A Simple Preparative Route to New Fluoroisopropenyl Carbamates and Ethers

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1,3-Dihalogenoprop-2-yl chloroformate and chloromethyl 1,3-dichloroprop-2-yl ether are used as versatile reagents for fluoroisopropenyl carbamylation and fluoroisopropenoxymethyl etherification, respectively.

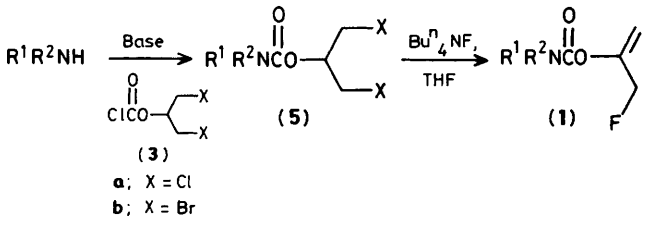
It is one of the most important yet difficult problems in potential drug design to increase the stability of enol esters, especially carbamates, since they are generally too susceptible to acid hydrolysis to utilize for new drug designs, although many drugs possess carbamate moieties, and isopropenyl carbamates in particular have very attractive features with a view to structure–activity studies.[1] One intriguing solution to the problem is the introduction of fluorine atom(s) into the isopropenyl group, and we have recently reported a convenient method for fluoroisopropenyl etherification of phenols[2] utilizing the intrinsic nature of the fluoride anion as a base[3] and as a nucleophile.[4] However, no methodology has been available until now for the preparation of fluoroisopropenyl carbamates (**1**). We have found that 1,3-dihalogenoprop-2-yl chloroformates (**3**)† are versatile reagents for carbamylation and also possess other useful functional groups.

1,3-Dihalogenoprop-2-yl carbamates (**5**) were readily prepared in good yields (>80%) from (**3**) and a secondary amine in the presence of triethylamine or pyridine. Fluoro-olefination[2a] was carried out with 3—4 equiv. of tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) at 50—65 °C, and the fluoroisopropenyl carbamates (**1**) were synthesized for the first time in moderate to good yields. The results are shown in Table 1.

The reaction was primarily influenced by steric effects of the alkyl groups in (**5**): with bulkier groups, the reaction proceeded smoothly to give (**1**) in good yields (**1a**,**b**, and **c**), whereas with less bulky substituents, the fluoride anion induced cleavage of the C–N bond and considerable amounts of free amines were formed as by-products [see (**1f** and **g**)].‡ We thought that this might be owing to attack at the carbonyl carbon by the naked fluoride anion, and in an effort to minimize these undesired side reactions we tried the fluoro-olefination reaction using the acetal-type analogue (**6**) prepared from chloromethyl 1,3-dichloroprop-2-yl ether (**4**)§ and a phenol.

The chloromethyl ether (**4**) is an excellent etherification reagent: phenol ethers (**6**) were prepared from (**4**) and the corresponding sodium phenoxides in good yields (>90%). Subsequent fluoro-olefination with 4—5 equiv. TBAF in THF at 50—60 °C gave the fluoroisopropenyl ethers (**2**), and the results are summarized in Table 2. The fluoro-olefination proceeded cleanly to give (**2**) in excellent yields, and the chemoselectivity is noteworthy: other functional groups were not affected under the fluoro-olefination conditions [see (**2e**)].

Next, we examined the stability of the fluoroisopropenyl carbamates (**1**) and fluoroisopropenoxymethyl ethers (**2**) using (**1a**), (**1e**), and (**2c**) as models. The carbamates (**1a**) and (**1e**) remained intact upon treatment with AcOH–H_2O, 2 M HCl–H_2O–THF, and 2 M NaOH–H_2O–THF at room temp., for 24 h, whereas the ether (**2c**) was 30% hydrolysed in 1 M HCl–H_2O–THF at room temp. for 24 h.



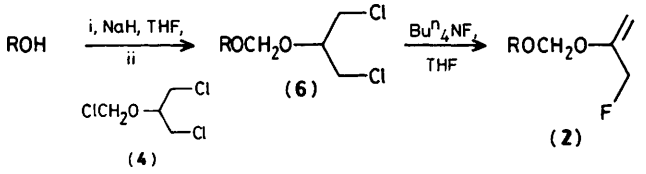
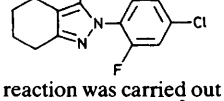


Table 1. The preparation of (**1**) from (**5**).[a]

	R^1	R^2	X	Temp. /°C	Time /h	% Yield of (**1**)[b]
a;	Pr^i	Cyclohexyl	Cl	65	8	72
b;			Br	50	18	81
c;	Pr^i	Pr^i	Cl	65	8	63
d;	Cyclohexyl	Cyclohexyl	Br	50	18	47
e;	Bu^t	$PhCH_2$	Cl	65	6	42
f;	Et	Et	Cl	50	18	31
g;	$-[CH_2]_5-$		Cl	65	8	0
h;	$-Me_2C[CH_2]_3CMe_2-$		Cl	65	8	55

[a] The reaction was carried out with (**5**) : Bu^n_4NF 1 : 3~4 in THF in the presence of 4 Å molecular sieves. [b] Isolated yield. All compounds gave satisfactory spectral data.

Table 2. The preparation of (**2**) from (**6**).[a]

	R	Time/h	% Yield of (**2**)[b]
a;	Ph	6	91
b;	4-MePh	6	95
c;	4-MeOPh	6	93
d;	1-Naphthyl	8	96
e;		6	72

[a] The reaction was carried out with (**6**) : Bu^n_4NF 1 : 4 in refluxing THF in the presence of 4 Å molecular sieves. [b] Isolated yield. All compounds gave satisfactory spectral data.

† (**3a**) and (**3b**) were prepared by the reaction of the corresponding 1,3-dihalogenopropan-2-ol and trichloromethyl chloroformate in toluene in the presence of triethylamine at 70 °C for 4 h (b.p.s, (**3a**): 95—101 °C, 17 mmHg; (**3b**): 70—74 °C, 1 mmHg). *Cf.* ref. 5.

‡ The fluoro-olefination reaction with alkyl(or aryl) 1,3-dichloroprop-2-yl carbonates gave the starting alcohols resulting from cleavage of the esters.

§ (**4**) was prepared by bubbling an excess of HCl gas into a mixture of 1,3-dichloropropan-2-ol and paraformaldehyde at 0 °C during 8 h (b.p., 48—50 °C, 2 mmHg). *Cf.* ref. 6.

Thus, the readily available reagents (**3**) and (**4**) coupled with the very efficient fluoro-olefination procedure with the naked fluoride anion offer a straightforward approach to fluoroisopropenyl carbamates (**1**) and ethers (**2**) which provide us with highly promising synthons for new drug designs.

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