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1,3-Bis(t-butyldimethylsiloxy)prop-2-yl 2,5-Dichlorobenzenesulphonate as a Convenient Unit for Fluoroisopropenyl Etherification of Phenols

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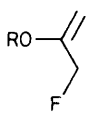
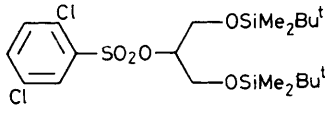
Phenols are converted into new fluoroisopropenyl ethers *via* etherification with 1,3-bis(t-butyldimethylsiloxy)prop-2-yl arenesulphonate followed by fluoro-olefination with Bu^n_4NF–RSO_2F.

The fluoroisopropenyloxy group is of interest in the design of specific synthons in drug design.[1,2]

We have attained the first synthesis of the fluoroisopropenyl phenyl ethers (**5**) utilizing 1,3-bis(t-butyldimethylsiloxy)prop-2-yl 2,5-dichlorobenzenesulphonate (**2**),† an excellent etherification reagent providing the necessary access to successive fluoro-olefination, and herein, we describe a facile preparation of aryl fluoroisopropenyl ether using the Bu^n_4NF–RSO_2F system in the crucial step.[4]



(**1**)

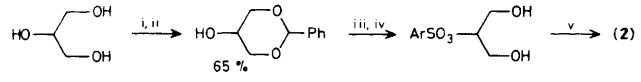


(**2**)

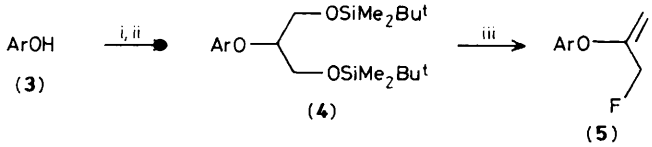
Bis(siloxy)isopropyl etherification of phenols was readily performed (Scheme 1) *via* reaction of sodium phenoxides with (**2**) in the presence of 18-crown-6 in refluxing tetrahydrofuran (THF). We next examined fluoro-olefination of the bis(siloxy)-isopropyl ether (**4**) and found that the Bu^n_4NF–RSO_2F system effected the desired transformation in which the use of 3—4 equiv. of RSO_2F (R = tolyl or methyl) and 5—6 equiv. of Bu^n_4NF at 50 °C in THF was crucial for optimum results. Table 1 summarizes the results of etherification and fluoro-olefination.

As shown in Table 1, a variety of phenols were converted into the bis(siloxy)isopropyl ethers (**4**) in good yield and the fluoro-olefination also proceeded to give the fluoroisopropenyl ethers (**5**) in high selectively in all cases except for a

† The use of (**2**) is preferable to other sulphonates examined (toluene-*p*-, methane-, 4-chlorobenzene-, 2,4,5-trichlorobenzene-, and trifluoromethane-sulphonate), since it showed the highest reactivity and adequate stability (the trifluoromethanesulphonate decomposed readily). It was prepared in the following manner:



For the first three steps see ref. 3. *Reagents:* i, PhCHO; ii, H^+; iii, $ArSO_2Cl$, pyridine, 89%; iv, $B(OEt)_3$, H_3BO_3, 80%; v, Bu^tMe_2SiCl, dimethylformamide, imidazole, 100%.



Scheme 1. *Reagents:* i, NaH, THF; ii, (**2**), 18-crown-6, THF; iii, Bu^n_4NF.

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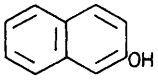
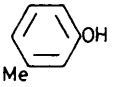
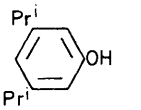
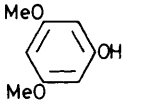
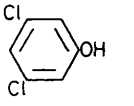
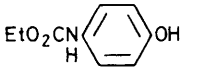
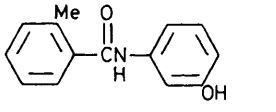
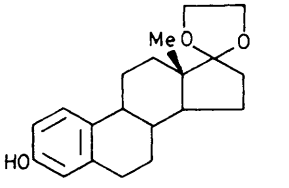
Table 1. Fluoroisopropenylation of phenols.[a]

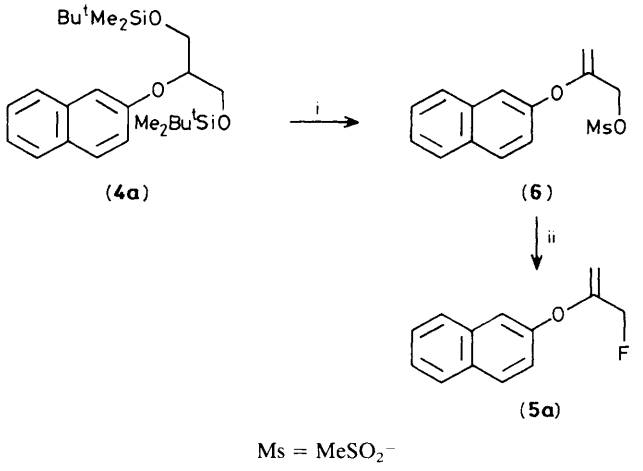
	(3)	(4),[b] % yield[c]	(5),[b] % yield[c]
a		99	70
b		74	40
c		84	70
d		70	42
e		95	52
f		75	42
g		78	61[d]
h		96	52

[a] Reaction conditions, see text. [b] All compounds have been fully characterized by spectroscopic methods. [c] Isolated yield. [d] 1,3-Difluoroprop-2-yl ether (14%) was formed.

single example.‡ However, phenyl fluoroisopropenyl ether was unstable under the reaction conditions, and it was obtained in poor yield (<5%), whereas substituents on the aromatic ring increased the stability of the product, and the fluoroisopropenyl ethers listed in Table 1 were reasonably stable. We examined the stability of the fluoroisopropenyl ether (**5g**) under acidic conditions, and found that it remained unaffected in acetic acid at room temperature and it was 50% hydrolysed in 2 M HCl–THF at room temperature after 12 h.

Close examination of the fluoro-olefination step has revealed that the reaction proceeds *via* the intermediate allyl methanesulphonate. For example, treatment of (**4a**) with Bu^n_4NF–$MeSO_2F$ in THF at 50 °C for 10 min gave (**6**) as an initial product, which was completely converted into (**5a**) after

‡ In the case of entry g in Table 1, 1,3-difluoroprop-2-yl ether was formed in 14% yield along with the desired product. However, it can be converted into (**5**) by potassium t-butoxide in THF at room temperature.



(4a) (6) (5a)

Ms = $MeSO_2$

Scheme 2. *Reagents:* i, Bu^nNF, MsF, THF, 50 °C; ii, F^-.

18 h (Scheme 2). Thus the nature of fluoride anion as a base[5] predominated over that as a nucleophile at the initial stage.

The present fluoroisopropenylation procedure offers a mild and selective preparation of new fluoroisopropenyl phenyl ethers inaccessible otherwise,[6] where the dual role of fluoride anion as base and as nucleophile appears most advantageous.§

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References

1 See for example, M. Schlosser, *Tetrahedron*, 1978, **34**, 3; 'Biomedical Aspects of Fluorine Chemistry,' eds. R. Filler and Y. Kobayashi, Kodansha Ltd., Elsevier Biomedical Press, Tokyo, New York, 1982; H. Yoshioka, C. Takaya, and N. Matsuo, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 809.
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4 M. Shimizu, Y. Nakahara, and H. Yoshioka, *Tetrahedron Lett.*, 1985, **26**, 4207.
5 For a review, see J. H. Clark, *Chem. Rev.*, 1980, **80**, 429; for recent examples, see R. J. P. Corriu and R. Pertz, *Tetrahedron Lett.*, 1985, **26**, 1311; M. Joucla and J. Le Brun, *ibid.*, 1985, **26**, 3001.
6 Mukaiyama prepared benzyl fluoroisopropenyl ether (**1**, R = $PhCH_2$) from the reaction of benzyl bromide with 1,3-difluoropropan-2-ol followed by dehydrofluorination with potassium t-butoxide; T. Mukaiyama, M. Oshima, H. Nagaoka, and M. Murakami, *Chem. Lett.*, 1984, 6154.

§ The following example represents a typical experimental procedure: To a solution of sodium 2-naphthoxide (0.66 mmol) prepared from 2-naphthol (96 mg, 0.66 mmol) and sodium hydride (53 mg, 60% in mineral oil, 1.32 mmol) in THF (6 ml) was added to a mixture of (**2**) (530 mg, 0.99 mmol) and 18-crown-6 (100 mg, 0.38 mmol) in THF (6 ml) at room temperature. After stirring at reflux for 14 h, the reaction mixture was quenched by adding saturated aq. NaCl followed by extraction with AcOEt (10 ml × 3). The combined extracts were dried and concentrated to leave an oil, which was purified on t.l.c. (eluant: 10% AcOEt in n-hexane), to give (**4a**) (296 mg, 99%) as a colourless oil. A mixture of (**4a**) (117 mg, 0.26 mmol) and mesyl fluoride (90 mg, 0.92 mmol) in THF (5 ml) was added to a solution of Bu^n_4NF (415 mg, 1.32 mmol) in THF (5 ml), in the presence of 4Å molecular sieve (1 g), and the mixture was stirred at 50 °C for 18 h. The brown mixture was filtered through Celite with the aid of AcOEt, and the filtrate was washed with saturated aq. NaCl. Drying and concentration gave an oil which was purified on t.l.c. (eluant: 1% AcOEt in n-hexane) to give (**5a**) (37 mg, 70%) as a colourless oil: n.m.r. ($CDCl_3$) δ 4.30 (d, 1H, *J* 1.8 Hz), 4.60 (unresolved dd, 1 H, *J* 1.8, 1.75 Hz), 4.95 (d, 2 H, *J* 46.8 Hz), 7.12—7.92 (m, 7 H).