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# SYNTHESIS OF 3-FLUORO-2-METHYL-1(2H)-ISOQUINOLINONE.

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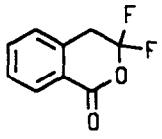
## SUMMARY

The title compound 9 is prepared in five steps from o-carboxy-benzaldehyde. In the key reaction, the amide functionality in N-methyl 2-(2,2-difluoroethenyl)-benzencarboxamide is silylated to afford the iminoester N-methyl 2-(2,2-difluoroethenyl)benzenetrimethyl silyl iminoester which cyclizes spontaneously to give the isoquinoline 9.

## INTRODUCTION

In 1985 Morikawa *et al.* described the synthesis of, *inter alia*, 3,3-difluoroisochroman-2-on **(1)** [1]. Their synthetic scheme relied on an iodolactonisation of methyl difluorovinyl benzoate **(2)**.

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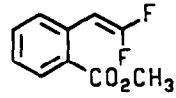


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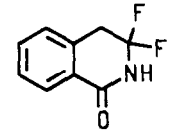


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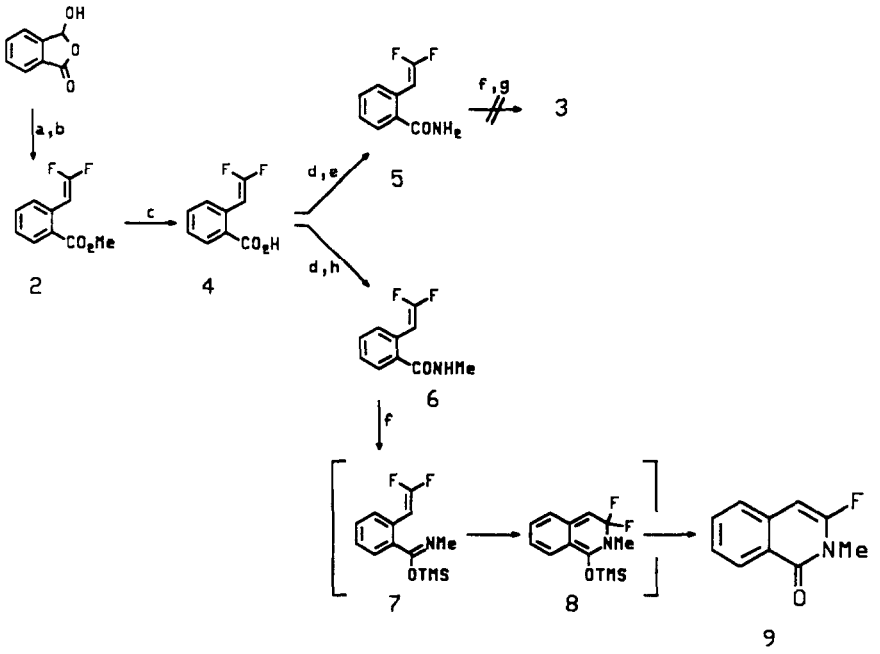
Recently we reported on our work directed towards the synthesis of these fluorinated lactone derivatives in general [2]. Our interest in the corresponding lactam analogue **3** with fluorine substitution next to the ring nitrogen atom has led us to investigate the utility of Morikawa's methodology for this purpose.

## SYNTHESIS

The difluorovinyl benzoic ester **2** [1] was hydrolyzed with trimethylsilyl iodide [3] to afford the corresponding carboxylic acid **4**. Sequential treatment of this acid with oxalyl chloride and then ammonia gave the amide **5**. In order to favour the desired N-C rather than O-C bond formation in the cyclisation step, the amide was silylated, and then treated with iodine according to the method of Knapp [4]. However, on work-up most of the starting material was recovered, together with a small amount of an unidentified compound. Longer reaction time and higher temperature led to destruction of the amide starting material.




a: *i*-$Pr_2NH$, MeI; b: $ClCF_2CO_2Na$, $Ph_3P$; c: $Me_3Si$-I; d: $(COCl)_2$, $HCONMe_2$; e: $NH_3$; f: $CF_3SO_3SiMe_3$, $Et_3N$, 4-$Me_2N$-$C_5H_4N$; g: $I_2$; h: $MeNH_2$ HCl, $Et_3N$.

Cyclisation could be achieved with the N-methyl analogue instead. Amide **6**, prepared by standard techniques from the acid **4**, was silylated; the course of the reaction was followed by $^{19}F$ NMR. The disappearance of the starting material **6** was accompanied by appearance of a product, whose $^{19}F$ NMR pattern did not correspond to the expected silyl iminoester **7**. Instead, the signals matched those of the unidentified product observed in the earlier attempted NH-amide cyclisation. The product was isolated and identified as 3-fluoro-2-methyl-1(2H)-isoquinolinone (**9**).

These findings suggest that the silyl iminoester **7** underwent rapid electrocyclic ring closure to give the intermediate **8**, which, on loss of trimethylsilyl fluoride, then gave the observed product **9** [5]. Both trimethylsilyl trifluoromethanesulfonate and triethylamine were required in this transformation.

## EXPERIMENTAL

NMR: Varian EM-390 or Bruker AM 360 spectrometer. $^1H$ chemical shifts are given in ppm relative to internal $Me_4Si$ ($\delta$); $^{19}F$ NMR shifts in ppm relative to internal $C_6F_6$ [$\Theta$=0; $\delta(CFCl_3)$= -163ppm]. UV: Cary 118 instrument. Microanalysis were conducted on a Perkin Elmer 240 CHN analyzer. All compounds described are new. Chromatography refers to the flash chromatography technique [6] on silica gel.

**2-(2,2-Difluoroethenyl)benzenecarboxylic acid (4).** A mixture of the ester **2** (3g, 15mmol) and $Me_3Si$-I (5mL, 35mmol) is heated under $N_2$ at 50°C for 1h, allowed to cool to room temperature, and then diluted with $Et_2O$. The solution is washed with 10% HCl containing enough $NaHSO_3$ to reduce all the iodine present, then with brine, and dried over $Na_2SO_4$ / $Na_2S_2O_5$. The solvent is removed *in vacuo* and the pale yellow residue is triturated with $CH_2Cl_2$ to give the title acid **4** as colourless needles. The supernatant is concentrated to yield a second crop of crystals; total amount 1.41g (51%); mp 123 - 125°C.
$^1H$ NMR ($CDCl_3$) $\delta$ 9.5-8.5 (1H, br, OH); 8.20 (1H, d, J= 7Hz, Ar); 7.7 - 7.2 (3H, m, Ar); 6.40 (1H, dd, J= 27, 5Hz, CH). $^{19}F$ NMR ($CDCl_3$, $C_6F_6$) $\Theta$ ABX: 80 (dd, J= 27, 5Hz) and 78 (br t, J= 27Hz).
Anal. Calcd. for $C_9H_6F_2O_2$: C 58.70, H 3.28; Found: C 58.32, H 3.40.

**2-(2,2-Difluoroethenyl)benzenecarboxamide (5).** To a solution of the acid **4** (0.370g, 2mmol) in dry $Et_2O$ (5mL) is added oxalyl chloride (0.22mL, 2.5mmol) and dimethylformamide (DMF, 1 drop). The mixture is stirred at room temperature for 45min. When gas evolution has ceased, a rapid stream of $NH_3$ is passed through the mixture for a few min. The mixture is then taken up in $Et_2O$ / $H_2O$, the resulting emulsion is filtered, the phases are separated and the aqueous layer is extracted with $Et_2O$. The combined organic phases are washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo.* The residue is purified by chromatography (eluant: $Et_2O$ / pentane, 19:1) to give the title amide **5**, (0.280g, 76%, recrystallized $CHCl_3$ / pentane); mp 133 - 135°C.
$^1H$ NMR ($CDCl_3$) $\delta$ 7.6-7.2 (4H, m, Ar); 6.3-5.8 (2H, br, $NH_2$); 5.90 (1H, dd, J= 27, 5Hz, CH). $^{19}F$ NMR ($CDCl_3$, $C_6F_6$) $\Theta$ ABX: 80 (dd, J= 27, 5Hz) and 79 (br t, J= 27Hz).
Anal. Calcd. for $C_9H_7F_2NO$: C 59.02, H 3.85; Found: C 59.16, H 4.06.

**N-Methyl 2-(2,2-difluoroethenyl)-benzenecarboxamide (6).** To a stirred solution of the acid **4** (0.650g, 3.5mmol) in dry $Et_2O$ (5mL) is added oxalyl chloride (0.39mL, 4.5mmol) and DMF (1 drop). The mixture is stirred for 1h at r.t., when no more gas is evolved. Methylamine hydrochloride (0.340g, 5mmol) and $Et_3N$ (7mL, 50mmol) are added. The mixture is stirred for 10min, then diluted with $Et_2O$ (20mL) and stirred further for 1h, poured into 1*N* HCl and extracted twice with $Et_2O$. The combined extracts are washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo.* The residue is purified by chromatography (eluant: $Et_2O$ / pentane; 3:2, then 4:1) to give amide **6** (0.380g, 55%), a pale yellow powder; mp 80 - 82°C.
$^1H$ NMR ($CDCl_3$) $\delta$ 7.7-7.2 (4H, m, Ar); 5.83 (1H, dd, J= 27, 5Hz, CH); 5.8 (1H, br, NH); 3.00 (3H, d, J= 5Hz, $CH_3$). $^{19}F$ NMR ($CDCl_3$, $C_6F_6$) $\Theta$ ABX: 80 (dd, J= 27, 5Hz) and 79 (br t, J= 27Hz). IR ($CHCl_3$) 3450 (NH), 1725 (C=C), 1660 (C=O) $cm^{-1}$.
Anal. Calcd. for $C_{10}H_9F_2NO$: C 60.91, H 4.60, N 7.10; Found: C 60.98, H 4.76, N 7.18.

**3-Fluoro-2-methyl-1(2H)-isoquinolinone (9).** To a solution of the amide **6** (0.150g, 0.76mmol) in $CH_2Cl_2$ (15mL) under $N_2$ are added $CF_3SO_3SiMe_3$ (0.16mL, 0.84mmol), $Et_3N$ (0.12mL, 0.84mmol), and 4-dimethylaminopyridine (1 cryst.). The mixture is stirred overnight at r.t., then diluted with $CH_2Cl_2$, washed

successively with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated *in vacuo.* The residue is purified by chromatography (eluant: $Et_2O$/hexane; 1:1) to give the title isoquinolinone derivative **9** (70mg,52%) as an off-white powder; mp 68-69°C. $^1H$ NMR ($CDCl_3$) $\delta$ 8.37 (1H, d, J= 7Hz, Ar); 7.8-7.2 (3H, m, Ar); 6.15 (1H, d, J= 7Hz, CH); 3.55 (3H, d, J= 3Hz, $CH_3$). $^{19}F$ NMR ($CDCl_3$, $C_6F_6$, 360MHz) $\Theta$ 60 (dq, J= 6.5, 3.0Hz). IR ($CHCl_3$) 1675, 1635 $cm^{-1}$. UV ($CH_3CN$) max ($\varepsilon$) 330 (3826), 282 (8888), 276 (8893), 244 (7351), 222 (16292), 207 (16102) nm; c= 3.8 $10^{-4}$ ($CH_3CN$).

Anal. Calcd. for $C_{10}H_8FNO$: C 67.79, H 4.55, N 7.91; Found: C 67.63, H 4.83, N 7.90.

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