

EVALUATION REPORT

by Prof. Dr. Valerij Christov Christov, PhD, DSc,

Pensioner, Konstantin Preslavsky University of Shumen

in regard to the thesis submitted for awarding the educational and scientific degree **Doctor (PhD)** field of higher education **4. Natural Sciences, Mathematics and Informatics**, professional field

4.2. Chemical Sciences, Organic Chemistry Doctoral Programme

Author: Martin Antoniev Ravutsov

Dissertation: "Sulfonamide-directed *Ortho*-metalation as a Tool for Regio- and Stereoselective Synthesis of Multifunctional Aromatic Compounds"

Scientific Advisors: Prof. Dr. Vladimir Dimitrov, PhD, DSc and Assoc. Prof. Dr. Georgi Dobrikov, PhD

Further to the Protocol of the meeting of the Scientific Jury from 25. 01. 2021, I was appointed by Order № ПД-09-20 / 21. 01. 2021 signed by the Director of the Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP) to be a member of the scientific jury (reviewer) for awarding the educational and scientific degree Doctor (PhD) on thesis named "Sulfonamide-directed *Ortho*-metalation as a Tool for Regio- and Stereoselective Synthesis of Multifunctional Aromatic Compounds", field of higher education **4. Natural Sciences, Mathematics and Informatics**, professional field **4.2. Chemical Sciences, Organic Chemistry** Doctoral Programme. It is Martin Antoniev Ravutsov`s thesis. Martin Ravutsov is a PhD student at Laboratory of Organic Synthesis and Stereochemistry, IOCCP. His scientific advisors are Prof. Vladimir Dimitrov, PhD, DSc and Assoc. Prof. Dr. Georgi Dobrikov, PhD from IOCCP.

The set of electronic materials submitted by Martin Ravutsov is in compliance with the Regulation on the Terms and Procedure for Acquisition of Academic Degrees and the Occupation of Academic Jobs at IOCCP.

Martin Ravutsov graduated from the Faculty of Chemistry and Pharmacy at Sofia University "St. Kliment Ohridski", bachelor's program "Chemistry", in 2011. In 2012 he graduated with honors the master's program in "Modern methods for synthesis and analysis of organic compounds" at the same faculty of the same university. Since 2013 he has been a full-time PhD student in the Laboratory "Organic Synthesis and Stereochemistry" of IOCCF-BAS. From 2016 to 2017 he was an Assis.-Prof. of organic chemistry, and from 2018 until now he has been a chemist in the same laboratory. He completed his education as a full-time PhD student and he was given right of defense.

The thesis presented for review includes research material on a topical issue in the field of organic synthesis and is aimed at developing approaches for obtaining chiral multifunctional compounds for use in asymmetric synthesis and medical chemistry. The PhD student focused on the development of reliable procedures for selective functionalization of naphthalene and ferrocene based on sulfonamide-directed *ortho*-lithiation. In this regard, the following two goals are set:

- Synthesis of chiral *P*-containing naphthalene ligands for Pd-catalyzed asymmetric allyl substitution; and
- Synthesis of ferrocensulfonamides with potential biological activity against *Mycobacterium tuberculosis*.

From the point of view of organic synthesis, these goals stimulate the use of new synthetic procedures, reagents, solvents and catalysts, the development of new isolation and purification techniques, as well as instrumental methods for characterization and structural elucidation of organic compounds. The main six objectives of the thesis are focused on:

- ✓ Synthesis of chiral naphthalene *P,O*-ligands by studying the regioselectivity of the reaction of directed *ortho*-lithiation of 1- and 2-naphthylsulfonamides;
- ✓ Evaluation of the catalytic activity of chiral naphthalene *P,O*-ligands in a model reaction of Pd-catalyzed asymmetric allyl substitution;
- ✓ Development of a synthetic approach for preparation of planar chiral 1,2-disubstituted ferrocene derivatives by *ortho*-lithiation reaction directed by a chiral sulfonamide group;
- ✓ Study of the diastereoselectivity of the reaction and the interaction of the obtained organolithium intermediates with different electrophiles and development of appropriate techniques for separation and isolation of the obtained diastereoisomers;
- ✓ Study of the structural characteristics of 1,2-disubstituted planar chiral ferrocene derivatives by applying physicochemical methods;
- ✓ Evaluation of the *in vitro* antimycobacterial activity of selected ferrocensulfonamides against *Mycobacterium tuberculosis* and design of potential new drug candidates by highlighting leading structures.

From the above it is clear that the goals and objectives of the thesis are undoubtedly in a modern, current and promising field of organic synthesis.

The thesis is written in English, is presented on 144 pages and contains 17 tables, 21 figures and 37 reaction schemes. The exposition of the thesis begins with an introduction (2 pages), which justifies the PhD student's interest in the chosen topic, after which the main goals and objectives of the thesis are defined. The following is a 44-page review of literature, citing 165 references. A review of the available literature on the *ortho*-metalation reaction (DoM) as a tool for regioselective

creation of complex and diverse polysubstituted aromatic and heteroaromatic structures is considered, considering the structure and properties of organolithium compounds as well as the known types of DoM mechanisms. The main attention is paid to the regioselective directed *ortho*-lithiation of naphthalenes and the diastereoselective *ortho*-lithiation of ferrocenes.

The reviewed literature review leaves a very good impression with the concise and competent exposition of the cited works and characterizes the PhD student as a trained specialist in the field and able to find, systematize and critically analyze the literature data. The way in which the literature review of the thesis is written shows that Martin Ravutsov is very well acquainted with the available literature, which is helped to plan clearly and accurately the experimental work and to select a methodology and approaches that allow successful realization of the goals of the thesis. Reading the thesis convinces me of the in-depth knowledge of the developed problems. In addition, the elegant way of exposing the material should be mentioned.

The thesis is constructed clearly, logically and is illustrated with appropriate schemes, figures and tables and contains original contributing research and results. The impression of the precisely conducted experiment, of the correctly described synthesis procedures and of the detailed spectral characterization of the compounds is very good.

It is obvious that Martin Ravutsov has knowledge and successfully applies in his work modern methods for the synthesis and research of organic compounds, i.e. the educational goals of the doctoral program have been fulfilled.

Martin Ravutsov's thesis is rather fundamental in the field of organic synthesis, albeit with a practical focus. The studies carried out have scientific and applied contributions with enrichment of the existing knowledge in the field of organic synthesis - in the direction of synthesis of new enantiomerically or diastereoisomerically pure organic and organometallic compounds, research of management of enantioselective catalytic variants of organic reactions and research of their biological activity. In my opinion, the main scientific contributions and merits of the thesis are the following:

- ✓ An effective method for regioselective *ortho*-lithiation of 1- and 2-naphthylsulfonamides has been developed;

- ✓ Chiral *P,O*-ligands were synthesized by regioselective *ortho*-lithiation of 2-naphthylsulfonamides, followed by reaction with diphenylphosphine, and their catalytic activity was evaluated in Pd-catalyzed asymmetric allylic substitution, whereby the products were obtained with low to moderate asymmetric induction;

- ✓ Optimized procedure for the synthesis of chirally modified ferrocenesulfonamides was developed allowing efficient introduction of different chiral substituents;

✓ A practical procedure for the synthesis of 1,2-disubstituted planar chiral ferrocenes has been developed based on optimization studies on the diastereoselective *ortho*-lithiation of ferrocene directed by chirally modified sulfonamide groups. Isolation of individual diastereoisomers bearing, apart from the sulfonamide substituent, other functionalities, including chiral groups, was achieved using efficient separation techniques;

- Convenient approach for configuration determination of the synthesized 1,2-disubstituted planar chiral ferrocene derivatives is developed by applying a number of NMR experiments. The planar configurations were confirmed by X-ray crystal structure analysis;

- The *in vitro* antibacterial activity of 11 new compounds against standard laboratory strain H₃₇Rv and multidrug-resistant strain 43 of *Mycobacterium tuberculosis* was determined.

The scientific results are formed in three articles published in *ChemSusChem* (Q1), *Organometallics* (Q1) (in press) and *Monatshefte für Chemie* (Q3). In two of the articles Martin Ravutsov is the first author, and in the third - the second. There are 3 citations to two of the articles. The results of the thesis have been reported at 12 scientific forums, of which 9 are international and 8 of them have been held abroad. In 8 of the reports the PhD student is the first author, and in four - the second.

The overall exposition of the thesis leaves no doubt about the reliability of the obtained experimental data and the way of their interpretation. I have no doubt in the significant contribution of the thesis in the implementation of the set goals and objectives, as the results obtained and the scientific contributions are the personal merit of PhD student Martin Ravutsov, of course, with the significant mentoring of his supervisors.

Methodologically original and contributing to better clarity is the placement at the end of the thesis of the section "Outlook of future studies", in which the focus of future research is on the following two aspects:

- Further optimization of the reaction conditions for *ortho*-lithiation of ferrocensulfonamide **4.30*exo*** as the most active compounds are derivatives of this substrate; and

- Study of the influence of other pharmacophore groups on antimycobacterial activity. The natural lactone ternatolide was selected as a potential candidate in this aspect, for the synthesis of which preliminary experiments of two approaches were carried out: a) from biorenewable furfuryl alcohol, and b) "green" method by reaction of Ir-catalyzed isomerization of the double C-C bond. In addition, the effect of aliphatic moieties on biological activity by modifying ferrocene derivatives with acyclic substituents will be investigated.

The thesis abstract accurately and correctly reflects in summary form the content of the thesis and is written in accordance with the established rules.

In general, the thesis and accompanying materials submitted for review meet the requirements of the regulations. I will refrain from technical remarks, which are always there, because they are not as important as, for example, remarks regarding chemical language and style - in some places in the thesis it is not clear and precise enough. In addition, in the author's abstract, some inaccuracies, such as the construction of some sentences (reverse word order), were obviously admitted in his translation from English.

Although I know Martin Ravutsov vaguely (mostly from our participation in conferences), I have no personal impressions of his qualities, but judging by his thesis, he undoubtedly has a very good theoretical and experimental background, based on which I can state that they were productive in the implementation of his research work, carried out under the guidance of Prof. Dr. Vladimir Dimitrov, PhD, DSc and Assoc. Prof. Dr. Georgi Dobrikov, PhD.

CONCLUSION

Martin Ravutsov's thesis is an in-depth and systematic study in the current field of organic synthesis and contains original research on the synthesis of chiral compounds with application in asymmetric synthesis and study of their *in vitro* antibacterial activity. The work performed is significant in volume and variety in nature, which gives reason to assume that the PhD student has gained sufficient experience and opportunities to conduct independent research in the field of organic synthesis.

The thesis contains scientific and applied scientific results, which represent an original contribution to science and meet all the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Rules for the implementation of the LDASRB and the Rules for the acquisition of scientific degrees and academic positions at IOCCF-BAS.. The thesis shows that the PhD student Martin Ravutsov has in-depth theoretical knowledge and professional skills in the scientific specialty of Organic Chemistry by demonstrating qualities and skills for independent research.

All the above motivates me to give without hesitation *a positive assessment* of the study, presented by the above peer-reviewed thesis, abstract, results and contributions, I would like to suggest the Honorable Scientific Jury to award *the educational and scientific degree **doctor (PhD)*** to **Martin Antoniev Ravutsov** in the field of higher education: **4. Natural Sciences, Mathematics and Informatics**, professional field **4.2. Chemical Sciences, Organic Chemistry** Doctoral Programme.

11. 02. 2021
Sofia

Reviewer:
(Prof. Dr. Valerij Christov, PhD, DSc)