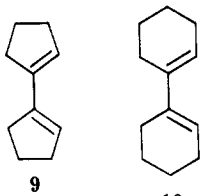
cyclobutacyclopropabenzene.[8] In contrast, a sizeable bathochromic shift is observed for the linear isomer [λ_{max} (cyclohexane) 284, 287.5, 294 nm]. Elemental analysis was provided by high-resolution mass spectrometry: calcd for $C_{11}H_{10}$ m/e 142.0783, found m/e 142.0785.

The dienes **9** and **10**, required for the synthesis of precursors **5** and **6**, can be prepared from the simple two-step



9 **10**

pinacol approach described by Greidinger and Ginsberg.[9] Dehydrohalogenation of **5** yielded **2** in 55% yield. The NMR spectrum is diplayed in Figure 1 (spectrum B). Other spectral properties are as follows: IR (CCl_4) 1651 cm^{-1}; UV (pentane) λ_{max} 270 (ϵ 920), and 279 nm (960); calcd for $C_{13}H_{14}$ m/e 170.1096, found m/e 170.1092.

Under similar conditions **6** yielded **3** in 83% yield; NMR (Figure 1, spectrum C); IR (CCl_4) 1660 cm^{-1}; UV (pentane) λ_{max} 273 (ϵ 908), 283 nm (915); calcd for $C_{15}H_{18}$ m/e 198.1408, found m/e 198.1406.

The results of studies on the chemical and physical properties of these cycloproparenes will be reported later.

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Registry No. **1**, 90968-12-0; **2**, 90968-13-1; **3**, 90968-14-2; **4**, 90968-15-3; **5**, 90968-16-4; **6**, 90968-17-5; **7**, 88180-95-4; **8**, 69573-29-1; **9**, 934-02-1; **10**, 1128-65-0.

(7) Davalian, D.; Garratt, P. J.; Mansuri, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 980.
(8) For a discussion of the electronic spectra of simple cycloproparenes, see: Halton, B. *Ind. Eng. Chem. Prod. Res. Rev.* **1980**, *19*, 349.
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A Safe Facile Synthesis of Difluorophosphonoacetic Acid

Summary: Copper(I) halide catalyzed acylation of [(diethoxyphosphinyl)difluoromethyl]zinc bromide with ethyl chloroformate provides a safe, easily scaled up preparation of ethyl difluoro(diethoxyphosphinyl)acetate from readily available precursors. Silyation of this ester, followed by hydrolysis, gives difluorophosphonoacetic acid.

Sir: Pronounced biological effects are often observed when hydrogen atoms in a biologically active molecule are replaced by fluorine.[1,2] Recently, we,[3,4] as well as others,[5]

(1) "Biomedicinal Aspects Of Fluorine Chemistry"; Filler, R., Kobayashi, Y., Eds.; Kodasha/Elsevier: New York, 1982.
(2) "Biochemistry Involving Carbon-Fluorine Bonds"; Filler, R., Ed.; ACS Symposium Series No. 28, 1978.
(3) Burton, D. J.; Pietrzyk, D. J.; Ishihara, T.; Fonong, T.; Flynn, R. M. *J. Fluorine Chem.* **1982**, *20*, 617.
(4) Fonong, T.; Burton, D. J.; Pietrzyk, D. J. *Anal. Chem.* **1983**, *55*, 1089.

Scheme I

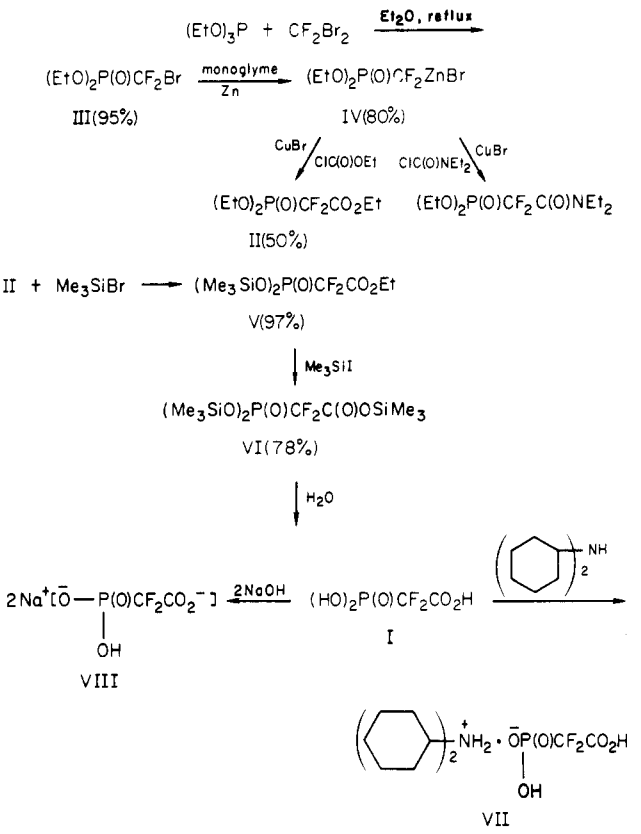

Table I. Ionization Constants

	$(HO)_2P(O)$-CF_2CO_2H	$(HO)_2P(O)$-CH_2CO_2H[22]	$(HO)_2P(O)$-$CF_2P(O)(OH)_2$[4]
pK_{a_1}	1.30 ± 0.10	2.0	1.46 ± 0.15
pK_{a_2}	1.95 ± 0.03	5.11 ± 0.04	2.14 ± 0.05
pK_{a_3}	6.16 ± 0.02	8.69 ± 0.05	5.78 ± 0.05
pK_{a_4}			8.16 ± 0.02

have been interested in fluorinated analogues of biologically important phosphonic acids. Thus, our attention was drawn to a comparison of the biological and chelation properties of phosphonoacetic acid[6-8] and difluorophosphonoacetic acid (I). Unfortunately, the preparation of I has not been described; only a poorly characterized ester of I has been reported[9] in low yield via the reaction of triethyl phosphite and tetrafluoroethylene oxide.[10]

We now report a safe, facile, easily scaled up preparation of ethyl difluoro(diethoxyphosphinyl)acetate (II) from readily available precursors (cf. Scheme I).

Diethyl (bromodifluoromethyl)phosphonate (III) is readily prepared from triethyl phosphite and dibromodifluoromethane.[11] Reaction of III with zinc dust gives the

(5) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930.
(6) Phosphonoacetic acid has been shown to effectively inhibit the replication of Herpes virus[7] and has been shown to suppress replication of DNA tumor viruses.[8]
(7) Hay, J.; Brown, S. M.; Jamieson, A. T.; Rixon, F. J.; Moss, H.; Dargon, D. A.; Subak-Sharp, J. H. *J. Antimicrob. Chemother.* **1977**, *3*, 63. Oda, H.; Mori, R.; Miyazono, J.; Iwasaha, T. *Arch. Virol.* **1979**, *62*, 175. Overly, L. R.; Robishaw, E. E.; Schleacher, J. B.; Ructer, A.; Shipkowitz, N. L.; Mao, J. *Antimicrob. Agents Chemother.* **1974**, *6*, 360.
(8) Allaudeen, H. S.; Bertino, J. R. *Biochim. Biophys. Acta* **1978**, *520*, 490. Elliot, R. M.; Bateson, A.; Kelly, D. C. *J. Virol.* **1980**, *33*, 539.
(9) Ginsburg, V. A.; Vasuk'eva, M. N. *Zh. Obshch. Khim.* **1967**, *37*, 2483 (English Translation, 2371).
(10) The ester was obtained in only 14% yield (impure). The major product of this route is the toxic diethyl fluorophosphate [$(EtO)_2P(O)F$]. Also, tetrafluoroethylene oxide is an explosive reagent and should be handled with caution.
(11) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329.

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stable [(diethoxyphosphinyl)difluoromethyl]zinc bromide (IV) which is acylated with acyl chlorides to yield (2-oxo-1,1-difluoroalkyl)phosphonates.[12] However, acylation of IV with ethyl chloroformate gave little or no II. However, catalysis with cuprous bromide gave a smooth reaction of IV and ethyl chloroformate to provide a good yield of II. Similar catalysis permitted the acylation of IV with diethylcarbamoyl chloride to give the corresponding amide derivative.[13]

Conversion of II to I was accomplished via selective silylation[14,15] of II at the phosphonic ester site to give V.[16] Further silylation of V with the more reactive iodotrimethylsilane gave the trisilylated ester VI.[17] Dissolution of VI in water immediately gave I in quantitative yield. I is extremely hygroscopic but may be isolated as a white crystalline monoamine salt[18] (VII) or as a stable monohydrate of the disodium salt[19] (VIII) of I.

Aqueous titration[20] of I gave two breaks with a stoichiometry of 1.993 (± 0.013) to 1 indicative of three acidic protons. Ionization constants of I were determined from titration of multiple independent titrations. The ionization constants were calculated by fitting the titration data to a titration function via a nonlinear least-squares program.[21] Table I summarizes the ionization constants of I relative to phosphonoacetic acid[22] and the analogous (difluoromethylene)bis[phosphonic acid].[23]

A typical preparation of II is described with operational details. To a 2-L flask equipped with a reflux condenser and cooled in an ice bath was added 267.0 g (1.0 mol) of III and 500 mL of dry monoglyme. Then 65.4 g (1.0 mol) of acid-washed zinc powder was added in one portion. The temperature was allowed to slowly rise until a vigorous exothermic reaction was initiated. After 4 days at room temperature, the solution was filtered in a Schlenk funnel (medium frit) and diluted with 250 mL of dry CH_3CN. Then 2.0 g (0.014 mol) of Cu^IBr were added followed by 115 mL (1.2 mol) of ethyl chloroformate. The reaction mixture was stirred overnight and the volume was reduced by rotary evaporation and then diluted with 500 mL of water. The insoluble inorganic salts were separated by suction filtration and washed with 100 mL of CH_2Cl_2. The aqueous portion was twice extracted with 200 mL of CH_2Cl_2. The organic fractions were combined, dried over Na_2SO_4, rotary evaporated, and flash distilled. Redistillation gave 131 g (50%) of II: bp 74–77 °C (0.2 mmHg); ^{19}F NMR ϕ^* −116.3 (d) $J_{P,F}$ = 96 Hz; ^{31}P NMR δ 2.91 (t); ^{13}C NMR δ 111.2 (td) (CF_2) $J_{C,F}$ = 272 Hz, $J_{C,P}$ = 204 Hz; ^1H NMR δ 1.38 (t) $J_{H,H}$ = 7.1 Hz, 1.40 (t) 7.0 Hz, 4.34 (dq) $J_{H,H}$ = 7.3 Hz, 4.40 (q) $J_{H,H}$ = 7.3 Hz; IR (neat) 1770 cm^{-1} (CO), 1290 (PO). Anal. Calcd for $C_8H_{15}F_2O_5P$: C, 36.93; H, 5.81. Found: C, 36.94; H, 5.69.

The described work now makes available a convenient source of difluorophosphonoacetic acid and its derivatives for detailed biological and chemical investigation. Future reports will detail additional studies in our laboratories in these directions.

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Registry No. I, 91410-83-2; II, 17843-01-5; III, 65094-22-6; V, 91410-84-3; VI, 91410-85-4; VII, 91410-86-5; VIII, 91410-87-6; CuBr, 7787-70-4; Zn, 7440-66-6; ClC(O)OEt, 541-41-3.

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(12) Burton, D. J.; Ishihara, T.; Maruta, M. *Chem. Lett.* **1982**, 755.
(13) bp 105 °C (0.2 mmHg); ^{19}F NMR ϕ^* −108.8 (d) $J_{P,F}$ = 100 Hz; ^{31}P NMR 3.92 (t); IR 1660 cm^{-1} (CO), 1280 (PO).
(14) Morita, T.; Okamato, Y.; Sakura, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2169.
(15) Sekine, M.; Futsuaki, T.; Yamada, Z.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2509.
(16) bp 75–80 °C (0.1 mmHg); ^{19}F NMR ϕ^* −118.2 (d) $J_{P,F}$ = 100 Hz; ^{31}P NMR δ −15.7 (t); ^1H NMR δ 0.35 (s), 1.37 (t) $J_{H,H}$ = 7.2 Hz, 4.37 (q) $J_{H,H}$ = 7.0 Hz.
(17) bp 88–92 °C (0.3 mmHg); ^{19}F NMR ϕ^* −118.0 (d) $J_{P,F}$ = 102 Hz; ^{31}P NMR δ −16.3 (t); ^1H NMR δ 0.35 (s) $P(OSiMe_3)_2$, (s) CO_2SiMe_3.
(18) mp 210–212 °C dec; ^{19}F NMR (H_2O) ϕ^* −112.5 (d) $J_{P,F}$ = 89 Hz; ^{31}P NMR δ 0.8 (t). Anal. Calcd for $C_{14}H_{26}F_2NO_5$: C, 47.06; H, 7.33; N, 3.92. Found: C, 47.17; H, 7.07; N, 3.76.
(19) Titration of VIII gave a M_r of 237.5; calcd M_r 238.0; mp (VIII) 271–275 °C dec.
(20) M_r of I from titration was found to be 176.5 (calcd 176.8). The anhydrous acid does not appear thermally stable above 100 °C and shows some decomposition at room temperature after several weeks.
(21) Cf. ref 3 and 4 for details of the titration procedure and calculation of K_a's.
(22) Heubel, P. C.; Popov, A. I. *J. Solution Chem.* **1979**, *8*, 615.
(23) Cf. ref 4—data corrected for Na^+ ion effects.

Organotin Chemistry. Preparation of 2,3-Disubstituted 1,3-Butadienes Using 2,3-Bis(trimethylstannyl)-1,3-butadiene and 1,4-Bis(trimethylstannyl)-2-butyne

Summary: 2,3-Bis(trimethylstannyl)-1,3-butadiene is a versatile synthon for the 2,3-dianion of 1,3-butadiene; mono and bis derivatizations with electrophiles such as halosilanes, disulfides, selenium, alkyl halides, aldehydes, and ketones have been carried out.

Sir: We report here procedures for the preparation of a wide variety of 2,3-disubstituted 1,3-butadienes using two new synthetic equivalents of the 2,3-dianion of 1,3-butadiene.[1] Treatment of either 2,3-dichloro-1,3-butadiene[2] or 1,4-dichloro-2-butyne[3] with 2 equiv of (trimethylstannyl)lithium gave the somewhat air-sensitive bis(trimethylstannyl)acetylene 1 (Scheme I). This compound was isomerized to the more stable butadiene 2,[4] an air-stable distillable liquid which can be stored in the freezer

(1) Other butadiene anions have been prepared. (a) Monoanions: Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967. Brown, P. A.; Jenkins, P. R. *Tetrahedron Lett.* **1982**, *23*, 3733. (b) Cuprate: Nunomato, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912. (c) Substituted 1,4-dilithio-1,3-butadienes: Reich, H. J.; Reich, I. L. *J. Org. Chem.* **1975**, *40*, 2248. Atwell, W. H.; Weyenberg, D. R.; Gilman, H. *J. Org. Chem.* **1967**, *32*, 885. Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1184. Braye, E. H.; Hübel, W.; Caplier, I. *J. Am. Chem. Soc.* **1961**, *83*, 4406.
(2) Gibbs, H. N.; Day, R. W. *Brit. Pat.* 1 084 742; *Chem. Abstr.* **1967**, *67*, P108184*k*. The reaction of 2,3-dichlorobutadiene with lithium diphenylphosphide gives 1,4-bis(diphenylphosphino)-2-butyne: Arthurs, M.; Nelson, S. M.; Walker, B. J. *Tetrahedron Lett.* **1978**, 1153.
(3) This compound as well as 1,4-dihydroxy-2-butyne has been frequently used as a precursor for 2- and 2,3-substituted butadienes: Bridges, A. J.; Fischer, J. W. *Tetrahedron Lett.* **1983**, *24*, 445. Jeganathan, S.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *21*, 4763. Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, 3323. Ishino, Y.; Nishiguchi, I.; Kim, M.; Hirashima, T. *Synthesis* **1982**, 740.
(4) Compound 1 can be reliably isomerized to 2 by treatment with a catalytic amount of $(CH_3)_3SnLi$ or CH_3Li in THF/HMPA (2 equiv) at 25 °C for 30 min. The minimum conditions needed for the isomerization vary with the batch of $(CH_3)_3SnLi$. One-pot conversion of 1,4-dichloro-2-butyne to 2 can be accomplished in 70% yield. To reproducibly obtain 1 free of 2, the original reaction mixture must be quenched with H_2O at −78 °C (84% yield). Trimethyltinlithium was prepared from $(CH_3)_3SnBr$ by the procedure of Tamborski, C.; Ford, F. E.; Soloski, E. J. *J. Org. Chem.* **1963**, *28*, 237. We found it necessary to employ lithium wire containing 1% sodium.

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