Reactions of methyl trifluoropyruvate 2-pyridylimines with trimethyl phosphite

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Reactions of methyl trifluoropyruvate 2-pyridylimines with trimethyl phosphite afford methyl 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylates.

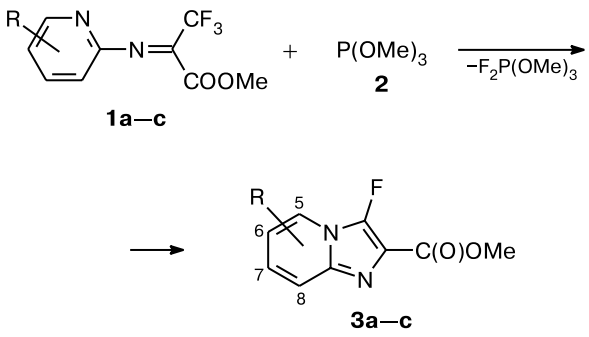
Key words: 2-pyridylimines, methyl trifluoropyruvate, 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylic acids, heterocyclization.

In this work, we studied the reactions of methyl trifluoropyruvate 2-pyridylimines **1** with trimethyl phosphite (**2**). This study was preceded by the known data on the reactions of hexafluoroacetone and methyl trifluoropyruvate *N*-acylimines with trimethyl phosphite. Hexafluoroacetone *N*-acylimines undergo an exothermic reaction with phosphite **2** to form [1+4] cycloadducts, which are transformed into cyclic oxazaphospholenes,[1,2] acyclic nitrile ylides,[3,4] or fluoro-containing carbamate,[5] depending on the reaction conditions and the nature of substituent at the N atom. Unlike hexafluoroacetone acylimines, the reaction of methyl trifluoropyruvate benzoylimine with trimethyl phosphite (**2**) produces trifluoromethyloxazole, whereas phosphite **2** is transformed into trimethyl phosphate.[6]

Thus, the formation of at least three products, *viz.*, diazaphospholenes, trifluoromethylimidazopyridines, and 2-aminodifluoroacrylates, should be expected from the reaction of compounds **1** and **2**. However, it turned out that 2-pyridylimines **1a—c** react anomalously with phosphite **2** to form only methyl 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylates **3a—c** (Scheme 1). Intramolecular ring closure occurs due to the defluorination of the trifluoromethyl group by the action of compound **2**. The latter, in turn, is fluorinated (according to the data of the ^{19}F and ^{31}P NMR spectra of the reaction mixture) to trimethoxydifluorophosphorane (δ_F 14.90, d, $J_{F,P}$ = 727 Hz; δ_P −71.00, t, $J_{P,F}$ = 727 Hz).

Methyl 3-fluoroimidazopyridine-2-carboxylates **3a—c** were obtained in 73—76% yields as crystalline solids, whose composition and structure were confirmed by elemental analysis, NMR spectroscopy, and chemical transformations. The signals of the F atom, *viz.*, doublets at δ −60 to −66 with the spin-spin coupling constant $J_{H,F}$ = 2.0 Hz caused by splitting on the H(8) atom, are characteristic in the ^{19}F NMR spectra; this is also confirmed by the ^{1}H NMR spectra using decoupling experiment and the ^{19}F NMR spectrum with selective decoupling on the H(8) proton (experiments were carried out for compound **3b**).

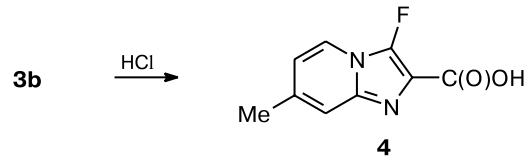
Scheme 1



1: R = H (**a**), 4-Me (**b**), 6-Me (**c**)
3: R = H (**a**), 7-Me (**b**), 5-Me (**c**)

Refluxing of ester **3b** in 30% HCl results in hydrolysis (Scheme 2), producing 3-fluoro-7-methylimidazopyridine-2-carboxylic acid **4** in 85% yield.

Scheme 2



Thus, we proposed a new approach to the formation of the imidazopyridine system, which is based on the reaction of available trifluoropyruvate 2-pyridylimines with trimethyl phosphite.

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Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer in $CDCl_3$ (**1a—c)** and DMSO-d_6 (**3a—c**, **4**) using residual signals from protons of the deuterated solvent as reference (^{1}H) and CF_3COOH as external standard (^{19}F). Melting points were determined in a glass capillary.

Methyl 3,3,3-trifluoro-2-(pyridine-2-imino)propionate (1a). Methyl trifluoropyruvate (7.8 g, 50 mmol), pyridine (7.8 g, 100 mmol), and $SOCl_2$ (6 g, 50 mmol) were successively added with stirring to a solution of 2-aminopyridine (4.7 g, 50 mmol) in benzene (50 mL). After the end of the exothermic reaction, the reaction mixture was stirred for 1 h, the precipitate that formed was filtered off, and the filtrate was concentrated and subjected to fractional distillation *in vacuo*. The yield was 9.1 g (78%), b.p. 89—90 °C (5 Torr). Found (%): C, 46.38; H, 3.21; N, 12.25. $C_9H_7FN_2O_2$. Calculated (%): C, 46.56; H, 3.04; N, 12.07. ^{1}H NMR, δ: 3.83 (s, 3 H, MeO); 7.25 (t, 1 H, H arom., J = 8.0 Hz); 7.37 (d, 1 H, H arom., J = 8.0 Hz); 7.82 (t, 1 H, H arom., J = 8.0 Hz); 8.45 (d, 1 H, H arom., J = 8.0 Hz). ^{19}F NMR, δ: 7.99 (s).

Methyl 3,3,3-trifluoro-2-(4-methylpyridine-2-imino)propionate (1b) was synthesized similarly to compound **1a**. The yield was 75%, b.p. 93—95 °C (5 Torr). Found (%): C, 48.61; H, 3.87; N, 11.25. $C_9H_7FN_2O_2$. Calculated (%): C, 48.79; H, 3.68; N, 11.38. ^{1}H NMR, δ: 2.40 (s, 3 H, Me); 3.85 (s, 3 H, MeO); 7.22 (dd, 1 H, H arom., J = 8.0 Hz, J = 5.0 Hz); 7.63 (d, 1 H, H arom., J = 8.0 Hz); 8.23 (d, 1 H, H arom., J = 5.0 Hz). ^{19}F NMR, δ: 8.00 (s).

Methyl 3,3,3-trifluoro-2-(6-methylpyridine-2-imino)propionate (1c) was synthesized similarly to compound **1a**. The yield was 80%, b.p. 96—97 °C (5 Torr). Found (%): C, 48.63; H, 3.85; N, 11.21. $C_9H_7FN_2O_2$. Calculated (%): C, 48.79; H, 3.68; N, 11.38. ^{1}H NMR, δ: 2.45 (s, 3 H, Me); 3.85 (s, 3 H, MeO); 7.12, 7.21, 7.70 (all d, 1 H each, H arom., J = 8.0 Hz). ^{19}F NMR, δ: 8.14 (s).

Methyl 3-fluoroimidazo[1,2-*a*]pyridine-2-carboxylate (3a). Trimethyl phosphite **2** (1.24 g, 10 mmol) was added with stirring to a solution of 2-pyridylimine **1a** (2.3 g, 10 mmol) in DMF (20 mL). After the end of the exothermic reaction, the reaction mixture was stirred for 1 h, H_2O (100 mL) was added, and the precipitate that formed was filtered off and recrystallized from 50% aqueous EtOH. The yield was 1.5 g (77%), m.p. 151—153 °C. Found (%): C, 55.48; H, 3.47; N, 14.25. $C_9H_7FN_2O_2$. Calculated (%): C, 55.67; H, 3.63; N, 14.43. ^{1}H NMR, δ: 3.85 (s, 3 H, MeO); 6.96 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 7.0 Hz, $J_{H(6),H(7)}$ = 8.0 Hz); 7.21 (t, 1 H, H(7), J = 8.0 Hz); 7.25 (dd, 1 H, H(8), $J_{H(8),H(7)}$ = 8.0 Hz, $J_{H,F}$ = 2.0 Hz); 8.16 (d, 1 H, H(5), $J_{H(5),H(6)}$ = 7.0 Hz). ^{19}F NMR, δ: −65.48 (d, $J_{F,H(8)}$ = 2.0 Hz).

Methyl 3-fluoro-7-methylimidazo[1,2-*a*]pyridine-2-carboxylate (3b) was synthesized similarly to compound **3a**. The yield was 77%, m.p. 139—141 °C. Found (%): C, 57.51; H, 4.47; N, 13.28. $C_{10}H_9FN_2O_2$. Calculated (%): C, 57.69; H, 4.36; N, 13.46. ^{1}H NMR, δ: 2.35 (d, 3 H, Me, $J_{H(Me),H(6)}$ = 1.0 Hz); 3.86 (s, 3 H, MeO); 6.84 (dd, 1 H, H(6), $J_{H(6),H(5)}$ = 7.0 Hz, $J_{H(6),H(8)}$ = 1.6 Hz); 7.24 (m, 1 H, H(8)); 8.05 (dd, 1 H, H(5), $J_{H(5),H(6)}$ = 7.0 Hz, $J_{H(5),H(8)}$ = 0.6 Hz). ^{19}F NMR, δ: −66.01 (d, $J_{F,H(8)}$ = 1.8 Hz).

Methyl 3-fluoro-5-methylimidazo[1,2-*a*]pyridine-2-carboxylate (3c) was synthesized similarly to compound **3a**. The yield was 75%, m.p. 128—129 °C. Found (%): C, 57.54; H, 4.55; N, 13.31. $C_{10}H_9FN_2O_2$. Calculated (%): C, 57.69; H, 4.36; N, 13.46. ^{1}H NMR, δ: 2.75 (d, 3 H, Me, $J_{H,F}$ = 6.5 Hz); 3.88 (s, 3 H, MeO); 6.61 (d, 1 H, H(6), $J_{H(6),H(7)}$ = 8.0 Hz); 7.11 (t, 1 H, H(7), J = 8.0 Hz); 7.28 (dd, 1 H, H(8), $J_{H(8),H(7)}$ = 8.0 Hz, $J_{H,F}$ = 2.0 Hz). ^{19}F NMR, δ: −61.98 (dq, $J_{F,H(8)}$ = 2.2 Hz, $J_{F,H(Me)}$ = 6.3 Hz).

3-Fluoro-7-methylimidazo[1,2-*a*]pyridine-2-carboxylic acid (4). A solution of compound **3b** (1.04 g, 5 mmol) in concentrated HCl (10 mL) was refluxed for 3 h, cooled, and neutralized with 25% NH_3. The precipitate that formed was filtered off. The yield was 0.7 g (72%), m.p. 243—245 °C (with decomp.). Found (%): C, 55.48; H, 3.47; N, 14.25. $C_9H_7FN_2O_2$. Calculated (%): C, 55.67; H, 3.63; N, 14.43. ^{1}H NMR, δ: 2.59 (s, 3 H, Me); 7.27 (d, 1 H, H(6), J = 8.0 Hz); 7.65 (s, 1 H, H(8)); 8.25 (br.s, 1 H, OH); 8.62 (d, 1 H, H(5), J = 8.0 Hz). ^{19}F NMR, δ: −64.04 (s).

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