



Assessment of Ph.D. Thesis

Author of Ph.D. Thesis: Zsófia Eszter Blastik

Name of Ph.D. Thesis: Azidoperfluoralkany: syntézy a aplikace
Azidoperfluoroalkanes: Synthesis and Applications

Supervisor of Ph.D. Thesis: Ing. Petr Beier, Ph.D.

The Thesis of Zsófia Eszter Blastik deals with azidoperfluoroalkanes and its applications. Apart of literature review, the Thesis contains four main parts, namely a new approach to the synthesis of azidoperfluoroalkanes, Huisgen cycloaddition („click“ reaction) of azidoperfluoroalkanes with selected alkynes, base-catalyzed cycloaddition of azidoperfluoroalkanes with ketoesters and ketones, and finally, a NMR study or protonation of azidoperfluoroalkanes in superacidic media.

In the Introduction, Ms. Blastik thoroughly reviews known data about compounds bearing trifluoromethyl or perfluoroalkyl group connected to nitrogen atom. This part makes the reader familiar with the chemistry related to the Ph.D. Thesis and is written in a clear and concise way.

Introduction is followed by Aims of the Thesis part, which shortly declares the targets intended to be achieved by the author.

The key part of the Thesis, results and discussion, is divided into four separate parts as mentioned above. The first part deals with novel convenient synthesis of azidoperfluoroalkanes using perfluorocarbanions or its precursors with umpoled azides, using Ruppert-Prakash reagent for trifluoromethylation with advantage. Author's synthetic effort resulted in a small library of azidoperfluoroalkanes, employed in further parts of the Thesis. Although the mechanism of the reaction is briefly discussed, no mechanistic studies were attempted. As a small drawback, the author did not pursue isolation of azidoperfluoroalkanes in a pure state (with the exception of precipitated azide bearing large perfluoroalkyl group) and was satisfied with using solutions of the products in an appropriate solvent. It would also quite interesting to find out whether the author's approach is limited to primary perfluoroalkyls, or if the secondary and tertiary perfluoroalkyls could also be used.

In the second part, catalytic Huisgen cycloaddition with terminal alkynes was studied yielding after optimization a large library of trifluoromethylated and perfluoroalkylated 1,2,3-triazoles. Scope and limitation of the reaction was again thoroughly studied and it was found that internal alkynes are not applicable for the synthesis. In analogy to non-fluorinated click reaction, the author find that regioselectivity can be governed by the choice of the catalytic system. Moreover, click reaction in the presence of iodine gave access to fully substituted triazoles after an appropriate coupling reactions.

The third part covers the cyclization of azidoperfluoroalkanes with enolates based on enolizable ketones. It clearly showed that the success and yield of the cyclization depends on stability of the key intermediary enolates with less enolizable ketons giving inferior yields. It is of

interest that for less enolizable ketones the catalytic intermediates became main products of the reaction.

The last part, performed in the course of the author's stay in Surya-Prakash laboratory in USA, concentrated on the study of protonation of azidoperfluoroalkanes in superacidic media. Using advanced NMR techniques and with the help of DFT computations, Ms. Blastik clarified the regioselectivity of protonation of azidoperfluoroalkanes.

The Conclusion and Outlook part summarizes both positive and negative results of the Thesis, the Experimental part experimental details of the Thesis.

The Thesis is written in very good English with minimal amount of errors, is well readable and clearly depicts many successful results, as well as a couple of failures. It points at authors' excellent theoretical and experimental knowledge of organic chemistry, as well as at high commitment and synthetic effort accomplished during her Ph.D. studies. Unfortunately, the original Thesis contained several critical errors, which required the addition of Errata to the Ph.D. Thesis.

In the revised version, I found only minimum minor errors, mainly related to nomenclature:

- 1) in *N*-alkylated compounds, *N* should be italicized;
- 2) (page 44 Scheme 43) in structure **76**, wrong curved arrows are given;
- 3) (page 53 row 8) the name triflic name is not allowed, should be trifluoromethanesulfonic acid;
- 4) (page 66) in the names azidoperfluoropropane and azidoperfluorooctane, locants are missing for the azido group;
- 5) (page 69 and further) when more nested parentheses are used, {{{ ... }}} should be used instead of simple parentheses;
- 6) (page 90) in compound **71r**, wrong prefix is used, instead of phenylthio, phenylsulfanyl should be used according to IUPAC;
- 7) (page 96) in compound **78**, relative stereochemistry should be expressed if known, probably (4a*R**,7a*R**);

I have also several questions and comments:

Questions:

Q1) (page 7) In the mechanism of fluorodesulfurization, the reaction is depicted as starting with X^+ , which is clear for NBS or HF (H^+), but how it should work for DeoxoFluor?

Q2) (page 15) Is there some information about the stability of Ar-NH-CF₃ grouping against HF elimination?

Q3) (page 32 Table 3) Is there some rationale for using sometimes method A, sometimes method B?

Q4) (page 98, part 8.5) What is meant by „CF₃N₃ was prepared according to modified reported procedure“ and how volatile products were condensed at ambient pressure to the NMR tube?

Q5) (Part 5.6.) Did you consider the use of silyl enol ethers for cyclizations with azides and is it known?

Comments:

C1) (page 44 Scheme 43) It would be probably better not to include the dehydration step into the catalytic cycle, as this is a parallel reaction.

C2) (page 12 Scheme 19) Symbol Q is normally used as the abbreviation of a two valent carbon moiety, e.g. -Q-.

C3) (page 12 Scheme 19) I am not sure if the synthesis including electrofluorination in anhydrous HF can be called „convenient“

C4) (page 22) The contribution of Dr. Voltrová to chapter 4 should be specified more clearly and in more detail, the Thesis should be the work of sole author.

C5) (page 46) I would hesitate to call „Table 7“ a table, it is a Scheme.

C6) (page 49) 4-*tert*-Butylcyclohexanone is achiral compound, not a racemate.

C7) (page 52) Similarly to C4, the contribution of other coworkers on the Thesis should be given in more detail and the relevant places.

C8) (page 56) ^{14}N NMR spectroscopy is normally not measured due to spin 1, which significantly widens the signals. Maybe the reader would deserve more explanation.

C9) (page 56 Table 10) Although quite high level calculations were used, the differences between the calculated and experimental shift are quite large. Could not be attributed to the absence of the solvent effect (SO_2ClF) in the computations? Maybe the results in the solvent simulated by the SCRF method could be closer?

C10) (page 62) The conclusions include the statement relating to the role of free CF_3^- anion, but the Thesis brings no experimental or theoretical data to confirm or deny it.

The results of the Thesis have been published in two papers in high level journals, the third manuscript is in preparation. The Thesis contains a large amount of high quality experimental data and significantly improved both the availability of fluorinated alkyl azides and the state of knowledge about their applications. Ms. Blastik showed high level knowledge of theoretical and experimental organic chemistry and I therefore **recommend** her Ph.D. Thesis as the basis for defending the **Ph.D.** title.

Prague, 9. 4. 2019

Prof. Ing. Jaroslav Kvíčala, CSc.