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2,2-Difluoroethylation of Heteroatom Nucleophiles via a Hypervalent Iodine Strategy
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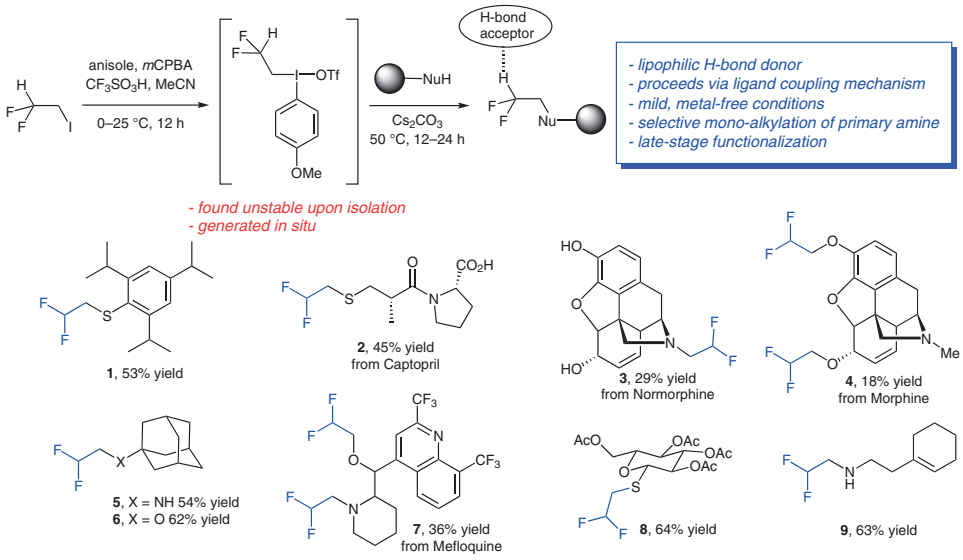
A Novel Method to Incorporate 2,2-Difluoroethyl Group as a Lipophilic Hydrogen-Bond Donor



Significance: In medicinal chemistry, fluorinated functional groups have been extensively explored as design motifs to improve physicochemical properties as well as biological profiles. Among these functional groups, the 2,2-difluoroethyl group occupies a unique niche as a lipophilic hydrogen-bond donor due to the increased acidity of the CF_2H proton while the molecule retains or enhances lipophilicity. Additionally, owing to the enhanced metabolic stability of C–F bonds, the 2,2-difluoroethyl group has been widely used as a stable bioisostere for alcohol, thiol and ether groups. In this article, the authors introduce a novel approach utilizing a hypervalent iodine reagent to incorporate a 2,2-difluoroethyl group into sulfur, nitrogen, and oxygen nucleophiles. This approach also enables the late-stage functionalization of pharmaceutically relevant molecules.

Comment: The authors successfully extended hypervalent iodine chemistry, previously applied in fluoroalkylation, to the 2,2-difluoroethylation of sulfur, nitrogen and oxygen nucleophiles. The key reagent, 2,2-difluoroethyl(aryl)iodonium salt, was generated in situ from the reaction of 1,1-difluoro-2-iodoethane, an aromatic ligand and an oxidant. Optimization studies revealed that the electron-donating anisole helped stabilize the salt and *m*CPBA was chosen as the most suitable oxidant. While more nucleophilic thiols and alcohols afforded the products in decent yields regardless of the electronic and steric properties of substituents, amines appeared to be more dependent on electronic property. Mechanistically, the highly selective monoalkylation of primary amines suggests a ligand coupling pathway rather than direct S_N2-type replacement. Overall, considering the relatively simple operation, the mild conditions, the broad functional group tolerance, and the significance of 2,2-difluoroethyl group in medicinal chemistry, this methodology is undoubtedly a valuable addition to medicinal chemistry toolbox.

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