ORGANIC LETTERS

2008
Vol. 10, No. 24
5565−5568

Fluoroalkylation of Imidazoles by Hypervalent Iodonium Salts

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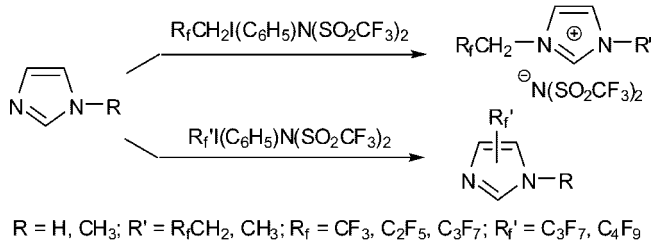
Received October 17, 2008

ABSTRACT



***N*-1*H*,1*H*-Perfluoroalkylation and regioselective *C*-perfluoroalkylation of imidazoles were obtained using the corresponding hypervalent iodonium salts.**

Imidazole derivatives play an important role in chemical and biological systems.[1] In the past decade, imidazolium-based ionic liquids have been investigated extensively.[2] More recently, the imidazole moiety has been incorporated into fuel cell membranes as a proton transporter at high temperatures.[3] In a variety of applications, either *N*- or *C*-alkylation of the imidazole moiety is often involved.

As the counterpart of alkylation, fluoroalkylation (including polyfluoroalkylation and perfluoroalkylation) of imidazoles has also attracted attention. *N*-Polyfluoroalkylation ($R_f(CH_2)_n$-type) of imidazoles was obtained by S_N2 reactions using polyfluoroalkyl triflates[2a] and halides.[4] To increase the S_N2 reactivities,[5] two or more -CH_2- spacers ($n \geq 2$) between the leaving group and the fluoroalkyl moiety R_f in the reactant were needed.

Site-specific *C*-trifluoromethylation of imidazoles has been known since 1973.[6] Regioselective *C*-perfluoroalkylation (R_f-type) of imidazoles was observed by photoinduced radical reactions using perfluoroalkyl halides (via a SET or $S_{RN}1$ mechanism).[7] Although some other methods are effective for the perfluoroalkylation of heteroaromatic compounds,[8] they have not been investigated for the *C*-perfluoroalkylation of imidazoles.

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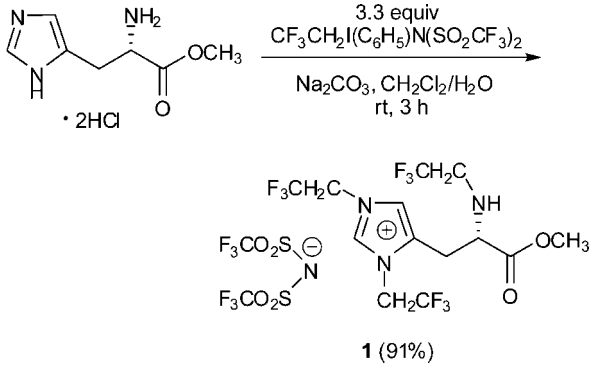
10.1021/ol802399z CCC: $40.75
Published on Web 11/19/2008

In the late 1970s, Yagupolskii[9] first used hypervalent iodonium salts for the electrophilic perfluoroalkylation of nucleophiles. Soon after that, Umemoto[10] investigated hypervalent iodonium salts as electrophilic perfluoroalkylating and 1*H*,1*H*-perfluoroalkylating agents for a variety of substrates. In the late 1990s, we introduced *N*,*N*-bis(trifluoromethylsulfonyl) imide into hypervalent iodonium salts for the trifluoroethylation of amino acids and small peptides in aqueous solutions.[11] Recently, we have extended this work to higher homologues.[12] The facile *N*-1*H*,1*H*-perfluoroalkylation of the imidazole moiety in two-phase solvents CH_2Cl_2/H_2O is shown in Scheme 1.

Scheme 1. *N*,*N*′,*N*″-Tritrifluoroethylation of L-Histidine Methyl Ester by an Iodonium Salt



In Scheme 1, three nitrogen atoms of L-histidine methyl ester were trifluoroethylated by the iodonium salt in one step to give compound **1**. The crystal structure of the cation moiety of **1** is shown in Figure 1.

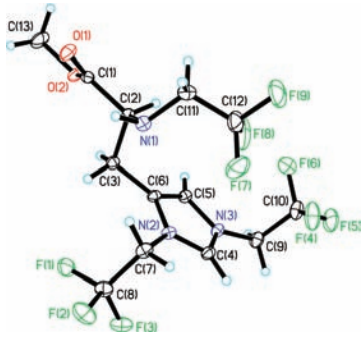
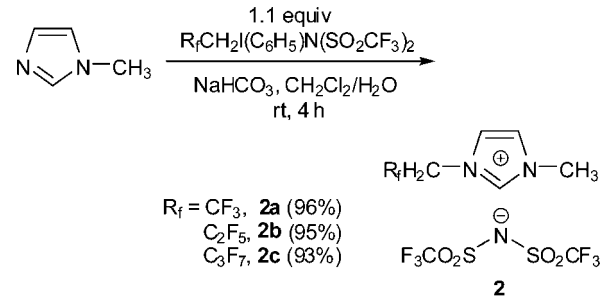


Figure 1. Crystal structure of cation moiety of compound **1**.

The facile *N*-trifluoroethylation of amino acids by the iodonium salt has resulted in the preparation of several pyridinium-based ionic liquids.[13] The extension of trifluoroethyl iodonium salt into its higher homologues[12] prompted us to prepare a series of imidazolium-based ionic liquids as shown in Scheme 2.

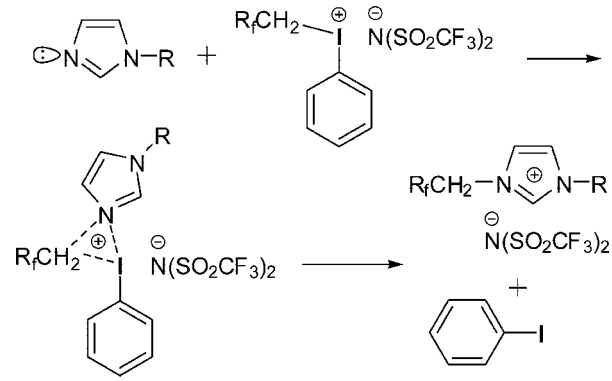
The reactions for *N*′-1*H*,1*H*-perfluoroalkylation of *N*-methyl imidazole are likely via an S_N2 process. The

Scheme 2. *N*′-1*H*,1*H*-Perfluoroalkylation of *N*-Methyl Imidazole



suggested mechanism is illustrated in Scheme 3. The lone pair electrons on the N′ atom interact with the empty antibonding orbital between iodine and sp^3 carbon (CH_2) to weaken and break the corresponding bonding orbital. With the leaving of iodobenzene, the new σ-bond between the N′ atom and sp^3 carbon (CH_2) is formed. Compared with the iodides R_fCH_2I, the process in Scheme 3 shows the increased S_N2 reactivity by hypervalent iodonium salts.

Scheme 3. Mechanistic Illustration of *N*′-1*H*,1*H*-Perfluoroalkylation of *N*-Alkyl Imidazole by Iodonium Salts



In contrast to 1*H*,1*H*-perfluoroalkyl iodonium salts that target the nitrogen atom(s) of imidazoles, perfluoroalkyl

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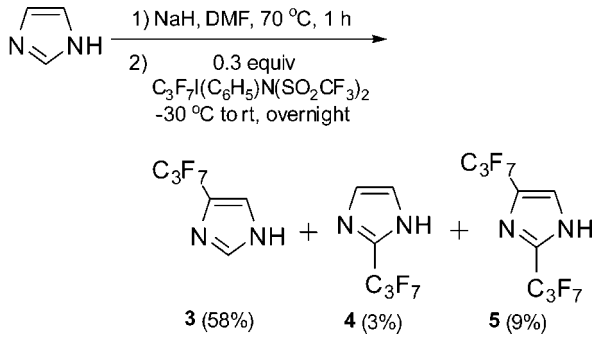
iodonium salts attack the carbon atoms of the substrates, as shown in Scheme 4.[14]

Scheme 4. *C*-Heptafluoropropylation of Imidazole



C_3F_7(C-4)-Imidazole **3** was obtained as the major product of the electrophilic substitution reaction. Its substitution position was varified by both the crystal structure shown in Figure 2 and the conformity of the ^{1}H NMR data with literature values.[6]

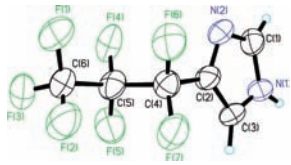


Figure 2. Crystal structure of C_3F_7(C-4)-imidazole **3**.

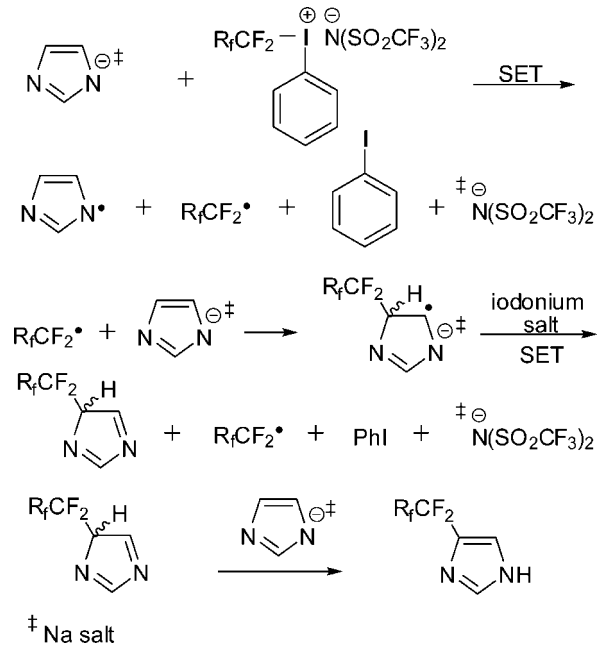
The *C*-perfluoroalkylation of imidazolate by the corresponding iodonium salt indicated a mechanism different from that of *N*-1*H*,1*H*-perfluoroalkylation. As illustrated in Scheme 5, the *C*-perfluoroalkylation of imidazolate by the corresponding iodonium salt is likely via a $S_{RN}1$ mechanism.[7b] As a result of the resonance structures of the imidazolate, the initial electrophilic attack at both C-4 and C-5 positions led to the same intermediate. Regaining aromaticity provided the driving force to shift the proton from the tetrahedral carbon in the intermediate to the nitrogen that was farther away from the electron-withdrawing perfluoroalkyl substituent, resulting in the major product.

C_3F_7(C-2)-Imidazole **4** was obtained as the minor isomer of the monosubstituted products. Its substitution position was determined by comparison of the ^{1}H NMR data with literature values.[6]

2,4-Diheptafluoropropylated imidazole **5** was also isolated. It seems that the monoperfluoroalkylation does not significantly deactivate the imidazole ring toward further electrophilic attack by the iodonium salt.

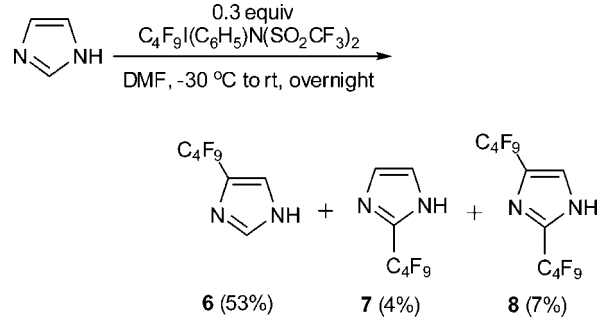
(14) Note: *C*-perfluoroalkylation of other aromatics, such as benzene, iodobenzene, and pyridine, proceeds readily. The reaction of $C_4F_9I(C_6H_5)N(SO_2CF_3)_2$ with benzene gives C_4F_9Ph in excellent yield.

Scheme 5. Mechanistic Illustration of *C*-Perfluoroalkylation of Imidazolate by Iodonium Salts



Pre-removal of the N(1)-H proton for regioselective *C*-perfluoroalkylation of imidazoles, which greatly shortened the reaction time in photoinduced radical perfluoroalkylation,[6] was not necessary here, as shown in Scheme 6.

Scheme 6. *C*-Nonafluorobutylation of Imidazole

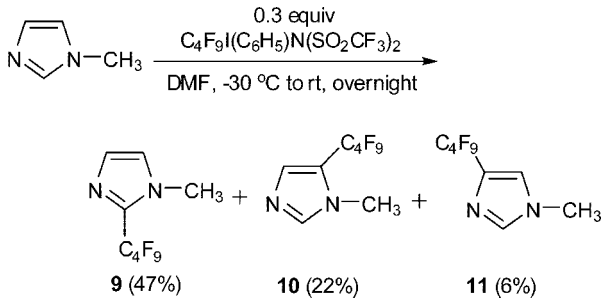


Similar regioselectivity of perfluoroalkylation was obtained without removing the N(1)-H proton of the imidazole. Although the initial electrophilic attack at C-5 was favored over that at C-4 due to resonance, the C-5 substituted isomer could be converted into the C-4 isomer by tautomerism. The two nitrogen atoms were affected differently by the electron-withdrawing perfluoroalkyl substituent and had different affinities toward the proton, which led to the major isomer **6**.

Regioselective *C*-perfluoroalkylation of *N*-methyl imidazole was carried out as shown in Scheme 7.

N-Methyl imidazole shows different regioselectivity toward perfluoroalkylation by the iodonium salt. C_4F_9(C-2)-

Scheme 7. *C*-Nonafluorobutylation of *N*-Methyl Imidazole



N-Methyl imidazole **9** was obtained as the major isomer. C_4F_9(C-5)-*N*-Methyl imidazole **10** was also isolated in modest yield, while C-4 perfluoroalkylation resulted in the minor isomer **11**. This supports the presumption that the initial electrophilic attack at C-5 was favored over the attack at C-4 due to resonance. The *N*-methyl group could affect the regioselectivity both electronically and sterically. On one hand, the methyl group increases the electron density in both C-2 and C-5 positions, which favors the formation of isomers **9** and **10** over isomer **11**; on the other hand, because of the steric effect of the methyl group, the C-2 position that is adjacent to N-2 bearing two lone pair electrons is favored over the C-5 position that is adjacent to C-4 bearing a proton. This could account for the regioselectivity between isomers **9** and **10** toward perfluoroalkylation by the iodonium salt. The electronic and steric effect of *N*-substituents on the regioselectivity of *C*-perfluoroalkylation of imidazoles will be further investigated in the future.

The substitution position in isomer **10** was verified by its crystal structure (in nitrate form) shown in Figure 3. The minor isomer **11** was also synthesized from **6** by removing the N(1)-H proton using NaH followed by methylation using methyl iodide, which confirmed the structure of **11** and led to the easy assignment of the major isomer **9**.

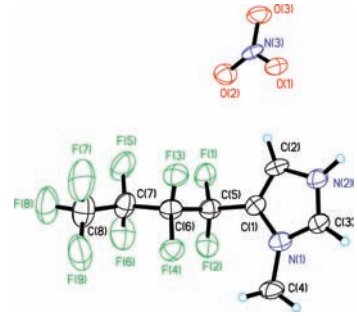


Figure 3. Crystal structure of **10**·HNO_3.

In summary, 1*H*,1*H*-perfluoroalkyl iodonium salts specifically target the nitrogen atom(s) of imidazole and its derivatives, whereas perfluoroalkyl iodonium salts attack the carbon atoms of imidazoles regioselectively. The *N*-substitution of imidazoles affects significantly the regioselectivity of *C*-perfluoroalkylation by the iodonium salts.

Acknowledgment. Financial support of this research by the National Science Foundation is gratefully acknowledged.

Supporting Information Available: Experimental procedures, NMR spectra of the numbered compounds, and cif files of the crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802399Z