New, Mild Method for Directed Introduction of a Fluorine Atom into Aromatic Molecules

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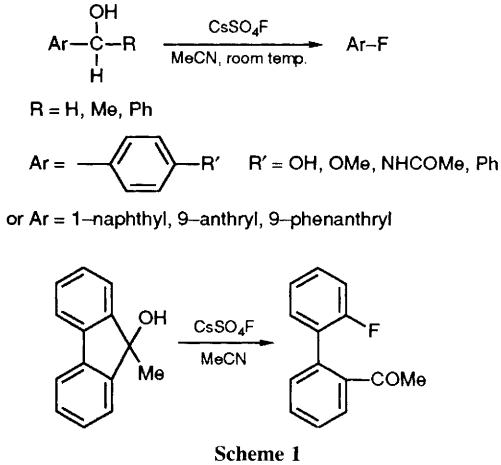
Hydroxyalkyl groups in various aromatic molecules are replaced with a fluorine atom by $CsSO_4F$ at room temperature thus regioselectively forming aryl fluorides in high to excellent yields.

The introduction of a fluorine atom into organic molecules, particularly aromatics, is a shared and important interest of organic chemists, and in view of the biological and chemical importance[1] of fluorine-containing organic molecules, rapid development of new reagents and methods for fluorofunctionalisation of organic compounds has taken place in the last few decades,[2] but the introduction of a fluorine atom into aromatics is still a partially resolved task.[3] The problem is not only connected with the use of an appropriate reagent and reaction conditions, but also with the regioselectivity of fluorination and side reactions. The Balz–Schiemann reaction[4] remains, so far, the classical and most widely used method for regioselective introduction of fluorine into an aromatic ring and was recently supplemented by the regioselective transformation of some aryl metallic derivatives to fluoroaromatics with F_2,[5] CF_3OF,[6] $MeCO_2F$[7] or caesium fluoroxysulfate ($CsSO_4F$).[8] We now report a new method for regioselective introduction of a fluorine atom into aromatic molecules, which is based on the reaction of α-hydroxyalkyl aromatic derivatives with $CsSO_4F$ under mild reaction conditions.

In a typical experiment, $CsSO_4F$ (1.4 mol equiv.) was added to a 0.5 mol dm^{-3} solution of 4-methoxybenzyl alcohol in MeCN, and the reaction suspension stirred at room temperature for an hour. After the usual work-up procedure 4-methoxyfluorobenzene in up to 70% yield was isolated. Directed fluorofunctionalization to 4-substituted fluorobenzenes was successfully achieved when electron donating



Scheme 1

substituents (OH, OR, NHCOMe or Ph) were bonded *para* to the hydroxymethyl group (Scheme 1), while the yield of regioselective fluorine introduction was even improved to over 80% when α-methyl or α-phenyl-4-substituted benzyl alcohol derivatives were used as substrates (the former is more convenient because acetaldehyde, as a leaving group resulting from RCHOH group cleavage, is more easily removed from the reaction mixture than the benzaldehyde, formed in the latter case; 82% of 4-hydroxy-, 85% of 4-methoxy-, 86% of 4-octylamino- and 81% of 4-pheny-fluorobenzene could be isolated). In the case of benzyl alcohol[9] and 4-trifluoromethylbenzyl alcohol only oxidation of the hydroxy group took place, and the corresponding aldehydes were further, in agreement with our previous observations,[9] readily converted to acid fluorides, while α-methyl or α-phenyl derivatives of both alcohols were selectively transformed to acetophenone and benzophenone or their 4-trifluoromethyl analogue, respectively.

We have further tested this unusual new reaction on other aromatic molecules and found that 1-fluoronaphthalene (69%) 9-fluoroanthracene (60%) or 9-fluorophenanthrene (85%) can be isolated after $CsSO_4F$ reaction with corresponding α-hydroxyalkyl substituted aromatics (Scheme 1), as well as 2,4-dimethoxyfluorobenzene (66%) from 2,4-dimethoxybenzyl alcohol. The method is also applicable for the regioselective fluorofunctionalisation of biphenyl or diphenyl ether derivatives. 9-Methyl-9-hydroxyfluorene was thus readily converted to 2-fluoro-2′-acetylbiphenyl (82%) and 9-phenyl-9-hydroxyxanthene to 2-benzoylphenyl 2-fluorophenyl ether, (71%), respectively (Scheme 1).

α-Hydroxyalkyl, as the key functional group, bonded to the aromatic molecule, can be easily obtained from different sources: by reduction of alkyl–aryl ketones; by Grignard reaction from aryl aldehydes and alkylmagnesium halides; or less conveniently, from arylmagnesium bromides and acetaldehyde. In order to make a detailed evaluation of the method and provide mechanistical elucidation of this easily handled and efficient regioselective introduction of a fluorine atom in aromatic molecules, further research is in progress.

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