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A New Approach to Synthesis of *gem*-Difluorocyclopropanes Substituted With Electron Withdrawing Group

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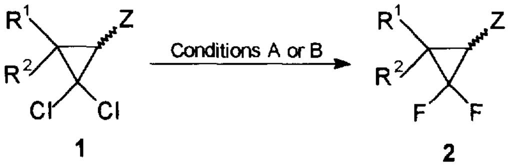
Abstract: *gem*-Dichlorocyclopropanes **1** react with tetra-n-butylammonium fluoride trihydrate in DMF or with potassium fluoride and tetra-n-butylammonium hydrogen sulphate in acetonitrile/water mixture, to afford *gem*-difluorocyclopropanes **2**, in moderate yields.

Cycloaddition of difluorocarbene to alkenes is the method of choice for the synthesis of *gem*-difluorocyclopropanes.[1] However, difluorocarbene is of all dihalocarbenes the least electrophilic species,[2-3] therefore it adds rather sluggishly to alkenes substituted with electron-withdrawing group (EWG). Practically, *gem*-difluorocyclopropanes can be synthesized from electrophilic alkenes if difluorocarbene is generated from phenyl(trifluoromethyl)mercury cleavage mediated by potassium iodide,[4-5] via decomposition of sodium chlorodifluoroacetate[6-8] or 3,3-difluoro-3H-diazirine.[9] However, all these reagents suffer from disadvantages: troublesome conditions of difluorocyclopropanation with mercury derivative, large excess of sodium salt needed, and explosive nature of diazirine precursors,[10] respectively.

We found at present that reaction of *gem*-dichlorocyclopropanes **1** with excess of commercial tetra-n-butylammonium fluoride (TBAF) trihydrate[11] in DMF at 0-5 °C for 4 h (conditions A), or with excess of potassium fluoride and tetra-n-butylammonium hydrogen sulphate (TBAHS)[12] in acetonitrile/water mixture, at ca 80 °C for 8 h (conditions B), afforded the expected products **2**, in moderate yields.



Under conditions given above practically all *gem*-dichlorocyclopropanes **1** were consumed, however formation of some tarry products, particularly under conditions B, was observed. Furthermore, taking into account rather small scale of synthesis of **2**,[13] and fact that some of these products are volatile, their partial loss during work up of reaction mixtures and purification is unavoidable. Concerning the availability of the starting *gem*-dichlorocyclopropanes **1**, 1,1-dichloro-2-alkoxycarbonylcyclopropanes **1a-c** are now easily synthesized *via* reaction of chloroform with the corresponding acrylates, carried out under phase-transfer catalytic (PTC) conditions, with tetramethylammonium salt as a catalyst.[14-15] Apart from substrates **1** listed in Table, some other

Table. *gem*-Difluorocyclopropanes **2** from **1**

1, **2**^{a}	R^1	R^2	Z	Yield of **2**^{b} (%) under conditions A	B	B.p. (°C/Torr)	or m.p. (°C)
a	H	H	t-BuO$_2$C	41	35	42/30	-
b	Me	H	i-PrO$_2$C	46	47	159/760	-
c	Me	Me	i-PrO$_2$C	40	-	179/760^c	-
d	H	H	PhSO$_2$	43	49	-	91
e	H	H	PhCO	41	12	121/27	-

^{a} The structure of **2** was proved by NMR spectra; satisfactory elemental analyses (C, H, S) were obtained for all **2** prepared.

^{b} Purity (by GC) ca 99%; purity of **2c** ≥ 97%.

^{c} Distilled product was purified by column chromatography (Merck silica gel 60, eluent pentane/ethyl acetate 1:1 mixture).

gem-dichlorocyclopropanes were allowed to react with fluoride anion:cyanoderivative **1**(R^1 = R^2 = H, Z = CN) has been destroyed, while 2-cyano-2-methyl-1,1-dichlorocyclopropane and 1,1-dichloro-2-phenylcyclopropane (**1**, R^1 = R^2 = H, Z = Ph) remained unchanged, irrespective of the conditions applied. Results mentioned above indicate that rather strong EWG and hydrogen atom α to this group have to be present in **1** for their successful transformation into **2**. Nucleophilic substitution at cyclopropane carbon usually takes place *via* series of elimination-addition steps.[16] Our preliminary experiments suggest that formation of **2** according to the same mechanistic pathway occurred, with fluoride anion playing the role of both base and nucleophile.

As result of our studies, compounds **2** become now fairly available, and fluoride anion was added to the pool of anions which enter nucleophilic substitution at cyclopropane carbon.

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11. Merck and Fluka TBAF · 3 H$_2$O was used.
12. The reaction of **1a** (9 mmol) with excess of KF (180 mmol) and catalytic amounts of TBAHS (ca 1 mmol) in acetonitrile/water (80 °C, 5 h) gave the mixture with consist of **2a** (13%) and unreacted **1a** (65%), as determined by GC. Prolonged heating did not increase amount of **2a**.
13. Preparation of **2**:
    Under conditions A: The solution of TBAF · 3 H$_2$O (7.6 g, 24 mmol) in DMF (10 mL) was added dropwise to mixture of **1a-e** (8 mmol) in DMF (10 mL) at ca 5 °C, during stirring (exothermic reaction). The process was carried out for 4 h, the mixture was diluted with water (ca 250 mL), extracted with pentanes (3 x 60 mL) (or CH$_2$Cl$_2$ for **2d**), conventionally worked up, and the products were isolated by distilation or crystallization (Table).
    Under conditions B: Dichlorocyclopropanes **1a-e** (9 mmol), KF (10.5 g, 180 mmol), water (7.5 mL), TBAHS (9.2 g, 27 mmol) and acetonitrile (50 mL) were stirred at 80 °C for 8 h, and worked up as described above.
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