COPPER-MEDIATED ELECTROPHILIC TRIFLUOROMETHYLATION OF AMINES

Alexandre Touron,[1] Uroš Todorović,[1] Laurent Severy,[1,2] Thibault Cantat,[1] Emmanuel Nicolas,[1] Lucile Anthore-Dalion[1]

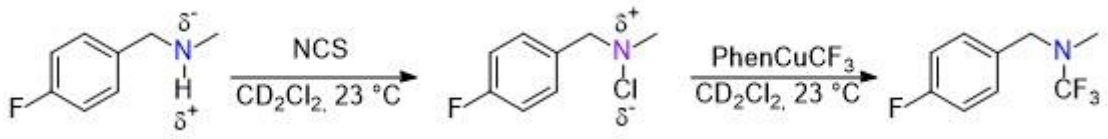
[1] Université Paris-Saclay, CEA-CNRS NIMBE (UMR 3685), 91191 Gif-Sur-Yvette, France

[2] CEA Grenoble, CEA-CNRS LCBM (UMR 5249), 38054 Grenoble, France

The trifluoromethyl group improves the lipophilicity and helps crossing biological barriers. Such properties make it an asset for the activity of drugs, in which the CF_3 moiety is, in most cases, bounded to a carbon atom,[1] albeit O–CF_3[2] and S–CF_3[3] linkages can also be found.

In contrast, despite the ubiquity of nitrogen atoms in drugs, N–CF_3 groups are rarer, notably because of the difficulty to form those bonds. It appears that a direct trifluoromethylation of free amines is difficult.[4] Thus, N–CF_3 bonds are generally formed by *de novo* syntheses using the natural nucleophilicity of the nitrogen atom.[5,6,7] The incorporation of a CF_3 as a whole adduct would require finding a new reactivity.

In this work, we used chloramines and their electrophilic nitrogen atoms coupled with a nucleophilic CF_3 source to form the N–CF_3 bond. The Ruppert-Prakash's reagent[8,9] in the presence of a fluoride source resulted mainly in gaseous CF_3Cl. In contrast, an alternative source of nucleophilic CF_3, [(phen)$CuCF_3$] (phen = 1,10-Phenanthroline)[10] was used and enabled the formation of the desired amine. We then developed a one-pot two-steps synthesis of trifluoromethylamines from free amines in 30 minutes at room temperature using *N*-chlorosuccinimide (NCS) as the chlorinating agent. The mechanism has also been studied with DFT calculations and electrochemical analyses.



References:

[1] R. E. Williams, *Top 200 Small Molecule Drugs by Retail Sales in 2023*, *J. Chem. Ed.* **2010**, 87, 1348-1349
[2] D. Moujalled, A. R. White, *CNS Drugs*, **2016**, 30, 227-243
[3] A. Jeanguenat, C. Lamberth, *Pest Manag. Sci.*, **2023**, 79, 2647-2663
[4] K. Niederman,, N. Früh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem. Int. Ed.* **2011**, 50, 1059-1063
[5] L. M. Yagupolskii, D. V. Fedyuk, K. I. Petko, V. I. troitskaya, V. I. Rudyk, V.V. Rudyuk, *J. Fluor. Chem*, **2000**, 106, 181-187
[6] W. Dmowski, M. Kamiński, *J. Fluor. Chem.* **1983**, 23, 207-218
[7] T. Scattolin, K. Deckers, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, 56, 221-224
[8] I. Ruppert, K. Schlich, W. Volbach, *Tet. Lett.* **1984**, 25, 2195-2198
[9] G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, 111, 393-395
[10] H. Morimoto, T. Tsubogo, N. D. Litvinas, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2011**, 50, 3793-3798