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One-pot Synthetic Approach to Dipyrromethanes and Bis(indolyl)methanes via Nitrosoalkene Chemistry

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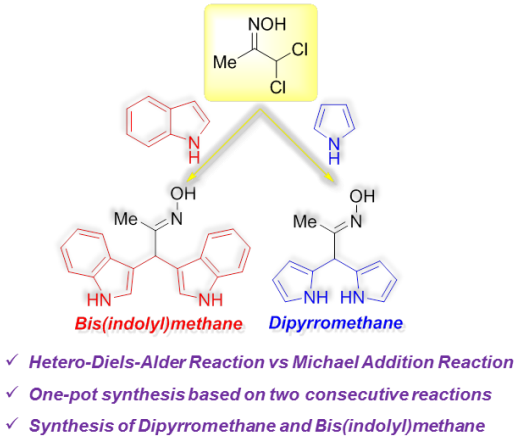
ABSTRACT:

A one-pot regio- and stereoselective synthesis of dipyrromethane and bis(indolyl)methane based on two consecutive reactions of nitrosoalkenes with pyrrole or indole, respectively, is described as an experiment to be carried out by upper-division undergraduate students in a laboratory classroom. Importantly, the ability of electrophilic conjugated nitrosoalkenes to react via Michael addition or hetero-Diels-Alder reactions with electron rich heterocycles, will provide an opportunity for students to acknowledge alternative reaction pathways underlying certain transformations. Reactions were performed under mild conditions using water as solvent, followed by purification through column chromatography on silica gel, and characterization of the desired products by NMR and IR spectroscopy. This laboratory experiment combines organic synthesis, determination of the purity of compounds (TLC analysis and melting point measurements) as well as structural analysis (interpretation of 1D NMR spectra). Several important organic chemistry concepts, such as stereo- and regioselectivity, *in situ* generation and reactivity of conjugated nitrosoalkenes, conjugated 1,4-addition reactions and cycloaddition reactions, are also discussed.



KEYWORDS: Upper-Division Undergraduate, Organic Chemistry, Hetero-Diels-Alder Reaction, Conjugate Addition, Hands-On Learning/Manipulatives, Heterocycles, NMR Spectroscopy, IR Spectroscopy, Organic Synthesis, Chromatography

Keywords (Audience): Upper-Division Undergraduate

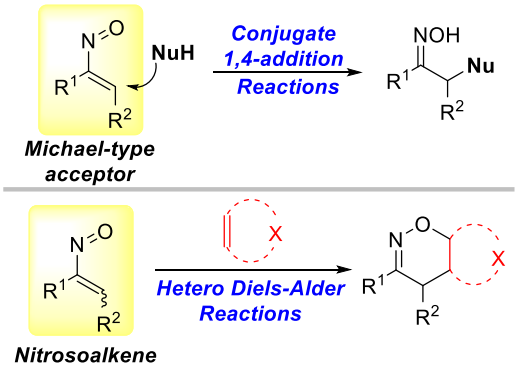
Keywords (Domain): Organic Chemistry, Hetero-Diels-Alder Reaction, Michael Addition Reaction

Keywords (Pedagogy): Hands-On Learning/Manipulatives

Keywords (Topic): Heterocycles, NMR Spectroscopy, IR Spectroscopy, Synthesis, Chromatography

In the past decades, the chemistry of conjugated nitrosoalkenes has been extensively explored in organic synthesis originating a plethora of new heterocyclic and non-heterocyclic compounds, some of which exhibiting promising biological activities.[1] These reactive intermediates are usually generated *in situ* through base-promoted dehydrohalogenation of α-halooximes. The conjugation of the nitroso-substituent with the C=C double bond conveys a strong electrophilic character to the system making the carbon C-4 strongly activated to nucleophilic attack. Thus, they can participate in conjugate 1,4-additions (Michael additions) with a variety of nucleophiles (Scheme 1).[2] On the other hand, they can also act as electron-deficient heterodienes participating efficiently in inverse electron-demand Diels-Alder reactions with electron rich olefins and electron rich heterocycles to afford 1,2-oxazines (Scheme 1).[1]

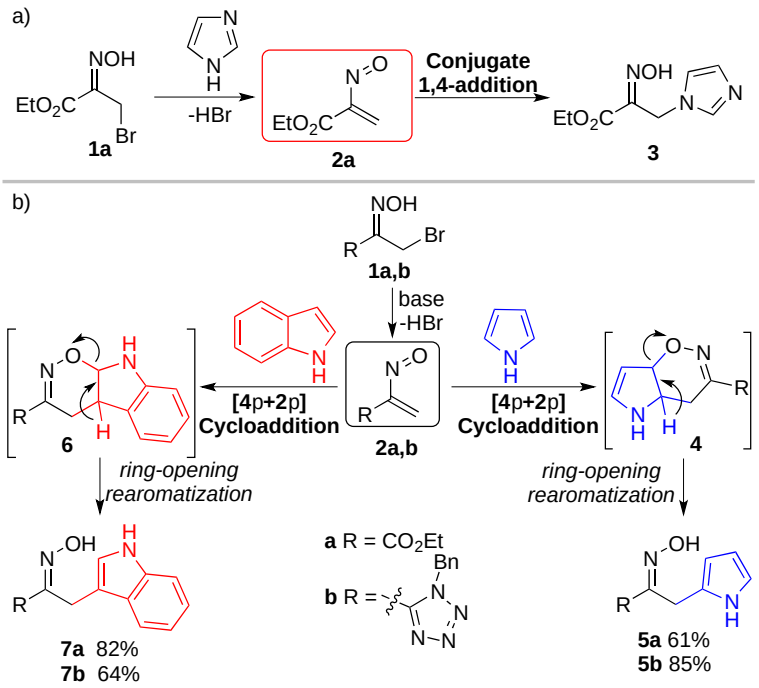
Scheme 1. **Typical reactivity of nitrosoalkenes.**



In the reaction of nitrosoalkenes with electron-rich heterocycles, both reactivities have been observed, with the mechanistic pathway being strongly influenced not only by the nitrosoalkene substituents but also the type of heterocycle. 1*H*-Imidazole reacts with ethyl bromopyruvate oxime **1a** via an elimination reaction to generate nitrosoalkene **2a** followed by conjugate addition reaction to give the corresponding alkylated product **3** (Scheme 2a).[3] On the other hand, the inverse electron demand Diels-Alder reaction of nitrosoalkenes **2a** and **2b**, generated *in situ* from the corresponding oximes **1**, with pyrrole and indole, gives open-chain oximes **5** and **7**, respectively, as single products. The synthesis of these products can be rationalized considering the formation of the Diels-Alder cycloadducts, the bicyclic 1,2-oxazines **4** and **6**, followed by oxazine ring-opening with concomitant rearomatization of the pyrrole or indole unit (Scheme 2b). In fact, the

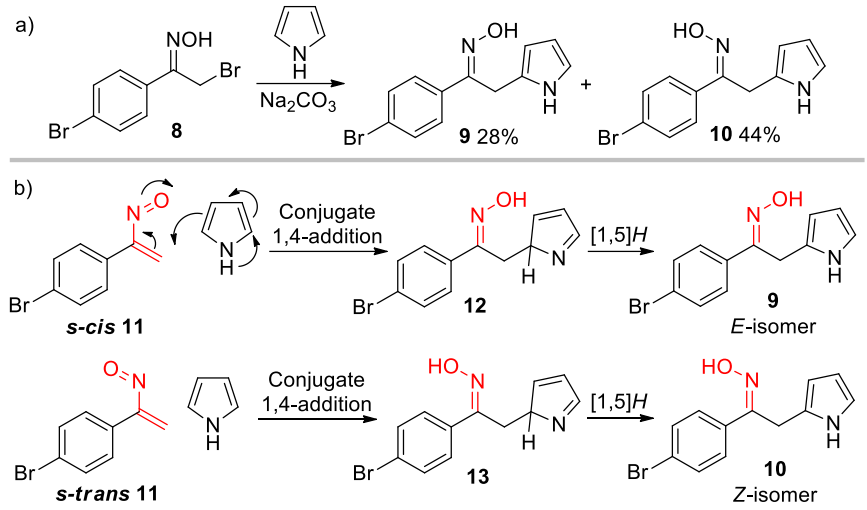
open-chain oximes were isolated as single isomers, with the hydroxyl and pyrrolylmethyl or indolylmethyl groups *cis* as expected for a mechanism pathway involving a hetero-Diels-Alder reaction and subsequent ring-opening reaction of the bicyclic 1,2-oxazine. In addition, pyrrole was functionalized at position 2 whereas the reaction with indole gave a 3-alkylated derivative which is in agreement with the expected and opposite regioselectivity of the hetero-Diels-Alder reaction.[4-8]

Scheme 2. Conjugate 1,4-addition and hetero Diels-Alder reaction of nitrosoalkenes with heterocycles.



Conversely, the reaction of *p*-bromophenyl oxime **8** with pyrrole, under the same reaction conditions, led to the formation of two isomeric oximes **9** and **10** (Scheme 3a).[9] This outcome is not consistent with a process involving a hetero-Diels-Alder reaction, which should lead exclusively to isomer **9**. Instead, a process involving as first step a conjugate addition reaction pathway occur leading to two isomeric oximes **12** and **13**. Starting from nitrosoalkene **11** at the *s-cis* conformation, oxime **12** was formed, whereas **11**-*s-trans* afforded oxime **13**. Oximes **12** and **13** undergo a 1,5-sigmatropic hydrogen shift, to give isomeric oximes **9** and **10**, respectively (Scheme 3b).[9] Interestingly, it was demonstrated that indole reacts with the same nitrosoalkene **11** via inverse electron-demand Diels-Alder reaction giving only one open-chain oxime.[10]

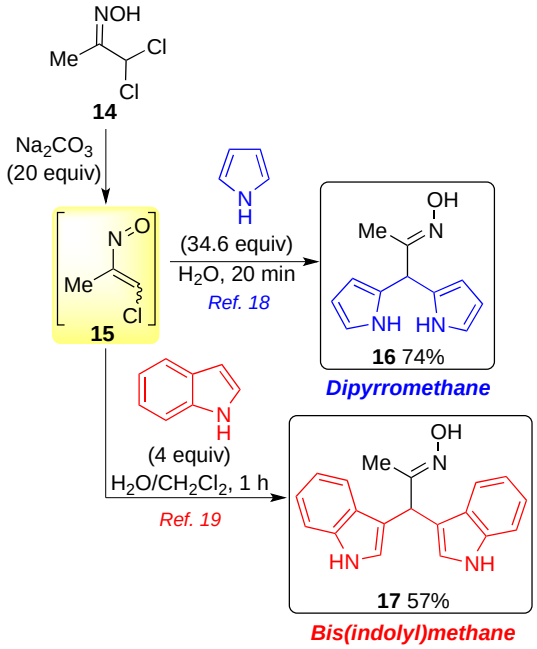
Scheme 3. Conjugate 1,4-addition reaction of 3-(*p*-bromophenyl)nitrosoalkene with pyrrole.



Dipyrromethanes (DPs) are valuable and versatile building blocks of a vast number of compounds such as porphyrins, *meso*-substituted corroles, chlorins, calix[4]pyrroles, and BODIPY dyes.[11,12] These compounds display remarkable photo- and biochemical properties suitable for several applications including photonic organic-based materials, optical anion sensors, as photosensitizers in photodynamic therapy and as theragnostic agents.[13-15] On the other hand, natural occurring and synthetic bis(indolyl)methanes (BIMs) have shown to exhibit a wide range of biological activities and have also been used as dyes and colorimetric sensors.[16,17]

The laboratory experiment described herein involves a regioselective one-pot synthetic approach to dipyrromethanes (*e.g.* **16**) and bis(indolyl)methanes (*e.g.* **17**) based on two consecutive reactions of nitrosoalkenes, generated *in situ* from 1,1-dichloro-2-propanone oxime (**14**), with pyrrole or indole, respectively (Scheme 4).[18-21]

Scheme 4. On-water synthesis of DP 16 and BIM 17 via two consecutive reactions of nitrosoalkenes with pyrrole or indole.



Pedagogical Goals and Assessment

The purpose of this laboratory experiment is to allow the students to carry out the synthesis of important scaffolds in organic synthesis in a straightforward procedure and under very mild conditions. The pedagogical aims of this experiment include deepening the knowledge about important organic chemistry concepts, such as regioselectivity, generation and reactivity of conjugated nitrosoalkenes, namely conjugated 1,4-addition reactions and cycloaddition reactions. The students will also acquire knowledge in one-pot reactions and atom economy as well as on TLC analysis, chromatography techniques, NMR and IR spectroscopy. Each experiment, the synthesis of DP **16** and BIM **17**, has been carried out successfully by 28 advanced undergraduate students (BSc Biochemistry and BSc Chemistry) within the organic chemistry course, working individually or in groups of two. After carrying out the experimental work and discussing the results, the students should be able to propose the mechanism for the synthesis of dipyrromethanes and bis(indolyl)methane based on the chemistry of nitrosoalkenes. The students will also acquire knowledge on purification and isolation of organic compounds by chromatographic techniques and demonstrate an understanding of the NMR and IR data that allowed them to structurally characterize the products.

The students' assessment is performed based on the laboratory reports as well as on instructor observation of the students' laboratory skill development, post-lab questions

focused on spectral analysis and reaction mechanisms, and exam questions (Supporting Information).

In general, the assessment of students confirmed that the pedagogic goals of the laboratory experiment were successfully achieved, well-illustrated by the results of the students' answers to the exam questions. In question 1, students acknowledged that the replacement of 1,1-dichloro-2-propanone oxime by 1,1-dibromo-2-propanone oxime, in the reaction with pyrrole, would lead to an enhancement of the reaction rate due to the presence of a better leaving group (Br). On the other hand, answers to questions 2 and 3 clearly show that the students not only understood the mechanism underlying the synthesis of dipyrromethanes and bis(indolyl)methane, but they were also able to apply the acquired knowledge to reactions with other dienophiles (*e.g.* furan, question 2) and heterodienes (*e.g.* azoalkenes, question 3). Moreover, the correct identification of the reaction products (cycloadduct vs open-chain oxime derivative) was accomplished by the students revealing knowledge regarding the regioselectivity of the proposed reactions as well as the aromaticity-nucleophilicity of the heterocycles (furan vs pyrrole). Also, students were capable of identifying the cycloadduct arising from the reaction of ethyl bromopyruvate oxime with 2,5-dimethylpyrrole, where the ring-opening reaction pathway to yield the open-chain oxime derivative is precluded, thus demonstrating mechanistic knowledge on the topic (question 4).

Although there are several experiments reported in this Journal illustrating basic concepts of Diels-Alder reactions, undergraduate laboratory experiments on the application of the hetero-Diels-Alder reaction are more limited.[21-27] Moreover, this synthetic methodology features several aspects that make it suitable for an undergraduate laboratory experiment. The total synthesis involves four consecutive reactions carried out in one pot, base-induced dehydrohalogenations, the hetero-Diels-Alder and Michael addition reactions, without the need of isolating or purifying any intermediate. The reactions are carried out at atmospheric pressure and room temperature using water as solvent, an environmentally friendly solvent. Furthermore, it illustrates the efficiency of hetero-Diels-Alder reactions carried out in aqueous medium. This has been suggested to be caused not only by the hydrophobic effect in which an entropy-driven aggregation of two nonpolar molecules dissolved in water occurs, but also to hydrogen-bonding interactions. In addition, it has been observed that aqueous solvents can enhance the selectivity and regioselectivity of

the reaction.[28] Indeed, the optimized on-water reaction conditions of these reactions afford the desired dipyrromethane and bis(indolyl)methane in higher yields with significantly shorter reaction times than those carried out in dichloromethane or in the absence of solvent.[18-20] Moreover, the synthetic methodology provides functionalized heterocyclic compounds in a regio- and stereoselective fashion.

EXPERIMENT OVERVIEW

In the classroom environment, upper-division undergraduate students may work either individually or in groups of two during three laboratory sessions of 3 hours. Each group carries out one reaction sequence, either using pyrrole or indole, to obtain dipyrromethane **16** or bis(indolyl)methane **17**, respectively (Scheme 4). Detailed experimental procedures are provided in the Supporting Information.

First Session

The first session involves the synthesis and isolation of dipyrromethane **16** or bis(indolyl)methane **17** through the *in situ* generation of 4-chloronitrosoalkene **15** and subsequent reaction with pyrrole or indole, respectively. To prepare dipyrromethane **16**, a solution of oxime **14** in pyrrole is added to a solution of sodium carbonate in water. The reaction mixture should be vigorously stirred at room temperature for 20 minutes. In the synthesis of bis(indolyl)methane **17**, the indole and a solution of oxime **14** in a co-solvent (dichloromethane) are added to the solution of sodium carbonate in water. The reaction is stirred vigorously for 1 hour at room temperature. Upon completion, the biphasic mixture is transferred to a separator funnel, extracted with ethyl acetate and the combined organic extracts dried. After removal of the solvent, the composition of the crude product is evaluated by thin layer chromatography (TLC) analysis and the appropriate eluent to be used in the following purification session is selected. The crude mixture should be stored in the refrigerator until the purification session.

Second Session

This session involves the purification of dipyrromethane **16** or bis(indolyl)methane **17**. The flash chromatography is prepared using silica gel and the eluent selected in the first session. After isolation of the product, the solvent is evaporated off affording dipyrromethane **16** as a light grey solid and bis(indolyl)methane **17** as an oil. However, compound **17** becomes a colorless solid upon addition of diethyl ether. The success of the isolation of the target compounds is confirmed by TLC analysis and the compounds are stored in a desiccator until next session.

Third Session

In this session, the yields and atom economy are calculated, and samples are prepared to record the IR and NMR spectra. Additionally, melting point measurements of the products can be carried out (optional).

HAZARDS

Students should be familiar with good laboratory practices to work safely in the laboratory. Personal protective equipment (PPE) is mandatory throughout the laboratory sessions. The entire experiment should be conducted in a fume hood. The experiments must be fully risk-assessed by all students. Proper procedures and precautions in handling waste and chemicals should be adhered to with reference to safety data sheets (SDS). All the reactants and solvents used in the experiments should be carefully handled and in a fume hood. Pyrrole [CAS 109-97-7], ethyl acetate [CAS 141-78-6], dichloromethane [CAS 75-09-2] and diethyl ether [CAS 60-29-7] are flammable liquid and vapor, toxic if swallowed, cause eye irritation or damage and harmful if inhaled. Indole [CAS 120-72-9] is a white solid harmful if swallowed, toxic in contact with skin, causes serious eye irritation and very toxic to aquatic life. Sodium carbonate [CAS 497-19-8] is a white solid which causes serious eye irritation. Hexane [CAS 110-54-3] causes neurotoxicity. Organic solvents waste should be disposed in appropriate waste collector containers. According to our experience, oxime **14** is unstable at room temperature and should be stored in the freezer. Dipyrromethane **16** and bis(indolyl)methane **17** should be stored in the dark.

RESULTS AND DISCUSSION

Synthesis

The synthesis of dipyrromethane **16** and bis(indoly)methane **17** was reproduced BSc students, individually or in groups of two, during three laboratory sessions (3 h/session). The students obtained dipyrromethane **16** in yields ranging from 30% to 55% and bis(indolyl)methane **17** with yields ranging from 34% to 49%. The atom economy was calculated as 53% and 63% for the synthesis of **16** and **17**, respectively. The TLC analysis of the crude mixture of reaction with pyrrole showed the presence of unreacted pyrrole, dipyrromethane **16** and some impurities (Fig. S1, see SI). Flash chromatography performed with the eluent ethyl acetate/hexane (1:1) allowed the isolation of pure dipyrromethane **16** as a light grey solid. Using the same purification method, bis(indolyl)methane **17** was isolated as a white solid. After purification, the purity of the products was assessed by TLC and ^{1}H NMR analysis of both compounds and by melting point measurements (optional).

Spectral Analysis

The identification and purity of the products was confirmed by the ^{1}H NMR spectra, by comparison with the previously reported data.[18,19] The analysis of the ^{1}H NMR spectra allows the consolidation of concepts such as chemical shift and multiplicity. For example, in the ^{1}H NMR spectrum of dipyrromethane **16** (Figure 1) it is possible to identify the presence of signals corresponding to two pyrrole units. Two N*H* protons emerge at 10.55 ppm as a broad singlet and the O*H* proton at 10.48 ppm. Also, signals corresponding to CH protons of pyrrole units appear between 5.79 and 6.62 ppm while the signal of the *meso*-proton (H-5) shows a chemical shift of 4.88 ppm. Protons of the methyl group appear as a singlet at 1.70 ppm (see SI). The ^{1}H NMR spectrum of bis(indolyl)methane **17** (Figure 2) shows signals corresponding to two indole units, with the N*H* protons at 10.90 ppm and the O*H* proton at 10.43 ppm. Additionally, the CH protons of the indole units can be observed at 7.13 ppm (H-5 and H-6), as well as the *meso*-proton (H-1) at 5.40 ppm. The protons of the methyl group appear as a singlet at 1.80 ppm (see SI).

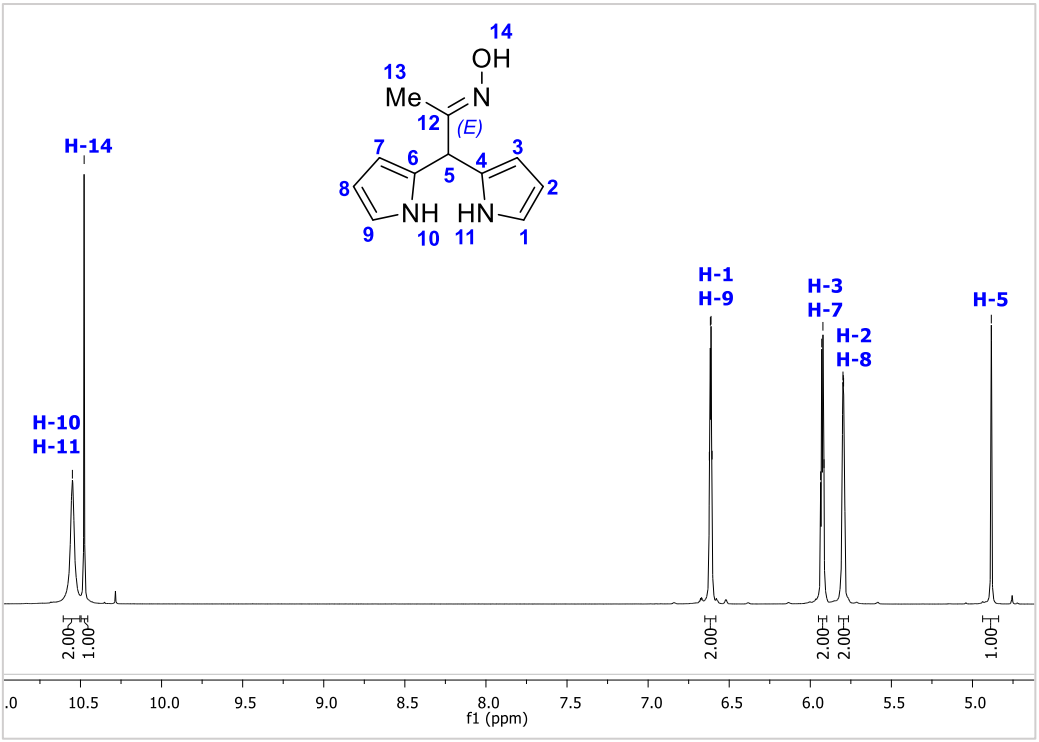


Figure 1. Representative parts of ^{1}H NMR spectrum of dipyrromethane **16**.

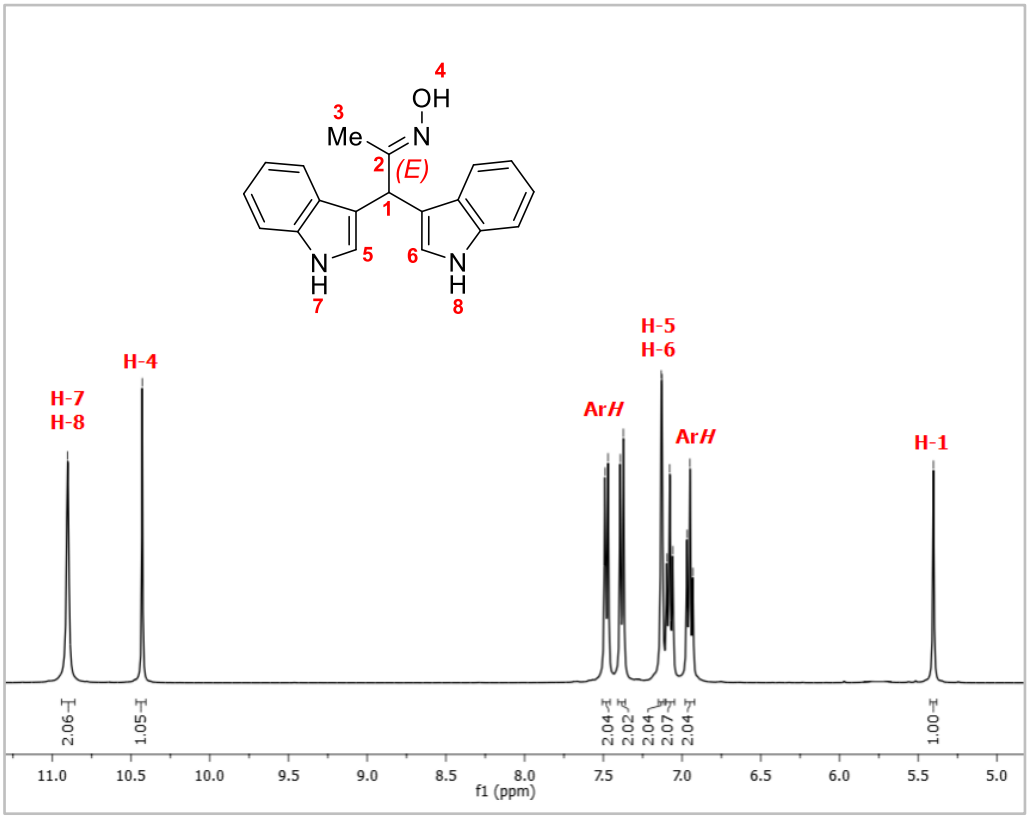


Figure 2. Representative parts of ^{1}H NMR spectrum of bis(indolyl)methane **17**.

CONCLUSIONS

The ability of electrophilic conjugated nitrosoalkenes to participate in Michael addition reactions or hetero-Diels-Alder reactions with electron rich heterocycles is illustrated and demonstrated in these laboratory experiments. The *in situ* generation and reactivity of conjugated nitrosoalkenes toward pyrrole or indole afforded the corresponding dipyrromethane and bis(indolyl)methane, respectively, in a stereo- and regioselective fashion.

These reactions carried out under mild conditions using water as solvent and with short reaction times, involve simple manipulations, easy isolation and handling procedures. The laboratory experiment includes the purification of the compounds through column chromatography, the determination of their purity and the structural analysis using NMR spectroscopy.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, instructions for students and spectra (IR, ^{1}H and ^{13}C NMR spectroscopy).

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Notes

The authors declare no competing financial interest.

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