A Convenient Synthesis of Dimethyl (Diazomethyl)phosphonate (Seyferth/ Gilbert Reagent)

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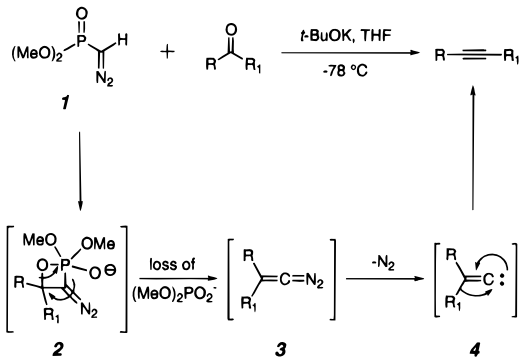
Dimethyl (diazomethyl)phosphonate (**1**, the Seyferth/ Gilbert reagent)[2ab] is a valuable reagent useful for efficient, one-carbon homologation of aldehydes and ketones to alkynes.[2c] It is presumed that the mechanism is Wittig-like and involves initial formation of adduct **2** as shown in Scheme 1. Elimination of dimethyl phosphate leads via the diazo intermediate **3** to an alkylidene carbene **4**, which undergoes a 1,2-rearrangement to give the alkyne. Although **1** has been a popular reagent for synthesis[3] and the one-carbon homologation itself proceeds quite efficiently, researchers often opt for alternative strategies[4] because of the multistep synthetic procedure required to prepare **1**.

We sought to synthesize **1** by a conventional diazo transfer technique. Ohira has investigated this idea and showed that the diazoketophosphonate $(MeO)_2P(O)C(N_2)$-Ac can serve as a precursor of **1** by deacylation with basic methanol.[5] Although the *in situ*-generated **1** is capable of converting aldehydes into terminal alkynes, reaction with ketones leads to methyl enol ethers through trapping of the intermediate carbene with the residual methanol.

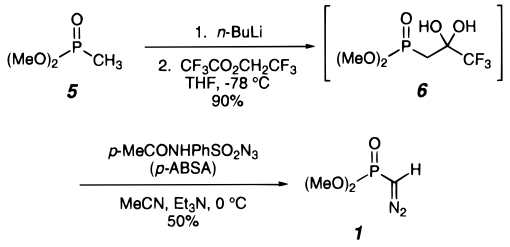
We report here a convenient synthesis of the Seyferth/ Gilbert reagent based upon a diazo transfer/deacylation strategy that permits isolation of **1**. We have used this procedure to synthesize both small (200 mg) and intermediate scale (2 g) quantities of **1** using commercially available starting materials. The sequence is illustrated in Scheme 2.

Dimethyl methylphoshonate (**5**) is temporarily trifluoroacetylated[6] to give intermediate **6**, which exists as the ketone hydrate.[7] This hygroscopic intermediate is best used directly without purification in the diazo transfer step. Although other azides can be used (e.g., methanesulfonyl azide and *p*-toluenesulfonyl azide), we have found that 4-acetamidobenzenesulfonyl azide (*p*-ABSA)[8] is the most convenient diazo transfer substrate for this reaction.[9,10] Not only is it commercially available and shock stable, but the resultant *p*-acetamidobenzenesulfonamide byproduct can be precipitated from the reaction solution. Detrifluoroacetylation occurs spontaneously under the diazo transfer reaction conditions. The resulting product is generally purified by filtration through silica gel and is of sufficiently high purity to be stored or used directly in homologation reactions. The preparation proceeds in over 50% overall yield and does not require purification of any intermediates. We believe this method to be a reproducible and improved procedure for the synthesis of **1**.

Scheme 1



Scheme 2



Experimental Section

Materials. Dimethyl methylphosphonate, 2,2,2-trifluoroethyl trifluoroacetate, *N*-acetylsulfanilyl chloride, and 4-acetamidobenzenesulfonyl azide were commercially available and used without further purification. THF was distilled over Na/ benzophenone. Acetonitrile was distilled over CaH_2. Acetone was reagent grade. All glassware was flame-dried under vacuum and back-filled with nitrogen. All reactions were carried out under a N_2 blanket.

***p*-Acetamidobenzenesulfonyl Azide (*p*-ABSA).** A 2 L round-bottomed flask equipped with a magnetic stirring bar was charged with sodium azide (5.70 g, 87.6 mmol) and acetone (1 L). This mixture was cooled to 0 °C, and *N*-acetylsulfanilyl chloride (20.0 g, 85.5 mmol) was added slowly (ca. 5 min) in small

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(2) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P *J. Org. Chem.* **1971**, *36*, 1379. (b) For an alternative preparation see: Ratcliffe, R.; Christensen, B. *Tetrahedron Lett.* **1973**, 4645. (c) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.

(3) For applications in natural product total synthesis see: (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511. (c) Heathcock, C. H.; Clasby, M.; Griffith, D. A.; Henke, B. R.; Sharp, M. J. *Synlett.* **1995**, 467. (d) Delpech, B.; Lett, R. *Tetrahedron Lett.* **1989**, *30*, 1521. For other applications see: (e) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. J. *J. Org. Chem.* **1983**, *48*, 5251. (f) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (g) Walborsky, H. M. Topolski, M. *J. Org. Chem.* **1994**, *59*, 5506.

(4) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. (b) Motherwell, W. B.; Lewis, R. T. *Tetrahedron* **1992**, *48*, 1465. (c) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem Commun.* **1992**, 721. (d) Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014.

(5) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(6) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1960.

(7) Although we have fully characterized **6** as shown, the (dehydrated) keto form is almost certainly the reactive species in the diazo transfer and deacylation steps. We have not studied this equilibrium in detail.

(8) Davies, H. M. L.; Smith, H. D.; Baum, J. S.; Shook, D. A. *Synth. Commun.* **1987**, *17*, 1709. In our preparations of *p*-ABSA we have used a slightly modified procedure (see Experimental Section).

(9) For examples of methanesulfonyl azide in diazo transfer reactions, see: Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

(10) Reproducibility of yields in the diazo transfer step varied to a greater degree using commercially available *p*-ABSA (20−50%) as compared to reactions in which the azide had been prepared in house (45−50%).

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portions. The reaction was allowed to warm to room temperature and stir for 48 h. The slurry was filtered and concentrated by rotary evaporation to give *p*-acetamidobenzesulfonyl azide (19.22 g, 94%). This was used without further purification in the diazo transfer step. All spectral data were consistent with an authentic sample.

Dimethyl (3,3,3-Trifluoro-2,2-dihydroxypropyl)phosphonate (6). A flame-dried 250 mL round-bottomed flask was charged with 40 mL of dry THF. Dimethyl methylphosphonate (**5**, 2.29 g, 2.00 mL, 18.4 mmol) was added, and the mixture was cooled to −78 °C. *n*-Butyllithium (7.66 mL of a 2.40 M solution in hexanes, 18.4 mmol) was added over 5 min, and the solution was allowed to stir at −78 °C for 15−30 min. 2,2,2-Trifluoroethyl trifluoroacetate (5.41 g, 3.73 mL, 27.6 mmol) was added rapidly (1−2 s), and the resulting mixture was stirred at −78 °C for 15 min. The solution was then warmed to room temperature. The crude reaction mixture was partitioned between diethyl ether (250 mL) and 3% HCl (10 mL).[11] The combined ether layers were washed with saturated $NaHCO_3$ (1 × 10 mL) and saturated NaCl (1 × 10 mL), dried with $MgSO_4$, and concentrated to give **6** as a pale yellow oil which was used without purification in the next step. (Intermediate **6**, in some runs, solidified to a low melting solid.) On one occasion this product was purified by chromatography on silica gel (EtOAc, I_2 for visualization) to provide an analytically pure sample: mp 57−61 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.50 (s), 3.82 (d, J = 11.2 Hz), 2.33 (d, J = 19.2 Hz). ^{31}P NMR ($CDCl_3$, 100.2 MHz, rel to ext H_3PO_4) δ 29.58. ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 122.4 (dq, J_{C-P} = 21 Hz, J_{C-F} = 265 Hz), 92.1 (m, J_{C-F} = 41 Hz), 53.1 (d, J_{C-P} = 6.5 Hz), 29.8 (d, J_{C-P} = 141 Hz). IR (thin film) 3256, 1462, 1257, 1183, 1100, 1077, 1039 cm^{-1}. Anal. Calcd for C, 25.22; H, 4.23. Found: C, 25.09; H, 3.86.

Dimethyl (Diazomethyl)phosphonate (1). The crude sample of **6** was immediately dissolved in dry CH_3CN (40 mL). 4-Acetamidobenzenesulfonyl azide (3.97 g, 16.5 mmol) was added, and the solution was cooled to 0 °C. Triethylamine (1.66 g, 2.29 mL, 16.5 mmol) was slowly added (ca. 5 min). The mixture was allowed to warm to room temperature and was stirred overnight. Solvent was removed by rotary evaporation from the resulting slurry, which contained precipitated 4-acetamidobenzenesulfonamide. The residual orange oily solid was suspended in $CHCl_3$ and filtered through a coarse glass frit to remove the 4-acetamidobenzenesulfonamide, which was washed with a small portion of additional $CHCl_3$. Column chromatography of the concentrated filtrate (SiO_2, EtOAc, I_2 for visualization) gave **1** (1.23 g, 8.25 mmol, 50%). Spectral data were identical with those from an authentic sample.

(11) In optimizing this procedure we found that minimal exposure to aqueous solutions at this stage resulted in greater yields in the diazo transfer step.

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