Interaction of pentafluorobenzoylpyruvic acid and its esters with *N*-nucleophiles. Synthesis of 4-oxoquinoline-2-carboxylic acids

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Abstract

Nitrogen-substituted 4-oxoquinoline-2-carboxylic acids have been prepared by the reaction of pentafluorobenzoylpyruvic acid with isopropyl-, cyclohexyl-, phenyl- and ethanol-amine. Ammonia and triethylamine, however, were found to react with pentafluorobenzoylpyruvic acid to form only the 2-carboxy-5,6,7-8-tetrafluorochromone; such behaviour has been found in the reactions of ethyl pentafluorobenzoylpyruvate with ammonia and cyclohexylamine.

1. Introduction

It is well known that non-fluorinated aroylpyruvic acids react with amines at α-carbonyl and/or carboxyl groups and serve as key precursors to a variety of biologically active heterocycles [1–3]. In our view, pentafluorobenzoylpyruvic acid is as interesting as its non-fluorinated analogues. It offers an available source of a fluorinated arene unit and may be used for its introduction into organic compounds. Some derivatives of pentafluorobenzoylpyruvic acid may give intramolecular cyclization products through the nucleophilic displacement of their fluorine *ortho*-atom. Moreover, pentafluorobenzoylpyruvic acid offers a convenient system for the study of the reactivity of a polycarbonyl compound with various reagents.

Of particular interest to us was the establishment of new syntheses of fluoro-containing 4-oxoquinoline structures from pentafluorobenzoylpyruvic acid and its derivatives.

Herein we wish to report some reactions of pentafluorobenzoylpyruvic acid (**1**) and ethyl pentafluorobenzoylpyruvate (**2**) with *N*-nucleophiles (ammonia, isopropyl-, cyclohexyl-, phenyl-, triethyl-amine) and also with ethanolamine.

2. Experimental details

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured on a Specord 75 IR spectrometer. ^{1}H NMR spectra were recorded on a Tesla BS-567 A instrument (^{1}H: 100 MHz) using TMS as an internal standard. ^{19}F NMR spectra were recorded on a Tesla BS-587 A instrument (^{19}F: 75 MHz) using $CDCl_3$ as an internal standard. ^{13}C NMR spectrum was recorded on a Tesla BS-587 A instrument (^{13}C: 20 MHz) using TMS as an internal standard. All chemical shifts are reported in ppm and wavenumbers in cm^{-1}.

Literature methods were used to prepare compound **2** [4] and compound **7** [5].

2.1. 2,4-Oxo-4-pentafluorophenylbutanoic acid (1) (nc)

A mixture of **2** (40.0 g, 129.0 mmol) and concentrated HCl (10 ml) in 200 ml of acetic acid was heated at 35–40 °C for 6 d. The reaction mixture was poured into water (600 ml) and 150 ml of hexane added to the mixture. The resulting precipitates were collected by filtration, dried under reduced pressure at 30–40 °C to give 23.7 g (65%) of **1** (m.p. 79 °C subl.). ^{1}H NMR (CD_3OD) δ: 3.45 (keto, 2H, m, CH_2); 5.30 (1H, w s., OH); 6.66 (enol, 1H, t, J = 1.6 Hz, CH) ppm. ^{19}F NMR (CD_3OD) (ratio keto/enol = 24:76) δ: −162.11 to −161.37 (keto, 2F, *meta*-fluorines, m); −161.71 to −160.98 (enol, 2F, *meta*-fluorines, m); −150.96 (keto, 1F, *para*-fluorine, t-t, J = 20.0, 4.1 Hz); −150.03 (enol, 1F, *para*-fluorine, t-t, *J* = 20.0, 4.1 Hz); −141.11 to −140.56 (keto, 2F, *ortho*-fluorines, m); −140.70 to −140.16 (enol, 2F, *ortho*-fluorines, m) ppm. IR (cm^{-1}): 3540, 3420, 2000, (OH); 1680 (C=O, acid); 1710 (sh) (C=O, keto); 1640, 1625 (C=O, enol); 1585, 1520 (C=C); 1000 (CF). Analysis: Found: C, 42.59; H, 1.10;

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F, 33.47%. Calc. for $C_{10}H_3F_5O_4$: C, 42.57; H, 1.07; F, 33.67%.

2.2. 2-Amino-3-(2-hydroxy-3,4,5,6-tetrafluorobenzoyl) acrylic acid (5) (nc)

A mixture of **1** (0.8 g, 1.06 mmol) and 50 ml of 25% ammonium hydroxide was heated under reflux for 10 min and concentrated to one-half. To the reaction mixture was added a concentrated solution of HCl until the pH value was 1–2. The resulting precipitate was collected and recrystallized from acetonitrile to give 0.15 g of **5** (yield, 51%; m.p. 223–225 °C. ^{1}H NMR (CD_3COCD_3) δ: 6.63 (1H, d, CH, J_{H-F} = 1.1 Hz); 7.92 (1H, w s, NH); 9.58 (1H, w s, NH); 11.08 (2H, w s, 2OH) ppm. ^{19}F NMR (CD_3COCD_3) δ: −172.13 (1F, d–d–d); −164.31 (1F, d–d–d); −151.22 (1F, d–d–d); −137.49 (1F, d–d–d) ppm. IR (cm^{-1}): 3315, 3455 (NH); 2650, 2500 (OH, NH_3^+); 1575 (COO^-); 1710 (C=O, acid); 1640 (C=O); 1610 (C=C). Analysis: Found: C, 43.09; H, 2.02; F, 26.93; N, 5.09%. Calc. for $C_{10}H_5F_4NO_4$: C, 43.03; H, 1.81; F, 27.23; N, 5.02%.

2.3. 2-Carboxy-5,6,7,8-tetrafluorochromone (4b) [4]

Method A

A mixture of **5** (1.0 g, 1.06 mmol) and concentrated HCl (10 ml) in 30 ml of acetic acid was heated under reflux for 10 h and concentrated to afford a precipitate which was collected, washed with 20 ml of water and dried to give 0.6 g (64%) of **4b** (m.p. 210–212 °C). The ^{1}H NMR and IR spectra of this compound were identical to those previously reported [4].

Method B

Into a solution of **1** (0.4 g, 1.42 mmol) in 15 ml of dioxan was bubbled anhydrous ammonia at 20 °C for 0.5 h and the mixture refluxed for 1 h. After cooling to room temperature, the solution was neutralized with 50 ml of 15% HCl. The resulting precipitate was collected, washed with water and dried to give 0.25 g (68%) of **4b** (m.p. 210–212 °C). The ^{1}H NMR and IR spectra were identical to those previously reported [4].

Method C

A mixture of **1** (0.1 g, 0.355 mmol) and 1 ml of triethylamine (0.73 g, 7.2 mmol) in 4 ml of dioxan was stirred for a 15-min period at 20 °C. The reaction mixture was poured into 15 ml of dilute HCl. The resulting precipitate was collected, washed with water and dried to give 0.04 g (43%) of **4b**. The filtrate was extracted with 15 ml of ethyl acetate. The organic layer was concentrated under reduced pressure and the residue was crystallized with hexane to give 0.02 g of **4b**. The overall yield of **4b** (m.p. 210–212 °C) was 65% (0.06 g). The ^{1}H NMR and IR spectra were identical to those previously reported [4].

2.4. 2-Ethoxycarbonyl-5,6,7,8-tetrafluorochromone (4c) [4]

Method A

A mixture of **2** (1.0 g, 3.22 mmol) and 10 ml of 10% ammonium hydroxide was shaken at room temperature for 10 min. The resulting precipitate was collected, washed with water and dried to give 0.93 g (100%) of **4c** (m.p. 125 °C). The ^{1}H NMR and IR spectra were identical to those previously reported [4].

Method B

Into a solution of **2** (1.0 g, 3.22 mmol) in 15 ml of dioxan was bubbled anhydrous ammonia for 0.5 h at 20 °C and the mixture then heated under reflux for 1 h. The resulting precipitate was collected, washed with water and dried to give 0.93 g (100%) of **4c** (m.p. 125 °C). The ^{1}H NMR and IR spectra were identical to those previously reported [4].

2.5. Methyl(5,5,5-trifluoro-2-hydroxy-4-oxopent-2-enoato)ammonium (8) (nc)

Into a solution of **7** (2.0 g, 10.0 mmol) in 50 ml of benzene was bubbled anhydrous ammonia at 20 °C for 1 h. The resulting precipitate was collected and dried to give 2.0 g (93%) of **7** (m.p. 84–86 °C). ^{1}H NMR (CD_3OD) δ: 3.79 (3H, s, CH_3); 4.94 (4H, s, NH_4^+); 5.86 (1H, s, CH) ppm. IR (cm^{-1}): 1725 (C=O, ester); 1630 (C=O); 1510 (C=C); 3170, 3070, 1495 (NH). Analysis: Found: C, 33.11; H, 3.66; F, 26.69; N, 7.00%. Calc. for $C_6H_5F_3O_4 \cdot NH_3$: C, 33.50; H, 3.75; F, 26.49; N, 6.51%.

2.6. 2-Cyclohexylamino-3-pentafluorobenzoylacrylic acid (9) (nc)

A mixture of **1** (3.0 g, 10.6 mmol) and 1.05 g (10.6 mmol) of cyclohexylamine in 20 ml of dioxan was heated under reflux for 1 h. The reaction mixture was poured into water (200 ml) and 100 ml of hexane was added. The resulting precipitate was collected and recrystallized from CCl_4 to give 2.5 g (65%) of **9** (m.p. 155–157 °C). ^{1}H NMR (DMF-d_7) δ: 1.05–2.1 (10H, m, $5CH_2$); 3.85 (1H, m, NCH); 5.62 (1H, s, CH); 6.22 (1H, w s, OH); 10.8 (1H, w s, NH) ppm. ^{19}F NMR (DMF-d_7) δ: −162.37 to −161.70 (2F, *meta*-fluorines, m); −154.29 (1F, *para*-fluorine, t, J = 20.7 Hz); −142.71 to −142.29 (2F, *ortho*-fluorines, m) ppm. IR (cm^{-1}): 3250 (NH); 1680 (C=O, acid); 2700 (CO_2^-, NH_2^+); 1640 (C=O); 1510 (C=C). Analysis: Found: C, 52.58; H, 4.20; F, 26.77%. Calc. for $C_{16}H_{14}F_5NO_3$: C, 53.00; H, 3.88; F, 26.20%.

2.7. 2-(2-Propyl)amino-3-pentafluorobenzoylacrylic acid (10) (nc)

In a similar manner, 3.0 g (10.6 mmol) of 1 and 0.63 g (10.7 mmol) of isopropylamine were refluxed in dioxan for 1 h. Recrystallization of the resulting precipitate

from CCl_4 gave 1.6 g of **10** (yield, 47%; m.p. 158–160 °C). ^{1}H NMR (DMF-d_7) δ: 1.32 (6H, t, J=6.6 Hz, $2CH_3$); 3.91–4.25 (1H, m, NCH); 5.56 (1H, s, CH); 6.07 (1H, w s, OH); 10.62 (1H w s, NH) ppm. ^{19}F NMR (DMF-d_7) δ: −162.41 to −161.66 (2F, *meta*-fluorines, m); −154.33 (1F, *para*-fluorine, t, J=20.5 Hz); −142.74 to −142.33 (2F, *ortho*-fluorines, m) ppm. IR (cm^{-1}): 3240 (NH); 1690 (C=O, acid); 2700, 1600–1565 (CO_2^-, NH_2^+); 1650 (C=O); 1515 (C=C). Analysis: Found: C, 46.60; H, 3.55; F, 28.74%. Calc. for $C_{13}H_{10}F_5NO_3 \cdot 1/2H_2O$: C, 47.00; H, 3.34; F, 28.60%.

2.8. 2-Phenylamino-3-pentafluorobenzoylacrylic acid (11) (nc)

In a similar manner, 0.6 g (2.13 mmol) of **1** and 0.2 g (2.14 mmol) of aniline were refluxed in 20 ml of dioxan for 1 h. The reaction mixture was poured into water (200 ml) and 100 ml of hexane was added. The resulting precipitate was collected by filtration to give a crude product (0.6 g, 78%) which was recrystallized twice from benzene to give 0.3 g (39%) of **11** (m.p. 176–178 °C). ^{1}H NMR (CD_3COCD_3; A, B isomers, ratio A/B=8:1) δ: 5.97 (A, 1H, t, J=1.6 Hz, CH); 6.06 (B, 1H, t, J=1.6 Hz, CH); 7.18–7.55 (5H, m, Ph); 11.88 (1H, w s, NH) ppm. ^{19}F NMR (CD_3COCD_3, A, B isomers, ratio A/B=8:1) δ: −161.84 (A, 2F, *meta*-fluorines, m); −161.67 (B, 2F, *meta*-fluorines, m); −153.17 (A, 1F, *para*-fluorine, t–t); −152.44 (B, 1F, *para*-fluorine, t–t); −141.98 (A, 2F, *ortho*-fluorines, m); −141.25 (B, 2F, ortho-fluorines, m) ppm. IR (cm^{-1}): 3200 (NH); 1680 (C=O, acid); 2700, 1550 (CO_2^-, NH_2^+); 1640 (C=O); 1510 (C=C). Analysis: Found: C, 53.88; H, 2.60; F, 26.20; N, 4.01%. Calc. for $C_{16}H_8F_5NO_3$: C, 53.80; H, 2.26; F, 26.59; N, 3.92%.

2.9. 1-Cyclohexyl-5,6,8-trifluoro-7-hydroxy-4(1H)-oxoquinoline-2-carboxylic acid (12) (nc)

A mixture of **9** (7.0 g, 19.3 mmol) and 8.0 g (143.0 mmol) of KOH in 200 ml of water was heated at 90–95 °C for 1 h. After cooling, the reaction mixture was added dropwise to a solution of concentrated HCl (25 ml) in 100 ml of water. The resulting precipitate was collected, washed with water and isopropyl alcohol, and dried to give 4.8 g (74%) of **12** (m.p. 295–297 °C). ^{1}H NMR (DMF-d_7) δ: 1.25–2.12 (1OH, m, $5CH_2$); 3.95 (1H, m, NCH); 6.41 (1H, s, CH); 9.1 (1H, w s, OH) ppm. ^{19}F NMR (DMF-d_7) δ: −161.20 (1F, d–d, F-6); −147.36 (1F, d–d, F-5); −140.95 to −140.55 (1F, m, F-8) ($J_{5-6}=J_{6-5}$=19.5; J_{5-8}=11.5; J_{6-8}=8.1 Hz) ppm. IR (cm^{-1}): 2650 (OH, CO_2^-, NH^+); 1725 (C=O, acid); 1640 (C=O); 1610, 1520 (C=C); 1565 (CO_2^-). Analysis: Found: C, 56.18; H, 4.46; F, 16.18%. Calc. for $C_{16}H_{14}F_3NO_4$: C, 56.31; H, 4.13; F, 16.70%.

2.10. 1-(2-Propyl)-5,6,8-trifluoro-7-hydroxy-4(1H)-oxoquinoline-2-carboxylic acid (13) (nc)

A mixture of **10** (0.5 g, 1.55 mmol) and 0.5 g (90.0 mmol) of KOH in 10 ml of water was heated at 90–95 °C for 1 h. After cooling, the reaction mixture was added dropwise to a solution of concentrated HCl (10 ml) in 50 ml of water. The resulting precipitate was collected, washed with water and dried to give 0.35 g (75%) of **13** (m.p. 210–212 °C). ^{1}H NMR (DMF-d_7) δ: 1.57 (6H, d–d, J_{H-H}=5.8; J_{H-F}=2.8 Hz, $2CH_3$); 4.43–4.59 (1H, m, NCH); 6.14 (2H, w s, OH); 6.36 (1H, s, CH) ppm. ^{19}F NMR (DMF-d_7) δ: −161.10 (1F, d–d, F-6); −147.16 (1F, d–d, F-5); −139.83 (1F, m, F-8) (J_{5-6}=19.6; J_{5-8}=11.5; J_{6-8}=7.8 Hz) ppm. IR (cm^{-1}): 2500 (OH, CO_2^-, NH^+); 1730 (C=O, acid); 1640 (C=O); 1590 (CO_2^-); 1505 (C=C). Analysis: Found: C, 51.67; H, 3.49; F, 19.13%. Calc. for $C_{13}H_{10}F_3NO_4$: C, 51.83; H, 3.35; F, 18.92%.

2.11. 1-Cyclohexyl-5,6,8-trifluoro-7-morpholinyl-4(1H)-oxoquinoline-2-carboxylic acid (14) (nc)

A mixture of **9** (9.0 g, 24.8 mmol) and 12.0 g (138.0 mmol) of morpholine in 40 ml of DMSO was heated at 90–100 °C for 1 h. To the solution was added 9.0 g (160.0 mmol) of KOH in 150 ml of water and the reaction mixture was heated at 90–100 °C for 1 h. After cooling, the reaction mixture was poured into solution of 50 ml of concentrated HCl in 150 ml of water. The resulting precipitate was collected by filtration and purified by recrystallization from DMF/water and then from DMF/acetonitrile to give 3.6 g (35%) of **14** (m.p. 176–178 °C). ^{1}H NMR (DMF-d_7+CD_3COOD) δ: 0.94–2.16 (10H, m, $5CH_2$); 3.44 (4H, w s, CH_2-N-CH_2); 3.80 (4H, t, J=4.0 Hz, CH_2-O-CH_2); 4.00 (1H, m, NCH); 6.36 (1H, s, CH) ppm. ^{19}F NMR (DMF-d_7) δ: −151.34 (1F, d–d, F-6); −147.14 (1F, d–d, F-5); −128.84 (1F, d, F-8) (J_{5-6}=18.6; J_{5-8}=12.2; J_{8-5}=10.8; J_{6-8}=4.4 Hz) ppm. IR (cm^{-1}): 3300, 3400, 2000 (OH, CO_2^-, NH^+); 1710 (C=O, acid); 1630 (C=O); 1610 (C=C); 1590 (sh) (CO_2^-). Analysis: Found: C, 58.61; H, 5.20; F, 13.40; N, 6.91%. Calc. for $C_{20}H_{21}F_3N_2O_4$: C, 58.53; H, 5.16; F, 13.89; N, 6.83%.

2.12. Methyl 2-phenylamino-5,5,5-trifluoro-4-oxopent-2-enoate (15) (nc)

A mixture of **7** (2.0 g, 10.0 mmol) and 0.93 g (10.0 mmol) of aniline in 10 ml of methanol was stirred at room temperature for 8 h. The reaction mixture was concentrated to afford a precipitate which was recrystallized from pentane to give 1.6 g (59%) of **15** (m.p. 60–61 °C). ^{1}H NMR ($CDCl_3$) δ: 3.72 (3H, s, CH_3); 5.91 (1H, s, CH); 7.01–7.39 (5H, m, Ph); 11.78 (1H, w s, NH) ppm. ^{13}C NMR ($CDCl_3$) δ: 53.23 (s, CH_3); 91.41 (s, CH=); 154.50 (s, =C−NPh); 163.05 (s, C=O, ester); 116.71 (q, J=288.09 Hz, CF_3); 178.32 (q, J=34.79

Hz, C=O) ppm. IR (cm^{-1}): 1730 (C=O, ester); 1620 (C=O); 1580 (C=C); 3380, 3250, 1560 (NH). Analysis: Found: C, 53.04; H, 4.01; F, 21.20; N, 4.92%. Calc. for $C_{12}H_{10}F_3NO_2$: C, 52.78; H, 3.69; F, 20.86; N, 5.13%.

2.13. 3-Pentafluorobenzoylidene-5,6-dihydro-1,4-oxazine-2-one (16) (nc)

A mixture of **1** (3.0 g, 10.6 mmol) and 0.65 g (10.7 mmol) of ethanolamine in 25 ml of dioxan was heated under reflux for 1 h. After cooling, the reaction mixture was poured into water (100 ml). The resulting precipitate was collected and recrystallized from methanol to give 1.5 g (46%) of **16** (m.p. 175–177 °C). ^1H NMR (CD_3COCD_3) δ: 3.48 (2H, d–t, $J_{H-H}=5.0$; $J_{H-F}=3.5$ Hz, CH_2N); 4.74 (2H, t, $J_{H-H}=5.0$ Hz, CH_2O); 6.1 (1H, t, $J=1.6$ Hz, CH); 10.69 (1H, w s, NH) ppm. ^{19}F NMR (CD_3COCD_3) δ: −162.38 to −161.62 (2F, *meta*-fluorines, m); −153.99 (1F, *para*-fluorine, t–t); −142.74 to −142.20 (2F, *ortho*-fluorines, m) ppm. IR (cm^{-1}): 3260, 1580 (NH); 1735 (O–C=O); 1640 (C_6F_5–C=O); 1625, 1510 (C=C). Analysis: Found: C, 46.51; H, 2.40; F, 30.56%. Calc. for $C_{12}H_6F_5NO_3$: C, 46.92; H, 1.97; F, 30.92%.

2.14. 5,6-Dihydro-3-oxo-4,7-oxazino[c]8,9,10,11-tetrafluoro-1(7H)-oxoquinoline (17) (nc)

A solution of **16** (5.6 g, 18.2 mmol) in 35 ml of DMSO was heated under reflux for 25 min. After cooling, the reaction mixture was added dropwise to water (100 ml). The resulting precipitate was collected and recrystallized from acetonitrile to give 2.4 g (46%) of **17** (m.p. 208 °C). ^1H NMR (DMF-d_7) δ: 4.70–4.95 (4H, m, $2CH_2$); 6.67 (1H, s, CH) ppm. ^{19}F NMR (DMF-d_7) δ: −162.51 (1F, d–d, F-6); −150.06 (1F, d–d–d, F-7); −146.24 (1F, d–d–t, F-8); −143.99 (1F, d–d–d, F-5) ($J_{6-7}=21.1$; $J_{7-6}=21.4$; $J_{6-5}=19.90$; $J_{5-6}=19.97$; $J_{6-8}=J_{8-6}=0$; $J_{7-8}=19.2$; $J_{8-7}=19.6$; $J_{7-5}=7.0$; $J_{5-7}=7.4$; $J_{8-5}=J_{5-8}=12.9$ Hz) ppm. IR (cm^{-1}): 1740 (O–C=O); 1630 (C=O); 1600, 1515 (C=C). Analysis: Found: C, 49.86; H, 2.22; F, 26.16%. Calc. for $C_{12}H_5F_4NO_3$: C, 50.19; H, 1.75; F, 26.46%.

2.15. Potassium 1-(2-hydroxyethylene)-5,6,7,8-tetrafluoro-4(1H)-oxoquinoline-2-carboxylate (18) (nc)

A mixture of **17** (0.5 g, 1.741 mmol) and 5.8 ml (1.689 mmol) of KOH (0.29 N solution in water) was stirred for 20 min. To the reaction mixture, 10 ml of water was added. The residual **17** was removed by filtration. The filtrate was concentrated to dryness under reduced pressure to leave 0.45 g (76%) of pure **18** (m.p. 240 °C decomp.). ^1H NMR (DMF-d_7 + D_2O) δ: 3.91 (2H, d–t, $J_{H-F}=1.9$ Hz; $J_{H-H}=6.0$ Hz, CH_2N); 4.65 (2H, m, CH_2O); 6.18 (1H, s, CH) ppm. ^{19}F NMR (DMF-d_7 + D_2O) δ: −163.78 (1F, t, F-6); −150.63 (1F, d–d–d, F-7); −145.59 (1F, d–d–t, F-8); −143.79 (1F, d–d–d, F-5) ($J_{6-5}=J_{5-6}=21.5$; $J_{7-5}=J_{5-7}=6.7$; $J_{7-8}=J_{8-7}=19.2$; $J_{5-8}=J_{8-5}=12.5$; $J_{8F-H}=1.9$ Hz) ppm. IR (cm^{-1}): 3310 (OH); 3050, 1590, 1510 (C=C); 1640 (C=O); 1610 (CO_2^-). Analysis: Found: C, 42.17; H, 1.98; F, 21.92%. Calc. for $C_{12}H_6F_4NO_4$: C, 41.98; H, 1.76; F, 22.14%.

2.16. 7-Cyclohexylamine-2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (20) (nc)

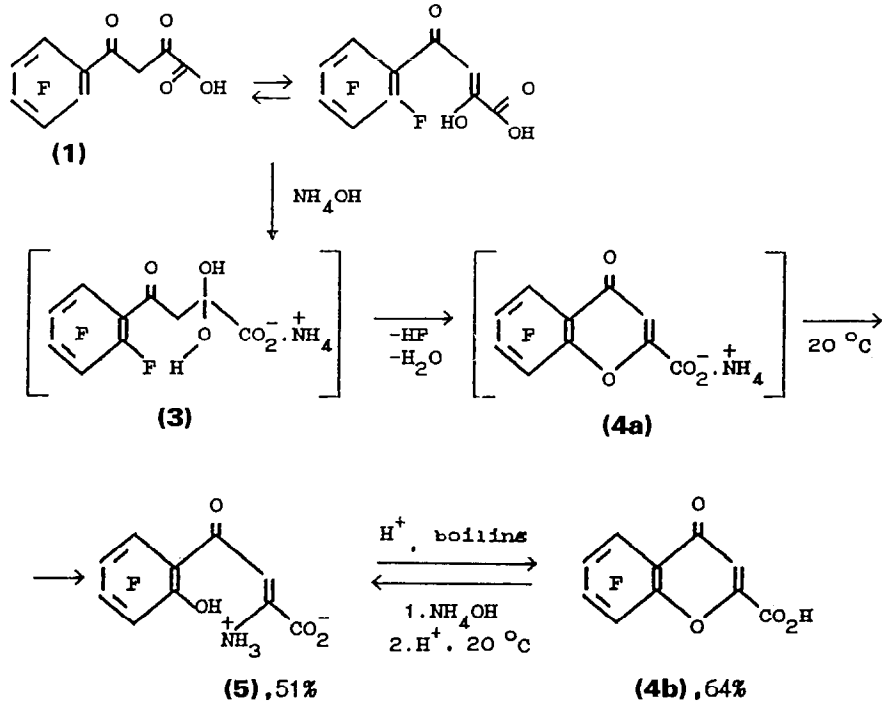
To a solution of **2** (0.8 g, 2.58 mmol) in 20 ml of CCl_4, a solution of cyclohexylamine (0.5 g, 5.04 mmol) in 20 ml of DMSO was added. The reaction mixture was heated to remove CCl_4 and the residue heated at 130 °C for 10 min. After cooling, 30 ml of water was added to the reaction mixture. The resulting precipitate was collected by filtration and purified by recrystallization twice from octane to give 0.6 g (63%) of **20** (m.p. 120–121 °C). ^1H NMR (CD_3CN) δ: 1.38 (3H, t, $J=7.0$ Hz, CH_2CH_3); 1.1–2.1 (1OH, m, $5CH_2$); 3.68 (1H, w s, HC–N); 4.40 (2H, q, $J=7.0$ Hz, CH_2CH_3); 5.0 (1H, w s, NH); 6.72 (1H, s, CH) ppm. ^{19}F NMR (CD_3CN) δ: −157.84 (2F, m, F-6 + F-8); −147.04 (1F, d–d, F-5) ($J_{5-8}=12.7$; $J_{5-6}=20.2$ Hz) ppm. IR (cm^{-1}): 3310, 1540 (NH); 1735 (C=O, ester); 1655 (C=O, chromone); 1610 (C=C). Analysis: Found: C, 58.33; H, 4.92; F, 15.47; N, 3.84%. Calc. for $C_{18}H_{18}F_3NO_4$: C, 58.54; H, 4.91; F, 15.43; N, 3.79%.

3. Results and discussion

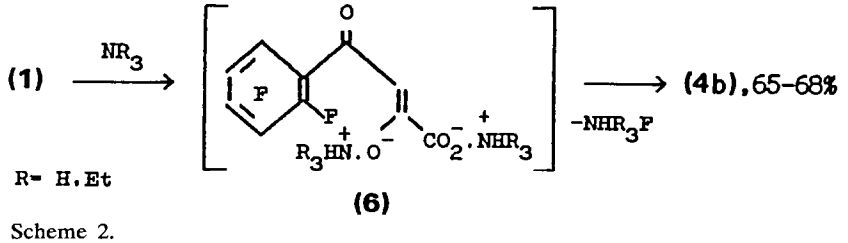
3.1. Interaction of pentafluorobenzoylpyruvic acid with ammonia and triethylamine

In this work, it has been found that pentafluorobenzoylpyruvic acid (**1**) forms 2-amino-3-(2-oxy-3,4,5,6-tetrafluorobenzoyl)acrylic acid (**5**) in reaction with ammonium hydroxide, obviously through the formation of the intermediates **3** and **4a** (Scheme 1).

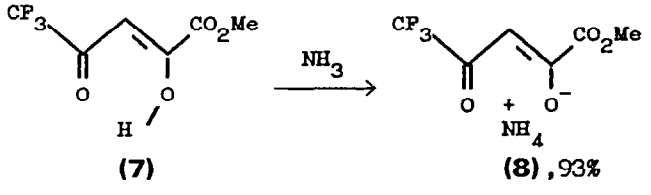
The same type of addition (O-nucleophile) to an α-carbonyl carbon atom is postulated for the interaction of non-fluorinated analogues with amines in alcohol [2, 3], but the ensuing nucleophilic displacement of the fluorine *ortho*-atom with the formation of **4a** is a specific feature of **1**. Compound **4a** could not be isolated; instead treatment of the reaction mixture with acetic acid at room temperature gave only **5** in moderate yield. The chromone derivative **4b** results from treatment of **5** with a boiling mixture of acetic and hydrochloric acids (Scheme 1). The IR, ^1H and ^{19}F NMR spectral data of compound **4b** were identical to those previously reported [4]. In contrast to **4b**, the ^1H NMR spectrum of compound **5** exhibited a vinylic proton as a doublet at δ 6.63 ppm with a coupling constant of 1.1 Hz between the CH hydrogen and the C_6F_4 fluorines. In addition, three resonances centred at δ 7.92, 9.58 and 11.08 ppm as wide singlet signals in the expected ratio



Scheme 1.



Scheme 2.



Scheme 3.

were found for the NH and OH hydrogen atoms of **5**.

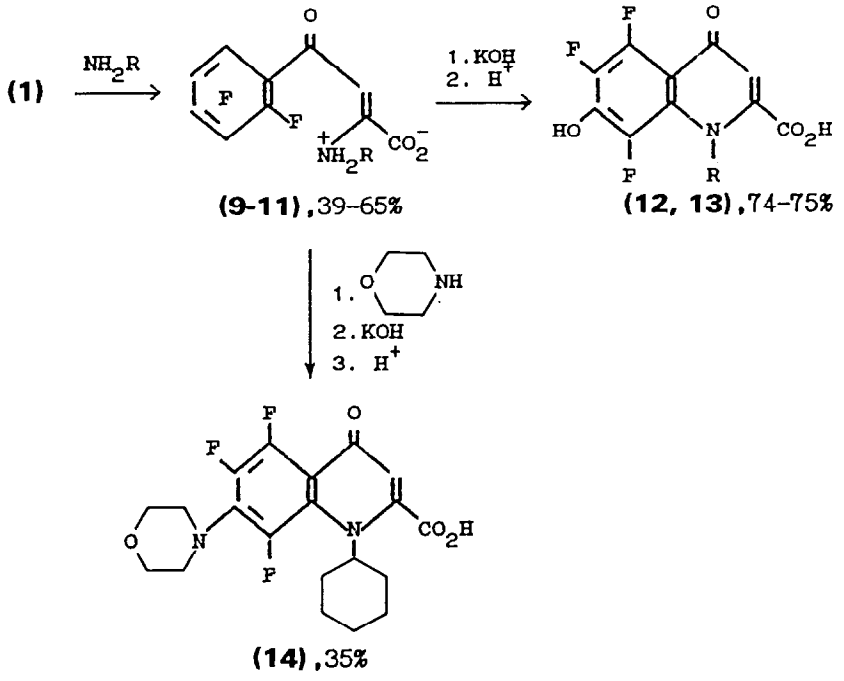
Interaction of either anhydrous ammonia or anhydrous triethylamine with **1** in dioxan afforded the same 2-carboxychromone **4b**, obviously through the formation of the intermediate **6** (Scheme 2). Evidently, in this case the absence of the hydroxide ion inhibits the opening of the **4b** chromone cycle.

In general, intramolecular cyclization with the formation of the chromone structure, but not the addition of NR_3 to the α-carbonyl carbon atom of **1**, predominates in all these reactions.

The formation of intermediate **6** is expected in view of our results with methyl trifluoroacetopyruvate (**7**) which has no active aromatic fluorine atom (Scheme 3). Compound **8** is highly stable and is not destroyed when heated in toluene.

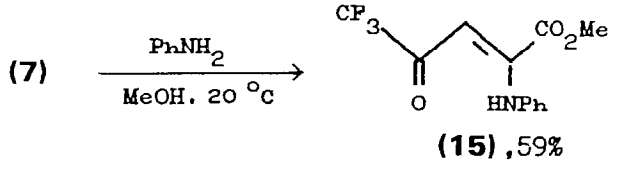
3.2. Interaction of pentafluorobenzoylpyruvic acid with isopropyl-, cyclohexyl- and phenyl-amines

In contrast, reaction of **1** with isopropyl-, cyclohexyl- and phenyl-amines in dioxan afforded compounds **9–11** (Scheme 4), the presence of some water in the reaction having no effect on the quality and yield of these products. This may result from the role of steric effects significantly lowering both the stability of compounds of type **6** and **8** and the reactivity of the amine. Hence molecular orbital control takes place in this reaction [6]. On the contrary, the reaction of **1** with ammonia (triethylamine) is determined by the charge. A similar trend is observed on comparing the reactions of methyl trifluoroacetopyruvate (**7**) with ammonia and phenyl-



Compound	R
9, 12	C_6H_{11}
10, 13	-CH(Me)$_2$
11	Ph

Scheme 4.



Scheme 5.

amine. Thus, under mild conditions, the amino compound **15** was obtained from **7** (Scheme 5).

The IR, ^1H and ^{19}F NMR spectral data for compounds **9–11** were found to be in complete agreement with the assigned structures. Thus, in ^{19}F spectra of compounds **9** and **10**, five resonance signals in the expected ratio were attributed to the fluorine atoms of the C_6F_5 group. The observation of two signals for each aromatic fluorine and for the vinylic proton in the ^{19}F and ^1H NMR spectra of **11** seems to support the presence of two stereoisomers. The ^1H NMR spectra of **9–11** showed a coupling between the CH hydrogen and the C_6F_5 fluorines ($J=1.6$ Hz) only for compound **11**.

The ^{13}C NMR spectrum of **15** exhibited two quartets at δ 116.71 ($J=288.09$ Hz) and 178.32 ppm ($J=34.79$ Hz) assigned to the CF_3 group and the carbonyl carbon atom connected to the fluoroalkyl substituent, respectively. In addition, four singlets were observed (at δ 163.05 ppm assigned to the ester carbonyl carbon, at δ 154.50 ppm assigned to the =C—NPh carbon, at δ 91.41 ppm assigned to the =CH carbon and at δ 53.23 ppm assigned to the methyl group). Such a spectrum could only arise from a compound containing a phenylamino substituent at the α-carbon atom.

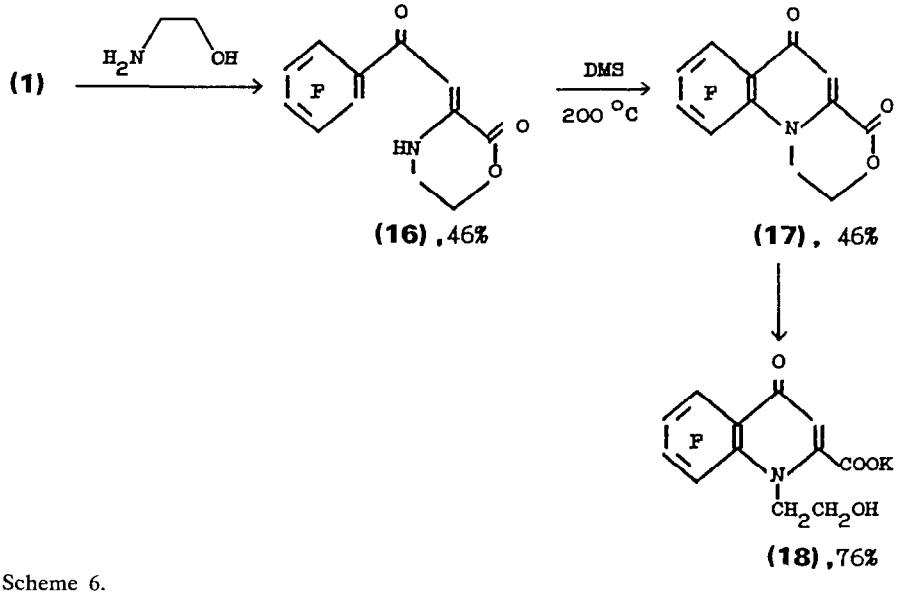
Compounds **12** and **13** were derived from **9** and **10**, respectively, under alkaline conditions (Scheme 4). Regiospecific displacement with water at the C-7 position of either **12** and **13** (O-nucleophile) took place.

The 7-morpholinyl compound **14** was independently prepared from **9** by a displacement reaction of **9** with morpholine, followed by alkaline treatment and subsequent acidic treatment.

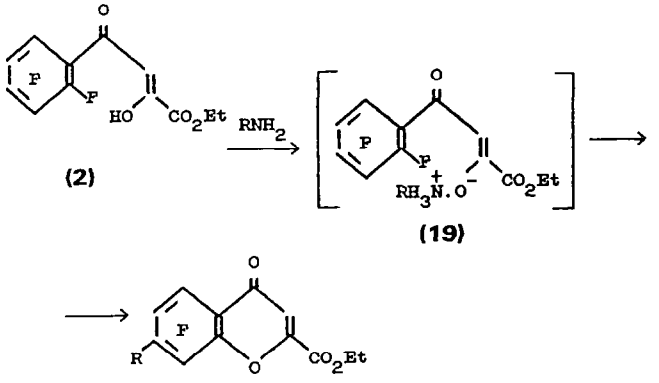
The structures of compounds **12–14** were assigned on the basis of their IR, ^1H and ^{19}F NMR spectra. In the ^{19}F NMR spectra of compounds **12–14**, three signals in the expected ratio were attributed to the C-5, C-6 and C-8 fluorine atoms of the C_6F_3 group.

3.3. Interaction of pentafluorobenzoylpyruvic acid with ethanolamine

A similar reaction of compound **1** with bifunctional ethanolamine in dioxan afforded compound **16**, which was then subjected to cyclization to give the heterocycle



Scheme 6.



Compound	R
4c	F
20	C_6H_{11}-NH

Scheme 7.

17 (Scheme 6). Compound **18** was derived from **17** under alkaline conditions.

In the ^{1}H NMR spectrum of compound **16**, a doublet of triplets at δ 3.48 ppm with coupling constants of 5.0 and 3.5 Hz between two CH_2 groups and the CH_2 group and the C_6F_5 fluorines, respectively, was found for the CH_2-N group. Two triplets at δ 4.74 ppm ($J_{H-H}=5.0$ Hz) and at δ 6.1 ppm ($J_{H-F}=1.6$ Hz) were assigned to the CH_2-O group and the vinylic proton, respectively. The ^{1}H NMR spectrum of compound **18** exhibited similar types of couplings. The ^{1}H NMR spectrum of compound **17** showed methylene protons as a four proton multiplet between δ 4.70 ppm and 4.95 ppm and also a vinylic proton as a singlet at δ 6.67 ppm.

3.4. Interaction of ethyl pentafluorobenzoylpyruvate with ammonia and cyclohexylamine

Treatment of ethyl pentafluorobenzoylpyruvate (2) with ammonia or cyclohexylamine gave only the chromone derivatives **4c** and **20** in a good yield (Scheme 7).

The presence of the ethoxycarbonyl group in compound **2** inhibits the formation of a condensation product of the latter with hexylamine as was found for the reaction of **1** with hexylamine; instead the nucleophilic replacement of its *ortho*-fluorine atom readily leads to the formation of a chromone structure. Such a preference is apparently the result of steric hindrance at the α-carbon position. The ethoxycarbonyl group, moreover, provided enhanced stability for the chromone structures of **4c** and **20** under these reaction conditions, compared to the carboxy group. It is possible to explain the difference in reactivity between 2-carboxychromone (**4b**) and 2-ethoxycarbonylchromone (**4c**) as arising from electronic effects, but we defer further discussion until more experimental information is available.

In conclusion, the reactions described demonstrate the preparation of 2-amino-substituted-3-pentafluorobenzoylacrylic acids and 1-amino-substituted-4(1*H*)-oxoquinoline-2-carboxylic acids from pentafluorobenzoylpyruvic acid. Interaction of pentafluorobenzoylpyruvic acid and its ester with *N*-nucleophiles is well established by the behaviour of the tricarbonyl compound and by the nucleophilic mobility of the *ortho*-fluorine atom of their C_6F_5 substituent.

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