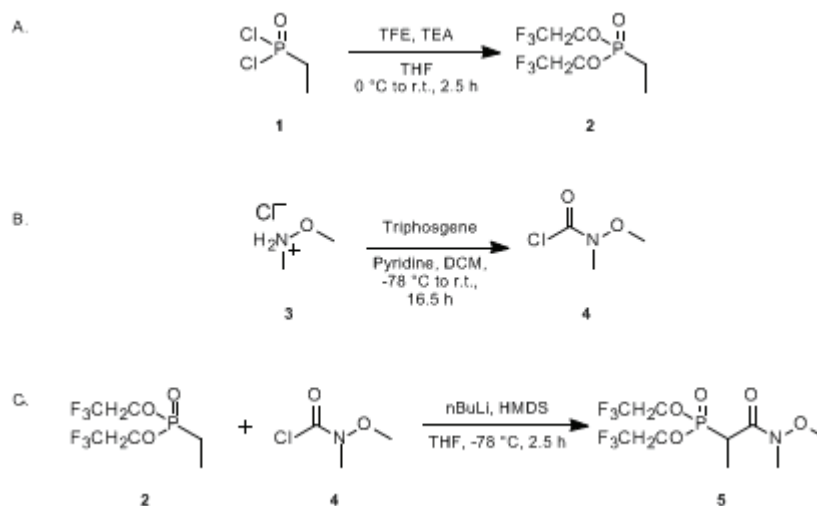


PREPARATION OF [1-(METHOXYMETHYL CARBAMOYL) ETHYL] PHOSPHONIC ACID BIS-(2,2,2-TRIFLUOROETHYL) ESTER: A USEFUL INTERMEDIATE IN THE SYNTHESIS OF Z-UNSATURATED N-METHOXY-N-METHYLAMIDES



Submitted by Amos B. Smith, III, Jason J. Beiger, Akin H. Davulcu, and Jason M. Cox¹.
Checked by Mark Lautens and Catherine Taillier.

1. Procedure

*A. Ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester (2).*² A flame-dried 2-L three-necked round-bottom flask equipped with a Teflon-coated magnetic stir bar, thermometer, rubber septum and argon inlet (Note 1) is charged with 24.1 mL (336 mmol, 2.01 eq.) of 2,2,2-trifluoroethanol (Notes 2, 3) and 500 mL of anhydrous THF (Note 4) under an argon atmosphere, and cooled to an internal temperature of 0 °C with an ice-NaCl bath for 10 min. The above flask is then charged dropwise with 51.3 mL (369 mmol, 2.20 eq.) of triethylamine (Note 5) over 10 min., and stirred at 0 °C for 15 min. A separate flame-dried 250-mL one-necked round-bottom flask equipped with a rubber septum and argon inlet is charged with 17.9 mL (167 mmol, 1.00 eq.) of ethylphosphonic dichloride 1 (Note 2) and 65 mL of THF under an argon atmosphere. The mixture is stirred, and transferred dropwise *via* cannula (Notes 3, 6) into the trifluoroethanol/triethylamine solution over 15 min while maintaining the internal temperature below 12 °C. The 250-mL flask is then rinsed with THF (2 × 10 mL), and the THF washes transferred by cannula to the larger flask over a five-minute period. The resulting white slurry is warmed to room temperature over 15 min., stirred at room temperature for 2.25 h, filtered through a sand-covered frit (Note 7), and concentrated by rotary evaporation (35 °C, 20 mmHg) to afford 43 g of a cloudy, nearly colorless liquid. The latter is transferred to a 100-mL one-necked round-bottom flask equipped with a Teflon-coated magnetic stir bar and a short path distillation head fitted with a distribution adapter and three 50-mL pear-shaped receiving flasks. After collecting a forerun (ca. 1 mL), the product is distilled under an aspirator vacuum (bp = 92–95 °C at 25 mmHg) to yield 40.85 g (89%) of ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester (2) as a clear colorless liquid (Note 8).

*B. N-Methoxy-N-methylcarbamoyl chloride (4).*³ A flame-dried 500-mL three-necked round-bottom flask equipped with a Teflon-coated magnetic stir bar, thermometer, rubber septum and argon inlet is charged with 10.1 g (34.1 mmol, 0.400 eq.) of triphosgene (Note 2) and 57 mL of anhydrous dichloromethane (Note 4) under an argon atmosphere, and cooled to an internal temperature of -78 °C with a dry ice-acetone bath for 20 min. The suspension is charged with 8.33 g (85.4 mmol, 1.00 eq.) of N,O-dimethylhydroxylamine hydrochloride 3 (Note 2) in three portions by briefly removing the septum and using a powder funnel with 5 min. elapsing between each portion while maintaining the internal

temperature below $-70\text{ }^{\circ}\text{C}$. The suspension is recooled to $-78\text{ }^{\circ}\text{C}$ and stirred for 30 min. A separate flame-dried, 100-mL round-bottomed flask equipped with a rubber septum and argon inlet is charged with 13.7 mL (171 mmol, 2.00 eq.) of pyridine (Note 5) and 28 mL of dichloromethane under an argon atmosphere. The mixture is stirred and transferred dropwise *via* cannula to the above hydroxylamine/triphosgene suspension over 1.5 h while maintaining the internal temperature below $-72\text{ }^{\circ}\text{C}$ (Note 6). The 100-mL flask is rinsed with dichloromethane ($2 \times 5\text{ mL}$), and the dichloromethane washes transferred by cannula to the larger flask over 5 min. The resulting yellow-orange slurry is slowly warmed to room temperature over 4 h, stirred at room temperature for 12.5 h, quenched with 100 mL of distilled water, and transferred to a 500-mL separatory funnel. The layers are separated, and the aqueous layer extracted with dichloromethane ($3 \times 50\text{ mL}$). The combined organic phases are sequentially washed (Note 5) with aqueous 0.5 M HCl ($2 \times 100\text{ mL}$), saturated aqueous NaHCO_3 ($1 \times 75\text{ mL}$), and brine ($1 \times 75\text{ mL}$), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation ($35\text{ }^{\circ}\text{C}$, 20 mmHg) to afford 11.3 g of a yellow liquid. The yellow liquid is transferred to a 50-mL one-necked round-bottom flask equipped with a Teflon-coated magnetic stir bar and a short path distillation head fitted with a distribution adapter and three 25-mL pear-shaped receiving flasks. After collecting a forerun (*ca.* 0.5 mL), the product is distilled under vacuum aspirator (bp = $67\text{--}69\text{ }^{\circ}\text{C}$ at 25 mmHg) to afford 8.87-9.18 g (84-87%) of *N*-methoxy-*N*-methylcarbamoyl chloride 4 as a clear colorless liquid (Note 9).

C. [1-(Methoxymethylcarbamoyl)ethyl] phosphonic acid bis-(2,2,2-trifluoroethyl) ester (5).⁴ A flame-dried 1-L three-necked round-bottom flask equipped with a Teflon-coated magnetic stir bar, thermometer, rubber septum and argon inlet is charged with 51.0 mL (128 mmol, 2.41 eq.) of a 2.5 M solution of *n*-butyllithium in hexanes (Note 2) and 40 mL of THF under an argon atmosphere, and cooled to an internal temperature of $-20 \pm 3\text{ }^{\circ}\text{C}$ with a dry ice-isopropanol-water bath for 20 min. In a separate flame-dried 100-mL one-necked round-bottom flask equipped with a rubber septum and argon inlet is charged with 29.2 mL (139 mmol, 2.64 eq.) of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (Note 2) and 40 mL of THF under an argon atmosphere. The mixture is stirred and transferred dropwise *via* cannula to the above *n*-butyllithium solution over 20 min while maintaining the internal temperature below $-15\text{ }^{\circ}\text{C}$ (Note 6). The 100-mL flask is then rinsed with THF (2 \times 10 mL), and the THF washes cannulated to the larger flask over 5 min. The resulting clear solution is stirred at $-20 \pm 3\text{ }^{\circ}\text{C}$ for 20 min., and cooled to an internal temperature of $-75\text{ }^{\circ}\text{C}$ with a dry ice-acetone bath. A separate flame-dried 100-mL one-necked round-bottomed flask equipped with a rubber septum and argon inlet is then charged with 14.5 g (52.9 mmol, 1.00 eq.) of ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester 2,² 9.00 g (72.9 mmol, 1.38 eq.) of *N*-methoxy-*N*-methylcarbamoyl chloride 4,³ and 50 mL of THF, and transferred dropwise *via* cannula to the above lithium HMDS solution over 30 min. while maintaining the internal temperature below $-68\text{ }^{\circ}\text{C}$ (Note 6). The smaller flask is rinsed with THF ($2 \times 10\text{ mL}$), and the THF washes transferred by cannula to the larger flask over 5 min. The resulting pale yellow solution is recooled to $-75\text{ }^{\circ}\text{C}$ and stirred for 2.5 h (Note 10), then slowly acidified over 5 min. with 130 mL of a 1.0 M solution of HCl, and gradually warmed to an internal temperature of $0\text{ }^{\circ}\text{C}$ over 30 min. The solution is diluted with 100 mL of distilled water, and transferred to a 1-L separatory funnel. The flask is rinsed with diethyl ether ($3 \times 50\text{ mL}$), transferred to the funnel, shaken, the layers separated, and the aqueous layer extracted with dichloromethane ($4 \times 100\text{ mL}$) (Note 11). The combined organic phases are dried (MgSO_4), filtered, and concentrated by rotary evaporation ($35\text{ }^{\circ}\text{C}$, 20 mmHg) to afford 19 g of a yellow oil (Note 12). The yellow oil is loaded onto a 80-mm diameter column, wet-packed (4:1 hexanes: ethyl acetate) with 450 grams (25 cm) of silica gel (Note 13), and sequentially eluted with a gradient of hexanes and ethyl acetate (2 L of 2:1, 2 L of 1:1, 1 L of 1:2). The desired product is collected in fractions of 75-mL volume, concentrated by rotary evaporation ($35\text{ }^{\circ}\text{C}$, 20 mmHg), and dried under vacuum ($25\text{ }^{\circ}\text{C}$, 0.01 mmHg) until a constant mass is obtained. The above described procedure affords 15.6 - 16.8 g (82-88%) of [1-(methoxymethylcarbamoyl)ethyl] phosphonic acid bis-(2,2,2-trifluoroethyl) ester 5 as a clear pale yellow oil (Note 14).

2. Notes

1. All flasks were flame-dried and maintained under an argon atmosphere during the course of the reactions. The argon was dried and purified by passing through Drierite[®] and then an Oxiclear[™] disposable gas purifier, which may be purchased from Aldrich Chemical Co., Inc. A gas manifold was then used to distribute argon to each of the attached flasks. An argon inlet was affixed to a flask by

inserting its needle through that flask's rubber septum while maintaining slightly positive pressure.

2. 2,2,2-Trifluoroethanol ($\geq 99\%$), ethylphosphonic dichloride (98%), triphosgene (98%), *N,O*-dimethylhydroxylamine hydrochloride (98%), 1,1,1,3,3,3-hexamethyldisilazane (99.9%) and the 2.5 M solution of *n*-butyllithium in hexanes were purchased from Aldrich Chemical Co., Inc. and used as received.

3. Liquids were added to flasks from plastic disposable syringes through stainless steel needles. Liquids were transferred between flasks *via* stainless steel cannulas. All needles and cannulas were oven-dried for at least one hour and cooled to room temperature in a desiccator prior to use.

4. HPLC grade dichloromethane (99.9%) and tetrahydrofuran (THF) (99.9%) were purchased from Fisher Scientific. Dichloromethane and THF were dried by purging with argon over activated molecular sieves and were stored under argon at room temperature. The checkers used THF distilled from Na/benzophenone ketyl and dichloromethane purified with a MBRAUN® Solvent Purification System.

5. Triethylamine (99%), pyridine (99.9%), dichloromethane, hexanes, ethyl acetate, sodium chloride, sodium bicarbonate, anhydrous magnesium sulfate, anhydrous sodium sulfate, and concentrated hydrochloric acid were purchased from Fisher Scientific and used as received. Triethylamine and pyridine were used by the checkers after distillation over KOH.

6. Alternatively, a flame-dried 100-mL additional funnel may be used to regulate the rate at which the reaction flask is charged with solution.

7. Alternatively, filtration of the resulting white slurry through a short plug of Celite could be performed to remove the ammonium salts.

8. Ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester **2** displays the following spectroscopic properties: IR (film): 2974 (weak), 1463, 1419, 1287, 1255, 1174, 1109, 1079, 1036, 964, 868, 844 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 4.30-4.47 (m, 4H), 1.93 (dq, $J_{\text{PH}} = 18.7$ and $J_{\text{HH}} = 7.7$ Hz, 2H), 1.22 (dt, $J_{\text{PH}} = 21.5$ and $J_{\text{HH}} = 7.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 122.6 (qd, $J_{\text{CF}} = 277.6$ and $J_{\text{CP}} = 7.7$ Hz), 61.8 (qd, $J_{\text{CF}} = 37.6$ and $J_{\text{CP}} = 6.1$ Hz), 18.9 (d, $J_{\text{CP}} = 143.4$ Hz), 5.9 (d, $J_{\text{CP}} = 7.7$ Hz); The checkers have not been able to get an elemental analysis due to volatility of compound **2**. However, the submitters reported the following data for **2**: Anal. Calcd for $\text{C}_6\text{H}_9\text{F}_6\text{O}_3\text{P}$: C, 26.29; H, 3.31. Found: C, 26.20; H, 3.06.

9. The following characterization data were obtained for *N*-methoxy-*N*-methylcarbamoyl chloride (**4**): IR (film): 2982, 2941, 1732 (broad), 1460, 1443, 1406, 1352, 1182, 1082, 995, 868, 669, 653 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 3.78 (s, 3H), 3.33 (s, 3H). The checkers have not been able to get an elemental analysis due to volatility of compound **4**. However, the submitters reported the following data for **4**: Anal. Calcd for $\text{C}_3\text{H}_6\text{ClNO}_2$: C, 29.17; H, 4.90. Found: C, 29.02; H, 4.89.

10. The reaction was monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates. The plates were eluted with a 1:1 mixture of hexanes and ethyl acetate. The R_f values of **2**, **4**, and **5**, are 0.55, 0.70, and 0.21, respectively. A potassium permanganate-based stain that was prepared by dissolving 3 g of KMnO_4 , 20 g of K_2CO_3 , and 5 mL of 5% aqueous NaOH in 300 mL of distilled water was suitable for visualizing the product on TLC.

11. If an emulsion occurs during the dichloromethane extractions, it may be broken with the addition of approximately 15 mL of brine. Checkers found that filtration of the biphasic mixture through a short plug of Celite was necessary to break the emulsion.

12. The crude mixture may be distilled under vacuum through a short path apparatus (bp = 105–107 °C at 0.01 mmHg) to yield phosphonate **5** as a slightly pale yellow oil. Purification by this method, however, resulted in a significantly lower yield (40–50%) due to thermal decomposition of **5**.

13. Silica gel may be purchased from Silicycle Chemical Division. The silica gel used by the submitters had the following specifications: pH: 6.5–7.0, particle size: 40–63 μm (230–400 mesh), spec. surface area: 500 m^2/g , pore diameter: 60 Å.

14. Phosphonate **5** exhibits the following spectroscopic properties: IR (film): 2976, 2949, 1651, 1455, 1418, 1393, 1259, 1173, 1072, 987, 962, 845 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 4.43-4.57 (m, 2H), 4.35-4.47 (m, 2H), 3.78 (s, 3H), 3.77 (m, 1H), 3.28 (s, 3H), 1.50 (dd, $J = 19.8$ and $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.3, 122.6 (qdd, $J_{\text{CF}} = 277.6$, $J_{\text{CP}} = 22.6$ and $J_{\text{CP}} = 8.8$ Hz), 63.1 (qd, $J_{\text{CP}} = 37.6$ and $J_{\text{CP}} = 5.0$ Hz), 61.8 (qd, $J_{\text{CP}} = 38.3$ and $J_{\text{CP}} = 6.1$ Hz), 61.7, 35.7 (d, $J_{\text{CP}} = 142.6$ Hz), 32.0, 12.4 (d, $J_{\text{CP}} = 7.7$ Hz); MS-ESI m/z (relative intensity): 284 ($\text{M}+\text{Na}^+$, 100%), 362 ($\text{M}+\text{H}^+$, 81%), 319 (27%), 301 (22%), 273 (25%), 245 (8%); High resolution mass spectrum (ES +) m/z 384.0393 [($\text{M}+\text{Na}^+$); calcd for $\text{C}_9\text{H}_{14}\text{F}_6\text{NNaO}_5\text{P}$: 384.0411]. Anal. Calcd for $\text{C}_9\text{H}_{14}\text{F}_6\text{NO}_5\text{P}$: C, 29.93; H, 3.91; N, 3.88. Found: C, 29.97; H, 3.93; N, 3.92.

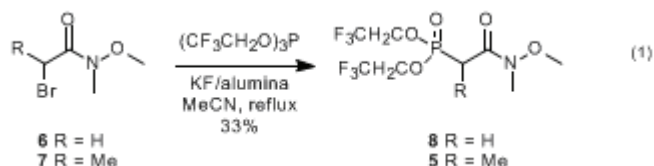
Waste Disposal Information

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

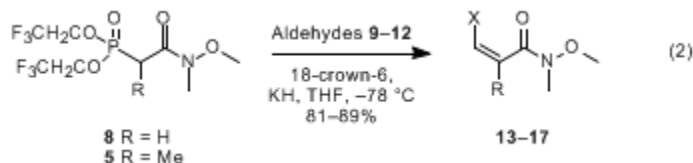
3. Discussion

The methods described herein illustrate a practical and convenient three-step synthesis of bis(2,2,2-trifluoroethyl)phosphonates in good overall yield (> 66%). This class of phosphonates, bearing an *N*-methoxy-*N*-methylamide functionality, is synthetically useful for the construction of *Z*-unsaturated *N*-methoxy-*N*-methylamides.⁴ It is well established that the Weinreb amide functionality may then be converted to aldehydes or ketones in good yields.⁵

The formation of bis(2,2,2-trifluoroethyl)phosphonate **5** was previously reported by Deslongchamps et al.⁴ following procedures developed by Tius and Busch-Petersen that employed KF/alumina to construct α -heterosubstituted Weinreb amides.⁶ They discovered that tris(2,2,2-trifluoroethyl) phosphite reacts with bromides bearing the *N*-methoxy-*N*-methylamide moiety (**6**, **7**) to furnish the respective phosphonates **8** and **5** in modest yield (eq. 1).



The procedure described herein proceeds in higher yield and circumvents the difficulty of handling and preparing the KF/alumina reagent. For example, although reactivity of the halide increases as the ratio of fluoride salt versus alumina is increased, the reagents became very hygroscopic and difficult to handle.⁷ Additionally, Ando et al. discovered that a trace amount of water was essential for promoting the reaction, and thorough drying of the KF/alumina reagent led to a significant reduction in reactivity.^{6,8} On the other hand, too much residual water was found to hydrolyze the chlorine analog of Weinreb amide **6**.⁶ Tius and Busch-Petersen also reported that continuous sonication of the reaction mixture was necessary to enhance the reactivity of the KF/alumina reagent.^{6,9}



Deslongchamps et al. subsequently demonstrated the utility of phosphonates **5** and **8** in the stereoselective formation of *Z*-unsaturated alkenes using the modified Still conditions.^{4,10} Bis(2,2,2-trifluoroethyl)phosphonates **8** and **5** react with aldehydes **9–12** to furnish the respective unsaturated *N*-methoxy-*N*-methylamides **13–17** in 81–89% yield, with only the *Z* isomer detectable by ¹H-NMR (eq. 2).⁴

Table 1 illustrates the several aldehydes (**9–12**) that Deslongchamps et al. employed to demonstrate the versatility of bis(2,2,2-trifluoroethyl)phosphonates **5** and **8** in the stereoselective synthesis of *Z*-unsaturated *N*-methoxy-*N*-methylamides **13–17**.⁴

Entry	Aldehyde	Phosphonate	Product	Yield
1		5		83
2		8		89
3		5		83
4		5		83
5		5		81

References and Notes

1. Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104.
2. For leading references on the preparation of ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester (**2**), see: Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1991**, *21*(22), 2391–2396. Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Org. Synth.* **1998**, *CV 9*, 88–91.
3. For leading references on the preparation of *N*-methoxy-*N*-methylcarbamoyl chloride (**4**), see: Tius, M.A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219–4222. Murakami, M.; Hoshino, Y.; Ito, H.; Ito, Y. *Chem. Lett.* **1998**, *2*, 163–164.
4. For leading references on the preparation of [1-(methoxymethylcarbamoyl)ethyl] phosphonic acid bis-(2,2,2-trifluoroethyl) ester **5**, and its use in the synthesis of *Z*-unsaturated *N*-methoxy-*N*-methylamides, see: Fortin, S.; Dupont, F.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5437–5439.
5. Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
6. Tius, M.A.; Busch-Petersen, J. *Synlett* **1997**, 531–532.
7. Ando, T.; Yamawaki, J.; Kawate, T.; Sumi, S.; Hanafusa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2504–2507.
8. Ando, T.; Kawate, T.; Yamawaki, J.; Hanafusa, T. *Chem. Lett.* **1982**, 935–938.
9. Ando, T.; Kawate, T.; Ichihara, J.; Hanafusa, T. *Chem. Lett.* **1984**, 725–728.
10. Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*(41), 4405–4408.

Appendix

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

n-Butyllithium:

Lithium, butyl- (8,9); (109-72-8)

Ethanamine, N,N-diethyl- (9); (121-44-8)

Ethanol, 2,2,2-trifluoro- (6,8,9); (75-89-8)

Ethylphosphonic acid bis-(2,2,2-trifluoroethyl) ester: 650-16-8
Phosphonic acid, ethyl-, bis(2,2,2-trifluoroethyl) ester (6, 8, 9); (650-16-8)

1,1,1,3,3,3-Hexamethyldisilazane:

Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)- (9); (999-97-3)

Methanamine, N-methoxy-, hydrochloride (9); (6638-79-5)

Methanol, trichloro-, carbonate (2:1) (9); (32315-10-9)

N-Methoxy-N-methylcarbamoyl chloride:

Carbamic chloride, methoxymethyl- (9); (30289-28-2)

[1-(Methoxymethylcarbamoyl)ethyl]phosphonic acid bis-(2,2,2-trifluoroethyl) ester:
Phosphonic acid, [2-(methoxymethylamino)-1-methyl-2-oxoethyl]-, bis(2,2,2-trifluoroethyl) ester (9);
(448219-33-8)

Phosphonic dichloride, ethyl- (6,7,8,9); (1066-50-8)

Pyridine (6,7,8,9); (110-86-1)