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Synthesis of difluorinated pyridinecarboxaldehyde via electrophilic fluorination

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Abstract

An efficient synthesis of novel 3,5-difluoropyridine-4-carboxaldehyde using *N*-fluoro-benzenesulfonimide (NSFi) is described. Difluorination was achieved through the reaction of 3,5-dihalo-1,3-dioxolane pyridine with *n*-butyllithium followed by *N*-fluorobenzenesulfonimide at −120 °C in good to high yields. Maintaining the low temperature during the transmetallation was found to be critical for the selective formation of the difluoro-susbstitution over the monofluoro one.
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Keywords: Difluoropyridine; 3,5-Difluoropyridine-4-carboxaldehyde

1. Introduction

Selectively fluorinated heterocyclic compounds are of a considerable importance in bioorganic and medicinal chemistry since these products possess unique properties [1] that allow a variety of applications [2] in the design of bioactive compounds [3]. Therefore, the development of efficient methodologies for the preparation of new selectively fluorinated compounds is still a challenge in heterocyclic chemistry.

The most commonly used methods for the synthesis of fluorinated heterocyclic compounds include the nucleophilic displacement of halogen substituents with a fluoride ion source (Halex reaction) [4] and fluorodiazotisation of appropriate amino-heterocycles (Balz-Schiemann process) [5,6]. However, the synthetic utility of these methods depends on the availability of the appropriate halo and amino heterocyclic precursors and, furthermore, in some cases harsh reaction conditions are required to achieve the fluorination. Alternatively, selective replacement of hydrogen by fluorine offers a more direct strategy for the synthesis of fluoro-heterocycles and a limited number of electrophilic fluorination processes involving the use of XeF_2 [7] and AcOF [8] have been reported in this context. Electrophilic fluorination using N-F reagents has grown in popularity and applications abound in recent years as methods for the selective fluorination of activated aromatics, alkenes, and enolates [9]. Despite increased use of these regents, reports of electrophilic N-F *difluorinations* in the literature are few in number.

Previously, we reported the synthesis of compounds **1**, **3a**, and **3b** (Fig. 1) [10]. These compounds were prepared as precursors for the synthesis of fluoropyridyl-porphyrins used as acetylcholine esterase (AChE) inhibitors in connection with treatment for Alzheimer's disease. The activity of AChE inhibition was higher for the porphyrin derivatives derived from more fluorine-substituted compound **3b** than for the porphyrin derivatives from **1**. However, these compounds (**3a** and **3b**) are sparingly soluble in water. Thus, we envisioned preparing difluorinated pyridine derivatives **2** in order to circumvent the solubility problem. In this vein, to the best of our knowledge, synthesis of 3,5-difluoropyridine-4-carboxaldehyde **2** has not been reported. Herein, we report a new efficient synthetic method of compound **2** via electrophilic difluorination using *N*-fluorobenzenesulfinimide (NFSi).

2. Results and discussion

Our initial attempt to synthesize 3,5-difluoropyridine-4-carboxaldehyde involved defluorination from 2,3,5,6-tetrafluoropyridine-4-carboxaldehyde. A trifluoropyridine derivative **3a** was synthesized starting with reduction of 2,3,5,

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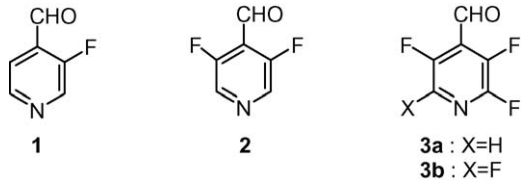
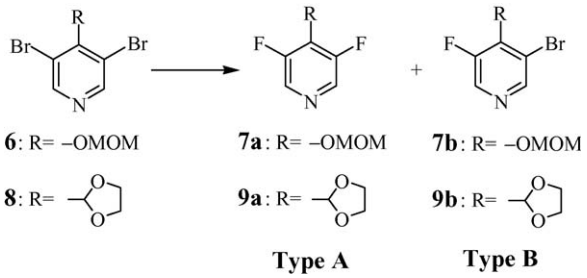


Fig. 1. Fluorinated pyridinecarboaldehydes.

6-tetrafluoropyridine-4-carbonitrile with diisobutyl-aluminum hydride (DIBAH) at low temperature [11], followed by reduction of highly volatile aldehyde to alcohol. Selective displacement of 6-fluorine in a tetrafluoropyridine ring with hydrazine provided 6-hydrazinopyridine-4-carbinol [12]. Sequential removal of hydrazine by copper sulfate and Swern oxidation of the subsequent alcohol gave 2,3,6-trifluoropyridine-carboxaldehyde **3a** in 78% yield. Unfortunately, this methodology could not be applied to the synthesis of 3,5-difluoropyridine-4-carboxaldehyde **2** due to the resistance of **3a** against further displacement with hydrazine at the 2-position.

The synthesis started with the formylation and methylation of 3,5-dihalopyridine at the 4-position. Lithiation of 3,5-dibromopyridines **4** using lithium diisopropylamide (LDA) and subsequent reaction with methyl formate introduced the formyl group (**5**) exclusively at the 4-position of the pyridine in good yields (Scheme 1) [13]. However, treatment of 3,5-dibromopyridine-4-carboxaldehyde **5** with 2.5 equiv. *n*-BuLi at −78 °C in THF followed by 2.5 equiv. of NFSi resulted only undesired side (polymerized) products. It may presumably be due to the deactivation of the pyridine ring by a substituted formyl group since this type of reaction involves the direct reaction of the F^+ reagent. Thus, electron-rich substituents are often necessary to promote the electrophilic fluorination reaction [14]. To circumvent the deactivation through the formyl substitution, we then decided to use methoxymethyl (MOM) ether pyridine derivatives **6** [13] and dibromo-1,3-dioxolanylpyridine derivatives **8** in the lithium–halogen exchange reaction (Scheme 1), followed by treatment with NFSi, to generate 3,5-difluoropyridine-4-carboxaldehyde **2** as depicted in Scheme 1. After converting the formyl group into a MOM ether group or 1,3-dioxolane group via conventional protection protocols, we examined an NFSi-mediated difluorination whether the yield could be improved by performing the reaction in a stepwise fashion using a variety of bases and reaction conditions listed in Table 1.

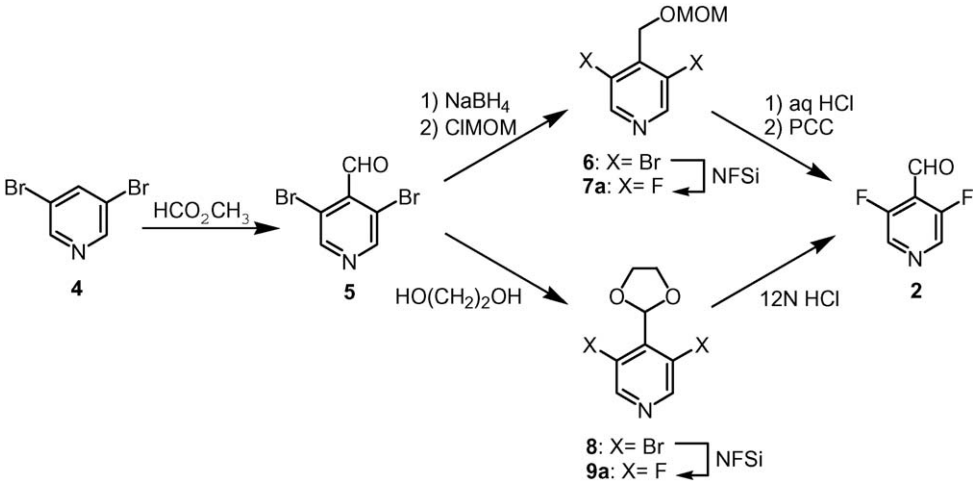
Table 1
Difluorination of pyridine derivatives with NFSi



Entry	Substrate	Base	Temperature (°C)	Yields[a] (%)	
				Type A	Type B
1	**6**	*n*-BuLi	−78	20	4
2	**6**	*n*-BuLi	−120	33	10
3	**6**	*s*-BuLi	−78	23	4
4	**6**	*s*-BuLi	−120	30	8
5	**6**	*t*-BuLi	−78	13	7
6	**6**	*t*-BuLi	−120	23	20
7	**8**	*n*-BuLi	−78	57	24
8	**8**	*n*-BuLi	−120	76	20
9	**8**	*s*-BuLi	−78	52	11
10	**8**	*s*-BuLi	−120	78	21
11	**8**	*t*-BuLi	−78	43	7
12	**8**	*t*-BuLi	−120	64	15

[a] Isolated yields; structures were determined by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and MS.

Interestingly, the yields and selectivity of the reaction were highly dependent upon the protecting group of the aldehyde. When compound **6** was subjected to the lithiation using *n*-BuLi, *s*-BuLi or *t*-BuLi followed by fluorination, the reaction yields were only moderate and a marginal degree of chemoselectivity was observed favoring the formation of difluorination product



Scheme 1.

(entries 1–6). In all the cases, performing the reaction at lower temperature (−120 °C) provided higher yields of the products (entries 2, 4, and 6). However, fluorination using compound **8** was much more desirable in terms of yields and selective formation of the desired difluorinated product was possible. When compound **8** was treated with *n*-BuLi at −78 °C followed by 2.5 equiv. of NFSi, a mixture of difluorinated compound **9a** and monofluorinated compound **9b** were obtained in 57% and 24% yield, respectively (entry 7). Surprisingly, lowering the reaction temperature to −120 °C afforded more selective formation of the desired difluoronated compound **9a** (76%), which is readily separable by conventional chromatography. Use of *s*-BuLi at −120 °C gave similar yields (78%) of the difluorinated product (entry 10). However, treatment with *t*-BuLi at −120 °C gave difluorinated compounds **9a** in a noticeably diminished yield (64%) than that of reaction using *s*-BuLi (entry 12). The noticeable difference in the reaction efficiency depending upon the protecting groups may presumably due to their different ability to stabilize the intermediate during the lithiation process. In this respect, 1,3-dioxolane protecting group was more efficient compared to the MOM ether group.

Deprotection of the 1,3-dioxolane in compound **9a** by the usual acid-catalyzed hydrolysis [15] or metal Lewis acid hydrolysis [16] was unsuccessful, presumably due to the strong electron-withdrawing effect of the 3,5-difluoro group adjacent to this protecting group. Fortunately, efficient deprotection could be achieved in 12 N aq HCl solution at reflux (Scheme 1). The resulting product 3,5-difluoro-pyridine-4-carboxaldehyde **2** was stable even under strongly acidic and high temperature (100 °C) conditions. Furthermore, MOM group in difluorinated compound **7a** was cleanly deprotected with dilute aq. HCl in methanol and treatment of the resulting alcohols with PCC or under Swern oxidation conditions provided compound **2** in 78% or 84% yields, respectively (Scheme 1).

3. Conclusion

In conclusion, we have successfully prepared 3,4-difluoropyridine-4-carboxaldehyde **2** via electrophilic fluorination. This result represents the first synthetically useful NFSi-mediated difluorination of unactivated pyridine carboxaldehyde **5**. Study on the synthetic applications of fluorinated aromatic compounds, in particular, for the design of bioactive compounds is in progress and the results will be reported in due course.

4. Experimental

N-fluorobenzenesulfonimide (NFSi) was obtained from Aldrich, and all reagents were purchased from commercial sources. Thin layer chromatography (TLC) analyses were performed on Merck F_{254} silica gel plates. Flash chromatography was carried out on Merck silica gel 60 (230–400 mesh). THF was distilled under nitrogen over sodium in a recycling still using benzophenone as indicator. Dichloromethane was distilled from P_2O_5. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Avance 600 (600 MHz). Tetramethylsilane (TMS) was used as an internal standard for ^1H and ^{13}C NMR, and CCl_3F was used as an external standard for ^{19}F NMR. All chemical shifts are quoted in δ (ppm), and coupling constants in Hz. Infrared (IR) spectra were recorded on a JASCO FT/IR-660 Plus spectrometer and are reported in wave numbers (cm^{-1}). Mass spectra were obtained on a JEOL, JMS-AX505WA spectrometer at 70 eV ionizing voltage (EI).

4.1. Preparation of 3,5-dibromo-4-[1,3]dioxolan-2-yl-pyridine, 8

Compound **5** (1.00 g, 3.78 mmol), ethane-1,2,-diol (0.5 mL, 8.7 mmol) and *p*-toluenesulfonic acid monohydrate (0.35 g, 1.84 mmol) in benzene (30 mL) were refluxed using Dean-Stark reflux condenser for 12 h. The reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure, and to the residue was added 10% aq NaOH solution (20 mL). The mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography (eluting with ethyl acetate/hexane, 1:5) to provide 1.14 g (98% yield) of the 3,5-dibromo-4-[1,3]dioxolan-2-yl-pyridine (**8**) as yellow solid: mp 74–75 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 4.10–4.12 (2H, m, H-4 and H-5 in dioxolan), 4.35–4.37 (2H, m, H-4 and H-5 in dioxolan), 6.30 (1H, s, H-2 in dioxolan), 8.66 (2H, s, H-2 and H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.2 (C-4 and C-5 in dioxolan), 102.9 (C-2 in dioxolan), 122.1 (C-3), 141.1 (C-2), 152 (C-4); IR (neat) 3020, 2898, 1525, 1407, 1217, 772 cm^{-1}; EIMS (70 eV, *m/z*): 311 $[M+4]^+$ (11), 309 $[M+2]^+$ (19), 307 $[M]^+$ (10).

4.2. Difluorination of compounds 6 and 8 with NFSi

4.2.1. A typical experimental procedure

To a stirred solution of 1.00 g of compound **6** or **8** in dry THF (60 mL) was added 2.5 equiv. *n*-, *s*-, or *t*-BuLi slowly under argon at −78 or −120 °C (ethanol/liquid N_2). The resulting mixture was stirred for 30 min and then 2.5 equiv. *N*-fluorobenzenesulfonimide in dry THF (15 mL) was added dropwise. The reaction mixture was stirred for an additional 3 h at −78 or −120 °C and then allowed to warm to room temperature. The reaction was quenched with sat aq NH_4Cl solution and the mixture was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude residue was purified by silica gel column chromatography (eluting with ethyl acetate/hexane, 1:2).

4.2.2. 3,5-Difluoro-4-methoxymethoxymethyl-pyridine, 7a

This product was prepared from **6** as described above: Red liquid; ^1H NMR (600 MHz, $CDCl_3$): δ 3.39 (3H, s, CH_3 in MOM), 4.71 (2H, s, CH_2–C4), 4.72 (s, 2H, CH_2 in MOM), 8.37 (2H, s, H-2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.30 (**C**H_3 in MOM), 55.69 (d, $^3J_{C-F}$ = 3 Hz, **C**H_2–C4), 96.32 (**C**H_2 in

MOM), 121.44 (t, $^2J_{C-F}$ = 16.4 Hz, C-4), 134.19 (dd, $^2J_{C-F}$ = 23.4 Hz and $^4J_{C-F}$ = 4.6 Hz, C-2 and C-6), 157.05 (dd, $^1J_{C-F}$ = 262.6 Hz, $^3J_{C-F}$ = 3 Hz, C-3 and C-5); ^{19}F NMR (470 MHz, $CDCl_3$): δ −131.67 (s, 2F, CF); IR (neat) 3020, 2927, 1520, 1423, 1219, 773 cm^{-1}; EIMS (70 eV, *m/z*): 189 $[M]^+$ (14), 159 $[M + H–OCH_3]$ (75), 128 $[M - OMOM]$ (100); HRMS (EI): calcd. for $C_8H_9O_2NF_2$: 189.0601, found: 189.0565.

4.2.3. 3-Bromo-5-fluoro-4-methoxymethoxymethylpyridine, **7b**

Red liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.41 (3H, s, CH_3 in MOM), 4.74 (2H, s, CH_2–C4), 4.75 (2H, s, CH_2 in MOM), 8.42 (1H, s, H-6), 8.59(1H, s, H-2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.80 (**C**H_3 in MOM), 61.66 (d, $^3J_{C-F}$ = 2.6 Hz, **C**H_2–C4), 96.86 (**C**H_2 in MOM), 123.40 (C-3), 133.31 (d, $^2J_{C-F}$ = 14.8 Hz, C-4), 137.20 (d, $^2J_{C-F}$ = 25 Hz, C-6), 148.19 (d, $^4J_{C-F}$ = 4.9 Hz, C-2), 158.29 (d, $^1J_{C-F}$ = 263.6 Hz, C-5); ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.56 (s, 1F, CF); IR (neat) 3020, 2927, 1520, 1423, 1219, 773 cm^{-1}; EIMS (70 eV, *m/z*) 250 $[M + 2]^+$ (14), 248 $[M]^+$ (12), 219 $[M - 2H–OCH_3]$ (38), 204 [M − H − MOM] (24), 188 [M − H − OMOM] (100); HRMS (EI): calcd. for $C_8H_9O_2NBrF$: 248.9801, found: 248.9806.

4.2.4. 4-[1,3]Dioxolan-2-yl-3,5-difluoropyridine, **9a**

This product was prepared from **8** as described above: Yellow solid; mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.05–4.08 (2H, m, H-4 and H-5 in dioxolan), 4.21–4.24 (2H, m, H-4 and H-5 in dioxolan), 6.26 (1H, s, H-2 in dioxolan), 8.35 (1H, s, H-2 and H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.3 (C-4 and C-5 in dioxolan), 96.3 (t, $^3J_{C-F}$ = 3.5 Hz, C-2 in dioxolan), 122.2 (t, J_{C-F} = 11.9 Hz, C-4), 135 (dd, $^2J_{C-F}$ = 23.8 Hz and $^4J_{C-F}$ = 5.3 Hz, C-2 and C-6), 157.4 (dd, $^1J_{C-F}$ = 265 Hz and $^3J_{C-F}$ = 3 Hz, C-3 and C-5); ^{19}F NMR (470 MHz, $CDCl_3$): δ −136.80 (s, 2F, CF); IR (neat) 3020, 1520, 1450, 1402, 1219, 773 cm^{-1}; EIMS (70 eV, *m/z*): 187 $[M]^+$ (66), 186 [M − H] (55), 142 $[M - H–CH_2CH_2O]$ (52); HRMS (EI): calcd. for $C_8H_7O_2NF_2$: 187.0445, found: 187.0408.

4.2.5. 3-Bromo-4-[1,3]dioxolan-2-yl-5-fluoropyridine, **9b**

Yellow liquid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.07–4.10 (2H, m, H-4 and H-5 in dioxolan), 4.24–4.27 (2H, m, H-4 and H-5 in dioxolan), 6.27 (1H, s, H-2 in dioxolan), 8.40 (1H, s, H-6), 8.56 (1H, s, H-2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 66.4 (C-4 and C-5 in dioxolan), 101 (C-2 in dioxolan), 121 (C-3), 132.6 (d, $^2J_{C-F}$ = 10 Hz, C-4), 138.2 (d, $^2J_{C-F}$ = 25.6 Hz, C-6), 148.6 (d, $^3J_{C-F}$ = 5.2 Hz, C-2), 158 (d, $^1J_{C-F}$ = 267.5 Hz, C-5); ^{19}F NMR (470 MHz, $CDCl_3$): δ −129.22 (s, 1F, CF); IR (neat) 3020, 1558, 1410, 1219, 1101, 773 cm^{-1}; EIMS (70 eV, *m/z*): 249 $[M + 2]^+$ (72), 247 $[M]^+$ (73), 204 $[M + 2–CH_2CH_2O]$ (52), 202 $[M–CH_2CH_2O]$ (52); HRMS (EI): calcd. for $C_8H_7O_2NBrF$: 246.9644, found: 246.9658.

4.3. Preparation of (3,5-Difluoro-pyridin-4-yl)methanol

Compound **7a** (100 mg, 0.53 mmol) was dissolved in 10% aq HCl solution (10 mL) and stirred for 1 h at 60 °C. The mixture was cooled to 0 °C and then treated with sat aq $NaCO_3$ solution (10 mL). The product was extracted with dichloromethane (3 × 30 mL), dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure at room temperature. The crude material was purified by silica gel column chromatography (eluting with ethyl acetate/hexane, 1:3) to provide 75 mg (97% yield) of the desired product as a white solid: mp 99–101 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.84 (2H, s, C4–CH_2), 8.35 (2H, s, H-2 and H-6); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.6 (t, $^3J_{C-F}$ = 3.6 Hz, **C**H_2–C4), 124.2 (t, $^2J_{C-F}$ = 16.5 Hz, C-4), 134.5 (dd, $^2J_{C-F}$ = 23.8 Hz and $^3J_{C-F}$ = 4.6 Hz, C-2 and C-6), 157.8 (dd, $^1J_{C-F}$ = 262 Hz and $^3J_{C-F}$ = 3.2 Hz, C-3 and C-5); ^{19}F NMR (470 MHz, $CDCl_3$): δ −132.72 (s, 2F, CF); IR (neat) 3020, 1522, 1425, 1402, 1217, 771 cm^{-1}; EIMS (70 eV, *m/z*): 145 $[M]^+$ (100), 116 $[M + H–CH_2OH]$ (40), 96 $[M–CH_2OH–F]$ (20); HRMS (EI): calcd. for $C_8H_9O_2NF_2$: 145.0339, found: 145.0344.

4.4. Preparation of 3,5-difluoro-pyridine-4-carbaldehyde, **2**

4.4.1. Method A: from (3,5-difluoro-pyridin-4-yl)methanol

4.4.1.1. Swern oxidation. To a solution of oxalyl chloride (0.15 mL, 1.73 mmol) in dichloromethane (10 mL) under N_2 at −60 °C was added dropwise a solution of DMSO (0.25 mL, 3.45 mmol) in dichloromethane (2 mL). The mixture was stirred for 10 min, and then a solution of (3,5-difluoro-pyridin-4-yl)methanol (100 mg, 0.69 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred for 20 min, and the mixture was warmed to room temperature. Next, Et_3N (0.6 mL, 4.31 mmol) was added flowed by H_2O. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic layer were washed with H_2O, 5% aq $NaHCO_3$ solution, and brine. Removal of the solvent afforded a crude residue, which was filtered through a plug of silica gel using dichloromethane and the filtrate was carefully concentrated under reduced pressure at room temperature. Finally, the product **2** (very volatile!) was purified through a bulb-to-bulb distillation. A white solid (83 mg, 84% yield) was obtained.

4.4.1.2. Oxidation with PCC. To a stirred suspension of PCC (450 mg, 2.1 mmol) and molecular sieve 4 Å (300 mg) in dichloromethane (100 mL) was added dropwise a solution of (3,5-difluoro-pyridin-4-yl)-methanol (100 mg, 0.69 mmol) in dichloromethane (5 mL). The reaction mixture was vigorously stirred at room temperature under N_2 for 1 h. The resulting dark brown slurry was filtered through a short column of silica and eluted with dichloromethane and carefully concentrated under reduced pressure at room temperature. Finally, the product **2** (very volatile!) was purified through a bulb-to-bulb distillation to provide 77 mg of a white solid (78% yield).

4.4.2. Method B: from compound **8**

Compound **8** (1.0 g, 5.3 mmol) was dissolved in 12 N aq HCl solution (15 mL) and the mixture was refluxed with stirring

for 2 h. The mixture was cooled to 0 °C and then treated with sat aq $NaCO_3$ solution (20 mL). The product was extracted with dichloromethane (3 × 30 mL), dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure at room temperature. Finally, the product **2** (very volatile!) was purified through a bulb-to-bulb distillation to yield 0.80 g (90% yield) as a white solid: mp 51–52 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55(2H, s, H-2 and H-6), 10.42 (1 H, s, CHO); ^{13}C NMR (150 MHz, $CDCl_3$): δ 118.42 (t, $^2J_{C–F}$ = 8.9 Hz, C-4), 136.07 (dd, $^2J_{C–F}$ = 22.8 Hz and $^3J_{C–F}$ = 4.7 Hz, C-2 and C-6), 157.05 (s, $^1J_{C–F}$ = 274.8 Hz, C-3 and C-5), 183.32 (CHO); ^{19}F NMR (470 MHz, $CDCl_3$): δ −132.86 (s, 2F, CF); IR (neat) 3020, 1716, 1421, 1219, 773 cm^{-1}; EIMS (70 eV, *m*/*z*): 144 $[M + 1]^+$ (18), 143 $[M]^+$ (100), 142 $[M - 1]^+$ (61), 114 [*M*–CHO] (25); HRMS (EI): calcd. for $C_6H_3ONF_2$: 143.0183, found: 143.0137.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2006.02.009.

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