**VIETNAM NATIONAL UNIVERSITY - HCMC**
**HO CHI MINH CITY UNIVERSITY OF TECHNOLOGY**

**SOCIALIST REPUBLIC OF VIETNAM**
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# DISSERTATION INFORMATION

Title: **Transition metal-free synthesis and functionalization of 5- and 6-membered heterocyclic compounds**

Major: **Chemical Engineering** Major code: **9520301**

PhD candidate: **Huynh Van Tien**

Advisors: **1: Prof.Dr. Phan Thanh Son Nam**

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***Major Contributions of This Dissertation:*** In this thesis, the new facile and more environmentally friendly pathways to achieve 4-phenylquinazolines, 2-phenylquinoxalines, *N*-arylindoles, and 2-arylthiochromenones were demonstrated. These heterocyclic compounds have contained important frameworks, capable of high biological activity.

For the synthesis of 4-phenylquinazolines, this thesis has successfully developed the synthesis of 4-substituted quinazoline derivatives via direct oxidative amination of C(sp3)-H bonds. The transformation proceeded readily in the presence of an organic peroxide without any added catalyst. The nature of the oxidant significantly affected the reaction, in which tert-butyl hydroperoxide in decane emerged as the peroxide of choice. Several nitrogen sources were explored, and ammonium acetate exhibited the best performance. A plausible reaction mechanism was proposed, in which acetic acid originating from ammonium acetate was essential for the formation of the 4-substituted quinazoline product. A variety of sp3 carbon sources could be utilized for the reaction, including *N*,*N*-dimethylaniline, *N*-methylaniline, *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide, and *N*,*N*-dimethyl-1-phenylmethanamine. Several 4-substituted quinazoline derivatives were synthesized via this approach in good yields. The fact that 4-substituted quinazolines derivatives were achieved via peroxide-mediated direct oxidative amination of

C(sp3)-H bonds without any added catalyst would offer a complementary synthetic pathway to previous protocols.

For the synthesis of 2-phenylquinoxalines, this thesis has reported a new pathway, in which 2-phenylquinoxalines were obtained via the condensations between o-phenylenediamines and phenylglyoxals in ethyl acetate without any added catalyst. The relevant conditions of reaction were exposed and a possible mechanism has been composed. A wide range of substituents could be utilized for the reaction. All quinoxaline derivatives were synthesized via this pathway in good and excellent yields. The significant points of this protocol are (1) metal-free, (2) green solvent, (3) short duration, (4) in room temperature, (5) excellent yields, and (6) wide range of applications. With these advantages, the procedure of synthesizing 2-phenylquinoxaline derivatives of the thesis will be applied in the field of organic synthesis and pharmaceuticals.

The third success in this thesis is the successful synthesis of N-arylindole derivatives. This study took advantage of nitroarene's oxidizing-substituent nucleophilic ability on the hydrogen atom to pair with a nitrogen atom containing an N-H bond without using a transition metal catalyst. Simple base NaOH and DMSO solvents were combined to mediate the amination of para C−H bond in nitrobenzene with N−H heterocycles. In addition, a plausible mechanism was also proposed. The substrate’s scope included indoles, pyrazoles, and pyrroles had been investigated. By the transition metal-free; room temperature, and simple base conditions, this strategy promises to tackle the previously mentioned disadvantages and become an efficient methodology in chemical fields.

The fourth point of the thesis is the successful development of a two-step one-pot procedure using elemental sulfur directly to synthesize thiocromenone derivatives. Whereby 2-arylthiocromenone derivatives were formed through the sulfurization of the 2'-chlorochalcones that were produced in the previous step between 2'-chloroacetophenones and aromatic aldehydes. A possible mechanism has been also offered and a large range of substrates have been investigated. The significances of this protocol are (1) direct use of elemental sulfur; (2) transition metal-free; (3) simple base, and (4) tolerance of many functionalities. Based on these advantages, this protocol would be mentioned in organic synthesis.

This thesis was successful in developing green pathways for the synthesis and functionalization of 5-, 6-membered heterocyclic compounds containing quinoxaline, quinazoline, N-indole, thiocromenone frameworks from common and abundant materials. All these protocols were taken place under simple conditions and especially without any added transition metal catalysts. These methodologies would be complementary to previous synthetic protocols and would be of interest to the pharmaceutical and chemical industries.

| **Advisor** | **Ph.D. candidate** |
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| Prof.Dr. Phan Thanh Son Nam | Huynh Van Tien |