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A new synthetic utility of iminophosphoranes. Synthesis of trifluoromethylated enamino and imino esters

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Abstract

A new synthetic utility of iminophosphoranes, including the reaction of iminophosphoranes with trifluoroacetic anhydride and organozinc compounds, to afford trifluoromethylated amino and imino esters is described.

Keywords: Iminophosphoranes; Synthesis; Trifluoromethylated enamino esters; Trifluoromethylated imino esters; NMR spectroscopy; IR spectroscopy

1. Introduction

The application of iminophosphoranes to the synthesis of heterocyclic compounds has been widely investigated, particularly for the synthesis of nitrogen-containing heterocyclic compounds [1–3]. Tetrazoles were obtained by reaction of iminophosphoranes with acyl halides and sodium azide [3]. However, under the same conditions, the trifluoromethyl analogue gave an imidoyl azide which upon treatment with silica gel afforded N-substituted 2,2,2-trifluoroacetamide [3].

To the best of our knowledge the application of fluorinated iminophosphoranes in organic synthesis has not been reported previously. Trifluoromethylated enamino esters are useful precursors for the synthesis of trifluoromethylated amino acids and trifluoromethylated nitrogen-containing heterocyclic compounds showing biological activity [4]. Few methods for their preparation have been reported, but the starting materials are not commercially available and must be prepared themselves [5,6]. Therefore an effective method for their preparation would be valuable.

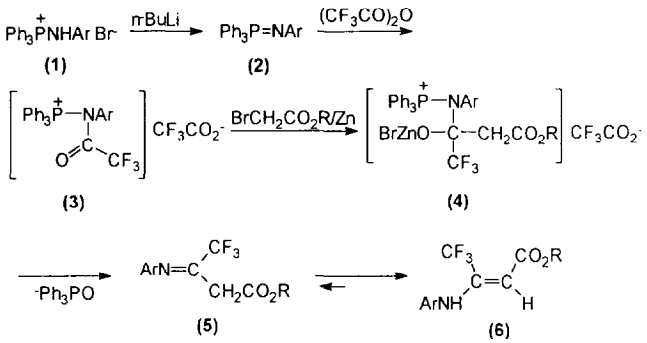
We now wish to report a new synthesis of iminophosphoranes including the reaction of iminophosphorane with trifluoroacetic anhydride and organozinc compounds to afford trifluoromethylated enamino and imino esters in 39%–75% yield (three steps). Enamino esters were obtained as the major tautomer (72%–89%) with exclusive *E*-configuration on the basis of their NMR spectra.

2. Results and discussion

The reaction sequence is shown in Scheme 1.

The iminophosphoranes **2**, generated from n-butyllithium and the corresponding amino phosphonium salts in tetrahydrofuran, were acylated by trifluoroacetic anhydride to give the fluorinated phosphonium salts **3**, which reacted with organozinc compounds with the elimination of triphenylphosphine oxide to give a tautomeric mixture of trifluoromethylated enamino and imino esters.

The study indicated that the enamino tautomer is the more stable and that the results listed in Table 1 reflect the thermodynamic equilibrium in the reaction conditions, whereas previous reports have suggested that the imino tautomer predominated [5,6]. Unfortunately this reaction could not be extended to the synthesis of *N*-alkyl derivatives. The electrophilicity of the carbonyl group in the *N*-alkyl derivatives may be lower than that in *N*-aryl ones due to the conjugative effect



Scheme 1.

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Table 1
Trifluoromethylated enamino and imino esters prepared

Compound 5+6	Ar	R	Yield [a] (%)	Ratio [b] 5/6
a	C_6H_5	CH_3	41	15:85
b	C_6H_5	C_2H_5	39	11:89
c	C_6H_5	i-C_3H_7	46	17:83
d	C_6H_5	t-C_4H_9	57	28:72
e	4-ClC_6H_4	CH_3	43	14:86
f	4-ClC_6H_4	C_2H_5	41	14:86
g	4-ClC_6H_4	i-C_3H_7	68	16:84
h	4-ClC_6H_4	t-C_4H_9	75	25:75

[a] Isolated yields.
[b] The ratios of **5** to **6** were estimated on the basis of NMR data.

of the aryl group, hence the organozinc reagents could not attack the carbonyl group in the *N*-alkyl derivatives and the reaction failed.

This one-pot synthesis of the title compounds starting from commercially available substances is very convenient and should be useful in the synthesis of fluorine-containing biologically active compounds.

3. Experimental details

Boiling (melting) points are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. ^{19}F NMR spectra were determined on a Varian EM-360 spectrometer (60M) with TFA as external standard; ^1H NMR spectra were carried out on a Bruker AM-300 (300M) instrument with TMS as reference: $CDCl_3$ was used as solvent *J*-Values are in Hz. Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer.

3.1. Preparation of the aminotriphenylphosphonium salt 1

Anilinotriphenylphosphonium bromide was prepared as described in the literature [7]. 4-Chloro-anilinotriphenylphosphonium bromide was prepared similarly in 79% yield; m.p. 152–153 °C. Analysis: Calc. for $C_{24}H_{20}BrClNP$ (468.76): C, 61.49; H, 4.30; N, 2.99%. Found: C, 60.98; H, 4.22; N, 2.94%. MS *m/z* (rel. int.): 390 (8); 389 ($M-{}^{79}Br$ 33); 388 (54); 387 (95); 386 (100); 262 (5). IR (KBr) (cm^{-1}): 3350; 1590; 1500; 1440; 1120. ^1H NMR ($CDCl_3$) δ: 10.50 (1H, d, $J=8.1$ Hz); 7.96–7.40 (15H, m); 7.03 (4H, s) ppm.

3.2. General procedure for the preparation of trifluoromethylated enamino and imino esters (5+6)a–h

n-Butyllithium (3 mmol) was added dropwise with stirring to a suspension of the aminotriphenylphosphonium salt **1** (3 mmol) in dry THF (20 cm^3) at −60 °C under nitrogen. The reaction mixture was stirred for 15 min at −50 °C until the solid had disappeared, cooled to −70 °C and trifluoroacetic anhydride (3 mmol) slowly added. After stirring at −70 °C for 10 min, bromoacetic ester (6 mmol) and zinc powder (8 mmol) were added. The mixture was allowed to warm to room temperature and stirred for 2 h at 50 °C. Filtration and evaporation of the filtrate gave a residue which was purified by column chromatography on silica gel by eluting with petroleum ether (b.p. 60–90 °C) to give the product as a mixture of tautomers.

Methyl 4,4,4-trifluoro-3-*N*-phenyliminobutanoate (**5a**) and methyl 4,4,4-trifluoroanilinobut-2-enoate (**6a**): Ratio **5a/6a** = 15:85; b.p. 85 °C/2 mmHg. Analysis: Calc. for $C_{11}H_{10}F_3NO_2$ (245.20): C, 53.88; H, 4.11; N, 5.71%. Found: C, 53.84; H, 3.90; N, 5.54%. MS *m/z* (rel. int.): 246 (7); 245 (M^+, 50); 214 (13); 213 (48); 186 (18); 172 (2); 144 (100). IR (film) (cm^{-1}): 3200; 1740; 1680; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5a**: 7.41–6.85 (5H, m); 3.71 (3H, s); 3.45 (2H, s) ppm. **6a**: 9.80 (1H, br); 7.41–6.85 (5H, m); 5.35 (1H, s); 3.76 (3H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: **5a**: −5.7 (3F, s) ppm. **6a**: −14.6 (3F, s) ppm.

Ethyl 4,4,4-trifluoro-3-*N*-phenyliminobutanoate (**5b**) and ethyl 4,4,4-trifluoro-3-anilinobut-2-enoate (**6b**): Ratio **5b/6b** = 11:89; b.p. 89 °C/2 mmHg. Analysis: Calc. for $C_{12}H_{12}F_3NO_2$ (245.20); C, 55.60; H, 4.67; N, 5.40%. Found: C, 53.53; H, 4.73; N, 5.19%. MS *m/z* (rel. int.): 260 (46); 259 (M^+, 100); 214 (38); 213 (34); 190 (70); 186 (11); 172 (18). IR (film) cm^{-1}): 3200; 1735; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5b**: 7.37–6.84 (5H, m); 4.18 (2H, q, $J=7.1$ Hz); 3.43 (2H, s); 1.26 (3H, t, $J=7.1$ Hz) ppm. **6b**: δ9.82 (1H, br); 7.37–6.84 (5H, m); 5.34 (1H, s); 4.22 (2H, q, $J=7.2$ Hz); and 1.31 (3H, t, $J=7.2$ Hz); 7.41–6.85 (5H, m); 5.35 (1H, s); 3.76 (3H, s); pp (3H, t, $J=7.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: **5b**: −5.7 (3F, s) ppm. **6b**: −14.6 (3F, s) ppm.

i-Propyl 4,4,4-trifluoro-3-*N*-phenyliminobutanoate (**5c**) and i-propyl 4,4,4-trifluoro-3-anilinobut-2-enoate (**6c**): Ratio **5c/6c** = 17:83; b.p. 90 °C/2 mmHg. Analysis: Calc. for $C_{13}H_{14}F_3NO_2$ (273.25): C, 57.14; H, 5.16; N, 5.13%. Found: C, 57.13; H, 5.23; N, 5.26%. MS *m/z* (rel. int.): 273 (M^+, 9); 231 (5); 189 (100); 144 (10); 120 (44); 92 (24). IR (film) (cm^{-1}): 3200; 1740; 1605; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5c**: 7.42–6.85 (5H, m); 5.14–5.00 (1H, m); 4.40 (2H, s); 1.24 (6H, d, $J=6.5$ Hz) ppm. **6c**: 9.83 (1H, br); 7.42–6.85 (5H, m); 5.32 (1H, s); 5.14–5.00 (1H, m); 1.29 (6H, d, $J=6.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: **5c**: −5.8 (3F, s) ppm. **6c**: −14.7 (3F, s) ppm.

t-Butyl 4,4,4-trifluoro-3-*N*-phenyliminobutanoate (**5d**) and t-butyl 4,4,4-trifluoro-3-anilinobut-2-enoate (**6d**): Ratio **5d/6d** = 28:72; b.p. 97 °C/2 mmHg. Analysis: Calc. for $C_{14}H_{16}F_3NO_2$ (287.28): C, 58.53; H, 5.61; N, 4.88%. Found: C, 58.36; H, 5.57; N, 4.45%. MS *m/z* (rel. int.): 288 (3); 287 (M^+, 9); 256 (27); 231 (57); 214 (22); 186 (18); 57 (100). IR (film) (cm^{-1}): 3200; 1735; 1665; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5d**: 7.40–6.85 (5H, m); 3.36 (2H, s); 1.45 (9H, s) ppm. **6d**: 9.81 (1H, br); 7.40–6.85 (5H, m); 5.28 (1H, s); 1.51 (9H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: **5d**: −5.7 (3F, s) ppm. **6d**: −14.6 (3F, s) ppm.

Methyl 4,4,4-trifluoro-3-*N*-(4-chloro-phenyl) iminobutanoate (**5e**) and methyl 4,4,4-trifluoro-3(4-chloro-anilino)but-2-enoate (**6e**): Ratio **5e/6e** = 14:86; b.p. 95 °C/2 mmHg. Analysis: Calc. for $C_{11}H_9ClF_3NO_2$ (279.65); C, 47.25; H, 3.24; N, 5.01%. Found: C, 47.44; H, 3.36; N, 4.96%. MS *m/z* (rel. int.): 281 (24); 280 ($M^+ + 1$, 11); 276 (76); 248 (16); 178 (100). IR (film) (cm^{-1}): 3300, 1740; 1705; 1490; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5e**: 7.52–6.82 (4H, m); 3.73 (3H, s); 3.44 (2H, s) ppm. **6e**: 9.73 (1H, br); 7.52–6.82 (4H, m); 5.38 (1H, s); 3.76 (3H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: **5e**: −5.1 (3F, s) ppm. **6e**: −14.7 (3F, s) ppm.

Ethyl 4,4,4-trifluoro-3-*N*-(4-chloro-phenyl) iminobutanoate (**5f**) and ethyl 4,4,4-trifluoro-3(4-chloro-anilino)but-2-enoate (**6f**): Ratio **5f/6f** = 14:86; b.p. 101 °C/2 mmHg. Analysis: Calc. for $C_{12}H_{11}ClF_3NO_2$ (293.67); C, 49.08; H, 3.78; N, 4.77%. Found: C, 48.93; H, 3.75; N, 4.86%. MS *m/z* (rel. int.): 295 (34); 293 (M^+, 100); 248 (19); 178 (47). IR (film) (cm^{-1}): 3200, 1740; 1680; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5f**: 7.37–6.85 (4H, m); 4.18 (2H, q, J = 7.1 Hz); 3.42 (2H, s); 1.26 (3H, t, J = 7.1 Hz) ppm. **6f**: 9.76 (1H, br); 7.37–6.85 (4H, m); 5.37 (1H, s); 4.22 (2H, q, J = 7.2 Hz); 1.37 (3H, t, J = 7.2 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: **5f**: −5.1 (3F, s) ppm. **6f**: −14.5 (3F, s) ppm.

i-Propyl 4,4,4-trifluoro-3-*N*-(4-chloro-phenyl) iminobutanoate (**5g**) and i-propyl 4,4,4-trifluoro-3(4-chloro-anilino)but-2-enoate (**6g**): Ratio **5g/6g** = 16:84; b.p. 103 °C/2 mmHg. Analysis: Calc. for $C_{13}H_{13}ClF_3NO_2$ (307.70): C, 50.75; H, 4.26; N, 4.55%. Found: C, 50.83; H, 4.27; N, 4.55%. MS *m/z* (rel. int.): 309 (4); 307 (M^+, 11); 248 (10); 238 (14); 196 (25); 43 (100). IR (film) (cm^{-1}): 3200; 1740; 1670; 1640; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5g**: 7.36–6.83 (4H, m); 5.23–4.93 (1H, m); 3.39 (2H, s); 1.24 (6H, d, J = 6.4 Hz) ppm. **6g**: 9.78 (1H, br); 7.36–6.83 (4H, m); 5.34 (1H, s); 5.23–4.93 (1H, m); 1.29 (6H, d, J = 6.4 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: **5g**: −5.3 (3F, s) ppm. **6g**: −14.5 (3F, s) ppm.

t-Butyl 4,4,4-trifluoro-3-*N*-(4-chloro-phenyl) iminobutanoate (**5h**) and t-butyl 4,4,4-trifluoro-3(4-chloro-anilino)but-2-enoate (**6h**): Ratio **5h/6h** = 25:75; b.p. 113 °C/2 mmHg. Analysis: Calc. for $C_{14}H_{15}ClF_3NO_2$ (321.73): C, 52.27; H, 4.70; N, 4.35%. Found: C, 52.44; H, 4.74; N, 4.41%. MS *m/z* (rel. int.): 323 (17); 321 (M^+, 42); 248 (48); 206 (40); 196 (100). IR (film) (cm^{-1}): 3200, 1740; 1665; 1600; 1300–1100. ^1H NMR ($CDCl_3$) δ: **5h**: 7.37–6.82 (4H, m); 3.35 (2H, s); 1.45 (9H, s) ppm. **6h**: 9.75 (1H, br); 7.37–6.82 (4H, m); 5.30 (1H, s); 1.51 (9H, s) ppm. ^{19}F NMR ($CDCl_3$) δ: **5h**: −5.1 (3F, s) ppm. **6h**: −14.5 (3F, s) ppm.

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References

[1] E. Zibiral, in J.I.G. Cadogan (ed.), *Organophosphorus Reagents in Organic Synthesis*, Academic Press, London, 1979, p. 241.
[2] N.I. Gusar, *Russ. Chem. Rev., 60* (1991) 146.
[3] E. Zibiral and J. Stroh, *Justus Liebig's Ann. Chem., 725* (1969) 29.
[4] K. Uneyama, O. Morimoto and F. Yamashita, *Tetrahedron Lett., 30* (1989) 4821.
[5] J. Froissard, J. Greiner, R. Pastor and A. Cambon, *J. Fluorine Chem., 17* (1981) 249.
[6] M. Iznaden and C. Portella, *Tetrahedron Lett., 29* (1988) 3683.
[7] I.J. Borowitz, K.C. Kirby, Jr., P.E. Rusek and E.W.R. Casper, *J. Org. Chem., 36* (1971) 88.