

AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF 1,1-DIFLUORO-2-HYDROXYALKYLPHOSPHONATES

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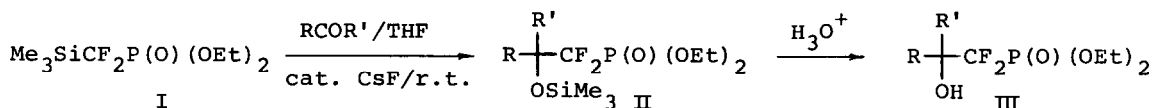
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Dedicated to Professor Hitosi Nozaki on the occasion of his 60th birthday.

Summary: The reaction of diethyl difluoro(trimethylsilyl)methylphosphonate with arenecarbaldehydes and aryl methyl ketones is effected with the aid of a catalyst, cesium fluoride, at room temperature to afford the title compounds.

(Diethylphosphinyl)difluoromethyl lithium is found to react with ketones or aldehydes to give 1,1-difluoro-2-hydroxyalkylphosphonates (III).¹ Though the reaction is applicable to various carbonyl compounds, the process failed to give the desired adduct in case of p-nitrobenzaldehyde and 4-pyridinecarbaldehyde, possibly due to the strong basicity of the lithium reagent. In the course of our exploratory study, it has been found that this defect can readily be overcome by the use of diethyl difluoro(trimethylsilyl)methylphosphonate (I) and cesium fluoride as a catalyst, which generates (diethylphosphinyl)difluoro-methyl carbanion species² under neutral conditions.



In a typical experiment, I (260 mg, 1.0 mmol) dissolved in tetrahydrofuran (THF) (3 ml) and benzaldehyde (106 mg, 1.0 mmol) was added successively to cesium fluoride (3 mg, 0.02 mmol) in THF (3 ml) at 0°C, and the reaction mixture was stirred overnight at room temperature.³ Treatment of the resulting mixture with conc-hydrochloric acid (0.02 ml) followed by work-up and chromatography (silica gel, hexane-ethyl acetate 2:1) afforded diethyl 1,1-difluoro-2-hydroxy-2-phenylethylphosphonate (III, R = Ph, R' = H, 171 mg, 58% yield).¹ Work-up without the acid treatment produced the trimethylsilyl ether II (R = Ph, R' = H) in 58% isolated yield after chromatographic purification. IR (neat) 1275, 1260 cm⁻¹; MS m/e (rel. %), 351 (3), 261 (4), 260 (29), 188 (1), 180 (16), 179 (100), 155 (23), 137 (2), 77 (19), 73 (64); ¹H-NMR (CDCl₃) δ ppm, 0.07 (9H, s), 1.26 (3H, t, J_{H-H} = 7 Hz), 1.37 (3H, t, J_{H-H} = 7 Hz), 4.04-4.24 (4H, m), 5.13 (1H, d-d-d, J_{H-P} = 3 Hz, J_{H-F} = 8 Hz, 18 Hz), 7.31-7.58 (5H, m); ¹⁹F-NMR (CDCl₃) δ ppm (from CF₃COOH), 36.29, 44.87 (2F, ABq-d-d, J_{F-F} = 305 Hz, J_{F-P} = 99.9 Hz, J_{F-H} = 8.5 Hz, 17.8 Hz).



Results with various arenecarbaldehydes and aryl methyl ketones are summarized in Table 1. Both p-nitrobenzaldehyde and 4-pyridinecarbaldehyde as well as highly enolizable acetophenone derivatives⁴ gave the corresponding adducts in good yields.

The adducts III thus obtained can easily be transformed into 1,1-difluoro olefins.¹

Table 1. Reaction of $\text{Me}_3\text{SiCF}_2\text{P(O)(OEt)}_2$ with ArCHO and ArCOCH_3

ArCHO	Yield(%) of III	ArCOCH ₃	Yield(%) of III
p-BuO-C ₆ H ₄ CHO	66	P-MeO-C ₆ H ₄ COCH ₃	67
C ₆ H ₅ CHO	58	p-NO ₂ -C ₆ H ₄ COCH ₃	38*
p-NO ₂ -C ₆ H ₄ CHO	87		
 -CHO	57	* A by-product, p-NO ₂ -C ₆ H ₄ C(Me)(CF ₂ H)O-P(O)(OEt) ₂ , ⁵ was produced (27%), which was detected before work-up.	
 -CHO	84		

REFERENCES AND NOTES

- (1) Preceding paper.
- (2) For C-SiMe₃ moiety as a masked carbanion, see (a) T. H. Chan, P. W. K. Lan, *Tetrahedron Lett.*, 2667 (1967); (b) E. Nakamura and I. Kuwajima, *Angew. Chem., Int. Ed. Engl.*, **15**, 498 (1976); (c) E. Nakamura, M. Shimizu, and I. Kuwajima, *Tetrahedron Lett.*, 1699 (1976); (d) E. Nakamura, T. Murofushi, M. Shimizu, and I. Kuwajima, *J. Am. Chem. Soc.*, **98**, 2346 (1976); (e) A. Hosomi, A. A. Shirahata, and H. Sakurai, *Tetrahedron Lett.*, 4043 (1978); (f) T. K. Sarkar and N. H. Anderwen, *ibid.*, 3513 (1978); (g) D. B. Grotjahn and N. H. Andersen, *J. Chem. Soc., Chem. Commun.*, 306 (1981).
- (3) Heating of the resulting mixture to reflux induced no β-elimination to give 1,1-difluoro-2-phenylethene.
- (4) Similar phenomena were observed by Kuwajima and his coworkers. In their case, trimethylsilylacetate reacts with aldehydes in the presence of quaternary ammonium fluoride to yield the Reformatsky-type products, whereas enolization is remarkable with ketones having α-hydrogen to give enol silyl ethers. See ref. 2c and 2d.
- (5) IR (neat) 1525, 1355, 1275 cm⁻¹; MS m/e (rel. %), 353 (M⁺, 2), 325 (1), 308 (1), 307 (3), 303 (12), 302 (92), 181 (43), 155 (100), 153 (29), 137 (2), 133 (52), 127 (98), 109 (37), 99 (90), 81 (40); ¹H-NMR (CDCl₃) δ ppm, 1.30 (3H, d-t, J_{H-P} = 1 Hz, J_{H-H} = 7 Hz), 1.33 (3H, d-t, J_{H-P} = 1 Hz, J_{H-H} = 7 Hz), 2.04 (3H, t, J_{H-F} = 1 Hz), 4.09 (2H, d-q, J_{H-P} = 7 Hz, J_{H-H} = 7 Hz), 4.10, 4.16 (2H, ABq-q-d, J_{AB} = 10 Hz, J_{H-P} = 7 Hz, J_{H-H} = 7 Hz), 6.08 (1H, t, J_{H-F} = 56 Hz), 7.68 (2H, d, J_{H-H} = 9 Hz), 8.23 (2H, d, J_{H-H} = 9 Hz).

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