

# Lodz University of Technology

Institute of Organic Chemistry

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Łódź, 2021-06-16

**Evaluation of the PhD thesis entitled:**  
**“Synthesis and reactivity of trifluoromethylated aziridines and  $\beta$ -lactams containing phosphonate moiety”**  
**by Monika Skibińska**

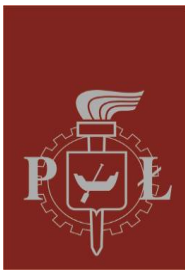
Ms. Monika Skibińska has performed her PhD work in the period of 2017-2021 within double doctoral degree program *Doctorate en Cotutell* financed by French Government Scholarship (BGF). Therefore, it has been realized in collaboration between Faculty of Pharmacy of University Paris-Saclay (France) and Faculty of Chemistry of Adam Mickiewicz University in Poznań (Poland) with Doctor Benoit Crousse (University Paris-Saclay) and Professor Henryk Koroniak (UAM) acting as supervisors of the thesis. During PhD studies Ms. Monika Skibińska carried out four internships at the University Paris-Saclay (lasting 18 months in total) where she was working on the projects described in the evaluated thesis and realized *INNChem* project. It should also be highlighted that the results obtained by Ms. Monika Skibińska during her PhD studies have been published in three papers in good international chemistry journals and in a book chapter.

PhD thesis of Ms. Monika Skibińska is entitled “Synthesis and reactivity of trifluoromethylated aziridines and  $\beta$ -lactams containing phosphonate moiety” and describes her studies on the development of new synthetic methodologies leading to selected nitrogen-based heterocycles with potential biological activity. The thesis has been divided into eight chapters with four of them dedicated to the discussion of the scientific results of her work. In the Chapter I, a brief introduction to three key structural motifs with significant importance to the evaluated thesis, namely trifluoromethyl, difluoromethylene and phosphonate moieties, is given. The content of the chapter is well-selected as it provides the reader with basic information relevant for subsequent parts of the thesis. Chapters II and III describe the actual results of the experimental work performed within Ms. Monika Skibińska PhD studies with each chapter focusing on specific research objectives. Importantly, a comprehensive introduction to the subject of a given project is provided in each of the cases. Chapters IV (General methods) and V (Experimental section) document instrumental and experimental methods utilized within the studies as well as



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spectroscopic data of the compounds obtained. Provided descriptions are very detailed and rise no questions with respect to their reproducibility. Assignments of NMR data are also of high quality confirming Ms. Monika Skibińska knowledge in this area. Literature references have been given in Chapter VI. This part of the thesis is well-prepared and contains 263 references providing very comprehensive and broad perspective on the covered areas of research. Chapter VII summarizes scientific achievements of Monika Skibińska that include publication record, active participation in conferences as well as accomplished internships. Abstracts in English, Polish and French are provided in the last chapter of the dissertation.

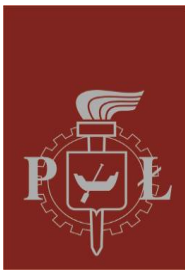
Chapter II describes studies focusing on the reactivity of  $\alpha$ -hydroxyphosphonates bearing trifluoromethyl-substituted aziridine ring. The synthesis of starting materials has been accomplished according to the methodology previously developed in Professor Koroniak research group. Aziridines obtained were subjected to nucleophilic ring opening with primary amines. Surprising reactivity that involved interesting phosphonate-phosphate rearrangement was observed yielding enol phosphate as the sole product. In the course of further studies, a method to transform  $\alpha$ -hydroxyphosphonates into  $\alpha$ -aminophosphonates (proceeding in a sequence retro-Abramov reaction followed by imine formation and aza-Pudovik addition) has been developed. A stereochemical model accounting for high diastereoselectivity obtained has been proposed. Very interesting reactivity of  $\alpha$ -hydroxyphosphonates bearing trifluoromethyl-substituted aziridine ring has been observed when the protecting group at the nitrogen atom of the aziridine ring was replaced from benzyl to benzyloxycarbonyl group with electron-withdrawing properties. This reactant under basic conditions underwent aza-Payne rearrangement resulting in the formation of the epoxide ring. Notably, the findings described within this Chapter were supported by detailed mechanistic studies performed with the aid of NMR spectroscopy. Given the importance of these results, more systematic studies on these transformations leading to expansion of their potential and synthetic applicability, would be highly appreciated. However, I understand that it is beyond the scope of the evaluated thesis.

The synthesis and functionalization of  $\beta$ -lactam derivatives is a common goal of three different research projects summarized within Chapter 3. The first method relies on the preparation of  $\alpha$ -unsubstituted- or  $\alpha$ -mono-substituted- $\beta$ -trifluoromethyl- $\beta$ -lactams via aza-Reformatsky reaction between  $\alpha$ -bromoesters and imines (derived from trifluoroacetaldehyde) and their subsequent reactions with selected electrophiles such as



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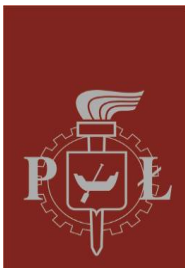
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aldehydes, alkyl halides and ethyl chloroformate. These transformations have been realized via intermediacy of the corresponding enolates. In the optimization studies of the reaction between benzaldehyde and  $\alpha$ -unsubstituted- $\beta$ -trifluoromethyl- $\beta$ -lactams interesting influence of the amount of base on the stereochemical outcome of the process has been observed. A rationalization of this intriguing diastereoselectivity reversal would be welcomed. Notably, the reaction with  $\alpha$ -mono-substituted- $\beta$ -trifluoromethyl- $\beta$ -lactams (described within Chapter III.2.4.2.4) has proceeded with excellent diastereoselectivity. I find this finding very valuable as this method provides stereocontrolled access to important group of  $\beta$ -lactams bearing a quaternary stereogenic center. Furthermore, the transformation is diastereoconvergent what increases its usefulness.  $\beta$ -Trifluoromethyl- $\beta$ -lactams containing phosphonate moiety constitute the next synthetic objective of the thesis. The developed method is based on the reaction between  $\alpha$ -unsubstituted- or  $\alpha$ -methyl- $\beta$ -trifluoromethyl- $\beta$ -lactams with diethyl chlorophosphonate. Attempts to use other phosphonate-group-containing electrophiles (diethyl chloromethylphosphonate or diethyl (2-bromoethyl)phosphonate) were either unsuccessful or resulted in: 1) epimerization of the C-3 stereogenic center or 2) the opening of the  $\beta$ -lactam framework. The final part of Chapter III describes a very elegant method for the synthesis of  $\beta$ -difluoromethylene- $\beta$ -lactams. It is based on dehydrofluorination of the  $\beta,\beta$ -disubstituted- $\beta$ -trifluoromethyl- $\beta$ -lactams with the idea arising from the previously observed side-product formation. This demonstrates that Ms. Monika Skibińska is a matured scientist paying attention to details that might not be of particular importance at the moment of their appearance. This is very important ability that that should be beneficial for her further development. The presence of quaternary stereogenic center in the  $\beta$ -position of the  $\beta$ -lactam ring proved crucial for the desired reactivity. In the course of further studies an interesting rearrangement reaction of the products has been identified and rational mechanistic explanation provided. Various methods for the functionalization of  $\beta$ -difluoromethylene- $\beta$ -lactam were also attempted (e.g. via  $S_NV$  reaction) with hydrogenolysis (resulting in the introduction of difluoromethyl substituent in the  $\beta$ -position) accomplished successfully.

In this part of the thesis there are some minor issues that require a comment:

- 1) Sentence "First the product **154a** after racemization of the hydroxyl group" (page 53) is not correct for two reasons. Firstly, compound **154a** is already racemic so it can only epimerize. Secondly, terms racemization/epimerization refer to processes taking place at the stereogenic center (and not at the functional group).





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- 2) Reactions described in Chapter III.2.4.2.4 have been defined as “substitution reactions” (page 79) while some of the described processes should be considered as nucleophilic additions.
- 3) Structures of compounds **104** (Scheme 13) and **301** (Scheme 71) are not correct.
- 4) Absolute configurations for racemic compounds should not be indicated (e.g. Figure 60).

These minor remarks do not influence my positive assessment of the PhD thesis as the scientific discussion is very detailed. The Author uses boxes entitled “In the literature” in order to indicate possible solutions to encountered synthetic problems and present literature state-of-art within the field. I find it as a useful feature of the thesis providing the reader with additional background information relevant for a given consideration. It also demonstrates the knowledge of Ms. Monika Skibińska and her way of thinking about synthetic organic chemistry. In my opinion, the PhD thesis of Monika Skibińska constitutes an interesting contribution expanding the methodological toolbox for the preparation of trifluoromethylated and phosphorylated three- and four-membered nitrogen heterocycles. Moreover, the thesis confirms her skills in structural elucidation of organic molecules by means of spectroscopic methods. In particular, the use of NMR techniques for the assignments of relative configuration is worth stressing out.

In summary, methodological achievements of Ms. Monika Skibińska in the field of organic chemistry clearly confirm her ability to conduct interesting research at high international level. Therefore, I am convinced that the dissertation meets the requirements for a doctoral degree, and I strongly recommend Adam Mickiewicz University in Poznań and University Paris-Saclay awarding Ms. Monika Skibińska the doctoral degree.

