Heteroatom Chemistry
Volume 9, Number 2, 1998

Studies on Organophosphorus Compounds 101. A Facile Synthetic Route to Trifluoromethylated Aminophosphonic Acids and Phosphonopeptides

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Received 24 March 1997; revised 16 June 1997

ABSTRACT

A series of dialkyl 1-(N-substituted amino)-2,2,2-trifluoroethylphosphonates was synthesized by Arbuzov-type reactions involving an N-substituted trifluoromethylimidoyl chloride and the appropriate trialkyl phosphite. The resulting C=N bond was successfully hydrogenated by $NaBH_4CN$ treatment. The subsequent deprotection of the amino group was conducted either by hydrogenolysis with Pd black or by use of cerium ammonium nitrate, depending on the structure of the substituent on the amino function. The free amino group thus obtained underwent a coupling reaction with an aminoacyl chloride in the usual manner.
 Heteroatom Chem 9:139–146, 1998

INTRODUCTION

The increasing and sustained interest in aminophosphonic acids and related peptides has had an explosive impact on the design and synthesis of functionalized aminophosphonic acids. Introduction of a fluorine atom into a biologically active compound usually results, as a rule, in an enhancement of the activity of the parent molecule. Utilizing fluorinated acetic acid, Flynn et al. [1] described the synthesis of β-fluorinated aminophosphonic acids, namely, β-monofluoro, β-difluoro-, and β-trifluoro-α-aminoethylphosphonic acid and their action as inhibitors of alanine racemace. Gruss and Hagele [2], on the other hand, reported a general method leading to nuclear fluorinated N-phenyl-phenylglycine and demonstrated that (N-*p*-trifluoromethoxyphenyl)-phenylglycine showed remarkable insecticidal activity toward harmful and parasitic insects. Recently, Hass and Hagele [3] reported an interesting reaction by which fluorinated hydroxyphosphonic acid esters and fluorinated N-(phenylamino)phosphonic acid ester can be formed conveniently from corresponding fluorinated aldehydes generated in situ. In our laboratory, we have previously introduced a method for the synthesis of 3-amino-2-hydroxy-1,1-difluoroalkylphosphonic acid [4]. Several synthetic methods for the preparation of 1-(N-substituted amino)- and 2-(N-substituted amino)-2,2,2-trifluoro-ethyl phosphonates were also introduced by us [5,6]. As far as we are aware, syntheses of fluorinated phos-

Dedicated to Prof. William Edwin McEwen on the occasion of his seventy-fifth birthday.

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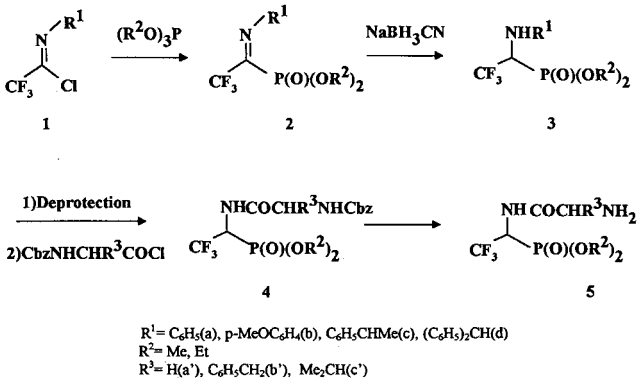
 CCC 1042-7163/98/020139-08

phonopeptides have not yet been studied. As a continuation of our systematic study, the preparation of phosphonopeptides bearing a trifluoromethyl group is reported in this article.

RESULTS AND DISCUSSION

Our synthetic approach leading to trifluoromethylated phosphonopeptides is based on the following sequence of reactions as shown in the following scheme.



The key intermediates, trifluoromethyl N-substituted imidoyl chlorides (**1**), were conveniently prepared by amidation of trifluoroacetic acid with a primary amine in the presence of carbon tetrachloride, triphenylphosphine, and triethylamine in a one-pot procedure as summarized (Table 1) [7].

The resulting trifluoromethyl N-substituted imidoyl chlorides (**1**) gave dialkyl 1-N-substituted imino-2,2,2-trifluoroethylphosphonates (**2**) via the Arbuzov rearrangement with trialkyl phosphites in good to excellent yields as depicted in Table 2.

Each Arbuzov-type reaction was performed by heating the trifluoroacetimidoyl chloride with the trialkyl phosphite at 80–100°C without a solvent. Heating was necessary, not only for each such thermal rearrangement, but also for the removal of the alkyl halide formed during the reaction. The reaction process was monitored either by ^{19}F NMR spectroscopy or by TLC [petroleum ether (60°C)/ethyl acetate 2:1]; while each N-phenyl-trifluoroimidoyl chloride exhibits an ^{19}F NMR chemical shift at δ 4.8, the product shows a chemical shift at δ 9.7 in ^{19}F NMR spectral studies. After 6 hours of reaction, the chemical shift at δ 4.8 disappeared, and a new peak at δ 9.7 was formed. For N-aralkyl derivatives, **2d** for example, the ^{19}F NMR chemical shift for the reactant (δ 6.0) disappeared only after 40 hours of reaction, with the formation of a new peak at δ 9.4 for the product. As we observed in our experiments, the reaction time required for the Arbuzov-type rearrangement depends directly on the nature of the substituent on the imino nitrogen. Generally speaking, N-aralkyl substituted derivatives need a longer (24–40 h) reaction time and higher (100°C) reaction temperature than the corresponding N-aryl derivatives that required only 6–10 hours of heating at 80°C. The presence of an electron-donating group on the N-phenyl group slows the reaction, while the presence of an electron-withdrawing group accelerates the process.

The 1-N-substituted imino-2,2,2-trifluoroethylphosphonates thus obtained can be converted smoothly to 1-N-substituted amino-2,2,2-trifluoroethylphosphonates quantitatively by treatment with $NaBH_3CN$ (Table 3).

Our unsuccessful attempts to effect the hydrogenolysis of the C = N bond and the simultaneous catalytic removal of the benzyl group of **2c** and **2d** could be rationalized by the presence of a bulky group around the C = N bond. Reduction of the C = N moiety by $NaBH_4$ treatment provided only a 17% yield. The use of an ethanolic $NaBH_3CN$ solution with a catalytic amount of acetic acid increased the yield markedly to 60%. Since the polarity of the substrate **2** is very close to that of the product **3,** a complete separation of **2** and **3** by column chromatography is not easy. However, the use of acetic acid solution of $NaBH_4CN$ works well in this reaction, providing the corresponding amino compounds in excellent yields.

For the removal of the N-protection group, various methods can be adopted, depending on the chemical structure of the protecting group. Deprotection of the N-methylbenzyl or the diphenylmethyl group was performed in 70–75% yield by reaction with palladium black (30–50%) in HCOOH-MeOH. Catalytic hydrogenolysis of **3c** by palladium black (30–50%) in anhydrous HCOOH-MeOH afforded a 71–75% yield. However, the yield of the hydrogenolysis product was sharply decreased to 50% when 88% aqueous HCOOH was used instead of anhydrous formic acid. However, no reaction was observed by use of palladium black or 50% Pd on carbon under similar conditions. The product isolated in each case is the 1-(N-formylamino)-2,2,2-trifluoroethylphosphonate, which provides the free 1-amino-2,2,2-trifluoroethylphosphonic acid by acid-catalyzed hydrolysis using 5% HCl-MeOH, followed by careful neutralization with aqueous NaOH. It should be pointed out that cerium ammonium nitrate (CAN) was successfully used to remove the *p*-methoxyphenyl group on the amino function, providing the N-dearylated product in fair to good yield [8,9]. This oxidative cleavage reaction of CAN for the deprotection of an N-anisyl moiety in the synthesis

TABLE 1 Preparation of Trifluoromethyl N-Substituted Imidoyl Chlorides $CF_3C(=NR^1)Cl$

	R^1	*BP* (°*C*) (*mm*)	*Yield* (%)	*IR* (ν, cm^{-1})	^{19}F *NMR* (*ppm*)
1a	C_6H_5	71–72 (24)	84	1700 (CN)	4.8
1b	4-$MeOC_6H_4$	91 (5)	80	1690 (CN)	5.8
1c	C_6H_5CHMe	92 (15)	80	1700 (CN)	6.0
1d	Ph_2CH	99–100 (0.1)	30	1690 (CN)	6.5

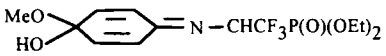
TABLE 2 Preparation of Dialkyl 1-(N-Substituted)-imino-2,2,2-trifluoroethylphosphonates $CF_3C(=NR^1)P(O)(OR^2)_2$

			Reaction		
Entry	R^1	R^2	*t*°	*h*	*Yield* (%)
2a	Ph	Et	80	6	94
2b	*p*-$MeOC_6H_4$	Et	80	10	95
2c	PhCHMe	Et	100	40	80
2d	PhCHMe	Me	100	40	82
2e	Ph_2CH	Et	100	40	67

TABLE 3 Preparation of dialkyl 1-(N-substituted) amino-2,2,2-trifluoroethylphosphonates $CF_3CH(NHR^1)P(O)(OR^2)_2$

Entry	R^1	R^2	*Mp* (°*C*)	*Yield* (%)
3a	Ph	Et	60	60
3b	*p*-$MeOC_6H_4$	Et	43–45	99
3c	PhCHMe	Et	oil	99
3d	PhCHMe	Me	38–40	99
3e	Ph_2CH	Et	oil	99

of trifluoromethylated 1-amino acids was reported by Watanabe et al. [9]. Our experimental results demonstrated that, upon reaction of **3b** with CAN in acetonitrile at 0°C, the N-dearylated product (**4b**) was usually contaminated with the hydroquinonimino derivative



as indicated by spectroscopic examination. The relatively electron-rich aromatic ring should be amenable to oxidative removal without prior ether cleavage. The product mixture, after chromatographic separation on silica gel, afforded the phosphonopeptide with Cbz-glycine using DCC-HOBT as the condensation reagent. Subsequent removal of the N-Cbz group by hydrogenolysis gave the trifluoromethylated phosphonopeptide with a free amino group (**5**). However, to our surprise, with Cbz-L-valinyl or Cbz-L-phenylalanyl chloride, the yield of condensation product with deprotected **3** is much lower than that with glycinyl chloride. The complicated reaction mixture was difficult to separate even by chromatography on silica gel.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken on a Shimadzu-440 spectrometer. ^1H and ^{31}P NMR spectra were recorded on a JEOL FX-90Q (90 Mz) and a Brucker AM-300 spectrometer, respectively. Chemical shifts for ^1H NMR spectra are reported in δ values downfield from TMS. ^{31}P NMR chemical shifts are reported in δ values downfield from 85% H_3PO_4. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3COOH as an external standard, positive for downfield shifts. EI–MS were obtained on a HP5989A mass spectrometer.

Dicyclohexylcarbodiimide (DCC) was kindly supplied by the Shanghai Institute of Biochemistry. Sodium Cyanoborohydride ($NaBH_3CN$) was purchased from Fluka Chemical Co., Switzerland. Anhydrous formic acid was prepared by refluxing 98% HCOOH with phthalic anhydride for 6 hours and then collecting the fraction boiling at 103–104°C [10]. Carbobenzyloxy chloride (CbzCl) was offered as a gift from the Experimental plant, Shanghai Institute of Biochemistry, as a 4.2 mmol/mL solution in toluene. The concentration of CbzCl was checked by converting it to $CbzNH_2$ and obtaining the weight. Cbz-Glycine (mp 119–121°C), Cbz-L-phenylalanine (mp 88–89°C), and Cbz-L-valine (mp 66–67°C) were prepared by reaction of CbzCl with the corresponding amino acid according to a standard method [11]. 1-Hydroxybenzotriazole (HOBt) was synthesized by reductive cyclization of O-nitrochlorobenzene with hydrazine hydrate and it was recrystallized from water, mp 155°C.

Palladium Black was prepared by dissolving 4.79 g $PdCl_2$ in 30 mL of conc. HCl and then adding 80 mL of H_2O and 35 mL of 38% aqueous HCHO solution in an ice-salt cooling bath. Under vigorous stirring, a solution of 35 g of KOH in 30 mL of water was introduced under 10°C. After that, the mixture was warmed to 60°C and kept at this temperature for 30 minutes. The precipitated palladium black was

successively washed six times with distilled water by decantation. Finally, the palladium black was collected on a Buchner funnel and washed repeatedly with 1 L of distilled water until the filtrate showed a pH of 7. The air-dried product was kept in a desiccator over $CaCl_2$ and silica gel until a constant weight (2.12 g) of palladium black was achieved.

N-(α-Methylbenzyl)-2,2,2-trifluoroacetimidoyl Chloride (**1c**). To a 250 mL three-necked flask equipped with a septum cap, thermometer, and stirrer was added triphenylphosphine (34.6 g, 132 mmol), triethylamine (5.87 g, 8.1 mL, 58 mmol), and carbon tetrachloride (21.3 mL, 220 mmol). The mixture was stirred vigorously with cooling to 0°C. After that, trifluoroacetic acid (5 g, 3.4 mL, 44 mmol) was introduced by a syringe through the rubber cap during 10 minutes, and then a solution of α-methylbenzylamine (6.42 g, 6.1 mL, 53 mmol) in carbon tetrachloride (21.3 mL, 220 mmol) was added. After the rubber cap had been replaced by a reflux condenser, the reaction mixture was heated gently. The triphenylphosphine had dissolved completely when the temperature reached 50°C, and the solution was kept at this temperature for 0.5 hour. The reaction occurred exothermally with the formation of a colorless precipitate consisting of $Et_3N.HCl$ and Ph_3PO. The oil bath was then removed, and stirring was continued. The exothermic reaction was allowed to continue for 3 minutes, and the mixture was then heated under reflux for 3 hours. After cooling to room temperature, the resultant mixture was filtered. The residue thus obtained was composed of Ph_3PO, $Et_3N.HCl$, and unreacted Ph_3P. The precipitate was washed thoroughly with petroleum ether until a colorless filtrate was obtained. The petroleum ether wash solutions were combined and concentrated, whereupon an additional precipitate was collected; **1c** was obtained 8.28 g, 80% yield, bp 92°C (15 mm Hg). IR (film) *ν*max: 1700 (C=N), 2950–3000 (CH), 1295, 1215, 1165 (C–F) cm^{-1}. ^1H NMR (CCl_4/TMS), δ 1.38 (d, 3H, J = 7 Hz, CH_3), 4.79 (q, 1H, J = 7 Hz, CH), 7.08 (s, 5H, Ph). ^{19}F NMR (CCl_4/TFA) δ 6.0 (s). MS, m/e (%) 105 (CHMePh, 100), 157 (M^+-Ph-1), 77 (Ph), 235 (M^+), 237 (M^- + 2). Anal. calcd for $C_{10}H_9ClF_3N$ (235.63): C, 50.96; H, 3.82; N, 5.94. Found: C, 50.92; H, 3.69; N, 5.81.

N-Phenyl-2,2,2-trifluoroacetimidoyl Chloride (**1a**). Compound **1a** was synthesized analogously as for **1c,** bp 71–72°C/24 mm Hg (Ref. [7] bp 55–56°C/11 torr). Yield 84%. IR (film) *ν*max: 1700 (C=N) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 7.08–7.12 (m, 2H, Ph), 7.26–7.49 (m, 3H, Ph). ^{19}F NMR (CCl_4/TFA) δ 4.8 (s).

N-(p-Anisyl)-2,2,2-trifluoroacetimidoyl Chloride (**1b**). Compound **1b** was synthesized analogously as for **1c,** colorless liquid by 91°C/5 mm (Ref. [7] bp 97–98°C/14 torr). Yield 80%. IR (film) *ν*max: 1690 (C=N) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 3.85 (s, 3H, OCH3), 6.97–7.02 (m, 2H, Ph), 7.30–7.37 (m, 2H, Ph). ^{19}F NMR (CCl_4/TFA), δ 5.8 (s).

N-(Diphenylmethyl-2,2,2-trifluoroacetimidoyl Chloride (**1d**). Compound **1d** was synthesized analogously as for **1c,** colorless liquid, bp 99–100°C/0.1 mm. Yield 3.77 g of 30%. IR (film) *ν*max: 1690 (C=N), 1150, 1205, 1275 (C–F) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 5.20 (s, 1H, CH), 7.38 (s, 10H, 2XPh). ^{19}F NMR (CCl_4/TFA) δ 6.50 (s). Anal. calcd for $C_{15}H_{11}ClF_3N$ (297.7): C, 60.51; H, 3.69; N, 4.71. Found: C, 60.62; H, 3.92; N, 4.48.

Diethyl 1-(N-p-Anisylimino)-2,2,2-trifluoroethylphosphonate (**2b**). To a 50 mL flask fitted with a $CaCl_2$ tube and reflux condenser was added an equivalent amount (5 mmol) of **1b** and triethyl phosphite. The mixture was stirred thoroughly at 80–100°C. The reaction was monitored by ^{19}F NMR spectroscopy, usually 10 to 40 hours being necessary, depending on the structure of the N substituent. The volatile components were removed under reduced pressure, and the resultant residue was subjected to chromatography on silica gel (EtOAc:Petroleum ether 1:1) giving a pale yellow oil; yield 1.62 or 95%. The product can be used directly for subsequent reduction. IR (film) *ν*max: 1680 (C=N), 1265 (P=O), 1140, 1190 (C–F), 1010 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 3.85 (s, 3H, OCH_3), 1.17 (q, 6H, J = 7 Hz, $2XOCH_2C\underline{H}_3$), 1.39 (d, 3H, J = 6 Hz, CH_3), 3.90 (m, 4H, $2XOCH_2$), 5.55 (q, 1H, H = 6 Hz, CH), 7.00 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$/TFA) δ 9.20 (s). ^{31}P NMR ($CDCl_3/H_3PO_4$) δ 2.10 (q, J = 9 Hz).

Diethyl 1-(N-Phenylimino)-2,2,2-trifluoroethylphosphonate (**2a**). Compound **2a** was prepared similarly as for **2b**. A pale yellow oil, yield 1.45 g or 94%. IR (film) *ν*: 1700 (C=N), 1260 (P=O), 1140, 1190 (C–F), 1020 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.03 (t, 6H, J = 6 Hz, $2XCH_3$), 3.77 (m, 4H, $2XOCH_2$), 6.76–6.96 (m, 2H, Ph), 7.03–7.30 (m, 3H, Ph). ^{19}F NMR (CCl_4/TFA). δ 9.70 (s). ^{31}P NMR ($CDCl_3/H_3PO_4$) δ 7.37 (q, J = 9.2 Hz). Ms, m/e (%): 172 [M^+-P(O)$(OEt)_2$, 100], 240 (M^+-CF_3), 309 (M^+). Anal. calcd for $C_{12}H_{15}F_3NO_3P$ (309.19): C, 46.60; H, 4.85; N, 4.59. Found: C, 46.48; H, 4.74; N, 4.62.

Diethyl 1-(N-α-Methylbenzylimino)-2,2,2-trifluoroethylphosphonate (**2c**). This compound was prepared similarly as for **2b**; yield 1.34 g or 80%. IR (film) *ν*max: 2940 (C–H), 1680 (C=N), 1260 (P=O),

1140, 1190 (C–F), 1005 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.17 (q, 6H, J = 7 Hz, $2XOCH_2C\underline{H}_3$), 1.39 (d, 3H, J = 6 Hz, CH_3), 3.90 (m, 4H, $2XOCH_2$), 5.55 (q, 1H, J = 6 Hz, CH), 7.00–7.15 (m, 5H, Ph). ^{19}F NMR (CCl_4/TFA) δ 9.40 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 2.10 (q, J = 9 Hz). MS, m/e (%): 77 (Ph), 105 (CHMePh), 199 (M^+-1-P(O)$(OEt)_2$, 100), 234 [$CF_3C{=}(NH_2)^+P(O)(OEt)_2$], 338 ($M^+$ + 1). Anal. calcd for $C_{14}H_{19}F_3NO_3P$ (337.27); C, 49.85; H, 5.64; N, 4.15. Found: C, 49.23; H, 5.51; N, 4.01.

Dimethyl 1-(N-α-Methylbenzylimino)-2,2,2-trifluoroethylphosphonate (**2d**). Compound **2d** was prepared similarly as for **2b**; yield 1.27 g or 82%. IR (film) *v*max: 2950 (C–H), 1712 (C=N), 1265 (P=O), 1190, 1145 (C–F), 1010 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.57 (d, 3H, J = 9 Hz, CH_3), 3.65 (dd, 6H, J = 9 Hz, J = 18 Hz, $2XOCH_3$), 5.56 (q, 1H, J = 9 Hz, CH), 7.07–7.27 (m, 5H, Ph). ^{19}F NMR (CCl_4/TFA) δ 8.00 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 4.37 (q, J = 8.67 Hz). MS, m/e (%): 77 (Ph), 105 (CHMePh), 199 [M^+-P(O)$(OMe)_2$, 100], 308 (M^+ − 1). Anal. calcd for $C_{12}H_{15}F_3NO_3P$ (309.22): C, 46.60; H, 4.85; N, 4.53. Found: C, 46.72; H, 4.78; N, 4.68.

Diethyl 1-(N-Diphenylmethylimino)-2,2,2-trifluoroethylphosphonate (**2e**). This compound was prepared similarly as for **2b**; yield 1.3 g or 67%. IR (film) *v*max: 2950 (CH), 1700 (C=N), 1250 (P=O), 1140, 1186 (C–F), 1010 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.17 (q, 6H, J = 7 Hz, $2XCH_2C\underline{H}_3$), 1.25 (q, 1H, J = 6 Hz, CH), 7.00–7.25 (m, 10H, 2Ph), 5.25 (s, 1H, $CHPh_2$). ^{19}F NMR (CCl_4/TFA) δ 8.80 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 3.45 (q, J = 7 Hz). MS, m/e (%): 77 (Ph), 167 ($CHPh_2$), 263 [M^+-P(O)$(OEt)_2$, 100], 400 (M^+ + 1). Anal. calcd for $C_{19}H_{21}F_3NO_3P$ (399.33): C, 57.14; H, 5.26; N, 3.50. Found: C, 56.82; H, 5.58; N, 3.42.

Diethyl 1-(N-Phenylamino)-2,2,2-trifluoroethylphosphonate (**3a**). Compound **2a** (1.4 g) was dissolved in absolute ethanol (5 mL) followed by addition of sodium cyanoborohydride (0.32 g, 5 mmol). The resulting mixture was stirred at room temperature (RT) for 20 hours and then poured into EtOAc (20 mL) and H_2O (15 mL). After agitation, the organic layer was removed, and the aqueous layer was extracted with EtOAc (2X 20 mL). The combined organic solution was dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography on silica gel using EtOAc/petroleum ether 1:1 as eluent. The product **3a** is a colorless solid, yield 60%, mp 60°C (Ref. [4] mp 60°C). IR (KBr) *v*: 3300 (N–H), 3000, 1610, 1505, 750 (Ph), 1250 (P=O), 1170 (C–F), 1020 (P–O–C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.33 (t, 6H, J = 7.0 Hz, $2XCH_3$), 4.12–4.23 (m, 6H, $2XOCH_2$, CH, NH), 6.73 (d, 2H, J = 7.1 Hz, Ph), 6.84 (t, 1H, J = 7.3 Hz, Ph), 7.20–7.27 (m, 2H, Ph). ^{19}F NMR (CCl_4/TFA) δ 9.2 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 15.2 (q, J = 8.7 Hz). MS, m/e (%): 311 (M^+ 96), 174 [M-P(O)$(OEt)_2$, 100]. Anal. calcd for $C_{12}H_{17}F_3NO_3P$ (311.25): C, 48.41; H, 8.36; N, 4.03. Found: C, 48.62; H, 8.30; N, 3.94.

Diethyl 1-(N-p-Anisylamino)-2,2,2-trifluoroethylphosphonate (**3b**). Compound **2b** (1.5 g) was dissolved in glacial acetic acid (5 mL), followed by addition of sodium cyanoborohydride (0.35, 5.5 mmol). The reduction occurred exothermically with evolution of hydrogen. The mixture was then stirred at RT for 10 hours and then evaporated to remove solvent. To the residue was added 20 mL of EtOAc and 15 mL of H_2O. The aqueous layer was treated with solid K_2CO_3 to pH 9. After agitation, the organic layer was separated, and the aqueous solution was extracted with EtOAc (2X 20 mL). The combined organic solution was dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography on silica gel using EtOAc/petroleum ether 1:2 as eluent. **3b** was obtained as a pale yellow solid, mp 43–45°C, yield 1.45 g or 99%. IR (nujol) *v*: 3250 (NH), 3000, 1650, 1505, 750 (Ph), 1245 (P=O), 1155, 1100 (C–F), 1020 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.29 (t, 6H, J = 7.0 Hz, $2XCH_3$), 3.77 (s, 3H, OCH_3), 4.02–4.30 (m, 6H, $2XOCH_2$, CH, NH), 6.70 (s, 4 H, Ph). ^{19}F NMR (CCl_4/TFA) δ 8.2. ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 15.48 (q, J = 8.5 Hz). MS, m/e (%), 134 [M-CF_3-P(O)$(OEt)_2$ − 1], 138 [P(O)$(OEt)_2$ + 1], 204 [M-P(O)$(OEt)_2$, 100], 341 (M^+), 342 (M^+ + 1). Anal. calcd for $C_{13}H_{19}F_3NO_4P$ (341.27): C, 45.75; H, 5.57; N, 4.10. Found: C, 46.02; H, 5.72; N, 3.95.

Diethyl 1-(N-α-Methylbenzylamino)-2,2,2-trifluoroethylphosphonate (**3c**). This compound was obtained analogously by the method used for **3b**. Colorless liquid, yield 1.2 g or 99%. IR (film) *v*: 3280 (NH), 2950 (CH), 1250 (P=O), 1160 (C–F), 1020 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.20 (t, 6H, J = 7.0 Hz, $2XOCH_2C\underline{H}_3$), 1.80 (d, 3H, J = 7.0 Hz, CH_3), 3.80–4.13 (m, 6H, $2XOCH_2$, CH, NH), 2.86–3.36 (m, 1H, $CHCF_3$), 7.08 (5H, Ph). ^{19}F NMR (CCl_4/TFA) δ 11.8 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 16.78 (q, J = 10.8 Hz). MS, m/e (%), 105 (CHMePh), 120 (NHCHMePh, 100), 186 [M-1-$CH_3P(O)(OEt)_2$], 201 [M^+-1-P(O)$(OEt)_2$], 340 (M^+ + 1). Anal calcd. for $C_{14}H_{21}F_3NO_3P$ (339.30): C, 49.56; H, 6.19; N, 4.13. Found: C, 49.95; H, 6.51; N, 4.11.

Dimethyl 1-(N-α-Methylbenzylamino)-2,2,2-trifluoroethylphosphonate (**3d**). Compound **3d** was

obtained analogously by the method used for **3b**. Colorless powder, mp 38–40°C, yield 1.1 g or 99%. IR (KBr) *v*: 3300 (NH), 2950 (CH), 1250 (P=O), 1160 (C–F), 1040 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.31 (d, 3H, J = 7.0 Hz, CH_3), 2.12–2.22 (m, 1H, CH), 3.46–4.07 (m, 8H, $2XOCH_3$, CF_3CH, NH), 7.14 (s, 5H, Ph). ^{19}F NMR (CCl_4/TFA) δ 11.1 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 19.28 (q, J = 10.9 Hz). MS, m/e (%), 105 (CHMePh, 100), 120 (NHCHMePh), 186 [M-1-CH_3-P(O)$(OMe)_2$], 201 [M^+-1-P(O)$(OMe)_2$], 312 (M + 1). Anal. calcd for $C_{12}H_{17}F_3NO_3P$ (311.25): C, 46.30; H, 5.47; N, 4.50. Found: C, 46.19; H, 5.49; N, 4.35.

Diethyl 1-(N-Diphenylmethylamino)-2,2,2-trifluoroethylphosphonate (**3e**). Compound **3e** was obtained analogously by the same method as for **3b**. Colorless liquid, yield 1.12 g or 99%. IR (film) *v*: 2590 (CH), 1250 (P=O), 1160 (C–F), 1020 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.23 (t, 6H, J = 7.0 Hz, $2XCH_3$), 2.16–2.49 (b, 1H, NH), 2.82–3.61 (m, 1H, CH), 4.00 (m, 4H, $2XOCH_2$), 5.18 (s, 1H, $CHPh_2$), 7.07–7.25 (m, 10H, 2XPh). ^{19}F NMR (CCl_4/TFA) δ 10.00 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 17.51 (q, J = 8.9 Hz). MS, m/e (%), 167 ($CHPh_2$), 182 ($NHCHPh_2$, 100), 262 [M^+-P(O)$(OEt)_2$], 400 (M^+ − 1). Anal. calcd for $C_{19}H_{23}F_3NO_3P$ (401.36): C, 56.85; H, 5.74; N, 3.49. Found: C, 56.41; H, 5.40; N, 3.44.

Diethyl 1-Amino-2,2,2-trifluoroethylphosphonate (**3**). In a 50 mL flask was added **3c** (900 mg, 2.65 mmol) or **3e** (1.06 g, 2.65 mmol), followed by a solution of HCOOH in MeOH (1:1) (10 mL). Under vigorous stirring, there was introduced carefully and gradually 1.1 g of freshly prepared palladium black. The air in the flask was evacuated by a water pump. The reaction mixture was stirred at RT overnight. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue was added EtOAc (20 mL), and this mixture was treated with an aqueous saturated solution of K_2CO_3 until the aqueous layer showed pH 8–9. The organic layer was then removed, and the water solution was extracted with EtOAc (2X 15 mL). The combined organic solution was dried (Na_2SO_4), filtered, and concentrated. The resultant oily liquid was identified as 1-formylamino -2,2,2-trifluoroethylphosphonate. IR (film) *v*: 3320 (NH), 1710 (C=O), 1260 (P=O), 1140 (C–F), 1040 (P–O–C) cm^{-1}. ^1H NMR (CCl_4/TMS) δ 1.40 (t, 6H, J = 7.0 Hz, 2X CH_3), 4.28 (m, 4H, $2XOCH_2$), 4.93–5.56 (m, 1H, CH), 8.31 (s, 1H, CHO), 8.64–8.80 (b, 1H, NH). ^{19}F NMR (CCl_4/TFA) δ 8.00 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 13.18 (q, J = 5.16 Hz). MS, m/e (%), 127 [M + 1 − P(O)$(OEt)_2$], 236 [M^+ + 2 − CHO], 264 (M^+ + 1, 100). The oily product thus obtained was dissolved in 15 mL of 5% HCl–MeOH solution and heated to reflux for 20 minutes. Removal of the solvent resulted in a residue that was then dissolved in 20 mL of EtOAc and treated with saturated K_2CO_3 solution to pH 8–9. The organic layer was separated, and the aqueous solution was extracted by EtOAc (2X 15 mL). The organic solution was combined, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography on a silica gel pretreated with triethylamine. Diethyl 1-amino-2,2,2-trifluoroethylphosphonate was obtained as a slightly yellow liquid, 461 mg or 74%. IR (film) *v*: 3300–3400 (NH), 2950 (CH), 1250 (P=O), 1150 (C–F) cm^{-1}. ^1H NMR (CCl_4/TFA) δ 1.24 (t, 6H, J = 7.0 Hz, $2XCH_3$), 1.80–2.12 (b, 2H, NH_2), 3.29–3.61 (m, 1H, CH), 4.03 (m, 4H, $2XCH_2$). ^{19}F NMR (CCl_4/TFA) δ 7.66 (s). ^{31}P NMR ($CDCl_3$/H_3PO_4) δ 17.04 (d, J = 12.6 Hz). Anal. calcd for $C_6H_{13}F_3NO_3P$ (235.15): C, 30.64; H, 5.53; N, 5.96. Found: C, 30.68; H, 5.49; N, 5.08.

Diethyl 1-amino-2,2,2-trifluoroethylphosphonate (*3) was obtained also from* **3b** by reaction with CAN. In a 50 mL pear-shaped flask was charged **3b** (0.8 g, 2.35 mmol) and acetonitrile (22 mL). Upon being cooled to 0°C, a solution of CAN (3.86 g, 7.05 mmol) in 23.5 mL water was added dropwise during 7 minutes. After having been stirred for 20 minutes, the reaction mixture was diluted with water (37 mL) and extracted with EtOAc (2X 37 mL). The organic solution was washed successively with 5% $NaHCO_3$ (15 mL), 10% $NaHSO_3$ (12 mL), and brine (12 mL). After having been dried (Na_2SO_4), the solvent was removed. A pale yellow, oily residue was obtained, 0.3 g of 55% yield. In addition to a positive ninhydrin test, the product was shown to be contaminated with hydroquinone derivatives. The spectroscopic data are basically identical with those obtained by hydrogenolysis of **3c** or **3e**.

Diethyl 1-(N-Cbzglycylamino)-2,2,2-trifluoroethylphosphonate (**4a′**). In a 50 mL pear-shaped flask was charged diethyl 1-amino-2,2,2-trifluoroethylphosphonate (0.3 g), Cbzglycine (0.23 g, 1.28 mmol), dichloromethane (10 mL), and HOBt (0.17 g, 1.26 mmol). After the mixture had been stirred for 10 minutes in ice bath, a CH_2Cl_2 (5 mL) solution of DCC (0.26 g, 1.26 mmol) was introduced dropwise. The reaction mixture was then stirred for 11 hours at 0°C and an additional 10 hours at RT. Formation of crystalline dicyclohexylurea was observed. Upon the removal of the urea derivative, the filtrate was concentrated, and then EtOAc (20 mL) was added. The mixture was filtered again, and the EtOAc solution was washed successively with 10% citric acid, 5% $NaHCO_3$, and then water. The solution was dried

(Na_2SO_4) and evaporated. The residual solution was chromatographed on a silica gel column using CH_2Cl_2/EtOH (10:0.2) as eluent. A slightly yellowish, oily liquid resulted; yield 0.15 g or 28%. IR (film) *v*: 1722, 1710 (C=O), 1537 (CONH II), 1260 (P=O) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.25–1.40 (m, 6H, $2XCH_3$), 3.90–4.20 (m, 6H, $2XOCH_2$, CH_2), 5.05 (s, 2H, $PhCH_2O$), 7.25 (s, 5H, Ph), 5.58 (b, 1H, $CONHCH_2$), 8.20 (b, 1H, $CONHCHCF_3$), 3.65 (m, 1H, CF_3CH). ^{19}F NMR (CCl_4/TFA) δ 8.80 (s). ^{31}P NMR ($CDCl_3/H_3PO_4$) δ 13.32 (d, J = 6.5 Hz). MS (%), 91 ($PhCH_2$, 100), 426 (M^+), 319 (M^+-$PhCH_2O$), 291 (M^+-$PhCH_2OCO$). Anal. calcd for $C_{16}H_{22}O_6F_3N_2P$ (426.33): C, 45.07; H, 5.16; N, 6.57. Found: C, 45.62; H, 5.61; N, 6.18.

Diethyl 1-(N-Cbzphenylalanylamino)-2,2,2-trifluoroethylphosphonate (**4b′**). Diethyl 1-amino-2,2,2-trifluoroethylphosphonate (0.2 g, 0.85 mmol) was mixed with Cbzphenylalanine (0.24 g, 0.8 mmol) in CH_2Cl_2 (20 mL), and then DCC (0.16 g, 0.8 mmol) was added with stirring at 0°C for 1 hour. Formation of DCU as a white crystalline powder was observed. After having been stirred overnight at ambient temperature, the solvent was removed under reduced pressure. EtOAc (20 mL) was added, and an additional portion of DCU precipitate thus formed was filtered off. The filtrate was successively washed with 10% citric acid, 5% $NaHCO_3$, and water, then dried (Na_2SO_4) and evaporated. The residual solution was chromatographed on a silica gel column using CH_2Cl_2/EtOH (10:0.5) as eluent. A pale yellow, oily liquid was obtained, yield 0.18 g or 43%. IR (film) *v*: 1722, 1699 (C=O), 1535 (CONH II), 1265 (P=O) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.36 (dd, 6H, $2XCH_3$), 3.13 (m, 2H, CH_2), 4.20 (m, 5H, $2XOCH_2CH_3$, $PhCH_2CH$), 5.12 (s, 2H, $PhCH_2O$), 5.46 (m, 1H, CF_3CH), 6.16 (b, 1H, CONHCH), 7.29 (s, 10H, 2XPh), 8.56 (b, 1H, $CONHCHCF_3$). ^{19}F NMR ($CDCl_3$/TFA) δ 9.20. ^{31}P NMR ($CDCl_3/H_3PO_4$) δ 13.31 (q, J = 8.6 Hz). MS, m/e (%): 91 ($PhCH_2$, 100), 254 [M-$CONHCHCF_3P(O)(OEt)_2$], 517 (M^+ + 1). Anal. calcd for $C_{23}H_{28}F_3N_2O_6P$ (516.45): C, 53.49; H, 5.43; N, 5.43. Found: C, 53.15; H, 5.36; N, 5.08.

Diethyl 1-(N-Cbzvalinylamino)-2,2,2-trifluoroethylphosphonate (**4c′**). This compound was obtained from diethyl 1-amino-2,2,2-trifluoroethylphosphonate and cbz-valine by the same method as for **4b′**. **4c′** is a pale yellow, oily liquid, yield 28%. IR (film) *v*: 1700 (C=O), 1550 (CONH II), 1255 (P=O), 1025 (P–O–C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.35 (dd, 6H, $2XCH_3$), 3.15 (m, 2H, CH_2), 5.52 (m, 1H, CF_3CH), 6.14 (b, 1H, CONHCH), 8.50 (b, 1H, $CONHCHCF_3$). ^{19}F NMR ($CDCl_3$/TFA) δ 8.88 (s). ^{31}P NMR ($CDCl_3/H_3PO_4$) δ 13.52. Anal. calcd for $C_{19}H_{28}F_3O_6N_2P$ (468.41); C, 48.68; H, 5.98; N, 5.98. Found: C, 48.99; H, 6.04; N, 5.44.

Diethyl 1-(N-Glycylamino)-2,2,2-trifluoroethylphosphonate (**5a′**). To **4a′** (0.12 g, 0.28 mmol) was added 0.6 mL of saturated dry HBr solution in glacial acetic acid, and the reaction tube was protected from atmospheric moisture with a $CaCl_2$ drying tube. The liberation of CO_2 was observed upon the completion of addition of the reagent. After the end of gas evolution (10–15 min), 8 mL of dry ether was introduced to precipitate the amine hydrobromide formed. Upon being chilled at −5°C in an ice-salt bath for several hours, the hydrobromide salt was collected by filtration and washed carefully with dry ether. The hydrobromide salt thus obtained was a colorless crystalline powder that turned to yellow on standing. For the conversion of the salt to the free amino compound, the salt was dissolved in absolute alcohol and treated with excess propylene oxide. After having been allowed to stand overnight, the resulting solution was concentrated to a minimum volume on a rotatory evaporator with bath temperature not to exceed 60°C. The residue was treated with a small amount of EtOH, and the colorless solid that resulted was collected by filtration; **5a′** was obtained, 74 mg, or 90% yield. IR (nujol) *v*: 3350 (NH_2), 1775, 1720 (C=O), 1600 (CONH II), 1250 (P=O), 1025 (P–O–C) cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 4.45 (s, 2H, CH_2), 5.10–5.80 (m, 1H, CHP), 6.74 (d, 4H, J = 9.2 Hz, $2XCH_2$), 7.17 (d, 1H, J = 2.0), 7.60 (b, 2H, NH_2), 8.00–8.20 (m, 1H, NH), 8.50 (b, 1H, $CONHCHCF_3$). HRMS 292.0124, calcd for $C_8H_{16}O_4N_2F_3P$, 292.0131.

ACKNOWLEDGMENT

The project was supported by the National Natural Science Foundation of China.

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