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Synthesis of tetrafluoroethylene- and tetrafluoroethyl-containing azides and their 1,3-dipolar cycloaddition as synthetic application†

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Tetrafluoroethylene-containing azides are accessed in two steps (one pot) from tetrafluoroalkyl bromides by metalation and reaction with electrophilic azides. Subsequent copper(I)-catalyzed azide–alkyne cycloaddition afforded *N*-tetrafluoroethyl and *N*-tetrafluoroethylene 4-substituted 1,2,3-triazoles. In addition, the protocol for the synthesis of 4,5-disubstituted 1,2,3-triazoles is presented.

Tetrafluoroethyl- and tetrafluoroethylene-containing compounds have been recently intensively investigated in agrochemistry, medicinal chemistry, and materials science as alternatives to well established fluorinated functional groups such as trifluoromethyl, perfluoroalkyl, and difluoromethyl.[1–9] For instance, tetrafluorinated sugar analogues were found to be significantly less hydrophilic than the parent carbohydrates, and thus exhibit enhanced protein–carbohydrate binding capabilities.[10–14] The tetrafluoroethylene motif is found in insecticides[15,16] and liquid crystals.[17,18] The tetrafluoroethyl- and triazole-containing molecule tetraconazole displays fungicidal activity.[19] Despite important recent advances in synthetic methods toward these compounds,[20–26] protocols affording CF_2CF_2-containing molecules of the unprecedented structure are still in demand. Our contribution to the field has been in the design and application of nucleophilic,[27–29] electrophilic[30] and radical[31] reagents for the CF_2CF_2 transfer which provided straightforward synthetic access to a variety of tetrafluoroethyl- and tetrafluoroethylene-containing compounds. In the latest report, tetrafluoroethyl bromides were reacted with i-PrMgCl·LiCl to afford metalated species stable at low temperature and displaying excellent reactivity with a range of electrophiles with one example of an electrophilic azide.[32] Azides are highly valuable compounds in organic synthesis – some fluoroalkyl azides are known,[33–40] including CF_3N_3 [41,42] and perfluoroalkyl analogues for which we have recently reported a new and practical synthetic method.[43] Perfluoroalkyl azides were investigated in copper(I)-catalyzed azide–alkyne cycloadditon (CuAAC)[44–46] furnishing *N*-perfluoroalkyl-1,2,3-triazoles.[43]

In this article, the synthesis of tetrafluoroethylene-containing azides is disclosed by metalation of tetrafluoroethyl bromides through organomagnesium or silicon species and their application in CuAAC is shown in the preparation of tetrafluoroethyl- and tetrafluoroethylene-containing triazoles.‡

Magnesiation of tetrafluoroethyl bromides (**1**) was performed with i-PrMgCl·LiCl (turbo Grignard reagent) in THF at −78 °C. We have earlier found that the metalated species are stable at this temperature and metalation times range from less than 5 min for R^1 = PhS and alkyl to half an hour or slightly longer for R^1 = imidazolyl, pyrazolyl and ArO.[32] An electrophilic azide source (tosyl or nonaflyl azide working equally well) was then added to the generated Grignard reagent and the temperature was allowed to rise to ambient temperature over a period of 3 hours. In this way, good yields of tetrafluoroethyl azides (**2**) were obtained with electron-neutral, -withdrawing or -donating groups on the aryl ring of the aryloxy substituent (R^1 = ArO) (Table 1). The 4-bromopyrazolyl derivative (**1h**) afforded the corresponding azide **2h** in moderate yield; however, the reaction was highly regioselective (only the bromine atom on the fluorinated carbon reacted). In contrast, the phenylthio derivative **1i**, under the same reaction conditions, provided selectively and in high conversion $PhSCF_2CF_2SPh$ instead of the expected azide **2i**. This outcome can be explained by high susceptibility of the Grignard intermediate to oxidation to radicals, partial fragmentation giving PhS radicals, which prefer to react with electrophilic $PhSCF_2CF_2$ radicals. Therefore, for the synthesis of **2i**, an alternative method was used starting from $PhSCF_2CF_2SiMe_3$.[47] Nucleophilic fluoroalkyl transfer, after activation with CsF, to either tosyl or nonaflyl azide afforded high yields of **2i** (Scheme 1).
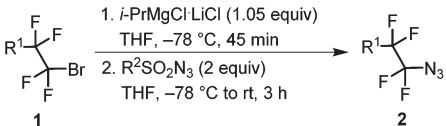
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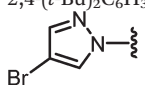*E-mail: beier@uochb.cas.cz*
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Table 1 Synthesis of tetrafluoroethylene-containing azides **2**
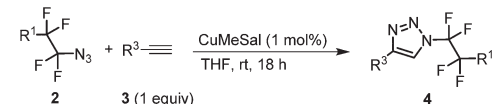
Entry	R^1	R^2	2, Yield (%)
1	PhO	p-Tol	**2a**, 92
2	4-FC$_6$H$_4$O	p-Tol	**2b**, 79
3	4-BrC$_6$H$_4$O	p-Tol	**2c**, 76
4	4-(MeO)C$_6$H$_4$O	n-C$_4$F$_9$	**2d**, 84
5	3-(Me$_2$N)C$_6$H$_4$O	n-C$_4$F$_9$	**2e**, 87
6	3-(CF$_3$)C$_6$H$_4$O	n-C$_4$F$_9$	**2f**, 73
7	2,4-(t-Bu)$_2$C$_6$H$_3$O	n-C$_4$F$_9$	**2g**, 71
8	(4-Br pyrazolyl)	n-C$_4$F$_9$	**2h**, 44
9	PhS	n-C$_4$F$_9$	**2i**, 0^a
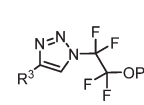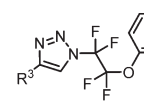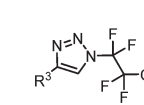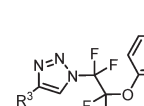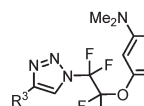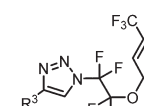
^{a} PhSCF$_2$CF$_2$SPh formed instead of **2i**.
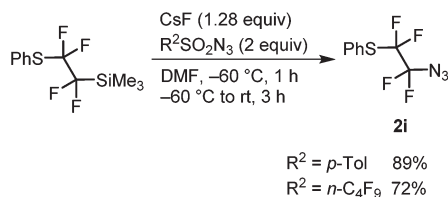
Scheme 1 Synthesis of (2-azido-1,1,2,2-tetrafluoroethyl)(phenyl)sulfane (**2i**).

Table 2 Synthesis of N-tetrafluoroalkyl triazoles **4**

R^3 = p-Tol **4aj** 85%
4-(NO$_2$)C$_6$H$_4$ **4ak** 78%
3-pyridyl **4al** 78%

p-Tol **4bj** 72%
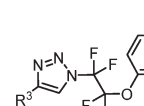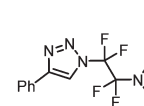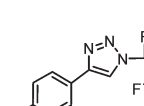4-(NO$_2$)C$_6$H$_4$ **4bk** 69%
3-pyridyl **4bl** 41%

Ph **4cm** 92%
p-Tol **4cj** 81%
4-(NO$_2$)C$_6$H$_4$ **4ck** 48%
3-pyridyl **4cl** 95%

R^3 = Ph **4dm** 82%, X-ray
4-(MeO)C$_6$H$_4$ **4dn** 86%
4-(NO$_2$)C$_6$H$_4$ **4dk** 77%

Ph **4em** 79%
4-(MeO)C$_6$H$_4$ **4en** 81%
4-(NO$_2$)C$_6$H$_4$ **4ek** 84%

4-(NO$_2$)C$_6$H$_4$ **4fk** 70%
4-(CF$_3$)C$_6$H$_4$ **4fo** 48%
CO$_2$Et **4fp** 73%
n-Bu **4fq** 81%

R^3 = Ph **4gm** 90%
4-(MeO)C$_6$H$_4$ **4gn** 85%
4-(NO$_2$)C$_6$H$_4$ **4gk** 83%
CO$_2$Et **4gp** 85%

4hm 64%
X-ray

4ij 59%
X-ray
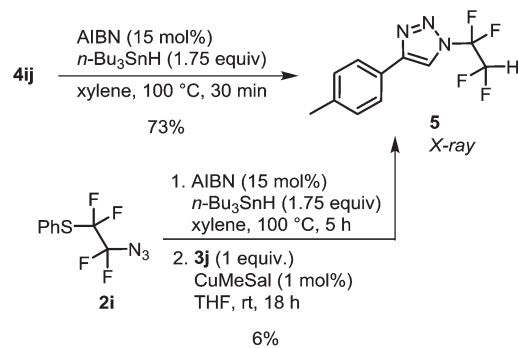
Scheme 2 Preparation of N-tetrafluoroethyl 4-substituted 1,2,3-triazole **5**.

With azides **2**, CuAAC was investigated. Our earlier work with azidotrifluoromethane and other azidoperfluoroalkanes[43] showed that copper(I) 3-methylsalicylate (CuMeSal) was a preferred catalyst in terms of catalytic activity, good solubility in organic solvents and high stability. Therefore, it was favored over other Cu(I) sources. In the reaction, equimolar amounts of aryl, heteroaryl or alkyl acetylenes and 1 mol% of CuMeSal afforded good to high yields of N-tetrafluoroalkylated 4-substituted 1,2,3-triazoles **4** (Table 2). The examples showing moderate yields resulted from isolation difficulties rather than a lack of reactivity or side reactions. Exclusive formation of 1,4-disubstituted triazoles was observed in all cases. Compounds of the type **4** are unknown in the literature with the exception of a triazole formed by thermal cycloaddition of N$_3$CF$_2$CF$_2$CO$_2$Me.[48] Reductive cleavage of the phenylsulfanyl group provided N-tetrafluoroethyl-containing triazole **5** in good yield (Scheme 2). However, attempts to prepare HCF$_2$CF$_2$N$_3$ from **2i** under the same reaction conditions met with limited success partially due to product volatility and also due to some unknown side reactions. Nevertheless, the *in situ* formed HCF$_2$CF$_2$N$_3$ transformed to N-tetrafluoroethyl triazole **5** (Scheme 2).

Finally, N-tetrafluoroethyl 4,5-disubstituted 1,2,3-triazoles were accessed in two steps from azides **2a** and **2d** and copper acetylides **6j** and **6m**, respectively. The reaction with iodine and a base afforded iodotriazoles **7aj** and **7dm**, respectively, in good to high yields which were amenable to Sonogashira or Suzuki–Miyaura cross-coupling reactions giving 4,5-disubstituted triazoles **8** and **9**, respectively (Scheme 3).

Crystallographic analysis of triazoles **4dm**, **4hm**, **4ij**, **5** and **7dm** confirmed their molecular structures (see the ESI†) and also showed an interesting difference in conformation at the N-CF$_2$CF$_2$-X unit. While in compounds **4hm** (X = N) and **4ij** (X = S) the N and X atoms are approximately *anti-periplanar*, in compounds **4dm**, **7dm** (X = O) and **5** (X = H) the N and X atoms are *gauche* as illustrated in Fig. 1. The reasons for this difference is unclear; however, an interplay between the steric
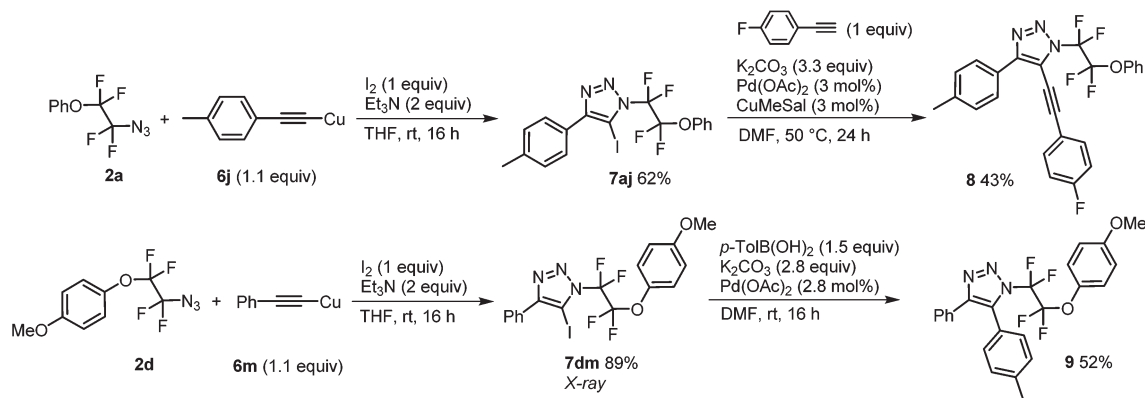
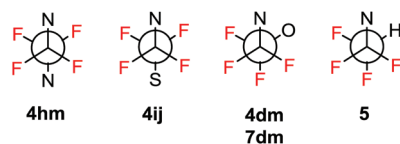**Scheme 3** Synthesis of 4,5-disubstituted 1,2,3-triazoles **8** and **9**.

Fig. 1 Schematic representation of the N–C–C–X conformation in the crystal structures of *N*-tetrafluoroethyl 1,2,3-triazoles.

repulsion of N and X atoms favoring *anti-periplanar* conformation and favorable vicinal fluorine–fluorine *gauche* conformation (three *vs.* two F, F *gauche* arrangements) should be taken into consideration.

In conclusion, magnesiation of tetrafluoroethyl bromides with i-PrMgCl·LiCl and subsequent reaction with tosyl or nonaflyl azides afforded tetrafluoroethylated azides. (2-Azido-1,1,2,2-tetrafluoroethyl)(phenyl)sulfane was prepared by fluoride-initiated nucleophilic fluoroalkyl transfer from the corresponding silane. The azides proved to be competent partners in copper(I)-catalyzed azide alkyne cycloadditions with terminal alkynes to generate *N*-tetrafluoroalkylated 4-substituted 1,2,3-triazoles. Reductive cleavage of the PhS group in the tetrafluoroethyl unit afforded *N*-tetrafluoroethyl azide. 4,5-Disubstituted triazoles were accessed by CuAAC of the triazoles with copper acetylides in the presence of iodine followed by transition metal-catalyzed cross-coupling reactions.

Acknowledgements

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