



Cite this: *Org. Biomol. Chem.*, 2017, **15**, 4962

Received 11th May 2017,
Accepted 18th May 2017

DOI: 10.1039/c7ob01151b

rsc.li/obc

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

Svatava Voltrová,^a Mickaël Muselli,^a Josef Filgas,^a Václav Matoušek,^b Blanka Klepetářová^a and Petr Beier^{✉*}^a

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 CF₂CF₂-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} electrophilic³⁰ and radical³¹ reagents for the CF₂CF₂ 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 CF₃N₃^{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 cycloaddition (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.‡

Magnesiumation 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 R¹ = PhS and alkyl to half an hour or slightly longer for R¹ = imidazolyl, pyrazolyl and ArO.³² An electrophilic azide source (tosyl or nonafllyl 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 (R¹ = 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 PhSCF₂CF₂SPh 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 PhSCF₂CF₂ radicals. Therefore, for the synthesis of **2i**, an alternative method was used starting from PhSCF₂CF₂SiMe₃.⁴⁷ Nucleophilic fluoroalkyl transfer, after activation with CsF, to either tosyl or nonafllyl azide afforded high yields of **2i** (Scheme 1).

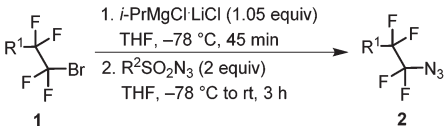
^aThe Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo náměstí 2, 166 10 Prague, Czech Republic.
E-mail: beier@uochb.cas.cz

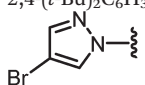
^bCF Plus Chemicals s.r.o., Kamenice 771/34, 625 00 Brno, Czech Republic

† Electronic supplementary information (ESI) available. CCDC 1545038–1545042. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob01151b

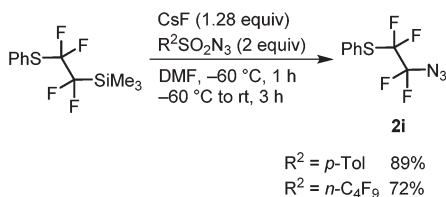


Table 1 Synthesis of tetrafluoroethylene-containing azides 2



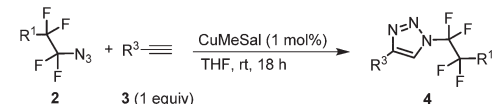
Entry	R ¹	R ²	2, Yield (%)
1	PhO	<i>p</i> -Tol	2a , 92
2	4-FC ₆ H ₄ O	<i>p</i> -Tol	2b , 79
3	4-BrC ₆ H ₄ O	<i>p</i> -Tol	2c , 76
4	4-(MeO)C ₆ H ₄ O	<i>n</i> -C ₄ F ₉	2d , 84
5	3-(Me ₂ N)C ₆ H ₄ O	<i>n</i> -C ₄ F ₉	2e , 87
6	3-(CF ₃)C ₆ H ₄ O	<i>n</i> -C ₄ F ₉	2f , 73
7	2,4-(<i>t</i> -Bu) ₂ C ₆ H ₃ O	<i>n</i> -C ₄ F ₉	2g , 71
8		<i>n</i> -C ₄ F ₉	2h , 44
9	PhS	<i>n</i> -C ₄ F ₉	2i , 0 ^a

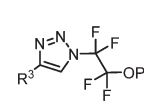
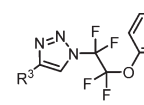
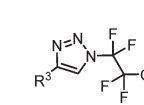
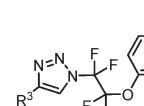
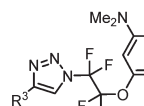
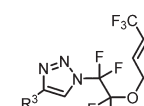
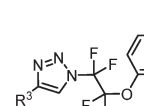
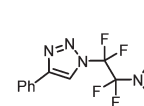
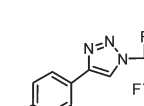
^a PhSCF₂CF₂SPh formed instead of **2i**.

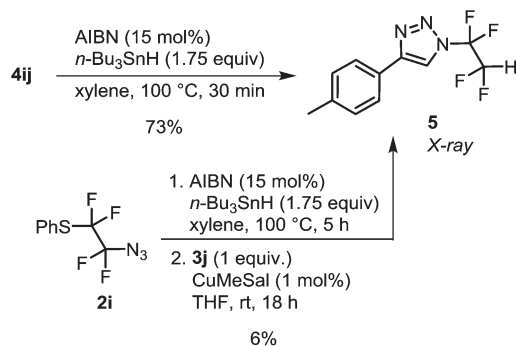
Scheme 1 Synthesis of (2-azido-1,1,2,2-tetrafluoroethyl)(phenyl) sulfane (**2i**).

With azides **2**, CuAAC was investigated. Our earlier work with azidotrifluoromethane and other azidoperfluoroalkanes⁴³ 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 N₃CF₂CF₂CO₂Me.⁴⁸ Reductive cleavage of the phenylsulfanyl group provided *N*-tetrafluoroethyl-containing triazole **5** in good yield (Scheme 2). However, attempts to prepare HCF₂CF₂N₃ 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 HCF₂CF₂N₃ 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

Table 2 Synthesis of *N*-tetrafluoroalkyl triazoles 4


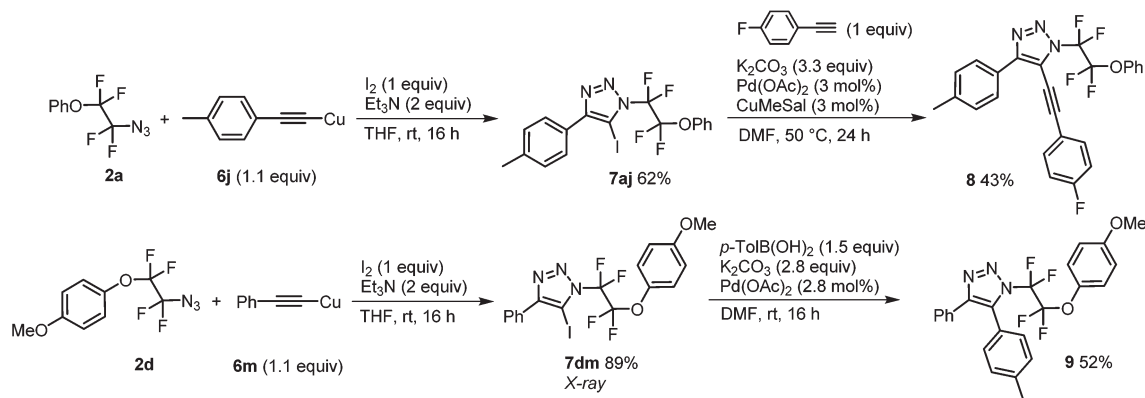
 R ³ = <i>p</i> -Tol 4aj 85% 4-(NO ₂)C ₆ H ₄ 4ak 78% 3-pyridyl 4al 78%	 <i>p</i> -Tol 4bj 72% 4-(NO ₂)C ₆ H ₄ 4bk 69% 3-pyridyl 4bl 41%	 Ph 4cm 92% <i>p</i> -Tol 4cj 81% 4-(NO ₂)C ₆ H ₄ 4ck 48% 3-pyridyl 4cl 95%
 R ³ = Ph 4dm 82%, X-ray 4-(MeO)C ₆ H ₄ 4dn 86% 4-(NO ₂)C ₆ H ₄ 4dk 77%	 Ph 4em 79% 4-(MeO)C 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% <i>n</i> -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**.

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*-CF₂CF₂-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**.

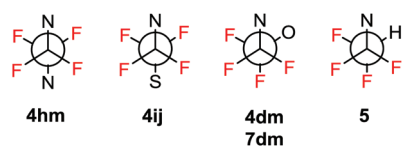


Fig. 1 Schematic representation of the N-C-C-X conformation in the crystal structures of *N*-tetrafluoroethyl 1,2,3-triazoles.

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 non-aryl 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

This work was supported by the Czech Academy of Sciences (Research Plan RVO: 61388963) and the Initial Training Network, FLUOR21, funded by the FP7 Marie Curie Actions of the European Commission (FP7-PEOPLE-2013-ITN-607787).

References

‡The CF Plus Chemicals s.r.o. (<http://www.cfplus.cz>) company, an ETH Zurich spin-off, commercializes the compounds used in this publication.

- P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2nd edn, 2013.
- Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- X. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826–870.
- C. Alonso, E. Martinez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.
- J. Wang, M. Sanchez-Rosello, J. L. Acena, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.
- I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, New York, 2009.
- J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465–7478.
- J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1–PR43.
- A. J. Boydell, V. Vinader and B. Linclau, *Angew. Chem., Int. Ed.*, 2004, **43**, 5677–5679.
- B. Linclau, A. J. Boydell, R. S. Timofte, K. J. Brown, V. Vinader and A. C. Weymouth-Wilson, *Org. Biomol. Chem.*, 2009, **7**, 803–814.
- T. Konno, T. Hoshino, T. Kida, S. Takano and T. Ishihara, *J. Fluorine Chem.*, 2013, **152**, 106–113.
- L. N'Go, S. Golten, A. Arda, J. Canada, J. Jimenez-Barbero, B. Linclau and S. P. Vincent, *Chem. – Eur. J.*, 2014, **20**, 106–112.
- K. E. van Straaten, J. R. Kuttiyatveetil, C. M. Sevrain, S. A. Villaume, J. Jimenez-Barbero, B. Linclau, S. P. Vincent and D. A. Sanders, *J. Am. Chem. Soc.*, 2015, **137**, 1230–1244.
- E. L. Plummer, *US 4737509*, 1988.
- E. L. Plummer, *US 4636523*, 1987.
- S. Yamada, S. Hashishita, T. Asai, T. Ishihara and T. Konno, *Org. Biomol. Chem.*, 2017, **15**, 1495–1509.
- P. Kirsch, M. Bremer, F. Huber, H. Lannert, A. Ruhl, M. Lieb and T. Wallmichrath, *J. Am. Chem. Soc.*, 2001, **123**, 5414–5417.



- 19 D. Bianchi, P. Cesti, S. Spezia, C. Garavaglia and L. Mirena, *J. Agric. Food Chem.*, 1991, **39**, 197–201.
- 20 Y. Sakaguchi, S. Yamada, T. Konno, T. Agou and T. Kubota, *J. Org. Chem.*, 2017, **82**, 1618–1631.
- 21 T. Konno, S. Takano, Y. Takahashi, H. Konishi, Y. Tanaka and T. Ishihara, *Synthesis*, 2011, 33–44.
- 22 Y. Watanabe and T. Konno, *J. Fluorine Chem.*, 2015, **174**, 102–107.
- 23 J. Zhu, C. Ni, B. Gao and J. Hu, *J. Fluorine Chem.*, 2015, **171**, 139–147.
- 24 M. O'Duill, E. Dubost, L. Pfeifer and V. Gouverneur, *Org. Lett.*, 2015, **17**, 3466–3469.
- 25 H. Saijo, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2014, **136**, 15158–15161.
- 26 M. Ohashi, Y. Ueda and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2017, **56**, 2435–2439.
- 27 Y. Chernykh, K. Hlat-Glembová, B. Klepetářová and P. Beier, *Eur. J. Org. Chem.*, 2011, 4528–4531.
- 28 J. Václavík, Y. Chernykh, B. Jurásek and P. Beier, *J. Fluorine Chem.*, 2015, **169**, 24–31.
- 29 Y. Chernykh, B. Jurásek and P. Beier, *J. Fluorine Chem.*, 2015, **171**, 162–168.
- 30 V. Matoušek, J. Václavík, P. Hájek, J. Charpentier, Z. E. Blastik, E. Pietrasiak, A. Budinská, A. Togni and P. Beier, *Chem. – Eur. J.*, 2016, **22**, 417–424.
- 31 Y. Chernykh and P. Beier, *J. Fluorine Chem.*, 2013, **156**, 307–313.
- 32 A. Budinská, J. Václavík, V. Matoušek and P. Beier, *Org. Lett.*, 2016, **18**, 5844–5847.
- 33 C. G. Krespan and B. E. Smart, *J. Org. Chem.*, 1986, **51**, 320–326.
- 34 C. G. Krespan, *J. Org. Chem.*, 1986, **51**, 332–337.
- 35 J. Dai, Z. Li, T. Wang and R. Bai, *Org. Biomol. Chem.*, 2016, **14**, 4382–4386.
- 36 S. A. Postovoi, Y. V. Zeifman and I. L. Knunyants, *Russ. Chem. Bull.*, 1986, **35**, 1183–1186.
- 37 T. G. Archibald and K. Baum, *J. Org. Chem.*, 1990, **55**, 3562–3565.
- 38 T. Hiramatsu, Y. Guo and T. Hosoya, *Org. Biomol. Chem.*, 2007, **5**, 2916–2919.
- 39 S. A. Lermontov, A. G. Polivanova and S. B. Shkavrov, *Russ. J. Gen. Chem.*, 2010, **80**, 1646–1651.
- 40 J. Dai, Z. Li, T. Wang, W. Bai and R. Bai, *Org. Lett.*, 2017, **19**, 1418–1421.
- 41 S. P. Makarov, A. Y. Yakubovich, A. S. Filatov, M. A. Enlin and T. Y. Nikiforova, *Zh. Obshch. Khim.*, 1968, **38**, 709–715.
- 42 K. O. Christe and C. J. Schack, *Inorg. Chem.*, 1981, **20**, 2566–2570.
- 43 Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová and P. Beier, *Angew. Chem., Int. Ed.*, 2017, **56**, 346–349.
- 44 M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015.
- 45 J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315.
- 46 E. Haldon, M. C. Nicasio and P. J. Perez, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550.
- 47 F. Toulgoat, B. R. Langlois, M. Medebielle and J. Y. Sanchez, *J. Org. Chem.*, 2007, **72**, 9046–9052.
- 48 S. A. Lermontov, S. V. Shkavrov and A. N. Pushin, *J. Fluorine Chem.*, 2000, **105**, 141–147.

