Expedient synthesis of highly substituted fused hetero-coumarins

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NMR spectra were recorded in CDCl₃ on a 300 MHz Brucker Avance spectrometer. Melting point were recorded on a Buchi 535 and were not corrected.

Synthesis of the 6-fluoro coumarin 12

Preparation of the enol triflate 10b:

\[ \text{1. NaH, DMF} \]
\[ \text{2.} \]

7.7 mL of ethyl cylohexanon-2-carboxylate (46 mmoles) are diluted in 100 mL of DMF under nitrogen at 0°C. Then 2.7 g of NaH (60% in oil) are cautiously added to the stirred solution and the reaction kept at 0°C till the end of gas evolution. N-phenyl-bis-(trifluoromethansulfonimid) (20 g; 56 mmoles) in 40 ml DMF is added dropwise and the reaction warmed to r.t. The reaction mixture is poured into NH₄Cl sat. followed by extraction with diethyl ether. Concentration in vacuum gives 18g of a light brown oil purified by chromatography (Hexane/ Ethyl acetate 85/15) and provides 12.87 g of 4b as a colorless oil (92%).

Preparation of 11 (2-(5-Fluro-2-methoxy-phenyl)-cyclohex-1-enecarboxylic acid ethyl ester):
Under nitrogen, 2.5 g of 10b (8.26 mmoles), and 1.5 g (8.6 mmoles) of 5-fluor-2-methoxyphenyl boronic acid 9a are solubilised in 30 mL of toluene. 10 ml of Na₂CO₃ (2M in water) and 10 mL of EtOH are added followed by 340 mg of Pd(TPP)₄. The reaction mixture is stirred at 80°C for 90 min. then poured into sat. NH₄Cl solution and extracted with ethyl acetate. After concentration the remaining oil is purified by flash chromatography (Hexane/Ethyl acetate: 4/1). 11 is obtained as a yellow oil (2.13 g; 89%).

NMR ¹H (300MHz) : 0.9 ppm (t, 3H), 1.75 ppm (broad m, 4H); 2.35 ppm (broad m, 2H); 2.45 ppm (broad m, 2H); 3.8 ppm (s, H), 3.9 ppm (q, 2H), 6.7 ppm (dd, 1H); 6.8 ppm (dd, 1H); 6.9 ppm (dt, 1H).

Fluoro coumarin 12 (2-Fluoro-7,8,9,10-tetrahydro-benzo[c]chromen-6-one):

2.13 g of 8 (7.3 mmoles) are stirred at 0°C in 60 mL CH₂Cl₂. BBr₃ (10 mL; 1M in CH₂Cl₂) is slowly added at 0°C and the reaction is further stirred 30 min. at this temperature and 30 min. at rt.

Then once again cooled to 0°C, MeOH (10mL) is added and the reaction mixture is finally extracted with CH₂Cl₂ from water.

After concentration, the remaining solid is suspended in hexane then filtrated and washed with hexane to give 990 mg (62%) of 9 (Mp: 106-107°C).

NMR ¹H (300MHz) : 1.8 ppm (broad m, 4H); 2.60 ppm (m, 2H); 2.75 ppm (m, 2H); 7.1 to 7.4 ppm (m, 3H, aromatics).
NMR $^{13}\text{C}$ (300MHz in ppm) : 22.58; 22.86; 25.70; 26.50; 11.40; 119.40; 119.80; 122.70; 125.70; 148.40; 149.50; 158.60; 161.70; 162.11.

Synthesis of the coumarino-pyrimidine 1

**Preparation of the boronic acid 9d:**
(to use as a general preparation for the boronic acids 9e and 9f)

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{O} \\
& \quad 1 \text{) BuLi} & \quad \text{B(OH)}_2 \\
& \quad 2 \text{) B(OMe)}_3
\end{align*}
\]

11g of 2-chloro-4,6-dimethoxy-pyrimidin-5(6H)one (63 mmoles) in 300 mL of THF under nitrogen are cooled to $-78^\circ$C. Then 44 mL of nBuLi (1.6 M in Hexanes; 69 mmoles) is added dropwise over a 30 min. period. The mixture is stirred at this temperature for an other hour, warmed to $-10^\circ$C and stirred 30 min. more. At $-78^\circ$C, 13.1 g of trimethylborate (126 mmoles) in 40 mL THF are added dropwise. The reaction is kept at $-78^\circ$C one hour after the end of addition and one more hour at 0°C. The mixture is then poured into water and extracted with ethyl acetate. After concentration the solid residue is taken in hexane, and filtered. After washing (hexane) and drying (40°C, 20 mmHg overnight) 9b is obtained as white crystals (10g; 75%). Mp : 148-149°C

NMR $^1\text{H}$ (300MHz) : 4.1 ppm (s, 6H); 6.4 ppm (s, 2H, (OH)$_2$).

**Preparation of 17 (2-(2-Chloro-4,6-dimethoxy-pyrimidin-5-yl)-cyclohex-1-enecarboxylic acid ethyl ester):**

\[
\begin{align*}
\text{Cl} & \quad \quad \text{B(OH)}_2 \\
\text{THO} & \quad \quad \text{O} \\
& \quad \quad \text{Pd(TPP)}_4
\end{align*}
\]

Under nitrogen, 13.2g of 10b (43.6 mmoles), and 10g (45.7 mmoles) of 9d are solubilised in 300 mL of toluene. 64 ml of Na$_2$CO$_3$ (2M in water) and 64 mL of EtOH are added followed by 2.0g of Pd(TPP)$_4$. The reaction mixture is stirred at 80°C for 3
hrs. Then poured into NH₄Cl sat. and extracted with ethyl acetate. After concentration
the remaining oil is purified by flash chromatography (Hexane/Ethyl acetate 1/1). 17
is obtained as a yellow oil (12 g; 85%).

NMR ¹H (Brucker, 300MHz) : 1.0 ppm (t, 3H), 1.75 ppm (broad m, 4H); 2.25 ppm
(broad, 2H); 2. 5 ppm (broad, 2H); 3.9 ppm (s, 6H), 3.95 ppm (q, 2H).

**Coumarino-pyrimidine (2-Chloro-4-methoxy-5,6,7,8-tetrahydro-10-oxa-1,3-diaza-
phenanthren-9-one)** 1:

![Chemical structure of Coumarino-pyrimidine](image)

2.7 g of 14 (8.3 mmoles) are stirred under reflux in 60 mL CH₂Cl₂ with BBr₃ (41mL;
1M in CH₂Cl₂) for 16 hours. Then cooled to 0°C, MeOH (20mL) is added and the
reaction mixture is finally extracted with CH₂Cl₂ from water.
After concentration, the remaining solid is suspended in hexane then filtrated and
washed with hexane to give after drying 1.57 g (71%) of 15 (Mp: 184-186°C).

NMR ¹H (300MHz) : 1.8 ppm (broad m, 4H); 2.60 ppm (m, 2H); 3.0 ppm (m, 2H);
4.15 ppm (s, 3H).
ESMS m/z (relative intensity) : 267 (MH⁺; 100)