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Synthesis of Phenyl Substituted Fluoro-Olefins

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Abstract: The anion derived from diethyl α -fluorobenzyl phosphonate (EtO)₂P(O)-CFHPh (2) and lithium diisopropylamide in THF underwent the reaction with aldehydes and ketones to afford a moderate to good yields of phenyl substituted fluoro-olefins RR'C=CFPh (6).

Biologically active molecules containing a vinylic fluorine atom are of special interest, as this moiety is present in a number of enzyme inhibitors.¹ The main methods currently afford vinyl fluorides in which the accompanying terminal group is a halogen,² ester,³ cyanide,⁴ or sulfone⁵ function. However, literature methods for the preparation of the phenyl substituted fluoro-olefins generally lack stereospecificity and generality. Thus, dehydrofluorination of erythro and threo vicinal difluorides PhCFHCFHPh with potassium t-butoxide produces α -fluoro cis and trans stilbene.⁶ Addition of elemental fluorine to propenylbenzene followed by subsequent dehydrofluorination gives cis and trans-1-fluoropropenylbenzenes.⁷ Dehydroiodination of 2-iodo-1-fluoro-1-phenylpropane also leads to the preparation of cis and trans-1-fluoropropenylbenzenes.⁸ Recently, we reported a method to α -fluoro- α , β -unsaturated diesters, which permits variation of the group at β -position *via* an intramolecular Wadsworth-Emmons reaction.⁹ Herein, we describe a general, one-pot synthesis of phenyl substituted fluoro-olefins RR'C=CFPh from the reaction of diethyl α -fluorobenzyl phosphonate (EtO)₂P(O)CFHPh (2) with aldehydes and ketones.

Sodium methoxide-catalyzed condensation of diethyl phosphite with benzaldehyde at room temperature¹⁰ or thermal non-catalyzed addition of diethylphosphite to benzaldehyde¹¹ at 110°C give the diethyl α -hydroxyphosphonate (EtO)₂P(O)CH(OH)Ph (1). The substitution of the α -hydroxy group by fluorine was achieved from the reaction of diethylaminosulphur trifluoride (DAST) with diethyl α -hydroxyphosphonate in dichloromethane solution¹² to give diethyl α -fluorobenzylphosphonate (EtO)₂P(O)CFHPh (2) (eq 1).

$$(EtO)_{2}P(O)H + PhCHO \xrightarrow{\text{Satd. CH}_{3}ONa, rt} (EtO)_{2}P(O)CH(OH)Ph$$

$$1 \qquad 1 \qquad 1 \qquad 1 \qquad (C_{2}H_{3})_{2}NSF_{3} / CH_{2}Cl_{2} \\ \hline 2) EtOH / Py \qquad 2 \qquad (EtO)_{2}P(O)CFHPh \qquad (1)$$

Our investigations indicated that organolithium reagents can be used as a base to abstract the α -proton from (EtO)₂P(O)CFHPh (2). Deprotonation was conveniently carried out with n-butyllithium, t-butyllithium, lithium bis(trimethylsilyl)amide, or lithium diisopropylamide at -78°C in THF. The acid-base reaction between

(EtO)₂P(O)CFHPh 2 and lithium diisopropylamide at -78°C could be detected by acylation of the product carbanion [(EtO)₂P(O)CFPh]⁻Li⁺ 3 with propionyl chloride to give (EtO)₂P(O)CF(COEt)Ph 4, a doublet (J_{F-C-P} = 76 Hz) at -170 ppm in the ¹⁹F NMR spectrum or by addition of methyl alcohol-*d* to the reaction mixture to afford (EtO)₂P(O)CFDPh 5, which was not isolated but was identified by a doublet of triplets at -200 ppm in the ¹⁹F NMR spectrum, with coupling constants of ³J_{F-C-P} = 83 Hz and ³J_{F-C-D} = 7 Hz, respectively (eq 2).



Treatment of diethyl α -fluorobenzyl phosphonate 2 with LDA in the presence of aldehydes or ketones in THF at -78°C was found to afford phenyl substituted fluoro-olefins RR'C=CFPh 6 in 76-48% isolated yields. The initial step in the synthesis of fluoro-olefins 6 is nucleophilic attack of the carbanion 3 at the carbonyl carbon of aldehydes or ketones to form 7, followed by intramolecular elimination of diethylphosphate to afford 6 (eq 3).



The results for the preparation of several phenyl substituted fluoro-olefins RR'C=CFPh **6** (a-o) are summarized in Table 1. The E/Z ratios were determined by integration of the vinyl fluoride signals in the ¹⁹F NMR spectrum. The E/Z assignments of stereochemistry are based on the reports that ³J_{H,F(trans)} is larger than ³J_{H,F(cis)} and ⁴J_{H,F(cis)} is larger than ⁴J_{H,F(trans)} in typical compounds that contain the unit -HC=CFCO₂Et¹³ and -HCC=CFCO₂Et^{9,14}, respectively. The stereoselectivity of the product PhCH=CFPh **6a** was examined in the current approach. The presence of hexamethylphosphoric triamide (HMPT) or N,N'dimethylpropyleneurea (DMPU) as cosolvent in the preparation of **6a** increased the Z-stereoselectivity from 54 to 76 and 62, respectively. However, The presence of lithium chloride (LiCl) in THF did not alter the E/Z ratio (46/54). The condensations of dialkyl(fluorocarbethoxymethyl)phosphonate⁹ anion $[(R^{1}O)_{2}P(O)CFCO_{2}Et]^{-}$ Li⁺ (R¹ = Et or i-Pr) with α -keto ester gave the different E/Z ratios of the product CH₃(CO₂Et)C=CFCO₂Et (**6p** and **6q**). Additional work is in progress to explore this effect.¹⁵

		$(R^{1}O)_{2}P(O)CFHR^{2} + R^{3}C(O)R^{4} -$		LDA / THF $R^3R^4C - CER^2$ 6			
				-78°C to rt			
no.	R ¹	R ²	R ³	R ⁴	Cosolvent	E/Z ^b	Yields (%) ^a
6a	Et	Ph	C ₆ H ₅	Н	_	46/54	71
6b	Et	Ph	C ₆ H ₅	н	HMPT	24/76	68
6 c	Et	Ph	C ₆ H ₅	н	DMPU	38/62	66
6d	Et	Ph	p-CH ₃ C ₆ H ₄	Н	_	50/50	66
6 e	Et	Ph	p-CH3OC6H4	Н	-	43/57	76
6 f	Et	Ph	p-ClC ₆ H ₄	н	-	50/50	65
6 g	Et	Ph	p-NO ₂ C ₆ H ₄	Н	-	49/51	65 ^c
6h	Et	Ph	o-CF3C6H4	Н	-	60/40	74
6 i	Et	Ph	C ₆ H ₁₁	н	-	47/53	72
6 j	Et	Ph	3-(HO)C6H3-4-(OCH3)	Н	-	20/80	71
6 k	Et	Ph	C ₆ H ₅	CH3	-	51/49	50
61	Et	Ph	C ₆ H ₅	C ₆ H ₅	-	_	48
6m	Et	Ph	C ₂ H ₅	CH3	-	48/52	52 ^c
6 n	Et	Ph	C_2F_5	OEtd	-	1/99	71
60	Et	Ph	-(CH ₂)5-		-	-	54c
6p	Et	CO ₂ Et	CH ₃	CO ₂ Et	_	45/55	65
6q	i-Pr	CO ₂ Et	CH ₃	CO ₂ Et	-	79/21	70

Table 1. Preparation of R³R⁴C=CFR² 6

^a Isolated yields are based on (R¹O)₂P(O)CFHR². ^b E/Z ratio was obtained by ¹⁹F NMR integration of vinyl fluorine signals. ^c ¹⁹F NMR yields, C₆H₅CF₃ as internal standard. ^d DIBAL was used as reducing agent to give the product C₂F₅CH=CFPh. All isolated products give satisfactory ¹⁹F, ¹H, ¹³C NMR, FTIR and GC/MS data.

In a typical experimental procedure, a 100 mL two-necked flask equipped with a septum port, a magnetic stirring bar, and a reflux water condenser topped with a nitrogen T-tube leading to a source of nitrogen and mineral oil bubbler was charged sequentially with 16 mL of dry THF, 8.0 mmol (1.96 g) of $(EtO)_2P(O)CFHPh$ and 10.0 mmol (1.12 g) of cyclohexanecarboxaldehyde. The contents of the flask were cooled to $-78^{\circ}C$ via a dry ice/i-PrOH slush bath. To the cooled solution, 10.5 mmol (7.0 mL) of a 1.5 M cyclohexane solution of lithium diisopropylamide mono(tetrahydrofuran) was added dropwise via syringe. The resultant solution was stirred at $-78^{\circ}C$ for 30 minutes and then allowed to warm to room temperature over

4 hours and stirred at that temperature overnight. The reaction mixture was poured into water (40 mL), and the water layer was extracted with ether (3 X 40 mL). The combined organic materials were washed with dilute hydrochloric acid until the washings were neutral to litmus paper. The resulting solution was washed successively with brine (30 mL) and water (30 mL), dried over MgSO₄, and concentrated in a vacuo. The residue was purified by flash chromatography column (100 g of silica gel, 200-425 mesh) eluting with n-hexane/ethyl acetate (24/1) mixture to give 1.18 g (72%) of (E,Z)-C₆H₁₁CH=CFPh (99% pure by GLPC analysis); ¹⁹F NMR (CDCl₃, δ): (E)-isomer -102.4 (d,³J_{FH}= 22 Hz), (Z)-isomer -121.0 (d,³J_{FH}= 39 Hz); ¹H NMR (CDCl₃, δ): (E)-isomer 1.11-1.76 (m), 2.23-2.30 (m), 5.25 (d,d,³J_{HF} = 22 Hz, ³J_{HH} = 10 Hz), 7.26-7.50 (m), (Z)-isomer 1.11-1.76 (m), 2.60-2.70 (m), 5.27 (d,d,³J_{HF} = 38 Hz, ³J_{HH} = 9 Hz), 7.26-7.50 (m); ¹³C NMR (CDCl₃, δ): 25.7-35.3, 123.9 (d, ²J_{C=CF} = 7 Hz), 127.5-133.2, 155.8 (d, ¹J_{CF} = 240 Hz), 157.1; GC/MS m/z (relative intensity %): (E)-isomer 204(M⁺, 32.16), 122(M⁺-C₆H₁₁+H, 100.0), (Z)-isomer 204(M⁺, 6.22), 122(M⁺-C₆H₁₁+H, 100.0); FTIR (CCl₄ solution): 3029 m (Ar-H), 1653 s (C=C), 1282 m (C-F); HRMS: Calc'd. 204.1314; Found: (E)-isomer, 204.1334; (Z)-isomer, 204.1342.

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REFERENCES

- 1. McCarthy, J.R.; Jarvi, E.T.; Matthews, D.P.; Edwards, M.L.; Prakash, N.J.; Bowlin, T.L.; Mehdi, S.; Sunkara, P.S.; Bey, P. J. Am. Chem. Soc. **1989**, 111, 1127.
- 2. Edwards, M.L.; Stemerick, D.M.; Jarvi, E.T.; Matthews, D.P.; McCarthy, J.R. Tetrahedron Lett. 1990, 39, 5571.
- 3. Thenappan, A.; Burton, D.J. J. Org. Chem. 1990, 55, 4639. Machleidt, H.; Wessendorf, R. Lieb. Ann.Chem. 1964, 674, 1.
- 4. Patrick, T.B.; Nadji, S. J. Fluorine Chem. 1990, 49, 147. Xu, Z.Q.; DesMarteau, D.D. J. C. S. Perkin Trans I 1992, 313.
- 5. McCarthy, J.R.; Matthews, D.P.; Edwards, M.L.; Stemerick, D.M.; Jarvi, E.T. Tetrahedron Lett. 1990, 38, 5449.
- 6. Zupan, M.; Pollak, A. J. Org. Chem. 1977, 42, 1559.
- 7. Merritt, R.F. J. Am. Chem. Soc. 1967, 89, 609.
- 8. Kuroboshi, M.; Hiyama, T. Tetrahedron Lett. 1991, 32, 1215.
- 9. Tsai, H.J.; Thenappan, A.; Burton, D.J. J. Org. Chem. 1994, 59, 7085.
- 10. Abramov, V.S. Doklady Akad. Nauk SSSR 1950, 73, 487.
- 11. Kharasch, M.S.; Mosher, R.A.; Bengelsdor, I.S. J. Org. Chem. 1960, 25, 1000.
- 12. Blackburn, G.M.; Kent, D.E. J. C. S. Perkin Trans I 1986, 913.
- 13. Merritt, R.F. J. Org. Chem. 1966, 31, 1859.
- 14. Allmendinger, T. Tetrahedron 1991, 47, 4905.
- 15. Eguchi, T.; Aoyama, T.; Kakinuma, K. Tetrahedron Lett. 1992, 33, 5545.

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