A Convenient Large-Scale Synthesis of 4-Fluoro-1-naphthaldehyde and Its Aromatic Nucleophilic Substitution Reactions[1]

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Introduction

The aromatic nucleophilic displacement of halides or the nitro group with strong nucleophiles in dipolar aprotic solvents is a well established method for functional group manipulation of aromatic compounds.[2] Unactivated or scarcely activated chlorobenzenes require high temperatures for this reaction to proceed.[3] The direct displacement reaction of unactivated fluoronaphthalene with sodium thioalkoxides in dimethyl sulfoxide has been reported to require a temperature of 80 °C.[4] The displacement of the nitro group from a singly activated phenyl ring at 25 °C in dipolar aprotic solvents with strong nucleophiles is well documented.[5] It has also been established that the fluoro group and the nitro group have similar reactivities for this mechanism (SnAr).[6] The displacement of a strongly activated nitro group with polyfluorinated alkoxides has been studied with 4-nitrobenzonitrile.[7]

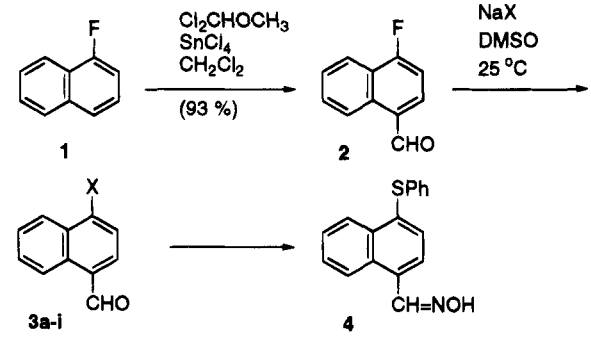
In this note we describe the regiocontrolled synthesis of 1,4-disubstituted naphthalenes and also demonstrate the greater reactivity of our system toward polyfluorinated alkoxides than the system studied by Gupton.[7]

Results and Discussion

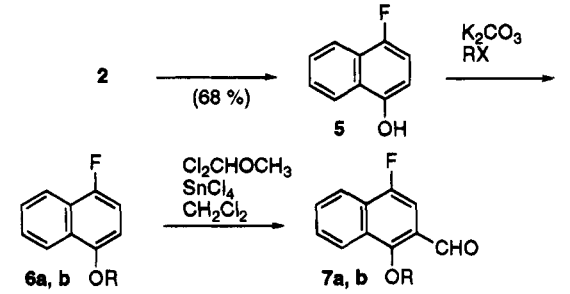
Nucleophilic Substitution Reactions of Fluoronaphthalenes. 1-Fluoronaphthalene was formylated on a 1 mol scale with dichloromethyl methyl ether and tin(IV) chloride in CH_2Cl_2 according to the method of Rieche[8] to yield 4-fluoro-1-naphthaldehyde (**2**) in 93% yield. Nucleophilic displacement reactions were carried out in DMSO at 25 °C (except for the sodium azide reactions which were run in DMF) (Scheme 1). Good yields were obtained with perfluoroalkoxides, thioalkoxides, sodium azide, and the sodium salts of phenolic groups (entries **3a–i**, Table 1). The 4-(phenylthio)-1-naphthaldehyde was oxidized by air to the carboxylic acid upon standing and was therefore immediately derivatized to the corresponding oxime **4** for isolation.

Compound **2** was converted to 4-fluoro-1-naphthol (**5**) by Baeyer–Villiger oxidation and subsequent hydrolysis of the formate ester utilizing the methodology of Rapoport[9] (Scheme 2). The normal product for the Baeyer–Villiger oxidation of an aldehyde is a carboxylic acid, but aryl aldehydes sometimes give formates.[9,10] This results from the migration of the aryl group of the peroxy reactive intermediate rather than the proton as is the usual case for aldehydes.[11] The 4-fluoro-1-naphthol was alkylated with an alkyl halide and potassium carbonate to yield the 4-fluoro-1-alkoxynaphthalenes **6a** and **6b**.

Scheme 1



Scheme 2



Compound **5** has been previously synthesized in five steps from 1-methoxynaphthalene with an overall yield of 24%,[12] or in one step as the minor isomer of a ortho–para mixture (in 13% yield) by the action of cesium fluorooxysulfate, which is not commercially available, on 1-naphthol.[13] In 1990 Umemoto[14] reported the use of *N*-fluoropyridinium triflate, which is more stable than CsO_4F and commercially available, though moderately expensive, but it also gave an ortho–para mixture when reacted with 1-naphthol with only a 9% yield of the para isomer **5**.

Formylation of the 4-fluoro-1-alkoxynaphthalenes with dichloromethyl methyl ether and tin(IV) chloride in CH_2Cl_2 gave 4-fluoro-1-alkoxy-2-naphthaldehydes **7a** and **7b** in good yield as the major products.

1-Fluoro-2-naphthaldehyde (**8**) was prepared according to the method of Shindo.[15] Most of the nucleophilic displacement reactions of **8** (Scheme 3) gave lower yields (entries **9b–e**, Table 1) than those obtained with the 1,4-isomer **2**. This result can be attributed to steric crowding.

(1) Presented at the 34th National Organic Symposium, Williamsburg, VA, June 11th, 1995

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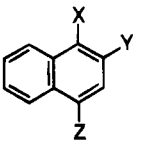
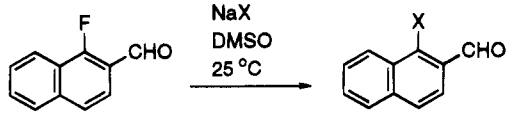
Table 1. Naphthalene Compounds Synthesized[a]



cmpd, no.	X	Y	Z	mp, °C	method	chromatography solvent	% yield
2	F	H	CHO	74–76	A	toluene	93
3a	SMe	H	CHO	61–64[b]	B	toluene	75
3b	S-n-Bu	H	CHO	62–64[c]	B	hexane:toluene/50:50	78
3c	OPh	H	CHO	54–57	B	hexane:EtOAc/98:2	85
3d	2-pyridinyloxy	H	CHO	141–142	B	EtOAc	49
3e	N_3	H	CHO	oil	B[d]	EtOAc	27[e]
3f	OCH_2CF_3	H	CHO	75–77	B	toluene	85
3g	$OCH_2CF_2CF_3$	H	CHO	66–68	B	toluene	44
3h	$OCH_2(CF_2)_2CF_3$	H	CHO	43–44	B	toluene	40
3i	$OCH(CF_3)_2$	H	CHO	130–132[c]	B	toluene	11[f]
4	SPh	H	CH=NOH	106–108[c]	C	hexane:EtOAc/50:50	90
5	F	H	OH	124–126[g]	D	CH_{2Cl2}	68
6a	F	H	OMe	oil	E	toluene	85
6b	F	H	O-Bu	oil	E	hexane	76
7a	OMe	CHO	F	90–92[h]	A	hexane:toluene/50:50	89
7b	O-n-Bu	CHO	F	oil	A	toluene	87
9a	S-n-Bu	CHO	H	oil	B	hexane:toluene/50:50	76
9b	OPh	CHO	H	59–62	B	hexane:toluene/80:20	34
9c	N_3	CHO	H	50–52	B[d]	hexane:toluene/60:40	17
9d	OCH_2CF_3	CHO	H	47–49[c]	B	hexane:toluene/50:50	63
9e	$OCH_2CF_2CF_3$	CHO	H	oil	B	hexane:toluene/70:30	27

[a] Satisfactory analytical data (±0.4% for C, H, N, etc.) were obtained for all compounds. [b] Literature[17] mp 63 °C. [c] Recrystallized from hexane. [d] Used DMF as reaction solvent instead of DMSO. [e] The azido products partially decomposed during chromatography. [f] Recovered 64% of starting material for a 31% conversion. [g] Literature[12] mp 127–128 °C. [h] Recrystallized from EtOH.

Scheme 3



8 **9a-e**

Comparison of the reactivity of 4-Nitrobenzonitrile and 4-Fluoro-1-naphthaldehyde with Polyfluoroalkoxides. In 1985 Gupton investigated the reactivity of polyfluoroalkoxides with 4-nitrobenzonitrile. Reaction with sodium 2, 2, 2-trifluoroethoxide occurred in high yield at 25 °C, but the more highly fluorinated nucleophiles $NaOCH_2CF_2CF_3$ and $NaOCH_2CF_2CF_2CF_3$ required heating for 18–20 h at 150 °C (in HMPA) to give only 55 and 50% products, respectively, and no reaction at all was reported with $NaOCH(CF_3)_2$.[7] All four of these perfluoroalkoxides reacted with 4-fluoro-1-naphthaldehyde (**2**) at 25 °C in our study. The three unbranched perfluoroalkoxides gave products in good to fair yields (entries **3f–h,** Table 1). Under these conditions $NaOCH(CF_3)_2$ gave 11% of the product **3i** and 64% recovered starting material **2** for a conversion of 31%.

Conclusions

The formylation of 1-fluoronaphthalene occurs regiospecifically in high yield to give 4-fluoro-1-naphthaldehyde (**2**), a versatile intermediate for the synthesis of a variety of substituted naphthalenes not previously reported in the literature. The nucleophilic displacement shows wide generality to give 4-substituted-1-naphthaldehydes in high yields.

Furthermore, 4-fluoro-1-naphthaldehyde can be derivatized to 4-fluoro-1-naphthol (**5**), another useful intermediate. Compound **5** can be alkylated in high yield to produce 4-fluoro-1-alkoxynaphthalenes. The aromatic ring can be further derivatized by electrophilic chemistry, as in our examples **7a** and **7b**.

This methodology for the regiocontrolled synthesis of 4-fluoro-1-naphthol from fluoronaphthalene is a significant improvement over the available literature routes, which either require multistep transformations[10] or utilize electrophilic fluorinating agents on 1-naphthol to produce the ortho isomer with the para product as a minor impurity.[13,14]

Experimental Section

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. H^1-NMR spectra were recorded in δ values with $CDCl_3$ or DMSO-d_6 as the solvent. Chromatography was performed (a) by filtering through a glass funnel, which has a sintered glass frit, packed with a layer of sand and a layer of silica gel using house vacuum (this method will be referred to as vacuum filtration chromatography) or (b) using a Waters 4000 prep system on two Porasil (Waters) 47 mm × 300 mm 15–20 μm prep pak cartridges. Vacuum filtration chromatography was used except where indicated otherwise. The analytical samples gave combustion values for C, H, N, S, F within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab and Galbraith Laboratories.

Method A. 4-Fluoro-1-naphthalenecarbaldehyde (2). To a solution of Cl_2CHOMe[16] (149.4 g, 1.3 mol) in 600 mL of CH_2Cl_2 at 0 °C under a N_2 atm was added $SnCl_4$ (338.7 g, 1.3 mol) dropwise. The solution was stirred at 0 °C for 1 h before adding a solution of 1-fluoronaphthalene (150 g, 1.03 mol) in 400 mL of CH_2Cl_2. The resulting mixture was allowed to warm to ambient temperature while being stirred overnight. The solution was poured into 2000 mL of ice–water. The layers were separated, and the organic layer was washed three more times with water and then dried (Na_2SO_4) and concentrated under reduced pressure to give 177.2 g of crude product. Vacuum filtration chromatography with toluene yielded 167.6 g (93%) of **2** as an off-white solid: mp = 74–76 °C; H^1-NMR ($CDCl_3$, 200 MHz) δ 7.28 (dd, J = 8.0, 9.7, 1H); 7.61–7.80 (m, 2H); 7.97 (dd, J = 5.5,

(16) Available from Fluka Chimie AG or can be prepared according to: Gross, H.; Reiche, A.; Hoft, E.; Beyer, E. *Organic Synthesis* **1967**, *47*, 47. Emmons, W., Ed.; John Wiley and Sons, New York, 1967.

8.0, 1H); 8.18 (d, J = 8.2, 1H); 9.31 (d, J = 8.4, 1H); 10.3 (s, 1H). Anal. Calcd for $C_{11}H_7FO$: C, 75.85; H, 4.05. Found: C, 75.86; H, 4.07.

Method B. 4-(Methylthio)-1-naphthalenecarbaldehyde[17] (3a). To a solution of NaSMe (50 g, 0.71 mol) in 800 mL of anhydrous DMSO stirred at 0 °C under a nitrogen atmosphere was added dropwise a solution of **2** (113 g, 0.65 mol) in 800 mL of anhydrous DMSO. After the addition was complete the reaction was allowed to stir another 30 min and then diluted with water and extracted three times with $CHCl_3$. The combined organic phases were washed with water and concentrated under reduced pressure to give 151.2 g of crude product. Vacuum filtration chromatography with toluene yielded 98.1g (75%) of **3a** as a light yellow solid. mp = 61–64 °C; H^1-NMR (DMSO-d_6, 200 MHz) δ 2.70 (s, 3H); 7.57 (d, J = 7.8, 1H); 7.64–7.73 (m, 2H); 8.10 (d, J = 7.8, 1H); 8.20 (d, J = 9.1, 1H); 9.23 (d, J = 9.6, 1H); 10.27 (s, 1H). Anal. Calcd for: $C_{12}H_{10}SO$: C, 71.25; H, 4.98. Found: C, 71.28; H, 4.99

Method C. 4-(Phenylthio)-1-naphthalenecarbaldehyde Oxime (4). 4-(phenylthio)-1-naphthaldehyde (0.5 g, 1.9 mmol) was prepared according to method B and without chromatography was immediately dissolved in 25 mL of EtOH:pyridine/5:1 with NH_2OH·HCl (0.9 g, 20.5 mmol) and heated at 65 °C for 1 h. The solution was concentrated under reduced pressure, and the product was purified by vacuum filtration chromatography with hexane:ethyl acetate/50:50 to obtain a yellow oil which crystallized upon standing. Recrystallization from hexane yielded 450 mg (90%) of **4** as white crystals. mp = 106–108 °C; H^1-NMR (DMSO-d_6, 200 MHz) δ 7.22–7.42 (m, 5H); 7.56–7.75 (m, 3H); 7.81 (d, J = 7.6, 1H); 8.30–8.42 (m, 1H); 8.70–8.80 (m, 1H); 8.83 (s, 1H); 11.60 (s, 1H). Anal. Calcd for: $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01; S, 11.48. Found: C, 72.95; H, 4.65; N, 4.97; S, 11.40.

Method D. 4-Fluoro-1-naphthol[12] (5). A mixture of **2** (80.68 g, 0.47 mol) and MCPBA (317 g of 50–60%, 0.92 mol) in 3 L of CH_2Cl_2 was stirred overnight under a N_2 atmosphere. A 1-L 20% aqueous solution of sodium thiosulfate was added and the solution was allowed to stir at ambient temperature for 45 min. before being poured it into 2 L of 20% aqueous sodium thiosulfate. The layers were separated, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic phases were washed sequentially with 4 L of 20% aqueous sodium thiosulfate and brine and then concentrated under reduced pressure. The residue was dissolved in 1 L MeOH/1 L THF and chilled to 0 °C under a N_2 atm. A solution of 65 g of KOH in 400 mL of MeOH was added as fast as possible without raising the temperature. The solution was stirred an additional 15 min after the addition was complete before the pH was adjusted to 1 with concd HCl. The solution was diluted with water and stirred for 1 h and then extracted twice with CH_2Cl_2. The extracts were combined, dried (Na_2SO_4), and then concentrated under reduced pressure. Purified by vacuum filtration chromatography with CH_2Cl_2 to obtain 51.8 g (68%) of **5** as a tan solid. mp = 124–126 °C; H^1-NMR (DMSO-d_6, 300 MHz) δ 6.77 (m, 1H); 7.11 (m, 1H); 7.55 (m, 1H); 7.92 (m 1H); 8.13 (m, 1H); 10.12 (m, 1H). Anal. Calcd for: $C_{10}H_7FO \cdot {}^1/_{20}\ H_2O$: C, 73.66; H, 4.39; F, 11.65. Found: C, 73.61.; H, 4.57; F, 11.80

Method E. 1-Butoxy-4-fluoronaphthalene (6b). A mixture of **5** (5 g, 0.03 mol) and K_2CO_3 (10 g, 0.072 mol) in 50 mL of 2-butanone was stirred under a N_2 atm for 15 min and then n-butyl bromide (3.2 mL, 0.03 mol) was added dropwise. The resulting solution was refluxed for 12 h. The solution was filtered and concentrated under reduced pressure and purified by vacuum filtration chromatography with hexane to obtain 5.0 g (76%) of **6b** as a green oil. H^1-NMR (DMSO-d_6, 200 MHz) δ 1.00 (t, J = 6.4, 3H); 1.42–1.64 (m, 2H); 1.78–1.97 (m, 2H); 4.15 (t, J = 5.5, 2H); 6.87–6.94 (m, 1H); 7.24 (t, J = 9.6, 1H); 7.57–7.70 (m, 2H); 8.0 (d, J = 8.4, 1H); 8.21 (d, J = 8.8, 1H). Anal. Calcd for $C_{14}H_{15}FO$: C, 77.04; H, 6.93; F, 8.70. Found: C, 77.10; H, 6.96; F, 8.45.

1-Azido-2-naphthalenecarbaldehyde (9c). Prepared from compound **8** (980 mg, 5.6 mmol) and NaN_3 according to method B except that DMF was used as the solvent. Chromatographed with a Waters 4000 prep system on two porasil 47 mm x 300 mm 15–20 μm prep pak cartridges with hexane:toluene/60:40 to obtain 190 mg (17%) of **9c** as a yellow solid. mp = 50–52 °C; H^1-NMR (DMSO-d_6, 200 MHz) δ 7.65–7.83 (m, 2H); 7.94–8.15 (m, 3H); 8.36–8.45 (m, 1H); 10 45 (s, 1H). Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.13; H, 3.62; N, 21.24.

1-(2,2,3,3,3-Pentafluoropropoxy)-2-naphthalenecarbaldehyde (9e). Prepared from compound **8** (1.07 g, 6.1 mmol) according to method B except that the anion of $CF_3CF_2CH_2OH$ was generated in situ from NaH. Chromatographed with a Waters 4000 prep system on two porasil 47 mm × 300 mm 15–20 μm prep pak cartridges with hexane:toluene/70:30 to obtain 500 mg (27%) of **9c** as a dark-yellow oil. H^1-NMR (DMSO-d_6, 200 MHz) δ 5.15 (t, J = 14.3, 2H); 7.65–8.00 (m, 4H); 8.05–8.17 (m, 1H); 8.20–8.30 (m, 1H); 10.47 (s, 1H). Anal. Calcd for $C_{14}H_9F_5O_2$: C, 55.28; H, 2.98. Found: C, 55.37; H, 2.92.

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Supporting Information Available: Elemental analysis and ^{1}H NMR spectra for all compounds, and experimental details for compound **6a** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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