R E V I E W

By Assoc. Prof. Dr. Georgi Kostadinov Stavrakov,
Faculty of Pharmacy, Medical University of Sofia

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: Krasimira Petkova Dikova

Subject: Betty-condensation – an instrument for preparation of chiral aminomethylnaphthols

Scientific Advisors: Prof. DSc. Vladimir Dimitrov and Assoc. Prof. Dr. Kalina Kostova

General description of the presented materials

According to order № РД-09-179/03.07.2020 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 assistant Krasimira Petkova Dikova, PhD student in independent training at IOCCP-BAS, in professional field 4.2. Chemical Sciences, Scientific Specialty "Organic Chemistry". The title of the thesis is: " Betty-condensation – an instrument for preparation of chiral aminomethylnaphthols". 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, 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 on the topic of the thesis; list of noticed citations; list of participations in scientific events; award for best poster; list of participations in projects; separation protocol between the authors Krasimira Dikova and Mariana Kamenova-Nacheva.

Brief biographical data about the PhD student

Krasimira Dikova graduated from Sofia University "St. Kliment Ohridski", Faculty of Chemistry in 2001 with a Master's degree in Chemistry, specialization in "Organic and Analytical Chemistry" with an average grade of "Very Good", and a diploma thesis with "Excellent" grade. In 2002 she started working in the laboratory "Organic Synthesis and Stereochemistry" at IOCCP-BAS and held the following positions: Chemist-specialist; Research Associate III grade; Assistant. The PhD student speaks English and Russian, works with high-performance liquid chromatograph; gas chromatograph, polarimeter and NMR spectrometer.

Krasimira Dikova is a co-author of 2 scientific publications, in which she is the first author. The results of her scientific work are presented at 11 scientific forums. She has participated in 16 research projects funded by the Bulgarian National Science Fund, SCOPES, 7th FP of the EU, pharmaceutical companies.

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. Asymmetric catalysis, on the other hand, is very promising because it is effective in a larger number of transformations than any of the other methods of the enantioselective synthesis.

The PhD thesis of Krasimira Dikova outlines two main goals: the diastereoselective synthesis of new chiral amino alcohols of the "Betti base" type and their use as ligands in the reaction of addition of dialkylzinc compounds to aldehydes. In the present work, the mechanism of diastereoselective three-component Betti condensation has been studied in detail. With the help of the latter, six types of chiral aminomethylnaphthols were synthesized, and used as asymmetric catalysts. Further on, chiral ligands based on natural compounds have been studied.

Knowledge of the problem

In the PhD thesis are cited 165 literature sources in renowned journals, which demonstrates that the doctoral student is well acquainted with the state of the problem. The literature review is structured in two sections. In the first part the Betti condensation is considered as a practical tool for the synthesis of functionalized aminomethylnaphthols. The peculiarities of this three-component condensation of aldehyde, naphthol and amine depending on the variation of the individual components are discussed in detail. The already known chiral variants of Betti condensation are also described in detail. The second part of the literature review is devoted to the enantioselective addition of dialkylzinc reagents to aldehydes catalyzed by chiral amino alcohols. The attention is focused on catalysis with chiral aminomethylnaphthols of the "Betti base" type. The enantioselective synthesis of diarylmethanols using arylboronic acids and dialkylzinc reagents catalyzed by chiral amino alcohols is also considered.

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.

In the PhD thesis is described the synthesis of ferrocene and ruthenocene substituted chiral aminonaphthols, which were subsequently converted to the corresponding dihydroxazines. Other ligands also synthesized by Betti condensations were chiral aminomethylnaphthols involving aldehydes with condensed aromatic rings, which were also transformed to the corresponding dihydroxazines. Finally, the amine component of the condensation reaction was successfully replaced with (*S*)-2-amino-4-methyl-pentanol. The absolute configuration of the synthesized chiral compounds was determined by NMR techniques and further confirmed by X-ray analysis. The newly obtained ligands were used as catalysts in the model reaction of enantioselective addition of diethylzinc to aldehydes.

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 165 pages and includes: introduction (2 pages), goals and tasks (1 page), literature review (55 pages), results and discussion (55 pages), conclusions (1 p.), experimental part (38 p.) and literature (5 p.). 165 literature sources are cited. The results of the dissertation are presented and discussed in three main sections: 1) Synthesis of chiral aminomethylnaphthols; 2) Application of the newly obtained compounds as chiral catalysts; 3) Study of chiral ligands based on natural compounds. A good impression is made by the correct description of the experimental procedures and the detailed characterization of the newly synthesized compounds.

Contributions and significance of development for science and practice

The PhD thesis of Krasimira Dikova is of fundamental importance to science. It would be of practical importance if the newly synthesized chiral substances are additionally explored for their properties as ligands and catalysts. The main contributions and merits of the dissertation can be summarized as follows:

- A series of new chiral aminomethylnaphthols was synthesized with high diastereoselectivity by means of three-component Betti condensation.
- It is demonstrated the possible application of functionalized chiral amines in the three-component Betti condensation.
- NMR spectroscopy was used to determine the configuration of the newly formed stereogenic centers.
- A high degree of enantioselectivity was achieved (up to 93% *ee*) when using the synthesized chiral aminomethylnaphthols as catalysts for enantioselective addition of diethylzinc to aldehydes.
- The effectiveness of a series of alkaloids as catalysts for the enantioselective addition of diethylzinc to ferrocenecarbaldehyde and to benzaldehyde has been studied.

Assessment of the publications and personal participation of the PhD student

The scientific results from the thesis of Krasimira Dikova have been partly published in two scientific publications. The PhD student is the first author in both articles, which confirms her personal participation in the elaboration and interpretation of the published results. There are eleven participants in scientific conferences in the form of poster presentations: four in national and seven in international scientific forums. In five of the presentations the doctoral student is the first author.

Abstract

The abstract of the thesis of Krassimira Dikova is 39 pages long and meets all the desired requirements. It correctly reflects the main results, notes the scientific contributions, participation in scientific forums and publications connected with the PhD thesis.

Critical remarks and recommendations

After a critical reading of the thesis, some remarks and questions arise, which in no way diminish the significance of the achieved results.

Subsection 3.1.2.3. "The Betti condensation mechanism" deals with the diastereoselectivity control during the reaction and, in my opinion, should be moved to section 3.1.3. with a changed title, namely: "Mechanism of the diastereoselective Betty condensation".

The literature quotations are placed repeatedly without following any rules in the middle of the sentences and not after a comma or a period, as accepted in scientific literature.

In Scheme 3-27, the chiral center of compound **3-68** is marked with 1, which I accept as a technical error that needs to be corrected. In Scheme 3-35 in the structure of quinidine is forgotten the nitrogen of the quinuclidine ring.

The Betti bases obtained with reduced leucine **4-33a/b** are amino diols that easily turns into racemic mixture over time, as demonstrated in the thesis. Although the competition of the two hydroxyl groups in combination with racemization, these compounds have been used as chiral catalysts and demonstrate expectedly low enantioselectivities. Why their oxazine derivatives **4-34a/b**, which lack the above-described disadvantages, were not used as catalysts?

Section 4.7 states: "1-Ferrocenyl-1-propanol (**4-38**) can be relatively easily transformed into dialkylamino derivative **A** with retention of the configuration". In this case, I expect the transformation to go through a Walden inversion of the configuration. I suggest the text to be changed to: "… dialkylamino derivative **A** while preserving the chiral center".

Personal impressions

I have known Krasimira Dikova personally since 2004. I have built my personal impressions both during our work in the laboratory "OSS" and subsequently as an employee of the Faculty of Pharmacy, MU-Sofia, continuing to have active cooperation with IOCCP, BAS. Krassimira Dikova is a good person and colleague who can always be relied on.

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 **Krasimira Petkova Dikova** 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 Krasimira Petkova Dikova in the field of higher education: 4. Natural sciences, mathematics and informatics; 4.2. Chemical sciences; Scientific Specialty "Organic Chemistry".

09.08.2020 Reviewer:……

Assoc. Prof. Georgi Stavrakov