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The crystal structure of 2-fluoro-1-(p-methoxyphenyl)-1-penten-3-yne, a fluorinated vinylacetylene prepared via Horner–Wadsworth–Emmons condensation

Tanya C. Sanders [a], James A. Golen [a], Paul G. Williard [b], Gerald B. Hammond [a,*,1]

[a] *Department of Chemistry, University of Massachusetts Dartmouth, North Dartmouth, MA 02747-2300, USA*

[b] *Department of Chemistry, Brown University, Providence, RI 02912, USA*

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Abstract

Horner–Wadsworth–Emmons condensation of (α-fluoropropargyl) phosphonate ester **3** and p-anisaldehyde provides a new method for the synthesis of monofluoro-conjugated enynes. Spontaneous crystallization of **4** yielded the Z isomer of 2-fluoro-1-(p-methoxyphenyl)-1-penten-3-yne. A comparison of bond angles and distances between **4** and vinylacetylene showed shorter bond distances along the enyne system in **4**. © 1997 Elsevier Science S.A.

Keywords: α-Fluorophosphonates; Fluorinated enzymes; X-ray; Horner–Wadsworth–Emmons condensation

The chemistry and biology of conjugated enynes (vinylacetylenes), enediynes and dienynes have received extensive coverage in recent years [1–4]. We were particularly interested in the new and attractive synthetic potentials uncovered by recent findings in the chemistry of enyne transition metal complexes. For example, cobalt-coordinated 1,3-enynes add chemo-, regio- and stereoselectively to nitrile oxides acting as 1,3-dipoles, to provide 5-alkynyl-2-oxazoline derivatives [5]. In the presence of Mn(III), these cobalt complexes react selectively with β-dicarbonyl compounds to yield substituted furans [6]. A ruthenium (II) enynyl complex has been shown to mediate the catalytic dimerization of 1-alkynes to (Z)-1,4-disubstituted butenynes [7]; enynes have also undergone regioselective insertion into ruthenium–hydrogen bonds [8,9]. Other stable interactions of 1-buten-3-ynes with rhenium have been reported [10,11]. We speculated that the substitution of a vinyl proton with fluorine might impart desirable chemical and physical properties to conjugated fluoroenynes acting as ligands. A measure of the ability of fluorinated 1-buten-3-ynes to function as desirable ligands can be obtained by the study of their experimental geometries as provided by X-ray analysis. Unfortunately, no information on the experimental geometries of fluorinated 1-buten-3-ynes is available. Only two crystal structures corresponding to phenyl-substituted enynes have been published thus far: 1,1,4-triphenyl-1-buten-3-yne and *cis*-4,5-diphenyl-4-hexen-2-yne [12]. We now wish to report the first X-ray structure of a fluorinated phenyl-substituted vinylacetylene, 2-fluoro-1-(p-methoxyphenyl)-1-penten-3-yne (**4**), prepared via a hitherto unknown sequence that included a Wittig-type condensation of a fluorinated synthon.

An inspection of the relevant literature on the preparation of fluorinated enynes revealed a handful of palladium-catalyzed cross-coupling reactions of fluorinated olefins that ultimately yielded 1,2-difluoro-1-buten-3-ynes [13–15]. The synthesis of monofluoroenynes, however, is much less documented. Two distinct approaches have been reported. Camps et al. introduced fluorine on a pre-existing enyne via a four-step sequence through an epoxide intermediate in 7% overall yield [16]. Eddarir et al. [17] used a palladium-catalyzed condensation of 1-bromo-1-fluoro-2-arylethylene with a terminal alkyne. Their approach was circumscribed to aromatic substituents on the olefinic carbon. For the preparation of monofluoro 1-buten-3-yne **4** we considered the possibility of reacting (α-fluoropropargyl) phosphonate **3** with p-anisaldehyde, using Horner–Wadsworth–Emmons conditions. This approach, of course, relied on the availability of an unsaturated fluorophosphonate **3**, the first synthesis of which was reported by our group [18]. The reaction sequence leading to **4** is shown in Scheme 1. α-Hydroxyphosphonate **2** [19], prepared through a base-promoted 1,2 O to C phos-

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[*] Corresponding author.

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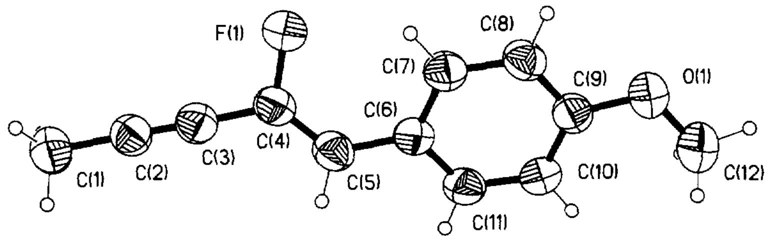
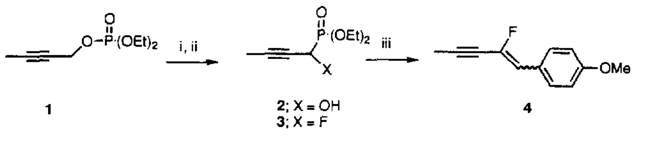


Fig. 1. A view of CH_3–C≡C–C(F)=CH–C_6H_4–OCH_3 showing the labeling of the non-H atoms. Displacement ellipsoids are shown at the 50% probability level and H atoms are drawn as small circles of arbitrary radii.



Scheme 1. Key: (i) LDA, toluene; (ii) DAST, CH_2Cl_2; (iii) NaH, THF, *p*-anisaldehyde.

phorus migration of but-2-ynyl phosphate **1**, was fluorinated to produce exclusively the desired α-fluoro isomer **3** in very good yield [20]. The anion of **3**, generated using NaH in THF, reacted with *p*-anisaldehyde to furnish the desired enyne **4** in approximate 1:1 *E*/*Z* ratio in 22% yield after purification [2]. Use of phase transfer conditions (NaOH, triethylbenzylammonium chloride) led to an improved yield (36%). Use of other reaction conditions (DBU/LiCl, K_2CO_3/18-Crown-6, KF/Al_2O_3, LDA, $NaN(TMS)_2$) led to no reaction, poorer yields or intractable mixtures. The instability of the α-fluorocarbanion might have accounted for the moderate yields observed.

Upon standing, a crystalline precipitate formed. Analysis of its X-ray crystal structure [3] revealed the molecular structure shown in Fig. 1 in which the fluorine atom and the phenyl ring are *cis* to each other. Interestingly, the reported crystalline phenyl-substituted enynes contain two and three phenyl substituents which appear to substantially increase their chances of crystallization. In our case, it appears that only one phenyl ring is needed to effect crystallization when a fluorine atom is present. A comparison of bond angles and distances between **4** and vinylacetylene [12] showed shorter bond distances along the enyne system in **4** (C(2)–C(3), 1.185 Å; C(3)–C(4), 1.418 Å; C(4)–C(5), 1.313 Å), perhaps indicating a higher degree of conjugation. A longer bond length is observed between the double bond and the phenyl ring (C(5)–C(6), 1.455 Å). Also, the bond angles on the olefinic carbon bonded to fluorine are quite distinctive (F(1)–C(4)–C(3), 111.6°; C(5)–C(4)–CF(1), 119.7°).

We are currently investigating optimal conditions for the generation of the α-carbanion from **3**, as well as the preparation of enediynes and tetrasubstituted enynes using the Horner–Wadsworth–Emmons reaction.

Acknowledgements

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[2] Preparation of 2-fluoro-1-(*p*-methoxyphenyl)-1-penten-3-yne. To a stirred mixture of NaH (0.027 g, 1.1 mmol), THF (19 ml) and **3** (0.198 g, 0.95 mmol) at room temperature, was added *p*-anisaldehyde (0.155 g, 1.1 mmol). The reaction was stirred for 4 h after which the mixture was quenched with water and extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by silica gel chromatography (hexane:EtOAc, 1:1) to yield **4** (0.040 g, 22%): *E* isomer ^{1}H-NMR ($CDCl_3$) δ 2.15 (d, J=5.4 Hz, 3H), 3.81 (s, 3H), 6.46 (d, J=17.3 Hz, 1H) 6.85–6.90 (m, 2H), 7.56 (d, J=8.9 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ −105.9 (s): *Z* isomer ^{1}H-NMR ($CDCl_3$) δ 2.05 (d, J=4.8 Hz, 3H), 3.81 (s, 3H), 5.88 (d, J=35.6 Hz, 1H) 6.85–6.90 (m, 2H), 7.43 (d, J=8.9 Hz, 2H); ^{19}F-NMR ($CDCl_3$) δ −103.5 (s). EIMS 190 (M^+, 100), 175 (33), 159 (11), 146 (99), 127 (32), 120 (11), 101 (9).

[3] Crystal data for **4**: $C_{12}H_{11}FO$, monoclinic, space group $P2_1/n$, $a=10.486$ (2), $b=7.4850$ (10), $c=13.406$ (2) Å, $\alpha=90$, $\beta=105.98$, $\gamma=90°$, $U=1011.5$ (3) Å^3, $Z=4$, $\mu=0.091$ mm^{-1}, $T=293$ (2) K. White prism 0.60×0.40×0.30 mm^3, Mo Kα radiation, Nicolet Siemens R3*m*/V diffractometer, 2685 intensities to $\theta=25.98°$, 1980 unique ($R_{int}=0.0199$) used for all calculations. Structure solution by direct methods, anisotropic refinement on F^2 (program SHELXTL-PLUS, G.M. Sheldrick, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA, 1990). H atoms refined as riding with fixed isotropic *U*. Final $wR(F^2)$ 0.1412, conventional $R(F)$ 0.0567 for 127 parameters.

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