture of diastereomers (in a 55:45 ratio). Oily product, $bp_{0.1}$=100°C. Major diastereomer: ^{31}P NMR ($CDCl_3$) [δ ppm, (*J* Hz)]: 10, d, 73.4; ^{19}F NMR ($CDCl_3$) [δ ppm, (*J* Hz)]: –208.4, d, 73.4; ^1H NMR ($CDCl_3$) [δ ppm, (*J* Hz)]: 1.4, m, 12H, $[(CH_3)_2CHO]_2P$; 1.7, d, 3H, 2.1, CH_3; 1.8–2, m, 2H, CH_2; 4.8, m, 2H, $[(CH_3)_2CHO]_2P$; ^{13}C NMR ($CDCl_3$) [δ ppm, (*J* Hz)]: 14.4, d, $^2J_{CF}$=15, C_2; 16.7, s, CH_3; 23.5, d, $^2J_{CF}$=7.6, C_3; 24, m, $[(CH_3)_2CHO]_2P$; 73.4, m, $[(CH_3)_2CHO]_2P$; 75.7, dd, $^1J_{CF}$=245.2, $^1J_{CP}$=222.6, C_1; 118.8, d, $^3J_{CF}$=6.8, CN. HRMS required for $C_{11}H_{20}O_3PFN$: 264.1164; found: 264.1178.
9. Jubault, P.; Feasson, C.; Collignon, N. *Tetrahedron Lett.* **1995**, *36*, 7073–7076.
10. Jubault, P.; Feasson, C.; Collignon, N. *Tetrahedron Lett.* **1996**, *36*, 3679–3682.
11. Jubault, P.; Goumain, S.; Feasson, C.; Collignon, N. *Tetrahedron* **1998**, *54*, 14767–14778.
12. Goumain, S.; Jubault, P.; Feasson, C.; Collignon, N. *Synthesis* **1999**, 981–984.
13. Thiem, J.; Meyer, B. *Org. Magn. Res.* **1978**, *11*, 50–51.