REVIEW

CURRENT AND FUTURE DEVELOPMENTS OF SYNTHETIC METHODS IN ORGANOFLUORINE CHEMISTRY

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SUMMARY

Although fluorine chemistry is rapidly approaching its 100th anniversary, organofluorine chemistry, as most of us know it, is only 40-50 years old. Interest and enthusiasm in this area of chemistry essentially traces its origins to the discovery and industrial applications of the Freons and polytetrafluoroethylene (Teflon). The unique properties of these materials attracted attention to this neglected area of organic chemistry - particularly industrially - and stimulated work on methods for the introduction of fluorine into organic molecules.

Much of the early work (1940-1960) was devoted industrially to individual perfluorinated target molecule preparation either *via* HF catalyzed fluorination or electrochemical fluorination. Although several excellent industrial processes were developed, these processes were often not general methods or not easily adaptable to functionalized derivatives. Partially fluorinated molecules were generally prepared *via* adaptation of the Swartz reaction or *via* halogen displacement reactions with fluoride ion. However, lack of specificity or solvent limitations for fluoride ion reactions limited the applicability of these methods.

In the mid-1950's, a search for selective and general methods for the introduction of fluorine was initiated. The first reagent that exhibited some selectivity and generality was sulfur tetrafluoride (SF_4) [1]. Carbonyl functionality, in substrates such as carboxylic acids, aldehydes, and ketones, was selectively converted into tri-

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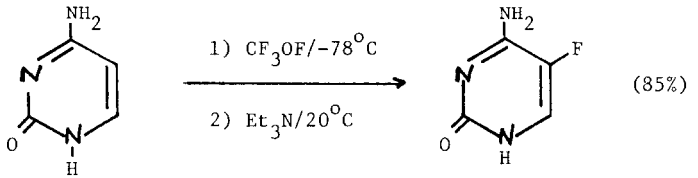
fluoromethyl or difluoromethylene analogues, respectively. The introduction of this reagent marks the beginning of the modern era of synthetic organofluorine chemistry. Recent modifications, such as the use of DAST, have received wide applicability in the preparation of fluorine-containing compounds by Middleton [2] and others, particularly with sensitive molecules [3] which require a mild reagent.

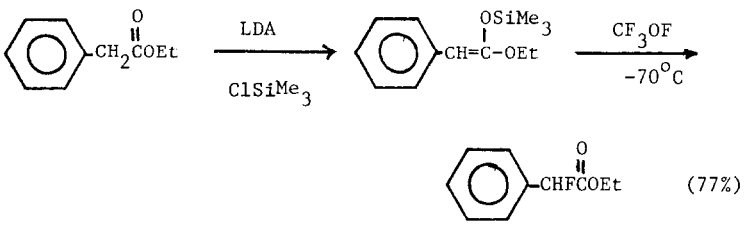
$$RCOOH + SF_4 \longrightarrow RCF_3$$

$$R_2CO + SF_4 \longrightarrow R_2CF_2$$

In the twenty-five years since the initial report of SF_4 chemistry, much of the synthetic methodology has been devoted to the development of selective methods for the regiospecific and stereospecific introduction of fluorine. Methods for controlled fluorination with reactive fluorinating agents, such as F_2 and CF_3OF, have been recently reported for the selective introduction of fluorine into uracils and uracil derivatives, steroids, and adamantanes [4]. Modifications of this



methodology has led to selective synthesis of α-fluorohydrins [5] and selective fluorination of tertiary carbon-hydrogen single bonds [6]. Middleton has also utilized such reagents to selectively introduce fluorine adjacent to the carbonyl group of ketones, aldehydes, esters, and amides [7].



As noted above, with selected examples, the emphasis on fluorination of carbon-hydrogen bonds is on selectivity. No longer is the goal

merely to introduce fluorine into the molecule, but the success is now gauged on the ability to introduce fluorine with regio- and stereochemical control. The future of such reagents will be dictated by the success with which they allow the investigator to achieve such control.

Another area of renewed interest has been in perfluoroalkylation reactions. Recent preliminary reports describe the use of (perfluoroalkyl) phenyl iodonium trifluoromethanesulfonates (FITS) - or sulfates (FIS) as selective cationic perfluoroalkylating agents of carbanions, alkenes, alkadienes, arenes, thiols, and carbonyl substrates [8].

$$C_8F_{17}I(Ph)OSO_2CF_3 + C_8H_{17}MgCl \xrightarrow[-78^oC]{THF} C_8F_{17}C_8H_{17} \quad (47\%)$$

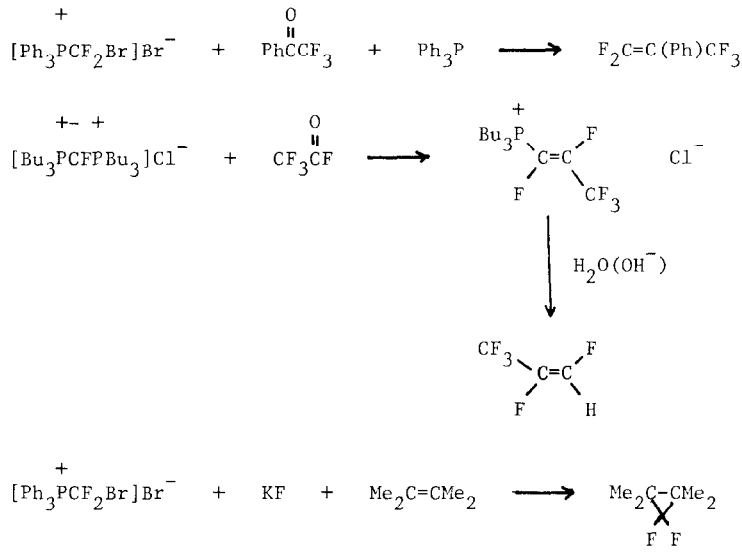
$$PhC(OSiMe_3)=CH_2 + i\text{-}C_3F_7I(Ph)OSO_2CF_3 \xrightarrow[CH_2Cl_2]{RT} PhCCH_2CF(CF_3)_2 \quad (79\%)$$

Other preliminary reports utilize ultrasound-promoted reactions to introduce the perfluoroalkyl group [9].

$$C_6F_{13}I + CO_2 + Zn \xrightarrow[2)\ HCl]{1)\ \text{ultrasound}} C_6F_{13}CO_2H \quad (77\%)$$

As yet these methods have only appeared in preliminary form and have not yet been widely utilized by other research groups. However, they appear to offer some new and novel routes for the introduction of a perfluoroalkyl group. They will undoubtedly stimulate similar or modified efforts by others in the future to achieve both regiospecific and stereospecific perfluoroalkylation processes as a route to partially fluorinated materials.

In our own laboratory, we have attempted to develop fluorine-containing reagents that would permit regio- and stereo-selective preparation of organofluorine compounds [10]. The methodology is based on the use of commercially available materials as precursors to the reagent - thus the fluorine is incorporated in the first step of the reaction - not in the final step like with F_2 and CF_3OF. Then, by proper choice of reagent and substrate typical organic chemistry methodology can be utilized to achieve the final product.



The key to this chemistry has been an understanding of the mechanism and transient intermediates involved in the formation of the reagents.

The future of synthetic organofluorine chemistry will see the additional development or modification of reagents that will permit the ready introduction of fluorine atom or a perfluoroalkyl group in a regiospecific and/or stereospecific manner. These new reagents will be predicated on commercially available fluorochemicals, and procedures will be developed that can be readily employed by any competent synthetic chemist - and not restricted to the investigator with expertise in fluorine chemistry. Renewed efforts will be undertaken to understand the mechanism of fluorinating agents or fluorine-containing transient intermediates, and serious attempts will be made to base organofluorine chemistry on firm mechanistic principles. For it's only as the understanding of the mechanism of the formation of these reagents or reactive intermediates increases that a rational conceptual design of selective synthetic reagents can be achieved.

CONCLUSION

The future of synthetic organofluorine chemistry is indeed full of promise. It's rapidly taking its place in the mainstream of synthetic organic chemistry and offers the synthetic chemist an unparalleled opportunity for significant contributions to this exciting area of research.

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