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Convenient synthesis of pentafluoroethyl thioethers *via* catalytic Sandmeyer reaction with a stable fluoroalkylthiolation reagent†

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Aromatic and heteroaromatic diazonium salts were smoothly converted into the corresponding pentafluoroethyl thioethers by reaction with Me_4NScF_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 preformed 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 Roesenthaler 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 sulfinat salts 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). Me_4NScF_5 appeared to be the reagent of choice, because according to a patent by Roesenthaler, 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 Me_4NScF_5 in the presence of 10 mol% CuSCN in acetonitrile at room temperature, conditions previously optimised for

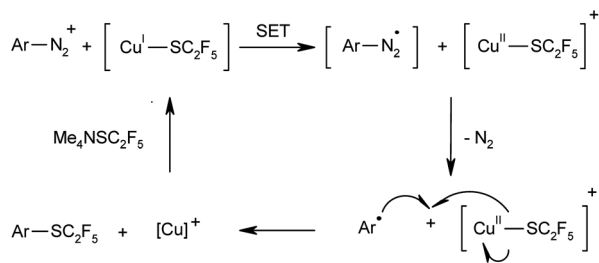
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Scheme 2 Sandmeyer pentafluoroethylthiolation of aromatic amines.

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.

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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. Roesenthaler, 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. Vicić, *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.

