R E V I E W

By Assoc. Prof. Dr. Irena Lyubomirova Philipova,
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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: Maya Trifonova Tavlinova-Kirilova

Subject: Chiral aminobenzyl-naphthols and -quinolinols and dihydro-1,3-naphthoxazines - synthesis and catalytic applications

Scientific Advisors: Assoc. Prof. Dr. Kalina Kostova and Assist. Prof. Mariana Kamenova-Nacheva, PhD

General description of the presented materials

According to order № RD-06/19.01.2024 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 Maya Trifonova Tavlinova-Kirilova, 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: " Chiral aminobenzyl-naphthols and -quinolinols and dihydro-1,3-naphthoxazines - synthesis and catalytic applications" 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: application form; autobiography; a copy of the diploma for completed master's degree; protocols from successfully passed exams according to an individual training plan; PhD thesis; 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; list of participations in projects; protocols from successfully passed exams according to an individual training plan. The documents are well organized.

Brief biographical data about the PhD student

Assistant Maya Tavlinova graduated from Sofia University "St. Kliment Ohridski", Faculty of Chemistry in 2000 with a Master's degree in Organic and Analytical Chemistry. During the period 2000-2005, she worked as a specialist chemist in the "Organic Synthesis and Stereochemistry" laboratory, and from 2005 she was appointed as an assistant in the same laboratory. Since June 2021, she has been enrolled as a PhD student of free training at the Institute of Organic Chemistry with Centre of Phytochemistry-BAS. Maya Tavlinova is the co-author of 3 scientific publications, in two of which she is the first author. She has participated in 23 scientific research projects funded by FNI, the SCOPES program of the Swiss Research

Support Fund, the 7th FP of the EU, the Horizon 2020 program of the EC, INFRAMAT, Pobelch Gle, EthnoHERBS, CNM Technologies-Germany, Operational Program Science and Education for Smart Growth (OP NOIR) to create a Center of Competence.

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

Assistant Professor Maya Tavlinova's thesis is in the field of stereoselective organic synthesis. Asymmetric synthesis, or the creation of stereoisomeric pure compounds, continues to be a highly topical area of organic chemistry. Obtaining structurally diverse multifunctional compounds in one step is an attractive area for developments. *Mannich* and *Betti* condensations provide possibilities for the synthesis of chiral aminonaphthols, aminobenzylnaphthols and their analogues with application as ligands and catalysts, as well as intermediates for obtaining biologically active substances. Of particular interest are applications where such compounds are used as ligands for enantioselective nucleophilic addition reactions to carbonyl compounds. The resulting chiral secondary alcohols can be used for the synthesis of biologically active compounds and are often a component of natural products. Any enantioselective process requires fine-tuning therefore a multitude of chiral ligands is justified from both a scientific and an industrial point of view. In this regard, the topic is definitely relevant and the achieved results are in a promising scientific field.

The main goal of the thesis is the application of the three-component condensations according to *Mannich* and *Betti* to obtain new chiral, non-racemic dihydro-1,3-naphthoxazines, *N*-substituted aminomethylnaphthols, aminobenzyl-naphthols and -quinolinols in order to use them as ligands in enantioselective reactions. The set goals and tasks are in a logical sequence: synthesis and proof of the structure of the new compounds, application of the synthesized enantiomerically pure aminobenzyl-naphthols and -quinolinols as ligands in the model reaction for the enantioselective addition of diethylzinc to aldehydes.

Knowledge of the problem

The literature review of the thesis covers 187 literature sources in renowned journals, which shows that the PhD student is well acquainted with the state of the problem. At the beginning of the literature review, the usefulness of multicomponent reactions for the preparation of structurally diverse multifunctional compounds by one-step transformation is substantiated. The next few chapters are devoted to *Mannich* condensation reactions. The mechanism and reaction conditions that determine the preferred reaction pathway of the reaction are described in detail. The enantioselective and catalytic variations of the reaction depending on the components and reaction conditions are thoroughly reviewed: aminomethylation of phenols and naphthols; preparation of bis-dihydro-1,3-oxazines using polyhydroxy aromatic systems; reactions using diamines. The next section considers *Betti* condensation as a specific case of *Mannich* condensation. The mechanism and features of this three-component reaction depending on the variation of the individual components are described in detail. Particular attention is paid to the synthesis of aminobenzyl-quinolinols and -isoquinolinols. The last part of the literature review is devoted to the enantioselective addition of diethylzinc to aldehydes catalyzed by chiral aminobenzylnaphthols ("*Betti* bases"). The section systematizes the current knowledge on the synthesis of functionalized secondary aminoalkylnaphthols possessing a rich structural diversity by varying the reaction components: aldehyde, naphthol, and chiral amine, as

well as their application as catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes.

Research methodology

Within the thesis a significant experimental work is demonstrated. A complex of chemical synthesis methods has been mastered: carrying out organometallic reactions in an inert medium, synthesis of new chiral ligands for asymmetric transformations, carrying out stereoselective reactions creating C-C bonds, isolating the products in pure form using column chromatography and recrystallization, characterization and proof of the structure of the newly synthesized substances through the application of NMR spectroscopy, mass spectrometry, specific angle of rotation; melting points and elemental analysis. Within the framework of the thesis, structurally diverse dihydro-1,3-naphthoxazines and dihydro-1,3-oxazinequinolinols were synthesized by *Mannich* condensation of naphthalen-2-ol or quinolinol, formaldehyde and chiral amines, which were subsequently reduced to the corresponding aminomethyl- naphthols and -quinolinols. By means of *Betti* condensation of quinoline analogues of naphthalene-2-ol with aromatic aldehydes and chiral amines, a series of aminobenzylquinolinols have been prepared. The *Mannich* condensation of naphthalene-2-ol with enantiomerically pure (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine and paraformaldehyde was also investigated, as well as of naphthalenediols with (*S*)-(-)-1-phenylethan-1-amine. The absolute configuration of some of the synthesized chiral compounds was determined using NMR techniques and further confirmed by X-ray structural analysis. The newly obtained ligands were applied as catalysts in the model reaction of enantioselective addition of diethylzinc to aldehydes.

Characteristics and evaluation of the thesis

The thesis is well organized and structured and meets the established requirements. The exposition of the material in the thesis is formed on 220 pages and includes: introduction (2 pages), goals and tasks (1 page), literature review (92 pages), results and discussion (60 pages), conclusions (3 page), experimental part (40 pages) and literature (9 pages). 187 literature sources are cited. The thesis is clearly written in good scientific language. A very good impression is made by the correct and detailed description of the synthetic experiments, as well as the detailed spectral characterization of the obtained compounds and the unambiguous establishment of the structure and stereochemistry of the new compounds by applying a combination of modern NMR techniques and X-ray diffraction analysis.

Contributions and significance of development for science and practice

The PhD thesis of Maya Tavlinova has a fundamental character in the field of organic synthesis, although with a practical focus. The results of the research conducted on the methods of synthesis of functionalized chiral *N*-substituted aminomethylnaphthols, aminobenzyl-naphthols and -quinolinols are presented with an emphasis on their application as catalysts in reactions of enantioselective addition of diethylzinc to aldehydes.

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

- A series of new dihydro-1,3-naphthoxazines and dihydro-1,3-oxazinquinolinols were synthesized, which were successfully transformed into the corresponding aminomethyl-naphthols and -quinolinols.

- The methyl ester of (*R*)-(−)-2-phenylglycine as well as (*R*)-(−)-2-phenylglycinol were used as amine components and source of chirality for the synthesis of chiral, non-racemic aminomethylnaphthols *via* the *Mannich* condensation of 2-naphthol and paraformaldehyde. It has been shown that the reaction proceeds with preservation of the configuration of the starting chiral component.

- *Mannich* condensation of naphthalene-2-ol, formaldehyde and enantiomerically pure (*R,R*)- or (*S,S*)-cyclohexane-1,2-diamine was carried out. Conditions for preferential formation of chiral, non-racemic imidazolidine bis-hydroxynaphthalene were optimized.

- A large number of chiral aminobenzylquinolinols have been synthesized and isolated in diastereomerically pure form by means of a three-component *Betti*-type condensation of quinoline analogues of naphthalene-2-ol with aromatic aldehydes and chiral amines.

- The newly synthesized chiral compounds were fully characterized using NMR spectroscopy, mass spectrometry, specific rotation angle and elemental analysis.

- An NMR approach was applied to determine the newly formed stereogenic center of aminobenzylquinolinol **4-40a**. The absolute configuration determined by this approach was confirmed using X-ray diffraction analysis.

- Chiral *N*-methylaminonaphthols, imidazolidines and aminobenzyl-quinolinols isolated in diastereomerically pure form were evaluated as ligands in the model reaction of enantioselective addition of diethylzinc to various aldehydes, achieving enantioselectivity up to 98% *ee*.

- Antimicrobial and antiviral activity of selected compounds was evaluated. Established antimicrobial activity against *Bacillus cereus* and *Staphylococcus aureus*.

Assessment of the publications

The scientific results of the thesis of Assistant Maya Tavlinova have been published in three scientific publications: two in *Bulg. Chem. Comm.* and one in *Crystals*. The PhD student is the first author in two of the articles, which confirms her personal involvement in the development and interpretation of the published results. Two citations to first article noted. The results of her scientific work have been presented at seven scientific forums with poster presentations. In two of the posters, Maya Tavlinova is the first author.

Personal participation of the PhD student

I have no doubts about the personal participation of Maya Tavlinova in the implementation of the tasks and the achievement of scientific results and contributions to the thesis, of course under the guidance of her supervisors.

Abstract

The abstract of the thesis is 40 pages long. It is written in accordance with the established rules and accurately and correctly reflects the main results achieved in the thesis in summary form. The conclusions and scientific contributions, publications and participation in scientific forums in connection with the thesis are noted.

Critical remarks and recommendations

I have no significant critical comments on the PhD thesis of Assistant Maya Tavlinova. The PhD thesis is carefully written. The following two questions arose:

- Using (*R*)-(−)-2-phenylglycine (**4-8**) in a modified *Mannich* reaction, no product formation was observed (Scheme 4-5). Do you have an explanation for the lack of reaction?

- In the addition reaction of Grignard reagent to Schiff base **4-26**, you used a large excess of phenylmagnesium bromide, I assume because of the presence of phenolic hydroxyl groups (section 4.4.2.). Have you tried to protect preliminarily the hydroxyl groups?

Personal impressions

I have known Maya Tavlinova personally since she joined the "Organic Synthesis and Stereochemistry" laboratory, and I have very good impressions of her as a diligent and experienced chemist. Her experimental training, strengthened by long-term work in the "OSS" laboratory, has helped to realize her research work, carried out under the guidance of Assoc. Prof. Kalina Kostova.

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 **Maya Trifonova Tavlinova-Kirilova** 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"** of Maya Trifonova Tavlinova-Kirilova in the field of higher education: 4. Natural sciences, mathematics and informatics; 4.2. Chemical sciences; Scientific Specialty "Organic Chemistry".

01.03.2024 Reviewer:……

Sofia /Assoc. Prof. Irena Philipova/