



รายงานวิจัยฉบับสมบูรณ์

โครงการ

การประยุกต์ใช้ไฮเปอร์แวลেন্টไอโอไดต์ในเคมีอินทรีย์สังเคราะห์:
การทำวิชันลฟังก์ชันนัลไลเซชันของสารประกอบโอเลฟิน

โดย รองศาสตราจารย์ ดร. ชุตีมา คุณากาญจน์

กรกฎาคม พ.ศ. 2558

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รองศาสตราจารย์ ดร. ชุติมา คุณหากาญจน์
ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัยและสำนักงานคณะกรรมการอุดมศึกษา
(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

กิตติกรรมประกาศ

ผู้วิจัยขอแสดงความขอบคุณ สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) ที่สนับสนุนเงินสนับสนุนงานวิจัยผ่านทุนวิจัยพื้นฐานเชิงยุทธศาสตร์ “สมุนไพร ยารักษาโรคและสารเสริมสุขภาพ” (สัญญาเลขที่ DBG5480017) ศูนย์ความเป็นเลิศด้านนวัตกรรมทางเคมี สำหรับเครื่องมือในการทำวิจัย ทุนมหาวิทยาลัยวิจัย มหาวิทยาลัยมหิดล ภายใต้ศูนย์วิจัยพัฒนาด้านเภสัชศาสตร์ชีวภาพและนวัตกรรมการบำบัด ทุนพัฒนาและส่งเสริมผู้มีความสามารถพิเศษทางวิทยาศาสตร์และเทคโนโลยี (ทุน พสวท.) สำหรับการสนับสนุนด้านทุนการศึกษาของนักศึกษา ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดลสำหรับสถานที่ในการทำวิจัย และ ขอขอบพระคุณ ศาสตราจารย์ ดร. วิชัย รั้วตระกูล ศาสตราจารย์ ดร. มนัส พรหมโคตร และ ผู้ช่วยศาสตราจารย์ ดร. จรุงณี สุวรรณ์ ในคำแนะนำต่างๆ ในงานวิจัย

บทคัดย่อ

รหัสโครงการ:

DBG5480017

ชื่อโครงการ:

การประยุกต์ใช้ไฮเปอร์แวลেন্টไอโอดีนในเคมีอินทรีย์สังเคราะห์:
การทำวินิลฟังก์ชันนัลไลเซชันของสารประกอบโอเลฟิน

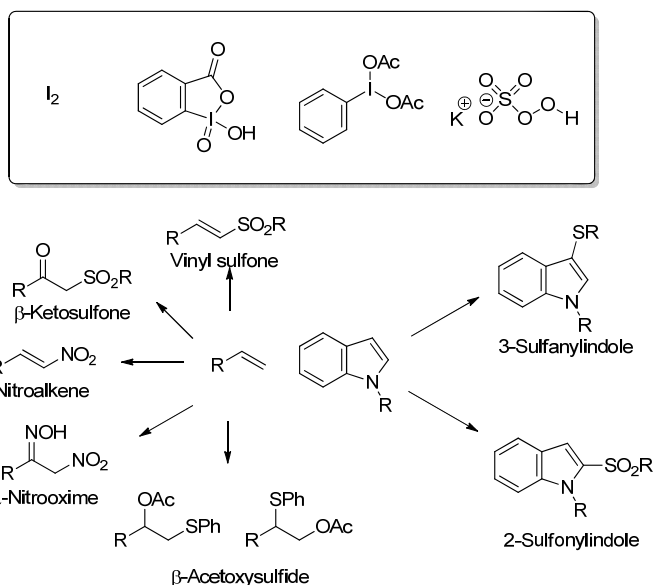
ชื่อนักวิจัย:

รองศาสตราจารย์ ดร. ชุตินา คูหากาญจน์
ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล
chutima.kon@mahidol.ac.th

ระยะเวลาโครงการ:

30 กันยายน 2554 – 29 กันยายน 2557

ไอโอดีน และ สารไฮเปอร์แวลেন্টไอโอดีน ได้ได้รับความนิยมในสาขาเคมีอินทรีย์อย่างยิ่งในปัจจุบัน เนื่องจากคุณสมบัติที่เป็นมิตรต่อสิ่งแวดล้อม สามารถนำมาใช้ทำปฏิกิริยาแทนตัวออกซิไดซ์ที่เป็นโลหะ มีความจำเพาะต่อปฏิกิริยา ทำปฏิกิริยาโดยใช้สถานะที่ไม่รุนแรง ใช้งานง่าย สามารถหาซื้อหรือเตรียมขึ้นจากสารตั้งต้นที่หาซื้อได้ง่าย ในการศึกษาจะเป็นการประยุกต์ใช้ไอโอดีน และสารไฮเปอร์แวลেন্টไอโอดีนในการเตรียมสารเบต้า-คีโตซัลโฟน สารเบต้า-อะเซทอกซีซัลไฟด์ สาร 2-ซัลโฟนิลอินโดล สาร 3-ซัลโฟนิลอินโดล สารไนโตรแอลคีน สารแอลฟา-ไนโตรออกซิม และ สารไวนิลซัลโฟน



คำหลัก: ไฮเปอร์แวลেন্টไอโอดีน โอเลฟิน สไตรีน อินโดล เบต้า-คีโตซัลโฟน เบต้า-อะเซทอกซีซัลไฟด์ 2-ซัลโฟนิลอินโดล 3-ซัลโฟนิลอินโดล ไนโตรแอลคีน แอลฟา-ไนโตรออกซิม ไวนิลซัลโฟน

Abstract

Project code: DBG5480017

Project Title: Synthetic Applications of Hypervalent Iodines in Organic Synthesis

Investigators:

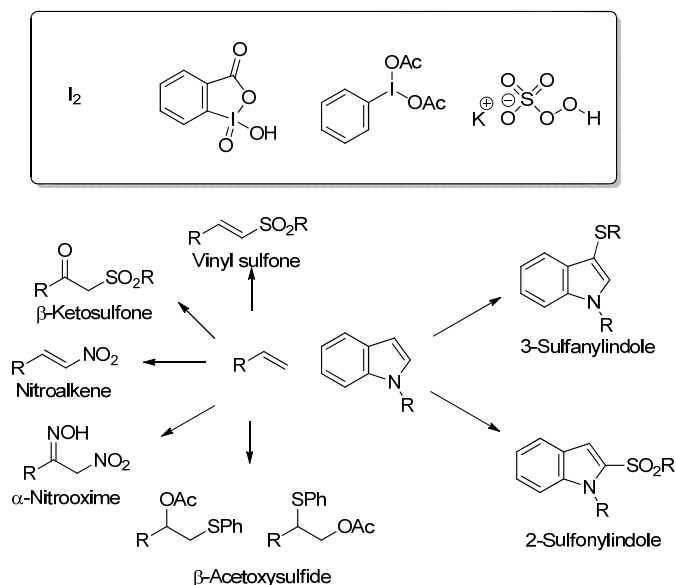
Assoc. Prof. Chutima Kuhakarn

Department of Chemistry, Faculty of Science, Mahidol University

chutima.kon@mahidol.ac.th

Project Period: 30 September 2011 – 29 September 2014

Iodine and hypervalent iodine reagents gained popularity in organic chemistry in recent years. The increasing interests of this class of reagents are mainly due to their environmentally benign properties as substitutes for metallic-based oxidizing reagents, selectivity, mild reaction conditions, ease of handling, commercial availability or readily prepared from commercially available starting materials. This work aims to develop new synthetic applications of iodine and hypervalent iodine reagent for the preparation of β -ketosulfones, β -acetoxysulfides, 2-sulfonylindoles, 3-sulfonylindoles, nitroalkenes, α -nitrooximes, vinylsulfones



Keywords: hypervalent iodine, olefins, styrenes, indoles, β -ketosulfones, β -acetoxysulfides, 2-sulfonylindoles, 3-sulfonylindoles, nitroalkenes, α -nitrooximes, vinylsulfones

Objectives

- 1) To develop new synthetic applications of iodine and hypervalent iodines in organic synthesis
- 2) To develop knowledge-based research in synthetic organic chemistry

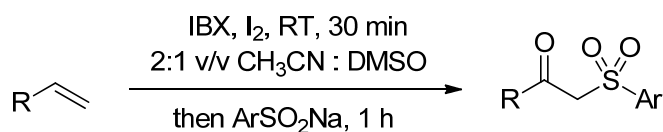
Methodology

- 1) Choose synthetic conversions which are novel and have never been reported (on the basis of scientific database)
- 2) Select a model compound for investigating optimized reaction conditions (solvents, temperature, reagents, reaction time, etc.)
- 3) Demonstrate the reaction efficiency and functional group compatibility by applying the optimized reaction conditions obtained from 2) to a collection of sterically and electronically different substrates
- 4) Summarize experimental results for the explanation of reaction mechanism
- 5) Preparation of manuscript for publication in international journals

Research Summary

1. IBX/I₂-Mediated Reaction of Sodium Arenesulfonates with Alkenes: Facile Synthesis of β -Ketosulfones

Among several methods for β -ketosulfone synthesis, the reaction of α -haloketones with sodium arenesulfonates is a direct and straightforward route. However, the drawback of the method is due to the virtually low solubility of sodium arenesulfonates in organic solvents. Therefore, a *one-pot* method involving an *in situ* generation of α -iodoketones from its precursors followed by alkylation of sodium sulfonates was found attractive. In this part, we have developed a facile *one-pot* synthesis of β -ketosulfones from alkenes mediated by a combination of *o*-iodoxybenzoic acid (IBX) and iodine in the presence of sodium arenesulfonates. The optimized reaction conditions are to employ alkene (1 equiv), IBX (2 equiv), I₂ (1.1 equiv) and *p*-TolSO₂Na (4.0 equiv) in CH₃CN:DMSO (2:1 v/v). An array of structurally β -ketosulfones can be synthesized directly from olefins including both styrene derivatives and aliphatic alkenes. The present procedure offers experimental simplicity, mild reaction conditions, and readily available starting materials and is an important alternative to existing methods for the synthesis of β -ketosulfones.



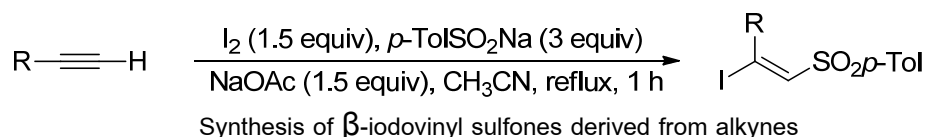
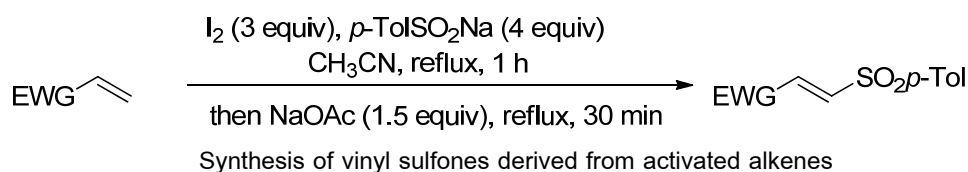
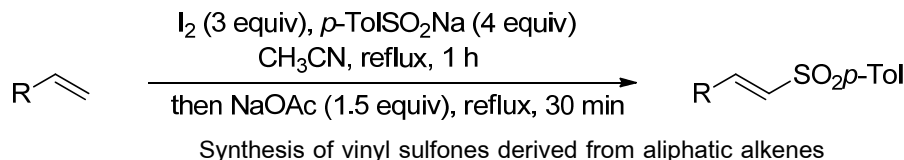
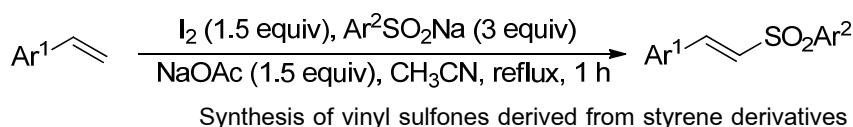
Synthesis of β -ketosulfones

This work was published in an international journal:

Samakkanad, N.; Katrun, P.; Techajaronjit, T.; Hleklai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "IBX/I₂-Mediated Reaction of Sodium Arenesulfonates with Alkenes: Facile Synthesis of β -Ketosulfones" *Synthesis*, **2012**, *44*, 1693-1699. (Q2; IF= 2.443)

2. An Improved Synthesis of Vinyl- and β -iodovinyl Sulfones by a Molecular Iodine-Mediated One-pot Iodosulfonation-Dehydroiodination Reaction

Vinyl sulfones are important scaffolds found in various biologically active compounds as well as useful synthetic intermediates in organic synthesis. As a result, there are a number of efforts aiming at developing efficient and mild methods for the synthesis of vinyl sulfones. In the present work, we developed an improved and convenient experimental procedure to prepare vinyl sulfones and β -iodovinyl sulfones from alkenes and alkynes by molecular iodine-mediated *one-pot* iodosulfonation followed by base-induced dehydroiodination reaction. The reaction integrates two reactions into a *one-pot* reaction and was found suitable with a variety of substrates. Vinyl sulfones derived from styrene derivatives except for those bearing strong electron releasing substituent were obtained in good to excellent yields. Aliphatic alkenes and activated alkenes gave the corresponding vinyl sulfone products in moderate to good yields. Arylacetylenes yielded the respective β -iodovinyl sulfones in good yields while low yield was observed with aliphatic terminal alkyne. The potentials of the method include simplicity, short reaction time, non-anhydrous reaction conditions, employing inexpensive, non-metallic reagent and integrating two reactions that are commonly accomplished separately into a single operation.

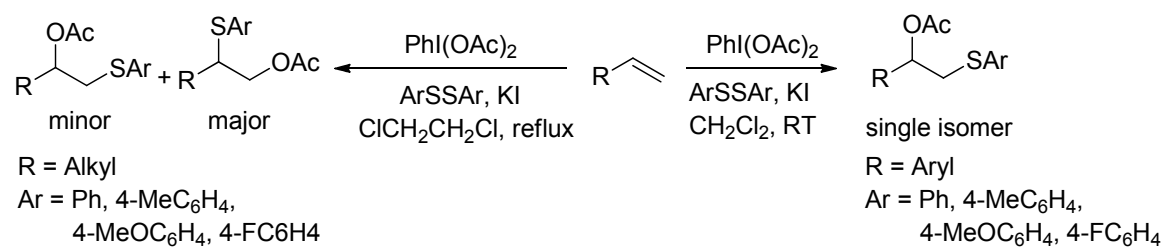


This work was published in an international journal:

Sawangphon, T.; Katrun, P.; Chaisiwamongkhon, K.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "An Improved Synthesis of Vinyl- and β -iodovinyl Sulfones by a Molecular Iodine-Mediated One-pot Iodosulfonation-Dehydroiodination Reaction" *Synth. Commun.*, **2013**, 43, 1692-1707. (Q3; IF = 0.984)

3. $\text{PhI}(\text{OAc})_2/\text{KI}$ Mediated 1,2-Acetoxyulfenylation of Alkenes: Facile Synthesis of β -Acetoxyulfides

1,2-Hydroxysulfides are important class of compounds. They are valued as crucial building blocks for the preparation of useful and higher functionalized organic molecules. In this work, we demonstrated a facile synthesis of 1,2-acetoxyulfides by using (diacetoxyiodo)benzene ($\text{PhI}(\text{OAc})_2$)/KI to promote the reaction of alkenes with diaryl disulfides. The reaction is highly regioselective for styrene derivatives while aliphatic alkenes lead to a mixture of two regioisomers. The method is simple, enables the use of both organosulfur groups of the disulfide, fast, and being conducted under non-anhydrous conditions.



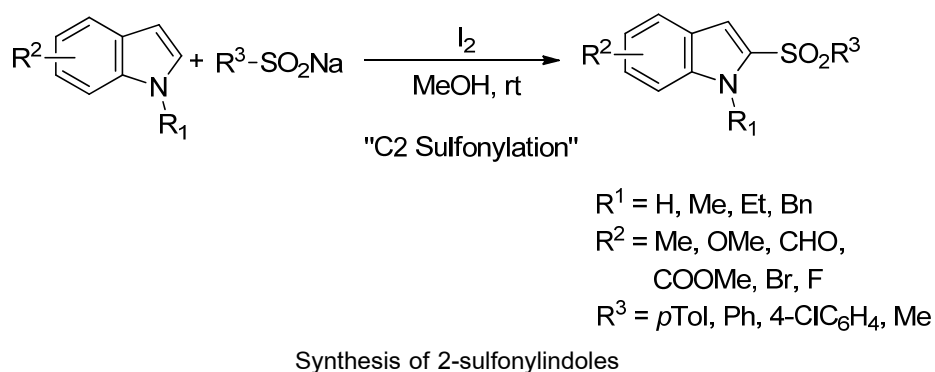
Synthesis of β -acetoxyulfides

This work was published in an international journal:

Muangkaew, C.; Katrun, P.; Kanchanarugee, P.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. " $\text{PhI}(\text{OAc})_2/\text{KI}$ Mediated 1,2-Acetoxyulfenylation of Alkenes: Facile Synthesis of β -Acetoxyulfides" *Tetrahedron*, **2013**, 69, 8847-8856. (Q2; IF 2.817)

4. Regioselective C2 Sulfonylation of Indoles Mediated by Molecular Iodine

Indole is an important structural scaffold omnipresent in naturally occurring compounds and pharmacologically important agents. Therefore, new approaches directing synthesis of indole nucleus and development of novel methods for indole functionalization have long inspired synthetic organic chemists. In particular, the 2-sulfanylindoles possess inhibitory effect toward nucleoside triphosphate hydrolase enzyme and a sulfonyl group in 2-sulfonylindoles serves as a temporary functional group which can be later removed by β -elimination. Previously reported methods available for accessing 2-sulfanylindoles and 2-sulfonylindoles are not straightforward. Therefore, an exploration of a facile method for a direct regioselective installation of the sulfur moiety to the indole scaffold would be highly desirable. In this part, we successfully developed a direct C2 sulfonylation of indoles in a highly regioselective manner via molecular iodine mediated reaction. The reactions undergo under mild reaction conditions in a neutral solvent allowing a broad scope of 2-sulfonylindole derivatives being prepared.

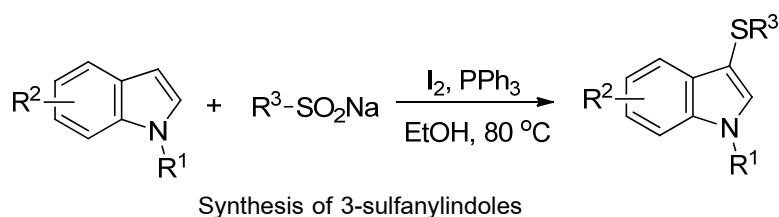


This work was published in an international journal:

Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C.
"Regioselective C2 Sulfonylation of Indoles Mediated by Molecular Iodine" *J. Org. Chem.*, **2014**, *79*,
1178-1185. (Q1; IF = 4.564)

5. Iodine–PPh₃-mediated C3-Sulfonylation of Indoles with Sodium Sulfinates

In continuation of our previous report on C2 sulfonylation of indoles mediated by molecular iodine, we next developed the C3 sulfonylation of indoles. The present work offers a convenient and simple protocol to access 3-(alkylsulfonyl)- and 3-(arylsulfonyl)indoles using sodium sulfinates as the reagents mediated by I₂-PPh₃ system. The reaction readily proceeded in refluxing ethanol within a few hours. In view of simplicity, high efficiency, non-anhydrous conditions, environmentally benign solvent and short reaction time, it is believed that this protocol should offer an alternative and rapid approach to 3-sulfonylindoles.

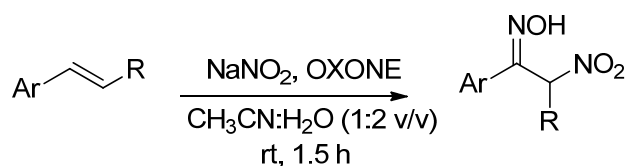


This work was published in an international journal:

Katrun, P.; Hongthong, S.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "Iodine–PPh₃-mediated C3-Sulfonylation of Indoles with Sodium Sulfinates" *RSC Advances*, **2014**, 4, 18933-18938. (Q1; IF = 3.708)

6. Convenient Synthesis of α -Nitrooximes Mediated by OXONE[®]

The 1,2-difunctionalizations of carbon–carbon double bonds of alkenes are among the most powerful transformations in chemical synthesis. They have been challenging synthetic transformations in organic chemistry as for the introduction of functional groups into an unactivated alkene moiety as well as enhancement of molecular complexity. In this part, we established a convenient and efficient synthesis of α -nitrooximes from alkenes employing commercially available reagents (NaNO_2 and OXONE[®]). The reaction readily proceeded at ambient temperature and conveniently employed inexpensive and environmentally benign reagents. The reaction offers an easy access for the 1,2-difunctionalization of alkenes through formation of C–N bonds.



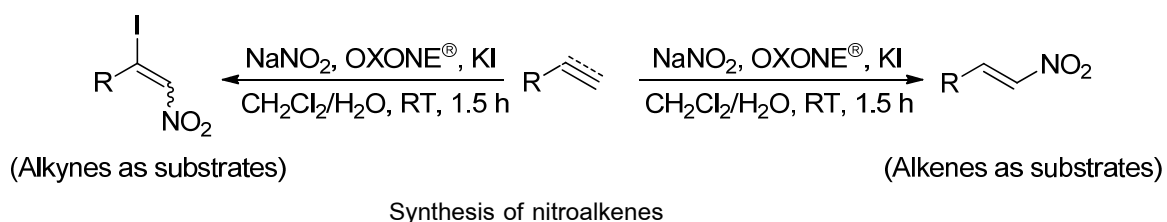
Synthesis of α -nitrooximes

This work was published in an international journal:

Chumnanvej, N.; Samakkanad, N.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "Convenient Synthesis of α -Nitrooximes Mediated by OXONE[®]" *RSC Advances*, **2014**, *4*, 59726-59732. (Q1; IF = 3.708)

7. Oxone®/KI-Mediated Nitration of Alkenes and Alkynes: Synthesis of Nitro- and β-Iodonitro-Substituted Alkenes

Nitroalkenes are an important class of nitro compounds which have synthetic utilities in organic synthesis for the preparation of a variety of organic compounds widely used in various fields. Nitroalkene-containing molecules have also been reported to exhibit important biological activities. Nitro group has an activating effect to the adjacent carbon-carbon double bonds enable the nitroalkenes to serve as Michael acceptors, and electron-deficient dienophile partners in cycloaddition reactions. Furthermore, the nitro group can be transformed into other important functionalities, allowing the nitro group to function as a transient activating functional group. As a part of our on-going interest on oxidative transformation reactions, we established an eco-friendly reaction using a combination of sodium nitrite (NaNO₂)/OXONE®/KI to effect nitration of alkenes and alkynes. Styrene derivatives lacking of electron-donating groups yielded the corresponding nitroalkenes in moderate to good yields while aliphatic alkenes and electron-deficient alkenes gave deficient results. Despite limited substrate scopes, in view of the convenient and mild reaction conditions (room temperature) as well as relatively inexpensive reagents, the present method is an important alternative to existing methods for the synthesis of nitroalkenes and β-iodonitroalkenes, which are an important class of compounds in organic chemistry.

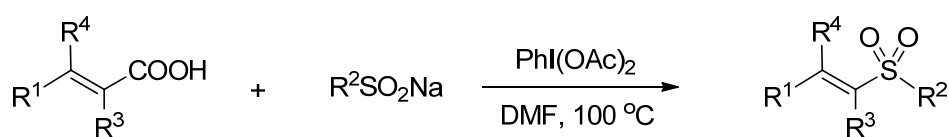


This work was published in an international journal:

Hlekhlai, S.; Samakkanad, N.; Sawangphon, T.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Jaipetch, T.; Kuhakarn, C. "Oxone®/KI-Mediated Nitration of Alkenes and Alkynes: Synthesis of Nitro- and β-Iodonitro-Substituted Alkenes" *Eur. J. Org. Chem.*, **2014**, 7433-7442. (Q1; IF = 3.154)

8. $\text{PhI}(\text{OAc})_2$ Mediated Decarboxylative Sulfonylation of β -Aryl- α,β -Unsaturated Carboxylic Acids: A Synthesis of (E)-Vinyl Sulfones

Decarboxylation accompanying by simultaneous functionalization reactions emerged as synthetically important transformation in current organic synthesis, leading to carbon-carbon and carbon-heteroatom bond formations. Vinyl sulfones are of particularly valuable units in organic synthesis due to chemical versatilities of the sulfonyl moiety which can be further manipulated into other useful functional groups. Thus, in this part, we developed the decarboxylative sulfonylation of unsaturated carboxylic acids mediated by (diacetoxyiodo)benzene (DIB). Our method offers several advantages, including being transition-metal-free, employing environmentally benign and stable reagents, involving simple handling under air-stable conditions. This is also first report of decarboxylative sulfonylation of δ -aryl- $\alpha,\beta,\gamma,\delta$ -diene carboxylic acid.



Synthesis of vinylsulfones via decarboxylative sulfonylation

This work was published in an international journal:

Katrún, P.; Hlekhlai, S.; Meesin, J.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. " $\text{PhI}(\text{OAc})_2$ Mediated Decarboxylative Sulfonylation of β -Aryl- α,β -Unsaturated Carboxylic Acids: A Synthesis of (E)-Vinyl Sulfones" *Org. Biomol. Chem.*, **2015**, 13, 4785-4794. (Q1; IF = 3.487)

Summary of the research project

The research project involves the development of synthetic applications of molecular iodine and hypervalent iodine reagents in organic synthesis. The outputs from the research project include the synthetic applications of molecular iodine and two hypervalent iodine reagents, including 2-iodoxybenzoic acid (IBX) and (diacetoxyiodo)benzene (DIB), for the functionalization of olefins and indole derivatives. We have successfully reported new synthetic methods to access vinylsulfones, β -ketosulfones, α -acetoxysulfides, nitroalkenes, α -nitrooximes, 2-sulfonylindoles and 3-sulfanylindoles. Total of eight international publications with peer review are the output of the research project.

Output of the research project

1. The output of the present project include eight international publications as listed below

- 1) Samakkanad, N.; Katrun, P.; Techajaronjit, T.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "IBX/I₂-Mediated Reaction of Sodium Arenesulfonates with Alkenes: Facile Synthesis of β -Ketosulfones" *Synthesis*, **2012**, 44, 1693-1699. (Q2; IF= 2.443)
- 2) Sawangphon, T.; Katrun, P.; Chaisiwamongkhol, K.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "An Improved Synthesis of Vinyl- and β -iodovinyl Sulfones by a Molecular Iodine-Mediated One-pot Iodosulfonation-Dehydroiodination Reaction" *Synth. Commun.*, **2013**, 43, 1692-1707. (Q3; IF = 0.984)
- 3) Muangkaew, C.; Katrun, P.; Kanchanarugee, P.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "PhI(OAc)₂/KI Mediated 1,2-Acetoxysulfonylation of Alkenes: Facile Synthesis of β -Acetoxysulfides" *Tetrahedron*, **2013**, 69, 8847-8856. (Q2; IF 2.817)
- 4) Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "Regioselective C2 Sulfonylation of Indoles Mediated by Molecular Iodine" *J. Org. Chem.*, **2014**, 79, 1178-1185. (Q1; IF = 4.564)
- 5) Katrun, P.; Hongthong, S.; Hlekhlai, S.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "Iodine-PPh₃-mediated C3-Sulfonylation of Indoles with Sodium Sulfonates" *RSC Advances*, **2014**, 4, 18933-18938. (Q1; IF = 3.708)
- 6) Chumnavej, N.; Samakkanad, N.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. "Convenient Synthesis of α -Nitrooximes Mediated by OXONE[®]" *RSC Advances*, **2014**, 4, 59726-59732. (Q1; IF = 3.708)
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3. International conference

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4. National conference

Poster presentation at The 3rd Thailand National Research Universities Summit, 2014: Prelude to World Class University) 31 July - 1 August 2014 Centara Grand & Bangkok Convention Centre, Bangkok, Thailand "Environmentally Friendly Molecular Iodine Mediated C2 Sulfonylation and C3 Sulfonylation of Indoles"

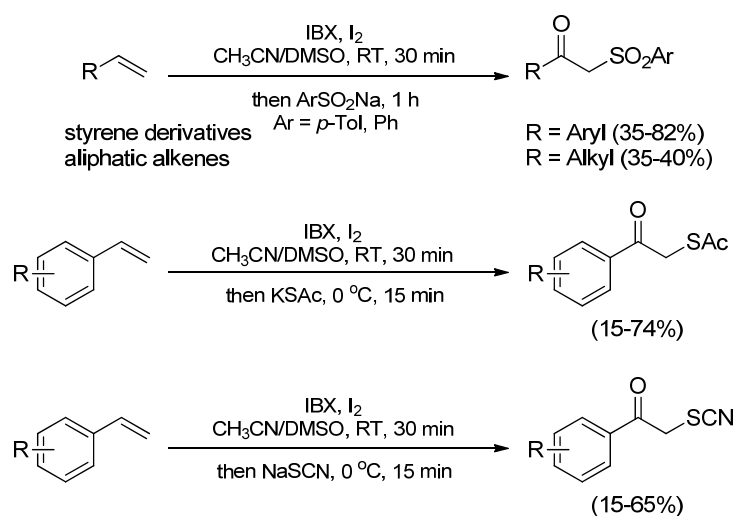
Facile and Convenient Synthesis of β -Ketosulfones, α -Oxothioacetates and α -Oxothiocyanates from Alkenes

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A combination of *o*-iodoxybenzoic acid/iodine (IBX/I₂) was found to promote the reaction of alkenes with sodium arenesulfonates, potassium thioacetates and sodium thiocyanates to produce the corresponding β -ketosulfones, α -oxothioacetates, and α -oxothiocyanates, respectively (Scheme 1). The salient features of the present method include experimental simplicity, mild reaction conditions and readily accessible starting alkenes. The methods are important alternatives to the existing methods for the synthesis of β -ketosulfones, α -oxothioacetates, and α -oxothiocyanates.



Scheme 1

Abstract

The 3rd Thailand National Research Universities Summit, 2014: Prelude to World Class University)

Cluster: Center for Biopharmaceutical Development and Innovative Therapy (Mahidol University)

Environmentally Friendly Molecular Iodine Mediated C2 Sulfonylation and C3 Sulfenylation of Indoles

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Abstract: Indole is a privileged structural motif found in many clinically used therapeutic drugs and natural products. Therefore, there has been long interest toward the development of new approaches for the synthesis of the indole framework as well as indole functionalization. In the present work, we have developed a convenient and highly efficient method for a direct C2 sulfonylation reaction of indole and derivatives mediated by molecular iodine using sodium aryl-, and alkylsulfonates as the reagents in methanol. Additionally, a combination of sodium aryl-, and alkylsulfonates in the presence of iodine-PPh₃ in ethanol was found to efficiently promote the C3 sulfenylation reaction of indole and derivatives. The salient features of the present protocol are simplicity, high efficiency, non-anhydrous conditions, environmentally friendly reagents and short reaction time.

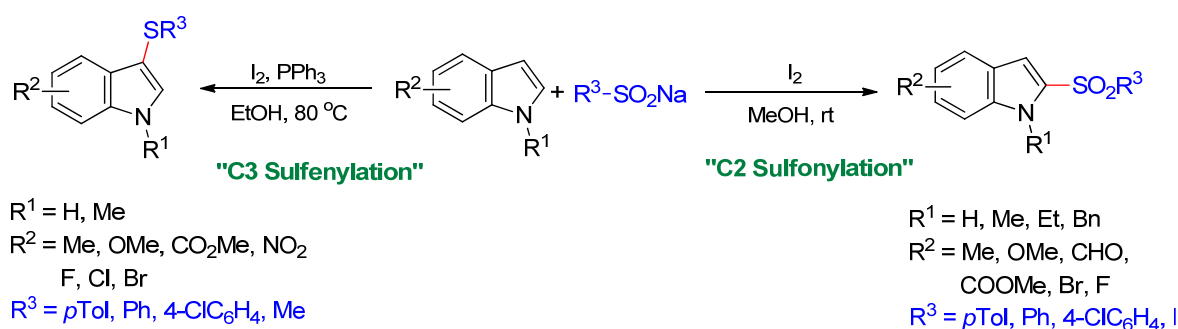


Figure 1. Synthesis of 2-sulfonyl and 3-sulfonyl indoles

Keywords: iodine, indoles, sulfones, sulfides, sulfonates