

# Reactions of trifluorovinyl lithium and 1-chloro-2,2-difluorovinyl lithium: the synthesis of fluorinated heterocycles

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## Abstract

Trifluorovinyl lithium (from 1,1,1,2-tetrafluoroethane [HFC-134a]) reacted with 2-trifluoromethylaniline at  $-78^{\circ}\text{C}$  to give 1,2,3-trifluoroquinoline in moderate to good yield. In a similar reaction, 1-chlorodifluorovinyl lithium (from 1-chloro-2,2,2-trifluoroethane [HCFC-133a]) yielded 2-chloro-1,3-difluoroquinoline. © 1997 Elsevier Science S.A.

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## 1. Introduction

Polyfluoroquinolines are potentially important compounds as precursors to quinolone anti-bacterial agents [1]. They are not simple to prepare; however, recent reports by Streckowski and coworkers [2,3] described the production of 4-fluoroquinoline systems by a “one pot” reaction of excess amounts of organolithium reagents with 2-trifluoromethylaniline **5**. If this methodology could be adapted to trifluorovinyl lithium **2** [4] and chlorodifluorovinyl lithium **4** systems, it would provide an approach to the synthesis of polyhalogenated quinolines.

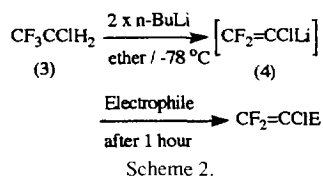
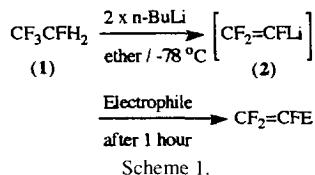
## 2. Results and discussion

We have recently reported [4] a new route for the generation of trifluorovinyl lithium **2** by the reaction of hydrofluorocarbon 1,1,1,2-tetrafluoroethane (134a) **1** with *n*-butyllithium (*n*-BuLi) at  $-78^{\circ}\text{C}$  (Scheme 1). This makes **2** much more accessible compared with previous routes [5]. The solvent used, reagent concentration and time elapsed before addition of the electrophilic trapping agent are all important factors in determining the reaction profile [4]. We discovered that the optimum reaction conditions required the addition of the electrophile to a dilute solution of trifluoro-

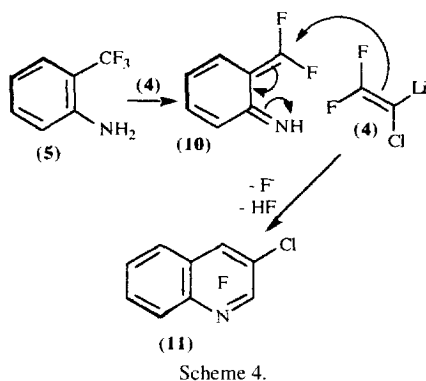
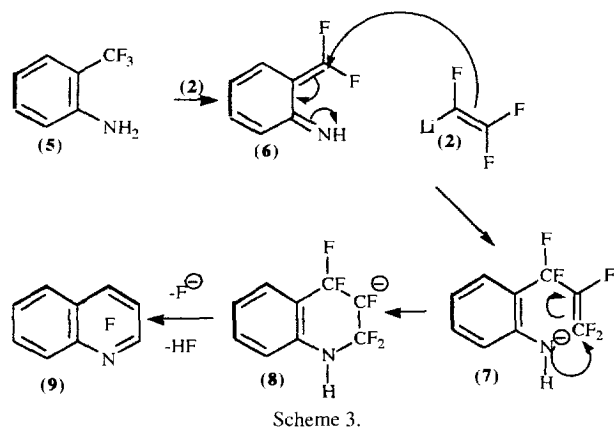
vinyl lithium **1** h after it had been generated “in situ” by the addition of *n*-BuLi in hexane to a dilute solution of **1** in dry ether at  $-78^{\circ}\text{C}$ .

We now report the successful generation and subsequent reaction of 1-chloro-2,2-difluorovinyl lithium **4**, previously reported by Tarrant et al. [5] using a much more complicated route, from the hydrochlorofluorocarbon 1-chloro-2,2,2-trifluoroethane (133a) **3** under the same conditions as described for **1** (Scheme 2).

When 2-trifluoromethylaniline **5** is reacted with an excess of **2** at  $-78^{\circ}\text{C}$ , 2,3,4-trifluoroquinoline **9** is produced. We suggest that, in the first step of the reaction, the vinyl lithium **2** reacts as a base with the aniline **5** forming the imine **6** in a manner analogous to that suggested by Streckowski et al. [3] (Scheme 3). The nucleophilic susceptibility of the difluorovinyl group [6] in the imine **6** means that this species is not



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isolated, but reacts with the excess **2** present to form the anion **7**, which intramolecularly cyclizes to generate the anion **8**. Loss of fluoride ion and hydrogen fluoride from **8** affords the quinoline **9** which has a mass peak at an  $m/z$  value of 183 [ $M^+$ ] in the mass spectrum and three fluorine signals in the  $^{19}\text{F}$  nuclear magnetic resonance (NMR) spectrum at  $-77$ ,  $-131$  and  $-165$  ppm. These signals are attributable to fluorine atoms ortho, para and meta to the nitrogen group in the quinoline ring. Four hydrogen signals are present in the  $^1\text{H}$  NMR spectrum and nine carbon signals in the  $^{13}\text{C}$  NMR spectrum, of which three have doublet coupling constants of 240 Hz or more. These combined data suggest that 2,3,4-trifluoroquinoline **9** is successfully synthesized (Scheme 3). Accurate mass measurement on a purified sample confirms the structure.

When the aniline **5** is reacted as described above with an excess of the vinyl lithium **4**, the product has mass peaks at  $m/z$  values of 201 and 199 (ratio 1 : 3) in the mass spectrum, indicating the presence of one chlorine atom, and two signals in the  $^{19}\text{F}$  NMR spectrum at  $-63$  and  $-107$  ppm, consistent with fluorine atoms ortho and para to the nitrogen atom in the quinoline ring. Four hydrogen signals are present in the  $^1\text{H}$  NMR spectrum and nine carbon signals in the  $^{13}\text{C}$  NMR spectrum, of which two have coupling constants of 240 Hz or more. The compound is assigned as 3-chloro-2,4-difluoroquinoline **11**. The chlorine atom in the 3 position proves that the attack by the second organolithium species **4** proceeds by

nucleophilic addition onto the difluoro-substituted end of the double bond in the intermediate imine **10** (Scheme 4).

### 3. Experimental details

Compounds **1** and **3** were provided by ICI Klea Business and *o*-trifluoromethylaniline and *n*-BuLi, 2.5 M in hexanes, were purchased from Aldrich. All the reactions involving **1** and **3** were performed under an atmosphere of dry nitrogen in three-necked, round-bottomed flasks fitted with a septum, a stopper and an acetone–solid  $\text{CO}_2$  condenser, and cooled in a  $\text{CO}_2$ –acetone bath unless stated otherwise. Crude reaction mixtures were purified by flash column chromatography using Sorbsil C60 (40–60 mm) H hydrated silica, followed by preparative thin layer chromatography using glass-backed Kieselgel 60  $\text{F}_{254}$  20 cm  $\times$  20 cm silica gel plates. The  $^{19}\text{F}$  NMR spectra were obtained on a JEOL FX90Q spectrometer with  $\text{CFCl}_3$  as internal standard, and the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker 8C300 spectrometer with tetramethylsilane (TMS) as internal standard. The mass spectral work was carried out on a Kratos Profile gas chromatography/mass spectrometry (GC/MS) machine.

#### 3.1. Preparation of trifluorovinyl lithium **2**

A 100  $\text{cm}^3$  flask was charged with anhydrous ether (40  $\text{cm}^3$ ) and an excess of **1** (2–3  $\text{cm}^3$ , 20–30 mmol). To this stirred mixture was added *n*-BuLi (2.5 M in hexanes, 8  $\text{cm}^3$ , 20 mmol) over 30 min using a syringe pump, and the reaction was left to stir for 1 h with the temperature maintained between  $-78$  and  $-70$   $^\circ\text{C}$ . This reaction mixture was then ready to use in the other experiments (reagents were added directly to this system unless otherwise stated).

#### 3.2. Preparation of 2,3,4-trifluoroquinoline **9**

2-Trifluoromethylaniline **5** (0.8 g, 5 mmol) was added to a solution of **2** (20 mmol) at  $-78$   $^\circ\text{C}$  and the reaction was left to stir for 3 h with slow warming to room temperature.

Hydrochloric acid (5%, 50  $\text{cm}^3$ ) was then added, the organic layer was separated and the aqueous layer was extracted with dichloromethane ( $3 \times 50$   $\text{cm}^3$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and the solvent was removed by vacuum transfer. Most of the impurities were removed by column chromatography using a hexane–ether solvent gradient, followed by preparative thin layer chromatography using hexane–ether (10 : 1) as eluent. Yield, 0.5 g; m.p., 49–54  $^\circ\text{C}$ . NMR spectra (in  $\text{CDCl}_3$ ):  $^1\text{H}$ : 7.65 (t, 1H,  $J=8.5$ ), 7.75 (t, 1H,  $J=8.5$ ), 7.95 (d, 1H,  $J=8.5$ ), 8.05 (d, 1H,  $J=8.5$ );  $^{13}\text{C}$ : 121 (s), 123 (dd,  $J=30.9$  and 10.7), 127 (s), 128 (s), 131 (s), 132 (ddd,  $J=264$ , 35.82 and 12.6), 141 (m,  $J=17.7$ , 5.2 and 4.8), 151 (m,  $J=240.8$ , 13.9 and 5.3), 152 (m,  $J=268.7$ , 8.0 and 7.9);  $^{19}\text{F}$ : 77 (t, 1F,  $J=27.4$  and 24.8), 131 (dd, 1F,  $J=24.8$  and 15.2), 165 (dd, 1F,  $J=27.4$  and 15.2). Mass spectrum: 183 ( $M^+$ ), 164

(M – F<sup>+</sup>). Precise mass *m/z*: 183.028845 (calculated mass: 183.029584).

### 3.3. Preparation of 1-chloro-2,2-difluorovinyl lithium **4**

A 100 cm<sup>3</sup> flask was charged with anhydrous ether (40 cm<sup>3</sup>) and excess **3** (2–3 cm<sup>3</sup>, 20–30 mmol). To this stirred mixture was added *n*-BuLi (2.5 M in hexanes, 8 cm<sup>3</sup>, 20 mmol) over 30 min using a syringe pump, and the reaction was left to stir for 1 h with the temperature maintained between –78 and –70 °C. This system was then ready to use in the other experiments (reagents were added to this reaction mixture).

### 3.4. Preparation of 3-chloro-2,4-fluoroquinoline **11**

The aniline **5** (1.61 g, 10 mmol) was added to a solution of **4** (40 mmol) at –78 °C and the reaction was left to stir for 3 h with slow warming to room temperature. Hydrochloric acid (5%, 40 cm<sup>3</sup>) was added to the organic layer, separated and the aqueous layer was extracted with dichloromethane (2 × 25 cm<sup>3</sup>). The combined organic layers were dried (MgSO<sub>4</sub>), filtered and the solvent was removed by vacuum transfer. Most of the impurities were removed by column chromatography using a hexane–ether solvent gradient, followed by preparative thin layer chromatography using hexane–ether (10 : 1) as eluent. Yield, 0.67 g; m.p., 84–87 °C. NMR spectra (in CDCl<sub>3</sub>): <sup>1</sup>H: 7.6 (dt, 1H, *J* = 1 and 7.5), 7.8 (dt, 1H, *J* = 1.5 and 7.5), 7.95 (d, 1H, *J* = 8.5), 8.05 (dd, 1H, *J* = 1 and 8.5); <sup>13</sup>C: 102 (dd, *J* = 42.8 and 17.9), 118 (dd, *J* = 14.4 and 2.9), 120 (d, *J* = 2.6), 127 (s), 128 (d, *J* = 1.47), 131 (s), 143 (dd, *J* = 18.3 and 6.8), 155 (dd, *J* = 239.4 and 5.4), 161 (dd, *J* = 269.7 and 7.1); <sup>19</sup>F: 63 (d,

1F, *J* = 21.3), 107 (d, 1F, *J* = 22.3). Mass spectrum: 201 (<sup>37</sup>ClM<sup>+</sup>), 199 (<sup>35</sup>ClM<sup>+</sup>), 164 (M – Cl<sup>+</sup>). Precise mass *m/e*: 199.000315 (calculated: 199.000033).

## 4. Conclusions

We have shown that 1,2,3-trifluoroquinoline and 2-chloro-1,3-difluoroquinoline can be synthesized from the readily available HFC-134a and HCFC-133a respectively. A wide range of substituted chlorodifluoroquinolines and trifluoroquinolines may therefore also be prepared using suitable aminobenzotrifluorides as starting materials.

## Acknowledgements

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