

REVIEW

By Assoc. Prof. Dr. Georgi Kostadinov Stavarakov,

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Subject: PhD thesis for the award of the educational and scientific degree "doctor", field of higher education 4. Natural sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences, Scientific Specialty "Organic Chemistry".

Author: Martin Antoniev Ravutsov

Title: Sulfonamide-directed *ortho*-metalation as a tool for region- and stereoselective synthesis of multifunctional aromatic compounds

Scientific Advisors: Prof. DSc. Vladimir Dimitrov

General description of the presented materials

According to order № ПД-09-20/21.01.2021 of the Director of IOCCP-BAS, I have been approved as a member of the academic board for awarding the educational and academic degree "Doctor" of Martin Antoniev Ravutsov, PhD student at IOCCP-BAS, in professional field 4.2. Chemical Sciences, Scientific Specialty "Organic Chemistry". The title of the thesis is: "Sulfonamide-directed *ortho*-metalation as a tool for region- and stereoselective synthesis of multifunctional aromatic compounds". At the first meeting of the academic board I was chosen as a reviewer of the PhD thesis.

The submitted set of documents and materials meets the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations on the terms and conditions for awarding scientific and academic degrees in IOCCP-BAS and includes the following documents: PhD thesis (in English), application form; autobiography; a copy of the diploma for completed master's degree; protocols from successfully passed exams according to an individual training plan; abstract in Bulgarian and English; list and copies of scientific publications; list of noticed citations; list of participations in scientific events; award for best poster; list of participations in scientific projects; separation protocol between the authors Martin Ravutsov and Zhanina Petkova.

Brief biographical data about the PhD student

Martin Ravutsov graduated from Sofia University "St. Kliment Ohridski", Faculty of Chemistry and Pharmacy in 2012 with a Master's degree in Chemistry, specialization in

“Modern methods of synthesis and analysis of organic compounds” with an average grade “Excellent”, and a diploma thesis with “Excellent” grade. In 2013 he started work on his PhD thesis in the laboratory "Organic Synthesis and Stereochemistry" at IOCCP-BAS. He held the following positions: Assistant (04.01.2016 – 31.12.2017) and Chemist (01.01.2018 – today). Martin Ravutso additionally qualified in “Radiocarbon Dating” in Rudjer Bošković Institute, Zagreb, Croatia. He speaks fluent English. The PhD student is a co-author of 3 scientific publications, in one of which he is the first author. The results of her scientific work are presented at 12 scientific forums. He participated in 10 research projects funded by Bulgarian National Science Fund, Bulgarian Academy of Sciences, IAEA, European Commission, National Program “Young Scientist and Post-doctorants”.

Relevance of the topic and expediency of the set goals and objectives

The asymmetric synthesis or the creation of stereoisomerically pure compounds continues to be an extremely relevant field of the Organic chemistry. The chiral synthesis is crucial for the production of a number of products of the pharmaceutical industry because different enantiomers or diastereomers of a compound often have different biological activity.

The PhD thesis of Martin Ravutsov outlines few main goals, namely: study of the directed *ortho*-lithiation within 1- and 2-naphthylsulfonamides and application of the reaction towards the synthesis of ligands, which catalytical activity was evaluated; synthesis of ferrocenesulfonamides and their application in reaction of directed *ortho*-lithiation towards planar chiral ferrocenes; Evaluation of the antibacterial activity of selected ferrocene sulfonamides against *Mycobacterium tuberculosis*.

Knowledge of the problem

In the PhD thesis are cited 165 literature sources in renowned journals, which demonstrate that the doctoral student is well acquainted with the state of the problem. The literature review is structured in two sections. In its first part is examined the structure of the organolithium compounds, the mechanism of the directed lithiation reactions and in particular the directed *ortho*-lithiation (DoL). The attempt to systematize the lithium-directing groups according to their strength and efficiency makes a good impression. The second part of the literature review is devoted to the region- and stereoselectivity of *ortho*-lithiation of naphthalene and ferrocenes. Particular attention is paid to the introduction of planar chirality on ferrocene derivatives *via* chiral directing group.

Research methodology

The research methodology includes the implementation of a large number of reactions, including under inert atmosphere, the isolation of the products in pure form by column chromatography or recrystallization, characterization of the structures of the newly synthesized substances by NMR techniques, mass spectrometry, elemental analysis, melting points and optical rotation. Following this mandatory for modern organic synthesis methodology allows the achievement of the goals of the scientific problems.

Within the dissertation, a large number of lithiation reactions have been performed, which require strict anhydrous and oxygen-free conditions for their successful implementation. Therefore, the PhD-student has mastered the techniques of working under an inert atmosphere with the help of an argon-vacuum line and the so-called Schlenk equipment. The lithiation conditions were optimized by combining the influence of different organolithium reagents, solvents, temperatures from -78 °C and -40 °C to 0 °C, addition of different complexing agents and subsequent reactions with different electrophiles. It has been achieved optimization of yields, regio- and stereoselectivity. This huge work is presented in several tables, from which a synthetic chemist can see systematic research, persistence and the acquisition of vast practical experience by the doctoral student.

Characteristics and evaluation of the thesis

The PhD thesis is well organized and structured according to the established requirements. The exposition of the material in the dissertation is formed on 144 pages and includes: introduction (2 pages), goals and tasks (1 page), literature review (44 pages), results and discussion (23 pages), conclusions (1 p.), experimental part (55 p.), literature (6 p.) and appendixes (5 pages). 165 literature sources are cited. The results of the dissertation are presented and discussed in two main sections: 1) Directed *ortho*-lithiation of chiral 1- and 2-naphthylsulfonamides; 2) Synthesis of 1,2-disubstituted planar-chiral ferrocene derivatives. A good impression is made by the correct description of the experimental procedures and the detailed characterization of the newly synthesized compounds.

A list of publications related to the dissertation and participations in scientific forums is missing.

Contributions and significance of the thesis for science and practice

The PhD thesis of Martin Ravutsov is of fundamental importance to science. It would be of practical applicability if the research on the biological activities of the newly obtained substances is deepened. The main contributions and merits of the dissertation can be summarized as follows:

- A method for *ortho*-lithiation of 1- and 2-naphthylsulfonamides was developed and applied for the synthesis of chiral ligands. The latter were evaluated in palladium-catalyzed asymmetric allylic substitution (AAS)
- Ferrocenesulfonamides were prepared and used for the synthesis of 1,2-disubstituted planar chiral ferrocene derivatives *via* diastereoselective *ortho*-lithiation.
- The configuration of the synthesized diastereoisomers was determined by NMR experiments and additionally confirmed by X-ray crystal structure analysis.
- The activity of chosen newly synthesized compounds against *Mycobacterium tuberculosis* was evaluated.

Assessment of the publications and personal participation of the PhD student

The scientific results from the thesis of Martin Ravutsov have been partly published in two scientific publications. The PhD student is the first author in one of them and second author in the other. A third paper connected with the thesis, in which Martin Ravutsov is first author is also accepted for publication in a renowned international journal. The aforesaid unequivocally proves the qualities of the dissertation and the personal participation of the PhD student.

Abstract

The abstract of the thesis of Martin Ravutsov is 35 pages long. It correctly reflects the main results, notes the scientific contributions, conclusions and cites correctly the literature.

A list of publications related to the dissertation and participations in scientific forums is missing.

Critical remarks and recommendations

Despite a thorough and critical reading of the dissertation, I have no significant remarks. Of course, I found a number of technical and spelling mistakes. I have marked them in the paper body of the thesis, which I will provide to the PhD student to make the appropriate corrections.

I have one question. Why is the dissertation of a Bulgarian, written at the Bulgarian Academy of Sciences, in English? My opinion as a lecturer is that in the globalizing world of science we must fight for the purity of the expression of the Bulgarian chemical language and every Bulgarian dissertation needs to contribute in this direction.

I recommend at the end of the dissertation and the abstract to be added a list of publications related to the dissertation.

Personal impressions

I have known personally Martin Ravutsov since 2013. I consider him to be an extremely pedantic, persistent and promising young scientist.

CONCLUSION

The PhD thesis contains **scientific and scientific-applied results, which represent an original contribution to science and meet all the requirements** of the Law for Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for application of LDASRB and the respective Regulations of BAS and IOCCP-BAS. The presented materials **fully** comply with the specific requirements of IOCCP -BAS.

The thesis unequivocally shows that the Ph.D. student **Martin Antoniev Ravutsov** has theoretical knowledge and professional skills in the scientific specialty "Organic Chemistry" by demonstrating qualities and skills for independent research.

Based on the above, I give my **positive assessment** of the PhD thesis **and propose to the esteemed academic board to award the educational and academic degree "Doctor"** to Martin Antoniev Ravutsov in the field of higher education: 4. Natural sciences, mathematics and informatics; 4.2. Chemical sciences; Scientific Specialty "Organic Chemistry".

Sofia, 15.02.2021 г.

Reviewer:.....

Assoc. Prof. Georgi Stavrakov