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Selective direct fluorination of quinoline derivatives

Richard D. Chambers[a,*], Darren Holling[a], Graham Sandford[a,*], Horst Puschmann[b], Judith A.K. Howard[b]

[a]*Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, UK*
[b]*Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, UK*

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Dedicated to Professor Lev M. Yagupolskii on the occasion of his 80th birthday.

Abstract

Direct fluorination of various quinoline derivatives in acidic reaction media gives fluorinated quinoline products arising from selective, efficient electrophilic substitution processes.

Keywords: Fluorine; Quinoline; Selective fluorination

1. Introduction

Selectively fluorinated quinoline derivatives can have valuable biological activity and a number of commercially significant pharmaceuticals [1], such as Ciprofloxacin (anti-bacterial) and 5-fluoroprimoquine [2] (anti-malarial) make use of such properties. However, syntheses of quinoline systems that bear a fluorine substituent on the benzenoid ring are not trivial and normally involve multi-step sequences either starting from non-quinolinoid precursors (Skraup synthesis [2]) or by fluorination of appropriate chloro-quinolines (Halex reaction [3]) or amino-quinolines (Balz–Schiemann reaction [4]). The selective replacement of hydrogen by fluorine offers a more direct strategy for the synthesis of fluoro-quinolines and a limited number of electrophilic fluorination processes involving the use of XeF_2, [5] CF_3OF [6] and AcOF [7] have been reported in this context.

Direct selective fluorination of heterocycles by elemental fluorine has remained undeveloped despite the fact that 5-fluorouracil, a potent anti-cancer agent, is synthesised on a commercial scale by direct fluorination methodology [1] thus indicating the feasibility and opportunities of such an approach. Also, direct fluorination of various pyridine derivatives [8] and the fluorination of quinoline and quinoxaline systems at sites adjacent to the heteroatom using fluorine/iodine mixtures [9] have been established.

We previously reported that direct selective fluorination of a range of aromatic systems could be achieved when acids, such as formic and sulphuric, were used as reaction media [10] and here, we report that direct fluorination of quinoline derivatives can also be performed in acidic media, thus, providing efficient and synthetically viable routes to these systems.

Fluorination of various quinoline derivatives was achieved by passing fluorine, diluted by nitrogen (10% v/v), through a cooled (0–5 °C) mixture consisting of the quinoline derivative and concentrated sulphuric acid. After work-up all the fluorinated products shown in the table were isolated by column chromatography except for compounds **3** and **11**. Conversions and yields, estimated by ^{19}F NMR analysis of the crude product mixture with reference to a trifluormethyl-benzene standard, of the fluorination reactions are collected in the Table 1.

In all cases, selective fluorination occurred on the benzenoid ring and we attribute this to deactivation of the heterocyclic ring towards electrophilic attack by the protonation of the heteroatom in the strongly acidic reaction medium. In contrast, in neutral medium, such as acetonitrile, the fluorination of quinoline gave many products and a significant amount of tarry material.

Hydrogen/deuterium exchange studies have established [11] that the positional order for electrophilic substitution in quinoline dissolved in strong acid media is $8 > 5$,

* Corresponding author. Tel.: +191-3744639.
E-mail addresses: graham.sandford@durham.ac.uk, r.d.chambers@durham.ac.uk (R.D. Chambers).

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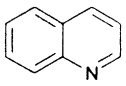
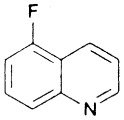
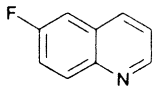
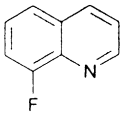
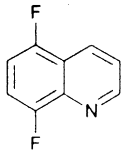
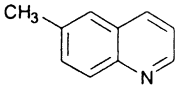
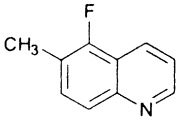
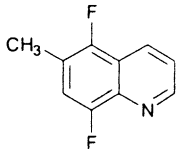
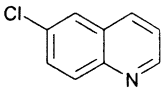
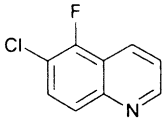
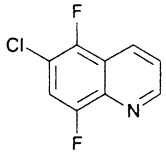
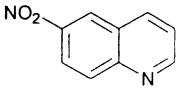
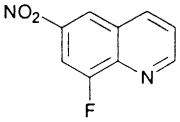
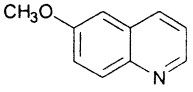
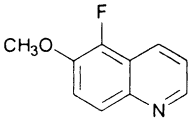
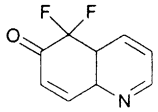
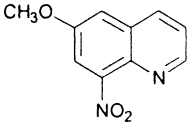
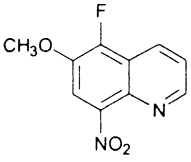
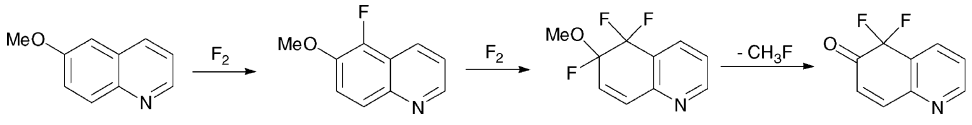
Table 1
Quinoline derivative $\xrightarrow[\text{conc.}H_2SO_4,\,5\,^{\circ}C]{10\%\,F_2\,\text{in}\,N_2\,(v/v)}$ fluoro − quinoline products

Substrate	Conversion	Product yield (%)	
 **1**	67	 **2**, 27%	 **3**, 8%
		 **4**, 14%	 **5**, 32%
 **6**	54	 **7**, 75%	 **8**, 5%
 **9**	59	 **10**, 75%	 **11**, 5%
 **12**	13	 **13**, 86%	
 **14**	51	 **15**, 74%	 **16**, 26%
 **17**	56	 **18**, 99%	

$6 > 7 > 3$, i.e. sites adjacent to the pyridyl ring (5 and 8) are the most reactive. Therefore, the results of direct fluorination reactions of quinoline derivatives give products that are consistent with an electrophilic aromatic substitution process. For example, fluorination of quinoline **1** yields products **2–5** resulting largely from substitution at the 5 and 8 positions and fluorination of 6-methylquinoline **6** gives 5 rather than 7-fluoro-substitution.



Scheme 1.

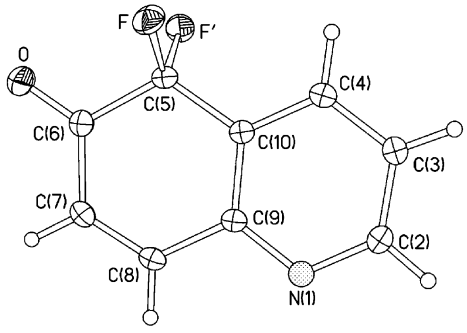


Fig. 1.

However, fluorination of 6-methoxyquinoline **14** gave a mixture of two products which could be identified as the mono- and difluorinated compounds **15** and **16**.[1] The yield of **16**, which was identified by X-ray crystallography (Fig. 1) could be increased by simply passing an excess of fluorine through the reaction mixture and a proposed mechanism for its formation is given in Scheme 1.

Direct selective fluorination of quinoline derivatives, therefore, provides effective methodology for the synthesis of fluorinated heterocyclic analogues and the application of this new methodology to the synthesis of related fluoro-heteroaromatic derivatives is in progress.

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[1] *5,5-Difluoro-5-hydroquinolin-6-one*: yellow solid; m.p. 105–107 °C; (found: C, 59.7; H, 2.8; N, 7.8. C_9H_5FNO requires C, 59.7; H, 2. 8; N, 7.7%); δ_H: 8.75 (1H, dq, $^3J_{HH}$ 4.8 $^4J_{HH}$ 1.2, H-2), 8.10 (1H, dm, $^4J_{HF}$ 8.1, H-4), 7.64 (1H, d, $^3J_{HH}$ 10.4, H-8), 7.44 (1H, dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 9.2, H-3), 6.46 (1H, dt, $^3J_{HH}$ 10.4 $^4J_{HF}$ 4.0, H-7); δ_F –102.4 (s); δ_C 186.2 (t, $^2J_{CF}$ 24.2, C-6), 152.8 (t, $^5J_{CF}$ 1.9, C-2), 149.3 (t, $^3J_{CF}$ 6.1, C-8a), 146.9 (s, C-8), 134.7 (t, $^3J_{CF}$ 2.7, C-4), 129.7 (t, $^2J_{CF}$ 24.3, C-4a), 126.8 (t, $^3J_{CF}$ 2.7, C-7), 124.4 (s, C-3), 104.9 (t, $^1J_{CF}$ 245.0, C-5); *m/z* (EI^+) 181 (M^+, 100%), 153 (82); X-ray crystallography (selected data). Temp. 100(2) K, λ = 0.71073 Å, orthorhombic, Pnma, a = 12.2462(9) Å, b = 6.6912(5) Å, c = 9.1757(7) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 751.87(10) Å^3, density (calc.) = 1.600 g/cm^{-3}, R(int) = 0.0527, crystal size = 0.4 mm × 0.4 mm × 0.4 mm.