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A SIMPLE CONVENIENT METHOD FOR PREPARATION OF DIFLUOROMETHYL ETHERS USING FLUOROSULFONYLDIFLUOROACETIC ACID AS A DIFLUOROCARBENE PRECURSOR

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SUMMARY

In the presence of catalytic amounts of sodium sulfate or cuprous iodide, a variety of alkyl and aryl difluoromethyl ethers were synthesized in moderate yields by the reaction of the corresponding alcohols and phenols with fluorosulfonyldifluoroacetic acid (1) in acetonitrile under mild conditions. Fluorosulfonyldifluoroacetate anion [$FO_2SCF_2CO_2^-$] (5) is believed to readily eliminate SO_2, CO_2 and F^-, thus liberating CF_2:; insertion of difluorocarbene into O-H bonds and its capture by fluoride ion then result in the formation of ethers and by-product CF_3H, respectively.

INTRODUCTION

The introduction of fluorine, either alone or in conjunction with the other halogens, into organic compounds has brought a revolution in the field of anesthesiology [1-3]. As a class, fluorinated ethers show the widest spectrum of unpredictable biological response. Compounds such as enflurane (CHF_2OCF_2CHFCl),

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isoflurane ($CHF_2OCHClCF_3$) [2] are excellent anesthetics and are in clinical use at the present time. Therefore, the search for simpler, more convenient synthetic methods for the preparation of new fluorinated ether type anesthetics is still attractive.

The key step for synthesizing a difluoromethyl ether is difluoromethylation of alcohols via a difluorocarbene insertion reaction. For example, Croix has described the preparation of the intermediate isofluorane precurser, difluoromethyl 2,2,2-trifluoroethyl ether, CF_3CH_2-$OCHF_2$, by autoclaving the corresponding fluoroalcohol with $CHClF_2$ in the presence of base [2,4]. An alternative method for synthesizing difluoromethyl ethers is from the photolysis of difluorodiazirine with alcohols in glass ampoules [5]. Owing to the unavailability of CF_2N_2, the application of this method is seriously limited. In connection with our previous work [6], describing fluorosulfonyldifluoroacetic acid, $FO_2SCF_2CO_2H$, (1), as a difluorocarbene precurser, we envisioned using it to synthesize difluoromethyl ethers. The acid is available because the corresponding acid fluoride is one of the starting materials for producing the commercial ion-exchange resins, Nafion H ® [7].

RESULTS AND DISCUSSION

Treatment of a range of alcohols and phenols, (2), with fluorosulfonyldifluoroacetic acid (1) in the presence of catalytic amounts (20 mol%) of sodium sulfate in acetonitrile at 45-55 °C for 1-2 h gave the corresponding difluoromethyl ether in moderate yield.

$$\underset{1}{FO_2SCF_2CO_2H} + \underset{2}{ROH} \longrightarrow \underset{3}{ROCF_2H} + \underset{4}{HCF_3} + SO_2 + CO_2$$

R = CH_3(a), C_2H_5(b), $(CH_3)_2CH$(c), $CH_3(CH_2)_9$(d), CF_3CH_2(e), $H(CF_2)_2CH_2$(f), $C_6H_5CH_2$(g), C_6H_5(h), p-$CH_3C_6H_4$(i), p-$NO_2C_6H_4$(j) C_6F_5(k), 2-naphthyl(l), o-HOC_6H_4(m), C_6H_5(n) [from thiophenol, the product, (3n), is $C_6H_5SCF_2H$].

Fluoroform (4)is the only by-product in the reaction. As described in our previous work [6], aprotic polar solvents, such as dimethylsulfoxide,diglyme, monoglyme, tetrahydrofuran and dimethylformamide could not be used and acetonitrile is the most suitable solvent for the reaction. Solvent,(acetonitrile) has to be well dried prior to use, otherwise, another product, difluoromethanesulfonyl fluoride FSO_2CF_2H, may be formed. Representative examples are listed in Table 1.

TABLE 1

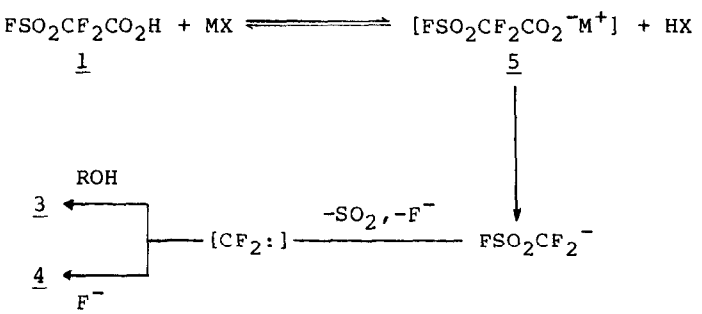
The reaction of 1 with 2 in CH_3CN

Entry	2	1/2	T(°C)	t(h)	Additive	conversion(%) of 1[a]	Product%[b] 3	4
1	2a	1:4	45	2	Na_2SO_4	91	57	30
2	2b	1:3	50	1	Na_2SO_4	94	53	32
3	2c	1:3	50	1	Na_2SO_4	95	58	30
4	2d	1:3	45	1	Na_2SO_4	90	68	20
5					CuI	90	52	40
6	2e	1:3	45	2	Na_2SO_4	84	38	60
7	2f	1:3	50	2	Na_2SO_4	98	43	50
8	2g	1:2.5	50	2	Na_2SO_4	88	60	24
9	2h	1:2	50	2	Na_2SO_4	85	10	78
10					CuI	80	42	43
11	2i	1:2	50	2	Na_2SO_4	85	15	70
12					CuI	85	44	40
13	2j	1:2	50	2	Na_2SO_4	80	10	77
14					CuI	80	38	50
15	2k	1:2	50	2	Na_2SO_4	80	11	72
16					CuI	74	32	53
17	2l	1:2	55	2	Na_2SO_4	80	12	70
18					CuI	80	48	40
19	2m	4:1	60	6	CuI	90	53[c]	-
20	2n	1:2	60	2	Na_2SO_4	85	28	63
21					CuI	85	44	42

[a] Conversion was determined by ^{19}F NMR. [b] Isolated yield.

[c] o-Bis(difluoromethoxy)benzene was not observed even with the higher molar ratio (10:1).

The results in Table 1 show that in the presence of Na_2SO_4 the yields of alkyl difluoromethyl ether varied from 40% to 60%, while that of aryl difluoromethyl ether was rather poor (~10%). It was found that by using cuprous iodide instead of sodium sulfate the yields of the ether could be improved significantly (30-40%). All these results can be rationalized in terms of the similar mechanism proposed earlier [6], i.e. the first step of the reaction involves the conversion of 1 to sodium (or cuprous) fluorosulfonyldifluoroacetate (5); 5 is unstable and decomposes readily to generate CF_2: with simultanous elimination of SO_2 and F^-. Difluorocarbene either inserts into an O-H bond, yielding the expected corresponding difluoromethyl ether, or captures F^- giving CF_3^- and then CF_3H.



M= K, Cu, etc. X= I, SO_4 etc.

The difference in yield of the aromatic difluoromethyl ether depending on whether sodium sulfate or cuprous iodide is used probably arises from the various effects of the salts on the decomposition of 1. No difference was observed when 1 was decomposed in the presence of catalytic amounts of sodium or potassium fluoride over 1.5 h at 60 °C (conversion, 100%; yield of 4, 93%). It was found that the rate of decomposition of 1 in the presence of Na_2SO_4 is faster than that with cuprous iodide, as shown in Table 2.

TABLE 2

Decomposition of 1(%) with catalytic amounts of salts at 60°C

Salt/t(h)	0.5	1	1.5	2
Na_2SO_4	34	83	100	-
CuI	21	64	85	100

Further studies of the effects of salts on the decomposition of 1 are in progress.

EXPERIMENTAL

All boiling points were uncorrected. NMR spectra (chemical shifts in ppm from external TMS for ^1H NMR and from external TFA for ^{19}F NMR; positive values indicate upfield shifts)were recorded on an EM-360 NMR spectrometer at 60MHz. Infrared spectra were measured on a Shimadzu IR -440 instrument. Mass spectra were recorded with a GC-MS-4021 spectrometer.

All solvents and reagents were dried and purified prior to use; 1 was prepared according to the literature method [8].

Synthesis of difluoromethyl ethers

The following procedure is typical: 2d, 9.5g (0.06mol), Na_2SO_4, 0.57g (0.004mol) and CH_3CN (30ml) were placed in a 100ml three-necked round-bottomed flask fitted with a magnetic stirrer, a dropping funnel and a refluxing condenser connected with a dry-ice trap; 1,3.6g (0.02mol) was then added with stirring at 45°C. After addition, the mixture was further stirred for 1h at this temperature. ^{19}F NMR analysis showed that the conversion was 90%. Sulfur dioxide was collected in the cold trap. The gas mixture was then passed into the solution of sodium hydroxide to eliminate CO_2. The gas remained was identified as

HCF_3 (90ml,20%) by GC-MS spectroscopy. The reaction mixture was poured into water, the aqueous layer was extracted three times with diethyl ether, the combined extracts were washed with water and dried over Na_2SO_4 and the ether was distilled off. Distillation under reduced pressure gave 3d, 2.4g (68%). Using CuI instead of Na_2SO_4, 3d, 2.2g (52%) and 4 (189ml, 40%) were obtained.

3d: b.p. 65°C/1.5mm. IR(film) 2930,2860,1469,1195-1210,1005-1015. MS M/e(rel.int.) 207(2.74),187(0.75),159(7.42),141(13.86),112(13.50), 97(32.98),83(67.66),71(89.57),51(100). ^1H NMR δ0.80-1.34(m, 19H), 3.46(t, 2H), 5.93(t, 1H). ^{19}F NMR δ 6.6(d, J_{H-F}=73Hz). Analysis: Found: C, 63.72; H, 11.05; F, 17.83. $C_{10}H_{22}OF_2$ requires C, 63.41; H, 10.67; F, 18.24.

3a: b.p. -4---6°C (lit[9] -4°C). ^{19}F NMR δ6.5(t, J_{H-F}=76Hz).

3b: b.p. 24-26°C (lit[10] 24°C/734mm). ^1H NMR δ0.8(t, 3H), 3.66(q, 2H), 5.66(t, 1H). ^{19}F NMR δ7.6(d, J_{H-F}=78Hz).

3c: b.p. 46°C (lit[11] 44.5°C). ^{19}F NMR δ7.6(d, J_{H-F}=78Hz).

3e: b.p. 28-30°C (lit[12] 29°C). ^{19}F NMR δ-13(t, J_{H-F}=12Hz, 3F), 5.4(d, J_{H-F}=74Hz).

3f: b.p. 90-92°C (lit [13] 92°C). ^{19}F NMR δ 6.8(d, J_{H-F}=76Hz).

3g: b.p. 120-122°C/2mm. (lit [14] 149°C/6mm).
^{19}F NMR δ 5.8(d, J_{H-F}=75Hz).

3h: b.p. 60°C/3mm. (lit [15] 37°C/13mm). ^1H NMR δ6.00(t, 1H), 6.90 (m, 5H). ^{19}F NMR δ 4.29 (d, J_{H-F}=78 Hz).

3i: b.p. 55-57°C/6mm. (lit [15] 28-29°C/3mm).
^{19}F NMR δ5.6(d, J_{H-F}=76Hz).

3j: m.p. 32-34°C. (lit [15] 32-32.5°C).
^{19}F NMRδ4.8(d, J_{H-F}=78Hz).

3k: b.p. 128-130°C. (lit[16] 129.5-130°C). ^{19}F NMR δ 4.6 (d, J_{H-F}=72Hz), 75.0(m, 2F), 85.0(m, 2F), 78.3(m, 2F).

3l: b.p. 110-112°C/3.5mm. (lit[15] 128-130°C/14mm). ^{19}F NMR δ 5.5 (d,J_{H-F}=77Hz).

3m: b.p. 75-76°C/10mm. (lit [17] 84°C/18mm). ^{19}F NMR δ 4.4(d, J_{H-F}=76Hz).

3n: b.p. 73-75°C/10mm. (lit [9] 62-63°C/7mm). ^{19}F NMR δ 13.2(d, J_{H-F}=74Hz).

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