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Review of the Doctoral Dissertation of MSc Joseph Patrick Milton entitled: *"Photochemical Generation of Carbenes and Radicals for C–C and C–X Bond Formations at the α-Position to the Carbonyl Moiety"*
submitted to the Scientific Council of the Institute of Organic Chemistry of the Polish Academy of Sciences in Warsaw for the purpose of obtaining the degree of Doctor of Chemical Sciences

The doctoral dissertation submitted for review by MSc Joseph Patrick Milton, prepared under the supervision of Prof. Dorota Gryko, is a monothematic work based on a series of original publications, enriched with a theoretical introduction and the author's own commentary. The subject of the dissertation is closely aligned with current, rapidly developing trends in modern organic chemistry, focusing on the development of photochemical methods for the generation of carbenes and radicals, and their application in the formation of C–C and C–X bonds at the α-position to the carbonyl group. This research topic addresses both the needs of sustainable synthesis and fundamental challenges in contemporary organic chemistry.

It is worth emphasizing that the research conducted under the guidance of Prof. Dorota Gryko has, for many years, been recognized and highly valued in the organic chemistry community, especially in the area of photochemistry and catalysis applied to the synthesis of heterocyclic compounds and biologically relevant systems. Prof. Gryko's team consistently publishes works of significant scientific value, contributing to the development of modern methods in organic synthesis.

In the introduction, the Author provides a highly competent and concise overview of the place of photochemistry in modern organic synthesis, highlighting the potential of this field for developing environmentally friendly methods and enabling the generation of reactive intermediates under conditions inaccessible by classical reactions. The thorough literature review, covering both classical and recent approaches to α-functionalization of carbonyl compounds, demonstrates the doctoral candidate's excellent command of the literature and his skill in critical analysis of sources.

The first of the works forming the basis of the dissertation is an extensive review article, published as a book chapter, in which the doctoral candidate systematically summarizes previous achievements in photochemical carbene generation from both diazo compounds and silyl ketones via the Brook rearrangement. The author discusses various reaction mechanisms, the potential of carbenes in cycloadditions, insertions, and ylide generation, as well as the role of direct photolysis and visible light. This publication serves as an excellent and comprehensive background for the author's own research and confirms his scientific maturity. The candidate's own experimental research is presented in three subsequent publications, each of which brings significant novelty and originality to contemporary organic synthesis. Particularly noteworthy is the work on photochemical cyclopropanation of diazo compounds in aqueous micellar systems. This work addresses the important issue of the toxicity of classical solvents (such as dichloromethane), replacing them with water and surfactants. It is important to note that while water as a reaction medium helps to avoid environmental problems, it also poses synthetic challenges—especially the competitive O–H insertion into the carbene, which can limit reaction yields. As the candidate points out, only a few methods for the photochemical use of diazo compounds in water are known in the literature, most of which require metal catalysts.

In this context, it should be acknowledged that the authors conducted a comprehensive optimization of reaction conditions, including the use of various surfactants, which is thoroughly documented in the Supporting Information. This optimization enabled the selection of the most effective system; however, a mechanistic explanation of the influence of hydrazones and ions present in solution on the selectivity of the reaction remains somewhat ambiguous. It seems advisable that, in the future, more in-depth mechanistic studies—such as kinetic, spectroscopic, or isotopic labeling experiments—be carried out to more precisely verify the proposed mechanism and clarify the role of individual components in the micellar system, particularly in terms of competing reaction pathways and the impact of the microenvironment on diastereoselectivity.

The next publication constitutes the first report on the use of 4-diazoisoquinoline-1,3(2H,4H)-diones in O–H, S–H, and C–H insertion reactions under LED irradiation. Of particular significance are the high yields of O–H insertion products with fluorinated alcohols, while less acidic alcohols proved to be significantly less reactive—a phenomenon the author explains by the proton transfer mechanism and the limited stabilization of the carbene. The synthesis and investigation of a new class of diazo compounds (4-diazo-2H-benzo[e][1,2]thiazin-3(4H)-one 1,1-dioxides) is a valuable addition and broadens the range of possible applications of these methods. It might be worth considering additional studies on the activation of less reactive alcohols, or comparing the efficiency of the reaction with the use of organometallic catalysts, as reported in the literature.

The third publication, concerns the stereoselective synthesis of amines by a photochemical HAT reaction with chiral N-sulfinyl imines. The optimized process allowed the synthesis of amines with very high enantiomeric purity (up to 99% ee) and high diastereoselectivity. The Author demonstrated a deep understanding of the factors influencing the reaction, although not all observed phenomena were fully explained (e.g., the low reactivity of certain imines and ketimines). I would gently suggest that, in the future, further mechanistic investigations (e.g., DFT calculations or kinetic studies) could help elucidate the reasons behind these observations.

It should be noted, however, that the section of the dissertation devoted to the discussion of results and their interpretation is limited to only seven pages of the author's own text. It is widely understood that scientific publications, which constitute the basis for the doctoral procedure, typically present only positive or best-documented results, whereas the dissertation itself provides space for more in-depth, personal reflection on the chosen reaction models, synthetic decisions, and the rationale behind particular research approaches. In this case, the reader misses a broader discussion of the motivations for selecting specific reaction models—whether they were based on the group's previous experience, literature premises, or other factors. Including a more detailed analysis of research strategies in the dissertation, addressing failures and limitations as well, would contribute to a more comprehensive understanding of the evolution of the adopted research hypothesis.

The experimental section constitutes a substantial part of the reviewed dissertation. It has been very well prepared and contains all necessary information.

The descriptions of the preparative procedures developed and the analytical techniques used have been presented in accordance with contemporary standards in organic chemistry and raise no concerns regarding their reproducibility. The target products have been properly characterized using appropriate analytical techniques.

The reviewed doctoral dissertation is written in correct language and demonstrates that the doctoral candidate correctly applies chemical and stereochemical nomenclature. The discussed topics have been accurately illustrated using clear reaction schemes and mechanisms. I read the dissertation with great interest. It is worth noting that the works forming the basis of the procedure are exceptionally consistent, allowing the evolution of the research hypothesis adopted at the beginning of the doctoral project to be clearly traced.

In summary, I state that the objective of the dissertation has been fully achieved. The reviewed dissertation demonstrates a very high standard of synthetic methodology and fully meets the requirements of contemporary organic chemistry. The research has produced valuable results, and the developed synthetic methodologies exhibit clear scientific novelty, significantly expanding the range of light-induced methods in organic synthesis. The dissertation is of high quality and unquestionably fulfills the criterion of originality.

Furthermore, I confirm that the dissertation meets all the formal requirements specified in the Act "Law on Higher Education and Science" (Journal of Laws of 2020, item 85, as amended, Title V, Chapter 2, Section 1), as well as the customary standards expected of candidates for the doctoral degree in the field of chemical sciences.

Based on the above, I submit to the Scientific Council of the Discipline “Chemical Sciences” at the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw, my recommendation to admit the Candidate, MSc Joseph Patrick Milton, to the subsequent stages of the doctoral procedure.

Signature Not Verified
Dokument podpisany przez Zbigniew Rafiński
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