

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2016, **3**, 949Convenient synthesis of pentafluoroethyl thioethers *via* catalytic Sandmeyer reaction with a stable fluoroalkylthiolation reagent†

C. Matheis,‡ B. Bayarmagnai,‡ K. Jouvin and L. J. Goossen*

Received 11th May 2016,

Accepted 3rd June 2016

DOI: 10.1039/c6qo00194g

rsc.li/frontiers-organic

Aromatic and heteroaromatic diazonium salts were smoothly converted into the corresponding pentafluoroethyl thioethers by reaction with $\text{Me}_4\text{NSC}_2\text{F}_5$ in the presence of catalytic amounts of elemental copper. This Sandmeyer-type reaction proceeds at room temperature under mild conditions and is applicable to a wide range of functionalised molecules. It enables the late-stage introduction of pentafluoroethylthio groups, a promising but largely unexplored substituent, into bioactive molecules.

Fluorine-containing groups are of exceptional importance in modern bioactive molecules. Approximately 40% of currently marketed agrochemicals and 25% of pharmaceuticals contain fluorine atoms.¹ The systematic introduction and screening of fluorinated residues has become a standard procedure in drug discovery. Thus, methods for the late-stage introduction of fluorinated substituents into functionalised molecules are highly sought-after. In the past decade, various powerful fluoroalkylation methods have been developed.² The attention has recently shifted towards fluoroalkyl thioethers, since the SCF_3 group induces even higher lipophilicity (Hansch constant 1.44 for SCF_3 vs. 0.88 for CF_3) and membrane permeability.³

Contemporary trifluoromethylthiolation reactions of arenes are based on electrophilic,⁴ nucleophilic,⁵ radical,⁶ or oxidative processes,⁷ usually starting from arylboronic acids or aryl halides.

Our contribution to the field of fluoroalkyl(thiol)ations has been the development of several Sandmeyer-type processes.⁸ We have demonstrated that a Sandmeyer-thiocyanation followed by a Langlois-type nucleophilic CN/CF_3 - or CF_2H -exchange allows the convenient synthesis of fluoroalkylthioethers.^{8f,9} For laboratory-scale applications, the use of pre-formed reagents such as $(\text{bpy})\text{CuSCF}_3$,¹⁰ AgSCF_3 ^{5a} and Me_4NSCF_3 are more convenient. The bench-stable reagent Me_4NSCF_3 was first synthesised by Roeschenthaler and Yagupolskii¹¹ and has successfully been employed in trifluoromethylthiolations of vinyl iodides,¹² boronic acids,^{7d} aryl

halides,¹³ aryl triflates,¹⁴ and aryl C–H bonds¹⁵ catalysed by Cu, Ni, or Pd complexes.

In medicinal chemistry, C_2F_5 derivatives have repeatedly been found to exhibit properties that are superior to those of their CF_3 counterparts. Whereas several methods have been reported for the introduction of pentafluoroethyl groups, there are only few reports on the corresponding pentafluoroethylthio compounds.¹⁶ Pentafluoroethyl thioarenes cannot be prepared by classical halogen/fluorine exchange reactions, *e.g.* Swarts-type processes. Traditional syntheses of SC_2F_5 moieties are based on the reaction of C_2F_5 radicals or carbanions with disulfides or thiols.¹⁷ However, these methods suffer from harsh reaction conditions and limited availability of sulfur-containing substrates.

Modern methods suitable for the late-stage introduction of SC_2F_5 groups include the Friedel–Crafts-type reaction of electron-rich arenes with a pentafluoroethyl sulfenamide reagent described by Billard *et al.*¹⁸ and the electrophilic perfluoroalkylthiolation of indoles with perfluoroalkyl sulfinates in the presence of stoichiometric copper chloride reported by Zhang *et al.*¹⁹ However, these methods are limited to electron-rich arenes and indoles. A generally applicable, regioselective method for the introduction of SC_2F_5 groups within a single step, based on widely available substrates and an inexpensive fluoroalkylation reagent, would be highly desirable.

We approached this challenge by investigating Sandmeyer-type pentafluoroethylthiolations (Scheme 1). $\text{Me}_4\text{NSC}_2\text{F}_5$ appeared to be the reagent of choice, because according to a patent by Roeschenthaler, it is easily accessible from tetramethylammonium fluoride, elemental sulfur and TMSC_2F_5 .^{11a,20}

In order to probe the viability of our approach, we treated 4-methoxybenzenediazonium tetrafluoroborate with $\text{Me}_4\text{NSC}_2\text{F}_5$ in the presence of 10 mol% CuSCN in acetonitrile at room temperature, conditions previously optimised for

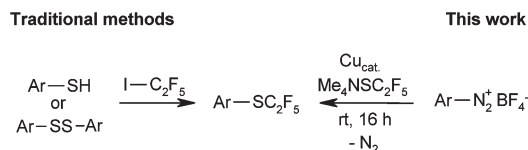
FB Chemie-Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Str. Geb. 54, D-67663 Kaiserslautern, Germany. E-mail: goossen@chemie.uni-kl.de;

Fax: +49 631 205 3921

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c6qo00194g

‡These authors contributed equally to this work.





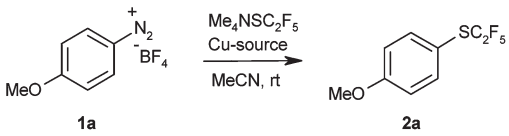
Scheme 1 Syntheses of pentafluoroethyl thioethers.

Sandmeyer trifluoromethylthiolations.^{8e} The pentafluoroethyl thioether was indeed observed, albeit in unsatisfactory yield. The main products were 4-methoxyphenyl thiocyanate and the protodiazotisation product anisole (Table 1, entry 1). It soon became clear that $\text{C}_2\text{F}_5\text{S}^-$ is substantially less nucleophilic than SCF_3^- , so that pentafluoroethylthiolation takes place only in reaction media free of other nucleophiles. Thus, most counter-ions of copper(i) precursors led to unwanted side product formation. However, the desired product was formed in high yield in the presence of elemental copper (entries 2–4).

The best results were obtained with 10 mol% of Cu (entries 5–7). This is remarkable, since there are only few examples of Sandmeyer reactions catalytic in copper. The markedly lower nucleophilicity of the pentafluoroethylthio group in comparison to the trifluoromethylthio group is reflected in the increased reaction times; the pentafluoroethylthiolation requires 15 hours to go to completion, whereas Sandmeyer trifluoromethylthiolations occur within less than one hour at room temperature (entry 8).^{8e} Without copper, no product formation was observed (entry 9).

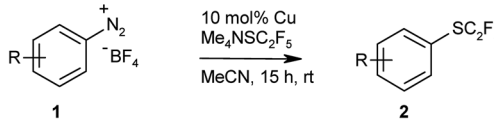
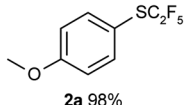
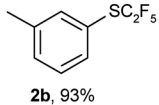
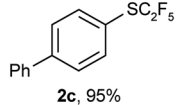
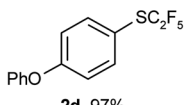
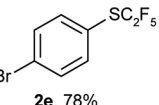
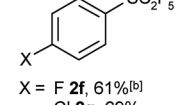
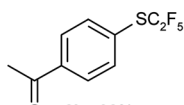
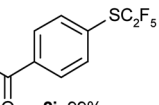
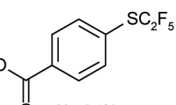
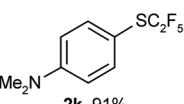
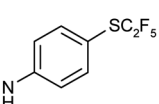
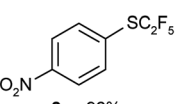
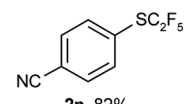
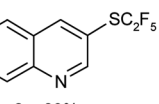
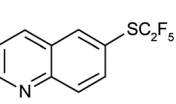
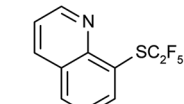
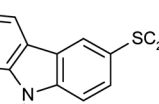
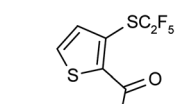
Having thus found an effective protocol for the Sandmeyer pentafluoroethylthiolation, we next investigated its scope. Various arenediazonium tetrafluoroborates were smoothly converted into the corresponding pentafluoroethyl thioethers in high yields (Table 2).

Table 1 Optimisation of the reaction conditions^a

		
Entry	Cu-source	Yield 2a [%]
1	10 mol% CuSCN	70
2	10 mol% CuOAc	15
3	10 mol% CuI	20
4	10 mol% Cu	99
5	5 mol% Cu	62
6	0.5 equiv. Cu	89
7	1.0 equiv. Cu	75
8 ^b	1.0 equiv. Cu	12
9	—	0

^a Reaction conditions: dropwise addition of 0.5 mmol of **1a** in 1 mL acetonitrile to 1.5 equiv. $\text{Me}_4\text{NSC}_2\text{F}_5$ and the copper source in 1 mL acetonitrile, 15 h at room temperature. Yields were determined by ^{19}F NMR using trifluoroethanol as an internal standard. ^b 1 h reaction time.

Table 2 Substrate scope of the Sandmeyer pentafluoroethylthiolation^a

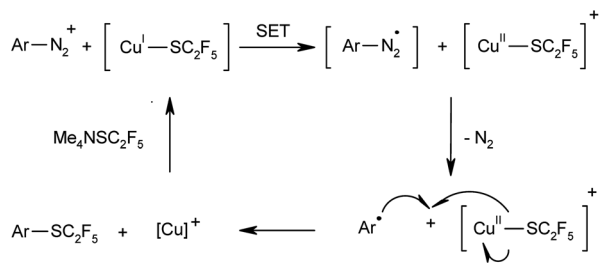
		
 2a , 98%	 2b , 93%	 2c , 95%
 2d , 97%	 2e , 78%	 2f , 61% ^[b] 2g , 69%
 2h , 98%	 2i , 99%	 2j , 94%
 2k , 91%	 2l , 82%	 2m , 96%
 2n , 82%	 2o , 89%	 2p , 82%
 2q , 71%	 2r , 72%	 2s , 98%

^a Reaction conditions: dropwise addition of 1.0 mmol of **1** in 2 mL MeCN to 1.5 mmol $\text{Me}_4\text{NSC}_2\text{F}_5$ and 0.1 mmol elemental copper in 2 mL MeCN, 15 h at room temperature. ^b Yields determined by ^{19}F NMR using trifluoroethanol as an internal standard.

Both electron-rich and electron-deficient substrates give similarly high yields, and various functionalities are tolerated including ester, ether, amino, keto, carboxylate, cyano, and even bromo groups. Various heterocycles were also pentafluoroethylthiolated in good yields. These examples clearly demonstrate the utility of the protocol for late-stage pentafluoroethylthiolations of functionalised intermediates. The products are obtained in reasonable purity after simple aqueous workup, and can be further purified by column chromatography.

It is safe to assume that in analogy to classical Sandmeyer halogenations and trifluoromethylthiolations of diazonium salts, the reaction proceeds *via* a single-electron transfer mechanism as depicted in Scheme 2. The use of metallic copper as source of Cu(I) species in these processes is rare but





Scheme 2 Sandmeyer pentafluoroethylthiolation of aromatic amines.

not unprecedented.^{8e,21} The addition of radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone suppressed the reaction, which confirms that the reaction involves radical intermediates. In order to exclude an alternative cationic pathway for extremely electron-poor substrates, analogous control experiments were conducted with 4-nitrobenzenediazonium tetrafluoroborate. In the absence of copper or in the presence of radical trapping reagents no product formation was detected, which supports a Sandmeyer type mechanism even for substrates in which other pathways are conceivable.

Conclusions

The Sandmeyer-type process reported herein allows the straightforward synthesis of pentafluoroethylthiolated compounds from the corresponding aromatic amines. The key advantages of this method are its mild reaction conditions (neutral, room temperature), the use of an inexpensive copper catalyst in only 10 mol% loading, and the exceptional functional group tolerance. As a result, this method is well-suited for the late-stage introduction of pentafluoroethylthio groups into drug-like molecules.

Acknowledgements

We thank the Heinrich-Böll-Stiftung e.V. (scholarship to B. B.) for financial support.

References

- (a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (b) P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589; (c) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- (a) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475–4521; (b) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (c) X.-F. Wu, H. Neumann and M. Beller, *Chem. – Asian J.*, 2012, **7**, 1744–1754; (d) T. Liu and Q. Shen, *Eur. J. Org. Chem.*, 2012, 6679–6687; (e) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264; (f) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683–730; (g) C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.
- (a) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani and E. J. Lien, *J. Med. Chem.*, 1973, **16**, 1207–1216; (b) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415–2428.
- (a) A. Tlili and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 6818–6819; (b) X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457–3460; (c) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782–8785; (d) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 1650–1653; (e) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9316–9320.
- (a) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312–7314; (b) C.-P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183–185; (c) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548–1552.
- L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237–18240.
- (a) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492–2495; (b) C. Chen, L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 12454–12457; (c) C.-P. Zhang and D. A. Vicic, *Chem. – Asian J.*, 2012, **7**, 1756–1758; (d) S.-Q. Zhu, X.-H. Xu and F.-L. Qing, *Eur. J. Org. Chem.*, 2014, 4453–4456.
- (a) B. Bayarmagnai, C. Matheis, E. Risto and L. J. Goossen, *Adv. Synth. Catal.*, 2014, **356**, 2343–2348; (b) G. Danoun, B. Bayarmagnai, M. Grünberg, C. Matheis, E. Risto and L. Goossen, *Synthesis*, 2014, 2283–2286; (c) C. Matheis, K. Jouvin and L. J. Goossen, *Org. Lett.*, 2014, **16**, 5984–5987; (d) B. Bayarmagnai, C. Matheis, K. Jouvin and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2015, **54**, 5753–5756; (e) C. Matheis, V. Wagner and L. J. Goossen, *Chem. – Eur. J.*, 2016, **22**, 79–82; (f) G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.*, 2014, **5**, 1312–1316.
- (a) B. Exner, B. Bayarmagnai, F. Jia and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 17220–17223; (b) K. Jouvin, C. Matheis and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 14324–14327; (c) C. Matheis, M. Wang, T. Krause and L. Goossen, *Synlett*, 2015, **26**, 1628–1632.
- (a) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548–1552; (b) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492–2495; (c) Y. Zhang, K. Gan and Z. Weng, *Org. Process Res. Dev.*, 2016, **20**, 799–802.
- (a) P. Kirsch, G. V. Roeschenthaler, B. Bissky and A. Kolomeitsev, *DE-A1 10254597*, 2003, Merck GmbH;



- (b) W. Tyrra, D. Naumann, B. Hoge and Y. L. Yagupolskii, *J. Fluorine Chem.*, 2003, **119**, 101–107.
- 12 M. Rueping, N. Tolstoluzhsky and P. Nikolaienko, *Chem. – Eur. J.*, 2013, **19**, 14043–14046.
- 13 (a) G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164–4172; (b) G. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2015, **54**, 6809–6813; (c) Y. Yang, L. Xu, S. Yu, X. Liu, Y. Zhang and D. A. Vicic, *Chem. – Eur. J.*, 2016, **22**, 858–863.
- 14 A. B. Dürr, G. Yin, I. Kalvet, F. Napoly and F. Schoenebeck, *Chem. Sci.*, 2016, **7**, 1076–1081.
- 15 C. Xu and Q. Shen, *Org. Lett.*, 2014, **16**, 2046–2049.
- 16 (a) M. Andrzejewska, *Eur. J. Med. Chem.*, 2002, **37**, 973–978; (b) A. Johansson, A. Poliakov, E. Åkerblom, K. Wiklund, G. Lindeberg, S. Winiwarter, U. H. Danielson, B. Samuelsson and A. Hallberg, *Bioorg. Med. Chem.*, 2003, **11**, 2551–2568; (c) A. Lishchynskiy and V. V. Grushin, *J. Am. Chem. Soc.*, 2013, **135**, 12584–12587.
- 17 N. Roques, *J. Fluorine Chem.*, 2001, **107**, 311–314.
- 18 S. Alazet and T. Billard, *Synlett*, 2014, 76–78.
- 19 L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai and W. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14965–14969.
- 20 (a) P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, Wiley-VCH, Weinheim, 2004, p. 145; (b) Me₄NSC₂F₅ was commercially available by CF Plus Chemicals s. r. o.
- 21 (a) N. Kornblum, G. D. Cooper and J. E. Taylor, *J. Am. Chem. Soc.*, 1950, **72**, 3013–3021; (b) C. Galli, *Chem. Rev.*, 1988, **88**, 765–792.

