Direct fluorination of the anthraquinone nucleus: scope and application to the synthesis of novel rhein analogues

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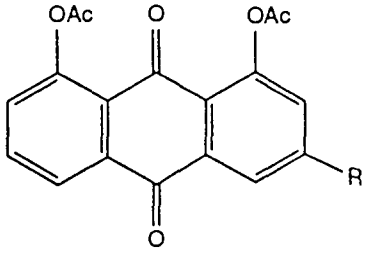
Abstract

Direct fluorination of the functionalised anthraquinone dimethyl rhein methyl ester with Selectfluor™ proceeds regioselectively, providing a concise approach to fluorinated compounds of potential medicinal interest. This represents a new use for Selectfluor™ which hitherto has only been used for fluorinating relatively activated compounds.

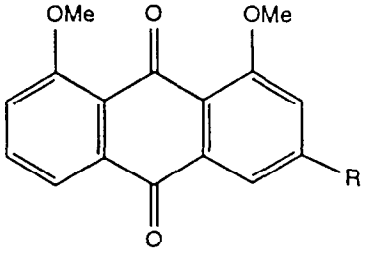
Introduction

Medical treatment of osteoarthritis (OA) commonly involves the use of non-steroidal anti-inflammatory drugs which realistically are not a cure, merely a means of pain relief [1]. One recent novel treatment for OA is the use of the anthraquinone carboxylic acid diacetyl rhein (**1**) [2], marketed in Italy since 1986.

Of some interest was the synthesis of analogues of **1**, particularly ring fluorinated analogues, for *in vitro* and *in vivo* profiling. Whilst synthesis of fairly simple anthraquinones can be brief [3], the *de novo* preparation of polysubstituted anthraquinone carboxylic acids commonly involves tedious multistep sequences [4], something we wished to avoid in this instance. Our strategy was to investigate the direct fluorination of a number of anthraquinones to assess the synthetic viability of a brief route to compounds of interest. A reagent which particularly appealed was the recently described Selectfluor™ (**6**) [5], a shelf-stable, easily handled, relatively non-hazardous reagent, available commercially†. A particular point to bear in mind is that the extremely poor solubility of anthraquinones in organic solvents at low temperatures†† makes the use of more reactive fluorinating species, e.g. $CsSO_4F$, non-viable on a multigram scale.

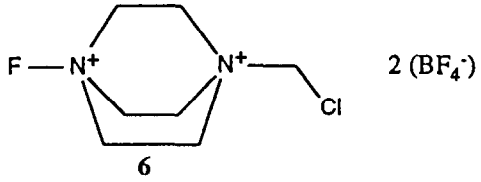


1 R = CO_2H **2** R = CH_2OAc



3 R = CO_2H **4** R = H

5 R = CO_2Me



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Results and discussion

Treatment of diacetyl rhein (**1**)* or dimethyl rhein (**3**) [6] with **6** (1 equiv.) in acetonitrile at reflux or in

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†Information on the reagent and its uses can be obtained from: The Commercial Development Manager, Corporate Technology – Europe, Air Products, PLC, European Technology Group, Chineham, Basingstoke, Hants RG24 0FE, UK.

††For example, the solubility of diacetyl rhein (**1**) in dimethyl formamide is *c.* 5 g l^{-1} at −15 °C.

*Diacetyl rhein is available commercially.

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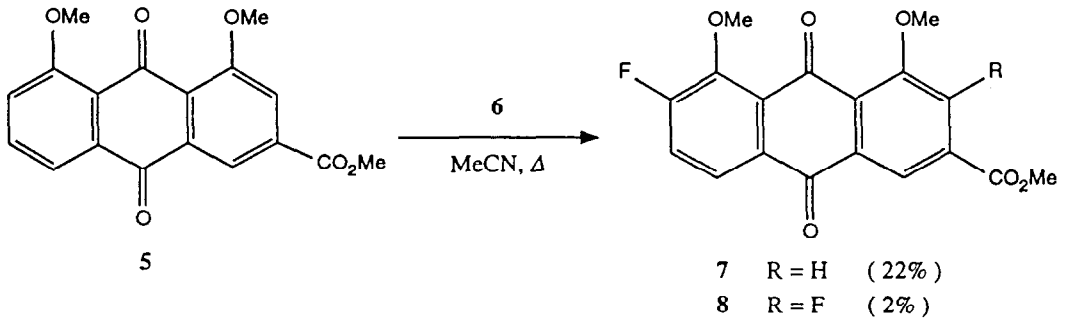

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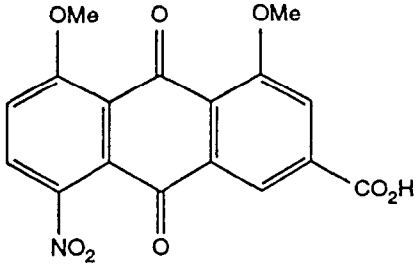
Scheme 1.

dimethylformamide at 100 °C failed to produce any fluorinated products, starting material being recovered in each instance. Reaction of triacetyl aloe emodin (**2**)*, with **6** in acetonitrile at reflux produced a mixture of two fluorinated products, but unambiguous identification was not possible. This was due to the chromatographic lability of the acetyl groups and the difficulty in assignment in the resulting mixture of non-, mono- and di-acylated materials. The more reactive dimethyl danthrone (**4**) unfortunately produced a multitude of fluorinated products under typical reaction conditions.

In a final search for some selectivity in this series (coupled with chromatographic stability of a product), reaction of dimethyl rhein methyl ester (**5**) with **6** was investigated. Reaction did proceed, albeit slowly (acetonitrile, reflux, 10 d), yielding after chromatography a monofluorinated compound **7** and a difluorinated compound **8** in 22% and 2% isolated yields, respectively (Scheme 1). The positions of incorporation of the fluorine were established by ^{1}H NMR techniques, including nuclear Overhauser effect difference experiments using the OMe and CO_2Me groups as sites for irradiation.

Whilst the yield of the monofluorinated product **7** is unremarkable, the brevity of this approach (three steps from **1**) to the fluorinated analogues of diacetyl rhein offers a considerable advantage over *de novo* syntheses. It is encouraging to report that Selectfluor™ (**6**) is able to fluorinate the somewhat deactivated anthraquinone nucleus (even with the methoxy substituents present, halogenation of **3** or **5** is a non-trivial matter indicating the lack of reactivity of the carboxylic acid series) even though selectivity seems to be confined to substrate **5**.

This short note adds to the growing literature on the use of **6**, and demonstrates that the reagent can fluorinate species other than enol acetates, silyl enol ethers, carbanions, xylenes or vinyl stannanes [5]. Two final points are of interest; firstly, the position of incorporation of the second fluorine in **8** is unusual in that it is a sterically encumbered site which one would not anticipate a reagent with the bulk of **6** being able to reach; secondly, nitration of dimethyl rhein (**3**) ($KNO_3/H_2SO_4/-10$ °C) provides the isomer **9** almost exclusively [7].



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Experimental

A stirred suspension of methyl 4,5-dimethoxy-9,10-anthraquinone-2-carboxylate (**5**) (10.0 g, 30.6 mmol) and Selectfluor™ (**6**) (21.0 g, 2.56 mmol F^+/g 53.4 mmol) in dry acetonitrile (125 cm^3) was brought to reflux and maintained at this temperature for 10 d. Additional portions of **6** were added during this time (8.0 g, 20.5 mmol after 66 h; 6.9 g, 17.7 mmol after 90 h; and 6.1 g, 15.6 mmol after 140 h). The suspension was allowed to cool to room temperature, the solid filtered off and washed well with dichloromethane. Concentration of the red filtrate *in vacuo* yielded a solid (18 g). This was suspended in dichloromethane (50 cm^3) and applied to a pad of 'flash' silica (10 cm × 8 cm), eluting with ethyl acetate. This provided a yellow foam that was rechromatographed on 'flash' silica, eluting with ethyl acetate–hexane (1:1), yielding firstly methyl 3,6-difluoro-4,5-dimethoxy-9,10-anthraquinone 2-carboxylate (**8**) (250 mg, 2%), m.p. 204.5–206 °C. Analysis: Found: C, 59.44; H, 3.39; F, 10.35%. $C_{18}H_{12}F_2O_6$ requires: C, 59.68; H, 3.34; F, 10.49%. IR ν_{max} (KBr) (cm^{-1}): 1718; 1675. ^{1}H NMR ($CDCl_3$, 300

*Aloe emodin is available commercially.

MHz) δ: 8.55 (1H, d, $J_{HF}=6.5$ Hz, H1); 8.05 (1H, dd, $J_{HH}=8.5$, $J_{HF}=5.0$ Hz, H8); 7.47 (1H, dd, $J_{HF}=10.5$, $J_{HH}=8.5$ Hz, H7); 4.13 (3H, d, $J_{HF}=1.0$ Hz, OMe); 4.12 (3H, d, $J_{HF}=1.5$ Hz, OMe); 4.01 (3H, s, CO_2Me) ppm. MS *m/z*: 363 ($[M+H]^+$, 100%); 347 (6). Eluted second was methyl 4,5-dimethoxy-6-fluoro-9,10-anthraquinone 2-carboxylate (7) (2.32 g, 22%), m.p. 199–201 °C. Analysis: Found: C, 62.70; H, 3.71; F, 5.81%. $C_{18}H_{13}FO_6$ requires: C, 62.80; H, 3.80; F, 5.52%. IR ν_{max} (KBr) (cm^{-1}): 1719; 1677. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.47 (1H, d, $J=1.5$ Hz, H1); 8.03 (1H, dd, $J_{HH}=8.5$, $J_{HF}=5.0$ Hz, H8); 7.95 (1H, d, $J=1.5$ Hz, H3); 7.43 (1H, dd, $J_{HF}=10.0$, $J_{HH}=8.5$ Hz, H7); 4.11 (3H, d, $J_{HF}=1.0$ Hz, 5-OMe); 4.09 (3H, s, 4-OMe); 4.00 (3H, s) ppm. MS *m/z*: 345 ($[M+H]^+$, 100%); 329 (10).

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References

1 For three recent reviews on approaches to tackling OA see: C.B. Caputo and A. Shaw, *Annu. Rep. Med. Chem., 22* (1987) 179; S.L. Carney, *Drug News Perspect., 6* (1993) 69; G. Di Pasquale, *Inflam. Dis. Ther., 12* (1993) 475.
2 C.A. Friedmann, *Ger. Offen. 2 711 493* (1977); [*Chem. Abs., 88* (1977) P37 504k].
3 For example: A.C. Bellaart and C. Koningsberger, *Recl. Trav. Chim. Pays-Bas, 79* (1960) 1289; K. Krohn, *Liebigs Ann. Chem.,* (1981) 2285.
4 For example: C.W. Smith, S.J. Ambler and D.J. Steggles, *Tetrahedron Lett., 34* (1993) 7447; P.T. Gallagher, T.A. Hicks, A.P. Lightfoot and W.M. Owton, *Tetrahedron Lett., 35* (1994) 289.
5 R.E. Banks, S.N. Mohialdin-Khaffaf, G.S. Lal, I. Sharif and R.G. Syvret, *J. Chem. Soc., Chem. Commun.,* (1992) 595; R.E. Banks (to Air Products and Chemicals, Inc.), *US Pat. 5 086 178* (1992); [*Chem. Abs., 116* (1992) P194 355b]; M.A. McClinton and V. Sik, *J. Chem. Soc., Perkin Trans. 1* (1992) 1891; G.S. Lal, *J. Org. Chem., 58* (1993) 2791; D.P. Matthews, S.C. Miller, E.T. Jarvi, J.S. Sabol and J.R. McCarthy, *Tetrahedron Lett., 34* (1993) 3057.
6 R. Robinson and J.L. Simonsen, *J. Chem. Soc., 95* (1909) 1085.
7 M. Brunavs, unpublished work.