

REVIEW

by Assoc. Prof. Dr. Yulian Dimitrov Zagranjarski

Sofia University "St. Kliment Ohridski", Faculty of Chemistry and Pharmacy, member of the scientific jury, according to order № RD-09-1179 / 03.07.2020 of the Director of IOCCP-BAS, of a dissertation paper to award the academic and scientific degree Doctor in the field of higher education 4. Natural sciences, mathematics and informatics professional field 4.2.

Chemical sciences, professional field "Organic Chemistry"

Author: assistant Krasimira Petkova Dikova

Topic: "Betti-condensation – an instrument for preparation of chiral aminomethylnaphthols"

Scientific advisers: 1. Prof. Vladimir Dimitrov

2. Assoc. Prof. Dr. Kalina Kostova

The dissertation, the abstract and the paper and electronic documents presented by the assistant Krasimira Petkova Dikova meet the requirements of the Academic Staff Development Act in the Republic of Bulgaria, and the Regulations on the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Positions at IOCCP-BAS and include the following documents: an application for admission to defense; an autobiography; a copy of the diploma for completed master's degree; protocols from successfully passed exams according to an individual training plan; dissertation work; an abstract in Bulgarian and English; a list and copies of scientific publications on the dissertation topic; a list of noticed citations; a list of participations in scientific forums; a list of participations in projects. The documents are well designed and systematized.

1. General presentation

Krasimira Petkova Dikova graduated from the Faculty of Chemistry and Pharmacy at Sofia University "St. Kl. Ohridski"- as a master in Chemistry in 2001. During the period 2002 – 2004, she worked as a chemist specialist in the laboratory "Organic Synthesis and Stereochemistry" and since 2004, she has been appointed as an assistant in this laboratory. Assistant Krasimira Dikova

speaks English and Russian, works with a highly effective liquid chromatograph; a gas chromatograph, polarimeter, standard and specialized chemical computer programs.

- Krasimira Petkova Dikova presented a dissertation paper, written on 165 pages, structured as follows:
- Content (4 pages)
- Introduction (2 pages).
- Goals and objectives (1 page) in which the goals of the dissertation are set.
- Literature review (55 pages). The review considers different variations and features of the Betty condensation reaction. Great attention is also paid to the enantioselective addition of dialkylzinc compounds to aldehydes catalyzed by chiral amino alcohols and aminomethylnaphthols of the "*Betti* bases" type.
- Results and discussion (55 pages) in which the results of the experimental work are discussed.
- Conclusions (1 page) - the contributions of the conducted research are presented.
- Experimental part (38 pages) - presents the experimental procedures by which the synthetic studies were performed, as well as the data for the spectral characterization of the newly obtained compounds.
- References - 165 literature sources are cited (5 pages). Most of the cited literature sources have been published after 2000, which shows the relevance of the studied issues.
- The dissertation is illustrated with 97 schemes, 15 figures and 39 tables.

2. Main contributions of the dissertation paper

The dissertation of Assistant Krasimira Dikova has a fundamental character in the field of organic synthesis and stereochemistry. The presented results definitely have a practical orientation. The dissertation of Assistant Krasimira Dikova clearly outlines three main goals, namely:

- synthesis of new chiral ligands of *Betti* type using ferrocene and ruthenocene carbaldehyde, as well as aromatic aldehydes 1-pyrenecarbaldehyde, 2-

fluorencarbaldehyde and 1-naphthaldehyde as aldehyde components with 2-naphthol or 3-methoxy-2-naphthol as naphthol components, and (*S*)-phenylethylamine or (*S*)-leucinol as the amino component;

- determination of the relative configuration of the newly formed stereogenic center by means of modern NMR techniques and X-ray diffraction analysis;
- application of the newly obtained diastereoisomerically pure aminomethylnaphthols as catalysts in the model reaction for enantioselective addition of diethylzinc to aldehydes;

The main contributions and merits of the dissertation can be summarized as follows:

- ✓ Metallocene-substituted chiral, non-racemic aminomethylnaphthols were synthesized and isolated by three-component *Betti* condensation of ferrocene- or ruthenocenecarbaldehyde, 2-naphthol or 3-methoxy-2-naphthol and (*S*)-(-)-phenylethylamine;
- ✓ Chiral, non-racemic aminomethylnaphthols were synthesized and isolated by three-component *Betti* condensation of 1-pyrenecarbaldehyde and 2-fluorencarbaldehyde, 2-naphthol and (*S*)-(-)-phenylethylamine;
- ✓ (*S*)-leucinol was used as the amino component and source of chirality for the synthesis of chiral, non-racemic aminomethylnaphthols by three-component *Betti* condensation with 1-naphthaldehyde and 2-naphthol.
- ✓ All chiral, non-racemic aminomethylnaphthols of the *Betti* type were transformed to the corresponding dihydrooxazines in almost quantitative yields.
- ✓ Chiral aminomethylnaphthols and their corresponding dihydrooxazines were characterized by ¹H and ¹³C NMR spectroscopy and two-dimensional spectra: a homonuclear correlation (COSY), a heteronuclear correlation with one-quantum coherence (HSQC), a heteronuclear two-cell correlation in several Overhauser nuclear effect (NOESY), a mass spectrometry, an elemental analysis and an angle of rotation.
- ✓ The relative configuration of all synthesized chiral aminomethylnaphthols and the corresponding dihydrooxazines was determined by means of modern NMR techniques and X-ray diffraction analysis (of some of the compounds).

- ✓ The applicability of the NMR spectroscopy as a method for determining the configuration of the newly formed stereogenic centers of the chiral aminomethylnaphthols has been proven. The validity of the approach has been proven by an X-ray diffraction analysis.
- ✓ All chiral, non-racemic aminomethylnaphthols of the *Betti* type were used in a model reaction as catalysts for the enantioselective addition of diethylzinc to aldehydes, achieving a high degree of enantioselectivity (up to 93% *ee*).
- ✓ In addition, it was studied the effectiveness of the natural alkaloids quinine and (–)-ephedrine, the amino alcohol (*S*)-prolinol, as well as the amino acids L-proline and L-phenylalanine as chiral catalysts for enantioselective addition of diethylzinc to various aldehydes.

The presented results show that assistant Krasimira Dikova has developed as a specialist in the field of organic synthesis, who skillfully handles modern instrumental methods.

3. Evaluation of the dissertation

The dissertation is written consistently and clearly and contains novel contributions to research and results. The scientific results have a certain value and are achieved through appropriate methods and approaches. The impression of the precisely conducted experiment, the correctly described synthesis procedures and the detailed spectral characterization of the compounds is very good. It can be noted that Dikova has mastered and successfully applied modern methods for synthesis and spectral study of organic compounds in her work, i.e. the academic goals of the doctoral program have been fulfilled.

The conducted researches have scientific and scientific-applied contributions enriching the existing knowledge in the field of organic synthesis - in the direction of synthesis of new chiral, non-racemic aminomethylnaphthols of *Betti*-type.

4. Scientometric indicators

The results of Krasimira Petkova Dikova's dissertation are summarized in two publications in peer-reviewed journals - *Bulgarian Chemical Communications* (Q4, IF 0.64 for 2019-2020) and *Polyhedron* (Q2, IF 2.27 for 2019-2020). The doctoral student is the first author in both articles, which confirms her personal participation in the elaboration and interpretation of the published results. There is only one quote from the first article, which I attribute to the recent appearance in

the international press. The results of the dissertation are presented in 11 poster presentations at international scientific forums. Krasimira Dikova is a participant in 16 research projects - European, national and industry-funded projects.

5. Abstract

The dissertation abstract consists of 39 pages, reflects fully and correctly the content of the dissertation and is written in accordance with the established rules.

6. Questions, critical remarks and recommendations

I have no significant critical remarks on the dissertation of Krasimira Petkova Dikova. However, some technical errors and inaccuracies are noted. I have a few remarks and questions:

- Schemes 4-5 (p. 72), 4-12 (p. 77), 4-16 (p. 80), 4-25 (p. 87) and 4-26 (p. 88), etc. are incorrectly written, and the reducing reagents should be written above the reaction arrow. Otherwise, their transformation has to be explained.
- On page 86, the term "N-Me derivatives" is used, which is incorrect.
- When chiral aminomethylnaphthols are used in the diethyl zinc model reaction, the volume of the used solvent is indicated on page 99, without specifying the concentration or the amount of the used diethyl zinc, which makes no sense.
- What does the phrase "the reaction was carried out in ethanol as solvent and heating in the range of 75 ° to 100 ° C" mean (page 68)? If the reaction was not carried out in a closed vessel, then this heating interval does not make sense.

CONCLUSION:

Krasimira Dikova's dissertation fully meets the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for its application (LDASRB) and the Regulations for the conditions and procedures for acquiring scientific degrees and holding academic positions at BAS and IOCCP-BAS.

Assistant Dikova's dissertation is a continuation of the traditional research of the group of Organic Synthesis and Stereochemistry. As part of the dissertation, Assistant Dikova has performed a large amount of experimental work in the current scientific field of synthesis and transformation of aminomethylnaphthol derivatives of *Betti* type.

The knowledge and skills acquired by doctoral student Krasimira Dikova during the elaboration of the dissertation and the achieved scientific results allow me to recommend to the esteemed Scientific Jury to award assistant Krasimira Dikova the academic and scientific degree "Doctor" in higher education: 4. Natural sciences, mathematics and informatics professional field 4.2. Chemical sciences, specialty "Organic chemistry".

26.08.2020

Sofia

Reviewer:

Assoc. Prof. Dr. Yulian Zagranyski