Institut de Chimie et Biochimie Moléculaires et Supramoléculaires

Dr. Thierry BILLARD
Directeur de Recherche CNRS - HDR

Synthèse de trifluoromethoxy- et difluoromethoxy-molécules. Applications à la chimie médicinale et l'imagerie médicale.

Synthesis of trifluoromethoxy- and difluoromethoxy-molecules. Applications to medicinal chemistry and medical imaging.

Dr Thierry Billard / Dr Fabien Toulgoat

Due to the particular properties of the fluorine atom, fluorinated molecules have become increasingly popular in recent years in a large number of application fields ranging from materials science to life sciences. Thus, fluorinated compounds have become essential in many current topics: batteries, polymers, agrochemistry, drugs, early diagnostics .... [1]

In order to propose new compounds that are increasingly efficient for "targeted applications", the development of new innovative fluorinated groups has become a hot topic. In this race for new fluorinated moieties, the merging of fluorinated groups and oxygen atom has emerged in recent years as an extremely efficient and promising solution.[2]

We have been involved in this field for several years by developing various reagents and methods to propose new pathways to innovative fluorinated molecules with very specific properties.[3] In particular, we recently described a new efficient reagent to directly introduce CF_3O moiety, in a "late-stage" strategy, onto organic substrates.[4] Furthermore, this reagent appeared to be an efficient $C(O)F_2$ generator able to be used in situ as an efficient reagent.[5]

This work will focus on the use of this reagent to propose new access to various molecules bearing a CF_3O or a CF_2O moieties. This will lead to develop various reactions such as, for instance, C-H functionalizations, couplings, flow chemistry. Furthermore, in order to develop "green synthesis" new activation mode will be also studied, with a particular focus on photochemistry, mechanochemistry and emerging mechanoredox.

These methodological developments will be applied to the functionalization of bioactive compounds in order to propose new compounds with dedicated properties which will be studied.

In addition, the laboratory is also specialized in radiochemistry with fluorine-18 isotope.[5-6] Consequently, some of the previously developed strategies will be used in the design of new diagnostic tools, particularly in the field of neurodegenerative diseases.

Bibliography :

[1] a) C. Zhang, K. Yan, C. Fu, H. Peng, C. J. Hawker, A. K. Whittaker, *Chem. Rev.* **2022**, *122*, 167-208; b) N. Sheikhi, M. Bahraminejad, M. Saeedi, S. S. Mirfazli, *Eur. J. Med. Chem.* **2023**, *260*, 115758; c) S. Han, Y. Lu, *Eur. J. Med. Chem.* **2023**, *258*, 115586; d) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633-10640; e) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.

[2] a) J. Liu, W. Lin, A. E. Sorochinsky, G. Butler, A. Landa, J. Han, V. A. Soloshonok, *J. Fluorine Chem.* **2022**, *257-258*, 109978; b) A. Loison, F. Toulgoat, T. Billard, G. Hanquet, A. Panossian, F. R. Leroux, *Tetrahedron* **2021**, *99*, 132458; c) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726-11735; *Angew. Chem. Int. Ed.* **2016**, *128*, 11900–11909.

[3] a) K. Grollier, A. De Zordo-Banliat, F. Bourdreux, B. Pegot, G. Dagousset, E. Magnier, T. Billard, *Chem. Eur. J.* **2021**, *27*, 6028-6033; b) K. Grollier, E. Chefdeville, E. Jeanneau, T. Billard, *Chem. Eur. J.* **2021**, *27*, 12910-12916; c) F. Brüning, C. R. Pitts, J. Kalim, D. Bornemann, C. Ghiazza, J. de Montmollin, N. Trapp, T. Billard, A. Togni, *Angew. Chem. Int. Ed.* **2019**, *58*, 18937-18941; d) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814-10817; *Angew. Chem.* **2013**, *125*, 11014-11017.

[4] a) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *Adv. Synth. Catal.* **2010**, *352*, 2831-2837; b) C. Bonnefoy, A. Panossian, G. Hanquet, F. R. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2023**, *29*, e202301513; c) C. Bonnefoy, E. Chefdeville, A. Panossian, G. Hanquet, F. R. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2021**, *27*, 15986-15991.

[5] C. Bonnefoy, E. Chefdeville, C. Tourvieille, A. Panossian, G. Hanquet, F. Leroux, F. Toulgoat, T. Billard, *Chem. Eur. J.* **2022**, *28*, e202201589.

[6] J. Colomb, G. Becker, S. Fieux, L. Zimmer, T. Billard, *J. Med. Chem.* **2014**, *57*, 3884-3890.

ICBMS UMR CNRS 5246
Bâtiment Raulin – 2 rue Victor Grignard

Tél. : +33 (0)4 72 44 81 29
thierry.billard@univ-lyon1.fr