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Ústav organické chemie a biochemie
Akademie věd České republiky, v. v. i.
Institute of Organic Chemistry and Biochemistry
of the Czech Academy of Sciences

Doctoral thesis report

Mgr. Ilaria Caivano

Charles University

Faculty of Science

"Synthesis of Aromatic Compounds Possessing the Fluorene Unit"

Reviewer:

RNDr. Ivo Starý, CSc.

IOCB Prague, CAS

Ilaria Caivano's PhD thesis focuses on the contemporary chemistry of interesting aromatic architectures and the study of their physicochemical properties. The main attention is paid to the synthesis of new functionalized spirobifluorenes and helical dispiroindenofluorenes, which combine the structural features of spirobifluorene and helicene in one molecule. The presented work is characterized by a large breadth of scope, as the subject of interest is also the detailed description of their structure, reaction mechanisms of their formation, optical properties of the prepared compounds, and attempts at the enantioselective synthesis of selected spirobifluorene-helicene hybrids. The present work is mainly experimental in nature.

Research on complex aromatic systems and their (chir)optical properties fits perfectly into modern trends in the field. One can even observe a renaissance of aromatic chemistry, inspired by the unprecedented development of modern synthetic methodologies and the discovery of new carbon allotropes (polyaromatics) in the last decades. The laboratory where Ilaria Caivano did her doctoral thesis cleverly combined the chemistry of spirobifluorenes and helicenes and recently developed efficient synthetic routes to these compounds. Ilaria Caivano then has continued on this course set and further developed an adequate synthetic methodology in a creative manner. The development of new emissive molecular systems, possibly chiral, is currently a "hot topic", especially in relation to their potential use in energy-saving display technologies. The work is thus in line with the most modern research trends on an international scene.

The doctoral thesis collects an above-average amount of literature data and own experimental results that are classically sorted. The "1 State of the Art" section (42 pp) comprehensively describes a variety of approaches to the synthesis of fluorene,

spirobifluorene, and dihydroindenofluorene derivatives. This literature review is detailed and well structured. It could serve as the basis for a useful review article.

In section "2 Aim of the Work" (3 pp) the general objectives and chosen methodologies are clearly described.

The key part of the thesis is "3 Results and Discussion" section (65 pp) describing her own experimental results. The extensive experimental data is organized into four parts. It is necessary to mention here that the author has chosen transition metal catalyzed alkyne cycloisomerization as the key reaction for building the target aromatic compounds and pays dominant attention to this highly efficient synthetic methodology. The most important results overlap with the subsections of the thesis: (a) A useful method for the preparation of a wide series of substituted spirobifluorenes has been developed and their basic photophysical properties have been measured. The author provides a convincing mechanistic rationale to explain the observed regioselectivity of intermolecular alkyne cycloisomerization. (b) A modular synthesis of a series of fluorinated helical dispiroindenofluorenes related to [5]-, [6]-, and [7]helicene has been developed to make these attractive compounds accessible in a straightforward way. It should be appreciated that the author attempted to apply enantioselective alkyne cycloisomerization to obtain these helicene-related molecules in a nonracemic form (however, with lower % ee). Considerable attention was paid to tuning the catalytic conditions of alkyne cycloisomerization, description of the structure of the compounds, and photophysical properties. (c) Finally, attention has been paid to the formation of unexpected minor by-products in the key cycloisomerization of alkynes to helical dispiroindenofluorenes, where the competitive dehydro-Diels-Alder reaction channel is discussed.

In section "4 Conclusion" (7 pp) the most important results obtained are concisely summarised.

In the "5 Experimental Part" (81 pages), the author describes the experiments performed in a standard way and also presents routine characterization of the prepared compounds, which generally corresponds to the needs of a scientific publication. The experiments are described in a convincing manner and the reviewer has no doubts about their validity, accuracy, and originality.

In the "7 References" section, the author lists 158 literature sources, which are continuously cited in the thesis.

Ilaria Caivano presents a doctoral thesis that is a useful scientific work and documents her ability to independently and successfully pursue modern academic research in the field of organic synthesis, chemistry of aromatics, photophysical characterisation, and catalysis by transition metal complexes. She presents her results clearly with a critical evaluation. The work contains only a small number of errors. Important parts of the doctoral thesis have already been published in peer-reviewed international journals (4 papers in *Tetrahedron*, *Catalysis*, *ChemPlusChem*, and *Catalysis Today*).

Formal comments:

The thesis is well written in English with minimal linguistic and formal errors.

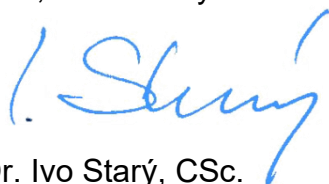
- (a) It is not ideal to combine three systems of numbering substances. It is a pity that the author did not use the simplest way, which is to use Arabic numerals in ascending order.
- (b) Intermediate **b** contains a pentavalent carbon atom, Scheme VIII, page 7.
- (c) The compound **LII** does not obey the Clar rule, Scheme XXI, page 13.
- (d) The word "cycloaddition" should be added after the term "[2+2+2]", the name of Scheme 15, page 64.
- (e) The correct abbreviation is UV-Vis (e.g. on page 78).

Questions for the defence:

- (a) Could the author explain what she means by the statement "... rigidity of the structure hinders recrystallization ...", page 19?
- (b) Could the author explain what she means by the statement "... sensitive to operational conditions ...", page 54?
- (c) Can the author explain why the ratio of *meta/ortho* regioisomers for substance **8I** is 17:1 (Scheme 13, page 55) when it was prepared from substance **3I** where the ratio is 5:1 (Scheme 8, page 50)?
- (d) Is the author really convinced of the mechanism where the sigma bond is formed between the electronegative oxygen of the nitro group and the carbanionic carbon of the lithiated biphenyl, intermediate **a**, Scheme 14, page 56?
- (e) The discussion of the configurational stability of compound **19** inferred from VT NMR spectra is questionable (lacking diastereotopic H), page 83-87. Why have the author not used racemisation on a chiral column at elevated temperature to determine the respective energy barrier (for a freely available computer simulation program, see Oliver Trapp's group, Munich)?
- (f) Although substance **27** was obtained in a nonracemic form (with known % ee), its chiroptical properties (specific rotation, ECD spectrum) have not been studied. Why?

In conclusion, I find that the doctoral thesis of Ilaria Caivano "Synthesis of Aromatic Compounds Possessing the Fluorene Unit" meets the standard requirements for doctoral theses in the field of organic chemistry, and therefore I unequivocally recommend this scientific work for defence.

Prague, 23 January 2022



RNDr. Ivo Starý, CSc.