

(DIETHYLPHOSPHINYLLITHIUM) DIFLUOROMETHYLLITHIUM.
— PREPARATION AND SYNTHETIC APPLICATION —

Michio Obayashi, Eiji Ito, Kiyohide Matsui, and Kiyosi Kondo

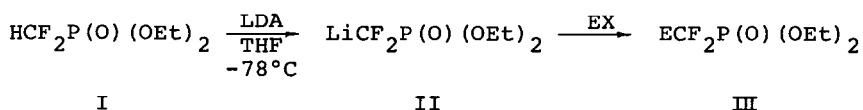
Sagami Chemical Research Center,
Nishiohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Dedicated to Professor Hitosi Nozaki on the occasion of his 60th birthday.

Summary: The action of lithium diisopropylamide on diethyl difluoromethylphosphonate gives the title reagent which reacts with various electrophiles to introduce difluoromethylene or difluoromethyl unit.

Remarkable enhancement of biological activity is often observed by introduction of halogen atoms into organic compounds. Examples in the pesticide field are decamethrin and NRDC-182¹ which have gem-dihaloethenyl unit in common. In view of the specific physiological activity of fluorine atom² it is of interest to study the difluoro analogs of biologically active substances. Although some synthetic methods are hitherto recorded,³ we wish to add a new procedure widely applicable to preparing compounds having difluoromethylene or difluoromethyl group from ketones and aldehydes.

The title reagent (II)⁴ was prepared by treatment of diethyl difluoromethylphosphonate (I)⁵ with 1.1 eq. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C. Addition of various electrophiles to the reagent solution followed by work-up and purification with silica gel column gave the corresponding products III. Results are given in the order of EX, E, % yield of III: Me₃SiCl, Me₃Si,⁶ 87; n-Bu₃SnCl, n-Bu₃Sn, 77; (EtO)₂P(O)Cl, (EtO)₂P(O), 74; EtBr, Et, 82; C₆H₁₃Br, C₆H₁₃, 66; CH₂=CHCH₂Br, CH₂=CHCH₂, 23; C₆H₅COCl, C₆H₅CO, 25.



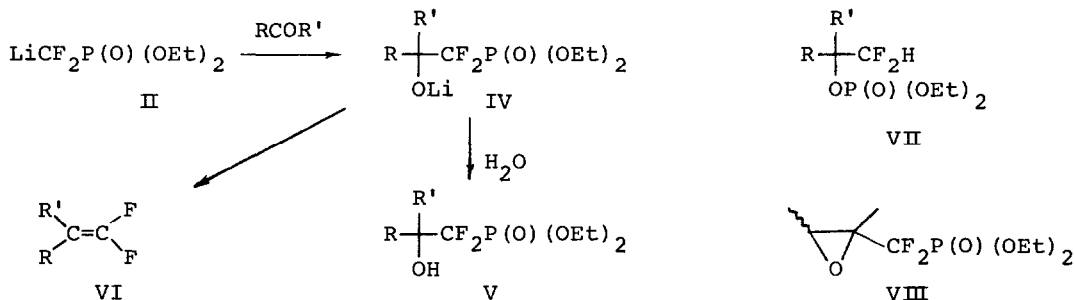


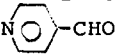
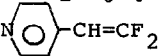
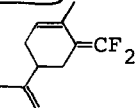
Table 1. Preparation of Diethyl 1,1-Difluoro-2-hydroxyalkylphosphonates (V)

RCOR'	Product V	Yield (%)
p-Me ₂ N-C ₆ H ₄ CHO	p-Me ₂ N-C ₆ H ₄ CH(OH)CF ₂ P(O)(OEt) ₂	71
p-BuO-C ₆ H ₄ CHO	p-BuO-C ₆ H ₄ CH(OH)CF ₂ P(O)(OEt) ₂ (Va)	76
C ₆ H ₅ CHO	C ₆ H ₅ CH(OH)CF ₂ P(O)(OEt) ₂ (Vb) ^a	83
p-NO ₂ -C ₆ H ₄ CHO	p-NO ₂ -C ₆ H ₄ CH(OH)CF ₂ P(O)(OEt) ₂ (Vc)	8 ^b
p-MeO-C ₆ H ₄ COCH ₃	p-MeO-C ₆ H ₄ C(CH ₃)(OH)CF ₂ P(O)(OEt) ₂	86
p-Cl-C ₆ H ₄ COCH ₃	p-Cl-C ₆ H ₄ C(CH ₃)(OH)CF ₂ P(O)(OEt) ₂	77 ^c
n-C ₁₀ H ₂₁ CHO	n-C ₁₀ H ₂₁ CH(OH)CF ₂ P(O)(OEt) ₂ (Vd)	90

^a See note 7. ^b VII (R = p-NO₂-C₆H₄, R' = H) was produced (14%).⁸

^c VII (R = p-Cl-C₆H₄, R' = CH₃) was by-product (6%).

Table 2. Preparation of 1,1-Difluoro Olefins VI

RCOR'	Product VI	Yield (%)
p-Me ₂ N-C ₆ H ₄ CHO	p-Me ₂ N-C ₆ H ₄ CH=CF ₂	67
p-BuO-C ₆ H ₄ CHO	p-BuO-C ₆ H ₄ CH=CF ₂ (VIa)	61
p-NO ₂ -C ₆ H ₄ CHO	p-NO ₂ -C ₆ H ₄ CH=CF ₂	0
 -CHO		0 ^a
p-MeO-C ₆ H ₄ COCH ₃	p-MeO-C ₆ H ₄ C(CH ₃)=CF ₂	62
p-Br-C ₆ H ₄ COCH ₃	p-Br-C ₆ H ₄ C(CH ₃)=CF ₂	54
C ₆ H ₅ COC ₃ H ₇	C ₆ H ₅ C(C ₃ H ₇)=CF ₂	62
p-NO ₂ -C ₆ H ₄ COCH ₃	p-NO ₂ -C ₆ H ₄ C(CH ₃)=CF ₂	0
m-NO ₂ -C ₆ H ₄ COCH ₃	m-NO ₂ -C ₆ H ₄ C(CH ₃)=CF ₂	0 ^b
C ₆ H ₅ COC ₆ H ₅	C ₆ H ₅ C(C ₆ H ₅)=CF ₂	64
n-C ₁₀ H ₂₁ CHO	n-C ₁₀ H ₂₁ CH=CF ₂	71
C ₉ H ₁₉ COCH ₃	C ₉ H ₁₉ C(CH ₃)=CF ₂	75
cyclododecanone	(CH ₂) ₁₁ C=CF ₂	73
Carvone		54

^a Isolated product was VII (R' = 4-pyridyl, R = H, 10%).

^b Isolated product was VII (R' = p-NO₂-C₆H₄, R = H, 14%), only.

When aldehydes were allowed to react with II and the work-up was carried out at room temperature, diethyl 2,2-difluoro-3-hydroxyalkylphosphonates (V) were produced (Table 1). Heating the THF solution of the intermediary adducts IV derived from aldehydes and ketones induced the Wadsworth-Emmons reaction to give 1,1-difluoro olefins VI as summarized in Table 2. Although the procedure is generally applicable to various ketones and aldehydes, those having nitro group or pyridine ring gave none of the desired products and sometimes underwent rearrangement to give phosphates VII.

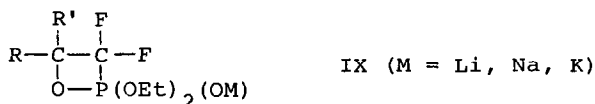
The transformation of Va-c (see Table 1) into VI was then attempted using various bases. Treatment of Va with LDA or BuLi gave VIa exclusively in 60-77% yields, whereas treatment with LiH produced only VII (R = p-BuOC₆H₄, R' = H) in 87% yield.⁹ The use of NaH, KH, or t-BuOK resulted in the formation of two products in variable ratios. On the other hand, Vb and Vc were converted into the corresponding phosphates of type VII solely with these bases.¹⁰

Alkylative transformation of V into VI was also exploited. Oxidation of Vb with pyridinium chlorochromate (89% yield) and treatment of the resulting ketone with butyllithium at -78°C followed by thermal elimination gave VI (R = Ph, R' = Bu) in 54% yield. Similarly, Vd was transformed into VI (R = n-C₁₀H₂₁, R' = Bu) by the two-step process (34% overall yield). Reaction of II with 3-chloro-2-butanone resulted in the Darzens-type reaction to give an epoxy phosphonate VIII in 51% yield.¹¹

REFERENCES AND NOTES

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- (2) Ciba Foundation, "Carbon-Fluorine Compounds-Chemistry, Biochemistry, and Biological Activities," Elsevier, Amsterdam (1972).
- (3) (a) S. A. Fuqua, W. G. Duncan, and R. M. Silverstein, Tetrahedron Lett., 1461 (1964); (b) idem, J. Org. Chem., 30, 1027 (1965); (c) idem, ibid., 30, 2543 (1965); (d) F. E. Herkes and D. J. Burton, ibid., 32, 1311 (1967); (e) D. G. Naae and D. J. Burton, J. Fluorine Chem., 1, 123 (1971/72); (f) idem, Synth. Commun., 3, 197 (1973); (g) G. A. Wheaton and D. J. Burton, Tetrahedron Lett., 895 (1976); (h) S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae, and H. S. Kesling, Chem. Lett., 983 (1979); (i) D. J. Burton, R. Takei, and S. Shin-Ya, J. Fluorine Chem., 18, 197 (1981).
- (4) Synthetic applications of LiCX₂P(O)(OEt)₂ (X = Cl, Br) are reported. (a) P. Savignac, J. Petrava, M. Dreux, and P. Coutrot, Synthesis, 535 (1975); (b) D. Seyferth and R. S. Marmor, J. Organomet. Chem., 59, 237 (1973); (c) A. Alexakis, J. F. Normant, and J. Villieras, ibid., 96, 471 (1975); (d) J. Villieras, P. Perriot, and J. F. Normant, Synthesis, 458 (1975); (e) P. Savignac and P. Coutrot, ibid., 197 (1976).

- (5) I was prepared from HCF_2Cl and $\text{NaOP}(\text{OEt})_2$ by the modification of the reported method. L. Z. Soborovskii and N. F. Baina, *J. Gen. Chem. USSR*, **29**, 1115 (1959). The use of THF as the solvent much improved the yield to give I in 77% yield.
- (6) IR (neat) 1255 cm^{-1} ; MS m/e (rel. %) 245 (7), 233 (30), 205 (43), 165 (53), 153 (22), 141 (91), 137 (52), 121 (69), 93 (24), 81 (23), 77 (63), 75 (75), 65 (43), 45 (46), 29 (45); $^1\text{H-NMR}$ (CDCl_3) δ ppm, 0.28 (9H, s), 1.36 (6H, t, $J_{\text{H-H}} = 7\text{ Hz}$), 4.24 (4H, d-q, $J_{\text{H-P}} = 7\text{ Hz}$, $J_{\text{H-H}} = 7\text{ Hz}$); $^{19}\text{F-NMR}$ (CDCl_3) δ ppm (from CF_3COOH), 51.98 (2F, d, $J_{\text{F-P}} = 94.0\text{ Hz}$). Found: C, 36.89; H, 7.29%. Calcd for $\text{C}_8\text{H}_{19}\text{F}_2\text{O}_3\text{PSi}$: C, 36.92; H, 7.36%.
- (7) Mp $76-77^\circ\text{C}$; IR (KBr) $3400, 1260\text{ cm}^{-1}$; MS m/e (rel. %) 294 (M^+ , 2), 277 (2), 188 (74), 161 (60), 160 (31), 137 (6), 132 (100), 109 (15), 107 (19), 81 (11), 79 (22), 77 (22), 29 (19); $^1\text{H-NMR}$ (CDCl_3) δ ppm, 1.26 (6H, t, $J_{\text{H-H}} = 7\text{ Hz}$), 4.13 (2H, d-q, $J_{\text{H-P}} = 7\text{ Hz}$, $J_{\text{H-H}} = 6\text{ Hz}$), 4.23 (2H, d-q, $J_{\text{H-P}} = 7\text{ Hz}$, $J_{\text{H-H}} = 7\text{ Hz}$), 4.56 (1H, d, $J_{\text{H-H}} = 6\text{ Hz}$), 4.89-5.28 (1H, m), 7.23-7.70 (5H, m); $^{19}\text{F-NMR}$ (CDCl_3) δ ppm (from CF_3COOH), 34.01, 47.00 (2F, ABq-d-d, $J_{\text{F-F}} = 306\text{ Hz}$, $J_{\text{F-P}} = 102\text{ Hz}$, 106 Hz , $J_{\text{F-H}} = 6.0\text{ Hz}$, 20.0 Hz); $\{^1\text{H}\}-^{31}\text{P-NMR}$ (CDCl_3) δ ppm (from H_3PO_4), 6.85 (1P, d-d, $J_{\text{P-F}} = 102\text{ Hz}$, 106 Hz). Found: C, 48.85; H, 5.80%. Calcd for $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_4\text{P}$: C, 48.99; H, 5.82%.
- (8) IR (neat) 1275 cm^{-1} ; Ms m/e (rel. %) 275 (8), 274 (56), 243 (49), 226 (51), 198 (64), 187 (7), 141 (42), 140 (23), 147 (19), 109 (65), 107 (46), 91 (100), 81 (25), 77 (29), 51 (11), 29 (18); $^1\text{H-NMR}$ (CDCl_3) δ ppm, 1.14 (3H, d-t, $J_{\text{H-P}} = 1\text{ Hz}$, $J_{\text{H-H}} = 7\text{ Hz}$), 1.25 (3H, d-t, $J_{\text{H-P}} = 1\text{ Hz}$, $J_{\text{H-H}} = 7\text{ Hz}$), 3.89 (2H, ABq-q-d, $J_{\text{AB}} = 0.75\text{ Hz}$, $J_{\text{H-H}} = 7.0\text{ Hz}$, $J_{\text{H-P}} = 7.1\text{ Hz}$), 4.01, 4.11 (2H, ABq-q-d, $J_{\text{AB}} = 10.2\text{ Hz}$, $J_{\text{H-H}} = 7.2\text{ Hz}$, $J_{\text{H-P}} = 7.2\text{ Hz}$), 5.35 (1H, d-d-t, $J_{\text{H-H}} = 4.1\text{ Hz}$, $J_{\text{H-P}} = 9.5\text{ Hz}$, $J_{\text{H-F}} = 10.6\text{ Hz}$), 5.87 (1H, d-t, $J_{\text{H-H}} = 4.1\text{ Hz}$, $J_{\text{H-F}} = 55.0\text{ Hz}$), 7.28-7.50 (5H, m); $^{19}\text{F-NMR}$ (CDCl_3) δ ppm (from CF_3COOH), 47.15, 48.85 (2F, ABq-d-d, $J_{\text{F-F}} = 290\text{ Hz}$, $J_{\text{F-H}} = 10.6\text{ Hz}$, $J_{\text{F-H}} = 55.0\text{ Hz}$); $\{^1\text{H}\}-^{31}\text{P-NMR}$ (CDCl_3) δ ppm (from H_3PO_4), -1.79 (1P, s). Found: C, 48.70; H, 5.87%. Calcd for $\text{C}_{12}\text{H}_{17}\text{F}_2\text{O}_4\text{P}$: C, 48.99; H, 5.82%.
- (9) The distinct difference between n-BuLi and LiH would arise from the salt effect of LiCl present in n-BuLi.
- (10) As the common stage leading to VI and VII, the four-membered transition state IX can be considered. Simultaneous elimination of phosphate will produce difluoro olefin, whereas hydrogen abstraction at the stage of IX probably from solvent THF will result in the formation of VII.



- (11) The use of this new process for preparation of various difluoro analogs of physiologically active substances is currently under way.