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Practical Alternative Synthesis of 1-(8-Fluoro-naphthalen-1-yl)piperazine

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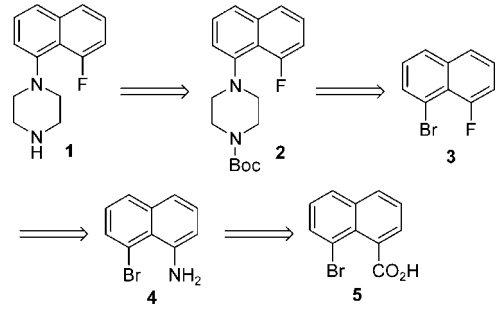
Abstract:

Convergent synthesis of 8-fluoronaphthalen-1-ylamine (6) was achieved through the reaction of 1*H*-naphtho[1,8-*de*][1,2,3]triazine (15) with HF-pyridine under mild conditions. This new synthesis for the preparation of 6 overcame many scale-up challenges that exist in the methods reported in the literature and provided a practical alternative synthesis of 1-(8-fluoronaphthalen-1-yl) piperazine (1).

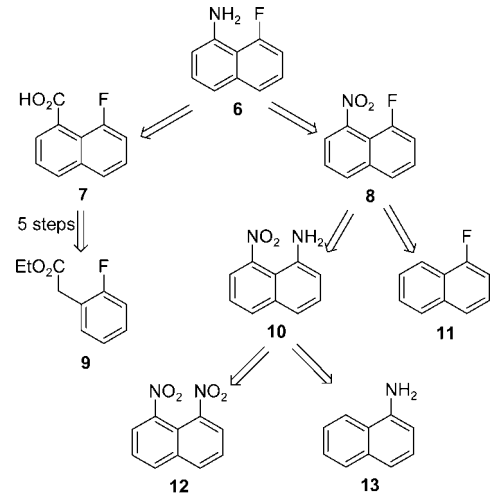
Owing to their unique properties, fluoro-organic compounds are increasingly important in the agrochemical and pharmaceutical industry.[1] However, selective introduction of fluoro substituents onto organic molecules continuously represents a significant challenge.[2,3b] In connection with our work, preparation of a significant quantity of 1-(8-fluoronaphthalen-1-yl)piperazine (**1**) was required as a key intermediate to support one of our drug discovery/development programs. The original synthesis[3] (Scheme 1) started with very expensive 8-bromo-1-naphthoic acid (**5**). The synthesis involved Curtius rearrangement, Balz–Schiemann diazotization/fluoro-dediazotization, and palladium catalyzed coupling with *N*-Boc-piperazine. Both of the Curtius and Balz–Schiemann reactions were highly energetic and would require considerable evaluation to ensure safe operation on a large scale. Additionally, a significant amount of the des-fluoro impurity (1-bromonaphthalene) was generated from the Balz–Schiemann reaction when the reaction was scaled up, and careful chromatographic purification was required to remove the impurity.

Alternatively, compound **1** could be prepared from 8-fluoronaphthalen-1-ylamine (**6**) (Scheme 2). In the literature, **6** was prepared from 1-fluoro-8-nitronaphthalene (**8**) by reduction.[4] Compound **8** was prepared either by nitration of 1-fluoronaphthalene (**11**)[5] or from 8-nitro-1-naphthalylamine (**10**)[4] through the Balz–Schiemann reaction. However, both routes required separations of regio-isomeric mixtures through chromatography[5,6]

Scheme 1. **Original synthesis of compound 1**



Scheme 2. **Retroalternative synthesis of 6 from literature**



or the use of heat- and shock-sensitive materials such as **12**,[7] which limited their use for large-scale preparation. It can also be envisaged that compound **6** be prepared from 8-fluoro-1-naphthalenecarboxylic acid (**7**) through Curtis or Hoffmann rearrangement. However, the preparation of compound **7** took five steps from ethyl (*o*-fluorophenyl)acetate (**9**).[2]

In looking for a practical and convergent synthesis of **1**, our efforts centered on the use of 1,8-diaminonaphthalene (**14**), which is inexpensive and provides the desired 1,8-disubstituted functionalities on naphthalene. Initial attempts of diazotization of **14** with 1 equiv of sodium nitrite in hydrogen fluoride–pyridine did not give any desired product. Considering the possible interference of the second amino group during the diazotization, protection of one of the amino groups of **14** with succinic anhydride or phthalic anhydride was carried out according to literature.[8] However, diazotization of both monoprotected derivatives under either aqueous or nonaqueous conditions gave

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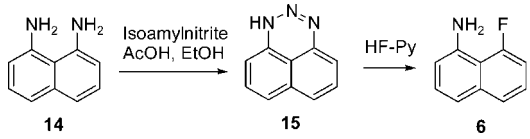
Table 1. **Conversion of 15 to 6 using HF–pyridine**



14 15 6

entry	temp, °C	time	HF-Py/**15** (w/w)	**6** yield, %	des-fluoro[a]
1	120	16 h	22 (≈0.28 M)	77	0.3
2	60	16 h	22	97	NA
3	rt	60 h	22	NA[b]	NA
4	60	16 h	3	83	9.5
5	rt	9 days	3	89	0.4
6	rt	3–7 days	5	87–90	0.3–0.4

[a] The amount of des-fluoro impurity was determined by ^{1}H-NMR. [b] The product was not isolated, HPLC of the reaction showed complete disappearance of starting material.

mostly unreacted starting material. The failure of the diazotizations was most likely caused by the steric hindrance of the succinimidyl or phthalimidyl group at the 8-position.

It was reported[9] that **14** can be converted to 1*H*-naphtho[1,8-*de*][1,2,3]triazine (**15**) by nonaqueous diazotization in ethanol/acetic acid in high yield (Table 1). Conversion of **15** to 8-chloro-1-aminonaphthalene in concentrated hydrochloric acid saturated with hydrogen chloride gas in the presence of copper under heating was reported in a German patent.[10] We postulated that **15** could be converted to the corresponding 1-amino-8-fluoronaphthalene (**6**) by using a fluoride source under acidic conditions, particularly hydrogen fluoride–pyridine (HF-Py).

Treatment of **15** with HF-Py (70%/30%, w/w) at 120 °C in a stainless steel Parr reactor indeed gave **6** cleanly in 77% isolated yield (entry 1, Table 1). The reaction worked equally well at 60 °C (entry 2). At room temperature, the reaction went cleanly, although it took more than 2 days to complete (entry 3). DSC analysis showed that **15** has an onset temperature of 240 °C with 818 J/g. Although still fairly energetic, the high onset temperature of **15** should provide a good safety margin for scale-up operation.

In efforts to optimize the reaction for scale up, the ratio of HF-Py/**15** (w/w) was decreased from 22 to 3. However at 60 °C, up to 9.5% of the des-fluoro impurity, 1-aminonaphthalene, was generated (entry 4, Table 1). This high level of des-fluoro impurity was not observed with HF-Py/**15** (w/w) ratio of 22 even at 120 °C (entry 1). At room temperature with HF-Py/**15** ratio of 3 (entry 5, Table 1), the amount of des-fluoro impurity was significantly reduced. However, the reaction took over 9 days to complete. During the scale-up, the reactions were run with HF-Py/**15** ratio of 5 for 3–7 days to give **6** in 87% to 90% yields with consistently low levels of the des-fluoro impurity (entry 6, table *1*). The competitive homolytic decomposition path way of **15** under higher concentration and/or higher temperature was likely the cause of the des-fluoro impurity formation.[11]

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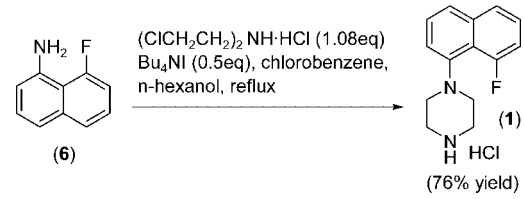
Scheme 3. **Conversion of 6 to 1 using bis(2-chloroethyl)amine HCl**



(6) (76% yield)

Treatment of **6** with 1.08 equiv of bis(2-chloroethyl)amine hydrochloride in the presence of 0.5 equiv of tetrabutyl ammonium iodide in chlorobenzene and 1-hexanol at reflux for 74 h gave directly the HCl salt of **1** in 76% yield with over 96% HPLC purity (Scheme 3).

The fluoro group at the 8-position seemed to slow down considerably the piperazine formation, as the corresponding reaction with 1-aminonaphthalene under comparable conditions could be finished within 8 h. The use of 0.5 equiv of tetrabutylammonium iodide is crucial to speed up the reaction, as well as allowing the direct isolation of the HCl salt of **1** without the contamination from the iodide salt. *N*-Arylpiperazines are commonly synthesized from the corresponding arylamines by using bis(2-chloroethyl)amine hydrochloride. However, the potential risk of generation and release of toxic bis(2-chloroethyl)amine freebase during the reaction and in the work-up make this methodology less appealing, especially for large scale operation.[12] The above optimized conditions allow the direct isolation of the product as hydrochloride salt and maintain acidic mediates throughout the reaction and the work-up. This should significantly reduce the risk of exposure to bis(2-chloroethyl)amine freebase during the operation.

In conclusion, a practical alternative synthesis of 1-(8-fluoronaphthalen-1-yl)piperazine (**1**) was developed. This synthesis starts with inexpensive 1,8-diaminonaphthalene and provides **1** as HCl salt in three steps in up to 60% overall yield. The discovery, that 1*H*-naphtho[1,8-*de*][1,2,3]triazine (**15**) can be used as a stabilized diazonium and can be converted to 8-fluoronaphthalene-1-ylamine (**6**) under mild conditions using hydrogen fluoride–pyridine, provides a convergent approach to **6** and overcomes many scale-up challenges present in the literature methods for the preparation of **6**. With an onset temperature of 240 °C, compound **15** should possess sufficient safety margin for its isolation and subsequent conversion to **6** using HF–pyridine at room temperature in large-scale operation.

Experimental Section

1*H*-Naphtho[1,8-*de*][1,2,3]triazine (15). To a 5 L, three-neck round bottom flask equipped with mechanical stirring, dropping funnel, and nitrogen outlet, 1,8-diaminonaphthalene (Aldrich, catalog no. D21405, 250 g, 1.58 mol) was dissolved in a mixture of acetic acid (500 mL) and ethanol (2500 mL) under nitrogen at room temperature. Isoamyl nitrite (Aldrich, catalog no. 150495, 208.1 mL, 1.55 mol, 0.98 equiv) was then added dropwise over a period of 3.5 h with temperature controlled between 18 and 21 °C with a cold-water bath. After

(12) Rudbeck, H. C; Johannsen, I.; Nielsen, O.; Ruhland, T.; Sommer, M. B.; Tanner, D.; Dancer, R. *Synthesis* **2005**, 3456–3462, and reference therein.

the addition, the resulting red suspension was stirred at room temperature for 19 h. The solid was collected by filtration, washed with ethanol (2 × 500 mL) and dried under vacuum to give a red crystalline solid (235.86 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 13.24 (s, 1H), 7.24 (m, 2H), 7.11 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 5.4 Hz, 2.6 Hz, 1H), 6.10 (d, J = 7.2 Hz, 1H). Anal. Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.62; H, 4.06; N, 24.46.

8-Fluoro-naphthalen-1-ylamine (6). To a 4000 mL Nalgene bottle with magnetic stirring, hydrogen fluoride–pyridine (Aldrich, catalog no. 18422-5, 70% HF/30% pyridine, 400 g) was added and cooled in an ice bath. (*Caution: To reduce the risk of exposure to hydrogen fluoride, people involved in handling the reaction are recommended to wear Viton gloves or Silver Shield/4H gloves, Silver Shield/4H apron, Silver Shield/4H sleeves, and safety face-shield.*) 1*H*-Naphtho[1,8-*de*][1,2,3]triazine (100 g, 0.59 mol) was added slowly in about five portions. After the addition, the Nalgene bottle was rinsed with additional 100 g of hydrogen fluoride–pyridine to wash down the solid sticking on the sidewall of the bottle (total hydrogen fluoride–pyridine used: 500 g, 17.5 mol, 30 equiv). The Nalgen bottle was capped. The bottle was vented through Tygon tubing attached to a small hole on the cap. The reaction solution was stirred at room temperature for 7 days. HPLC showed that all starting material disappeared, with 94% product purity. The reaction bottle was cooled in an ice bath, and ice chips (total 500 g) were added. Once the temperature was below 10 °C, KOH (45 wt %, 1.35 L) was slowly added with temperature controlled below 35 °C. During the neutralization period, 500 g of ice chips was added occasionally for effective cooling (about 1.5 h for the addition). The final pH of the mixture was about 11. The mixture was diluted with EtOAc (500 mL) and stirred for 20 min. The mixture was then transferred to a 6 L separatory funnel through suction. The aqueous layer was separated and removed. The organic layer and emulsion interface were filtered through Celite to remove solid. The filtering cake was washed with ethyl acetate (2 × 200 mL). The bilayer filtrate (now nicely separated) was separated. The organic layer was washed twice with a mix of saturated sodium chloride (300 mL), water (300 mL) and saturated sodium bicarbonate (300 mL) (*directly wash the organic layer with saturated sodium bicarbonate generated emulsion*) and then saturated sodium chloride (300 mL). The organic layer was then degassed by bubbling nitrogen for 20 min to remove oxygen and prevent oxidation of the product. The solution was stirred under nitrogen with activated carbon (Sigma-Aldrich, 242276, Darco, G-60, 100 mesh, 50 g) for 5 h and additional activated carbon (50 g) overnight. The activated carbon was removed by filtration through Celite; the solid cake was washed with EtOAc (2 × 300 mL). The filtrate (red-wine color) was concentrated to give an oil, which was azeotroped with chlorobenzene twice (2 × 500 mL) to remove residue water. The oil was solidified after sitting at room temperature overnight. The solid was further dried under vacuum to give a red-brown solid (86.1g, 90.4%). ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 7.48 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 7.27 (m, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.03 (m, 2H), 6.65 (dd, J = 7.6 Hz, 1.2Hz, 1H), 5.66 (s, 2H). Anal. Calcd for $C_{10}H_8FN$: C, 74.52; H, 5.00; N, 8.69. Found: C, 74.36; H, 4.92; N, 8.79.

1-(8-Fluoro-naphthalen-1-yl)piperazine Hydrochloride (1). 8-Fluoro-1-aminonaphthalene (168.86 g, 1.048 mol), bis(2-chloroethyl)amine hydrochloride (Aldrich, catalog no. B38503, 202.0 g, 1.13 mol, 1.08 equiv), tetrabutylammonium iodide (Aldrich, catalog no. 140775, 193.5 g, 0.524 mmol, 0.5 equiv), and hexyl alcohol (Aldrich, 100 mL) in anhydrous chlorobenzene (Aldrich, 1950 mL) was stirred in a 3 L, three-neck round bottom flask equipped with mechanical stir, Dean–Stark trap (50 mL), and condenser. The mixture was degassed by bubbling nitrogen for 20 min. The mixture was then heated to reflux under nitrogen for 74 h to give a light brown suspension. The progress of the reaction was checked by HPLC (after 23 h, product/starting material = 70.5/27.6; after 74 h, product/starting material = 93.8/0). The suspension was slowly cooled to room temperature and gently stirred overnight to give a brown suspension. The solid was collected by filtration, washed with chlorobenzene (300 mL) and toluene (300 mL), and dried under vacuum at room temperature for 24 h to give a yellow solid (232.19 g). The crude HCl salt of **1** was slurried twice in acetonitrile (500 mL) for 5 h. The solid was collected by filtration, washed with acetonitrile (70 mL), and dried under vacuum to give the HCl salt of **1** as a yellow solid (213.52 g, 76.4%). ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm): 9.34 (bs, 2H), 7.70 (dd, J = 8.2 Hz, 0.8Hz, 1H), 7.62 (m, 1H), 7.43 (m, 2H), 7.22 (m, 1H), 7.10 (dd, J = 7.5 Hz, 0.8 Hz, 1H), 3.33 (m, 4H), 3.11 (m, 2H), 3.00 (m, 2H). HPLC: 96.4% purity (Tr = 10.28 min, wavelength at 215 nm; YMC PackPre C18, 150 × 4.6 mm, 3 μm; solvent A, 0.2% $HClO_4$ in 90:10 water/ACN; solvent B, ACN; gradient, 90% A to 5% A in 30 min, then hold for 5 min; flow rate, 1.0 mL/min). Anal. Calcd for $C_{14}H_{15}FN_2 \cdot 1.05HCl \cdot 0.6H_2O$: C, 60.19; H, 6.22; N, 10.03; Cl, 13.32. Found: C, 59.95; H, 6.09; N, 10.16; Cl, 13.62.

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