Chelate synthesis of 3-ethoxycarbonyl-4-hydroxy-2-trifluoromethylpyridine from ethyl acetoacetate and trifluoroacetonitrile

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Ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate was synthesized by treatment of ethyl acetoacetate with CF_3CN in the presence of $Ni(acac)_2$. Condensation of the diphenylboron chelate of the former with dimethylformamide dimethylacetal followed by refluxing in ethanol yielded 3-ethoxycarbonyl-4-hydroxy-2-trifluoromethylpyridine.

Key words: ethyl acetoacetate, trifluoroacetonitrile, $Ni(acac)_2$, catalysis, ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate, boron chelates, dimethylformamide dimethylacetal, 3-ethoxycarbonyl-4-hydroxy-2-trifluoromethylpyridine.

Heterocycles containing a CF_3 group attract attention as potential biologically active compounds.[1,2] It has previously been found[3] that the reaction of trifluoroacetonitrile with acetylacetone in the presence of catalytic amounts of nickel acetylacetonate, ($Ni(acac)_2$), results in 3-acetyl-4-amino-5,5,5-trifluoro-3-penten-2-one, which is a convenient building block for synthesizing trifluoromethyl derivatives of pyridines and pyrimidines.[3,4]

In a continuation of the studies on the synthesis of *N*-heterocycles, we elaborated a facile method for obtaining the hitherto unknown 3-ethoxy-4-hydroxy-2-trifluoromethylcarbonylpyridine from trifluoroacetonitrile and ethyl acetoacetate. It was found that ethyl acetoacetate readily adds to CF_3CN in the presence of 1 mol.% of $Ni(acac)_2$ to give ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate (**1**) (Scheme 1). The reaction occurs more slowly than in the case of acetylacetone and requires 4—6 h to come to completion. The process occurs in neutral media and hence is not accompanied by deacetylation of enaminone **1**, which occurs in aqueous-alcoholic media in the presence of basic catalysts.[5] In attempts to avoid the deacetylation by performing the reaction in anhydrous media in the presence of Na metal, the formation of compound **1** is accompanied by strong resinification.

Enaminone **1** purified by sublimation *in vacuo* is a white crystalline compound soluble in ether, benzene, and chloroform, weakly soluble in pentane, and insoluble in water. The ^1H NMR spectrum of compound **1** contains one set of signals, and one proton of the NH_2 group participates in the formation of an intramolecular hydrogen bond (IHB) (δ = 10.5, while for free NH, δ = 6.0). A narrow band at 3480 cm^{-1} in the IR spectrum of compound **1** (NH stretching vibration region) corresponds to the free NH group, while a broad band at 3100—3250 cm^{-1} corresponds to that involved in an IHB. It can be believed that enaminone **1** exists in solutions as a *E*-form, since the acetyl group is more likely to participate in IHB than the ethoxycarbonyl group.

Compound **1** reacts with $BuOBPh_2$ to give boron chelate **2**, a light-yellow crystalline compound soluble in ether, benzene, and acetone and poorly soluble in hexane. In the ^1H NMR spectrum of chelate **2**, the signal of MeCO is shifted downfield (δ 2.62) relative to the free ligand (δ 2.31), while in the ^{13}C NMR spectrum, the signal of MeCO chelate **2** is observed at a higher field (δ ~191) than in the case of enaminone **1** (δ ~197) (*cf.* the data on the changes in the chemical shifts of the C atom of the carbonyl group in α-oxoketene aminals due to chelate formation[6,7]). These data suggest that coordination with B involves the NH_2 and acetyl groups, like in the case of 4-amino-5,5,5-trifluoro-3-penten-2-one described by us.[8]

In the previous communications, we presented an original strategy for synthesizing functionalized 4-hydroxypyridines (pyridones) *via* diphenyl- or difluoroboron chelates of diacetylketene *N,N*- and *N,S*-acetals,[9,10] as well as 4-amino-5,5,5-trichloro-3-penten-2-one and its acetyl derivative.[11] The key step in these syntheses involves condensation of amide acetals at the Me group directly linked with the boron-chelate ring. It was found that complex **2** can be used in similar transformations. In fact, chelating protects standard nucleophilic centers and activates nontraditional ones in functionalized enaminones. For example, dimethylformamide dimethylacetal (DMF DMA) reacts with enaminone **1** at the NH_2 group to give formamidine **3**, which was isolated as a mixture of *E*- and *Z*-isomers (the ^1H NMR spectrum displays a double set of signals with a ≈2 : 1 ratio), whereas the reaction of DMF DMA

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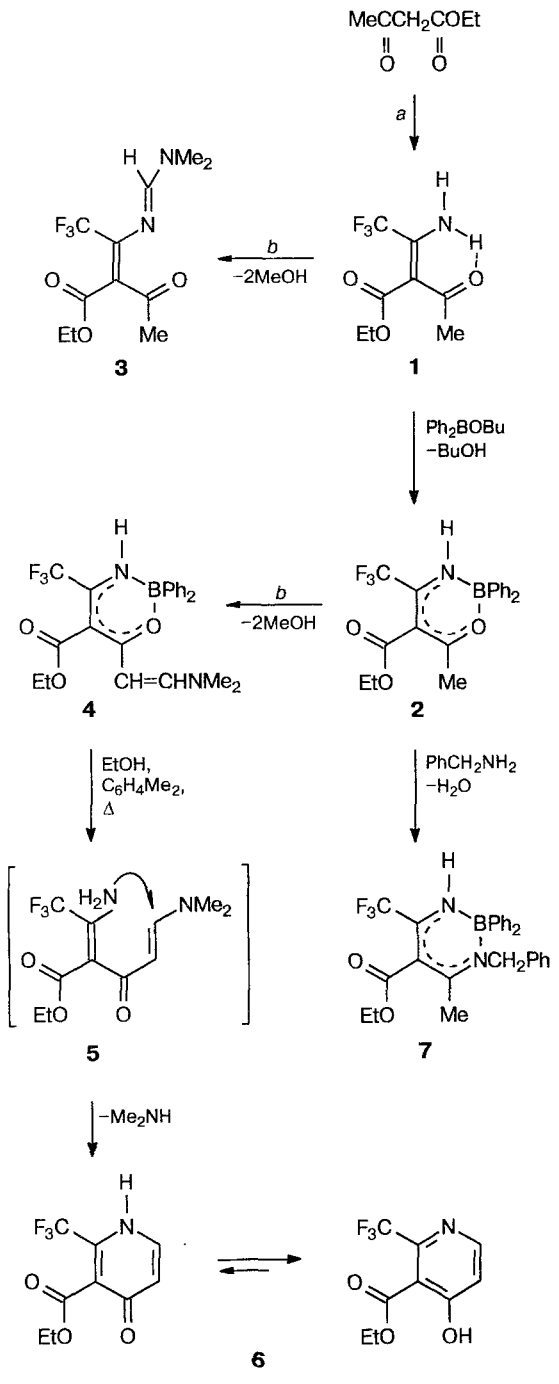
Scheme 1



Reagents and conditions. *a*. $CF_3C{\equiv}N$, $Ni(acac)_2$, CH_2Cl_2, ~20 °C. *b*. $(MeO)_2CHNMe_2$.

with chelate **2** gives a product of condensation at the Me group, complex **4**. Decomposition of the latter by refluxing in ethanol is accompanied by cyclization of the free ligand **5** liberated into hydroxypyridine **6**. The structure of pyridine **6** was confirmed by spectral methods. Judging by ^{13}C chemical shifts (in DMSO-d_6), compound **6** (C(4), δ 162.70 and C(6), δ 151.23) is similar to 4-methoxypyridine (δ 164.9 and 150.7) and strongly differs from 1-methyl-4-pyridone (δ 176.7 and 141.4).[12] In addition, the chemical shifts of C(4) and C(6) for compound **6** differ only slightly from those for 3-acetyl-4-hydroxy-2-trichloromethylpyridine, which possesses a similar structure (δ 162.41 and 148.52), in which the equilibrium pyridone ⇄ hydroxypyridine is strongly shifted to the right.[11] It can therefore be believed that the hydroxypyridine structure, which is stabilized by an intramolecular hydrogen bond O—H...O, is also more typical of compound **6**.

Chelate **2** is characterized by a transformation on treatment with primary amines to give β-diiminate complexes. For example, heating compound **2** with benzylamine gives chelate **7** (*cf.* similar reactions of boron chelates obtained from 4-amino-5,5,5-trifluoro-3-penten-2-one[8] and its 3-acetyl derivative[13]).

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz), and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument (75.47 MHz) relative to $SiMe_4$. IR spectra were recorded on a UR-20 spectrophotometer. Mass spectra were obtained on a Varian MAT-60 mass spectrometer.

Ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate (1). Ethyl acetoacetate (15.0 g, 0.12 mol), $Ni(acac)_2$ (0.35 g), and CH_2Cl_2 (20 mL) were placed in a three-necked flask equipped with a condenser cooled by a mixture of acetone with solid CO_2, a magnetic stirrer, and an inlet for CF_3CN. The CF_3CN (16.38 g, 0.17 mol) was slowly passed over a period of 4—6 h, and the reaction mixture was kept for 12 h. The solvent was evaporated *in vacuo*, and pentane was added to the solid residue. The precipitate was filtered off, washed with pentane, and dried by sublimation *in vacuo* (100 °C at 1—2 Torr) to give 18.98 g (73 %) of compound **1**, m.p. 64—65 °C (*cf.* the literature data:[5] m.p. 62—63 °C).

IR (CH_2Cl_2), ν/cm^{-1}: 3480 (NH), 3250—3100 (NH), 1720 (C=O), 1640, 1600 (the region of multiple bonds). ^1H NMR ($CDCl_3$), δ: 1.21 (t, 3 H, $\underline{CH_3}CH_2$); 2.18 (s, 3 H, $\underline{CH_3}CO$); 4.14 (q, 2 H, CH_2O); 6.0 (br.s, 1 H, NH); 10.5 (br.s, 1 H, NH).

Diphenylboron complex of ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate (2). Ph_2BOBu (9.1 g, 38 mmol) was added under argon to compound **1** (7.9 g, 35 mmol) in hexane (20 mL), and the reaction mixture was stirred for 3—4 h (the reaction was monitored by TLC). The mixture was concentrated *in vacuo*, and pentane (30 mL) was added to the residue. Filtration gave 8.25 g (68 %) of chelate **2**, m.p. 131—132 °C. MS, *m/z*: 312 $[M-Ph]^+$. IR (KBr), ν/cm^{-1}: 3250 (NH); 1700 (C=O). ^1H NMR, $CDCl_3$, δ: 1.29 (t, 3 H, $\underline{CH_3}CH_2$); 2.62 (s, 3 H, $\underline{CH_3}CO$); 4.21 (q, 2 H, CH_2O); 7.22—7.42 (m, 10 H, 2 Ph); 7.65 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 13.55 (qt, $^1J_{C,H}$ = 128 Hz, $^2J_{C,H}$ = 2.8 Hz, CH_3); 24.90 (q, $^1J_{C,H3}$ = 131 Hz, $\underline{C}H_3CO$); 61.36 (tq, $^1J_{C,H}$ = 147 Hz, $^2J_{C,H}$ = 4.6 Hz, OCH_2); 101.48 (d, $J_{C,H}$ = 7 Hz, C(2)); 118.79 (qd, $^1J_{C,F}$ = 281 Hz, $^3J_{C,H}$ = 7 Hz, CF_3); 127.13, 127.79, 131.75, 146.0 (2 Ph); 157.05 (qd, $^2J_{C,F}$ = 35 Hz, $^2J_{C,H}$ = 4 Hz, C(3)); 164.10 (s, O—C=O); 191.48 (q, $^2J_{C,H}$ = 6.5 Hz, $CH_3\underline{C}O$). Found (%): C, 61.65; H, 4.92;

F, 14.91; N, 3.31. $C_{20}H_{19}BF_3NO_3$. Calculated (%): C, 61.72; H, 4.92; F, 14.65; N, 3.60.

Ethyl 2-acetyl-3-(dimethylaminomethylene)amino-4,4,4-trifluoro-2-butenoate (3). DMF DMA (0.78 g, 6.6 mmol) was added to a solution of compound **2** (1.0 g, 4.4 mmol) in ether (10 mL), and the mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on a column with SiO_2 using benzene as the eluent to give 0.78 g (63 %) of compound **3**, m.p. 32—35 °C. MS, *m/z*: 280 $[M]^{+\cdot}$. ^1H NMR, $CDCl_3$, δ: 1.24 t and 1.29 t (3 H, CH_3; here and below, the first value refers to the minor isomer); 2.38 s and 2.25 s (3 H, CH_3CO); 3.07 (s, 6 H, $(CH_3)_2N$); 4.16 q and 4.24 q (2 H, CH_2O); 7.34 s and 7.36 s (1 H, CHN). Found (%): C, 47.27; H, 5.37; N, 10.28. $C_{11}H_{15}F_3N_2O_3$. Calculated (%): C, 47.14; H, 5.47; N, 10.77.

Diphenylboron complex of ethyl 2-(1-amino-2,2,2-trifluoroethylidene)-5-dimethylamino-3-oxo-4-pentenoate (4). A mixture of compound **2** (2.7 g, 7 mmol) and DMF DMA (2.47 g, 21 mmol) in ether (20 mL) was refluxed for 2—3 h. The crystals that precipitated after concenrating *in vacuo* were filtered off and washed with pentane to give 2.86 g (93 %) of complex **4**, m.p. 160—161 °C. MS, *m/z*: 367 $[M—Ph]^+$. IR (KBr), ν/cm^{-1}: 3320 (NH), 1680 (C=O). ^1H NMR, $CDCl_3$, δ: 1.25 (t, 3 H, $\underline{CH_3}CH_2O$); 3.02 (s, 3 H, CH_3N) and 3.24 (s, 3 H, CH_3N); 4.15 (q, 2 H, CH_2O); 6.35 (d, 1 H, CH=C, J = 12 Hz); 6.91 (br.s, 1 H, NH); 7.12—7.50 (m, 10 H, 2 Ph); 8.05 (d, 1 H, NCH=, J = 12 Hz). Found (%): C, 61.82; H, 5.71; F, 12.91. $C_{23}H_{24}BF_3N_2O_3$. Calculated (%): C, 62.18; H, 5.44; F, 12.83.

3-Ethoxycarbonyl-4-hydroxy-2-trifluoromethylpyridine (6). A mixture of compound **4** (0.9 g, 2 mmol), ethanol (1 mL), and xylene (~20 mL) was heated for 14—15 h at 115—120 °C, the solvent was distilled off *in vacuo*, and the residue was chromatographed on a column with SiO_2 (using initially benzene and then chloroform as eluents) to give 0.4 g (85 %) of compound **6**, m.p. 115—116 °C (from benzene-hexane). MS, *m/z*: 235 $[M]^+$. IR (CH_2Cl_2), ν/cm^{-1}: 1680 (CO). ^1H NMR, $CDCl_3$, δ: 1.42 (t, 3 H, CH_3); 4.80 (q, 2 H, CH_2O); 7.10 (d, 1 H, H(5), J = 5.70 Hz); 8.5 (d, 1 H, H(6), J = 5.7 Hz); 11.29 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 13.77 (q, $^1J_{C,H}$ = 127 Hz, CH_3); 61.63 (t, $^1J_{C,H}$ = 149 Hz, OCH_2); 114.53 (dd, $^1J_{C,H}$ = 167 Hz, $^2J_{C,H}$ = 8 Hz, C(5)); 118.11 (s, C(3)); 121.33 (q, $^1J_{C,F}$ = 275 Hz, CF_3); 143.68 (q, $^2J_{C,F}$ = 33 Hz, C(2)); 151.23 (d, $^1J_{C,H}$ = 183 Hz, C(6)); 162.70 (d, $^3J_{C,H}$ = 7.3 Hz, C(4)); 164.23 (t, $^3J_{C,H}$ = 3.5 Hz, C=O). Found (%): C, 45.96; H, 3.67; F, 24.04; N, 5.78. $C_9H_8F_3NO_3$. Calculated (%): C, 45.96; H, 3.43; F, 24.24; N, 5.95.

Diphenylboron complex of ethyl 3-amino-2-(1-benzylimino-ethyl)-4,4,4-trifluoro-2-butenoate (7). A mixture of chelate **2** (0.50 g, 1.3 mmol) and benzylamine (0.41 g, 3.9 mmol) in benzene (10 mL) was refluxed for 2 h. The solvent was distilled off *in vacuo*, and the residue was chromatographed on a column with SiO_2 using chloroform as the eluent to give 0.39 g (64 %) of complex **7**, m.p. 114—115 °C. MS, *m/z*: 401 $[M—Ph]^+$. IR (KBr), ν/cm^{-1}: 3360 (NH); 1710 (C=O). ^1H NMR ($CDCl_3$), δ: 1.26 (t, 3 H, $\underline{CH_3}CH_2$); 2.40 (s, 3 H, CH_3); 4.16 (q, 2 H, CH_2O); 4.77 (s, 2 H, $Ph\underline{CH_2}$); 6.67 (br.s, 1 H, NH); 6.7—6.8 and 7.08—7.48 (m, 15 H, 3 Ph). Found (%): C, 67.99; H, 6.11; N, 6.10. $C_{27}H_{26}BF_3N_2O_2$. Calculated (%): C, 67.78; H, 5.44; N, 5.86.

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