1-Trifluoromethyl-1-diethoxyphosphoryl Carbene: A New Synthon for the Preparation of CF_3-Containing α-Hydroxy and α-Amino Phosphonic Acid Derivatives

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Abstract: The first synthesis of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate has been developed starting from readily available compounds. The synthetic utility of this compound is demonstrated via its Rh-catalyzed insertion into O–H and N–H bonds to produce CF_3-substituted α-hydroxy phosphonic and α-amino phosphonic acid derivatives

Key words: diazo compounds, fluorine, aminophosphonates, hydroxyphoshonate, insertion reactions

The phosphonate (PO_3^{2-}) moiety is a common structural fragment present in a wide range of biologically active compounds. Despite structural and electronic differences between phosphonate and carboxylic functionalities (in terms of size, shape, acidity, and geometry) the phosphonate functionality is regarded as a bioisostere of the carboxylic group. Therefore, α-amino and α-hydroxyphoshonates are important analogues of the corresponding carboxylic acids, and their synthesis and biological activity have been a focus of attention in synthetic and medicinal chemistry.[1] Many of them can serve as haptens in catalytic enzyme antibody generation and as transition state analogue inhibitors of different proteolytic enzymes exhibiting a wide spectrum of biological properties including antimicrobial, antitumor, antihypertensive, and antibacterial activities.[2] On top of this, the introduction of fluorine or fluoroalkyl substituents into biological relevant compounds has become an important tool in the drug discovery process.[3] Special attention is paid to trifluoromethyl-containing compounds due to the unique properties of the trifluoromethyl group, such as high electro-negativity, electron density, steric hindrance, and hydrophobic character[4] that can profoundly improve the pharmaco-kinetic properties of potential drugs.

Among the range of fluorination methods available the building block strategy represents the most attractive route for the incorporation of fluorinated moieties into organic molecules. In this context, along with our interest in new fluorinated building blocks,[5] we wish to disclose a convenient method for the preparation of novel trifluoromethyl-containing α-diazophosphonate **4** as well as the results of the initial investigation of its reactivity under rhodium-catalyzed conditions. Taking into account the synthetic potential of alkyl-3,3,3-trifluoro-2-diazopropionate[6] (Scheme 1), its nearest carboxylate analogue, we believe that **4** will attract considerable attention from both synthetic and medicinal chemists.

Thus, we found that the diazo compound **4** can be easily synthesized from α-trifluoromethyl-α-aminophoshonate **3** via diazotization of the latter with isopropyl nitrite in chloroform under mild conditions (Scheme 2). Despite the fact that the synthesis of **3** has been described by several research teams[7] its synthesis is not trivial and includes multi-step procedures with overall yields around 30%. A recently published synthesis of the NCbz derivative **2** based on commercially available ethyl trifluorohemiacetal[8] has inspired us to utilize this approach for the synthesis of **3**. A slight modification of the described procedure for the preparation of **2**, followed by quantitative deprotection of the amino function allowed us to increase the overall yield of **3** up to 74%. For the key diazotisation step several classical methods have been tested (e.g. $NaNO_2$/HCl, $NaNO_2$/H_2SO_4, $NaNO_2$/AcOH), however, in all cases the yields of the desired compound **4** did not exceed 28%. The best result was obtained when **3** was treated with isopropyl nitrite; in this case **4** was synthesized in 67% yield. The product is a stable light-yellow liquid, which can be distilled under reduced vacuum. Its synthesis was also successfully performed on a 20 g scale.

Both OH- and NH-insertion reactions of metallocarbenoid intermediates derived from their corresponding diazo compounds have found widespread use in the synthesis of biologically active compounds including the construction of bicyclic β-lactams,[9a] α-amino and α-hydroxy acids,[9b] peptides,[9c–e] and depsipeptides[6j] etc. We examined the reactivity of diazophosphonate **4** in such transformations under rhodium-catalyzed conditions.

Thus, we found that **4** readily reacts with different alcohols and carboxylic acids under reflux in anhydrous benzene (5–10 h) in the presence of catalytic amounts (2–3 mol%) of $Rh_2(OAc)_4$ to afford regioselectively the corresponding OH-insertion products **5** in good yields (Scheme 3, Table 1). The nature of the substituents does not significantly affect the outcome of the process. In the case of NBoc-protected phenylalanine (Table 1, entry 6)

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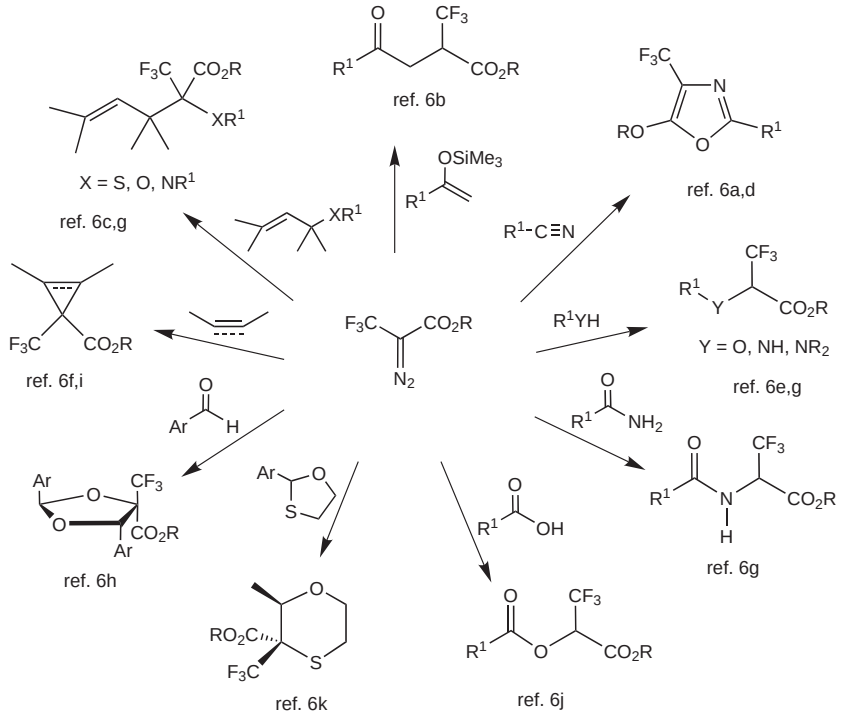
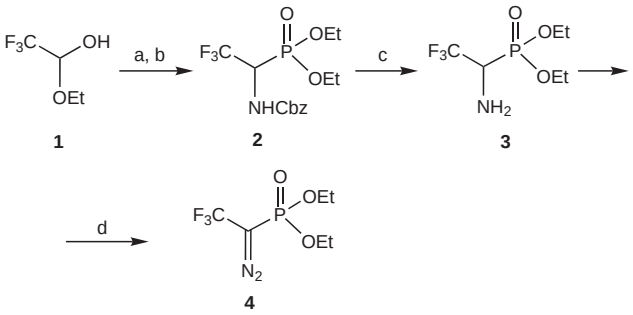
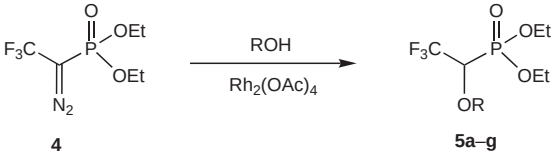


Scheme 1 Synthetic transformations of alkyl-3,3,3-trifluoro-2-diazopropionate.[6]



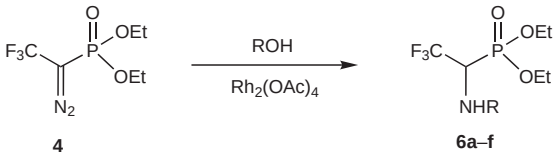
Scheme 2 Synthesis of diethyl 1-diazo-2,2,2-trifluoroethyl-phosphonate. *Reagents and conditions*: a) $CbzNH_2$, CH_2Cl_2, Et_3N, 5 Å MS, r.t., 14 d, 88%; b) i) $(CF_3CO)_2O$, py, ii) $HP(O)(OEt)_2$, Me_3SiCl, –20 °C, 84%; c) H_2, Pd/C, MeOH, r.t, 12 h, 100%; d) *i*-PrONO, $CHCl_3$, 30 min, 67%.

phosphorylated depsipeptide **5f** was isolated as a mixture of diastereomers in approximately a 1:1 ratio. Compound **5e** (Table 1, entry 5) has proved to be hydrolytically unstable; under standard purification by column chromatography it loses the trifluoroacetic group to give the corresponding 2-hydroxy-3,3,3-trifluoroethylphosphonate.



Scheme 3

Diazophosphonate **4** demonstrates comparable reactivity in reactions with different amino compounds under analogous reaction conditions yielding the corresponding α-trifluoromethyl-α-aminophosphonate derivatives **6** (Scheme 4, Table 2). Attempts to induce diastereoselectivity in the reaction of **4** with (1*R*)-menthyl carbamate proved to be unsuccessful; the insertion product **6e** (entry 5, Table 2) was isolated as a mixture of diastereomers in a 1:1 ratio.



Scheme 4

In conclusion we have developed a simple preparative pathway to new diethyl-1-diazo-2,2,2-trifluoroethylphosphonate (**4**);[10] this is the first example of an α-trifluoromethylated α-diazo-phosphonate. The synthetic utility of this compound was demonstrated via its Rh-catalyzed insertion into OH and NH bonds to produce CF_3-substituted α-hydroxy phosphonic and α-amino phosphonic acid derivatives.[11]

Acknowledgment

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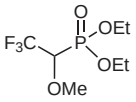
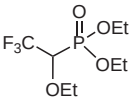
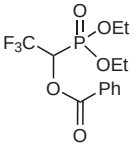
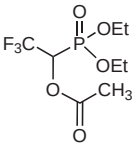
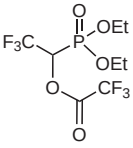
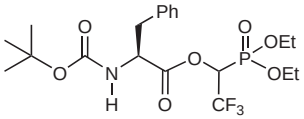
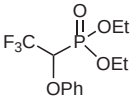
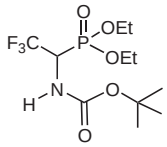
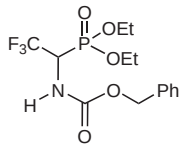
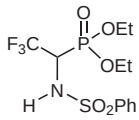
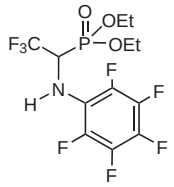
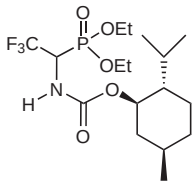
Table 1 Reaction of **4** with Alcohols and Carboxylic Acids

Entry	ROH	Product	Yield (%)[a]
1	MeOH		88
2	EtOH		93
3	PhC(O)OH		64
4	MeC(O)OH		84
5	$CF_3C(O)OH$		86[b]
6	BocPheOH		62
7	PhOH		78

[a] Isolated yield given after column chromatography.
[b] Yield determined by ^1H NMR spectroscopy.

Table 2 Reaction of **4** with NH_2-Functionalized Compounds

Entry	RNH_2	Product	Yield (%)[a]
1	$BocNH_2$		59
2	$CbzNH_2$		62
3	$PhSO_2NH_2$		64
4	$C_6F_5NH_2$		63
5	$MenthOC(O)NH_2$		50[b]

[a] Isolated yield given after column chromatography.
[b] Diastereomeric mixture in a 1:1 ratio.

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(10) **Diethyl (1-Diazo-2,2,2-trifluoroethyl)phosphonate (4)** The reaction was conducted in a 500 mL flask equipped with a condenser, a funnel, and magnetic stirrer. *i*-PrONO (9.5 g, 0.106 mol) was added to a vigorously stirred solution of aminophosphonate (19.6 g, 0.083 mol) in $CHCl_3$ (300 mL). After the addition of approximately 1.0 g of *i*-PrONO an exothermic reaction began; the rest of the nitrite was added dropwise providing a mild refluxing reaction mixture for 20 min. After stirring for an additional 40 min (the temperature was reduced to r.t.) the solvent was removed under reduced pressure and the residue was distilled in vacuo to afford 13.7 g (67%) of diazo compound **4** as light yellow liquid. Bp 47–50 °C (1 Torr). IR (KBr): 2160, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.40 (t, 6 H, *J* = 7.1 Hz), 4.15–4.30 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ = 15.9, 63.6, 118.6 (m), 124.1 (dq, J_{C-F} = 271.0 Hz, J_{C-P} = 12.1 Hz). ^{31}P NMR ($CDCl_3$): δ = 9.23. ^{19}F NMR ($CDCl_3$): δ = 23.0.

(11) **OH- and NH-Insertion; General Procedure** A solution of diazo compound **4** (1.1 mmol) in anhydrous benzene (3 mL) was added to a solution of the hydroxy or amino compound (1.0 mmol) and dirhodium tetraacetate (2 mol%) in benzene (10 mL). The reaction mixture was stirred under reflux for 4 h. After evaporation of the solvent under reduced pressure the crude product was purified by column chromatography on silica gel (EtOAc–hexanes).

Diethyl (2,2,2-Trifluoro-1-methoxyethyl)phosphonate (5a) Yield: 88%; oil. ^1H NMR ($CDCl_3$): δ = 1.38 (t, 6 H, *J* = 7.0 Hz), 3.65 (s, 3 H), 3.78–3.9 (m, 1 H), 4.20–4.30 (m, 4 H). ^{31}P NMR ($CDCl_3$): δ = 11.8 (app. q, *J* = 8.9 Hz). ^{19}F NMR ($CDCl_3$): δ = 6.7 (app. t, *J* = 8.5 Hz). Anal. Calcd for $C_7H_{14}F_3O_4P$: C, 33.61; H, 5.64. Found: C, 33.75; H, 5.75.

1-(Diethoxyphosphoryl)-2,2,2-trifluoroethyl *N*-(*tert*-Butoxycarbonyl)-1-phenylalaninate (5f) Yield: 62%; oil; dr 1:1. ^1H NMR ($CDCl_3$): δ = 1.35–1.45 (m, 6 H), 1.45 (s, 9 H), 3.10 (ddd, 1 H, *J* = 4.1, 6.4, 14.0 Hz), 3.28 (app. dt, 1 H, *J* = 5.5, 14.0 Hz), 4.20–4.37 (m, 4 H), 4.78 (m, 1 H), 4.98 (m, 1 H), 5.68–5.83 (m, 1 H), 7.20–7.30 (m, 2 H), 7.30–7.41 (m, 3 H). ^{31}P NMR ($CDCl_3$): δ = 8.7 (app. q, *J* = 7.4 Hz), 9.3 (app. q, *J* = 7.4 Hz). ^{19}F NMR ($CDCl_3$): δ = 7.63 (app. t, *J* = 7.3 Hz), 7.84 (app. t, *J* = 7.3 Hz). Anal. Calcd for $C_{20}H_{29}F_3NO_7P$: C, 49.70; H, 6.00; N 2.90. Found: C, 49.51; H, 6.21; N 2.75.

Diethyl (2,2,2-Trifluoro-1-phenoxyethyl)phosphonate (5g) Yield: 78%; oil. ^1H NMR ($CDCl_3$): δ = 1.40 (t, 6 H, *J* = 7.1 Hz), 4.20–4.40 (m, 4 H), 4.88–5.00 (m, 1 H), 7.05–7.15 (m, 3 H), 7.40–7.50 (m, 2 H). ^{31}P NMR ($CDCl_3$): δ = 10.6 (app. q, *J* = 8.9 Hz). ^{19}F NMR ($CDCl_3$): δ = 7.10 (app. t, *J* = 8.2 Hz). Anal. Calcd for $C_{12}H_{16}F_3O_4P$: C, 46.16; H, 5.17. Found: C, 46.27; H, 5.21.

Diethyl {1-[(*tert*-Butoxycarbonyl)amino]-2,2,2-trifluoroethy}phosphonate (6a) Yield: 59%; white crystals; mp 81.5–82.5 °C. ^1H NMR ($CDCl_3$): δ = 1.41 (t, 6 H, *J* = 8.1 Hz), 1.52 (s, 9 H), 4.20–4.30 (m, 4 H), 4.65–4.80 (m, 1 H), 5.20 (m, 1 H). ^{31}P NMR ($CDCl_3$): δ = 13.6 (app. q, *J* = 6 Hz). ^{19}F NMR ($CDCl_3$): δ = 8.05 (app. t, *J* = 7.5 Hz). Anal. Calcd for $C_{11}H_{21}F_3NO_5P$: C, 39.41; H, 6.31; N, 4.18. Found: C, 39.47; H, 6.31; N, 4.15.

Diethyl {1-[(Phenylsulfonyl)amino]-2,2,2-trifluoroethyl}phosphonate (6c) Yield: 64%; white solid; mp 115–117 °C. ^1H NMR ($CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.1 Hz), 1.39 (t, 3 H, *J* = 7.1 Hz), 4.10–4.30 (m, 4 H), 4.35–4.57 (m, 1 H), 7.05–7.15 (m, 1 H), 7.30–7.65 (m, 3 H), 7.92–7.97 (m, 2 H). ^{31}P NMR ($CDCl_3$): δ = 12.3 (app. q, *J* = 7.4 Hz). ^{19}F NMR ($CDCl_3$): δ = 8.03 (app. t, *J* = 8.0 Hz). Anal. Calcd for $C_{12}H_{17}F_3NO_5PS$: C, 38.40; H, 4.57; N, 3.73. Found: C, 38.21; H, 4.44; N, 3.67.

Diethyl {1-[(Pentafluorophenyl)amino]-2,2,2-trifluoroethyl}phosphonate (6d) Yield: 63%; white solid; mp 55–56 °C. ^1H NMR ($CDCl_3$): δ = 1.40 (dt, 6 H, *J* = 0.7, 7.1 Hz), 4.20–4.38 (m, 4 H), 4.38–4.50 (m, 1 H). ^{31}P NMR ($CDCl_3$): δ = 13.2 (app. q, *J* = 7.4 Hz). ^{19}F NMR ($CDCl_3$): δ = 8.06 (app. t, *J* = 7.8 Hz, 3 F), –78.0 (d, *J* = 21.8 Hz, 2 F), –85.2 (dt, *J* = 5.8, 21.8 Hz, 2 F), –88.9 (t, *J* = 21.8 Hz, 1 F). Anal. Calcd for $C_{12}H_{12}F_8NO_3P$: C, 35.93; H, 3.01; N, 3.49. Found: C, 36.25; H, 3.22; N, 3.47.