A Facile Regioselective Aromatic Fluorination of *N*-Aryl-*N*-hydroxyamides with Diethylaminosulfur Trifluoride (DAST)

Yasuo Kikugawa,* Kazuhiro Matsumoto, Kimiyo Mitsui and Takeshi Sakamoto

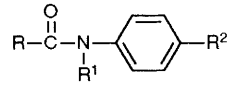
Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02 Japan

Treatment of *N*-aryl-*N*-hydroxyamides with diethylaminosulfur trifluoride (DAST) under conventional reaction conditions results in removal of the hydroxy function and introduction of a fluorine atom at the *para* position of the aromatic ring, in high yield.

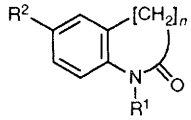
Introduction of fluorine into organic molecules has become increasingly important in a wide variety of fields. The Balz–Schiemann reaction[1] and its variants continue to be the most widely used methods today for the practical synthesis of fluoroaromatics, but the methods have some limitations. Direct fluorinating agents,[2] even when commercially available, often require special equipment and experience for safe handling and may pose significant hazards for the nonspecialist.

While investigating the reaction of *N*-aryl-*N*-hydroxyamides (**1a–6a**) with diethylaminosulfur trifluoride (DAST),[3] we have found that removal of the hydroxy function is coupled to the introduction of fluorine at the *para* position of the aromatic ring by nucleophilic fluorination in high yield. DAST is often used for replacement of the hydroxy group with fluorine and is a commercially available reagent which is easily handled by conventional techniques. A typical experimental procedure is as follows: DAST (0.15 ml, 1.13 mmol) was added, *via* a syringe, to a mixture of *N*-hydroxy-*N*-phenylbenzamide **2a** (200 mg, 0.94 mmol) and dichloromethane (30 ml) over 10 min at 0 °C under argon. The stirring was continued for

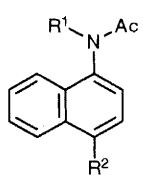
1–6	R^1	R^2
a	OH	H
b	H	F



1; R = Me, **2**; R = Ph



3; *n* = 1, **4**; *n* = 2



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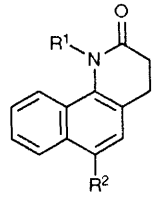

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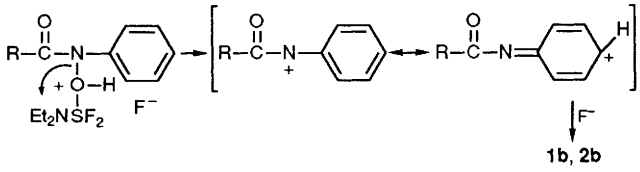

Scheme 1

5 min, then 10% $NaHCO_3$ (20 ml) was added. The aqueous layer was extracted with dichloromethane (2 × 20 ml). The combined extracts were washed with brine (30 ml), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (20 g) eluting with benzene–ethyl acetate (20:1) to give *N*-(4-fluorophenyl)-benzamide **2b** (167 mg, 83%), m.p. 183–184 °C (lit.[4] m.p. 183–185 °C). Several *N*-aryl-*N*-hydroxyamides were reacted with DAST in this way, and the results are presented in Table 1. According to NMR spectroscopy, fluorination occurs exclusively at the *para* position.

The most plausible reaction route is as follows: initially, DAST reacts at the *N*-hydroxy group to afford an oxygen–sulfur bond, heterolytic cleavage of which results in a positive charge on the nitrogen and canonical forms involving the benzene ring. A fluoride ion does not form a bond at nitrogen, but at the *para* position, to which the positive charge is mainly dispersed.

The merits of this method include regioselective introduction of a fluorine atom on an aromatic ring, a commercially available reagent, high yields, short reaction times and technical simplicity. In combination with known methods[5] for the synthesis of nitrogen heterocyclic compounds bearing the *N*-hydroxy group, this method allows the preparation of otherwise difficultly accessible aromatic and heteroaromatic fluoro compounds (run 6).

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Table 1 Aromatic fluorination of *N*-aryl-*N*-hydroxyamides with DAST

Run	Substrate	Product[a]	Yield (%)
1	**1a**	**1b**	71
2	**2a**	**2b**	83
3	**3a**	**3b**	81
4	**4a**	**4b**	75
5	**5a**	**5b**	79
6	**6a**	**6b**	70

[a] All the products except **6b** are known and gave satisfactory physical data. The position of the fluorine atom in **6b** was determined by comparison of its NMR spectrum with that of **5b**.

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