Synthesis, Stability, and Reactivity of Azidofluoroalkanes

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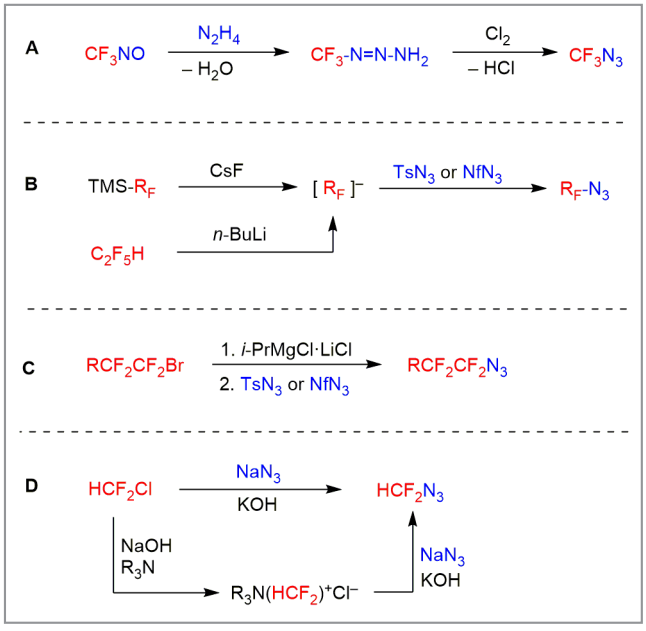
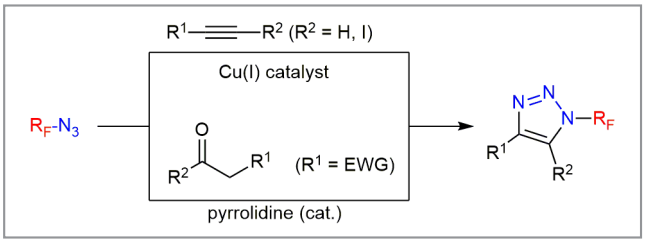
Organic azides constitute a very important class of compounds in synthetic, medicinal and biological chemistry and their preparation is often based on nucleophilic displacement of carbon-bound leaving groups starting from alkali metal azides. The synthetic utility of organic azides is very broad, encompassing reactions with electrophiles, nucleophiles (such as Staudinger reaction with phosphines), thermal or photo decomposition to nitrenes, and azide–alkyne cycloaddition to 1,2,3-triazoles. For the latter, when catalyzed by Cu(I) salts, the term 'click reaction' has been coined because of its reliability, high efficiency and broad substrate scope, and it has been widely used in synthetic chemistry, diversity-oriented synthesis, medicinal chemistry and materials science. Some organic azides, such as azidothymidine, even display interesting biological activities. However, a word of caution frequently appears in the literature when organic azides are described – low-molecular-weight azides are better avoided owing to their potentially explosive character.

The group of Dr. Petr Beier at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences, Prague (Czech Republic) has been active in the chemistry of fluorinated C1 and C2 building blocks and methodology development for some time, and recently the idea of investigating the properties and reactivity of fluorinated azides such as azidotrifluoromethane and azidodifluoromethane arose. "This chemistry was not completely new," acknowledged Dr. Beier. "Indeed, almost 60 years ago, Makarov prepared CF_3N_3 in two steps from toxic trifluoronitrosomethane, hydrazine and chlorine, a synthesis later repeated by Christe (Scheme 1A), thereby allowing for some basic characterization of the compound to be carried out, including ^{19}F NMR, IR and Raman spectra. However, the difficult synthetic access to CF_3N_3 involving toxic and corrosive starting gases, and perhaps also a fear of its possibly explosive nature, precluded further use of this azide and investigations of its chemical reactivity." Clearly, a new synthetic route to CF_3N_3 starting from commercial starting materials was needed. "Our initial attempts to produce CF_3N_3 from trifluoroiodomethane and sodium azide under thermal or photolytic conditions were unsuccessful. However, switching polarity of the synthons to the fluorinated carbanion derived from $TMSCF_3$ and an electrophilic azide (tosyl azide or nonaflyl azide) (Scheme 1B) was fruitful and allowed the preparation and full characterization (including ^{13}C NMR and high-resolution MS spectra) of CF_3N_3 and its longer carbon chain analogues (Scheme 1B)," explained Dr. Beier. He continued: "These are all volatile compounds and were isolated by distillation as solutions in organic solvents. Importantly, their stability was found to be sufficient for safe laboratory work (in contrast to their non-fluorinated counterparts) by test-heating their solutions to 150 °C for a prolonged time (*Angew. Chem. Int. Ed.* **2017**, *56*, 346–349). Related tetrafluoroethylene-containing azides were prepared by magnesiation of the corresponding bromides and reaction with electrophilic azides (*Org. Lett.* **2016**, *18*, 5844–5847; *Org. Biomol. Chem.* **2017**, *15*, 4962–4965) (Scheme 1C). For azidodifluoromethane, a modified published procedure based on the reaction of difluorocarbene with azide in aqueous conditions was used (Scheme 1D). The chemistry of azidodifluoromethane was also not investigated in the literature. We have fully characterized HCF_2N_3 and found that it was stable (*Eur. J. Org. Chem.* **2018**, 5087–5090)."

Click reactions of the azidofluoroalkanes with alkynes and organocatalyzed reactions with 1,3-diones or β-keto esters afforded 4-substituted and 4,5-disubstituted 1,2,3-triazoles, respectively (*Chem. Select* **2018**, *3*, 7045–7048) (Scheme 2).



Scheme 1 Synthetic approaches to azidoperfluoroalkanes and azidodifluoromethane

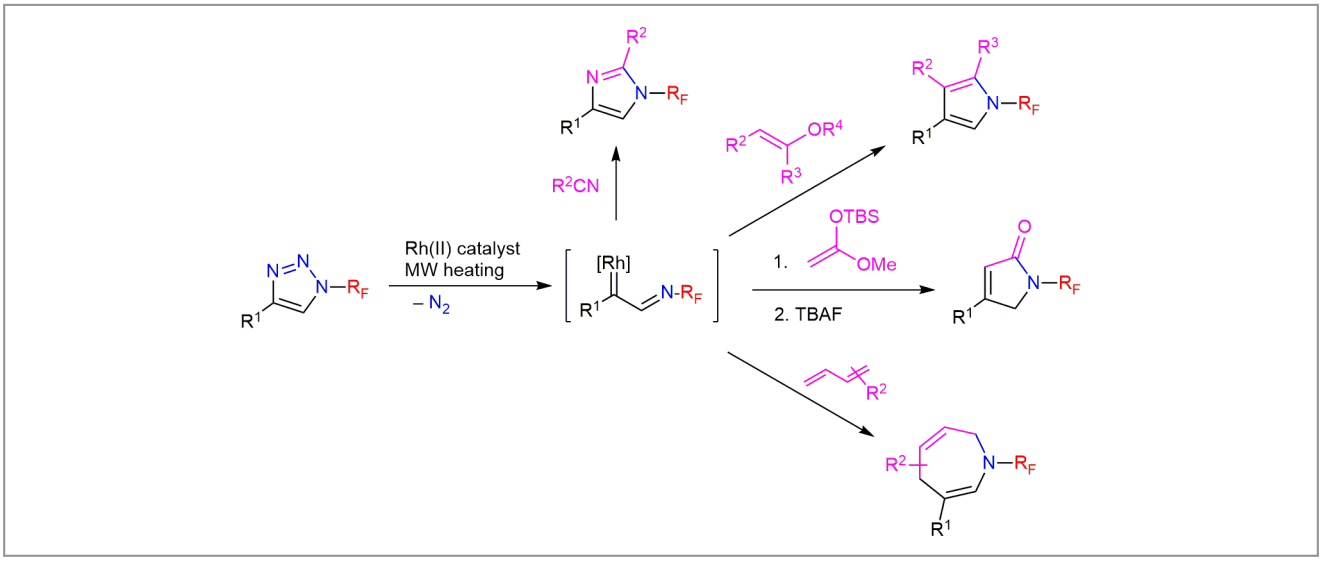


Scheme 2 [3+2] Cycloadditions with azido(per)fluoroalkanes

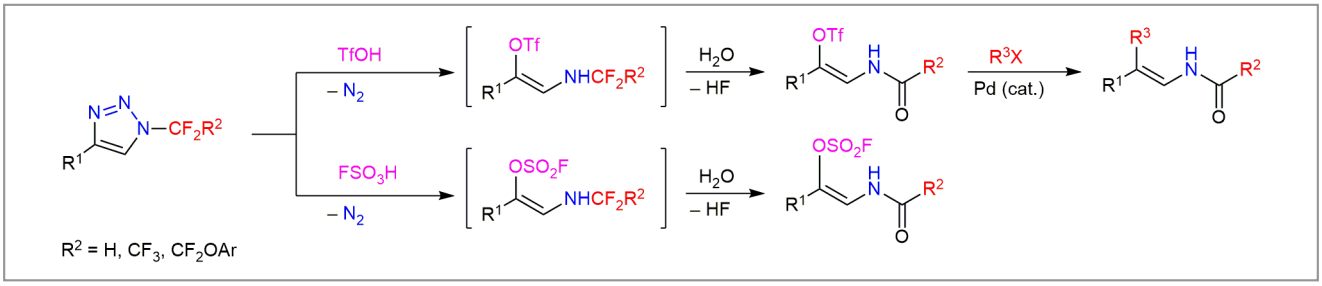
Dr. Beier explained that these 1-perfluoroalkylated 1,2,3-triazoles are very rare and some of them were prepared previously as mixtures of isomers. An important feature of azidofluoroalkanes when compared to azidoalkanes is their better stability and higher reactivity in click reactions with alkynes.

"1-Sulfonyl-1,2,3-triazoles are known to undergo rhodium-catalyzed transannulation to various nitrogen heterocycles under microwave heating and we were delighted to see that the chemistry can be expanded to 1-perfluoroalkyl (but not 1-difluoromethyl) 1,2,3-triazoles, thereby allowing synthetic access to a variety of previously unknown N-fluoroalkylated nitrogen heterocycles such as imidazoles, pyrroles, imidazolones, pyrrolones (*Chem. Commun.* **2018**, *54*, 3258–3261) and azepines (*J. Org. Chem.* **2018**, *83*, 15195–15201) (Scheme 3)," said Dr. Beier.

He continued: "Recently we found that 1-fluoroalkylated 1,2,3-triazoles in the presence of triflic or fluorosulfonic acid undergo a cascade reaction involving triazole protonation, ring opening and loss of nitrogen to a vinyl cation intermediate which reacts stereospecifically with the conjugate base of the strong acid to enamino triflate or fluorosulfonate, respectively." The group found that these are unstable under the reaction conditions, eliminate HF and hydrolyze to previously unreported β-enamido triflates or fluorosulfonates, respectively (Scheme 4) (*Chem. Eur. J.* **2019**, in press). "This reaction



Scheme 3 Rhodium(II)-catalyzed transannulation of N-perfluoroalkyl-1,2,3-triazoles



Scheme 4 Transformation of *N*-fluoroalkyl-1,2,3-triazoles into β-enamido triflates and fluorosulfonates

has a broad scope, is stereospecific, metal-free and takes place under mild conditions," said Dr. Beier. "The fluorinated group on nitrogen transforms into an amide protecting group (such as the trifluoroacetamido group) and the products are stable solids with a high synthetic utility, for example in cross-coupling reactions of the triflate group to give stereodefined enamides."

Dr. Beier concluded: "Our study shows that starting from a neglected chemical curiosity (CF_3N_3) we were able to develop a rich chemistry that afforded new products via exciting and unprecedented transformations. Physical and chemical properties of azidofluoroalkanes are currently under intensive investigation in our group."

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About the author

Dr. P. Beier

Petr Beier was born in 1978 in Ostrava (Czech Republic). After his undergraduate studies at the University of Pardubice (Czech Republic) he joined the group of Prof. David O'Hagan at St. Andrews University (UK) where he received his PhD in 2004. Then he moved to the Loker Hydrocarbon Research Institute and the University of Southern California, Los Angeles (USA), where he was a postdoctoral fellow in the group of Prof. Surya Prakash. In 2007 he joined the Institute of Organic Chemistry and Biochemistry at the Academy of Sciences in Prague (Czech Republic) for a junior group leader position and since 2012 he has worked at the same institute as a senior group leader. His research interests are synthetic methodology in organofluorine chemistry and chemistry of main group elements, C1 and C2 synthons, asymmetric synthesis, and investigation of reaction mechanisms. He has received the Alfred Bader Prize for Organic Chemistry from the Czech Chemical Society (2013) and the Royal Chemical Society Fluorine Prize (2017).