



HAL
open science

Study of a Stable “Trifluoromethoxide Anion Solution” Arising from 2,4-Dinitro-Trifluoromethoxybenzene

Clémence Bonnefoy, Emmanuel Chefdeville, Armen Panossian, Gilles
Hanquet, Frédéric R. Leroux, Fabien Toulgoat, Thierry Billard

► **To cite this version:**

Clémence Bonnefoy, Emmanuel Chefdeville, Armen Panossian, Gilles Hanquet, Frédéric R. Leroux, et al.. Study of a Stable “Trifluoromethoxide Anion Solution” Arising from 2,4-Dinitro-Trifluoromethoxybenzene. *Chemistry - A European Journal*, 2021, 27 (64), pp.15986-15991. 10.1002/chem.202102809 . hal-03582991

HAL Id: hal-03582991

<https://hal.science/hal-03582991>

Submitted on 11 Oct 2022

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.

Study of a stable “trifluoromethoxide anion solution” arising from 2,4-dinitro-trifluoromethoxybenzene.

Clemence Bonnefoy,^[a] Emmanuel Chefdeville,^[b] Armen Pannosian,^[c] Gilles Hanquet,^[c] Frédéric R. Leroux,^[c] Fabien Toulgoat*^{[a],[d]} and Thierry Billard*^{[a],[e]}

- [a] Clemence Bonnefoy, Dr Fabien Toulgoat, Dr Thierry Billard
Institute of Chemistry and Biochemistry (ICBMS-UMR CNRS 5246)
Univ Lyon, CNRS, Université Lyon 1
43 Bd du 11 Novembre 1918, 69622 Lyon (France)
E-mail: Thierry.billard@univ-lyon1.fr
- [b] Emmanuel Chefdeville
NMR Centre
Univ Lyon, Université Lyon 1, CNRS
43 Bd du 11 novembre 1918, 69622 Lyon (France)
- [c] Dr Armen Pannosian, Dr Gilles Hanquet, Dr Frédéric R. Leroux
Université de Strasbourg, Université de Haute-Alsace
CNRS, UMR 7042-LIMA, ECPM
67000 Strasbourg (France)
- [d] Dr Fabien Toulgoat
CPE Lyon
Campus LyonTech-La Doua, 43 Bd du 11 novembre 1918, 69616 Villeurbanne (France)
- [e] Dr Thierry Billard
CERMEP – In vivo imaging
Groupement Hospitalier Est
59 Bd Pinel, 69677 Lyon (France)

Abstract: Despite recent advances, trifluoromethoxylation remains a challenging reaction. Here we describe an efficient trifluoromethoxylation substitution, using an inexpensive and easy-to-handle reagent. By mixing DMAP with a slight excess of 1,4-dinitro-trifluoromethoxybenzene (DNTFB), a stable solution of trifluoromethoxide anion is obtained and can be used to perform a S_N2 reaction without any silver additives. A precise study of the properties and behavior of this unusual stable solution of CF_3O^- species is also performed.

Introduction

Due to the intrinsic properties of the fluorine atom,^[1] fluorinated molecules generally possess specific characteristics that can find very valuable applications in various fields.^[2] More particularly, fluorinated motifs are well sought after in medicinal^[2a-f] or agrochemical^[2g-i] chemistry due to the improved metabolic stability^[2d] and lipophilicity generally brought by these substituents.^[1b, 3]

Because of this interest, the development of innovative fluorinated groups, capable of modulating molecular properties, is, nowadays, an active research field.^[4] In this quest, the association of fluorinated groups with heteroatoms, and in particular chalcogens, has emerged.^[5]

The trifluoromethoxy group has a specific place and has already found applications in some bioactive compounds such as, for instance, Riluzole,^[6] used in the treatment of amyotrophic lateral sclerosis, Pretomanid,^[7] an anti-tuberculosis drug, Sonidegib,^[8] an inhibitor of the Hedgehog signaling pathway used to treat

cancer, Thifluzamide,^[9] a fungicide, or Triflumuron,^[10] an insect growth regulator (Figure 1).

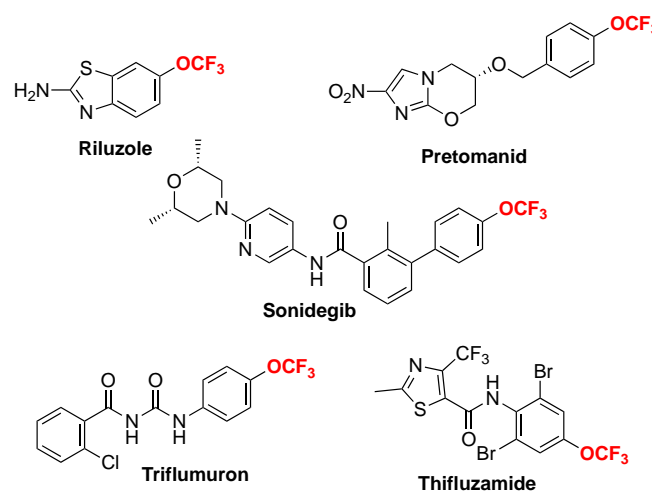


Figure 1. Examples of bioactive CF_3O -containing molecules.

Despite such an interest in this group, the synthesis of CF_3O -compounds suffers from restricted methods and remains difficult.^[5a-d] In particular, the direct introduction of the CF_3O motif onto organic substrates is still poorly described.^[5b-d] Even though, recently, a few reagents have been developed to perform radical trifluoromethoxylation, their use is limited to aromatic substrates and suffers from regioselectivity problems.^[11] Therefore, direct nucleophilic trifluoromethoxylation remains the most widely used

strategy. Nevertheless, as the trifluoromethoxide anion can easily collapse into difluorophosgene and fluoride anion, the use of reagents capable of releasing the CF_3O^- species in situ is required. Thus, several " CF_3O^- anion generators" have been described in the literature (Figure 2).

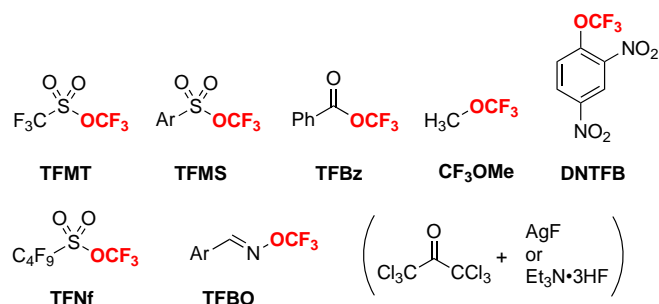


Figure 2. Reagents able to release or generate the CF_3O^- anion.

However, **TFMT**^[12] and **CF₃OMe**^[13] are highly volatile, even gaseous, at room temperature. **TFMS**,^[14] **TFBO**^[14a, 15] and **TFNF**^[16] are synthesized from expensive electrophilic trifluoromethylating reagents. **TFBz**^[17] is synthesized from a toxic phosgene derivative (triphosgene). Finally, **CF₃OAg** prepared from previous reagents or from triphosgene and fluoride source (AgF or $\text{Et}_3\text{N}\cdot 3\text{HF}$) has also been described but suffers from the same problem of using toxic reagents.^[18]

A few years ago, we described the release of CF_3O^- anion from **DNTFB** (2,4-dinitro-trifluoromethoxybenzene),^[19] a non-volatile, inexpensive and easy-to-handle compound, via a $\text{S}_{\text{N}}\text{Ar}$ reaction with the fluoride anion. However, this reagent seemed to have a very limited scope when considering $\text{S}_{\text{N}}2$ reactions.

In order to propose an efficient method to perform trifluoromethylations with a simple, inexpensive and safe reagent, we decided to reinvestigate **DNTFB** chemistry.

Results and Discussion

During our research, Sanford et al. published a nice work based on the new use of **DNTFB** as trifluoromethylating reagent.^[20] These results confirm our belief that **DNTFB** could be a relevant reagent in CF_3O chemistry. Here we would like to publish our preliminary studies on this reagent to provide additional informations to Sanford's results to better understand the reactivity of **DNTFB** and the properties of the resulting trifluoromethoxide anion solution.

In our initial study, we used TBAT (tetrabutylammonium triphenyldifluorosilicate) as the fluoride source to perform the nucleophilic activation of **DNTFB**.^[19] Nevertheless, even if this was effective, the scope of substrate application remains limited. Moreover, the cost of TBAT led us to look for other nucleophiles. Inspired by the Zincke reaction^[21] and the described demethylation reaction of trifluoromethyl methyl ether,^[13] amines (and phosphine) were naturally considered (Figure 3).

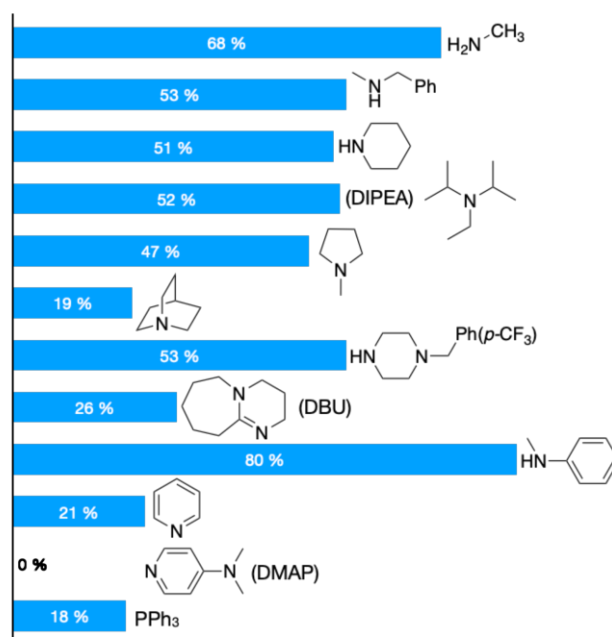
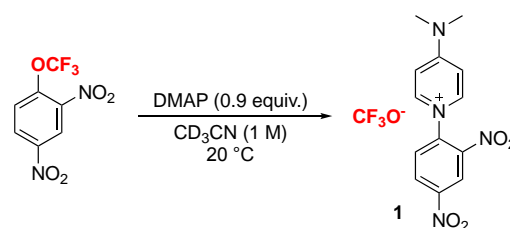


Figure 3. Residual **DNTFB** in presence of various nucleophile. Conditions: **DNTFB** (1 equiv.), nucleophile (1 equiv.), MeCN, 20 °C, 2h.

After 2h of reaction, quinuclidine, DBU, pyridine, DMAP and PPh_3 resulted in the highest degradations of **DNTFB**, with at least 75% of conversion. With a complete conversion, DMAP emerged as the best choice. In addition, the concomitant appearance of a broad singlet at -23 ppm (82%) in ^{19}F NMR was observed. Such a chemical shift is in agreement with a trifluoromethoxide anion species.^[22] These results are also similar to the observations made by Sanford et al.^[20]

To fully characterize the formed product by NMR analysis, this reaction was repeated in CD_3CN in presence of a slight excess of **DNTFB** (Scheme 1).



Scheme 1. Generation of the trifluoromethoxide anion (1).

The ^1H , ^{13}C and ^{19}F NMR analyses were found to be consistent with the proposed structure. Furthermore, while no CF_3 signal from the trifluoromethoxide anion is reported in the ^{13}C NMR analysis described in the literature,^[13, 20, 22] we were able to detect a broad singlet at -121 ppm in fluorine-decoupled ^{13}C NMR which could correspond to the CF_3 signal (Figure 4). With such results in hands, this reaction was followed by ^{19}F NMR to determine the kinetic of the CF_3O^- formation (Figure 5).

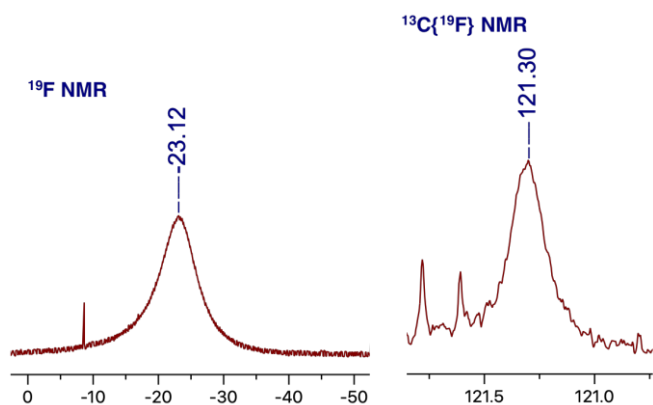


Figure 4. ^{19}F NMR and $^{13}\text{C}\{^{19}\text{F}\}$ NMR of CF_3O^- species **1** (in CD_3CN).

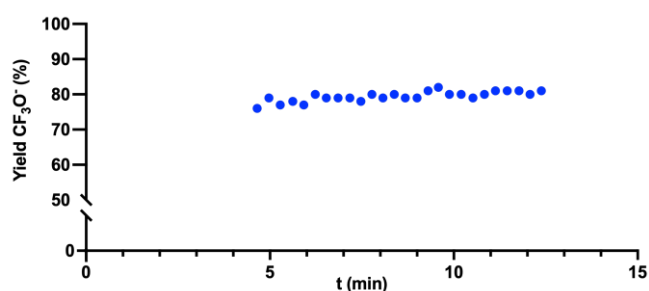


Figure 5. ^{19}F NMR monitoring of the formation of **1**. Preparation: **DNTFB** (0.58 mmol, 1 equiv.), DMAP (0.51 mmol, 0.9 equiv.), CD_3CN (0.5 mL, 1M). Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

In about 5 min (the time to introduce the NMR tube in the spectrometer, just after the preparation of the mixture, and to start the acquisition), the CF_3O^- species is already formed with an almost optimal amount.

To continue our study on the behavior of this CF_3O^- species, formed in situ, its stability in solution was studied (Figure 6).

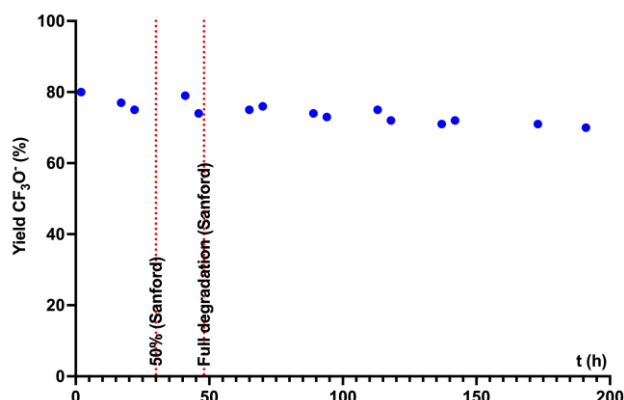


Figure 6. ^{19}F NMR monitoring of **1** (1 M). Preparation: **DNTFB** (1.16 mmol, 1 equiv.), DMAP (1.02 mmol, 0.9 equiv.), CD_3CN (1 mL, 1M). Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

Contrary to Sanford's observations,^[20] the solution proved to be stable over a long time since only 10% loss was observed over 3 days. It should be noted that our solution was prepared without using of a glove box. The main explanation for such a difference could come from the ratio **DNTFB** / DMAP. Indeed, we observed that in presence of an excess of DMAP, the degradation of the CF_3O^- species occurred. With 2 equivalents of DMAP, the complete degradation of CF_3O^- in solution is rapidly observed after 2h (Figure 7).

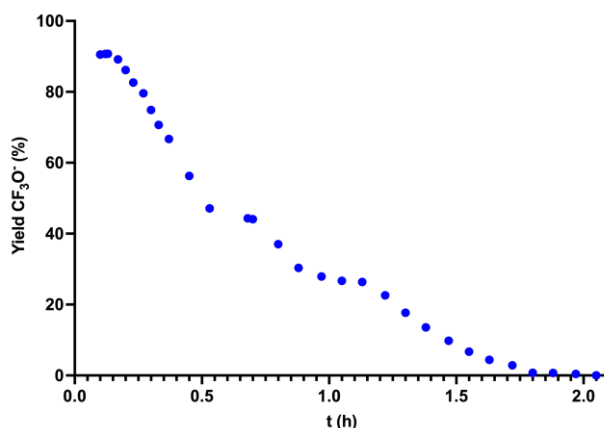


Figure 7. ^{19}F NMR monitoring of a solution (1M) of **DNTFB** (1 equiv.) / DMAP (2 equiv.). Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

Furthermore, this degradation does not require a stoichiometric amount of DMAP because the amount of CF_3O^- species decreases immediately after the addition of 0.4 equiv. of DMAP onto a preformed solution of **1**, disappearing completely after 21h. Interestingly, only a slight excess of DMAP is required to initiate this degradation. Indeed, with only 0.1 equiv. in excess of DMAP, the degradation of CF_3O^- is also observed over 24h. This observation led us to systematically prepare the CF_3O^- solution with 0.9 equiv. of DMAP to be sure to never to have an excess, even minimal (for example because of a weighing uncertainty). Indeed, in the presence of an excess of DMAP, a new fluorinated product was observed in solution in CD_3CN . This degradation product is not the logically expected 2,4-dinitro-fluorobenzene as can be seen from the comparison of ^1H and ^{19}F NMR spectra (Figure 8A). This compound was identified by NMR (Figure 8) as compound **2**, resulting from the nucleophilic attack of the fluoride anion on a carbon bearing a nitro group. In particular, the presence of 4 nitrogen atoms was demonstrated by $^{15}\text{N}\{^1\text{H}\}$ NMR (Figure 8C).

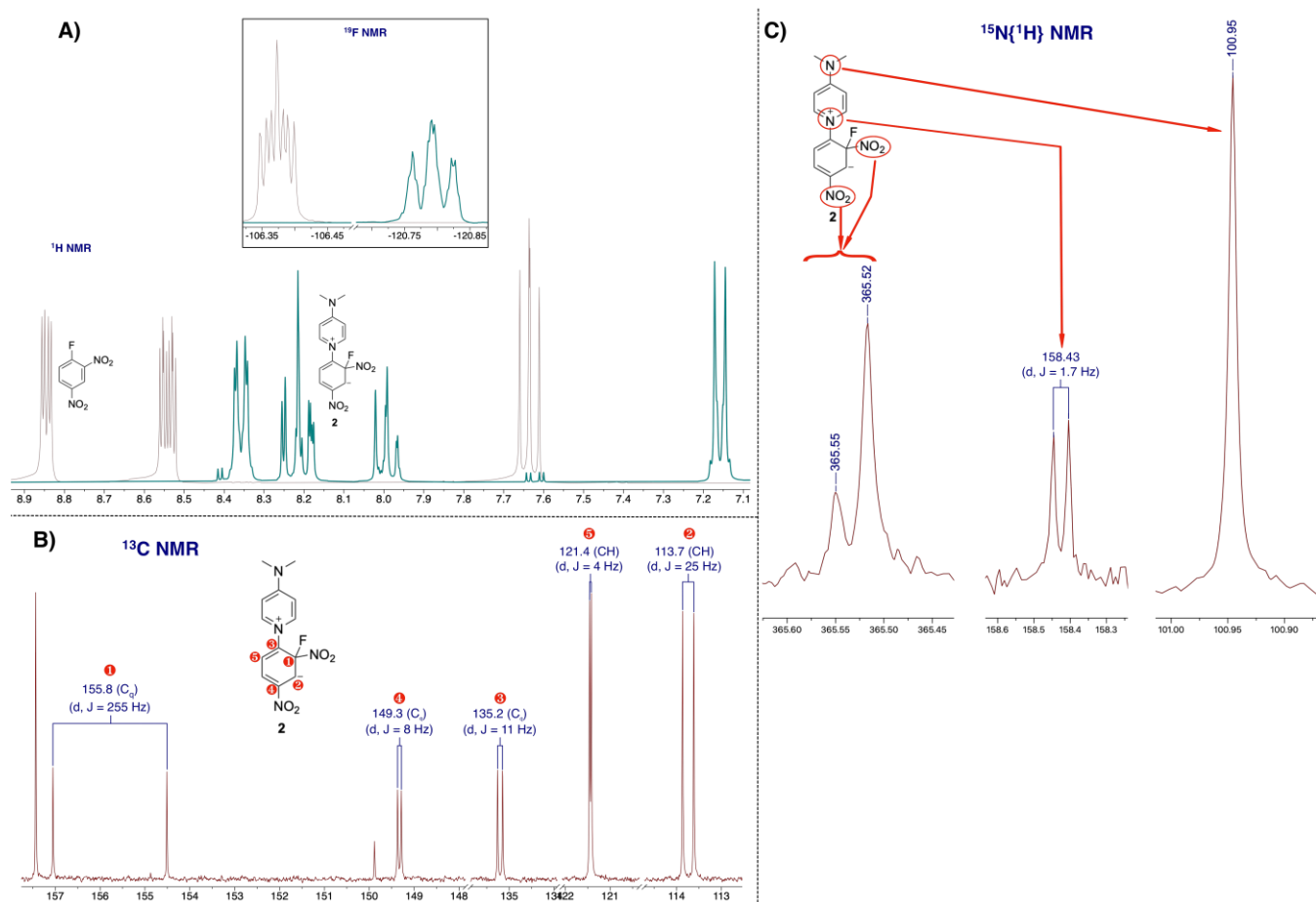
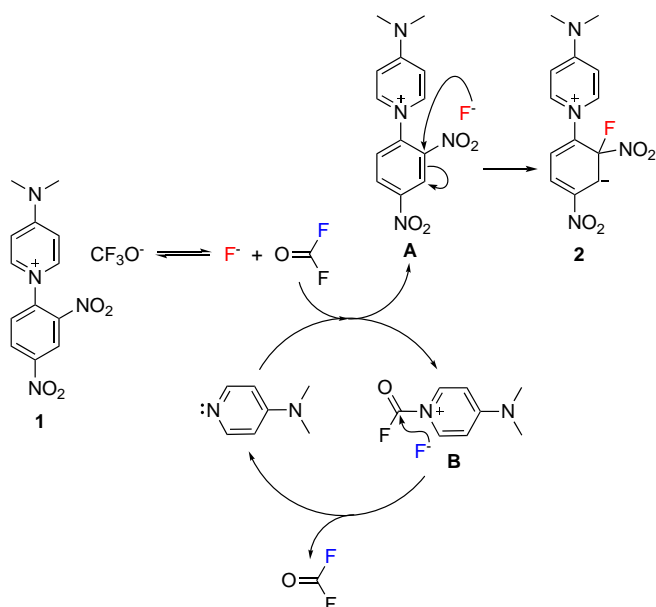


Figure 8. NMR spectra in CD_3CN of **2**. A) ^{19}F and ^1H NMR comparisons with 2,4-dinitro-fluorobenzene. B) ^{13}C NMR (characteristic selected peaks). C) $^{15}\text{N}\{^1\text{H}\}$ NMR



This degradation of **1** in presence of DMAP could come from the trapping of difluorophosgene, arising from the rapid equilibrium implying the trifluoromethoxide anion, thus releasing the transient species **A** and **B**. Intermediate **A** provides the product **2**, whereas **B** gives difluorophosgene, which can be evacuated in gaseous form, and regenerates DMAP. This would contribute to explain the degradation of **1** observed even in presence of small amount of DMAP (Scheme 2).

Finally, as some trifluoromethoxylation reactions may require heating, the thermal stability of the trifluoromethoxide species **1** was also studied.

If the species totally disappeared after 1h at 80 °C, the solution seems to be relatively stable at 40 °C during 24h; only 15% of degradation being observed (Figure 9).

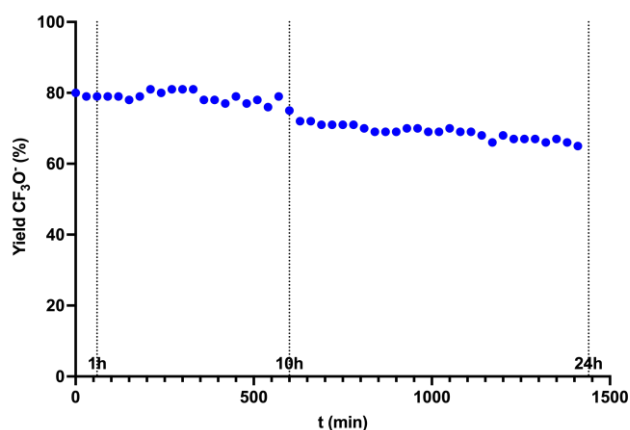
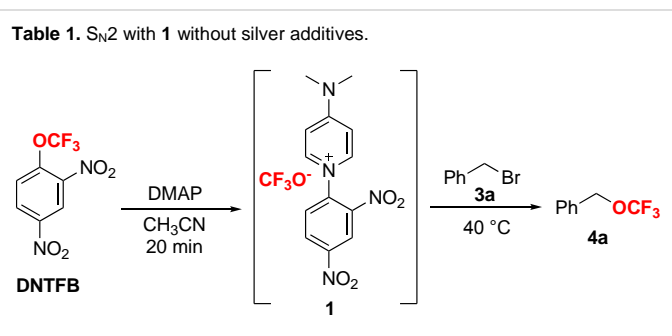


Figure 9. ^{19}F NMR monitoring of a solution of **1** (1 M) at 40 °C. Preparation: **DNTFB** (1.16 mmol, 1 equiv.), DMAP (1.04 mmol, 0.9 equiv.), CD_3CN (1 mL, 1M). Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

This trifluoromethoxide anion, stable in solution and easy and fast to prepare, in hand, we started to determine its reactivity in $\text{S}_{\text{N}}2$ reaction, as described previously.^[19] To provide an alternative to most trifluoromethoxylation reactions that are silver mediated,^[12-14, 16-20] a metal free method, as in the results of Tang^[15] or our previous DNTFB/TBAT^[19] process, was considered.

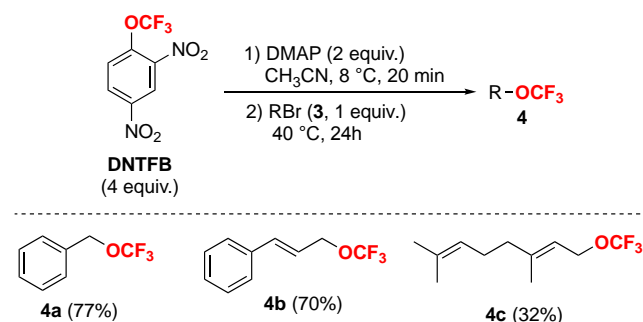


Entry	DNTFB (equiv.)	DMAP (equiv.)	T (°C)	t (h)	4a (%) ^[a]
1	1	0.9	20	24	21
2	1	0.9	40	24	26
3	2	1.9	40	24	43
4	3	2.9	40	24	48
5	4	2.9	40	24	76
6	4	2.9	40	16	77
7	4	2.9	40	5	55
8	5	2.9	40	16	77
9	4	2	40	16	69
10	4	2	40	24	77
11	4	1	40	24	45

[a] Yields determined by ^{19}F NMR with PhCF_3 as internal standard.

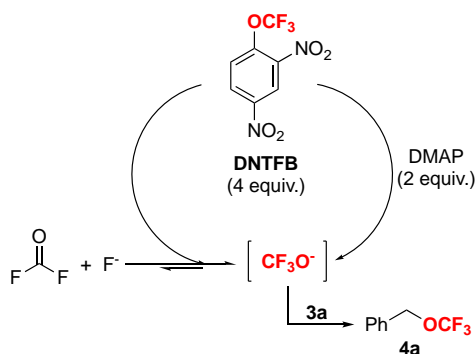
In this context, benzyl bromide was used as model substrate and was added to 1 equivalent of solution of **1**, prepared in situ, to give only 21% of the expected trifluoromethyl ether **4a** in 24h, at room temperature (entry 1). Heating to 40 °C led only to a very slight increase in yield (entry 2). Increasing the number of equivalents of **1**, the amount of **4a** increased to 48% with 3 equiv. (entries 3-4). More interestingly, heightening **DNTFB** amount alone gave a good result (entry 5). A similar result was obtained in only 16h (entry 6), but in 5h the yield dropped to 55% (entry 7). An additional equivalent of **DNTFB** (5 equiv.) did not induce a significant increase in yield (entry 8). On the other hand, a decrease of DMAP (2 equiv.) led to a good result but in 24h instead of 16h (entries 9-10). However, a single equivalent of DMAP dropped the yield to 45% (entry 11). Therefore, the optimal conditions were 4 equiv. of **DNTFB**, 2 equiv. of DMAP at 40 °C for 24h (entry 10). Nevertheless, we noticed that under these conditions, the observed yield was not exactly reproducible ([60%-79%] range) depending on the laboratory temperature (from 20°C to >30°C during hot summer weather). Reproducibility was recovered by preforming **1** in an ice bath (ca 8 °C).

These conditions were successfully extended to cinnamyl bromide (**4b**) (Scheme 3). Geranyl bromide (**4c**) was also trifluoromethoxylated with moderate yield but in accordance with modest results in literature.^[12b]



Scheme 3. Trifluoromethoxylation with **DNTFB** / DMAP system.

From a mechanistic point of view, the 2 equiv. of DMAP yield an excess of CF_3O^- (ca 2 equiv.) that can react with **3a**. This anion also undergoes degradation (certainly accelerated by temperature, as shown in Figure 9) to difluorophosgene and fluoride anion. The latter can then react with the unreacted **DNTFB** to regenerate the reactive species CF_3O^- (Scheme 4).



Scheme 4. Proposed mechanism for trifluoromethoxylation.

Conclusion

In this study, we have demonstrated that the system **DNTFB** / **DMAP** system could generate, in situ, a stable solution of trifluoromethoxide anion. A precise study of this solution was carried out in order to determine the parameters of its stability and its conditions of use. Indeed, the ratio **DNTFB** / **DMAP** appeared as a crucial parameter to obtain a stable solution of trifluoromethoxide anion. This study provided important complementary data to Sanford's preliminary results. Furthermore, this system appeared as an interesting alternative to perform trifluoromethoxylation by nucleophilic substitution, without silver additive. This is the second effective method described for performing such a reaction without any metal. This "trifluoromethoxide anion solution" should be a valuable reagent in organic fluorine chemistry and a more complete study of its reactivity will be published in due course.

Experimental Section

Typical procedure for trifluoromethoxylation reaction: In a 10 mL vial under nitrogen, **DNTFB** (310 μ L, 2 mmol, 4 equiv.) was added in one portion into a stirred solution of **DMAP** (120 mg, 1 mmol, 2 equiv.) in 1.5 mL of anhydrous CH_3CN . The vial is closed and the reaction mixture is stirred in an ice bath (ca 8 $^\circ\text{C}$) during 20 min (of note, the reaction mixture becomes orange immediately after **DNTFB** addition and quickly turns into yellow). Then, the tube is opened to add the alkyl bromide (0.5 mmol, 1 equiv.) and closed immediately after. The reaction mixture is stirred 24 h at 40 $^\circ\text{C}$. Then, the reaction is cooled down and yield is determined by ^{19}F NMR analysis with 30 μL of trifluoromethylbenzene anhydrous as internal standard.

Acknowledgements

The authors are grateful to the French National Research Agency (ANR) (grant number 20-CE07-0004-02, Ap-PET-I). The CNRS and the French Ministry of Education and Research are thanked for funding. The French Fluorine Network (GIS-FLUOR) is also acknowledged for its support.

Keywords: Fluorine • Trifluoromethoxylation • 2,4-dinitro-trifluoromethoxybenzene • Trifluoromethoxide anion • Nucleophilic substitution

- [1] a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2013**; b) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3-11.
- [2] a) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518; b) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880; c) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797-11819; d) B. M. Johnson, Y.-Z. Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*, 6315-6386; e) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633-10640; f) M. Cheng, C. Guo, M. L. Gross, *Angew. Chem. Int. Ed.* **2020**, *59*, 5880-5889; g) P. Jeschke, *Pest Management Science* **2010**, *66*, 10-27; h) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16-29; i) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; j) P. Jeschke in *Organofluorine Chemistry* (Eds.: K. Szabó, N. Selander), Wiley - VCH, Weinheim, Germany, **2021**, pp. 363-395; k) B. Améduri, *Macromol. Chem. Phys.* **2020**, *221*, 1900573; l) *Fascinating Fluoropolymers and Their Applications* (Eds.: B. Améduri, S. Fomin), Elsevier, Amsterdam, Netherlands, **2020**; m) J. Lv, Y. Cheng, *Chem. Soc. Rev.* **2021**, *50*, 5435-5467; n) M. Pagliaro, R. Ciriminna, *J. Mater. Chem.* **2005**, *15*, 4981-4991; o) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496-3508; p) D. Chopra, T. N. G. Row, *CrystEngComm* **2011**, *13*, 2175-2186.
- [3] A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525-616.
- [4] *Emerging Fluorinated Motifs: Synthesis, Properties and Applications* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**.
- [5] a) P. Tang, X. Jiang in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 195-205; b) P. Tang, X. Jiang in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 207-224; c) J. W. Lee, K. N. Lee, M.-Y. Ngai in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 225-250; d) C. Chen, G. Liu in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 251-265; e) J.-H. Lin, J.-C. Xiao in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 267-288; f) X.-H. Xu, F.-L. Qing in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 289-307; g) H. Liu, H. Ge, Q. Shen in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 309-341; h) W. Yi, Z. Song, J. Liu, Y. Mumtaz, W. Zhang in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 343-371; i) M. N. Hopkinson in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 373-401; j) Y. Liang, D. Cahard, N. Shibata in *Emerging Fluorinated Motifs* (Eds.: D. Cahard, J. A. Ma), Wiley, Weinheim, Germany, **2020**, pp. 403-447; k) H. Ge, H. Liu, Q. Shen in *Organofluorine Chemistry* (Eds.: K. Szabó, N. Selander), Wiley - VCH, Weinheim, Germany, **2021**, pp. 99-172; l) T. Besset, T. Poisson in *Emerging Fluorinated Motifs*, **2020**, pp. 449-475; m) V. Krishnamurti, C. Barrett, G. K. S. Prakash in *Emerging Fluorinated Motifs*, **2020**, pp. 477-549; n) P. Beier in *Emerging Fluorinated Motifs*, **2020**, pp. 551-570; o) G. Haufe in *Emerging Fluorinated Motifs*, **2020**, pp. 571-609; p) P. Kirsch in *Emerging Fluorinated Motifs*, **2020**, pp. 611-619; q) N. D. Ball in *Emerging Fluorinated Motifs*, **2020**, pp. 621-674; r) E. Magnier in *Emerging Fluorinated Motifs*, **2020**, pp. 675-690; s) T. Billard, F. Toulgoat in *Emerging Fluorinated Motifs*, **2020**, pp. 691-721; t) T. Milcent, B. Crousse in *Emerging Fluorinated Motifs*, **2020**, pp. 723-761; u) S. Schiesser, H. Chepliaka, J. Kollback, T. Quennesson, W. Czechtizky, R. J. Cox, *J. Med. Chem.* **2020**, *63*, 13076-13089; v) F.-G. Zhang, J.-A. Ma in *Emerging Fluorinated Motifs*, **2020**, pp. 763-808; w) F. Toulgoat, F. Liger, T. Billard in *Organofluorine Chemistry* (Eds.: K. Szabó, N. Selander), Wiley - VCH, Weinheim, Germany, **2021**, pp. 49-97; x) K. Grollier, A. Taponard, T. Billard, *Eur. J. Org. Chem.* **2020**, 6943-6954; y) K. Grollier, A. De Zordo-Banliat, F. Bourdreux, B. Pegot, G. Dagousset, E. Magnier, T. Billard, *Chem. Eur. J.* **2021**, *27*, 6028-6033.
- [6] a) G. Bensimon, L. Lacomblez, V. Meininger, *N. Engl. J. Med.* **1994**, *330*, 585-591; b) T. Fang, A. Al Khleifat, J.-H. Meurgey, A. Jones, P. N. Leigh, G. Bensimon, A. Al-Chalabi, *Lancet Neurol.* **2018**, *17*, 416-422.

- [7] a) C. K. Stover, P. Warrener, D. R. VanDevanter, D. R. Sherman, T. M. Arain, M. H. Langhorne, S. W. Anderson, J. A. Towell, Y. Yuan, D. N. McMurray, B. N. Kreiswirth, C. E. Barry, W. R. Baker, *Nature* **2000**, *405*, 962-966; b) F. Conradie, A. H. Diacon, N. Ngubane, P. Howell, D. Everitt, A. M. Crook, C. M. Mendel, E. Egizi, J. Moreira, J. Timm, T. D. McHugh, G. H. Wills, A. Bateson, R. Hunt, C. Van Niekerk, M. Li, M. Olugbosi, M. Spigelman, *N. Engl. J. Med.* **2020**, *382*, 893-902.
- [8] a) S. Buonamici, J. Williams, M. Morrissey, A. Wang, R. Guo, A. Vattay, K. Hsiao, J. Yuan, J. Green, B. Ospina, Q. Yu, L. Ostrom, P. Fordjour, D. L. Anderson, J. E. Monahan, J. F. Kelleher, S. Peukert, S. Pan, X. Wu, S.-M. Maira, C. Garcia-Echeverria, K. J. Briggs, D. N. Watkins, Y.-m. Yao, C. Lengauer, M. Warmuth, W. R. Sellers, M. Dorsch, *Sci. Transl. Med.* **2010**, *2*, 51ra70-51ra70; b) S. Pan, X. Wu, J. Jiang, W. Gao, Y. Wan, D. Cheng, D. Han, J. Liu, N. P. Englund, Y. Wang, S. Peukert, K. Miller-Moslin, J. Yuan, R. Guo, M. Matsumoto, A. Vattay, Y. Jiang, J. Tsao, F. Sun, A. C. Pferdekamper, S. Dodd, T. Tuntland, W. Maniara, J. F. Kelleher, Y.-m. Yao, M. Warmuth, J. Williams, M. Dorsch, *ACS Med. Chem. Lett.* **2010**, *1*, 130-134; c) M. R. Migden, A. Guminski, R. Gutzmer, L. Dirix, K. D. Lewis, P. Combemale, R. M. Herd, R. Kudchadkar, U. Trefzer, S. Gogov, C. Pallaud, T. Yi, M. Mone, M. Kaatz, C. Loquai, A. J. Stratigos, H.-J. Schulze, R. Plummer, A. L. S. Chang, F. Cornélis, J. T. Lear, D. Sellami, R. Dummer, *Lancet Oncol.* **2015**, *16*, 716-728.
- [9] a) N. Hayakawa, M. Baba, N. Suwa, K. Yamagishi (Nissan Chemical Industries, Ltd.), WO9731908, **1997** [*Chem. Abstr.* 127:220654]; b) A. K. Sharma, D. P. Singh, J. Kumar, A. Singh, A. N. Tewari, K. P. Singh, S. S. Karwasra, A. S. Grewal, *Indian J. Agric. Sci.* **2014**, *71*.
- [10] a) T. Miura, R. M. Takahashi, *J. Econ. Entomol.* **1979**, *72*, 692-694; b) G. Zobebelein, I. Hammann, W. Sirrenberg, *Z. Angew. Entomol.* **1980**, *89*, 289-297.
- [11] a) B. J. Jelier, P. F. Tripet, E. Pietrasiak, I. Franzoni, G. Jeschke, A. Togni, *Angew. Chem. Int. Ed.* **2018**, *57*, 13784-13789; b) W. Zheng, J. W. Lee, C. A. Morales-Rivera, P. Liu, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2018**, *57*, 13795-13799; c) J. W. Lee, K. N. Lee, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2019**, *58*, 11171-11181; d) J. W. Lee, S. Lim, D. N. Maienshein, P. Liu, M.-Y. Ngai, *Angew. Chem. Int. Ed.* **2020**, *59*, 21475-21480; e) S. Dix, P. Golz, J. R. Schmid, S. Riedel, M. N. Hopkinson, *Chem. Eur. J.* **2021**, doi:<https://doi.org/10.1002/chem.202101621>.
- [12] a) T. Billard, *Methanesulfonic Acid, 1,1,1-Trifluoro-, Trifluoromethyl Ester* in Encyclopedia of Reagents for Organic Synthesis [Online], John Wiley & Sons, Ltd, **2016**, <http://dx.doi.org/10.1002/047084289X.rm01930>; b) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *J. Fluorine Chem.* **2010**, *131*, 200-207.
- [13] J. J. Newton, B. J. Jelier, M. Meanwell, R. E. Martin, R. Britton, C. M. Friesen, *Org. Lett.* **2020**, *22*, 1785-1790.
- [14] a) X. Jiang, P. Tang, *Chin. J. Chem.* **2021**, *39*, 255-264; b) M. Lei, H. Miao, X. Wang, W. Zhang, C. Zhu, X. Lu, J. Shen, Y. Qin, H. Zhang, S. Sha, Y. Zhu, *Tetrahedron Lett.* **2019**, *60*, 1389-1392.
- [15] Y. Li, Y. Yang, J. Xin, P. Tang, *Nat. Commun.* **2020**, *11*, 755.
- [16] Z. Lu, T. Kumon, G. B. Hammond, T. Umemoto, *Angew. Chem. Int. Ed.* **2021**, *60*, 16171-16177.
- [17] M. Zhou, C. Ni, Y. Zeng, J. Hu, *J. Am. Chem. Soc.* **2018**, *140*, 6801-6805.
- [18] a) A. Turksay, T. Scattolin, S. Bouayad-Gervais, F. Schoenebeck, *Chem. Eur. J.* **2020**, *26*, 2183-2186; b) J. Saiter, T. Guérin, M. Donnard, A. Panossian, G. Hanquet, F. R. Leroux, *Eur. J. Org. Chem.* **2021**, *2021*, 3139-3147.
- [19] O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *Adv. Synth. Catal.* **2010**, *352*, 2831-2837.
- [20] G. Duran-Camacho, D. M. Ferguson, J. W. Kampf, D. C. Bland, M. S. Sanford, *Org. Lett.* **2021**, *23*, 5138-5142.
- [21] a) T. Zincke, *Justus Liebigs Ann. Chem.* **1904**, *330*, 361-374; b) T. Zincke, G. Heuser, W. Möller, *Justus Liebigs Ann. Chem.* **1904**, *333*, 296-345; c) T. Zincke, G. Weißpfenning, *Justus Liebigs Ann. Chem.* **1913**, *396*, 103-131; d) W.-C. Cheng, M. J. Kurth, *Org. Prep. Proced. Int.* **2002**, *34*, 585-608.
- [22] W. B. Farnham, B. E. Smart, W. J. Middleton, J. C. Calabrese, D. A. Dixon, *J. Am. Chem. Soc.* **1985**, *107*, 4565-4567.
- ...

