Fluorination

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Fluorodecarboxylation for the Synthesis of Trifluoromethyl Aryl Ethers

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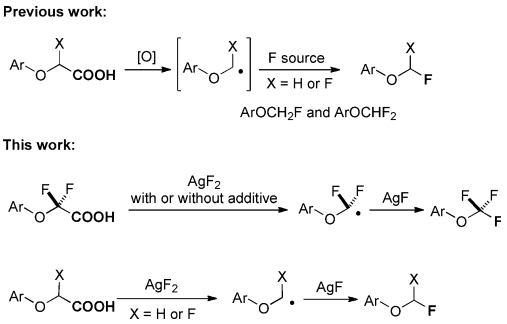
Abstract: *The synthesis of mono-, di-, and trifluoromethyl aryl ethers by fluorodecarboxylation of the corresponding carboxylic acids is reported. AgF_2 induces decarboxylation of aryloxydifluoroacetic acids, and AgF, either generated in situ or added separately, serves as a source of fluorine to generate the fluorodecarboxylation products. The addition of 2,6-difluoropyridine increased the reactivity of AgF_2, thereby increasing the range of functional groups and electronic properties of the aryl groups that are tolerated. The reaction conditions used for the formation of trifluoromethyl aryl ethers also served to form difluoromethyl and monofluoromethyl aryl ethers.*

Fluoromethyl aryl ethers are increasingly being investigated for agrochemical, pharmaceutical, and materials science.[1] Indeed, the introduction of a fluorine atom in a molecule allows one to tune the structure and electronic properties of the molecule as a means to modulate both pharmacokinetic and pharmacodynamic properties.[2] For example, the trifluoromethoxy group in a trifluoromethoxy aryl ether is oriented perpendicular to the aryl ring instead of being oriented closer to the plane of the aryl ring as in a methyl aryl ether. This difference in conformation results from the small degree of conjugation of the lone pair of electrons on the oxygen atom with the aryl ring because of the electron-withdrawing power of the CF_3 group and hyperconjugation of the electron pair with the C–F σ* orbitals.[3] Although many agrochemicals and pharmaceuticals containing trifluoromethyl aryl ethers have already been approved or are being developed, convenient methods to form these structures would greatly increase the applications of this class of molecule.[4]

Synthetic methods to form fluoromethyl aryl ethers are less developed than the methods to prepare other fluoroalkyl compounds.[1] Although several routes to mono- and difluoromethyl ethers are documented,[5,6] methods to form trifluoromethyl aryl ethers are less developed.[4–6] The traditional synthesis of trifluoromethyl ethers is typically achieved by nucleophilic substitution of the corresponding trichloromethyl ethers with fluoride, deoxyfluorination of fluoroformates, and fluorodesulfurization reactions of sulfonate esters, all of which require harsh reaction conditions.[7] Several new strategies have been developed recently, but none of the resulting procedures are broadly applicable. The limitations include either unstable reagents which require handling at low temperature, substrates that must contain a directing group, formation of mixtures of isomeric products, complex experimental conditions, or excess quantities of multiple reagents. Thus, the development of new strategies for the formation of aryl fluoromethyl ethers would be valuable for a range of synthetic applications.[8,9]

In principle, fluorodecarboxylation could provide a general method to access aryl trifluoromethyl ethers, as well as the analogous monofluoro- and difluoromethyl ethers (Scheme 1) from reactants which are readily accessible by a simple substitutions with phenols.[10] However, determining the appropriate reagents to induce the decarboxylation of α-fluoro carboxylic acids, as well as an appropriate source of F• to quench the fluoroalkyl radical, is challenging. The first fluorodecarboxylation reaction was reported with an alkyl carboxylic acid in 1969 by Grakauskas and co-workers with F_2 as both the oxidant and the source of fluorine.[11] Later, Patrick and co-workers improved the scope of the reaction by conducting reactions with the more easily handled XeF_2.[12] Recently, the groups of Sammis, Li, Gouverneur, Groves, MacMillan, and Ye all have reported decarboxylative fluorinations of alkyl, aryl, or aryloxy carboxylic acids by Hunsdiecker-type fluorinations and photoredox fluorinations.[13–16] However, the decarboxylative fluorination to generate trifluoromethyl ethers has not been reported.[17]



Scheme 1. Fluorodecarboxylation for the synthesis of fluoromethyl aryl ethers.

Decarboxylation reactions are strongly dependent on the electronic properties of the substrates because the process occurs by oxidation of the carboxylate. Thus, decarboxylation of α-fluoro- and α,α-difluorocarboxylates, particularly those containing accompanying aryloxy groups to form difluoromethyl and trifluoromethyl ethers, are distinct from decarboxylation reactions of simple alkyl groups. Indeed, the

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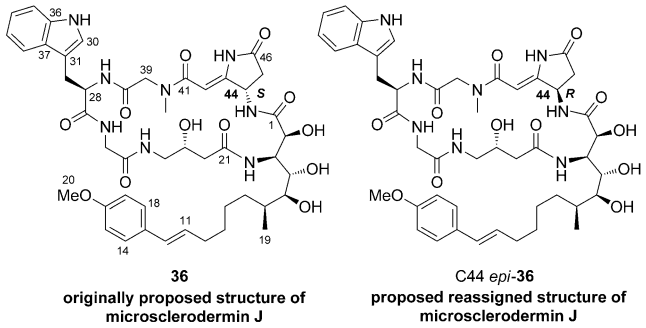
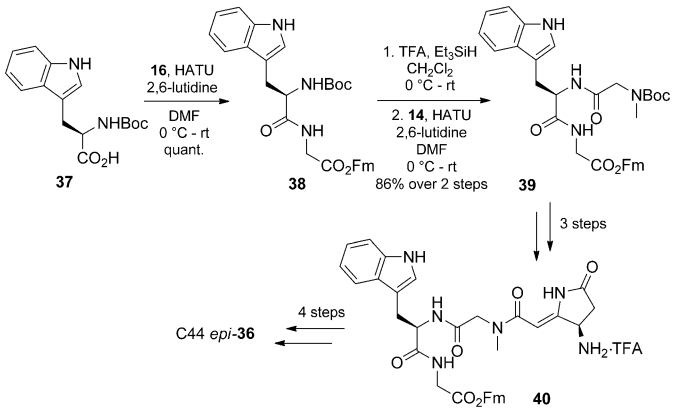


Scheme 8. Originally proposed structure of microsclerodermin J, **36**, and proposed reassigned structure of microsclerodermin J, C44 *epi*-**36**.



Scheme 9. Synthesis of the reassigned structure of microsclerodermin J, C44 epi-**36**.

C44 *epi*-**36** to that of natural microsclerodermin J was aided by a copy of the ^{13}C NMR spectrum provided by Li. This spectrum was critical to our analysis, as there were minor inaccuracies in the data listings given in the original isolation paper (see the Supporting Information for a copy of the ^{13}C NMR spectrum and a list of inaccuracies in the published ^{13}C NMR data for microsclerodermin J).[2a] This comparison showed a complete match between the ^{13}C NMR spectra of synthetic C44 *epi*-**36** and the natural material, with the differences in chemical shift not exceeding 0.1 ppm. From these data, it was confirmed that microsclerodermin J also has the *R* configuration at the C44 stereocenter.

To conclude, the first total synthesis of the proposed structure **31** of dehydromicrosclerodermin B was accomplished. The originally proposed C45 configuration for the parent compound **1** was reassigned from 45*S* to 45*R*, and this configuration was confirmed by synthesizing C45 *epi*-**31**, whose data were in complete agreement with those for naturally derived dehydromicrosclerodermin B. We also reassigned the C44 configuration of an analogous member of the family—microsclerodermin J—as 44*R* by completing the first total synthesis of C44 *epi*-**36**. Owing to our unsuccessful efforts to construct the sensitive pyrrolidinone aminal moiety through a hydroxybromination sequence, alternative hydration strategies will be pursued in the future for the total synthesis of microsclerodermin B.

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Keywords: cross-coupling · cyclic peptides · pyrrolidinones · structure elucidation · total synthesis

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[9] Similar rotameric NMR data were observed for protected cyclic peptides **25**, **26**, **29** and **30**.

[10] The original copies of the ^{1}H NMR data provided by Li for natural dehydromicrosclerodermin B and natural microsclerodermin J were not informative owing to the presence of broad peaks. Consequently, comparison was best achieved by using ^{13}C NMR data.

[11] The original stereochemical assignment of the pyrrolidinone unit of microsclerodermins A and K is also questionable. However, owing to the presence of the C46 hydroxy group in these microsclerodermins, their synthesis was not pursued in the current study.

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