Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7371–7373

Selective fluorination of 1-hydroxyisoquinolines using Selectfluor™

David A. Price,* Kim James, Simon Osborne and Gareth W. Harbottle

Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

Received 13 June 2007; revised 30 July 2007; accepted 6 August 2007
Available online 10 August 2007

Abstract—The highly regioselective fluorination of 1-hydroxyisoquinoline is described using Selectfluor™ (F–TEDA–BF_4) under a variety of conditions.

As part of our research it became necessary to access multigram quantities of 7-bromo-4-fluoro-1-hydroxyisoquinoline (Fig. 1). The bromo and hydroxy functionalities were to be further manipulated to allow the synthesis of key targets in a medicinal chemistry programme. In particular, conversion of the hydroxy moiety to a chlorine for displacement with a variety of amines was a key reaction for high throughput chemistry.

The fluorine, however, was not required for further synthetic work but was a key part of the pharmacophore for the biological target of interest.[1] The use of fluorine in molecules of pharmacological interest can profoundly alter their biological properties and there has been widespread research into methodologies for the introduction of this atom.[2] There have been two excellent reviews recently published on the use of Selectfluor™ (F–TEDA–BF_4)[3] and a Letter describing the fluorination of organonitriles,[4] which has prompted us to disclose our results on the use of this reagent.

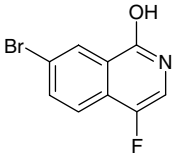
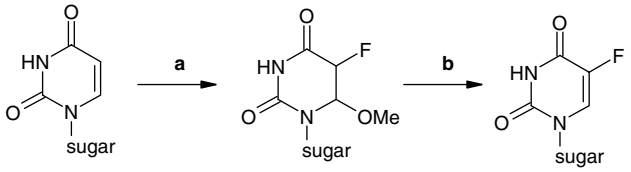


Figure 1. 7-Bromo-4-fluoro-1-hydroxyisoquinoline.

From an initial survey of the literature the direct electrophilic fluorination of 7-bromo-1-hydroxyisoquinoline looked problematic with little chance of success, however, the simplicity of the approach warranted investigation. The direct fluorination of aromatic rings often involves hazardous reagents (e.g., gaseous F_2)[5] or fluorinating agents that require preparation due to a lack of commercial sources.[6] Alternatives such as the thermal decomposition of diazonium tetrafluoroborates were unattractive and these methods are rarely applicable to heteroaromatic systems.

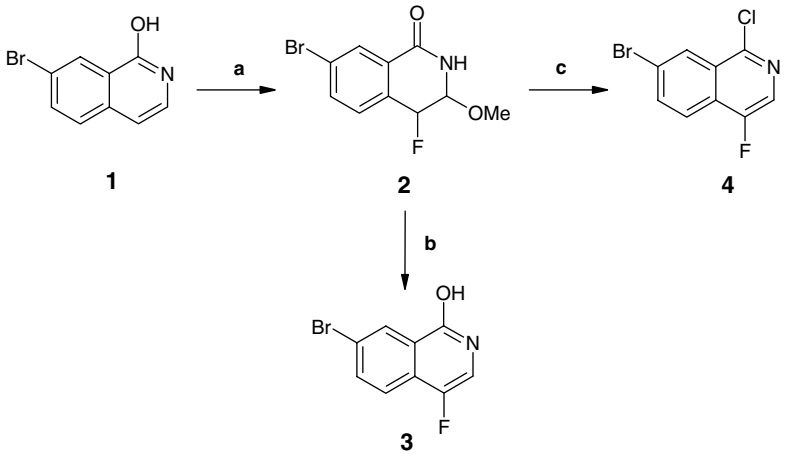
The development of Selectfluor™ has been a major advance in the chemistry of fluorine-containing compounds. There are numerous examples of the use of Selectfluor™ for electrophilic fluorination of electron rich phenyl rings, however, the use of this reagent for heterocyclic fluorination is extremely scarce.[7] The literature even teaches away for the use of this reagent with pyridine derived systems.[8] There has been work reported on the simultaneous fluorination and oxidation of indole systems,[9] but as far as we are aware, there is only the work of Sankar Lal, which demonstrated that a



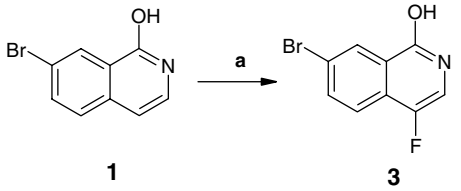
Scheme 1. Reagents and conditions: (a) Selectfluor™, MeCN/methanol (1:1 v:v), reflux, 85%; (b) pyridine, reflux.

* Corresponding author. Fax: +44 1304 644690; e-mail: david.a.price@pfizer.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.024



Scheme 2. Reagents and conditions: (a) Selectfluor™, MeCN/methanol, rt, 100%; (b) 1 N HCl, CH_2Cl_2, 83%; (c) $POCl_3$, CH_2Cl_2, rt, 95%.



Scheme 3. Reagents and conditions: (a) Selectfluor™, MeCN, reflux, 45%.

pyrimidinone base could be fluorinated in a two-step procedure (Scheme 1).[10]

These results prompted us to investigate the possibility of using Selectfluor™ to perform our required transformation. Using modified conditions (room temperature rather than reflux) we found complete consumption of the starting 6-bromo-1-hydroxyisoquinoline **1** and generation of a quantitative yield of an inseparable mixture of diastereoisomers of methanol adduct **2**. On prolonged standing at room temperature (typically >3 days) these diastereoisomers spontaneously re-aromatized to give the required product **3** as a single regioisomer. The rearomatisation could be more conveniently undertaken by stirring adduct **2** in 1 N hydrochloric acid in dichloromethane. With this knowledge in hand that acidic media assists in rearomatisation we were pleased to find that phosphorus oxychloride not only accomplished the rearomatisation but also converted the 1-hydroxy to the required chloro substituent **4** for subsequent amine displacement (Scheme 2).

With access to multigram quantities of intermediate **4** achieved we were intrigued by the possibility of a direct fluorination of the heterocycle without the need for rearomatisation; as far as we are aware this is unprecedented in the literature. Pleasingly, simply heating 7-bromo-1-hydroxyisoquinoline in acetonitrile with a slight excess of Selectfluor™ under reflux generated the required fluorinated heterocycle **3** in moderate yield (Scheme 3).[11] The transformation is highly regiospecific with only the 4-fluoro isomer being produced in the reaction and for the project's needs could be easily performed on a 50 mmol scale.

Disappointingly, all attempts to further optimise this reaction by varying the number of equivalents of Selectfluor™ and using different solvents were unsuccessful. Studies were also made on the use of microwave heating of the reaction and again these showed no improvement over the initial conditions developed.

Extension of this methodology to the fluorination of 2-pyridone was also unsuccessful with a highly complex reaction profile that was difficult to separate and obtain analytical data on the components. This result suggests 1-hydroxyisoquinoline may be a rare example of a heterocyclic system, that is, suitable for fluorination with Selectfluor™. The hydroxyl substituent activates the heterocyclic ring for electrophilic reaction while the fused phenyl prevents fluorination *ortho* to the hydroxy and ensures only a single regioisomer as product.

In conclusion, we have demonstrated an efficient methodology for the two-step fluorination of 7-bromo-1-hydroxyisoquinoline, which can yield multigram quantities of this versatile intermediate. In addition, we have shown that 7-bromo-1-hydroxyisoquinoline can be directly fluorinated in a single step in moderate yield using Selectfluor™, which to the best of our knowledge is the first example of this transformation.

Acknowledgement

The authors wish to thank the analytical services group at Pfizer Global Research and Development for all their assistance in generating the required spectral data.

References and notes

1. Wermuth, C. G. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: San Diego, 2001.
2. *New Fluorinating Agents in Organic Synthesis*; German, L., Zemskov, S., Eds.; Springer: Berlin, 1989.

3. (a) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res* **2004**, *37*, 31; (b) Nyffeler, P. T.; Gonzalez Duron, S.; Burkhart, M. D.; Vincent, S. P.; Wong, C. *Angew. Chem., Int. Ed* **2005**, *44*, 192.
4. Peng, W.; Shreeve, J. M. *Tetrahedron Lett.* **2005**, *46*, 4905.
5. Purrington, S. T.; Kagan, S. B. *Chem. Rev.* **1986**, *86*, 997.
6. Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925.
7. Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1.
8. Banks, R. E.; Murtagh, V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995; Vol. 1.
9. Takeuchi, Y.; Tarui, T.; Shibata, N. *Org. Lett.* **2000**, *2*, 639.
10. Sankar Lal, G.; Pastore, W.; Pesaresi, R. *J. Org. Chem.* **1995**, *60*, 7340.
11. Selectfluor™ (17.9 g, 52 mmol) was added in one portion to a suspension of 7-bromo-1-hydroxyisoquinoline (11.2 g, 50 mmol) in acetonitrile (100 ml) at room temperature. The reaction was heated under reflux for 12 h, cooled to room temperature and the solvent removed under reduced pressure. The resulting yellow oil was dissolved in ethyl acetate (200 ml) and washed with water (100 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to furnish a yellow oil. The oil was purified by column chromatography on silica gel eluting with ethyl acetate–pentane (40:60 v:v) to yield 7-bromo-4-fluoro-1-hydroxyisoquinoline as a white solid, 5.5 g, 45%. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.26$ (1H, s), 7.97 (1H, d, $J = 6.5$ Hz), 7.68 (1H, d, $J = 6.5$ Hz), 7.41 (m, 1H). LRMS: $m/z = 242$ [MH^+].