Baylis–Hillman Route to Several Quinolone Antibiotic Intermediates

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Received 29 August 2005; revised 24 October 2005

Abstract: Treatment of methyl propiolate and 2,4,5-trifluoro-, 2-fluoro-, 2-fluoro-5-methoxy- or 2,3,4,5-tetrafluorobenzaldehydes with a $ZrCl_4/Bu_4NI$ combination induces an aldol reaction to furnish β-iodo-α-(hydroxyalkyl)acrylates. These can be used for the preparation of several quinolone intermediates, 1-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acids and 9,10-difluoro-3-methyl-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid through the oxidation, amination and hydrolysis reactions.

Key words: Baylis–Hillman reaction, quinolone antibiotics, β-iodo-α-(hydroxyalkyl)acrylates, Dess–Martin periodinane, α-methylene-β-keto ester

Since the discovery of nalidixic acid by Lesher in 1962,[1] many clinically important antibacterial agents such as norfloxacin,[2] ciprofloxacin,[3] temafloxacin,[4] difloxacin[5] and ofloxacin[6] having the 1-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acid moiety and collectively known as quinolones have been discovered.[7] These agents have been shown to inhibit the topoisomerase enzyme DNA gyrase.[8]

The synthetic chemistry of quinolone backbone consists basically of variations on just a few pathways. The original method was the well-precedented Gould–Jacobs reaction[9] between suitably substituted anilines and a substituted ethylenemalonate analogue at high temperature. Access to novel quinolones was greatly expanded subsequently by the introduction of the Grohe–Heitzer cycloacylation synthesis.[10] In this process, a suitable benzoic acid derivative is first elaborated into benzoylmalonate ester. The active methylene function is then condensed under dehydrating conditions with an ortho ester. The resulting enol ether is subjected with a suitable primary amine, and this product can be cyclized in a tandem addition–elimination reaction at the *ortho* position of aromatic ring.

The Baylis–Hillman (BH) reaction, i.e., coupling of an activated alkene or alkyne with an aldehyde or ketone, has recently become a very attractive goal for the carbon–carbon bond-forming reactions.[11] Lu[12] and Paré[13] reported an efficient $ZrCl_4/Bu_4NI$- or Et_2AlI-promoted BH-type coupling of aldehydes with propiolic esters to produce β-iodo-α-(hydroxyalkyl)acrylates, originally discovered by Taniguchi et al.[14] Our interest in BH chemistry[15] led us to investigate an alternative route for the synthesis of quinolone skeleton. We herein report a new synthesis of several quinolone key intermediates from the BH-type reaction of 2-fluorobenzaldehydes **1a–c** or 2,3,4,5-tetrafluorobenzaldehyde (**7**) with methyl propiolate.

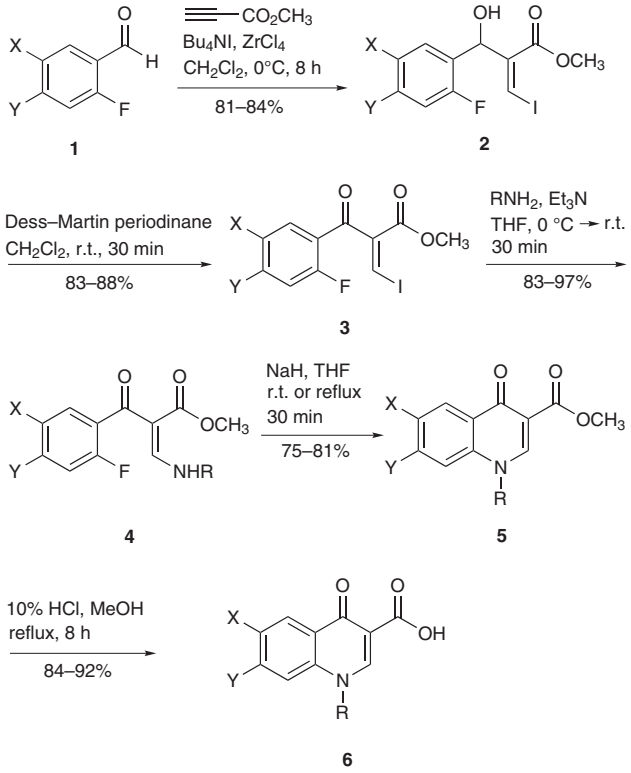
The requisite BH adducts **2a–c** were prepared by the reaction of methyl propiolate with Bu_4NI, followed by an aldol process with aldehydes **1a–c** in the presence of $ZrCl_4$ in 81–84% yields.[12] The ratios of *Z*/*E* were 90:10 to 93:7 as determined by the ^1H NMR spectral analyses of olefinic protons in comparison with literature values.[12] Dess–Martin periodinane[16] was able to transform the BH adducts **2a–c** into the α-methylene-β-keto esters **3a–c** in 83–88% yields as a single isomer.[17] The keto esters **3a–c** were reacted with a primary amine such as cyclopropyl-, ethyl-, 4-fluorophenyl-, and 2,4-difluorophenylamine in an addition–elimination sequence to afford methyl 2-(substituted amino)methylene 3-aryl-3-oxopropanoates **4a–f** in 83–97% yields. The ratios of *Z*/*E* were 72:28 to 92:8 by the ^1H NMR spectral analyses of vinyl protons. On cyclization of **4a–e** with sodium hydride in THF at room temperature for 30 minutes or at reflux temperature for **4f**, methyl 4-oxo-1,4-dihydroquinoline-3-carboxylates **5a–f** were obtained in 75–81% yields (Scheme 1).

The requirement for the presence of certain electron-withdrawing groups *para* to the leaving group does not force the generality of this cyclization reaction, it works well with hydrogen or electron-donating methoxy substituted compounds. Esters **5a–f**, on heating with aqueous 10% HCl in MeOH for eight hours, gave most of the known 4-oxo-1,4-dihydroquinoline-3-carboxylic acids **6a–f** in 84–92% yields. Thus an overall 41% yield for **6a** was achieved.[18]

Repetition of this reaction sequence with 2,3,4,5-tetrafluorobenzaldehyde (**7**) and 2-aminopropan-1-ol afforded 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (**12**) through the compounds **10** and **11** in five steps and 40% overall yield (Scheme 2).[18]

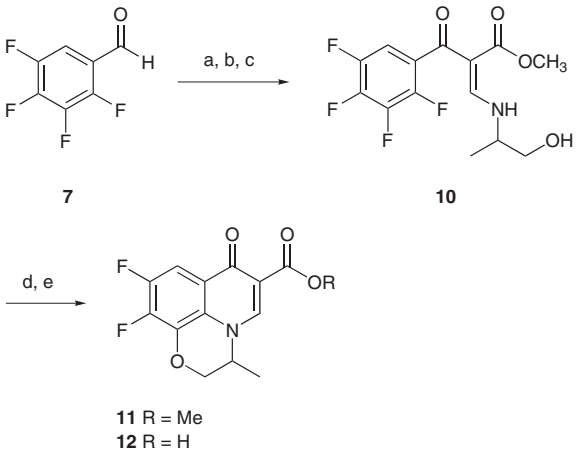
In conclusion, the first examples of the use of Baylis–Hillman type reaction of methyl propiolate with 2-fluorobenzaldehydes for the preparation of quinolone antibiotics intermediates have been described. This methodology provides a simple and general access to a variety of quinolone derivatives. Since the experimental conditions are extremely simple, we hope that this methodology could be in some cases a good complement to the existing procedures.

SYNTHESIS 2006, No. 6, pp 0963–0968
Advanced online publication: 27.02.2006
DOI: 10.1055/s-2006-926360; Art ID: F14405SS



1, 2, 3	X	Y	4, 5, 6	X	Y	R
a	F	F	**a**	F	F	*c*-Pr
b	H	H	**b**	F	F	Et
c	MeO	H	**c**	F	F	4-FC_6H_4
			d	F	F	2,4-$F_2C_6H_3$
			e	H	H	*c*-Pr
			f	MeO	H	*c*-Pr

Scheme 1



Scheme 2 *Reagents and conditions*: a) ≡–CO_2CH_3, $Bu_4NI/ZrCl_4$, CH_2Cl_2, 0 °C, 8 h → **8** (85%); b) Dess–Martin periodinane, CH_2Cl_2, r.t., 30 min → **9** (85%); c) $H_2NCH(Me)CH_2OH$, Et_3N, THF, 30 min → **10** (92%); d) NaH, dioxane, reflux, 4 h → **11** (76%); e) 10% HCl, MeOH, reflux, 8 h → **12** (80%)

Silica gel 60 (70–230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical TLC was carried out on Merck silica gel 60 F_{254} TLC plates. Melting points were taken using an electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. IR spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^1H NMR spectra were measured on a Gemini 300 spectrometer using $CDCl_3$ or DMSO-d_6. All chemical shifts are reported in ppm relative to TMS and coupling constants (J) are expressed in Hz.

2,4,5-Trifluoro-, 2-fluoro- and 2-fluoro-5-methoxybenzaldehydes were obtained from Aldrich, and 2,3,4,5-tetrafluorobenzaldehyde was prepared from the oxidation of commercially available 2,3,4,5-tetrafluorobenzyl alcohol according to the literature procedure.[19] Petroleum ether (PE) used refers to the fraction boiling in the range 30–60 °C.

Methyl 2-[(2,4,5-Trifluorophenyl)(hydroxy)methyl]-3-iodoprop-2-enoate (2a); Typical Procedure

To a mixture of 2,4,5-trifluorobenzaldehyde (**1a**; 1.60 g, 10 mmol), methyl propiolate (0.98 mL, 11 mmol) and Bu_4NI (4.06 g, 11 mmol) in anhyd CH_2Cl_2 (40 mL) was added $ZrCl_4$ (2.80 g, 12 mmol) at 0 °C. The mixture was stirred at 0 °C under N_2 for 8 h. Then, H_2O (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel eluting with hexane–EtOAc (8:1) to afford **2a** (3.13 g, 84%) as a white solid, which was recrystallized from Et_2O–hexane. The product was an approximate 90:10 mixture of the *Z* and *E* isomers; mp 59–61 °C.

IR (KBr): 3490, 1712, 1598, 1518, 1507, 1330 cm^{-1}.

(*Z*)-**2a**

^1H NMR ($CDCl_3$): δ = 3.12 (d, *J* = 5.0 Hz, 1 H), 3.80 (s, 3 H), 5.78 (d, *J* = 5.0 Hz, 1 H), 6.88–6.97 (m, 1 H), 7.25–7.34 (m, 1 H), 7.36 (s, 1 H).

(*E*)-**2a**

^1H NMR ($CDCl_3$): δ = 3.77 (s, 3 H), 4.16 (d, *J* = 11.0 Hz, 1 H), 5.91 (d, *J* = 11.0 Hz, 1 H), 6.88–6.97 (m, 1 H), 7.25–7.34 (m, 1 H), 8.15 (s, 1 H).

Anal. Calcd for $C_{11}H_8F_3IO_3$: C, 35.51; H, 2.17. Found: C, 35.29; H, 2.02.

Methyl 2-[(2-Fluorophenyl)(hydroxy)methyl]-3-iodoprop-2-enoate (2b)

To a mixture of 2-fluorobenzaldehyde (**1b**; 1.24 g, 10 mmol), methyl propiolate (0.98 mL, 11 mmol) and Bu_4NI (4.06 g, 11 mmol) in anhyd CH_2Cl_2 (40 mL) was added $ZrCl_4$ (2.80 g, 12 mmol) at 0 °C. The mixture was stirred at 0 °C under N_2 for 8 h. The work-up procedure was the same as described above to afford **2b** (2.72 g, 81%) as a light yellow solid, which was crystallized from Et_2O–PE. The product was an approximate 93:7 mixture of the *Z* and *E* isomers; mp 41–43 °C.

IR (KBr): 3507, 1709, 1596, 1588, 1489, 1302 cm^{-1}.

(*Z*)-**2b**

^1H NMR ($CDCl_3$): δ = 3.05 (d, *J* = 5.0 Hz, 1 H), 3.77 (s, 3 H), 5.86 (d, *J* = 5.0 Hz, 1 H), 7.01–7.08 (m, 1 H), 7.14–7.19 (m, 1 H), 7.28 (s, 1 H), 7.29–7.35 (m, 1 H), 7.39–7.45 (m, 1 H).

(*E*)-**2b**

^1H NMR ($CDCl_3$): δ = 3.73 (s, 3 H), 4.28 (d, *J* = 10.4 Hz, 1 H), 5.97 (d, *J* = 10.4 Hz, 1 H), 7.01–7.08 (m, 1 H), 7.14–7.19 (m, 1 H), 7.29–7.35 (m, 1 H), 7.39–7.45 (m, 1 H), 8.10 (s, 1 H).

Anal. Calcd for $C_{11}H_{10}FIO_3$: C, 39.31; H, 3.00. Found: C, 39.18; H, 2.89.

Methyl 2-[(2-Fluoro-5-methoxyphenyl)(hydroxy)methyl]-3-iodoprop-2-enoate (2c)

To a mixture of 2-fluoro-5-methoxybenzaldehyde (**1c**; 1.54 g, 10 mmol), methyl propiolate (0.98 mL, 11 mmol) and Bu_4NI (4.06 g, 11 mmol) in anhyd CH_2Cl_2 (40 mL) was added $ZrCl_4$ (2.80 g, 12 mmol) at 0 °C. The mixture was stirred at 0 °C under N_2 for 8 h. The work-up procedure was the same as described for the preparation of **2a** to afford **2c** (3.08 g, 84%) as a light yellow solid, which was crystallized from Et_2O–PE. The product was an approximate 93:7 mixture of the *Z* and *E* isomers; mp 56–58 °C.

IR (KBr): 3407, 1712, 1609, 1595, 1496, 1288 cm^{-1}.

(*Z*)-**2c**

^1H NMR ($CDCl_3$): δ = 3.25 (d, *J* = 3.4 Hz, 1 H), 3.77 (s, 6 H), 5.80 (d, *J* = 3.4 Hz, 1 H), 6.76–6.82 (m, 1 H), 6.91–6.98 (m, 2 H), 7.23 (s, 1 H).

(*E*)-**2c**

^1H NMR ($CDCl_3$): δ = 3.74 (s, 6 H), 4.27 (d, *J* = 10.7 Hz, 1 H), 5.93 (d, *J* = 10.7 Hz, 1 H), 6.76–6.82 (m, 1 H), 6.91–6.98 (m, 2 H), 8.09 (s, 1 H).

Anal. Calcd for $C_{12}H_{12}FIO_4$: C, 39.37; H, 3.30. Found: C, 39.10; H, 3.12.

Methyl 3-(2,4,5-Trifluorophenyl)-2-(iodomethylene)-3-oxopropanoate (3a); Typical Procedure

To a mixture of **2a** (595 mg, 1.6 mmol) in anhyd CH_2Cl_2 (75 mL) was added Dess–Martin periodinane (850 mg, 2 mmol). The mixture was stirred at r.t. for 30 min. After evaporation of CH_2Cl_2, Et_2O (100 mL) was added. Precipitated periodinane by-products were removed by filtration and the filtrate was concentrated to dryness. The residue was flash-chromatographed on silica gel eluting with hexane–EtOAc (6:1) to afford **3a** (521 mg, 88%) as a liquid.

IR (KBr): 1721, 1678, 1620, 1510, 1431, 1338 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.77 (s, 3 H), 6.97–7.05 (m, 1 H), 7.83–7.92 (m, 1 H), 8.18 (s, 1 H).

Anal. Calcd for $C_{11}H_6F_3IO_3$: C, 35.70; H, 1.63. Found: C, 35.58; H, 1.56.

Methyl 3-(2-Fluorophenyl)-2-(iodomethylene)-3-oxopropanoate (3b)

To a mixture of **2b** (538 mg, 1.6 mmol) in anhyd CH_2Cl_2 (75 mL) was added Dess–Martin periodinane (850 mg, 2 mmol). The mixture was stirred at r.t. for 30 min. The work-up procedure was the same as described above to afford **3b** (460 mg, 86%) as a liquid.

IR (KBr): 1715, 1674, 1608, 1481, 1454, 1319 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 3 H), 7.10–7.17 (m, 1 H), 7.24–7.29 (m, 1 H), 7.52–7.59 (m, 1 H), 7.65–7.71 (m, 1 H), 8.06 (s, 1 H).

Anal. Calcd for $C_{11}H_8FIO_3$: C, 39.55; H, 2.41. Found: C, 39.41; H, 2.28.

Methyl 3-(2-Fluoro-5-methoxyphenyl)-2-(iodomethylene)-3-oxopropanoate (3c)

To a mixture of **2c** (586 mg, 1.6 mmol) in anhyd CH_2Cl_2 (75 mL) was added Dess–Martin periodinane (850 mg, 2 mmol). The mixture was stirred at r.t. for 30 min. The work-up procedure was the same as described for the preparation of **3a** to afford **3c** (484 mg, 83%) as a white solid after crystallization with Et_2O–hexane; mp 103–105 °C.

IR (KBr): 1743, 1655, 1591, 1495, 1460, 1326 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.82 (s, 6 H), 7.04–7.09 (m, 2 H), 7.14–7.16 (m, 1 H), 8.07 (s, 1 H).

Anal. Calcd for $C_{12}H_{10}FIO_4$: C, 39.58; H, 2.77. Found: C, 39.40; H, 2.51.

Methyl 2-Cyclopropylaminomethylene-3-(2,4,5-trifluorophenyl)-3-oxopropanoate (4a); Typical Procedure

To a stirred solution of **3a** (296 mg, 0.8 mmol) in anhyd THF (4 mL) was added cyclopropylamine (0.06 mL, 0.9 mmol) and Et_3N (0.11 mL, 0.8 mmol) under ice cooling. The mixture was stirred at r.t. for 30 min, and concentrated to dryness under reduced pressure. The residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford a solid, which was crystallized from a mixture of Et_2O–hexane to give **4a** (208 mg, 87%). The product was an approximate 92:8 mixture of the *Z* and *E* isomers; mp 124–125 °C (Lit.[20] mp 124–127 °C).

^1H NMR ($CDCl_3$): δ (major isomer) = 0.82–0.96 (m, 4 H), 2.95–3.01 (m, 1 H), 3.60 (s, 3 H), 6.83–6.92 (m, 1 H), 7.15–7.23 (m, 1 H), 8.20 (d, *J* = 13.7 Hz, 1 H), 10.90 (br s, 1 H).

Methyl 2-Ethylaminomethylene-3-(2,4,5-trifluorophenyl)-3-oxopropanoate (4b)

According to the method as described above, **3a** (296 mg, 0.8 mmol) was treated with $EtNH_2$ (70%, 0.07 mL, 0.9 mmol) to give **4b** (211 mg, 92%). The product was an approximate 88:12 mixture of the *Z* and *E* isomers; mp 127–128 °C.

IR (KBr): 3233, 1690, 1625, 1563, 1509, 1433 cm^{-1}.

^1H NMR ($CDCl_3$): δ (major isomer) = 1.36 (t, *J* = 7.3 Hz, 3 H), 3.45–3.52 (m, 2 H), 3.59 (s, 3 H), 6.84–6.92 (m, 1 H), 7.15–7.24 (m, 1 H), 8.12 (d, *J* = 14.0 Hz, 1 H), 10.92 (br s, 1 H).

Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.45; H, 4.08; N, 4.67.

Methyl 2-(4-Fluorophenylaminomethylene)-3-(2,4,5-trifluorophenyl)-3-oxopropanoate (4c)

According to the method as described for the preparation of **4a**, **3a** (296 mg, 0.8 mmol) was treated with 4-fluoroaniline (0.09 mL, 0.9 mmol) to give **4c** (257 mg, 91%). The product was an approximate 85:15 mixture of *Z* and *E* isomers; mp 104–105 °C.

IR (KBr): 3226, 1693, 1626, 1564, 1515, 1442 cm^{-1}.

^1H NMR ($CDCl_3$): δ (major isomer) = 3.66 (s, 3 H), 6.87–6.96 (m, 1 H), 7.11–7.33 (m, 5 H), 8.50 (d, *J* = 13.4 Hz, 1 H), 12.54 (br d, *J* = 12.8 Hz, 1 H).

Anal. Calcd for $C_{17}H_{11}F_4NO_3$: C, 57.80; H, 3.14; N, 3.96. Found: C, 57.69; H, 3.01; N, 3.81.

Methyl 2-(2,4-Difluorophenylaminomethylene)-3-(2,4,5-trifluorophenyl)-3-oxopropanoate (4d)

According to the method as described for the preparation of **4a**, **3a** (296 mg, 0.8 mmol) was treated with 2,4-difluoroaniline (0.09 mL, 0.9 mmol) to give **4d** (247 mg, 83%). The product was an approximate 72:28 mixture of *Z* and *E* isomers; mp 118–119 °C (Lit.[20] mp 116–119 °C).

^1H NMR ($CDCl_3$): δ (major isomer) = 3.66 (s, 3 H), 6.95–7.03 (m, 3 H), 7.28–7.41 (m, 2 H), 8.49 (d, *J* = 13.4 Hz, 1 H), 12.48 (br d, *J* = 13.7 Hz, 1 H).

Methyl 2-Cyclopropylaminomethylene-3-(2-fluorophenyl)-3-oxopropanoate (4e)

According to the method as described for the preparation of **4a**, **3b** (668 mg, 2 mmol) was treated with cyclopropylamine (0.15 mL, 2.2 mmol) to give **4e** (495 mg, 94%). The product was an approximate 88:12 mixture of *Z* and *E* isomers; mp 95–96 °C.

IR (KBr): 3206, 1682, 1632, 1580, 1550, 1484, 1442 cm^{-1}.

^1H NMR ($CDCl_3$): δ (major isomer) = 0.82–0.94 (m, 4 H), 2.93–3.01 (m, 1 H), 3.55 (s, 3 H), 6.98–7.05 (m, 1 H), 7.14–7.19 (m, 1 H), 7.32–7.38 (m, 2 H), 8.20 (d, *J* = 13.4 Hz, 1 H), 10.98 (br s, 1 H).

Anal. Calcd for $C_{14}H_{14}FNO_3$: C, 63.87; H, 5.36; N, 5.32. Found: C, 63.70; H, 5.27; N, 5.15.

Methyl 2-Cyclopropylaminomethylene-3-(2-fluoro-5-methoxyphenyl)-3-oxopropanoate (4f)

According to the method as described for the preparation of **4a**, **3c** (728 mg, 2 mmol) was treated with cyclopropylamine (0.15 mL, 2.2 mmol) to give **4f** (569 mg, 97%). The product was an approximate 75:25 mixture of *Z* and *E* isomers; mp 96–98 °C.

IR (KBr): 3228, 1705, 1635, 1570, 1493, 1428 cm^{-1}.

^1H NMR ($CDCl_3$): δ (major isomer) = 0.83–0.91 (m, 4 H), 2.90–3.01 (m, 1 H), 3.57 (s, 3 H), 3.79 (s, 3 H), 6.86–6.93 (m, 3 H), 8.18 (d, *J* = 13.7 Hz, 1 H), 10.91 (br s, 1 H).

Anal. Calcd for $C_{15}H_{16}FNO_4$: C, 61.43; H, 5.50; N, 4.78. Found: C, 61.28; H, 5.32; N, 4.53.

Methyl 1-Cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (5a); Typical Procedure

To a stirred solution of **4a** (180 mg, 0.6 mmol) in anhyd THF (3 mL) was slowly added in portions NaH (95%, 18 mg, 0.7 mmol) at 0 °C and the mixture was stirred at r.t. under N_2 for 30 min. H_2O (2 mL) was added to the mixture and concentrated under reduced pressure to precipitate a solid, which was collected by filtration and washed with cold H_2O to afford **5a** (126 mg, 75%); mp 226–228 °C (Lit.[21] mp 226–228 °C).

^1H NMR (DMSO-d_6): δ = 1.12–1.14 (m, 2 H), 1.24–1.28 (m, 2 H), 3.62–3.66 (m, 1 H), 3.75 (s, 3 H), 8.05 (dd, *J* = 10.7, 8.9 Hz, 1 H), 8.14 (dd, *J* = 11.9, 6.7 Hz, 1 H), 8.50 (s, 1 H).

Methyl 6,7-Difluoro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (5b)

Following the procedure described above, compound **5b** was prepared in 75% yield as a white solid using **4b**; mp 184–186 °C.

IR (KBr): 1688, 1645, 1620, 1493, 1323, 1289 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.35 (t, *J* = 7.0 Hz, 3 H), 3.76 (s, 3 H), 4.39 (q, *J* = 7.0 Hz, 2 H), 8.03–8.12 (m, 2 H), 8.74 (s, 1 H).

Anal. Calcd for $C_{13}H_{11}F_2NO_3$: C, 58.43; H, 4.15; N, 5.24. Found: C, 58.30; H, 4.05; N, 5.02.

Methyl 6,7-Difluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (5c)

Following the procedure described for the preparation of **5a**, compound **5c** was prepared in 77% yield as a white solid using **4c**; mp 238–240 °C.

IR (KBr): 1736, 1707, 1650, 1622, 1503, 1333, 1289 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.75 (s, 3 H), 7.04 (dd, *J* = 11.6, 6.4 Hz, 1 H), 7.49–7.55 (m, 2 H), 7.73–7.78 (m, 2 H), 8.14 (dd, *J* = 10.7, 8.6 Hz, 1 H), 8.50 (s, 1 H).

Anal. Calcd for $C_{17}H_{10}F_3NO_3$: C, 61.27; H, 3.02; N, 4.20. Found: C, 61.13; H, 2.89; N, 4.04.

Methyl 6,7-Difluoro-1-(2,4-difluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (5d)

Following the procedure described for the preparation of **5a**, compound **5d** was prepared in 81% yield as a white solid using **4d**; mp 204–204.5 °C.

IR (KBr): 1734, 1702, 1650, 1625, 1509, 1471, 1288 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.75 (s, 3 H) 7.20 (dd, *J* = 11.6, 6.4 Hz, 1 H), 7.39–7.45 (m, 1 H), 7.66–7.73 (m, 1 H), 7.86–7.94 (m, 1 H), 8.15 (dd, *J* = 10.7, 8.6 Hz, 1 H), 8.63 (s, 1 H).

Anal. Calcd for $C_{17}H_9F_4NO_3$: C, 58.13; H, 2.58; N, 3.99. Found: C, 57.89; H, 2.75; N, 3.72.

Methyl 1-Cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (5e)

Following the procedure described for the preparation of **5a**, compound **5e** was prepared in 79% yield as a white solid using **4e**; mp 238–239 °C.

IR (KBr): 1713, 1624, 1608, 1593, 1480, 1315 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.07–1.12 (m, 2 H), 1.23–1.29 (m, 2 H), 3.63–3.70 (m, 1 H), 3.75 (s, 3 H), 7.48–7.53 (m, 1 H), 7.81–7.87 (m, 1 H), 8.09 (d, *J* = 8.6 Hz, 1 H), 8.23 (dd, *J* = 8.2, 1.4 Hz, 1 H), 8.53 (s, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.29; H, 5.27; N, 5.51.

Methyl 1-Cyclopropyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (5f)

Following the procedure described for the preparation of **5a**, compound **5f** was prepared at reflux temperature for 30 min in 81% yield as a white solid using **4f**; mp 244–246 °C.

IR (KBr): 1723, 1621, 1610, 1590, 1493, 1323 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.09–1.15 (m, 2 H), 1.21–1.25 (m, 2 H), 3.67–3.69 (m, 1 H), 3.75 (s, 3 H), 3.87 (s, 3 H), 7.45 (dd, *J* = 9.2, 3.1 Hz, 1 H), 7.64 (d, *J* = 3.1 Hz, 1 H), 8.05 (d, *J* = 9.2 Hz, 1 H), 8.46 (s, 1 H).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.81; H, 5.40; N, 4.95.

1-Cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6a); Typical Procedure

A suspension of **5a** (84 mg, 0.3 mmol) in a mixture of 10% HCl (2 mL) and MeOH (2 mL) was stirred at reflux temperature for 8 h. After addition of H_2O (2 mL), the resulting precipitate was collected by filtration and washed with cold H_2O to give **6a** (68 mg, 85%), which was recrystallized from a mixture of $CHCl_3$ and EtOH (1:1); mp 284–286 °C (Lit.[22] mp 287–289 °C).

^1H NMR (DMSO-d_6): δ = 1.17–1.36 (m, 4 H), 3.78–3.85 (m, 1 H), 8.28 (dd, *J* = 10.4, 8.9 Hz, 1 H), 8.38 (dd, *J* = 12.0, 7.0 Hz, 1 H), 8.77 (s, 1 H), 14.69 (br s, 1 H).

1-Ethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6b)

Following the procedure described above, compound **6b** was prepared in 86% yield as a white solid using **5b**; mp 303–305 °C (Lit.[23] mp ca. 300 °C).

^1H NMR (DMSO-d_6): δ = 1.40 (t, *J* = 7.0 Hz, 3 H), 4.58 (q, *J* = 7.0 Hz, 2 H), 8.24–8.34 (m, 2 H), 9.08 (s, 1 H), 14.86 (br s, 1 H).

6,7-Difluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6c)

Following the procedure described for the preparation of **6a**, compound **6c** was prepared in 84% yield as a white solid using **5c**; mp 258–260 °C (Lit.[24] mp 252–256 °C).

^1H NMR (DMSO-d_6): δ = 7.27 (dd, *J* = 11.3, 6.7 Hz, 1 H), 7.54–7.60 (m, 2 H), 7.78–7.82 (m, 2 H), 8.38 (dd, *J* = 9.5, 9.2 Hz, 1 H), 14.42 (br s, 1 H).

6,7-Difluoro-1-(2,4-difluorophenyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6d)

Following the procedure described for the preparation of **6a**, compound **6d** was prepared in 92% yield as a white solid using **5d**; mp 239–241 °C (Lit.[25] mp 240 °C).

^{1}H NMR (DMSO-d_6): δ = 7.43–7.47 (m, 2 H), 7.68–7.76 (m, 1 H), 7.87–7.95 (m, 1 H), 8.32–8.39 (dd, *J* = 10.4, 8.5 Hz, 1 H), 8.96 (s, 1 H), 14.44 (br s, 1 H).

1-Cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6e)

Following the procedure described for the preparation of **6a**, compound **6e** was prepared in 85% yield as a white solid using **5e**; mp 280–282 °C (Lit.[10] mp 284 °C).

^{1}H NMR (DMSO-d_6): δ = 1.17–1.22 (m, 2 H), 1.29–1.36 (m, 2 H), 3.82–3.90 (m, 1 H), 7.68–7.73 (m, 1 H), 8.00–8.06 (m, 1 H), 8.31 (d, *J* = 8.6 Hz, 1 H), 8.38 (dd, *J* = 8.1, 1.7 Hz, 1 H), 8.77 (s, 1 H), 15.09 (br s, 1 H).

1-Cyclopropyl-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (6f)

Following the procedure described for the preparation of **6a**, compound **6f** was prepared from **5f** in 90% yield as a white solid; mp 213–214 °C.

IR (KBr): 3424, 1721, 1613, 1547, 1470, 1447, 1285 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.16–1.23 (m, 2 H), 1.25–1.35 (m, 2 H), 3.83–3.90 (m, 1 H), 3.93 (s, 3 H), 7.63 (dd, *J* = 9.5, 3.1 Hz, 1 H), 7.71 (d, *J* = 3.1 Hz, 1 H), 8.26 (d, *J* = 9.5 Hz, 1 H), 8.69 (s, 1 H), 15.26 (s, 1 H).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.62; H, 4.82; N, 5.28.

Methyl 2-[(2,3,4,5-Tetrafluorophenyl)(hydroxy)methyl]-3-iodoprop-2-enoate (8)

To a mixture of 2,3,4,5-tetrafluorobenzaldehyde (**7**; 1.78 g, 10 mmol), methyl propiolate (0.98 mL, 11 mmol) and Bu_4NI (4.06 g, 11 mmol) in anhyd CH_2Cl_2 (40 mL) was added $ZrCl_4$ (2.80 g, 12 mmol) at 0 °C. The mixture was stirred at 0 °C under N_2 for 8 h. Then, H_2O (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The resulting mixture was chromatographed on silica gel eluting with hexane–EtOAc (8:1) to afford **8** (3.31 g, 85%) as a white solid, which was recrystallized from Et_2O–hexane. The product was an approximate 90:10 mixture of the *Z* and *E* isomers; mp 63–65 °C.

IR (KBr): 3491, 1713, 1600, 1524, 1487, 1296 cm^{-1}.

(*Z*)-**8**

^{1}H NMR ($CDCl_3$): δ = 3.25 (d, *J* = 5.8 Hz, 1 H), 3.80 (s, 3 H), 5.80 (d, *J* = 5.8 Hz, 1 H), 7.06–7.15 (m, 1 H), 7.45 (s, 1 H).

(*E*)-**8**

^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H), 4.20 (d, *J* = 10.4 Hz, 1 H), 5.94 (d, *J* = 10.4 Hz, 1 H), 7.06–7.15 (m, 1 H), 8.20 (s, 1 H).

Anal. Calcd for $C_{11}H_7F_4IO_3$: C, 33.87; H, 1.81. Found: C, 33.78; H, 1.76.

Methyl 3-(2,3,4,5-Tetrafluorophenyl)-2-(iodomethylene)-3-oxopropanoate (9)

To a mixture of **8** (624 mg, 1.6 mmol) in anhyd CH_2Cl_2 (75 mL) was added Dess–Martin periodinane (850 mg, 2 mmol). The mixture was stirred at r.t. for 1 h. After evaporation of CH_2Cl_2, Et_2O (100 mL) was added. Precipitated periodinane by-products were removed by filtration and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel eluting with hexane–EtOAc (6:1) to afford **9** (528 mg, 85%) as a liquid.

IR (KBr): 1720, 1688, 1628, 1524, 1484, 1362 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.79 (s, 3 H), 7.67–7.69 (m, 1 H), 8.24 (s, 1 H).

Anal. Calcd for $C_{11}H_5F_4IO_3$: C, 34.05; H, 1.30. Found: C, 33.87; H, 1.19.

Methyl 2-(2,3,4,5-Tetrafluorobenzoyl)-3-(1-hydroxyprop-2-ylamino)acrylate (10)

To a stirred solution of **9** (349 mg, 0.9 mmol) in anhyd THF (5 mL) was added 2-aminopropan-1-ol (0.12 mL, 1.5 mmol) and Et_3N (0.12 mL, 0.9 mmol) under ice cooling. The mixture was stirred at r.t. for 30 min, and concentrated to dryness under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOAc (3:2) to afford **10** (278 mg, 92%) as a liquid. The product was an approximate 82:18 mixture of *Z* and *E* isomers.

IR (KBr): 3440, 1696, 1681, 1632, 1567, 1525, 1482 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (major isomer) = 1.36 (d, *J* = 6.1 Hz, 3 H), 2.05 (br s, 1 H), 3.55–3.67 (m, 2 H), 3.60 (s, 3 H), 3.74–3.80 (m, 1 H), 6.93–6.99 (m, 1 H), 8.20 (d, *J* = 14.3 Hz, 1 H), 10.92 (br s, 1 H).

Anal. Calcd for $C_{14}H_{13}F_4NO_4$: C, 50.16; H, 3.91; N, 4.18. Found: C, 50.10; H, 3.87; N, 4.16.

Methyl 9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (11)

To a stirred solution of **10** (268 mg, 0.8 mmol) in anhyd dioxane (3 mL) was slowly added in portions NaH (95%, 50 mg, 2.0 mmol) at 0 °C, and the mixture was stirred at reflux temperature under N_2 for 4 h. H_2O (3 mL) was added to the mixture and concentrated under reduced pressure to precipitate a solid, which was collected by filtration and washed with H_2O and Et_2O–hexane solution (1:1) to afford **11** (180 mg, 76%); mp 258–260 °C.

IR (KBr): 1724, 1624, 1569, 1530, 1487, 1448 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.43 (d, *J* = 6.7 Hz, 3 H), 3.76 (s, 3 H), 4.45 (dd, *J* = 11.3, 2.4 Hz, 1 H), 4.60 (dd, *J* = 11.3, 2.4 Hz, 1 H), 4.81 (m, 1 H), 7.60 (dd, *J* = 11.0, 7.9 Hz, 1 H), 8.72 (s, 1 H).

Anal. Calcd for $C_{14}H_{11}F_2NO_4$: C, 56.95; H, 3.76; N, 4.74. Found: C, 56.72; H, 3.59; N, 4.60.

9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (12)

A suspension of **11** (89 mg, 0.3 mmol) in a mixture of 10% HCl (2 mL) and MeOH (2 mL) was stirred at reflux temperature for 8 h. After addition of H_2O (2 mL), the resulting precipitate was collected by filtration and washed with cold H_2O to give **6a** (67 mg, 80%), which was recrystallized from a mixture of $CHCl_3$ and EtOH (1:1); mp 309–311 °C (Lit.[6a] >300).

^{1}H NMR (DMSO-d_6): δ = 1.48 (d, *J* = 6.7 Hz, 1 H), 4.50 (dd, *J* = 11.3, 2.4 Hz, 1 H), 4.70 (dd, *J* = 11.3, 2.4 Hz, 1 H), 5.02 (m, 1 H), 7.83 (dd, *J* = 10.4, 7.6 Hz, 1 H), 9.01 (s, 1 H), 14.81 (br s, 1 H).

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