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NOVEL SYNTHESIS OF F-1-ALKENE-1-PHOSPHONATE DERIVATIVES FROM F-ALKANOYL CHLORIDES AND THEIR EFFICIENT USE FOR PREPARING FLUORO-α,β-ENONES[1]

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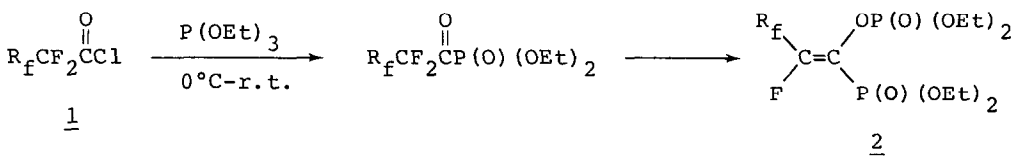
Abstract: (Z)-1-[(diethoxyphosphinyl)oxy]-F-1-alkene-1-phosphonates were synthesized in good yields from F-alkanoyl chlorides and triethyl phosphite, and were proved to be useful precursors for the preparation of fluoro-α,β-enones.

Electron-deficient olefinic compounds, such as vinyl ketones,[2] vinyl phosphorus compounds,[3] vinyl sulfoxides,[4] and nitroolefins[5] have been used as valuable intermediates in organic transformations. However, the synthetic application of fluorine-containing analogs, whose olefinic linkages are more electron-deficient, is limited because of the paucity of effective methods for preparing such compounds.

In this communication, we report a new synthesis of F-1-alkene-1-phosphonate derivatives from F-alkanoyl chlorides, which can serve as useful precursors for the preparation of fluoro-α,β-enones.

When F-alkanoyl chlorides (1)[6] were treated with triethyl phosphite (2 equiv) at 0°C to room temperature for 2 h, diethyl (Z)-1-[(diethoxyphosphinyl)oxy]-F-1-alkene-1-phosphonates (2)[7] were obtained in good yields. Use of no solvent gave the best results. This reaction produced no trace of the corresponding F-acylphosphonates in spite of the amount of triethyl phosphite and its addition mode being changed, in contrast to the reaction between ordinary carboxylic acid halides and trialkyl phosphites which generally gives acylphosphonates.[8]



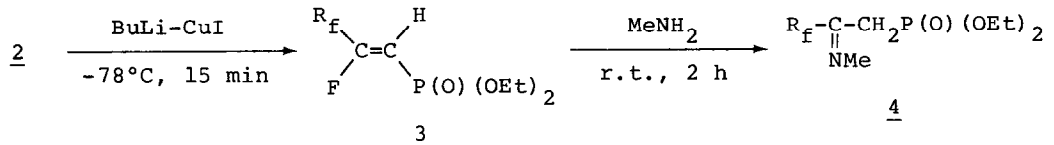
1 2

R_f=CF_3 (77%); R_f=n-C_6F_{13} (60%)
R_f=C_2F_5 (74%); R_f=n-C_8F_{17} (66%)

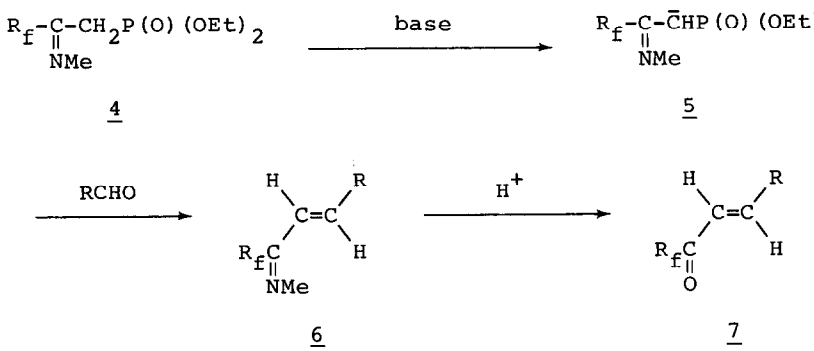
The exclusive formation of the phosphonates 2 can be understood by the intermediacy of F-acylphosphonate and its extremely high reactivity toward a nucleophile. Probably, the F-acylphosphonate formed initially by the Arbuzov-type reaction is successively attacked by another phosphite molecule on its carbonyl oxygen atom,[9]

followed by elimination of a fluoride ion to form the product. This mechanism is supported by the observation that the reaction of 1 with triethyl phosphite in the presence of diethyl phosphite as proton source gave mainly 1H-1-[(diethoxyphosphinyl)oxy]-F-alkanephosphonates,[7] which produced 2 quantitatively on treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C.

The phosphonates (2) thus obtained can readily be reduced by butylcopper(I) reagent at -78°C to the corresponding (Z)-1H-F-1-alkene-1-phosphonates (3)[7] in high yields.[10] Either THF or diethyl ether could be used as solvent. The addition of tetramethylethylenediamine (TMEDA) to the solvent improved the reproducibility of the reaction. It is noteworthy that no butylated product was obtained at all and that the enol phosphate moiety in 2 was selectively reduced with complete retention of configuration. These reduced phosphonates 3 underwent the Michael addition reaction when treated with an excess of methylamine at room temperature for 2 h, giving nearly quantitative yields of fluorinated β-(methylimino)-alkanephosphonates (4).[7,12]

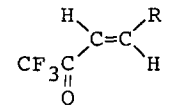
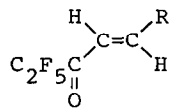
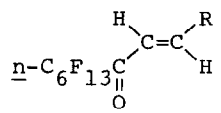


The compounds of this type (4)[13] are expected to be an efficient Horner-Wittig type reagent for the preparation of fluorinated α,β-unsaturated ketones. In fact, the conversion of the phosphonates 4 into their anion form (5) and the subsequent treatment of the anion with an aldehyde, followed by acidic hydrolysis, afforded good to excellent yields of the expected product (7).[7] Table I summarizes the results of the reaction of 4, along with the vinylic H-H coupling constants of 7.



Butyllithium, LDA, and sodium hydride could equally be used as base for generating the phosphonate anions 5. The anions (5) smoothly reacted with various aldehydes including crotonaldehyde at room temperature to give 7, but ketones failed to react with 5 even at elevated temperatures, only fluoro β-oxoalkanephosphonates[7] being obtained after hydrolytic workup. Of much significance is

Table I. Preparation of Fluorinated α,β-Unsaturated Ketones[a]

Enone 7		R	Yield of 7[b] %	J (H-H)[c] Hz
	7a	n-C_6H_{13}	68	16.5
	7b	Ph	74	15.6
	7c	Pr	87	15.0
	7d	i-Pr	77	15.0
	7e	n-C_6H_{13}	90	15.2
	7f	c-C_6H_{11}	87	15.3
	7g	Ph	95	15.6
	7h	trans-CH_3CH=CH	80	15.0
	7i	n-C_6H_{13}	94	15.2
	7j	Ph	93	15.3

[a] LDA was used as base. [b] Isolated by means of preparative TLC, column chromatography, or distillation. [c] Determined by ^1H and ^{19}F NMR analyses.

that the reaction with aldehydes proceeds stereoselectively. As shown in Table I, only E-isomers of fluorinated α,β-unsaturated ketones (7) were obtained. α,β-Unsaturated imines (6),[7] whose stereochemistry was confirmed as E, could be isolated when the reaction mixture was not treated with acid. No trace of the Z-isomer was detected in the reaction mixture.

The typical procedure for the present olefination reaction is as follows: To a solution of LDA (1.2 equiv) in diethyl ether was added diethyl 3,3,4,4,4-pentafluoro-2-(methylimino)butanephosphonate (4, R_f=C_2F_5) at -78°C. After stirring for 0.5 h at the same temperature, freshly distilled benzaldehyde (1.0 equiv) was gradually added to the resulting mixture at -78°C. This reaction mixture was then warmed up to room temperature and was stirred overnight. After addition of 5% hydrochloric acid, the whole mixture was stirred at room temperature for 2 h, and was subjected to extraction with pentane (30 ml x 3). The extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Column chromatography on silica gel gave pure 4,4,5,5,5-pentafluoro-1-phenyl-1-buten-3-one (7g) in 95% yield.

References and Notes

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10. The reduction of 2 with butylcopper(I) reagent was conducted in the following manner. Butyllithium (42.5 mmol) in hexane (1.5 M) was added to a mixture of cuprous iodide (25.0 mmol) and TMEDA (25.0 mmol) in THF (50 ml) under nitrogen at -78°C. To this solution, after stirring for 0.5 h, was gradually added the phosphonate 2 (10.0 mmol) in THF (5 ml). The whole mixture was stirred for 15 min at the same temperature and was quenched with a saturated aqueous ammonium chloride solution.[11] Extraction with ether followed by distillation *in vacuo* or column chromatography on silica gel gave only one stereoisomer 3 in 60-79% yields.
11. Quenching with an excess of aqueous methylamine solution directly afforded fluoro β-(methylimino)alkanephosphonates (4) in 60-70% yields.
12. The phosphonate 4 carrying $R_f=CF_3$ exists preferentially in the form of enamine, being equally effective for the subsequent olefination reaction.
13. The use of fluorine-free β-(alkylimino)ethanephosphonates for the formylolefination of aldehydes and ketones has been described: W. Nagata and Y. Hayase, J. Chem. Soc. C, 460 (1969); A.I. Meyers, K. Tomioka, and M.P. Fleming, J. Org. Chem., 43, 3788 (1978).

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