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A Mild, Selective Method for Preparation of Vicinal Fluoro Ethers Using "F-Teda-BF_4"

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Abstract: Vicinal alkoxy fluorides are efficiently formed by room temperature reaction of phenyl substituted alkenes with commercially available 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis tetrafluoroborate (Selectfluor^{TM} F-Teda BF_4) in CH_3CN in the presence of various alcohols. The reaction follows Markovnikov-type regioselectivity, while stereoselectivity in the case of phenyl substituted benzocyclenes strongly depends on the ring size and the structure of the alcohol.

The enhanced biological activity of fluorine containing organic molecules[1] is responsible for very intense research in this field of organic chemistry, focused mainly on development of new reagents and methods for the selective introduction of a fluorine atom into organic molecules under mild reaction conditions. Much work has been done in last two decades connected with this still only partly solved problem[2], and an important break through was acchieved by the introduction of a variety of N-fluoro compounds as versatile fluorinating reagents[3].

Several attemps were made to prepare organic molecules with the fluoro ether functional block, which carries potential bioactivity and is a useful precursor for other fluoro containing products. Vicinal fluoro methoxy derivatives were selectively obtained by low temperature reaction of in situ prepared acetyl hypofluorite with methoxy-organo mercury precursors derived from alkenes[4]. Highly explosive perchloryl fluoride in methanol was used for methoxy fluorination of prostacycline derivatives[5], while the selectivity of alkoxy fluorination of alkenes with relatively expensive xenon difluorine in the presence of alcohols depend on the catalyst used[6]. Caesium fluoroxysulphate is reported to be an easy handling reagent for selective preparation of vicinal fluoro ethers from alkenes at room temperature[7], but the reagent is still not commercially available. Very recently a new family of 1-alkyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane salts were promoted as selective, easy handling fluorinating reagents[8] and reasonably priced chemicals are commercially available under the trade name Selectfluor^{TM} reagents[9]. We now report 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis tetrafluoroborate (commercial: F-Teda BF_4) as an versatile reagent for the fluoro alkoxylation of alkenes under mild reaction conditions.

In a typical experiment 2 mmol of alkene (1 or 3) was disolved in a mixture of 20 ml of acetonitrile and 2 ml of alcohol and under stirring 2 mmol of F-TEDA BF_4 was added. The reaction mixture was stirred for an hour at room temperature, then diluted with 40 ml of CH_2Cl_2, washed with a 10% aqueous solution of $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, evaporated under

SCHEME 1

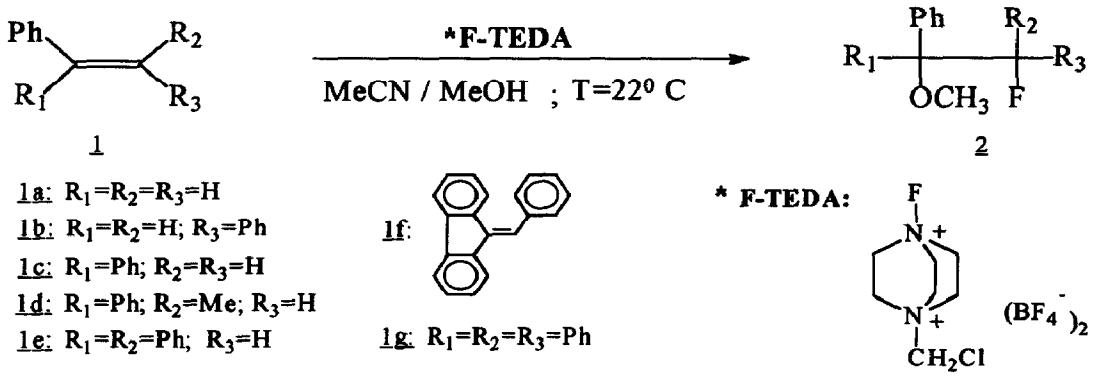

TABLE 1: Effect of the Structure of the Alkene (1a - g) on Relative Rates[10] (k_{rel}, Relative to 1,1-Diphenylethene) of Formation of Vicinal Fluoro Ethers (2a - g) with F-TEDA at 22°C

ALKENE (1)	k_{rel}	k_{rel}	ALKENE (1)
Styrene (1a)	<0.001	2.8	Triphenylethene (1e)
trans-Stilbene (1b)	0.77	0.53	9-Benzylidene fluorene (1f)
1,1-Diphenyl-1-propene (1d)	8.6	0.11	Tetraphenylethene (1g)

reduced pressure and analysed by ^1H and ^{19}F nmr spectroscopy. The amount of fluorinated products was determined from ^{19}F nmr spectra of the crude reaction mixture using octafluoronaphthalene as additional standard, and pure products were isolated by flash or thin layer chromatography on silica gel and their structures established on the basis of ^1H, ^{19}F nmr, MS, IR and when necessary, also by X-ray difraction analysis . The purity of all the new compounds was comfirmed by combustion elemental analysis.

Under the mentioned reaction conditions almost quantitative formation of vicinal fluoro methoxy derivatives following Markovnikov-type regioselectivity (2b-g, Scheme) was observed with alkenes 1b-g, while in the case of styrene (1a) an one hour reflux of the reaction mixture was necessary for the formation of 2-fluoro-1-methoxy-1-phenylethane (2a) in over 90% yield. This fact stimulated us to established the effect of the structure of the alkene on its reactivity with F-Teda BF_4 at room temperature, using measurement of relative rates[10] (k_{rel}) as a correlation factor. The values of k_{rel}, measured relative to 1,1-diphenyl ethene (1c), are shown in **Table 1**. Styrene is almost unreactive in comparision to 1,1-diphenyl ethene at 22°C, while the reactivity of trans stilbene is not considerably different. On the other hand, the additional methyl group in the alkene (1d) enhanced reactivity towards F-Teda BF_4 by almost nine times, and the phenyl group (1e) by nearly three times, while 9-benzylidene fluorene (1f) is twice and tetraphenylethene (1g) nine times less reactive than 1,1-diphenylethene.

Cyclic alkenes are often used as test compounds for the study of stereochemistry and the kinetics of addition across a double bond, and a considerable effect of ring size on

SCHEME 2

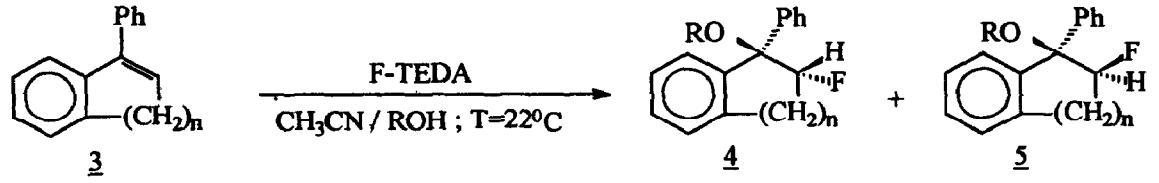

TABLE 2: Effect of the Structure of theBenzocyclene(3a-c) and Alcohol on Stereoselectivity and Relative Rates (k_{rel}, Relative to 1,1-Diphenyl-1-propene) of Formation of Vicinal Fluoro Ethers with F-TEDA at 22°C

ALKENE	n	R	Stereoselectivity anti(4):syn(5)	k_{rel}
3a	1	Me	0.37:1	3.2
3b	2	Me	1.6:1	3.7
3c	3	Me	100:1	1.3
3c	3	Et	0.77:1	1.2
3c	3	i-Pr	0.16:1	1.4

stereoselectivity and relative reactivity was generally established. Drastic reduction of reaction rate of bromination of the cycloheptene homologue in comparision with five and six membered ring derivatives of benzocyclenes was observed and attributed to a loss of additional mesomeric stabilisation caused by the different geometry of the bromo carbocationic intermediate[13]. This facts stimulated us to test the stereochemistry and relative reactivity of phenyl-substituted benzocyclenes (3, Scheme 2) with F-Teda-BF_4. We found that variation of ring size in the target molecules drastically changes the stereochemical course of methoxy fluorination across the double bond, being in the case of 3-phenyl-1H-indene (3a) predominantly syn, in 4-phenyl-1,2-dihydronaphthalene (3b) mainly anti and finally in the case of 9-phenyl-6,7-dihydro-5H-benzocycloheptene (3c) exclusively anti. In the latter case the structure of the alkoxy group as a external nucleophile also plays an important role on the stereochemistry of the reaction. The use of ethanol as nucleophile species resulted in a considerable excess of syn adduct formation, while i-propanol caused almost stereoselective syn addition (Table 2). The structures of stereoisomers in the 2-fluoro-1-alkoxy-1-phenyl benzocycloalkane diastereoisomeric pairs formed (4 and 5, Scheme 2) were established on the basis of characteristic differences in their ^1H and ^{19}F nmr spectra[7b], but when these data were not enough for unequivocal postulation of the correct structure, we grew a single crystal of at least one isomer of a particular pair and the structure was confirmed by X-ray difraction analysis[14].

We also measured relative rate factors as a function of the structure of the benzocyclene and found that benzocyclenes 3 are more reactive than their open chain analogue 1,1-diphenyl-1-propene, and 4-phenyl-1,2-dihydronaphthalene (3b) was found to be the most reactive one (Table 2). As

evident, relative rates factors of all three substrates are in the same range of magnitude, contrary to the values established for bromination of 3 with Br_2 in methanol[13] where the bromination reaction of 3c is five hundredfold slower than that of 3a and 3b. The Markovnikov-type regiospecificy of the reported reactions strongly supports the hypothesis that fluoro carbocationic intermediates, established also in the case of some other N-F reagents[3b], are involved in reactions of F-Teda with alkenes 1 and 3, but such a small effect of the structure of benzocyclene 3 on the relative rate of the reaction cauld be the consequence of the fact that the fluorine atom coused different stabilisation in carbocationic intermediate, or that the formation of a fluorocarbocationic intermediate is not the key rate determining process in this case.

The present report confirms that F-Teda BF_4 is one of the most suitable reagent for the fluorination of alkenes. The study of its reactions in the presence of more sophisticated alcohols, with the stress on those possessing an assymetric centre, and kinetic measurements connected with the reported reactions are in progress.

REFERENCES

1) a) Filler,R.; Kobayashi,Y. (eds.) "Biomedicinal Aspects of Fluorine Chemistry": Elsevier: Amsterdam, **1982**; b) Banks, R.E.; Sharp,D.W.A. and Tatlow,J.C. (eds.) "Fluorine: The First Hundred Years": Elsevier: Lausane, **1986**; c) Welch,J.T. *Tetrahedron* **1987**, *43*, 3123; d) Mann,J. *Chem.Soc.Rev.* **1987**, *16*, 381; e) J.T. Welch and S. Eswarakrishnan, "Fluorine in Biorganic Chemistry", John Wiley, New York, **1991**.
2) a) German,L.; Zemskov,S. (eds.) *"New Fluorinating Agents in Organic Syntheses"*, Springer-Verlag, Berlin, **1989**; b) Wilkinson,J.A. *Chem.Rev.* **1992**, *92*, 505.
3) For extensive lists of primary references see a) Umemoto,T.; Fukami,S.; Tomizawa,G.; Harasawa,K.; Kawada,K.; Tomita,K. *J.Am.Chem.Soc.* **1990**, *112*, 8563; b) DesMarteau,D.D.; Ze-Qi Xu; Witz,M. *J.Org.Chem.* **1992**, *57*, 629; c) Differdng,E.; Bersier,P.M. *Tetrahedron* **1992**, *48*, 1595.
4) Hebel,D.; Rosen,S. *J.Org.Chem.* **1987**, *52*, 2588.
5) Djurič,S.W.; Garland,R.B.; Nysted,L.N.; Pappo,R.; Plume,G.; Swenton,L. *J.Org.Chem.* **1987**, *52*,978.
6) Shellhamer,F.D.; Curtis,M.C.; Dunham,H.R.; Hollingsworth,R.D.; Ragains,L.M.; Richardson,E.R.; Heasley,L.V.; Shackelford,A.S.; Heasley,E.G. *J.Org.Chem.* **1985**, *50*, 2751; Shellhamer,F.D.; Carter,L.S.; Dunham,H.R.; Spitsbergen,P.M.; Heasley,L.V.; Chapman,D.R.; Druelinger,L.M. *J.Chem.Soc. Perkin Trans. II*, **1989**, 159.
7) a)Stavber,S,; Zupan,M. *Tetrahedron*, **1986**, *42*, 5035; *b)J.Org.Chem.* **1987**, *52*, 919; *c)Tetrahedron* **1990**, *46*, 3093.
8) a)Banks,R.E.; Mohialdin-Khaffaf,S.N.; Lal,G.S.; Sharif,I.; Syvret,R.R. *J.Chem.Soc. Chem. Commun.* **1992**, 595; b) Lal,G.S. *J.Org.Chem.* **1993**, *58*, 2791; Matthews,D.P.; Miller,S.C.; Jarvi,E.T.; Sabol,J.S.; McCarthy,J.R. *Tetrahedron Lett.* **1993**, *34*, 3057.
9) Banks,R.E. *U.S. Patent, 5,086,178,* **1992**; produced by Air Products and Chemicals,Inc.; Allentown,PA18195, USA.
10) Applying the known competitive technique, relative reactivities expressed by relative rate factors (k_{rel}) were calculated from the equation[11]:

$$k_{rel} = \frac{k_A}{k_B} = \frac{\log (A\text{-}X)/A}{\log (B\text{-}Y)/B}$$

derived from the Ingold-Shaw relation[12], where A and B are the amounts (in mmols) of starting material and X and Y the amounts of products derived from them.
11) Pearson,R.E.; Martin,J.C. *J.Am.Chem.Soc.* **1963**, *85*, 3142.
12) Ingold,C.K.; Shaw,F.R. *J.Chem.Soc.* **1927**, *130*, 2918.
13) Dubois,J.E.; Hegarty,A.F. *J.Chem.Soc. (B)*, **1969**, 638.
14) Leban,I. *unpublished results.* All spectroscopic detailes and X-ray crystallographic data relating to the new compounds will be published elsewhere.

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