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A new synthesis of 2-fluoro-1-naphthols

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Dedicated to Prof. R.D. (Dick) Chambers on the occasion of his 70th birthday.

Abstract

A general synthesis of 2-fluoro-1-naphthols in two steps from 1-indanones is reported. The 1-indanones are first converted to difluoromethyl 2-fluoro-1-napthyl ethers by reaction with difluorocarbene source, trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA). These ethers are then converted in high yield to the respective naphthols by heating with a mixture of acetic acid and 48% HBr.

Keywords: Difluorocarbene; Indanone; Fluoroaromatics

1. Introduction

The only reported syntheses of 2-fluoro-1-naphthol (**1a**) appear to be those that involve electrophilic fluorination of 1-naphthol by various electrophilic fluorination reagents, which include fluoroxytrifluoromethane [1], $CsSO_4F$ [2,3], *N*-fluoro-*N*-alkylsulfonamides [4], *N*-fluoropyridinium triflate [5], 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (also known as F-TEDA) [6–8], and 4,6-bis(trifluoromethyl) *N*-fluoropyridinium-2-sulfonate (**2**) [9]. These reactions generally lead to preferential formation of the 2-fluoro isomer, although mixtures of both the 2-fluoro and the 4-fluoro isomers were usually reported (Scheme 1). In one contrary example, only the 2-fluoro isomer (in 63% yield), along with a small amount of 2,2-difluoro-3,4-dihydro-2H-naphthalen-1-one, was obtained when 1-naphthol was treated with Umemoto's counteranion-bound *N*-fluoropyridinium reagent (**2**) (Scheme 2) [9].

In the present paper, we report a novel method for the specific synthesis of 2-fluoro-1-naphthols. It will be shown that two different aspects of difluorocarbene chemistry combine to provide an efficient and broadly applicable synthesis of 2-fluoro-1-naphthols from 1-indanones.

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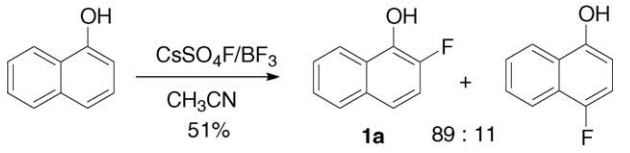
2. Results and discussion

Recently, we reported the sequential reaction of aryl alkyl ketones with two equivalents of difluorocarbene, generated thermally (under fluoride catalysis) from acid free trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) [10], to form difluoromethyl 2,2-difluorocyclopropyl ethers, via the intermediate formation of difluoromethyl enol ethers (Scheme 3) [11].

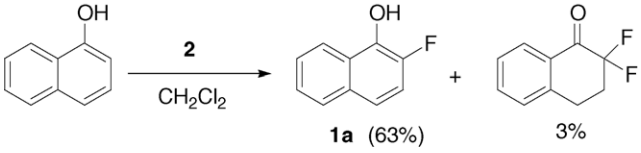
2.1. Synthesis of 2-fluoro-1-naphthyl difluoromethyl ethers

In principle, when the reaction depicted in Scheme 3 is carried out using 1-indanone (**3a**) as substrate, the analogous product (**5a**) should be formed (Scheme 4). However, it is well known that difluorocarbene adducts of both cyclopentadiene [12,13] and indene [14] undergo relatively facile aromatization reactions via thermal dehydrofluorination processes. As indicated in Table 1, a small amount of intermediate compound **5a** with the difluorocyclopropane ring intact could be observed when the reaction with TFDA was carried out in refluxing toluene, but when it was carried out in refluxing xylene none was observed. Under these conditions, the reaction led directly to the aromatized, dehydrofluorinated product, (**6a**) in a very good yield.

When carried out using substituted 1-indanones as substrates, the reaction provides a convenient, general



Scheme 1.



Scheme 2.

synthesis of difluoromethyl ethers of 2-fluoro-1-naphthols, as can be seen in Scheme 5 and Table 1. Together with formation of major fluoronaphthol product **6**, small amounts of intermediate enol ethers **4** or difluorocyclopropanes **5** (generally detected in the NMR spectra of the crude product) were sometimes detected in these reactions.

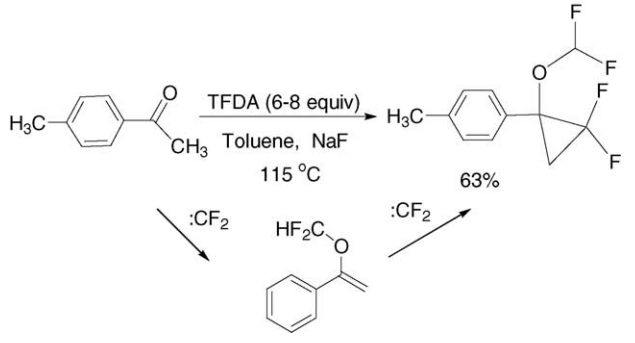
An analogous reaction with 1,3-indanedione proceeded to give enol ether **7** as the major product, together with small amounts of cyclopropane product **8** (Scheme 6). Unlike the case for the indanone-derived cyclopropane products **5**, product **8** has no mechanistically viable aromatization process accessible to it.

It has also been found that 2-indanones undergo chemistry analogous to that of the 1-indanones, but this work is still in the preliminary stages and will be reported separately.

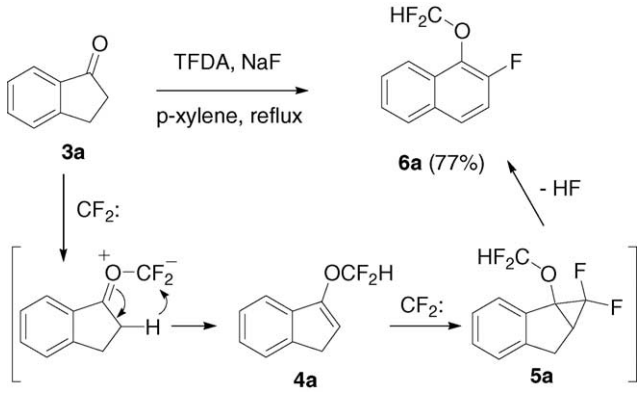
2.2. Conversion of difluoromethyl ethers to naphthols

Finding a good method for conversion of the difluoromethyl ether products, **6**, to their naphthol analogues, **1**, proved to be an experimental challenge, with these ethers being stable to highly acidic conditions such as refluxing 6 M HCl and 48% HBr. Use of electrophilic catalysis, such as refluxing aqueous $AgNO_3$, treatment with solid $AlCl_3$, BF_3 in refluxing THF or SbF_3 in CH_2Cl_2 led either to no reaction or decomposition.

Finally, it was found that heating difluoromethyl ethers **6a–c** in a sealed tube containing a mixture of acetic acid and 48% aqueous HBr at 120 °C overnight led to formation of



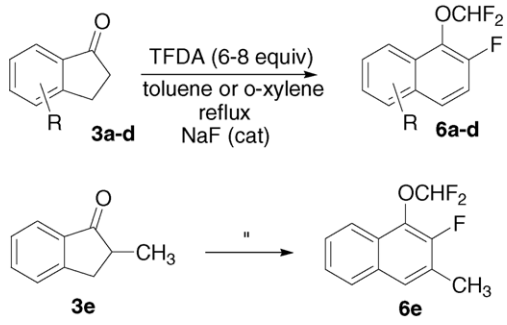
Scheme 3.



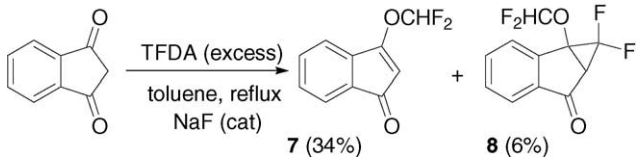
Scheme 4.

Table 1
Conversions of 1-indanones to difluoromethyl 2-fluoro-1-naphthyl ethers

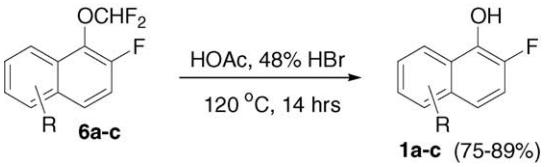
Indanone substrate	R group	Solvent	TFDA (equiv.)	Product	Yield (%)	Side product
3a	H	Toluene	6	**6a**	35	**5a** (6%)
3a	H	Xylene	8	**6a**	77	–
3b	6-methyl	Toluene	6	**6b**	38	–
3b	6-methyl	Xylene	6	**6b**	80	–
3c	5-chloro	Xylene	6	**6c**	20	–
3c	5-chloro	Xylene	8	**6c**	39	–
3d	5-methoxy	Toluene	6	**6d**	53	–
3d	5-methoxy	Xylene	8	**6d**	45	–
3e	2-methyl	Xylene	6	**6e**	37	**4e** (13%)



Scheme 5.



Scheme 6.



Scheme 7.

the respective 2-fluoro-1-naphthols, **1a–c** in yields ranging from 75 to 89% (Scheme 7). The methoxy-substituted difluoromethyl ether, **6d**, did not give satisfactory results in this reaction, whereas **6e** was not attempted.

3. Conclusion

In conclusion, a two step, regiospecific synthesis of 2-fluoro-1-naphthols from 1-indanones is reported. This synthesis should be broadly applicable to the synthesis of most substituted 2-fluoro-1-naphthols for which the appropriate 1-indanone precursors are available.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained at 300 MHz (^{1}H), 75 MHz (^{13}C) and 282 MHz (^{19}F) using $CDCl_3$ as solvent, tetramethylsilane as an internal reference standard for H and C and $CFCl_3$ as external reference for F. Toluene and xylene were distilled from sodium metal under nitrogen immediately before their use as solvents. $FSO_2CF_2COOSiMe_3$ (TFDA) was prepared according to the literature [10]. Sodium fluoride (NaF) was oven dried before use. All other reagents and solvents were obtained from commercial sources and were used without additional purification.

4.2. General procedure for preparation of 1-difluoromethoxy-2-fluoronaphthalenes from substituted 1-indanones, *3a–e*

A 15 mL three-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, and a water-cooled condenser bearing a nitrogen (N_2) inlet. The flask was charged with solvent (either toluene or *p*-xylene), sodium fluoride (0.06 equiv.) and 1.0 mmol of the appropriate 1-indanone, **3a–e**. The solution was heated to reflux and slow N_2 bubbling was initiated and continued for 1 h. Then, TFDA (0.50 g, 2 mmol, 2.0 equiv.) (free of acid according to ^{19}F NMR) was added slowly using a syringe pump via a Teflon® needle at the rate of 0.25 mL/h. After 3 h, an additional two batches of acid-free TFDA (0.50 g, 2.0 mmol, 2.0 equiv.) were added. (Alternatively, two batches of 1.0 g, 4 mmol, 4.0 equiv. were added, according to Table 1). The reaction mixture was then heated for an additional 3 h at reflux. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexanes/AcOEt: 20/1) to give the desired products, **6a–e**.

4.2.1. Reaction of *3a*

In the case of its reaction in toluene, a mixture of 1-difluoromethoxy-2-fluoro-naphthalene, **6a** (35%) and 1α-difluoromethoxy-1,1-difluoro-1,1α,6,6α-tetrahydro-cyclopropa[α]indene, **5a** (6%) (**6a**:**5a** = 100:17) was obtained, in addition to recovered 1-indanone. In the case of its reaction in xylene, only **6a** was obtained.

1-Difluoromethoxy-2-fluoronaphthalene (**6a**): ^{1}H NMR, δ: 6.73 (dd, J = 74.6 and 73.5 Hz, 1H), 7.34 (t, J = 9.7 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 7.70–7.78 (m, 1H), 7.85 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H); ^{19}F NMR, δ: −80.9 (dd, J = 73.2 and 6.1 Hz, 2F), −131.5 (m, 1F); HRMS (EI) calculated: $C_{11}H_7F_3O$, M^+, 212.0449, found: 212.0500.

1α-Difluoromethoxy-1,1-difluoro-1,1α,6,6α-tetrahydro-cyclopropa[α]indene (**5a**): ^{1}H NMR δ: 2.80 (dd, J = 7.4 and 17.3 Hz, 1H), 3.15 (d, J = 17.2 Hz, 1H), 3.50 (dd, J = 7.7 and 17.7 Hz, 1H), 6.35 (dd, J = 71.8 and 75.8 Hz, 1H), 7.21–7.26 (m, 1H), 7.29–7.36 (m, 2H), 7.48–7.56 (m, 1H); ^{19}F NMR, δ: −82.4 (m, 2F), −137.5 (dd, $J_{d(F–F)}$ = 155.6 Hz, $J_{d(F–H)}$ = 18.3 Hz, 1F), −149.9 (d, $J_{d(F–F)}$ = 155.6 Hz, 1F); HRMS (EI), calculated: $C_{11}H_8F_4O_2$, M^+, 232.0511, found: 232.0514.

4.2.2. Reaction with *3b*

1-Difluoromethoxy-2-fluoro-7-methylnaphthalene (**6b**): yellow oil; ^{1}H NMR ($CDCl_3$), δ: 2.38 (s, 3H), 6.55 (t, J = 74.5 Hz, 1H) 7.06 (dd, J = 9.4 and 10.6 Hz, ^{1}H), 7.15 (dd, J = 8.5 and 1.8 Hz, ^{1}H), 7.47 (dd, J = 4.9 and 9.0 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR, δ: 22.3, 115.5 (d, J = 11.3 Hz), 117.2 (t, J = 265 Hz), 120.6 (d, J = 6 Hz), 127.4, 127.5, 127.9, 128.6 (d, J = 3 Hz), 129.6, 138.0, 150.0, 153.5; ^{19}F NMR, δ: −80.7 (dd, J = 73.3 and 6.1 Hz, 2F), −131.8 (m, 1F); HRMS (EI) calculated: $C_{12}H_9F_3O$, M^+, 226.0605, found: 226.0607.

4.2.3. Reaction with *3c*

6-Chloro-1-difluoromethoxy-2-fluoronaphthalene (**6c**): white needles; mp 59–61 °C; ^{1}H NMR, δ: 6.73 (t, J = 74.0 Hz, 1H), 7.37 (dd, J = 9.0 and 9.9 Hz, 1H), 7.54 (dm, J = 9.1 Hz, 1H), 7.65 (dd, J = 4.7 and 9.1 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 9.1 Hz, 1H); ^{19}F NMR, δ: −81.1 (dd, J = 73.2 and 9.2 Hz, 2F), −130.6 (m, 1F); LRMS calculated: $C_{11}H_6ClF_3O$ M^+, 246, 196 M–CF_2.

4.2.4. Reaction with *3d*

1-Difluoromethoxy-2-fluoro-6-methoxynaphthalene (**6d**): yellow needles; mp 62–64 °C; ^{1}H NMR, δ: 3.91 (s, 3H), 6.70 (t, J = 74.6 Hz, 1H) 7.11 (d, J = 2.4 Hz, 1H), 7.22–7.32 (m, 2H), 7.58 (dd, J = 4.6 and 9.0 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H); ^{13}C NMR, δ: 55.6, 106.0, 117.1

(t, J = 266 Hz), 117.0 (d, J = 22.5 Hz), 120.7, 123.4 (k, J = 6 Hz), 124.3, 126.1 (d, J = 2.6 Hz), 132.6, 148.7, 151.9, 158.0 (d, J = 2.5 Hz); ^{19}F NMR, δ: −81.0 (dd, J = 73.3 and 6.1 Hz, 2F), −135.4 (m, 1F); HRMS (EI) calculated: $C_{12}H_9F_3O_2$, M^+, 242.0555, found: 242.0561.

4.2.5. Reaction with **3e**

Following the procedure described above, 110 mg of a light yellow oil mixture of products, 1-difluoromethoxy-2-fluoro-2-methylnaphthalene, **6e** (37%) and 3-difluoromethoxy-2-methyl-1H-indene, **4e** (13%) (**6e**:**4e** = 100:36) was obtained.

1-Difluoromethoxy-2-fluoro-2-methylnaphthalene (**6e**): 1H NMR δ 2.49 (t, J = 1.1 Hz, 3H), 6.72 (t, J = 74.6 Hz, 1H), 7.45–7.58 (m, 3H), 7.76 (d, J = 7.7 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H); ^{19}F NMR δ −80.7 (dd, J = 73.2 and 6.1 Hz, 2F), −135.3 (m, 1F); HRMS (EI) calculated: $C_{12}H_9F_3O$, M^+, 226.0605, found: 226.0663.

3-Difluoromethoxy-2-methyl-1H-indene (**4e**): 1H NMR δ 2.11 (s, 3H), 3.30 (s, 2H), 6.50 (t, J = 74.6 Hz, 1H), 7.17–7.40 (m, 4H); ^{19}F NMR δ −79.7 (d, J = 74.2 Hz, 2F); HRMS (EI) calculated: $C_{11}H_{10}F_2O$, M^+, 196.0700, found: 196.0707.

4.3. Reaction of TFDA with 1,3-indandione

Following the general procedure described above, 15 mg of 1α-difluoromethoxy-1,1-difluoro-1α,6α-dihydro-1*H*-cyclopropa[α]inden-6-one (**8**) and 66 mg of 3-difluoromethoxy-inden-1-one (**7**) were obtained.

1α-Difluoromethoxy-1,1-difluoro-1α,6α-dihydro-1H-cyclopropa[α]indene-6-one (**8**): yellow oil, yield 6%; ^{1}H NMR δ 6.32 (dd, J = 13.4 and 2.3 Hz, 1H), 6.82 (ddd, J_1 = 70.7 Hz, J_2 = 71.9 Hz, J_3 = 1.2 Hz, 1H), 7.64–7.71 (m, 1H), 7.76–7.90 (m, 2H), 8.12 (d, J = 7.8 Hz, 1H); ^{19}F NMR δ −82.0 (m, 2F), −110.4 (dm, J = 354.0 Hz, 2F); HRMS (EI) calculated: $C_{11}H_6F_4O_2$, M^+, 246.0304, found: 246.0295.

3-Difluoromethoxyinden-1-one (**7**): yellow solid, mp 69–71 °C, yield 34%; ^{1}H NMR δ 5.20 (t, J = 1.5 Hz, 1H), 6.66 (t, J = 71.5 Hz, 1H), 7.19–7.23 (m, 1H), 7.27–7.39 (m, 2H), 7.40–7.44 (m, 1H); ^{13}C NMR δ 101.3, 114.9 (t, J = 265.6 Hz), 119.1, 122.0, 130.8, 131.3, 132.9, 138.3, 169.8, 193.6; ^{19}F NMR δ −86.7 (d, J = 73.2 Hz, 2F); LRMS: $C_{10}H_6F_2O_2$, M^+ 196, (M–CF_2) 146.

4.4. General procedure for preparation of 2-fluoro-1-naphthols, **1a–c**

A sealed tube containing 0.33 mmol of difluoromethylether (**6a–c**), glacial acid (2.5 mL), and 48% hydrogen bromide (1.5 mL) was heated to 120 °C overnight. The tube was then cooled and opened carefully. The reaction mixture was poured into water, and the aqueous layer was extracted three times with diethyl ether. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated. The pure naphthol products, **1a–c**, were obtained by flash chromatography.

2-Fluoro-1-naphthol (**1a**): white solid, 52 mg (85%); mp 72–74 °C (lit 71–73 °C) [1]; ^{1}H NMR 5.91 (s, 1H), 7.22–7.32 (m, 1H), 7.34–7.47 (m, 1H), 7.53–7.62 (m, 1H), 7.72–7.83 (m, 2H), 8.02–8.11 (m, 1H); ^{19}F NMR −145.8 (m, 1F); IR(CH_2Cl_2) 3562, 3044, 2966, 1605, 1058, 941, 867, 816; MS: 162 (M^+, 83), 149(50), 133(100), 114(29), 85(23).

6-Methyl-2-fluoro-1-naphthol (**1b**): white solid, yield 75%; mp 83–85 °C; ^{1}H NMR 2.58 (s, 3H), 5.42 (s, 1H), 7.16–7.36 (m, 3H), 7.68 (d, 15 Hz, 1H), 7.94–7.98 (m, 1Hz); ^{19}F NMR −145.0 (dd, 7.6 Hz, 29.6 Hz, 1F); ^{13}C NMR 22.19, 114.50, 114.79, 116.04, 120.33, 120.43, 120.57, 120.66, 127.74, 128.09, 135.99; MS: 176(M^+, 100), 147(38), 133(66), 128(36), 64(18); HRMS: 176.0629, required, $C_{11}H_9FO$, 176.0637.

5-Chloro-2-fluoro-1-naphthol (**1c**): white solid, yield 89%; mp 96–98 °C; ^{1}H NMR 5.56 (s, 1H), 7.24–7.32 (m, 2H), 7.41–7.46 (m, 1H), 7.77–7.79 (m, 1H), 8.10–8.16 (m, 1H); ^{19}F NMR −145.3 (m, 1F); ^{13}C NMR ($CDCl_3$), 116.7, 117.1, 119.7, 119.8, 123.6, 123.7, 126.5, 126.5, 126.5, 127.0; MS, 196 (M^+, 100), 198(33), 148(9), 133(46), 113(12); HRMS: 196.0091, required, $C_{10}H_6FClO$, found 196.0091.

Acknowledgment

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