Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1537–1540

A simple route to 6- and 7-fluoro-substituted naphthalene-1-carboxylic acids

Thomas M. Krülle,* Oscar Barba, Susan H. Davis, Graham Dawson, Martin J. Procter, Thomas Staroske and Gerard H. Thomas

Prosidion Limited,† Watlington Road, Oxford OX4 6LT, UK

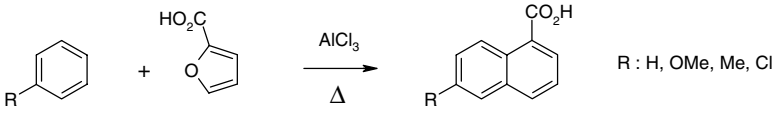
Received 5 November 2006; revised 19 December 2006; accepted 4 January 2007
Available online 7 January 2007

Abstract—A simple one-pot method for the synthesis of 6-fluoro- and 6,7-difluoro-1-naphthoic acid is described. 6-Fluoro-1-naphthoic acid can be converted into 7-fluoro-1-naphthoic acid in three straightforward steps.

Fluorine substitution at the site of metabolic oxidation in aromatic and heteroaromatic rings is a tool in medicinal chemistry, which may increase the stability of compounds.[1] Although fluorinated benzene derivatives are used extensively and are often commercially available, fluorinated naphthalene derivatives have seen only a limited use. Synthetic routes via tetralones are an unambiguous and well established way to achieve 6- or 7-fluoro substitution patterns in 1-naphthyl derivatives.[2–5] Subsequent cyanide addition to the ketone group for example, followed by dehydration, aromatisation and then nitrile hydrolysis allows the introduction of a carboxylic acid at C-1.[6] Employment of fluorophenyl acetic acids achieves an early introduction of the carboxylate moiety but the aromatisation step is more complicated and some transformations involve the use of diastereomeric mixtures.[7]

We herein describe a convenient and simple synthetic route to achieve 6- and 7-fluoro substitution in 1-naphthoic acids. In addition to its simplicity, this method is particularly attractive as it circumvents the handling of potentially carcinogenic β-aminonaphthalenes in a Balz-Schiemann introduction of the fluorine atoms to the naphthalene core.[8,9] The direct formation of 1-naphthoic acids using benzene derivatives, 2-furanoic acid and aluminium chloride has been described previously[10] (Scheme 1). The use of methyl furoate instead of the acid seems to increase the overall yield in the case of chlorobenzene although the ester is partially hydrolysed during the work-up.[11]

We found that the application of this procedure to fluorobenzene[12] gives remarkably pure 6-fluoro-1-naphthoic acid **1**[13] in one step without the need for chromatographic purification or further derativisation.[14] 1,2-Difluorobenzene underwent a similar cyclisation with 6,7-difluoro-1-naphthoic acid **2**[15] being obtained in a slightly lower yield. Interestingly, this reaction does not allow the incorporation of a bromine atom into the final naphthalene. Attempted cyclisations with bromobenzene and 1-bromo-4-fluorobenzene yielded 1-naphthoic acid **3**[16] and 6-fluoro-1-naphthoic acid **1**, respectively. In the case of the more sterically hindered

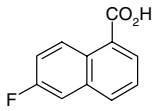
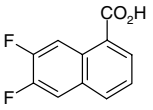
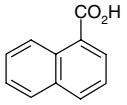
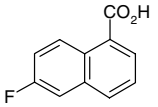
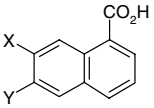


Scheme 1.

* Corresponding author. Tel.: +44 1865 782644; e-mail: tkrulle@prosidion.com
† Prosidion Limited is a subsidiary of OSI Pharmaceuticals, Inc.

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.022

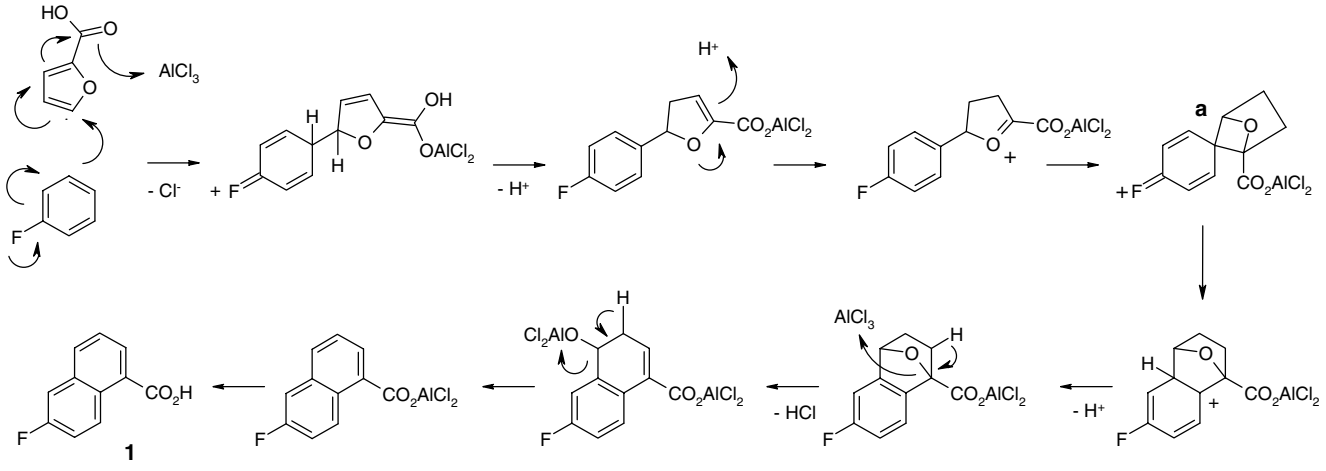
Table 1.

Starting material (solvent)	Product		Yield (%)
Fluorobenzene		**1**	23
1,2-Difluorobenzene		**2**	12
Bromobenzene		**3**	10
1-Bromo-4-fluorobenzene		**1**	10
1,3-Difluorobenzene	No cyclisation		—
1-Chloro-2-fluorobenzene		X : Cl, Y : F **4** X : F, Y : Cl **5**	24

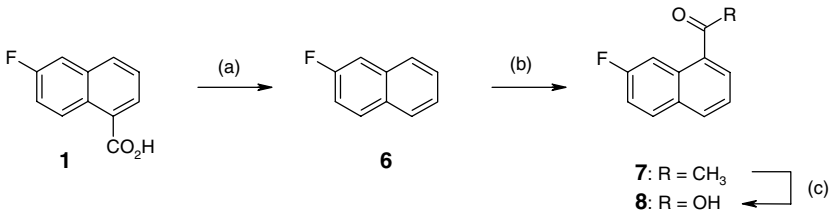
1,3-difluorobenzene, no naphthoic acid product could be isolated under comparable reaction conditions. The analogous treatment of 1-chloro-2-fluorobenzene provided an inseparable mixture of naphthoic acids **4** and **5**[17] in a ratio of 1.7:1. This implies that a fluorine atom directs the regioisomeric outcome of this reaction slightly more than a chlorine atom (Table 1).

One important aspect of this cyclisation reaction is the ease of extraction of 1-naphthoic acids into saturated sodium hydrogen carbonate solution. This physical property is the basis for the simple work-up and isolation of the final products in all cases listed in Table 1.[18] It is noteworthy that the extension of the bicarbonate extraction duration and the use of larger aliquots improved the yield of isolated 6-fluoro-1-naphthoic acid **1** from 23% to 56%. In the case of the failed 1,3-difluorobenzene reaction the bicarbonate extraction led to an almost quantitative recovery of 2-furanoic acid.

The remarkable selectivity by which this reaction produces 6-substituted 1-naphthoic acids can be explained by an initial electrophilic substitution at the *para*-position of the benzene ring (Scheme 2). Successive rearomatisation, tautomerisation and protonation of the furan ring then allows a second electrophilic attack to form a highly strained spiro-intermediate that rearranges to a bicyclic system by the migration of the more electron rich bond **a** to the *meta*-position. A second equivalent of aluminium chloride promotes the β-elimi-



Scheme 2. Proposed mechanism.



Scheme 3.

nation to form the dihydronaphthalene intermediate that aromatises under these conditions. Aqueous work-up hydrolyses the aluminium adduct and liberates 1-naphthoic acid **1**.

The relative ease by which the naphthalene scaffold can be assembled in this way makes the synthesis of other β-substituted naphthalenes feasible. For example a classical copper/quinoline decarboxylation[19] of 6-fluoro-1-naphthoic acid **1** gave the 2-fluoronaphthalene **6** in a good yield (Scheme 3). Friedel–Crafts acylation[20,21] of 2-fluoronaphthalene **6** takes place regioselectively at the 8-position to form ketone **7**,[22,23] we found that a slow increase of the reaction temperature over a period of several hours provides a quantitative conversion. Successive oxidation with sodium hypochlorite finally allowed the isolation of 1-naphthoic acid **8** in four simple steps overall.

In conclusion, we have developed a very convenient method for the preparation of gram quantities of 6-fluoro- and 6,7-difluoro-1-naphthoic acids (**1** and **2**, respectively) in a one-pot process. Decarboxylation of 6-fluoronaphthoic acid **1** followed by the regioselective Friedel–Crafts acylation of 2-fluoronaphthalene **6** provided an easy access to a 1,7-disubstituted naphthalene derivative **7** which could be oxidised to 7-fluoro-1-naphthoic acid **8** with bleach.

Acknowledgement

We would like to thank Professor George W. J. Fleet[‡] for his valuable suggestions with regards to a plausible mechanism.

References and notes

1. Boehm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Mueller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643.
2. Martinez, G. R. *Tetrahedron: Asymmetry* **1995**, *6*, 1491–1494.
3. Cui, D.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007–4010.
4. Vercouillie, J.; Abarbi, M.; Parrain, J.; Duchene, A.; Thibonnet, J. *Synth. Commun.* **2004**, 3751–3762.
5. Owton, M. W.; Brunavs, M. *Synth. Commun.* **1991**, 981–987.
6. Nussbaumer, P.; Dorfstaetter, G.; Leitner, I.; Mraz, K.; Vyplel, H.; Stuetz, A. *J. Med. Chem.* **1993**, *36*, 2810–2816.
7. Tagat, J. R.; McCombie, S. W.; Nazareno, D. V.; Boyel, C. D.; Kozlowski, J. A.; Chackalamannil, S.; Joisen, H.; Wang, Y.; Zhou, G. *J. Org. Chem.* **2002**, *67*, 1171–1177.
8. Dewar, M. J. S.; Grisdale, P. J. *J. Am. Chem. Soc.* **1962**, *84*, 3541–3546.
9. Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, *89*, 386–390.
10. Price, C. C.; Chapin, E. C.; Goldman, A.; Krebs, E.; Shafer, H. M. *J. Am. Chem. Soc.* **1941**, *63*, 1857–1861.
11. Price, C. C.; Huber, C. F. *J. Am. Chem. Soc.* **1942**, *64*, 2136–2139.
12. *6-Fluoronaphthalene-1-carboxylic acid* **1**: Anhydrous aluminium chloride (65 g, 487 mmol) was added carefully to a suspension of furan-2-carboxylic acid (25 g, 260 mmol) in fluorobenzene (250 mL) at 0 °C. After 1 h the ice bath was removed and the mixture was slowly heated to 75 °C and then kept at this temperature for a further 12 h. The mixture was added to a 2 N HCl solution (1.5 L) before extraction into ether (3 × 300 mL). The combined ether layers were washed with water (250 mL) and then extracted with saturated $NaHCO_3$ solution (3 × 250 mL). The alkaline solution was then made acidic with concd HCl solution and re-extracted with EtOAc (3 × 250 mL). Concentration in vacuo after drying ($MgSO_4$) gave a solid residue which was stirred in the presence of toluene (50 mL) for 12 h. Filtration gave the title compound (11.4 g, 23%) as an off-white solid, mp 234–236 °C. ^{1}H NMR: δ_H (DMSO-d_6, 500 MHz): 7.56 (1H, ddd, J_1 2.8 Hz, J_2 8.6 Hz, J_3 9.5 Hz, H-7), 7.66 (1H, dd, $J_1 = J_2$ 7.8 Hz, H-3), 7.84 (1H, dd, J_1 2.8 Hz, J_2 9.9 Hz, H-5), 8.16 (2H, m, H-2, H-4), 8.97 (1H, dd, J_1 6.0 Hz, J_2 9.5 Hz, H-8), 13.27 (1H, br s); MS: ESI$^-$, *m/z* 189.19 [M−H]$^-$.
13. Lowe, J. A.; Nagel, A. A.; US Patent No. 4,831,031; *Chem. Abstr*. **1989**, *111*, 153842.
14. Jacobs, T. L.; Winstein, S.; Henderson, R. B.; Bond, J.; Ralls, J. W.; Seymour, D.; Florsheim, W. H. *J. Org. Chem.* **1946**, *11*, 229–238.
15. ^{1}H NMR **2**: δ_H (DMSO-d_6, 500 MHz): 7.66 (1H, dd, $J_1 = J_2$ 7.7 Hz, H-3), 8.13 (1H, dd, J_1 8.4 Hz, J_2 8.9 Hz, H-5), 8.21 (1H, d, *J* 8.4 Hz, H-4), 8.27 (1H, d, *J* 7.4 Hz, H-2), 8.91 (1H, dd, J_1 8.4, J_2 8.9 Hz, H-8), 13.70 (1H, br s). HRMS: ESI$^-$, calcd for $C_{11}H_5F_2O_2$ [M−H]$^-$ 207.0257, found 207.0262.
16. N1909, Sigma–Aldrich.
17. ^{1}H NMR **4**: δ_H (DMSO-d_6, 500 MHz): 7.67 (1H, dd, $J_1 = J_2$ 7.6 Hz, H-3), 8.07 (1H, d, *J* 10.2 Hz, H-5), 8.19 (1H, d, *J* 8.1 Hz, H-4), 8.22 (1H, dd, J_1 1.0, J_2 7.3 Hz, H-2), 9.16 (1H, d, *J* 7.9 Hz, H-8); **5**: 7.64 (1H, dd, $J_1 = J_2$

[‡] Central Research Laboratories, University of Oxford.

7.8 Hz, H-3), 8.20 (1H, d, *J* 7.5 Hz, H-4), 8.28 (1H, d, *J* 7.0 Hz, H-2), 8.37 (1H, d, *J* 8.0 Hz, H-5), 8.85 (1H, d, *J* 12.7 Hz, H-8). HRMS: ESI$^-$, calcd for $C_{11}H_5ClFO_2$ $[M-H]^-$ 222.9962, found 222.9967.

18. The work-up described in Ref. 12 has been used consistently for all the examples listed in Table 1.
19. Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189–3190.
20. Price, C. C.; Voong, S. *J. Org. Chem.* **1949**, *14*, 111–117.
21. Ansems, R. B. M.; Scott, L. T. *J. Am. Chem. Soc.* **2000**, *122*, 2719–2724.
22. Harnik, M.; Jensen, E. V. *Israel J. Chem.* **1965**, *3*, 79–82.
23. ^{1}H NMR **7**: δ_H ($CDCl_3$, 500 MHz): 2.80 (3H, s, CH_3), 7.34 (1H, ddd, J_1 2.7 Hz, J_2 8.0 Hz, J_3 8.9 Hz, H-6), 7.49 (1H, dd, $J_1 = J_2$ 7.8 Hz, H-3), 7.88 (1H, dd, J_1 5.9 Hz, J_2 9.0 Hz, H-5), 7.86, 7.89 (2H, 2d, J_1 8.2 Hz, J_2 7.4 Hz, H-2, H-4), 8.62 (1H, dd, J_1 2.5 Hz, J_2 12.3 Hz, H-8). HRMS: ESI$^+$, calcd for $C_{12}H_{10}FO$ $[M+H]^+$, 189.0715 found 189.0712.