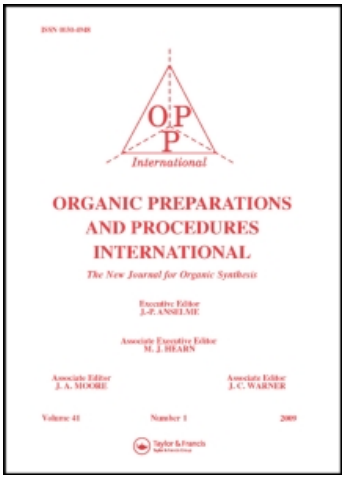


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# MICHAELIS-BECKER SYNTHESIS OF *bis*(2,2,2-TRIFLUOROETHYL)PHOSPHONO ESTERS

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## MICHAELIS-BECKER SYNTHESIS OF *bis*(2,2,2-TRIFLUOROETHYL)PHOSPHONO ESTERS

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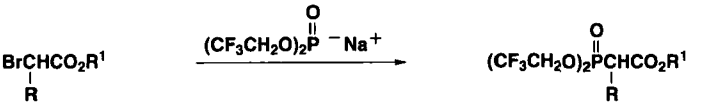
The Michaelis-Becker reaction is a well known method for the synthesis of alkylphosphonates,[1] although the yields of phosphono esters tend to be relatively low.[1c] Although the Arbuzov reaction generally provides phosphono esters in significantly higher yields,[1c] *bis*(2,2,2-trifluoroethyl)phosphono esters are inaccessible *via* the Arbuzov reaction due to the non-nucleophilic nature of $(CF_3CH_2O)_3P$. *bis*(2,2,2-Trifluoroethyl)phosphono esters have found widespread use in the synthesis of Z-α,β-unsaturated esters in the Horner-Wadsworth-Emmons condensation.[1b,2a] The two principal literature methods for synthesis of *bis*(2,2,2-trifluoroethyl)phosphono esters have involved variations of Still's procedure of phosphonate ester interchange,[2] or modifications of that reported by Patois and Savignac *et al.* of acylation of an alkylphosphonate anion,[3] both of which rely upon an existing phosphonate starting material. This paper describes the use of the Michaelis-Becker reaction to prepare *bis*(2,2,2-trifluoroethyl)phosphono esters **2a-d**.




**1a-d** **2a-d**

a) R = H, $R^1 = CH_2CH_3$ b) R = $CH_3$, $R^1 = CH_2CH_3$ c) R = $CH_2CH_3$, $R^1 = CH_2CH_3$ d) R = $CH_3$, $R^1$ = Cl

The surprising nucleophilic reactivity of the anion of *bis*(2,2,2-trifluoroethyl)phosphite toward bromo esters in the Michalis-Becker reaction provides an interesting approach for the preparation of *bis*(2,2,2-trifluoroethyl)phosphono esters. Our best results were obtained with unhindered bromo ester **1a**, which was converted to the corresponding phosphonate **2a** in 30% yield. With the secondary bromo esters **1b-d**, lower yields (16-20%) of phosphonates **2b-d** were realized, with significant recovery of starting materials. In an attempt to optimize the yields, we examined the variation of base (NaH, KO-*t*Bu, LDA, *n*-BuLi) temperature (reflux to -78°) and solvent (THF, THF/HMPA).[4] Optimum yields are summarized in Table 1.

## EXPERIMENTAL SECTION

$^1H$, $^{13}C$ and $^{31}P$ NMR spectra were recorded on a 400 MHz Varian Gemini 2000 Spectrometer. $^1H$ and $^{13}C$ NMR chemical shifts are reported in δ values downfield from TMS as internal standard, while $^{31}P$ NMR chemical shifts are reported downfield from 85% $H_3PO_4$ as an external standard. Reactions were conducted under an atmosphere of dry argon. THF was distilled from sodium/benzophenone prior to use. *bis*(2,2,2-trifluoroethyl)phosphite was purchased from Aldrich Chemical Co.



**TABLE 1.** Optimized Yields of Phosphono Esters **2a-d**[a]

| Cmpd | Solvent | Temp (°C) | Method | Yield (%) |
|---|---|---|---|---|
| **2a** | THF | -42 | A | 30[b] |
| **2b** | THF/HMPA | rt | B | 18[b] |
| **2c** | THF/HMPA | rt | B | 20[b,c] |
| **2d** | THF | -42 | A | 16[d] |

a) NaH was used as the base; b) Ref. 3a; c) Ref. 2a; d) Ref. 2e.

**Ethyl [*bis*(2,2,2-Trifluoroethoxy)phosphinyl]acetate (2a).**- *bis*(2,2,2-Trifluoroethyl)phosphite (0.80 mL, 5.0 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 400 mg, 10 mmol) in anhydrous THF (20 mL) at -42° followed by the immediate addition of ethyl bromoacetate (0.44 mL, 4.0 mmol). The reaction mixture was allowed to warm to rt and stirred for 5 h. The reaction mixture was quenched with saturated $NH_4Cl$. The organic layer was washed with $H_2O$ (20 mL). The aqueous extract was washed with ether (3 x 25 mL). The combined organic extract was washed with saturated NaCl and dried ($MgSO_4$). After removal of the solvent by rotary evaporation, the final product was purified by flash chromatography using hexane:ethyl acetate (80:20) producing compound **2a** as a clear oil (400 mg, 30%). $^1H$ NMR ($CDCl_3$): δ 4.49-4.40 (m, 4H), 4.22 (q, 2H, $J$ = 7.1 Hz), 3.14 (d, 2H, $J$ = 21.2 Hz), 1.28 (t, 3H, $J$ = 7.1 Hz). $^{13}C$ NMR ($CDCl_3$): δ 164.6 (d, $J$ = 4.6 Hz), 122.4 (2, dq, $J$ = 277.3, 8.2 Hz), 62.6 (2, dq, $J$ = 38.1, 5.3 Hz), 62.3, 34.00 (d, $J$ = 145.0 Hz), 13.9. $^{31}P$ NMR ($CDCl_3$): δ 23.2.

**Ethyl [*bis*(2,2,2-Trifluoroethoxy)phosphinyl]propionate (2b).**- *bis*(2,2,2-Trifluoroethyl)phosphite (0.79 mL, 5.0 mmol) was added to a solution of sodium hydride (400 mg, 10 mmol), in THF (20 mL)

and HMPA (1.5 ml, 8.6 mmol) at rt. Immediately thereafter, ethyl 2-bromopropionate (0.50 mL, 3.9 mmol) was added to the solution in a dropwise manner and the reaction mixture was stirred for 5 h. The reaction mixture was quenched with saturated $NH_4Cl$. The organic layer was washed with $H_2O$ (20 mL). The aqueous extract was washed with ether (3 x 25 mL). The combined organic extracts were washed with saturated NaCl and dried ($MgSO_4$). After the solvent had been removed *in vacuo*, the product was purified by flash column chromatography. Elution with hexane:ethyl acetate (80:20) produced compound **2b** as a thick oil (240 mg, 18%). $^1H$ NMR ($CDCl_3$): δ 4.44-4.02 (m, 4H), 4.21 (q, 2H, *J* = 7.1 Hz), 3.17 (dq, 1H, *J* = 22.6, 7.5 Hz), 1.79 (dd, 3H, *J* = 19.3, 7.4 Hz), 1.27 (t, 3H, *J* = 7.1 Hz). $^{13}C$ NMR ($CDCl_3$): δ 168.1 (d, *J* = 3.1 Hz), 123.5 (dq, *J* = 277.0, 3.1 Hz), 123.4 (dq, *J* = 277.0, 3.1 Hz), 62.6 (2, dq, *J* = 38.2, 5.3 Hz), 62.2, 40.5 (d, *J* = 140.4 Hz), 14.0, 11.8 (d, *J* = 3.1 Hz). $^{31}P$ NMR ($CDCl_3$): δ 26.7.

**Ethyl [*bis*(2,2,2-trifluoroethoxy)phosphinyl]butyrate (2c).**- To a solution of sodium hydride (393 mg, 9.8 mmol) in THF (20 mL) and HMPA (1.5 ml, 8.6 mmol) at rt was added dropwise *bis*(2,2,2-trifluoroethyl) phosphite (0.79 mL, 5.0 mmol), followed immediately by dropwise addition of ethyl 2-bromobutyrate (0.50 mL, 3.4 mmol). After 9 h at rt, the reaction mixture was quenched by addition of saturated aqueous ammonium chloride. The aqueous layer was removed and the organic layer was washed with water (20 mL). The aqueous solution was washed with ether (3 x 25 mL). The organic extract was washed with saturated sodium chloride and dried ($MgSO_4$). After removal of the solvent by rotary evaporation, the product was purified by flash chromatography, eluting with hexane:ethyl acetate (80:20) producing compound **2c** as a clear oil (250 mg, 20%). $^1H$ NMR ($CDCl_3$): δ (ppm) 4.45-4.32 (m, 4H), 4.22 (q, 2H, *J* = 7.1 Hz), 3.00 (ddd, 1H, *J* = 21.6, 9.5, 5.0 Hz), 1.90-2.04 (m, 2H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.01 (t, 3H, *J* = 7.4 Hz). $^{13}C$ NMR ($CDCl_3$): δ 167.7 (d, *J* = 3.1 Hz), 122.3 (dq, *J* = 276.7, 8.0 Hz), 122.3 (dq, *J* = 276.8, 7.8 Hz) 62.7 (dq, *J* = 38.0, 5.9 Hz), 62.4 (dq, *J* = 38.2, 6.1 Hz), 62.1, 47.1 (d, *J* = 136.6 Hz), 20.8 (d, *J* = 5.4 Hz), 14.1, 12.6. $^{31}P$ NMR ($CDCl_3$): δ 25.8.

**Methyl [*bis*(2,2,2-Trifluoroethoxy)phosphinyl]propionate (2d).**- *bis*(2,2,2-Trifluoroethyl)phosphite (0.75 mL, 4.7 mmol) was added dropwise to a mixture of THF (25 mL) and sodium hydride (415mg, 10.4 mmol) at -42°. Methyl 2-bromopropionate (0.38 mL, 3.4 mmol) was added immediately to the solution in a dropwise manner. The reaction mixture was allowed to warm to rt and was stirred overnight. After standard aqueous workup, the product was purified by flash chromatography, eluting with hexane:ethyl acetate (80:20) producing compound **2d** as an oil (0.191 g, 16%). $^1H$ NMR ($CDCl_3$): δ 4.25-4.35 (m, 4H), 3.77 (s), 3.19 (dq, 1H, *J* = 22.7, 7.5 Hz), 1.51 (dd, 3H, *J* = 19.32, 7.42 Hz). $^{31}P$ NMR ($CDCl_3$): δ 26.7.

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