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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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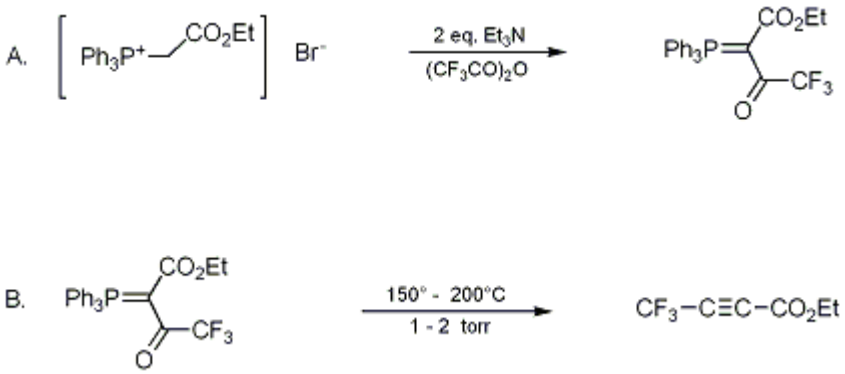
α-ACETYLENIC ESTERS FROM α-ACYLMETHYLENEPHOSPHORANES: ETHYL 4,4,4-TRIFLUOROTETROLATE

[2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester]



Submitted by B. C. Hamper[1]
Checked by T. Harrison and Larry E. Overman.

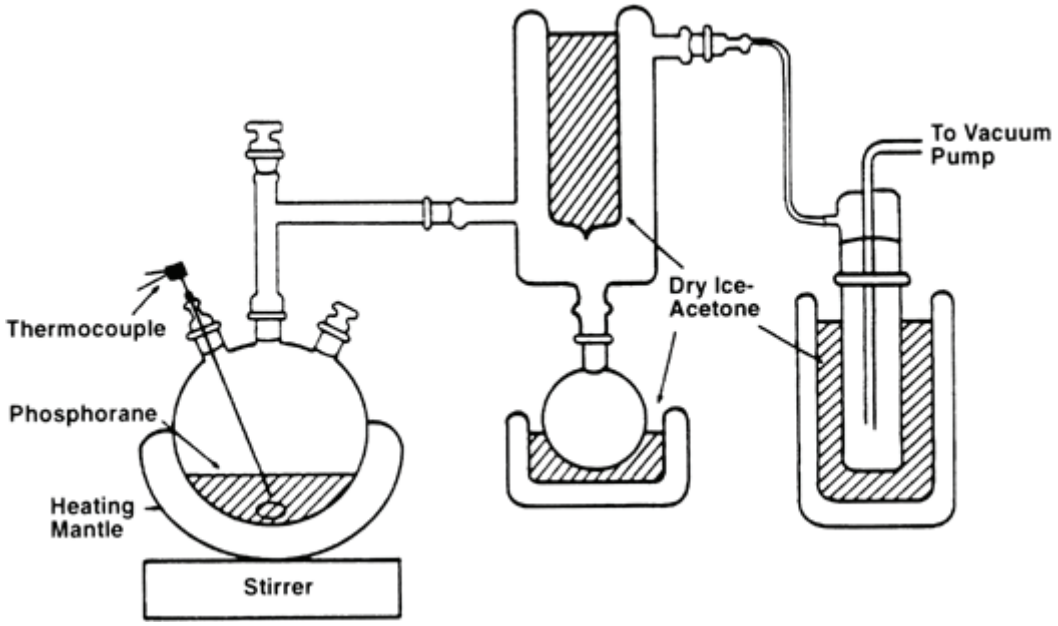
1. Procedure

A. *Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate*. A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 215 g (0.5 mol) of (carbethoxymethyl)triphenylphosphonium bromide and 1.1 L of anhydrous tetrahydrofuran (THF) (Note 1) and (Note 2). The stirred suspension is cooled in an ice water bath and treated with 150 mL (1.1 mol) of triethylamine (Note 3) added dropwise over 5 min. After the mixture is stirred for an additional 30 min at 5°C, it is treated dropwise with 78 mL (116 g, 0.55 mol) of trifluoroacetic anhydride (Note 4) in such a manner that the reaction temperature is maintained between 5–10°C, which results in a total addition time of approximately 1 hr. The mixture is allowed to stir for 2 hr and subsequently filtered, the precipitate is washed three times with cold THF and the filtrate is concentrated under reduced pressure to afford a yellow oily residue. Trituration of the residue with 600 mL of water affords a crystalline product which is collected, washed three times with 100 mL of water, and dried by suction to afford 208 g of a yellowish colored solid (Note 5). The solid is dissolved in 900 mL of hot methanol; the solution is filtered, treated with 500 mL of water, and placed in a refrigerator overnight. The crystalline product is collected, washed three times with 100 mL of cold water and dried under reduced pressure to afford 200–208 g (89–93%) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate as a very pale-yellow, crystalline solid (Note 6).

B. *Ethyl 4,4,4-trifluorotetrolate*. A 1-L, three-necked, round-bottomed flask is equipped with an efficient magnetic stirrer, a heating mantle, a thermocouple (Note 7) and a large bore gas exit tube (Figure 1, (Note 8)). To this flask are added 200 g (0.45 mol) of ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate and 40 g of potassium carbonate (Note 9). The gas exit tube is connected to a Dewar condenser, modified with a side arm connection, which has a round-bottomed flask for collection of the product in a dry ice-acetone bath. A second trap is placed between the reaction setup and the vacuum pump, all the traps are cooled with dry ice-acetone, and the system is evacuated to 1–2 mm. The reaction flask is carefully heated to 150°C (Note 10) at which point the phosphorane melts and the acetylene evolution begins. The molten phosphorane is stirred and heated from 160°C to 220°C over a period of 5 hr. Heating is carefully increased during the reaction in order to control the rate of distillation of the acetylenic product. From the round-bottomed flask in the cold trap is obtained 65–67 g (87–89%) of a clear, slightly yellow, liquid. The thermolysis product is dried with magnesium sulfate and filtered through Celite. Distillation at atmospheric pressure through a short-path distillation

apparatus affords about 1.0 g of forerun and 59–61 g (79–82%) of ethyl 4,4,4-trifluorotetrolate as an analytically pure, colorless liquid, bp_{760} 97–100°C (Note 11).

Figure 1



2. Notes

1. Anhydrous tetrahydrofuran was obtained from Aldrich Chemical Company, Inc., in SureSeal bottles and was used without further purification. (Carbethoxymethyl)triphenylphosphonium bromide may be obtained from Aldrich Chemical Company Inc., or prepared as described in *Org. Synth., Coll. Vol. VII* **1990**, 232. The in situ preparation described in (Note 2) was used by the checkers.

2. We have found it more convenient to prepare (carbethoxymethyl)triphenylphosphonium bromide in situ in the same reaction vessel from triphenylphosphine and ethyl bromoacetate. This effectively provides a one-pot preparation for the α-acylmethylenephosphorane from triphenylphosphine and allows facile incorporation of various esters, by employing different bromoacetate esters, in the acetylenic product. The yield and purity of the resultant phosphorane is unaffected by the following one-pot procedure.

A 2-L, four-necked, round-bottomed flask is equipped with a nitrogen line attached to a bubbler, a 250-mL pressure-equalizing funnel, an overhead stirrer and a thermometer. The flask is charged with 132 g of triphenylphosphine (0.503 mol) and 500 mL of anhydrous tetrahydrofuran and cooled in an ice water bath to 5°C. The stirred solution is treated dropwise with 56 mL of ethyl bromoacetate (84 g, 0.503 mol) added at such a rate that the temperature is maintained between 8°C and 10°C. The total addition time is about 15 min. After the mixture is stirred overnight, it is diluted with an additional 600 mL of anhydrous tetrahydrofuran and the precipitate is washed from the sides of the flask. The resultant suspension of (carbethoxymethyl)triphenylphosphonium bromide is cooled in an ice-water bath and used directly in the same pot to prepare α-acylmethylenephosphoranes as detailed in section A.

3. Triethylamine was supplied by Eastman Kodak Company and Fisher Scientific Company.

4. Trifluoroacetic anhydride was obtained from Aldrich Chemical Company, Inc.

5. The yellow crystalline solid is analytically pure (>95% by NMR and HPLC analysis), mp 124–127° C. We have found that the yield of the acetylenes can be adversely affected by small amounts of impurities in the α-acylmethylenephosphoranes and prefer to recrystallize the phosphoranes prior to thermolysis. The yield from the recrystallization step is greater than 95%.

6. The phosphorane softens above 120°C and melts between 125–130°C (lit.[2,3] mp 125–127°C). Spectral properties of the phosphorane are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, 3 H, J = 7.2), 3.81 (q, 2 H, J = 7.2), 7.49 (dt, 6 H, J = 7.9, 3.3), 7.57 (m, 3 H), 7.67 (dd, 6 H, J = 12.9, 7.9); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5, 59.8, 70.1 (d, $^1J_{CP}$ = 110), 117.9 (dd, $^1J_{CF}$ = 288, $^3J_{CP}$ = 14.6), 123.7 (d, $^1J_{CP}$ =

93.3), 128.8 (d, $^{2}J_{CP}$ = 13.0), 132.2 (d, $^{4}J_{CP}$ = 3.0), 133.2 (d, $^{3}J_{CP}$ = 10.0), 165.6 (d, $^{2}J_{CP}$ = 13.0), 174.4 (dd, $^{2}J_{CF}$ = 34.0, $^{2}J_{CP}$ = 5.8); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 19.8. Anal. Calcd for $C_{24}H_{20}O_3F_3P$: C, 64.87; H, 4.54. Found: C, 64.96; H, 4.60.

7. A stainless steel-covered thermocouple is preferred since it is less likely to break than a mercury thermometer. As the phosphorane begins to melt, large chunks of solid remain as the mixture is initially stirred, and these can lodge between a thermometer and the walls of the flask. The thermocouple has the added advantage that the steel rod can be used to help break up the melting phosphorane, taking care to avoid breaking the flask.

8. The large bore gas exit tube (Figure 1) used between the reaction flask and the Dewar condenser is a glass tee equipped with the appropriate 24/40 ground glass joints. Alternatively, the connection can be made using large bore, thick wall Tygon or vacuum tubing.

9. In the absence of potassium carbonate, the thermolysis product is slightly acidic and the pH of a water wash of freshly collected product is about 1.

10. *CAUTION! Care must be taken not to heat the phosphorane too rapidly, particularly before the solid has melted. The temperature of the molten material is not at equilibrium until the mixture has completely melted. If it is heated too rapidly, it is difficult to control the rate of acetylene production. It is best to heat slowly until a stirred, molten material is obtained and to continue heating at such a rate as to control acetylene formation.* We have obtained excellent results applying initially 30 volts to a 380-watt, 115-volt, 1-L heating mantle obtained from Glas-Col Apparatus Company. Alternatively, more even and controlled heating can be obtained by using a large oil bath.

11. Previous literature reports[3] bp 96–98°C. Spectral properties of the acetylene are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (t, 3 H, J = 7.1), 4.32 (q, 2 H, J = 7.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 63.5, 69.9 (q, $^{2}J_{CF}$ = 54.0), 75.5 (q, $^{3}J_{CF}$ = 6.0), 113.4 (q, $^{1}J_{CF}$ = 259), 150.7; IR (neat) cm^{-1}: 2987, 2275 (w); 1731. Anal. Calcd for $C_6H_5O_2F_3$: C, 43.49; H, 3.03. Found: C, 43.14; H, 3.07.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

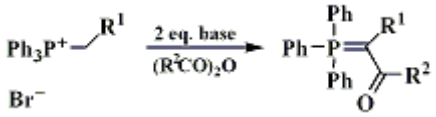
Thermolysis of α-acylmethylenephosphoranes is the most convenient method for preparation of acetylenes with perfluoroalkyl substituents.[3,4] Many of these acetylenes, particularly the trifluoromethyl analogs, are particularly volatile and thermolysis allows preparation and collection of material which is free of solvents or impurities of similar boiling point. In addition, the acetylenes are prepared from readily available starting materials with overall conversions for the two steps of greater than 75% in many cases. Attempts to prepare trifluorotetrolic acid by carbonylation of the lithium acetylenide of 3,3,3-trifluoropropyne have been unsuccessful.[5] However, the treatment of lithium acetylenides with chloroformates affords perfluoroalkyl-substituted propiolates (the perfluoroalkyl group is a C_4 chain length or longer) in 38–43% yield along with an unusual by-product.[6] Benzyl trifluorotetrolate, which was employed in the synthesis of a trifluoromethyl analog of geraniol, has been prepared from ethyl trifluoroacetoacetate via a pyrazolone in an overall yield of 55%.[7] A number of (difluoroalkyl) propiolates, employed in Diels-Alder cycloaddition reactions, have been prepared by treatment of the corresponding ketones with diethylaminosulfur trifluoride (DAST).[8] The corresponding (difluoroalkyl) propiolic acids have also been prepared by carbonylation of the magnesium bromoacetylenide.[9]

The utility of the phosphorane route to electron-deficient acetylenes depends on the facile synthesis of the α-acylmethylenephosphorane intermediates. Previously they had been prepared by a two-step procedure from the available phosphonium salts, requiring isolation of the Wittig reagent [e.g., (ethoxycarbonylmethylene)triphenylphosphorane] intermediate.[3,4] Acylation of the Wittig reagent affords, via transylidation,[10] a 1:1 mixture of components which must be separated prior to thermolysis. In addition, at least half of the Wittig reagent is lost by conversion to the starting phosphonium salt. The addition of a suitable base, such as triethylamine, to the reaction mixture avoids the undesired transylidation reaction and affords complete conversion to the desired α-acylmethylenephosphorane. For acyl halides which have an acidic hydrogen α to the carbonyl group, treatment with base can give rise to ketenes which readily react with Wittig reagents to afford allenes.[11] This route, using

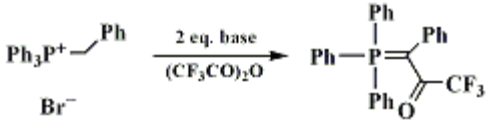
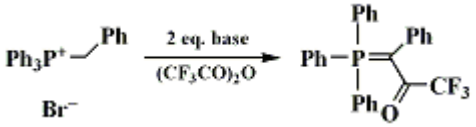
triethylamine as a base, has been explored to prepare allenes that are either substituted or unsubstituted in the α-position.

For acyl halides or anhydrides which do not afford ketenes in the presence of base (such as perfluoroacyl halides), however, the α-acylmethylenephosphoranes can be prepared directly in one step from the phosphonium salts by using two equivalents of base by the present procedure (Table I).[2] Both tetrahydrofuran and methylene chloride have been used as solvents; in the case of the title compound, tetrahydrofuran provides the best results. Good yields of the phosphoranes are generally obtained when R^1 is an electron-withdrawing group such as ester or nitrile. The yields of phosphoranes obtained for the thiomethyl or phenyl cases can be improved by using 1,4-diazabicyclo[2.2.2]octane (DABCO) rather than triethylamine as the base.

TABLE I
PREPARATION OF (α-ACYLMETHYLENE)PHOSPHORANES FROM α-SUBSTITUTED METHYLPHOSPHONIUM SALTS[2]



R^1	R^2	Solvent	Base	Yield (%)
CO_2Et	CF_3	CH_2Cl_2	Et_3N	54
CO_2Me	CF_3	THF	Et_3N	99
CO_2Et	CF_2CF_3	THF	Et_3N	69
CN	CF_3	THF	Et_3N	75
SCH_3	CF_3	THF	Et_3N	49

Ph	CF_3	CH_2Cl_2	Et_3N		24
Ph	CF_3	CH_2Cl_2	DABCO		57

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

potassium carbonate (584-08-7)

acetylene (74-86-2)

methanol (67-56-1)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Ethyl bromoacetate (105-36-2)

Tetrahydrofuran,
THF (109-99-9)

geraniol (106-24-1)

triethylamine (121-44-8)

triphenylphosphine (603-35-0)

trifluoroacetic anhydride (407-25-0)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

Diethylaminosulfur trifluoride (38078-09-0)

(ethoxycarbonylmethylene)triphenylphosphorane (1099-45-2)

Ethyl 4,4,4-trifluorotetrolate,
2-Butynoic acid, 4,4,4-trifluoro-, ethyl ester (79424-03-6)

Ethyl 4,4,4-trifluoro-2-(triphenylphosphoranylidene)acetoacetate (83961-56-2)

(carbethoxymethyl)triphenylphosphonium bromide (1530-45-6)

trifluorotetrolic acid

lithium acetylenide

3,3,3-trifluoropropyne (661-54-1)

Benzyl trifluorotetrolate

ethyl trifluoroacetoacetate

magnesium bromoacetylenide

METHYLPHOSPHONIUM