

Traceless N -Polyfluoroalkylation of Weakly Nucleophilic Nitrogen Containing Compounds

Laura Santos, Florian Audet, Morgan Donnard, Armen Panossian, Jean-pierre

Vors, David Bernier, Sergii Pazenok, Frédéric Leroux

▶ To cite this version:

Laura Santos, Florian Audet, Morgan Donnard, Armen Panossian, Jean-pierre Vors, et al.. Traceless N -Polyfluoroalkylation of Weakly Nucleophilic Nitrogen Containing Compounds. Chemistry - A European Journal, 2023, 10.1002/chem.202300792 . hal-04100627

HAL Id: hal-04100627 https://hal.science/hal-04100627

Submitted on 17 May 2023 $\,$

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Announcing

Gold Open Access

Preprints welcome

flagship journal

Publishing charges waived

Edited by active scientists

our new

WILEY VCH

Excellence in Chemistry Research





Meet the Editors of ChemistryEurope



Luisa De Cola Università degli Studi di Milano Statale, Italy



Ive Hermans University of Wisconsin-Madison, USA



Ken Tanaka Tokyo Institute of Technology, Japan

Research Article doi.org/10.1002/chem.202300792



Traceless *N*-Polyfluoroalkylation of Weakly Nucleophilic Nitrogen Containing Compounds

Laura Santos⁺,^[a] Florian Audet⁺,^[a] Morgan Donnard,^[a] Armen Panossian,^[a] Jean-Pierre Vors,^[b] David Bernier,^[b] Sergii Pazenok,^[c] and Frédéric R. Leroux^{*[a]}

Abstract: Here we report an efficient access to high-value *N*-polyfluoroalkyl anilines, primary polyfluoroalkylamines and *N*,*N*-bis(polyfluoroalkyl)amines, via *N*-polyfluoroalkylation of sulfonamides and phthalimide derivatives using sulfuryl fluoride (SO_2F_2). The in situ formation of polyfluoroalkyl fluorosulfonates from commercially available fluorinated alcohols and economical sulfuryl fluoride is highly advantageous given that some polyfluoroalkyl halides are ozone-depleting

Introduction

The addition of polyfluoroalkyl chains on an amino functional group can mitigate its metabolic degradation but also reduce the basicity of the nitrogen atom to circumvent potential toxicity issues and increase bioavailability.^[1,2] In addition, the lipophilicity of the active ingredient can be tuned by the introduction of a fluorinated chain.^[1,3] These properties participate in making, for instance, the N-trifluoroethyl motif a useful bioisostere of the peptide bond.^[4,5] Thus, polyfluoroalkylamines and N-polyfluoroalkylanilines are key components for the preparation of pharmaceuticals and agrochemicals and therefore have significant industrial value. For example, the highly potent butanolide insecticide flupyradifurone (Sivanto®), approved in Europe in 2015, required 2,2-difluoroethylamine for its preparation,^[6] quazepam (Doral®) is a N-trifluoroethylated benzodiazepine derivative used as a treatment for insomnia (Scheme 1a).^[7]

- [a] Dr. L. Santos,⁺ F. Audet,⁺ Dr. M. Donnard, Dr. A. Panossian, Dr. F. R. Leroux Laboratoire d'Innovation Moléculaire et Applications (UMR7042) Université de Strasbourg, Université de Haute-Alsace, CNRS 25 rue Becquerel, 67000 Strasbourg (France) E-mail: frederic.leroux@unistra.fr
- [b] Dr. J.-P. Vors, Dr. D. Bernier
 Bayer S.A.S.
 14 impasse Pierre Baizet, 69263 Lyon (France)
- [c] Dr. S. Pazenok
 Bayer CropScience AG
 Alfred Nobel Straße 50, 40789 Monheim (Germany)
- [⁺] These authors contributed equally to this work.
- Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202300792
- © 2023 The Authors. Chemistry A European Journal published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

substances (ODS) regulated by the Montreal protocol. This general method is applied to the polyfluoroalkylation of a variety of sulfonamides, *N*-sulfonyl carbamates and phthalimide with a wide tolerance of functional groups. The process thus provides viable access for industry to *N*-(polyfluoroalkyl)anilines as well as primary and secondary *N*-(polyfluoroalkyl)amines, which are very valuable but not easily accessible building blocks for life science applications.

One strategy, among others, to access *N*-polyfluoroalkyl building-blocks or ingredients,^[8] is the electrophilic *N*-polyfluoroalkylation of precursors containing a nitrogen atom substituted by an electron-withdrawing group (EWG), such as sulfonamides, *N*-sulfonyl carbamates and phthalimide, followed by cleavage of the appropriately selected EWG. However, they are generally weaker nucleophiles than their parent amine. In addition, because the presence of a fluorine atom in the alpha position relative to the electrophilic center has been shown to significantly decrease their rates, *N*-polyfluoroalkylation reactions are particularly difficult.^[9] In this context, developing an efficient method for the *N*-polyfluoroalkylation of nitrogen derivatives bearing a sulfonyl group as EWG would be particularly attractive.

Indeed, on the one hand, sulfonamides are, as such, interesting functional groups with potential pharmaceutical and agrochemical applications. Since 2008, more than 110 drugs containing at least one sulfonamide group have been marketed.^[10] Interest in this moiety has arisen from its ability to act as a bioisostere of a carboxylate anion,^[11] a hydroxyl^[12] or an α -ketoamide group.^[13]

On the other hand, the most commonly used methods for the *N*-polyfluoroalkylation of sulfonamides are the use of polyfluoroalkyl halides^[14] and polyfluoroalkyl sulfonates (Scheme 1b).^[15] However, some polyfluoroalkyl halides, such as 2-chloro-1,1,1-trifluorethane, are ozone-depleting reagents (ODS) regulated by the Montreal protocol^[16] while polyfluoroalkyl sulfonates, such as triflates, are generally pre-synthesized with poor atom economy and high cost. More environmentally friendly polyfluoroalcohols have been used to induce the *N*polyfluoroalkylation of sulfonamides by the Mitsunobu reaction. Despite the diversity at the fluoroalkyl chain level, low yields were obtained, and the use of phosphine and azo reagents was expensive for industrial application (Scheme 1b).^[17] Moreover, these methods have only been applied to a rather limited Research Article doi.org/10.1002/chem.202300792



Scheme 1. Bioactive ingredients containing a *N*-polyfluoroalkyl moiety, synthetic approaches to incorporate polyfluoroalkyl chains at the nitrogen atom of sulfonamides and alternative SO_2F_2 -based method towards monoor bis(polyfluoroalkyl)amino compounds.

number of sulfonamides in agrochemical or pharmaceutical research programs.

To the best of our knowledge, there is no systematic study of the *N*-polyfluoroalkylation of sulfonamides to gain insight into the optimal reaction conditions and the extent of the transformation. In this context, one cannot anticipate the outcome of a planned *N*-polyfluoroalkylation reaction on a sulfonamide moiety using only the few benchmarks available in the current literature.

Given the limitations of the above methods for the preparation of *N*-polyfluoroalkylated sulfonamides, there is still a demand for an approach that would be economical, environmentally friendly, and more generally applicable to access a high structural diversity of polyfluoroalkylated sulfonamides. Therefore, we focused our attention on SO_2F_2 -mediated *N*-polyfluoroalkylation methods.^[18]

Sulfuryl fluoride is a commodity chemical that has been used as a fumigant for over 50 years and is produced on a multi-ton scale.^[19] In the last decade, it has gained interest as a reagent for organic synthesis with the development of sulfur fluoride exchange (SuFEx) chemistry.^[20] In addition, polyfluorinated alcohols have the potential to react with SO_2F_2 in the presence of a suitable base to form a polyfluoroalkyl fluorosulfonate R_F-OSO₂F. This rather stable triflate surrogate can react with a suitable amino group in a one-pot reaction, which is highly advantageous given the limitations of polyfluoroalkyl halides and sulfonates mentioned previously.^[14,15] Compared to the use of triflates that generate triflic acid, which is persistent and belongs to the newly defined PFAs, this synthesis attractively achieves traceless N-alkylation. Sulfuryl fluoridemediated fluoroalkylation methods have been applied to alkylamines or thiols, but weaker N-nucleophiles such as anilines have proven to be poor substrates under the reported conditions.^[18a,21] Our group has begun to investigate SO_2F_2 mediated N-polyfluoroalkylation of challenging substrates that are highly relevant to agrochemical and pharmaceutical applications. In 2022, we reported the N-(polyfluoro)alkylation of ambident and weakly nucleophilic imino-thiazolidinones.^[18c] This first example of N-polyfluoroalkylation of weakly nucleophilic nitrogen compounds paved the way for a general method for N-polyfluoroalkylation of sulfonamides and derived Nsulfonyl carbamates using sulfuryl fluoride (SO₂F₂), which is presented here (Scheme 1c).

Results and Discussion

We started our investigation by evaluating the *N*-polyfluoroalkylation of *N*-sulfonyl nucleophiles using saccharin **1** a, an ambident nucleophile (N = 10.78 on the Mayr scale)^[22] as model substrate. Application of the conditions that gave the highest reaction rate in our previous work on the *N*-polyfluoroalkylation of thiazolidinone using SO₂F₂ (i.e., DBU as a base and DMAc as solvent)^[18c] gave only trace amounts of the desired product (Table 1, entry 1).

The switch from DBU as a base to DIPEA led to a 68% yield at 25 °C (Table 1, entry 2). Two isomers were formed in a ¹⁹F NMR ratio of 64:36, assigned to N- and O-trifluoroethylation adducts 2a and 2b, respectively. The difference in reactivity between DBU and DIPEA in sulfuryl fluoride-mediated fluoroalkylation reactions was previously observed by Sammis et al. for thiols.^[21] The use of DBU as a base was shown to lead to the formation of a symmetric bis(trifluoroethyl)sulfate intermediate that selectively reacts with thiols in the presence of other nucleophilic functional groups such as an amine, alcohol or carboxylic acid.^[21] Consistent with this report, the bis(trifluoroethyl)sulfate intermediate generated with DBU also showed weak reactivity with saccharin 1a as nucleophile. Increasing the temperature to 50 °C, while using DIPEA as the base, led to an excellent yield of 95% and an isomer ratio of 61:39 (Table 1, entry 3). Toluene and acetonitrile as solvents were found to be less effective, both in terms of yield and selectivity (Table 1, entries 4 and 5). Et₃N led to a slightly 5213765,

Research Article doi.org/10.1002/chem.202300792





decreased trifluoroethylation yield and an unchanged isomeric ratio compared to DIPEA (Table 1, entry 6). Interestingly, the economical inorganic base K_2CO_3 provided the desired products with an NMR yield of 86% and a significant increase in selectivity toward *N*-trifluoroethylation with a ratio of 85:15 (Table 1, entry 7). K_3PO_4 also gave an excellent overall NMR yield of 95% but with a selectivity of 61:39 (Table 1, entry 8).

Thus, the ambivalent nucleophile saccharin **1a** showed excellent trifluoroethylation yields using inexpensive K_2CO_3 or K_3PO_4 as bases. However, different ratios of *N*- vs *O*-alkylation were obtained. We then applied these conditions to a model sulfonamide substrate, *N*-phenylbenzenesulfonamide, for which only the *N*-trifluoroethylation is possible. The use of K_2CO_3 as a base gave 85% of the desired product **2**k by ¹⁹F NMR, while the use of K_3PO_4 induced a reduced yield of 40%. Therefore, K_2CO_3 was retained as the base of choice for the *N*-polyfluoroalkylation of sulfonamides.

With optimized conditions for N-polyfluoroalkylation of sulfonamides in hand, we next explored the scope of the reaction (Scheme 2). First, our model substrate, saccharin, was trifluoroethylated in 73% ¹⁹F NMR yield (2a) using standard conditions and was isolated as a mixture with the O-alkylation product (2 b). The polyfluoroalkylation was also extended to its imide analogue, phthalimide. Four variously fluorinated derivatives of ethanol and propanol were used to fluoroalkylate phthalimide and led to the targeted products (2c-2f) in good to quantitative yields. In these cases, DBU was used as the base and the reaction time could be reduced to 30 min. These results are consistent with the previously reported alkylation of phthalimide using non-fluorinated alcohols, where DBU was DIPEA.^[18b] more efficient than *tert*-Butyl ((4nitrophenyl)sulfonyl)-carbamate could also be fluoroalkylated in good yields, up to 91%, using the same four polyfluorinated alcohols (2g-j). To avoid cleavage of the Boc group, the temperature was reduced to 30 °C and an additional equivalent of base was added.

Subsequently, variations of the sulfonyl part were evaluated on sulfonamide derivatives.

The model sulfonamide, N-phenylbenzenesulfonamide (2k), was trifluoroethylated in a 69% isolated yield. Substituted benzenesulfonyl derivatives bearing -NO₂ (21), -CF₃ (2p) or -Cl (2q) as electron-withdrawing groups (EWGs) in the para position were trifluoroethylated in good to excellent yields. Other fluorinated chains (difluoroethyl, tetrafluoropropyl and pentafluoropropyl) were also tested with 4-nitrobenzenesulfonyl derivatives and afforded moderate to good yields (2m to 20). Similarly, benzenesulfonyl derivatives substituted at the 4position by electron-donating groups (EDGs) were also tested. The methoxy substitution (2r) gave 89% yield in ¹⁹F NMR. Methyl substitution (2s) provided the desired product in a similar 85% yield. Replacement of the substituted phenyl with a heteroaromatic guinoline gave a moderate yield of 51% (2t). Finally, methyl (2u) and trifluoromethyl (2v) sulfonamides were also tolerated and led to the desired trifluoroethylated products in 62%-64% yields. Thus, the variation of the electron richness on the sulfur substituent gave a range of yields that could not be correlated simply with the nature of the substituent. This could be due to the fact that an EWG (respectively an EDG) would facilitate (resp. disfavor) the deprotonation of the nitrogen atom of the substrate but decrease (resp. increase) its nucleophilicity.

We then explored the amino part (\mathbf{R}^2) using a phenyl or a 4nitrophenyl substituent as group \mathbf{R}^{1} . We started by studying benzene-derived EDGs on the \mathbf{R}^2 moiety. A methoxy group at the para position gave a good trifluoroethylation yield of 74% (2w) and 88% (2x), with benzenesulfonyl and p-nitrobenzenesulfonyl groups as \mathbf{R}^1 , respectively. The introduction of a methyl group at the para (2y) or ortho (2z) positions had no impact on the trifluoroethylation yield. Next, the influence of EWGs on the aniline motif N-R² was investigated. A methyl ester in the ortho position (2aa) led to an excellent yield of 95%. Substitution with a trifluoromethyl group at the para (2 ab) or meta (2 ac) positions gave yields of 77% and 88%, respectively. Similarly, with a cyano group in the para (2 ad, 74% yield) or meta (2 ae, 76% yield) positions, the desired trifluoroethyl products were obtained in good yields. Nitro substitution was also tested at the meta position and trifluorethylation occurred in good 77% yield (2 af). In addition, halides were also well tolerated at the aniline moiety. lodine (2 ag, 80% yield) or bromine (2 ah, 78% yield) at the para position on the aniline afforded the desired trifluoroethylated products in efficient yields. A chlorine atom in the meta position gave an excellent 94% yield (2ai). Four different fluorinated chains (2aj-am) were introduced on the pchloroaniline-derived sulfonamide. Excellent yields were obtained with CF₃ (2aj, 95% yield) and CHF₂ (2ak, 89% yield) as $R_{F_{7}}$ while a good yield of 78% was achieved with $CF_{2}CF_{3}$ (2 al). A more moderate result of 46% yield was obtained for the tetrafluoropropyl chain (2 am). Finally, fluorine on meta (2 an) or para (2ao) positions of the aniline part was well tolerated with yields of 96% and 81%, respectively, for the trifluoroethylated products. Overall, the N-polyfluoroalkylation reaction is equally efficient with electron-poor and electron-rich aniline-derived

Chemistry Europe

European Chemical Societies Publishing Research Article doi.org/10.1002/chem.202300792



Scheme 2. Scope of *N*-polyfluoroalkylated sulfonamides.^[a] [a] All reactions were carried out at a concentration of 40 mg/mL of **1**. Isolated yields are reported. [b] DBU (4 eq.) was used as base, 25 °C, 30 min. [c] Reactions performed at 30 °C using 5 eq. of K_2CO_3 . [d] ¹⁹F NMR yield using α, α, α -trifluorotoluene as an internal standard is given in parentheses. [e] Additional trifluoroethanol (1 eq.) and K_2CO_3 (1 eq.) were used, total reaction time: 24 h. [f] Additional trifluoroethanol (2 eq.) and K_2CO_3 (2 eq.) were used, total reaction time: 48 h. * The asterisk highlights the position of the alkylation in the regioisomeric product **2 aw**.

sulfonamides. Furthermore, steric hindrance induced by *ortho* substitution had no impact on the reaction outcome.

To extend the scope of this method, sulfonamides derived from heterocyclic amines were also evaluated. Excellent yields

were obtained for isoxazole (**2ap**, 85% yield), benzothiophenes (**2aq**, **2ar**, 79% yield for both), indole (**2as**, 83% yield), furan (**2at**, 74% yield) and pyrazole (**2au**, 85% yield), whereas pyridine (**2av**, 13% yield) was less successful. Sulfonylated

© 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Research Article doi.org/10.1002/chem.202300792

European Chemical Societies Publishing

aminobenzothiazole afforded a mixture of regioisomers, with the endocyclic nitrogen preferentially polyfluoroalkylated in 35% yield (**2aw**). This regioselectivity is consistent with previously reported *N*-alkylations of similar ambident nucleophiles.^[18c] The methylamine-derived sulfonamide also gave a low yield of 32% (**2ay**). Interestingly, a bis-sulfonamide could be trifluoroethylated in a moderate yield of 41% (**2az**).

Having in hand an efficient method to synthesize Npolyfluoroalkylated sulfonamides, we investigated whether we could remove the sulfonyl group to access the corresponding N-polyfluoroalkyl anilines. Substituted anilines are widespread in medicinal chemistry but the N-(β -fluoroalkyl) aniline moiety remains underutilized, even though N-fluoroalkylanilines have shown greater metabolic stability toward P450-mediated oxidation than N-alkylanilines.^[23] In addition, the introduction of a fluorinated chain can tune the lipophilicity of the drug candidate as well as the pK_a of the neighboring functions.^[1,3] Several methods have already been reported to access Npolyfluoroalkyl anilines. However, these methods usually require air-sensitive metal catalysts^[24] or the use of expensive,^[25] hazardous,^[26] toxic,^[27] and often not commercially available starting materials. These drawbacks explain the scarcity of polyfluoroalkylated anilines in active ingredients. Given the limitations of these methods, there is still a strong demand for a new approach with high robustness, low cost, and high tolerance to functional groups. While sulfonyl groups are notoriously difficult to remove,[28] the 4-nitrobenzenesulfonyl (nosyl, Ns) group can be cleaved via an S_NAr reaction.^[29] The use of thioglycolic acid as nucleophile and potassium carbonate as a base in DMF was optimal to efficiently obtain N-polyfluoroalkyl anilines (Scheme 3).

N-Trifluoroethylated anilines with substitution on the arene ring were obtained in equally high yields, whether they were electron-enriched - derivatives of p-anisidine (3a, 91%), ptoluidine (3b, quant.) or o-toluidine (3c, 91%)- or electrondepleted - derivatives bearing ester (3d, 82%), trifluoromethyl (3e-f, up to 90%), cyano (3g-h, up to quant.) or nitro (3i, quant.) groups. Similarly, halide-substituted polyfluoroalkylated anilines were obtained in good to excellent yields, up to 99% (3j-s). It should be noted that bromine or iodine are well tolerated and could then be used for further diversification by conventional C-C or C-N metal-catalyzed cross-coupling. This would not be possible using previously reported methods $^{\mbox{\tiny [24a,b,e,f,h]}}$ where halide is used in the metal-catalyzed Narylation of fluoroalkylamines. Interestingly, compounds 31-p, with four different fluorinated chains, were obtained in yields ranging from 97% to quantitative ($R_{\rm F}$ corresponding to CF₃, CHF_2 , CF_2CF_3 or CF_2CHF_2), showing that the nature of the fluorinated chain on the aniline had no impact on the efficiency of the nosyl removal. N-Polyfluoroalkylated heterocyclic amines were also accessed in moderate to quantitative yields. N-Trifluoroethyl derivatives of 3-aminobenzothiophene (3t) and 5aminoindole (3 u) were obtained in 83% and guantitative yields, respectively. Furan 3v and pyrazole 3w were obtained in 65% and 38% yields, respectively. These lower yields can be attributed to the difficulties in purifying these compounds. It



Scheme 3. Synthesis of *N*-polyfluoroalkylated anilines and amino-heterocycles via nosyl cleavage.^[a] [a] Isolated yields are reported.

should be noted that a wide range of functional groups are tolerated on the (hetero)aromatic ring for this reaction.

To illustrate the usefulness of this method for obtaining various N-polyfluoroalkyl compounds, we decided to synthesize primary polyfluoroalkyl amines. To our knowledge, the main route to access polyfluoroalkylated primary amines is the amination of polyfluoroalkyl halides or sulfonates.^[30] However these reactions are highly corrosive and require high temperatures and pressure systems to proceed. Polyfluoroalkylated primary amines can also be accessed by reduction of the corresponding amide^[31] or imine^[32] but these reactions using aluminium-based reductants have previously been reported to have safety issues.^[33] Hydrogenation of nitrile, azido or nitro groups have also been developed, but also require high pressure to perform the reaction.^[34] Finally, Gabriel synthesis has been presented as the safest way to access these fluorinated amines.^[35] However, the reported examples are limited to fluoroalkyl nosylate and halides as electrophiles, and

5213765,

these reagents are respectively expensive for industrial applications or classified as ozone depleting gases (freons).

We decided to use our four *N*-polyfluoroalkylated phthalimides (**2c**-**f**) obtained via the SO_2F_2 -mediated polyfluoroalkylation process, to access the primary *N*-polyfluoroalkylamines via a Gabriel reaction. Cleavage of the polyfluoroalkylated phthalimides with hydrazine hydrate gave the desired four polyfluorinated primary amines (**4a**-**d**) which were isolated as HCI salts in good to quantitative yields (Scheme 4a).

Since primary polyfluoroalkyl amines can be obtained from N-polyfluoroalkyated phthalimides, we wondered if we could access symmetrical or unsymmetrical N.Nbis(polyfluoroalkyl)amines, which are also important intermediates in the preparation of active pharmaceuticals. Basic alkylamines are often associated with toxicity problems (hERG inhibition and P-gp efflux) that can be decreased by lowering the pK_a of the amine.^[1,2] For example, CB2 agonist analogs^[36] or receptor modulators bearing androgen an N.Nbis(trifluoroethyl)amine motif have been shown to be very potent and selective among a range of N,N-bis(alkyl)amine motifs.^[37] Only a few methods for the preparation of N,Nbis(polyfluoroalkyl)amines are described in the literature, but they are mainly limited to the synthesis of symmetrical ones. First, primary polyfluoroalkylamines can be reacted with polyfluoroalkyl sulfonates or ozone-depleting polyfluoroalkyl halides under harsh conditions.^[38] Other approaches for the synthesis of bis(N-polyfluoroalkyl)amines are based on a twostep process involving the formation of an amide, imide or

Scheme 4. Synthesis of primary polyfluoroalkylamines by Gabriel synthesis and bis(*N*-polyfluoroalkyl) amines through two successive SO₂F₂-mediated *N*-polyfluoroalkylations of *N*-sulfonyl compounds.^[a] [a] Isolated yields are reported and ¹⁹F NMR yields are in parentheses (calculated using α , α -trifluorotoluene or fluorobenzene as internal standards). (i) Polyfluoroalkyl alcohol (2.5 eq.), K₂CO₃ (4 eq.), SO₂F₂ (balloon), DMAc, 50 °C, 3 h. (ii) Thioglycolic acid (4 eq.), K₂CO₃ (8 eq.), DMF, rt., 16 h.

imine functional group followed by its reduction in the presence of a hydride-based reducing agent such as LiAlH₄.^[31,39] However, these strategies face safety issues with explosions already reported during the reduction of fluorinated amides.^[33]

We therefore investigated whether we could perform a second polyfluoroalkylation reaction on N-polyfluoroalkylated 4-nitrophenylsulfonamides 5a-b to afford the desired N,Nbis(polyfluoroalkyl)amines 7 a-e after denosylation. Compounds 5 a-b, obtained after Boc cleavage of N-polyfluoroalkylated Nsulfonyl carbamates 2g-j (see Supporting Information for details), exquisitely underwent a second polyfluoroalkylation to give 6a-e in excellent to quantitative yields. Finally, nosyl cleavage was again very efficient, providing the desired secondary amines, isolated as HCl salts, in NMR yields up to 92% (7 a-e) (Scheme 4b). This method provided a reliable route to symmetrical and unsymmetrical N.Nbis(polyfluoroalkyl)amines in high yields under mild reaction conditions and from readily available starting materials.

Conclusion

In conclusion, we have developed a general method for the (SO_2F_2) -mediated *N*-polyfluoroalkylation of weakly nucleophilic nitrogen containing compounds, including sulfonamides, carboxylic sulfimides, *N*-sulfonyl carbamates and imides. This process occurs under mild and operationally simple conditions and a wide variety of functional groups are tolerated. The in situ formation of an electrophilic reactive species from fluorinated alcohols is highly advantageous since several polyfluoroalkyl halides are ozone-depleting substances (ODS). *N*-Polyfluoroalkyl-amines were obtained after simple sulfonyl or phthalimide cleavage in excellent yields.

Experimental Section

The data that support the findings of this study are available in the Supporting Information of this article.

Acknowledgements

The authors thank the CNRS (Centre National de la Recherche Scientifique, France), the Université de Strasbourg and Université de Haute-Alsace. The authors are grateful to Bayer S.A.S. for Ph.D. grants to L.S. and F.A. The French Fluorine Network (GIS Fluor) is also acknowledged. Finally, the authors also thank Dr. Emeric Wasielewski (NMR platform) and Matthieu Chessé (analytical facilities) of the LIMA (UMR7042 CNRS-Unistra-UHA), as well as the analytical facilities of the Fédération de Chimie "Le Bel" (FR2010) of the Université de Strasbourg, who contributed, by their valuable technical and scientific support, to the achievement of this research project.

Chem. Eur. J. 2023, 29, e202300792 (6 of 8)

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: alkylation · fluorine · nucleophilic substitution · sulfonamides · sulfuryl fluoride

- [1] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, J. Med. Chem. 2015, 58, 8315–8359.
- [2] K. Fjelbye, M. Marigo, R. P. Clausen, E. B. Jørgensen, C. T. Christoffersen, K. Juhl, MedChemComm 2018, 9, 893–896.
- [3] N. A. Meanwell, J. Med. Chem. 2018, 61, 5822-5880.
- [4] M. Sani, A. Volonterio, M. Zanda, ChemMedChem 2007, 2, 1693–1700.
- [6] R. Nauen, P. Jeschke, R. Velten, M. E. Beck, U. Ebbinghaus-Kintscher, W. Thielert, K. Wölfel, M. Haas, K. Kunz, G. Raupach, *Pest Manage. Sci.* 2015, 71, 850–862.
- [7] T. Roth, E. I. Tietz, M. Kramer, M. Kaffeman, J. Int. Med. Res. 1979, 7, 583– 587.
- [8] T. Milcent, B. Crousse, in *Emerging Fluorinated Motifs*, John Wiley & Sons, Ltd, 2020, pp. 723–761.
- [9] The rate constant of the substitution reaction of the alkyl bromide by sodium thiophenolate in MeOH at 34.6 °C is reported to be 182× $10^4 \text{ sec}^{-1} \text{ mol}^{-1}\text{L}$ for CH₃CH₂Br and 25×10⁴ sec⁻¹ mol⁻¹L for FCH₂CH₂Br: J. Hine, W. H. Jr. Brader, J. Am. Chem. Soc. **1953**, 75, 3964–3966.
- [10] A. S. Kalgutkar, R. Jones, A. Sawant, in *Metabolism, Pharmacokinetics and Toxicity of Functional Groups*, Royal Society of Chemistry, **2010**, pp. 210–274.
- [11] P. H. Bell, R. O. Jr. Roblin, J. Am. Chem. Soc. 1942, 64, 2905-2917.
- [12] a) Y. K. Yee, P. R. Bernstein, E. J. Adams, F. J. Brown, L. A. Cronk, K. C. Hebbel, E. P. Vacek, R. D. Krell, D. W. Snyder, *J. Med. Chem.* **1990**, *33*, 2437–2451; b) P. Lin, D. Marino, J.-L. Lo, Y. T. Yang, K. Cheng, R. G. Smith, M. H. Fisher, M. J. Wyvratt, M. T. Goulet, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1073–1076.
- [13] R.-J. Lu, J. A. Tucker, T. Zinevitch, O. Kirichenko, V. Konoplev, S. Kuznetsova, S. Sviridov, J. Pickens, S. Tandel, E. Brahmachary, Y. Yang, J. Wang, S. Freel, S. Fisher, A. Sullivan, J. Zhou, S. Stanfield-Oakley, M. Greenberg, D. Bolognesi, B. Bray, B. Koszalka, P. Jeffs, A. Khasanov, Y.-A. Ma, C. Jeffries, C. Liu, T. Proskurina, T. Zhu, A. Chucholowski, R. Li, C. Sexton, J. Med. Chem. 2007, 50, 6535–6544.
- [14] a) S. Brand, N. R. Norcross, S. Thompson, J. R. Harrison, V. C. Smith, D. A. Robinson, L. S. Torrie, S. P. McElroy, I. Hallyburton, S. Norval, P. Scullion, L. Stojanovski, F. R. C. Simeons, D. van Aalten, J. A. Frearson, R. Brenk, A. H. Fairlamb, M. A. J. Ferguson, P. G. Wyatt, I. H. Gilbert, K. D. Read, J. Med. Chem. 2014, 57, 9855–9869; b) J. T. Bagdanoff, Y. Ding, W. Han, Z. Huang, Q. Jiang, J. X. Jin, X. Kou, P. Lee, M. Lindvall, Z. Min, Y. Pan, S. Pecchi, K. B. Pfister, D. Poon, V. Rauniyar, X. M. Wang, Q. Zhang, J. Zhou, S. ZHU, Aminoheteroaryl Benzamides as Kinase Inhibitors, 2015, WO2015066188 A1; c) D. Blomberg, K. Brickmann, A. Holmén, R. Hovland, P. Johannesson, Å. Mansson, A. T. Plowright, V. Schnecke, P. Sörme, P. Stahlberg, E. Wellner, New Acetyl Coenzyme a Carboxylase (Acc) Inhibitors and Uses in Treatments of Obesity and Diabetes Mellitus 087, 2009, WO2009082346 A1; d) Ya. S. Alekseenko, K. I. Petko, Ukr. Khim. Zh. 2016, 82, 114–117.
- [15] a) Y. Xue, E. Chao, W. J. Zuercher, T. M. Willson, J. L. Collins, M. R. Redinbo, *Bioorg. Med. Chem.* 2007, *15*, 2156–2166; b) G. Schwertz, M. S. Frei, M. C. Witschel, M. Rottmann, U. Leartsakulpanich, P. Chitnumsub, A. Jaruwat, W. Ittarat, A. Schäfer, R. A. Aponte, N. Trapp, K. Mark, P. Chaiyen, F. Diederich, *Chem. Eur. J.* 2017, *23*, 14345–14357; c) H. Toyama, S. Sato, H. Shirakawa, M. Komai, Y. Hashimoto, S. Fujii, *Bioorg. Med. Chem. Lett.* 2016, *26*, 1817–1820; d) Y. Rew, M. DeGraffenreid, X. He, J. C. Jaen, D. L. McMinn, D. Sun, H. Tu, S. Ursu, J. P. Powers, *Bioorg. Med. Chem. Lett.* 2012, *22*, 3786–3790; e) J. M. Cid, H. Lavreysen, G.

Tresadern, L. Pérez-Benito, F. Tovar, A. Fontana, A. A. Trabanco, ACS Chem. Neurosci. 2019, 10, 1043–1054; f) N. J. Willetts, M. R. Cordingley, P. J. Crowley, S. J. Riley, M. D. Turnbull, Herbicidal Compounds, 2009, WO2009063180 A1; g) C. C. Mccomas, N. J. Liverton, J. Habermann, U. Koch, F. Narjes, P. Li, X. Peng, R. Soll, H. Wu, A. Palani, S. He, X. Dai, H. Liu, Z. Lai, C. London, D. Xiao, N. Zorn, R. Nargund, Tetracyclic Heterocycle Compounds and Methods of Use Thereof for the Treatment of Viral Diseases, 2013, WO2013033971 A1; h) S. Routier, F. Suzenet, S. Chalon, F. Buron, J. Vercouillie, R. Melki, L. Boiaryna, D. Guilloteau, L. Pieri, Compounds for using in imaging and particularly for the diagnosis of neurodegenerative diseases, 2018, WO2018055316 A1.

- [16] O. US EPA, "Ozone-Depleting Substances," can be found under http:// www.epa.gov/ozone-layer-protection/ozone-depleting-substances, 2015.
- [17] a) Q. Li, H. Sham, K. W. Woods, B. A. Steiner, I. S. L. Gwaltney, K. J. Barr, H. M. Imade, S. Rosenberg, *Cell Proliferation Inhibitors*, **2003**, US6521658B1; b) H. Kubota, I. Tsukamoto, K. Kamijo, K. Kato, T. Hideki, Y. Fukuda, H. Azami, H. Morita, *Sulfonamide Compound or Salt Thereof*, **2009**, WO2009157399 A1; c) C. E. Augelli-Szafran, D. Lu, H. Wei, J. Zhang, M. S. Wolfe, D. J. Selkoe, *Sulfonamide-Containing Compounds*, **2012**, WO2012047926 A3.
- [18] a) M. Epifanov, P. J. Foth, F. Gu, C. Barrillon, S. S. Kanani, C. S. Higman, J. E. Hein, G. M. Sammis, J. Am. Chem. Soc. 2018, 140, 16464–16468;
 b) J. Y. Mo, M. Epifanov, J. W. Hodgson, R. Dubois, G. M. Sammis, Chem. Eur. J. 2020, 26, 4958–4962; c) L. Santos, M. Donnard, A. Panossian, J.-P. Vors, P. Jeschke, D. Bernier, S. Pazenok, F. R. Leroux, J. Org. Chem. 2022, 87, 2012–2021; d) M. Epifanov, J. Y. Mo, R. Dubois, H. Yu, G. M. Sammis, J. Org. Chem. 2021, 86, 3768–3777.
- [19] M. P. Sulbaek Andersen, D. R. Blake, F. S. Rowland, M. D. Hurley, T. J. Wallington, *Environ. Sci. Technol.* 2009, 43, 1067–1070.
- [20] a) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* 2019, 48, 4731–4758; b) J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* 2014, 53, 9430–9448; *Angew. Chem.* 2014, 126, 9584–9603; c) S. Kitamura, Q. Zheng, J. L. Woehl, A. Solania, E. Chen, N. Dillon, M. V. Hull, M. Kotaniguchi, J. R. Cappiello, S. Kitamura, V. Nizet, K. B. Sharpless, D. W. Wolan, *J. Am. Chem. Soc.* 2020, 142, 10899–10904.
- [21] P. J. Foth, F. Gu, T. G. Bolduc, S. S. Kanani, G. M. Sammis, Chem. Sci. 2019, 10, 10331–10335.
- [22] M. Breugst, T. Tokuyasu, H. Mayr, J. Org. Chem. 2010, 75, 5250-5258.
- [23] a) A. S. Travis, in *The Chemistry of Anilines*, John Wiley & Sons, Ltd, **2007**, pp. 835–870; b) M. Bhakta, P. F. Hollenberg, K. Wimalasena, *Chem. Commun.* **2005**, 265–267; c) S. T. Seger, P. Rydberg, L. Olsen, *Chem. Res. Toxicol.* **2015**, *28*, 597–603; d) F. P. Guengerich, *Toxicol. Rev.* **2021**, *37*, 1–23.
- [24] a) A. T. Brusoe, J. F. Hartwig, J. Am. Chem. Soc. 2015, 137, 8460–8468;
 b) A. T. Brusoe, J. F. Hartwig, Palladium-Catalyzed Arylation of Fluoroalkylamines, 2016, WO2016183101 A1; c) H. Wang, Y.-H. Tu, D.-Y. Liu, X.-G. Hu, Org. Biomol. Chem. 2018, 16, 6634–6637; d) X. Hu, H. Wang, Method for Preparing N-Fluoroalkyl Anilines by Cross-coupling of Aromatic Boronic Acid and Fluoroalkyl Amine, 2018, CN108997133 A; e) S. Chen, H. Wang, W. Jiang, P.-X. Rui, X.-G. Hu, Org. Biomol. Chem. 2019, 17, 9799–9807; f) R. T. McGuire, A. A. Yadav, M. Stradiotto, Angew. Chem. Int. Ed. 2021, 60, 4080–4084; Angew. Chem. 2021, 133, 4126–4130; g) C. A. Malapit, M. Borrell, M. W. Milbauer, C. E. Brigham, M. S. Sanford, J. Am. Chem. Soc. 2020, 142, 5918–5923; h) E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, D. W. C. MacMillan, Science 2016, 353, 279–283; i) S. U. Dighe, F. Juliá, A. Luridiana, J. J. Douglas, D. Leonori, Nature 2020, 584, 75–81.
- [25] H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto, Y. Kikugawa, J. Fluorine Chem. 2010, 131, 477–486.
- [26] a) H. Luo, G. Wu, Y. Zhang, J. Wang, Angew. Chem. Int. Ed. 2015, 54, 14503–14507; Angew. Chem. 2015, 127, 14711–14715; b) S. Hyde, J. Veliks, B. Liégault, D. Grassi, M. Taillefer, V. Gouverneur, Angew. Chem. Int. Ed. 2016, 55, 3785–3789; Angew. Chem. 2016, 128, 3849–3853; c) S. Ren, G. Xu, Y. Guo, Q. Liu, C. Guo, RSC Adv. 2021, 11, 20322–20325.
- [27] a) M. Steinman, J. G. Topliss, R. Alekel, Y.-S. Wong, E. E. York, J. Med. Chem. 1973, 16, 1354–1360; b) J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, H. M. Hill, R. A. Corbitt, M. A. McCall, W. H. Moore, Ind. Eng. Chem. 1954, 46, 2213–2220.
- [28] T. Javorskis, E. Orentas, J. Org. Chem. 2017, 82, 13423-13439.
- [29] a) S. P. Miller, Y.-L. Zhong, Z. Liu, M. Simeone, N. Yasuda, J. Limanto, Z. Chen, J. Lynch, V. Capodanno, *Org. Lett.* 2014, *16*, 174–177; b) P. Yang, X. Wang, L. Peng, F. Chen, F. Tian, C.-Z. Tang, L.-X. Wang, *Org. Process Res. Dev.* 2017, *21*, 1682–1688; c) T. Kim, S. Matsushita, S. Matsudaira, T.

Chem. Eur. J. 2023, 29, e202300792 (7 of 8)

 $\ensuremath{\mathbb O}$ 2023 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Doi, S. Hirota, Y.-T. Park, M. Igarashi, M. Hatano, N. Ikeda, J. Ham, M. Nakata, Y. Saikawa, *Org. Lett.* **2019**, *21*, 3554–3557.

- [30] a) J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, D. J. Wallace, J. Sagal, M. A. McCall, D. G. Hedberg, Ind. Eng. Chem. 1956, 48, 209–213;
 b) N. Lui, S. Pazenok, Y. G. Shermolovich, Method for Producing 2.2-Difluoroethylamine, 2011, WO2011012243 A1; c) Y. Moriyama, Manufacturing Method of 2,2,2-Trifluoroethylamine, 2008, JP2008162990 A; d) X. Han, F. Qing, C. Zhang, X. Jia, H. Quan, J. Fluorine Chem. 2021, 242, 109690.
- [31] a) H. Yamanaka, Y. Takagami, M. Kuwabara, K. Fukunishi, M. Nomura, Nippon Kagaku Kaishi 1987, 1987, 1796–1801; b) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, J. C. Tatlow, J. Chem. Soc. 1952, 4014–4019; c) N. Lui, S. Antons, W. A. Moradi, Method for Producing 2,2-Difluoroatehylamine and Salts Thereof, Starting with Difluoroacetone Nitrile, 2011, WO2011069994 A1; d) A. Donetti, E. Cereda, A. Ezhaya, R. Micheletti, J. Med. Chem. 1989, 32, 957–961; e) Z. B. Papanastassiou, R. J. Bruni, J. Org. Chem. 1964, 29, 2870–2872; f) D. R. Husted, A. H. Ahlbrecht, J. Am. Chem. Soc. 1953, 75, 1605–1608.
- [32] a) H. Zhang, Catalytic Preparation Method of Trifluoroethylamine Compound, 2018, CN109096121 A; b) V. A. Soloshonok, A. G. Kirilenko, V. P. Kukhar, G. Resnati, Tetrahedron Lett. 1994, 35, 3119–3122; c) 瞿军, 沈润 溥, 陆文辉, 吴宏祥, 章学兵, 时立, 范文昌, 吴春雷, Preparation Method of Trifluoroethylamine, 2013, CN103274947 A.
- [33] Chem. Eng. News Archive 1955, 33, 1368–1370.
- [34] a) H. Gilman, R. G. Jones, J. Am. Chem. Soc. 1943, 65, 1458–1460; b) I. L. Knunyants, L. S. German, I. N. Rozhkov, B. L. Dyatkin, Russ. Chem. Bull. 1966, 15, 226–228; c) F. W. Swamer, Hydrogenation of Perfluoroalkyl Nitriles, 1970, US3532755 A; d) T. Reissner, A. G. Altenhoff, C. Mueller, Method for Producing 2,2-Difluoroethylamine, 2016, WO2016023773 A1;

e) S. Antons, N. Lui, A. Gerlach, Process for Preparing 2,2-Difluoroethylamine by Hydrogenating 1,1-Difluoro-2-Nitroethane, 2011, US20110082318 A1.

- [35] a) N. Lui, J.-D. Heinrich, Method for Producing 2,2-Difluoroethylamine Starting from 2,2-Difluoro-1-Chloroethane, 2012, WO2012101044 A1;
 b) M. Kuwabara, H. Sunada, K. Fukunishi, M. Nomura, H. Yamanaka, Nippon Kagaku Kaishi 1985, 1985, 796–798.
- [36] D. Pagé, E. Balaux, L. Boisvert, Z. Liu, C. Milburn, M. Tremblay, Z. Wei, S. Woo, X. Luo, Y.-X. Cheng, H. Yang, S. Srivastava, F. Zhou, W. Brown, M. Tomaszewski, C. Walpole, L. Hodzic, S. St-Onge, C. Godbout, D. Salois, K. Payza, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3695–3700.
- [37] A. van Oeveren, M. Motamedi, N. S. Mani, K. B. Marschke, F. J. López, W. T. Schrader, A. Negro-Vilar, L. Zhi, J. Med. Chem. 2006, 49, 6143–6146.
- [38] a) F. L. Scott, R. E. Oesterling, Preparation of Secondary Fluoroalkyl Amines, 1964, US3134816 A; b) H. Bürger, B. Krumm, G. Pawelke, J. Fluorine Chem. 1989, 44, 147–153; c) A. J. Elliott, G. W. Astrologes, Preparation of Trifluoroethylamine, 1986, US4618718 A.
- [39] a) D. R. Husted, A. H. Ahlbrecht, Bis (1, 1-Dihydroperfluoroalkyl) Amines and Salts Thereof, 1957, US2795615 A; b) R. H. Meen, G. F. Wright, J. Org. Chem. 1954, 19, 391–402; c) A. V. Solov'ev, N. P. Kolesnik, R. Ya. Musyanovich, Yu. G. Shermolovich, Russ. J. Org. Chem. 1998, 34, 957– 959.

Manuscript received: March 10, 2023 Accepted manuscript online: March 14, 2023 Version of record online: April 20, 2023

15213755, 0, Downloaded from https://ctemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cthem.202300792 by Cochrane France, Wiley Online Library on [17/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

RESEARCH ARTICLE

N-polyfluoroalkylation reactions are challenging due to the high cost, toxicity or environmental impact of commonly used polyfluoroalkylation reagents. We report the sulfuryl fluoride (SO₂F₂)-mediated *N*-polyfluoroalkylation of weakly nucleophilic nitrogen compounds from readily available fluorinated alcohols. This method opens access to a variety of *N*-polyfluoroalkylated building blocks that are highly valuable for life science applications. Dr. L. Santos, F. Audet, Dr. M. Donnard, Dr. A. Panossian, Dr. J.-P. Vors, Dr. D. Bernier, Dr. S. Pazenok, Dr. F. R. Leroux*

Traceless *N*-Polyfluoroalkylation of Weakly Nucleophilic Nitrogen Containing Compounds