

REVIEW

of the official reviewer for dissertation work of Amankulova Dinara on the theme: "Development of a method for non-catalytic synthesis of *meta*-aryloxyphenols from 1,3-cyclogexanedione", submitted for the degree of Doctor of Philosophy (PhD) in the Educational Program "8D07105 - Chemical technology of organic substances.

№	Criteria	Eligibility (one of the options must be checked)	Justification of the position of the official reviewer
1.	The topic of the thesis (as of the date of its approval) corresponds to the directions of development of science and/or state programs	<p>1.1 Compliance with priority areas of science development or government programs:</p> <p>1) The thesis was completed within the framework of a project or target program financed from the state budget (indicate the name and number of the project or program)</p> <p>2) The thesis was completed within the framework of another state program (indicate the name of the program)</p> <p><u>3) The dissertation corresponds to the priority direction of the development of science, approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan (indicate the direction)</u></p>	The dissertation was carried out aligning with the priorities of scientific development, as approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan. Specifically, it pertained to Scientific research in the field of natural sciences.
2.	Importance for science	The work makes /does not make a significant contribution to science, and its importance is well disclosed /not disclosed	The development of efficient and practical methods for the synthesis of meta-(aryloxy)phenols is of great importance due to their wide range of applications, including their use as synthetic intermediates and in medical and industrial applications. In this regard, work continues to develop more efficient and environmentally friendly methods for their synthesis, which will make it possible to use them more widely in various fields of chemistry. The work presented makes a significant contribution to science and its importance is well disclosed.

3.	The principle of independence	Self-reliance level: 1) High; 2) Medium; 3) Low; 4) No independence	The author made a significant contribution to the development and implementation of experiments, the solution of theoretical and practical problems, and the interpretation of the results. She also played a key role in the preparation and writing of a review article published in the journal "Molecules". Furthermore, the author synthesized 24 out of the 51 compounds discussed in an article published in the journal "Tetrahedron".
4.	The principle of inner unity	4.1 Justification of the relevance of the thesis: 1) Justified; 2) Partially justified; 3) Not justified.	The development of efficient and practical methods for the synthesis of meta-(aryloxy)phenols is of great importance due to their diverse range of applications, including their use as synthetic intermediates and in medicinal and industrial applications. As such, continued efforts are being made to develop more efficient and environmentally friendly methods for their synthesis, which will allow for their wider use in various fields of chemistry.
		4.2 The content of the thesis reflects the topic of the thesis: 1) Reflects; 2) Partially reflects; 3) Does not reflect	The content of the dissertation fully reflects the topic of the dissertation. The content of the dissertation fully reflects the topic of the dissertation. All sections of the dissertation address issues related to the non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione. The literature review presents methods for the synthesis of meta-aryloxyphenols using catalytic systems.
		4.3. The purpose and objectives correspond to the topic of the thesis: 1) correspond; 2) partially correspond; 3) do not correspond	The objective of the present dissertation research is to develop an efficient and novel method for the synthesis of meta-(aryloxy)phenols from 1,3-cyclohexanedione. To accomplish this goal, the following tasks were undertaken: - formation of 3-chlorocyclohex-2-en-1-one from cyclohexan-1,3-dione by utilizing the Vilsmeier reagent; - conduction of research on the conditions of obtaining 3-(aryloxy)cyclohex-2-en-1-one by nucleophilic substitution reaction; - introduction of a directing group by C(2) bromination of 3-(aryloxy)cyclohex-2-en-1-one; - conduction of research on the conditions of synthesis of meta-(aryloxy)phenols by oxidative aromatization; - representation technological schemes for the developed methods for the synthesis of intermediate and final compounds and calculate the material balance of production.
		4.4 All sections and provisions of the thesis are logically interconnected: 1) completely interconnected; 2) the interconnection is partial; 3) there is no interconnection	The thesis has internal unity; all sections and provisions of the dissertation are interconnected. The relevance of the research follows from the introductory part of the dissertation. The literature review examines the main ways to obtain meta-(aryloxy)phenols by catalytic methods. This is followed by the purpose of the study

			and the objectives to achieve the purpose. The objects of research and methods, novelty, theoretical and practical significance of the work are presented.
		4.5 The new solutions (principles, methods) proposed by the author are reasoned and evaluated in comparison with the known solutions: 1) there is a critical analysis; 2) partial analysis; 3) the analysis does not represent one's own opinions, but quotes from other authors	The new approach proposed by the author to the synthesis of meta-(aryloxy)phenols via cyclohexane-1,3-dione is reasoned and evaluated in comparison with known solutions. The results obtained were published in highly rated journals.
5.	Scientific novelty principle	5.1 Are the scientific results and provisions new? 1) completely new; <u>2) partially new (25-75% are new);</u> 3) not new (less than 25% are new)	Scientific results and provisions are new. A new and efficient method for the non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione in four steps. All steps don't required high temperature and don't involve any heavy metals or ligands were developed. The method has been successfully utilized to synthesize eight distinct meta-aryloxy phenols, four of which have not been previously documented in the literature. Additionally, the method has yielded 16 intermediate products, 14 of which have not been previously reported in literature. The chemical structures of newly synthesized compounds have been characterized for the first time using a combination of analytical techniques. New scientific results are reflected in the articles: Duvvuru B., Amankulova D., Gauden S., Haffemayer T., Clive D.L. A mild alternative to the classical Ullmann coupling for preparation of 3-aryloxy phenols // Tetrahedron - 2023. - Vol. 133. - Article Number 133264. https://doi.org/10.1016/j.tet.2023.133264 ; Amankulova D., Berganayeva G., Kudaibergenova B., Zhetpisbay D., Sharipova A., Dyusebaeva M. Recent Advances in the Synthesis and Applications of m-Aryloxy Phenols // Molecules. – 2023. – Vol. 28, 2657. https://doi.org/10.3390/molecules28062657
		5.2 Are the dissertation findings new? 1) completely new; <u>2) partially new (25-75% are new);</u> 3) not new (less than 25% are new)	The conclusions obtained in the dissertation are completely new. - 3-Chloro-cyclohex-2-en-1-one has been synthesized from cyclohexan-1,3-dione by utilizing Vilsmeier reagent. - Bromination reaction of 3-(aryloxy)cyclohex-2-en-1-one at position C(2) was performed for further directional aromatization to exclude the synthesis of para- and ortho- substituted phenols. 8 Compounds were synthesized by developed approach with average yield 72%; 7 of them have not been previously described in the literature.

			<p>- A novel synthetic approach was developed for the synthesis of meta-aryloxy phenols via aromatization reaction. Through systematic experimentation, DBU was identified as an effective base for aromatizing 2-bromo-3-(aryloxy)cyclohex-2-en-1-one to achieve the desired meta-aryloxy phenols. 8 Final compounds were synthesized by developed approach with average yield 66%; 4 of them have not been previously described in the literature.</p> <p>The conclusions of the dissertation are new and are reflected in the articles: Duvvuru B., Amankulova D., Gauden S., Haffemayer T., Clive D.L. A mild alternative to the classical Ullmann coupling for preparation of 3-aryloxy phenols // Tetrahedron - 2023. - Vol. 133. - Article Number 133264. https://doi.org/10.1016/j.tet.2023.133264</p>
		<p>5.3 Technical, technological, economic or management decisions are new and reasonable:</p> <p>1) completely new; 2) partially new (25-75% are new); 3) not new (less than 25% are new)</p>	<p>Technical and technological solutions are partially new (25-75% are new). I think so, since well-known equipment and technology are used for a new purpose.</p>
6.	The validity of the main findings	<p>All main conclusions are/are not based on scientifically significant evidence or well-grounded (for qualitative research and areas of training in the arts and humanities)</p>	<p>All major conclusions are based on scientifically sound evidence.</p> <p>- The chemical structures of the synthesized compounds were confirmed using multiple analytical techniques, including infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance spectroscopy.</p> <p>- Technological schemes detailing the developed methods for synthesizing intermediate and final compounds were presented. Additionally, material balances of production were calculated to assess the efficiency of the synthesis processes.</p>
7.	The main provisions for the defense	<p>It is necessary to answer the following questions for each provision separately:</p> <p>Provision 1</p> <p>7.1 Is the provision proven?</p> <p>1) proven; 2) rather proven; 3) rather not proven; 4) not proven</p> <p>7.2 Is it trivial?</p> <p>1) yes; 2) no</p> <p>7.3 Is it new?</p>	<p>1. A novel approach for synthesizing <i>meta</i>-(aryloxy)phenols via cyclohexane-1,3-dione has been devised, comprising a four-step synthesis protocol. The method has yielded eight <i>meta</i>-(aryloxy)phenols in high quantities, with an average yield of 66% for all eight compounds.</p> <p>2. The method avoids the need for operations to bypass the <i>ortho</i>-, <i>para</i>-directing effect of oxygen, resulting in a simplified and streamlined synthesis process. The required 1,3-functional group relationship is inherent in the readily available cyclohexane-1,3-dione starting material, allowing for easy access to the desired <i>meta</i>-(aryloxy)phenols</p>

	<p>1) yes; 2) no 7.4 Application level: 1) narrow; 2) medium; 3) wide 7.5 Is it proven in the article? 1) yes; 2) no</p> <p>Provision 2 7.1 Is the provision proven? 1) proven; 2) rather proven; 3) rather not proven; 4) not proven 7.2 Is it trivial? 1) yes; 2) no 7.3 Is it new? 1) yes; 2) no 7.4 Application level: 1) narrow; 2) medium; 3) wide 7.5 Is it proven in the article? 1) yes; 2) no</p> <p>Provision 3 7.1 Is the provision proven? 1) proven;</p>	<p>3. The synthesis method does not entail the use of heavy metals or ligands, rendering it a more ecologically sound and safer substitute to conventional techniques.</p> <p><i>Comments:</i></p> <p>Provision 1 7.1 The provision has been proven. A novel approach for synthesizing meta-(aryloxy)phenols via cyclohexane-1,3-dione has been devised, comprising a four-step synthesis protocol. The method has yielded eight meta-(aryloxy)phenols in high quantities, with an average yield of 66% for all eight compounds. 7.2 The new approach to the synthesis of meta-(aryloxy)phenols via cyclohexane-1,3-dione is not trivial. It includes a four-stage synthesis flow. Using this method, eight meta-(aryloxy)phenols are synthesized in yields greater than 66%. 7.3 The approach to the synthesis of meta-(aryloxy)phenols via cyclohexane-1,3-dione is new. It includes a four-stage synthesis flow. Using this method, eight meta-(aryloxy)phenols are synthesized in yields greater than 66%. The method avoids the need for operations to bypass the ortho-, para- directing effect of oxygen, resulting in a simplified and streamlined synthesis process. 7.4 Application level is medium. The developed method can also be used as a platform for the synthesis of novel meta-substituted phenolic compounds with tailored steric and electronic properties, which can be optimized for specific industrial and medicinal applications. 7.5 The provision has been proven in the articles. Duvvuru B., Amankulova D., Gauden S., Haffemayer T., Clive D.L. A mild alternative to the classical Ullmann coupling for preparation of 3-aryloxy phenols // Tetrahedron - 2023. - Vol. 133. - Article Number 133264. https://doi.org/10.1016/j.tet.2023.133264 ; Amankulova D., Berganayeva G., Kudaibergenova B., Zhetpisbay D., Sharipova A., Dyusebaeva M. Recent Advances in the Synthesis and Applications of m-Aryloxy Phenols // Molecules. – 2023. – Vol. 28, 2657. https://doi.org/10.3390/molecules28062657</p> <p>Provision 2</p>
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		<p>2) rather proven; 3) rather not proven; 4) not proven 7.2 Is it trivial? 1) yes; 2) no 7.3 Is it new? 1) yes; 2) no 7.4 Application level: 1) narrow; 2) medium; 3) wide 7.5 Is it proven in the article? 1) yes; 2) no</p>	<p>7.1 The provision has been proven. A novel approach for synthesizing meta-(aryloxy)phenols via cyclohexane-1,3-dione has been devised, comprising a four-step synthesis protocol. The method avoids the need for operations to bypass the ortho-, para- directing effect of oxygen, resulting in a simplified and streamlined synthesis process. The required 1,3-functional group relationship is inherent in the readily available cyclohexane-1,3-dione starting material, allowing for easy access to the desired meta-(aryloxy)phenols. This method contains formation of 3-chlorocyclohex-2-en-1-one from cyclohexan-1,3-dione by utilizing the Vilsmeier reagent; conduction of research on the conditions of obtaining 3-(aryloxy)cyclohex-2-en-1-one by nucleophilic substitution reaction; introduction of a directing group by C(2) bromination of 3-(aryloxy)cyclohex-2-en-1-one; conduction of research on the conditions of synthesis of meta-(aryloxy)phenols by oxidative aromatization</p> <p>7.2 The new approach to the synthesis of meta-(aryloxy)phenols via cyclohexane-1,3-dione is not trivial. It includes a four-stage synthesis flow. Using this method, eight meta-(aryloxy)phenols are synthesized in yields greater than 66%.</p> <p>7.3 The approach to the synthesis of meta-(aryloxy)phenols via cyclohexane-1,3-dione is new. It includes a four-stage synthesis flow. Using this method, eight meta-(aryloxy)phenols are synthesized in yields greater than 66%.</p> <p>7.4 Application level is medium. The developed method can also be used as a platform for the synthesis of novel meta-substituted phenolic compounds with tailored steric and electronic properties, which can be optimized for specific industrial and medicinal applications.</p> <p>7.5 The proven has been proven in the articles. Duvvuru B., Amankulova D., Gauden S., Haffemayer T., Clive D.L. A mild alternative to the classical Ullmann coupling for preparation of 3-aryloxy phenols // Tetrahedron - 2023. - Vol. 133. P.133264. https://doi.org/10.1016/j.tet.2023.133264 Amankulova, D., Berganayeva, G., Kudaibergenova, B., Zhetpisbay, D., Sharipova, A., Dyusebaeva, M. Recent Advances in the Synthesis and Applications of m-Aryloxy Phenols // Molecules. – 2023. – Vol. 28, 2657. https://doi.org/10.3390/molecules28062657</p>
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Amankulova D., Dyusebaeva M.A. Efficient and metal-free synthesis of m-aryloxy phenols via a three-step process // Farabi Alemi: International Scientific Conference of Students and Young Scientists. – Almaty: KazNU, - 2023. – P. 261.

Provision 3

7.1 The provision has been proven. The synthesis method does not entail the use of heavy metals or ligands, rendering it a more ecologically sound and safer substitute to conventional techniques.

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8.	The principle of reliability Reliability of sources and information provided	8.1 Choice of methodology - is justified or the methodology is described in sufficient detail 1) yes; 2) no	The methodology used in the dissertation is justified and described in detail in the experimental part of the work. All 4 stages of synthesis are described in detail and justified.
		8.2 The results of the thesis were obtained using modern methods of scientific research and methods of processing and interpreting data using computer technologies: 1) yes; 2) no	The work used modern methods of scientific research, such as mass spectrometry, IR spectroscopy, ^1H , ^{13}C NMR spectroscopy.
		8.3 Theoretical conclusions, models, identified relationships and patterns have been proven and confirmed by experimental research (for areas of training in pedagogical sciences, the results have been proven on the basis of a pedagogical experiment): 1) yes; 2) no	Theoretical conclusions regarding the production of meta-aryloxyphenols are confirmed by experimental results. Good yields of reaction products are obtained - above 66%. As a result of the experiments, 8 different meta-aryloxyphenols were obtained, 4 of which were not previously described in the literature.
		8.4 Important statements are confirmed / partially confirmed / not confirmed by references to current and reliable scientific literature	The results obtained in the work - the obtained meta-(aryloxy)phenols - their characteristics and indicators are confirmed by references to relevant and reliable scientific literature.
		8.5 Used literature sources are sufficient /not sufficient for a literature review	The list of references used includes 128 titles. This is quite enough to prepare a literature review.
9	Practical value principle	9.1 The thesis has theoretical value: 1) yes; 2) no	The theoretical significance of the developed method lies in the discovery of a new and efficient approach for the synthesis of meta-(aryloxy)phenols from 1,3-cyclohexanedione. This approach offers a unique alternative to the conventional

			methods that involve the use of heavy metals or ligands and require additional steps to bypass the ortho-, para- directing effect of oxygen.
		9.2 The thesis is of practical importance and there is a high probability of applying the results obtained in practice: 1) yes; 2) no	Meta-(aryloxy)phenols have a wide range of applications in various fields, including pharmaceuticals, agrochemicals, and dyes. The developed method can also be used as a platform for the synthesis of novel meta-substituted phenolic compounds with tailored steric and electronic properties, which can be optimized for specific industrial and medicinal applications.
		9.3 Are the practice suggestions new? 1) completely new ; 2) partially new (25-75% are new); 3) not new (less than 25% are new)	The efficient method for the non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione in four steps are completely new. All steps don't required high temperature and don't involve any heavy metals or ligands were developed.
10.	The quality of writing and design	Academic writing quality: 1) high ; 2) average; 3) below average; 4) low.	The quality of academic dissertation writing is high. <i>As a note, I believe that for 4 meta-(aryloxy)phenols not previously described in the literature, the Mass spectra and IR spectra could be presented in the Appendix.</i>

1) to award the degree of Doctor of Philosophy (PhD) in the educational program 8D07105 "Chemical technology of organic substances" Amankulova Dinara Erkinovna on the topic "Development of a method for non-catalytic synthesis of meta-aryloxyphenols from 1,3-cyclohexanedione".

Official Reviewer:

Professor of Sh. Ualihanov
Kokshetau University,
Candidate of Chemical Sciences
(place of work, academic title)

06.11.2023



Seilkhanov

(signature)

Seilkhanov Tulegen Muratovich
(FULL NAME)

