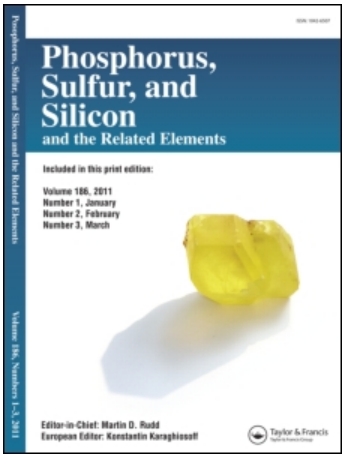

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 95. A NOVEL SYNTHESIS OF 2-TRIFLUOROMETHYL-2-(SUBSTITUTED AMINO)ETHYLPHOSPHONATES

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Reactions of alkyl phosphonates with trifluoroacetimidoyl chlorides using an appropriate base followed by subsequent reduction of the intermediates provides 2-trifluoromethyl-2-(substituted amino)-ethylphosphonates.

Key words: 2-trifluoromethylated 2-AEP derivatives, alkylphosphonates, trifluoroacetimidoyl chlorides, reduction.

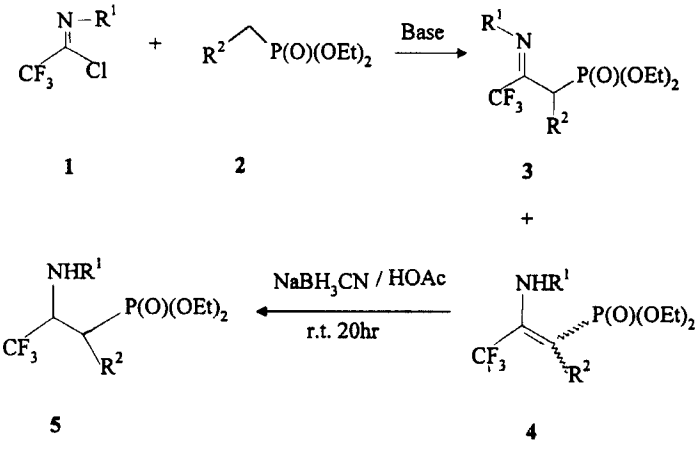
INTRODUCTION

Since the first isolation of 2-aminoethylphosphonic acid (2-AEP) from several organisms,[1] synthesis of 2-AEP derivatives is the subject of active investigation because those compounds exhibit interesting biological activities. In recent years trifluoromethylated organic molecules received increasing attention owing to some special properties of the trifluoromethyl moiety.[2] Introduction of a trifluoromethyl group into biologically active molecules often results in exciting and promising improvements. In this communication, we wish to report a novel synthetic approach to a new type of trifluoromethylated 2-AEP derivatives.

RESULTS AND DISCUSSION

We developed a new and convenient method for the synthesis of α, β-unsaturated trifluoromethyl ketones,[3] which involved the intermediates of trifluoromethylated imino phosphonates and their enamine isomers. It can be envisaged to obtain trifluoromethylated 2-AEP derivatives by subsequent reduction of those intermediates.

When R^2 is hydrogen or alkyl, BuLi was used as deprotonating agent. The carbanion thus formed displaced the chlorine of imidoyl chloride at $-70°C$, providing a mixture of imino phosphonate **3** and enamine **4** in the ratio of 5:2. The doublet of the methylene hydrogens (R^1 = Ph, R^2 = H) at δ = 2.83 ppm ($J_{P—H}$ = 24 Hz) and the signal at δ = 8.9 ppm (br, NH) in the ^1H NMR spectra revealed the formation of imine **3** and enamine **4**, respectively.



1 2 3 + 4 5

TABLE I

Preparation of compound 5

entry	R^1	R^2	base	Temp(°C)*	Yield(%)	m.p.(°C)
a	Ph	H	BuLi	-70/20	52	78
b	$PhCH_2CH_2$	H	BuLi	-70/20	48	oil
c	Ph	Me	BuLi	-70/20	60	81-82
d	$PhCH_2CH_2$	Me	BuLi	-70/20	56	oil
e	Ph	MeOC(O)	NaH	20/20	70	73-74
f	p-ClC_6H_4	MeOC(O)	NaH	20/20	64	58-60

* Reaction temperature for the first step addition-elimination process / the reduction temperature.

When R^2 was methoxycarbonyl, NaH could be used as base and the resultant carbanion displaced the chlorine of compound **1** at r.t. Workup in the usual manner after 30 min gave a mixture of imine **3** and enamine **4** in the ratio of 4:1. However, enamine **4** was exclusively obtained after 6 hrs due to the thermodynamic stability resulting from the conjugation between the carbonyl group with the C=C double bond.

The mixture of intermediates **3** and **4**, which was difficult to separate by column chromatography, was subjected to reduction without isolation. Sodium borohydride was found to be inert to these intermediates and the reduction proceeded very slowly in ethanol even with sodium cyanoborohydride as the reducing reagent. However, the reduction products were obtained in moderate to good yields when acetic acid was used as the reaction media; it enhanced the electrophilic activity of the substrate by its protonation to the imino and amino group.

EXPERIMENTAL

The melting points are uncorrected. IR spectra were taken on a Shimadzu-440 spectrophotometer. ^1H, ^{31}P NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ and chemical shifts are

reported in ppm downfield from TMS and 85% H_3PO_4 respectively. ^{19}F NMR spectra were obtained on a Varian EM 360A spectrometer using CF_3CO_2H as an external standard, positive for downfield shifts. EI-MS were recorded on a HP5989A mass spectrometer. Coupling constants are reported in Hz.

N-Substituted trifluoroacetimidoyl chlorides were synthesised by Uneyama's methods.[4] Alkyl phosphonates were prepared in the usual manner. BuLi, NaH and $NaBH_3CN$ were purchased as standard reagent from Aldrich, Merck and Fluka Co., respectively. Other reagents were commercially available from a local source (Shanghai Chemical Co.). THF was freshly distilled from sodium benzophenone ketyl prior to use.

Diethyl 2-(N-phenyl)amino-3,3,3-trifluoropropylphosphonate (**5a**): To an oven dried 100 ml 3-necked flask fitted with stirring bar, thermometer, rubber septum and charged with dry N_2, was added dry THF (20 ml) and diethyl methylphosphonate (0.76 g, 5 mmol). After cooling to −70°C (dry ice-acetone bath), BuLi (1.6 N in hexane, 3.2 ml, 5 mmol) was added dropwise to the solution. After stirring at −70°C for 15 min, a solution of N-phenyl trifluoroacetimidoyl chloride (1.04 g, 5 mmol) in THF (5 ml) was added dropwise. Stirring was continued at −70°C for 30 min and the mixture was then warmed to r.t. THF was removed under reduced pressure and acetic acid (10 ml) was added. Sodium cyanoborohydride (0.31 g, 5 mmol) was added to the resulting mixture in one portion at 0°C. After stirring at r.t. overnight, the mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc (20 ml) and water (20 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 20 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude product, which was subjected to column chromatography (EtOAc: petroleum ether, 1:1), providing pure **5a** as a white solid (0.85 g, 52%). m.p. 78°C. IR (film): ν 1250 (P═O), 1020 (P—O—C), 1190 (C—F) cm^{-1}. ^1H NMR, δ: 1.06, 1.14 (2t, J = 7.0, 7.1, 6H, 2Me), 2.00–2.19 (m, 2H, CH_2P), 3.18–4.19 (m, 6H, $2OCH_2$, CF_3CH, NH), 6.62–7.16 (m, 5H, Ph). ^{19}F NMR: δ 9.0 (s). ^{31}P NMR: δ 26.3 (s). MS: m/e 325 (M^+, 69%), 305 (M—HF, 30%), 256 (M—CF_3, 40%), 118 ($PhNCH{=}CH_2^+$, 100%). Anal calcd for $C_{13}H_{19}F_3NO_3P$: C, 48.00; H, 5.85; N, 4.31. Found: C, 48.12; H, 5.78; N, 4.26.

Diethyl 2-(N-phenethyl)amino-3,3,3-trifluoropropylphosphonate (**5b**): Analogous to the preparation of **5a** using N-phenethyl trifluoroacetimidoyl chloride instead of N-phenyl trifluoroacetimidoyl chloride. The product was obtained as a yellowish oily liquid in 48% yield. IR (film): ν 3350 (N—H), 1250 (P═O), 1030 (P—O—C), 1170 (C—F) cm^{-1}. ^1H NMR: δ 1.31 (t, J = 7, 6H, 2Me), 1.86–2.18 (m, 3H, NH, CH_2P), 2.80 (t, J = 7.2, 2H, $\underline{CH_2}Ph$), 2.95–3.13 (m, 2H, NCH_2), 3.44–3.51 (m, 1H, $CHCF_3$), 7.17–7.31 (m, 5H, Ph). ^{19}F NMR: δ 2.0 (s). ^{31}P NMR: δ 27.6 (s). MS: m/e 354 (M + 1, 10%), 262 (M—$PhCH_2$, 100%). Anal calcd for $C_{15}H_{23}F_3NO_3P$: C, 50.85; H, 6.50; N, 3.95. Found: C, 51.02; H, 6.46; N, 4.02.

Diethyl 1-methyl-2-(N-phenyl)amino-3,3,3-trifluoropropylphosphonate (**5c**): Analogous to the preparation of **5a** using diethyl ethylphosphonate instead of diethyl methylphosphonate. The product was obtained as a white solid in 60% yield, m.p. 81–82°C. IR(film): ν 3000 (C—H), 1250 (P═O), 1170 (C—F), 1025 (P—O—C) cm^{-1}. ^1H NMR: δ 1.17–1.40 (m, 9H, 3Me), 2.42–2.55 (m, 1H, CHP), 3.15 (br, 1H, NH), 3.93–4.58 (m, 5H, $2OCH_2$, $CHCF_3$), 6.69–7.33 (m, 5H, Ph). ^{19}F NMR: δ 5.31 (s), 5.34 (s). ^{31}P NMR: δ 29.0 (s), 29.7 (s). MS: m/e 339 (M^+, 32%), 319 (M—HF, 11%), 270 (M—CF_3, 18%), 201 (M—$HP(O)(OEt)_2$, 100%). Anal calcd for $C_{14}H_{21}F_3NO_3P$: C, 49.56; H, 6.19; N, 4.13. Found: C, 49.78; H, 6.02; N, 4.08.

Diethyl 1-methyl-2-(N-phenethyl)amino-3,3,3-trifluoropropylphosphonate (**5d**): The product **5d** was prepared from diethyl ethylphosphonate and N-phenethyl trifluoroacetimidoyl chloride analogous to the synthesis of **5a**. A yellow oily liquid was obtained in 56% yield. IR (film): ν 3350 (N—H), 3000 (C—H), 1250 (P═O), 1020 (P—O—C) cm^{-1}. ^1H NMR: δ 1.22–1.48 (m, 9H, 3Me), 2.26–2.40 (m, 2H, NH, CHP), 2.84–2.90 (m, 2H, $\underline{CH_2}Ph$), 3.01–3.25 (m, 2H, NCH_2), 3.30–3.50 (m) and 3.62–3.78 (m) (total 1H, CF_3CH), 4.10–4.39 (m, 4H, $2OCH_2$), 7.23–7.37 (m, 5H, Ph). ^{19}F NMR: δ 6.2 (s), 6.6 (s). ^{31}P NMR: δ 31.1 (s), 30.0 (s). MS: m/e 368 (M + 1, 78%), 276 (M—$PhCH_2$, 100%). Anal calcd for $C_{16}F_{25}F_3NO_3P$: C, 52.32; H, 6.81; N, 3.81. Found: C, 52.28; H, 6.72; N, 4.00.

Diethyl 1-methoxycarbonyl-2-(N-phenyl)amino-3,3,3-trifluoropropylphosphonate (**5e**): To an oven dried 3-necked flask fitted with stirring bar, thermometer, rubber septum and charged with dry N_2 was added NaH (80% in mineral oil, 150 mg, 5 mmol) and dry THF (20 ml). After cooling to −10°C, diethyl 1-methoxycarbonylmethylphosphonate (1.05 g, 5 mmol) was added dropwise and the reaction temperature was kept below 0°C. N-Phenyl trifluoroacetimidoyl chloride (1.04 g, 5 mmol) was then added dropwise at 0°C. Stirring was continued at r.t. for 1 hr and THF was removed from the mixture under reduced pressure. Acetic acid (10 ml) was added to the residue and sodium cyanoborohydride (0.46 g, 7.5 mmol)

was added in one portion at 0°C. After stirring at r.t. overnight, usual workup analogous to the procedure for compound **5a** gave a white solid in 70% yield, m.p. 73–74°C. IR (film): ν 1740 (C═O), 1250 (P═O), 1025 (P—O—C) cm^{-1}. ^1H NMR: δ 1.02, 1.25 (2t, J = 7.1, 7.0, 6H, $2OCH_2\underline{CH_3}$), 3.47 (dd, J_{P-H} = 21.7, J_{H-H} = 10.1, 1H, CHP), 3.78 (s, 3H, OMe), 3.83 (dq, J_{H-H} = 7.0, J_{P-H} = 9.9, 1H, $1/2OCH_2$), 3.96 (dq, J_{H-H} = 7.1, J_{P-H} = 10.3, 1H, $1/2OCH_2$), 4.14 (dq, J_{H-H} = 7.1, J_{P-H} = 8.9, 2H, OCH_2), 4.47 (d, J = 8.9, 1H, CF_3CH), 4.70 (br, 1H, NH), 6.75–6.82 (m, 3H, Ph), 7.18–7.23 (m, 2H, Ph). ^{19}F NMR: δ 1.90 (s), 2.95 (s). ^{31}P NMR: δ 17.2 (s), 17.8 (s). MS: m/e 383 (M^+, 90%), 314 (M—CF_3, 50%), 245 (M—HP(O) $(OEt)_2$, 100%). Anal calcd for $C_{15}H_{21}F_3NO_5P$: C, 47.00; H, 5.48; N, 3.66. Found: C, 47.12; H, 5.76; N, 3.48.

Diethyl 1-methoxycarbonyl-2-N-(p-chlorophenyl)amino-3,3,3-trifluoropropylphosphonate (**5f**): Analogous to the preparation of compound **5e** using N-(*p*-chlorophenyl)trifluoroacetimidoyl chloride instead of N-phenyl trifluoroacetimidoyl chloride. The product was obtained as a white solid in 64% yield, m.p. 58–60°C. IR (film): ν 3400 (N—H), 1730 (C═O), 1240 (P═O), 1160 (C—F), 1020 (P—O—C) cm^{-1}. ^1H NMR: δ 1.06, 1.29 (2t, J = 7.1, 7.1, 6H, $2OCH_2\underline{CH_3}$), 3.45 (dd, J_{P-H} = 21.6, J_{H-H} = 9.5, 1H, CHP), 3.78 (s, 3H, OMe), 3.80–3.99 (m, 2H, OCH_2), 4.15 (dq, J_{H-H} = 7.1, J_{P-H} = 7.9, 2H, OCH_2), 4.54–4.64 (m, 2H, CHNH), 6.69–6.72 (m, 2H, Ar), 7.13–7.17 (m, 2H, Ar). ^{31}P NMR: δ 16.97 (s), 17.59 (s). ^{19}F NMR: δ 1.90 (s), 2.90 (s). MS: m/e 417 (M^+, 88%), 279 (M—HP(O) $(OEt)_2$, 100%). Anal calcd for $C_{15}H_{20}ClF_3NO_5P$: C, 43.11; H, 4.79; N, 3.35. Found: C, 43.24; H, 4.67; N, 3.48.

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