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A MILD, CONVENIENT, HALOGEN-EXCHANGE ROUTE TO GEM-DIFLUORIDES AND TRIFLUORIDES.

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Summary: Reaction of gem -dihalides $R^1R^2CX_2$ (X= Cl or I) and of $PhCCl_3$ with $AgBF_4$ at room or sub-ambient temperatures affords the corresponding gem-difluorides and trifluoride in unoptimised yields of 35-84%.

The appearance of several recent publications describing the construction of CF and CF_2 moieties[1-5] has prompted us to reveal our own method for the introduction of CF_2 and CF_3 groups. Previously reported routes to gem -difluorides employ harsh reaction conditions, low temperatures, or in situ generated fluorination reagents.[1,6-9] This limits the range of precursors that can be used in these transformations, and causes concern over their viability for substrates with sensitive side-groups.

We now wish to report a mild method for the conversion of gem -dihalides and trihalides into the corresponding fluorides at room or sub-ambient temperatures using the readily available reagent silver tetrafluoroborate. Although there are scattered reports of this reagent being used to effect exchange-fluorination as a side reaction with certain mono-halides,[10-13] it does not appear to have been recognised previously that the process can be used for the preparation of di- and tri-fluorides.

When silver tetrafluoroborate was stirred with various gem -dihalides or trichloromethylbenzene, the corresponding fluorides were obtained in moderate to good yields (Equations 1 & 2, and Table 1). Dichloromethane was the principal solvent used, but the reactions also proceeded satisfactorily in diethyl ether, or in Freon 21 ($CHFCl_2$) at 0°C. It is important to minimise the amount of adventitious water in the reaction mixture. Hence, dried solvents were used and the silver tetrafluoroborate was handled rapidly in a dry box. Even so, the formation of hydrolysis products with the benzylic dichlorides could not be completely suppressed (Table 1, entries 2 & 8).

$$R^1R^2CX_2 + 2AgBF_4 \longrightarrow R^1R^2CF_2 + 2AgX + 2BF_3\uparrow \qquad (1)$$

$$PhCCl_3 + 3AgBF_4 \longrightarrow PhCF_3 + 3AgCl + 3BF_3\uparrow \qquad (2)$$

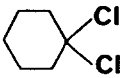
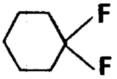
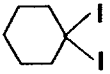
The starting dihalides were obtained by standard synthetic methods: the dichlorides from the requisite ketone plus PCl_5 or SO_2Cl_2, and the diiodides from the derived hydrazone plus I_2/Et_3N. Thus our method represents an alternative to those previously reported for the transformation of a carbonyl into a CF_2 group.

Thus, these preliminary results indicate that silver tetrafluoroborate is capable of bringing about the conversion of both benzylic and non-benzylic CX_2 groups to CF_2,[14] of CX_2 groups in both cyclic and acyclic systems to CF_2, of both non-terminal (ketone-derived) and terminal (aldehyde-derived) CX_2 groups to CF_2, and of benzylic CX_3 groups to CF_3. It should be noted, however, that under our standard conditions an aliphatic trichloride did not afford the corresponding trifluoride. Also, the non-benzylic terminal dichlorides RCH_2CHCl_2 ($R=Ph, Bu^t$) failed to react even in dichloromethane at reflux, but difluorination was successfully achieved by switching to the corresponding diiodide (Table 1, entry 1). This suggests that where chlorides are reluctant to react, the use of iodides may be successful.

It seems likely that these reactions proceed <u>via</u> cationic intermediates, generated by silver-induced dehalogenation, which undergo nucleophilic fluorination by tetrafluoroborate anion (Scheme 1). Consistent with this mechanism is the observation that exchange did not occur with either 2,2-dichlorocyclohexanone or 1,1-dichloro-2-methyl-2-phenylcyclopropane, substrates which are reluctant to undergo S_N1-like reactions. Also, when a half equivalent of silver salt was used <u>no</u> mono-fluoride was isolated. Supporting a mechanism involving a fluorine-stabilised cation (Scheme 1).

We are continuing to investigate the synthetic scope and mechanistic aspects of these fluorinations.

Table 1. Exchange-fluorination by reaction with $AgBF_4$ [a]

	Substrate	Product [b]	Yield (%) [c]
1	$PhCH_2CHI_2$ [d]	$PhCH_2CHF_2$ [f]	35
2	$PhCHCl_2$	$PhCHF_2$ [g]	40
3	$PhCH_2CCl_2CH_3$	$PhCH_2CF_2CH_3$	50
4	$PhCH_2CI_2CH_3$	$PhCH_2CF_2CH_3$ [h]	84
5	$C_3H_7\text{-}CCl_2\text{-}C_7H_{15}$	$C_3H_7\text{-}CF_2\text{-}C_7H_{15}$	60
6			40
7			49[e]
8	$PhCCl_2Ph$	$PhCF_2Ph$ [i]	40
9	$PhCCl_3$	$PhCF_3$	48

a. <u>Reaction Conditions.</u> Substrate stirred with $AgBF_4$ (1.1 molar equiv. per halide) in CH_2Cl_2 for 1h at room temperature, filtered through celite and silica, and solvent removed by distillation.

b. All products except $C_3H_7CF_2C_7H_{15}$ are known compounds and the structures shown were supported by ^1H, ^{13}C, and ^{19}F NMR spectra.

c. Isolated, or evaluated by NMR from mixtures with other products (entries 1,2, and 8) or with residual CH_2Cl_2 (entries 6 and 9).

d. Reaction also proceeds in Et_2O; the corresponding dichloride did not react.

e. Reaction in $CHFCl_2$ at 0°C.

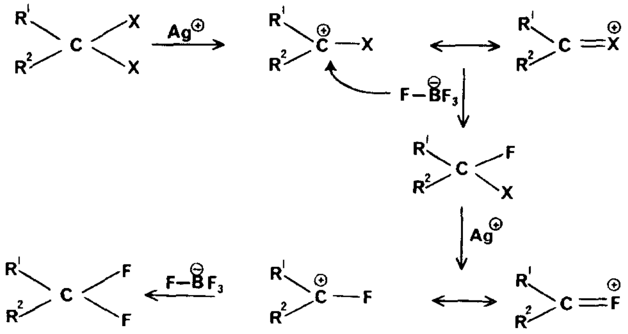
f. Other products also formed.

g. PhCHO also formed.

h. Small amounts of vinyl iodides also formed.

i. Ph_2CO also formed.

Scheme 1



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