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Direct fluorination of coumarin, 6-methyl-coumarin and 7-alkoxy-coumarins

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Abstract

Direct fluorination of coumarin in acid media led to complex mixtures of products arising from electrophilic substitution processes. Fluorination of 6-methyl- and 7-alkoxy-coumarins was, however, more selective and preparatively useful quantities of various fluorinated systems were obtained.

Keywords: Selective fluorination; Fluorine; Heterocycles; Coumarin; Electrophilic substitution

1. Introduction

Efficient methodology for the synthesis of selectively fluorinated heteroaromatic systems is a high research priority in organofluorine chemistry [1,2], partly because of the increasing number of valuable, biologically active life science products that contain fluorinated heteroaromatic moieties [3].

Synthetic procedures for the preparation of fluorinated heterocycles include substitution of diazo groups (Balz–Schiemann reaction) or chlorine (halogen exchange) by fluorine or cyclisation strategies involving acyclic fluorinated 'building blocks' [1,2,4–6]. However, synthesis of the necessary functionalised precursors can sometimes be very complex and time consuming and, therefore, a more convenient approach to the synthesis of fluorinated heteroaromatic derivatives is, potentially, the selective transformation of carbon–hydrogen bonds to carbon–fluorine bonds in reactions involving electrophilic fluorinating agents.

At Durham [7,8], we are developing the use of elemental fluorine as a viable reagent for organic synthesis and, in the context of synthesizing fluorinated heteroaromatic derivatives, we have reported direct fluorination reactions of quinoline derivatives [9] and halogen mediated direct fluorination of various pyridine and quinoxaline systems [10].

Various papers describing the synthesis of fluorinated coumarins (2*H*-chromen-2-ones), involving Balz–Schiemann [11], halogen exchange [12] and cyclisation approaches [13–16] (Pechmann, Knoevenagel, etc.) have been published. Electrophilic fluorination of coumarin by acetyl hypofluorite, giving 3-fluoro-coumarin, was described by Rozen et al. [17] and reaction of various substituted coumarin systems with Selectfluor™ also yielded appropriate 3-fluoro derivatives [18]. Rozen also demonstrated [19] that reaction of coumarin with fluorine in a mixture of chloroform, trichlorofluoromethane and ethanol at low temperature gave a difluorinated product which, after dehydrofluorination during purification, yielded 3-fluoro-coumarin in overall good yield.

Acids, such as formic and sulfuric acid, are effective reaction media for fluorination processes [7] and, here, we extend our studies on direct fluorination of heteroaromatic

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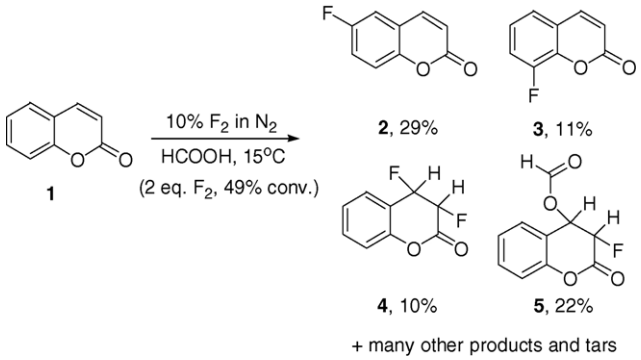


Scheme 1.

systems and report our investigations concerning the fluorination of various coumarin derivatives in acidic reaction media.

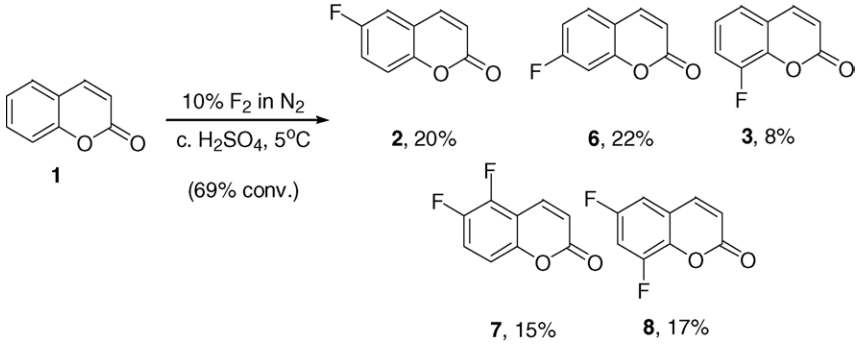
2. Results and discussion

Fluorination of coumarin **1** in formic acid gave a very complex mixture consisting of many products from which four major products **2**–**5** could be identified and their yields estimated by ^{19}F NMR, by comparison with literature data [17,19] (Scheme 1). Whilst products arising from fluorination on the aryl ring predominate, significant quantities of products from electrophilic addition of fluorine or formyl fluoride to the carbon-carbon double bond of the heterocyclic ring were observed.

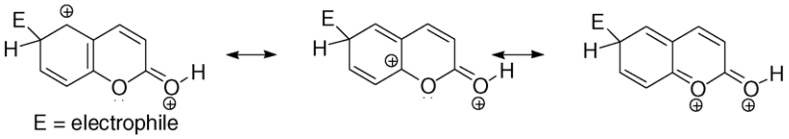
Fluorination of coumarin **1** in sulfuric acid gave five major products, as observed by ^{19}F NMR, but, in this case, no tarry material was obtained (Scheme 2). In this reaction medium, only trace quantities of products arising from fluorination of the hetero-ring were observed, indicating that protonation of the oxygen atom by the strongly acidic medium is sufficient to deactivate the hetero-ring towards electrophilic attack by fluorine.

Isolation of pure fluorocoumarin products from the complex product mixture was extremely difficult but column chromatography, followed by preparative HPLC, allowed the isolation of trace quantities of **3** and **7**, which were both identified unambiguously by X-ray crystallography (Fig. 1). Other products were identified by ^{19}F NMR, by comparison to literature data [11,17,19,20], although pure samples could not be obtained.

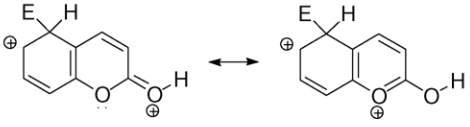
It has previously been established that electrophilic substitution on coumarin under highly acidic conditions occurs preferentially at the 6- and 8-positions, although substitution at other sites can compete effectively [11,21]. A consideration of the natures of the carbocationic intermediates, in which charge is located on carbon sites adjacent to ring oxygen providing significant enhanced stabilisation, explains this preferred regiochemistry (for substitution at position 6, for example, see Scheme 2). On the other hand, electrophilic attack at the 5 and 7 positions would result in some charge delocalisation on heterocyclic ring oxygen and



Substitution at 6-position in strong acid media



Substitution at 5-position in strong acid media



Scheme 2.