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Photochemical locking and unlocking of an acyl nitroso dienophile in the Diels–Alder reaction

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ABSTRACT

Photochromic Diels–Alder cycloadducts consisting of acyl nitroso dienophiles, which are known nitroxyl (HNO) donors, and dithienyldienes are presented. The dithienylethene-type photochromic cycloadducts were found to exhibit reversible electrocyclic ring closing and ring opening reactions to 'lock' or 'unlock' the retro Diels–Alder reaction, respectively. The release of an acyl nitroso dienophile via a retro Diels–Alder reaction at 92 °C was shown to occur only from the open or 'unlocked' form of a photochromic dithienylcyclopentene and not from the closed or 'locked' isomer.

Introduction

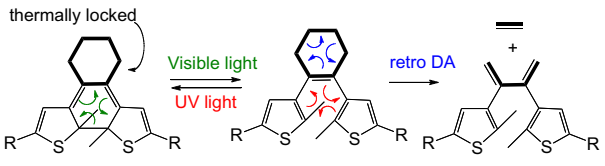
The one-electron reduced and protonated cousin of NO, nitroxyl (HNO), has been rapidly emerging as a novel pharmacological agent.[1] Recent studies demonstrating HNO production in vitro have ignited interest due to its possible endogenous production.[2,3] Furthermore, HNO has many beneficial pharmacological properties, including positive inotropy,[4] vasodilation,[5,6] cardioprotection,[7] and anti-cancer properties.[8] HNO and NO have several key differences in their reactivity. HNO exhibits high reactivity with thiols and is resistant to scavenging by superoxide.[9] This uniqueness has led to the theory that HNO production is actually elevated under pathophysiological conditions and compensates for compromised NO signaling during oxidative stress, where thiol levels are low and superoxide is high.

HNO is a very reactive species and must be generated by a donor molecule. Very recently, Cardioxyl Pharmaceuticals demonstrated that an HNO donor does indeed produce beneficial hemodynamic effects during heart failure.[10] In order to elucidate and exploit the therapeutic utility of HNO, new donors are needed.

It is known that acyl nitroso compounds generate HNO but they must be generated in situ because they are highly reactive.[11] King et al. developed hetero-Diels–Alder (DA) cycloadducts that thermally decompose (via a retro DA reaction) under physiological conditions to release HNO via acyl nitroso formation.[12,13]

Light is an effective trigger to release reactive species from inactive molecules, offering precise spatial and temporal control. Indeed, Miyata and Nakagawa have developed photo-enhanced HNO-releasing hetero DA adducts utilizing photoactive nitro substituted aryl groups.[14] However, such molecules may be limited for biological use due to cellular damage from the wavelengths required (UV-A; 330–380 nm). Branda et al. developed a photochromic dithienylethene capable of releasing a chemical species through a 'photogated' retro DA reaction.[15] Specifically, the thermal retro DA reaction was able to occur only after the photochemical electrocyclic ring opening reaction, (Scheme 1).

Dithienylethene photochromic molecules are ideal molecular switches for biological applications because they are extraordinarily stable against thermal opening/closing reactions, and the HNO release should be promoted by >450 nm irradiation.[16] This is desirable in order to prevent unwanted release of the chemical species, and the lower energy irradiation reduces cellular damage. In this regard, such a 'photogated' retro DA reaction to release an acyl nitroso species would offer the precise spatial and temporal



Scheme 1. Demonstration of the photogated retro Diels–Alder process using photochromic dithienylethenes.

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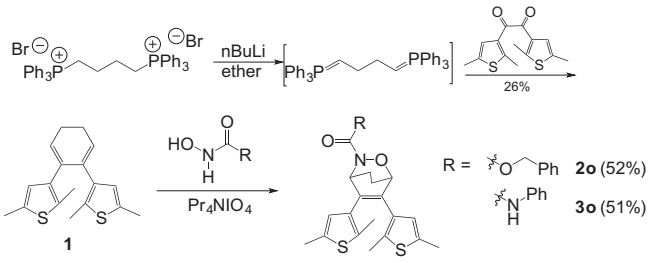


Scheme 2. Synthesis of photochromic carbamate, **2o** and urea, **3o.**

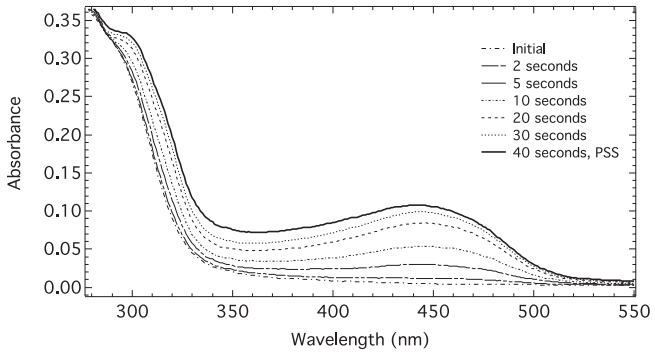
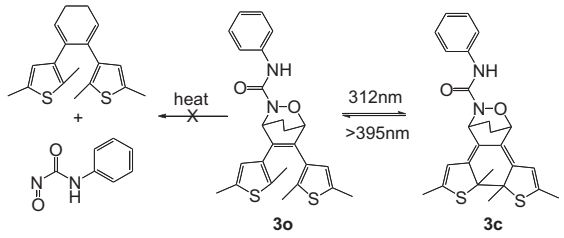


Figure 1. Changes in UV/Vis absorption spectra for **3o** (6.8×10^{-5} M) in acetonitrile solution upon irradiation with 312 nm light.



Scheme 3. The photochemical ring closing reaction of **3o** thermally 'locks' the acyl nitroso dienophile as the DA adduct in **3c**. No retro DA reaction takes place from the 'unlocked' **3o.**

control for the generation of nitroxyl. In this Letter, we describe the photochemical locking and unlocking of DA cycloadducts derived from dithienyldienes and acyl nitroso species. The DA adduct derived from 5,5-dimethylcyclopentadiene was shown to effectively undergo a retro DA reaction to release an acyl nitroso dienophile.

Results and discussion

We first sought the known cyclohexadiene, 2,3-bis(2′,5′-dimethyl-3′-thienyl)cyclohexadiene (**1**), to test the photochromic nature of a DA cycloadduct containing an acyl nitroso dienophile. Each compound was synthesized according to Scheme 2 following the method of Branda[17] to synthesize the cyclohexadiene, **1**. In our hands, the generation of the bis(ylide) was best obtained using nBuLi in diethyl ether at room temperature. The racemic cycloadducts **2o** and **3o** were obtained using tetrapropylammonium periodate oxidation in 52% and 51% yields, respectively.[18]

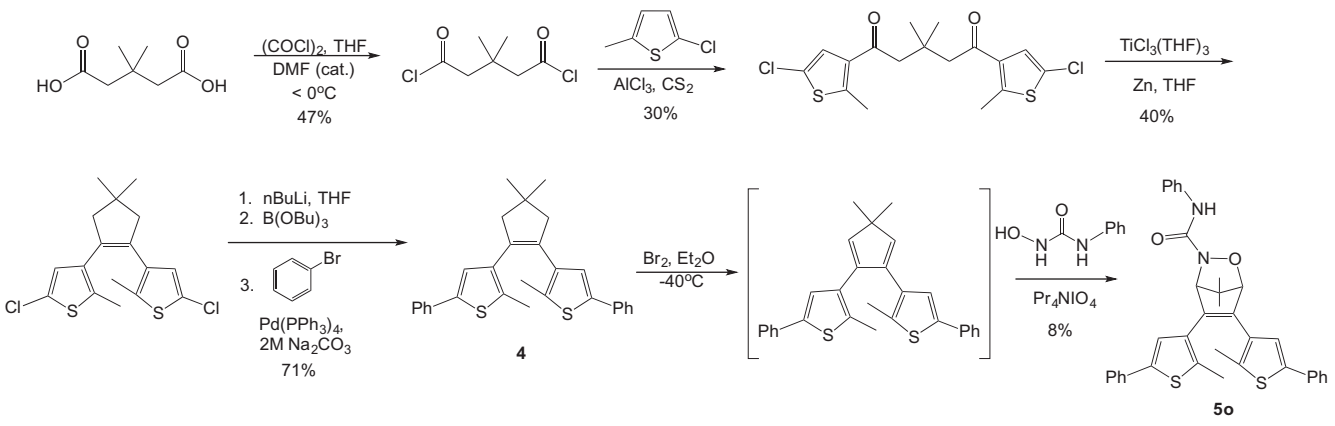
The DA cycloadducts have the appropriate 6π-electron backbone to undergo the characteristic conrotatory electrocyclic ring closing reaction. We studied the cycloadducts derived from both N-hydroxylbenzylcarbamate, **2**, and N-hydroxylphenylurea, **3**. Previous work by Feringa and co-workers[19] has shown that the bis (dimethylthienyl) compounds display incomplete ring closing and begin degrading with extended UV irradiation. This is addressed later with the 5-phenylthiophene substituted system. We found **2** began degrading almost immediately upon irradiation with 312 nm light in acetonitrile solution. A new peak corresponding to the typical closed isomer appears at 440 nm but immediately a peak at 390 nm becomes evident (Fig. S1).

The cycloadduct derived from N-hydroxylurea, however, was more stable upon irradiation at 312 nm and only displays the major peak at 443 nm with no second peak (Fig. 1). The ring closing reaction (Scheme 3) was also monitored by NMR (ca. 1×10^{-3} M in CD_3CN). The photostationary state (PSS) of **3** was found to contain 32% of the closed isomer, **3c**. This is very similar to the system by Branda,[17] suggesting that the dienophile plays little role in the photostationary state.

Upon irradiation with light >395 nm the ring closed isomer slowly reverts back to the ring open isomer **3o** (Fig. S2) after 58 s. However, even after only one cycle of opening and closing, degradation is observed and full closing is never regained.

When **3o** was heated to reflux in toluene or xylenes no cycloreversion was observed, indicating that this system cannot be used as a nitroxyl source.

To address the inability of the system derived from cyclohexadiene to undergo a retro DA reaction and stability issues of **3** we turned to synthesizing **5o** from cyclopentene **4** as shown in Scheme 4. Adding phenyl substituents at the 5-positions of the thiophene is known to greatly increase the stability and fatigue resistance of the photochromic ring opening and ring closing.[16] Furthermore, the molecular design replaces the cyclohexadiene bridge with a 5,5-dimethylcyclopentadiene. Kirby showed that cycloadducts of cyclopentadiene and nitroso species dissociate readily at 80 °C.[18,20] Later, King postulated that the rate of



Scheme 4. Synthesis of the racemic photochromic urea cycloadduct, **5o.**

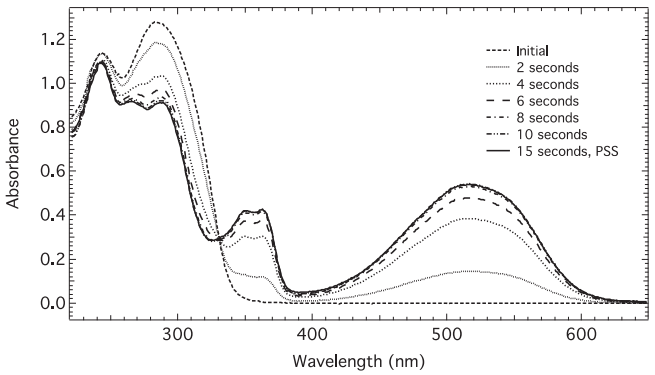


Figure 2. Changes in UV/Vis absorption spectra for **5o** (4.5×10^{-5} M) in acetonitrile solution upon irradiation with 312 nm light.

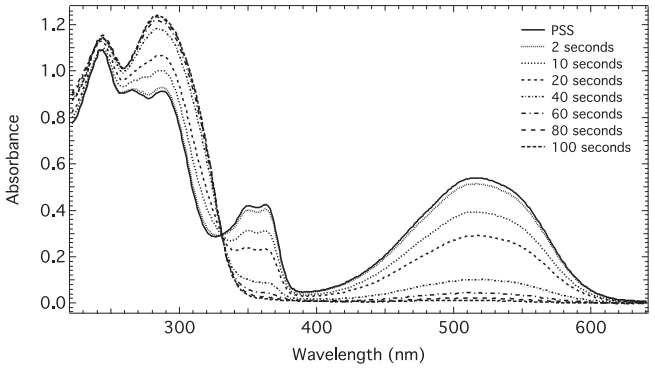


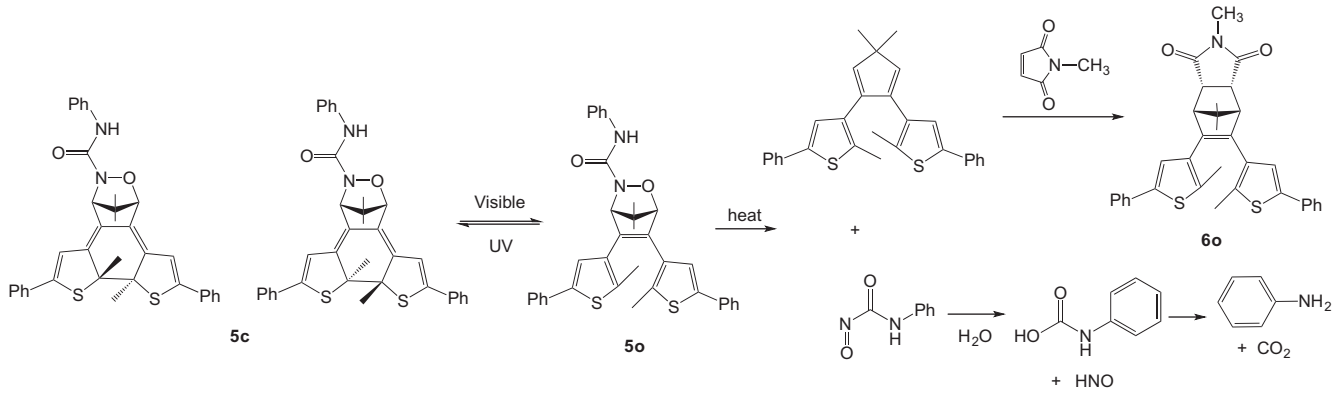
Figure 3. Changes in UV/Vis absorption spectra for **5c** (4.5×10^{-5} M) in acetonitrile solution upon irradiation with >395 nm light.

dissociation of the cycloadducts was more dependent on steric rather than electronic factors of the acyl nitroso species.[13] We envisioned that the bulky N-phenyl nitroso and 5,5-dimethylcyclopentadiene cycloadduct would facilitate the retro DA due to steric factors.

The synthesis began with converting commercially available 3,3-dimethylglutaric acid to the acyl chloride using oxalyl chloride and catalytic DMF in THF at 0 °C in 47% yield.[21] Next, Friedel-Crafts acylation using 2 equiv of 2-chloro-5-methylthiophene with aluminum chloride in carbon disulfide produced the (bis)thienyl in 30% yield.[19] McMurry coupling using titanium chloride tetrahydrofuran complex and powdered zinc yielded the cyclopentene in 40% yield.[19] Suzuki coupling of bromobenzene provided 1,2-bis(2-methyl-5-phenylthiophen-3-yl)cyclopent-1-ene (**4**) in 71% yield. The next step was to produce the diene using bromine in diethyl ether.[15] In our hands, this reaction never went to completion and starting material remained by TLC analysis. Attempts to isolate the diene by column chromatography led to degradation, so the DA reaction was performed on the crude diene after simple extraction and workup. Adding 1-hydroxy-3-phenylurea to an acetonitrile/dichloromethane solution containing the crude diene and tetrapropylammonium periodate at 0 °C produced the racemic cycloadduct **5o** in 8% yield. Purification was accomplished via silica gel chromatography with EtOAc/hexanes (1:9) containing 1% triethylamine. The product was characterized by ^{1}H, ^{13}C, IR, and HRMS.

Irradiation of **5o** with 312 nm light in acetonitrile produced a deep red/violet solution with a new band in the visible spectrum (Fig. 2). Photobleaching is accomplished upon irradiation of the sample with >395 nm light (Fig. 3). **5** displays moderate fatigue resistance and degrades 11% after three full cycles. The time required to achieve ring closing and ring opening was 15 and 100 s, respectively. ^{1}H NMR spectroscopic studies performed in deuterated DMSO were carried out to observe the ratio of ring closed to ring opened isomers. Due to the asymmetry in the closed ring form (Scheme 5), diastereomers are produced. Observation of the four new bridgehead protons from these diastereomers allowed for the quantification of the photostationary state. After 210 s of irradiation of a 2×10^{-3} M DMSO solution the photostationary state was reached with 90% closed isomer. This is a main advantage of **5** over **3,** given that the closed form is the inactive isomer toward the retro DA reaction and a 'locked' system, **5c** (Scheme 5), was produced.

Our attention now turned to the retro DA reaction on the 'unlocked' **5o**. Previous studies by Kirby have shown the cycloreversion to produce cyclopentadiene and an acyl nitroso compound takes place at 80 °C in several hours in benzene or ethyl acetate.[18] ^{1}H NMR spectroscopic studies in either deuterated toluene or DMSO (Fig. S3 and Scheme S1) were used to follow the retro DA reaction. To a deuterated toluene solution of **5o** (1.47×10^{-2} M) was added 1 equiv of N-methylmaleimide. Heating was increased stepwise from 60 °C to 92 °C at which point a noticeable change in the NMR spectrum occurred (Fig. 4). After 24 h at 92 °C the maleimide adduct **6o** (Scheme 5) was present as shown in Figure 4c. The bridgehead and bridge protons of **6o** become evident at 2.83 and 2.92 ppm (Fig. 4c, up arrow), showing the splitting of the expected endo isomer.[22] Due to the symmetry of **6o**, the thiophene protons produce the singlet at 7.38 ppm (Fig. 4c, up arrow). Finally, the down arrows in Figure 4a show the disappearance of the



Scheme 5. Demonstration of the photochemical 'locking' (**5c**) and 'unlocking' (**5o**) of the retro DA reaction. Upon release of the acyl nitroso dienophile nitroxyl is likely generated in aqueous systems. The released cyclopentadiene is trapped with N-methylmaleimide to give cycloadduct **6o.**

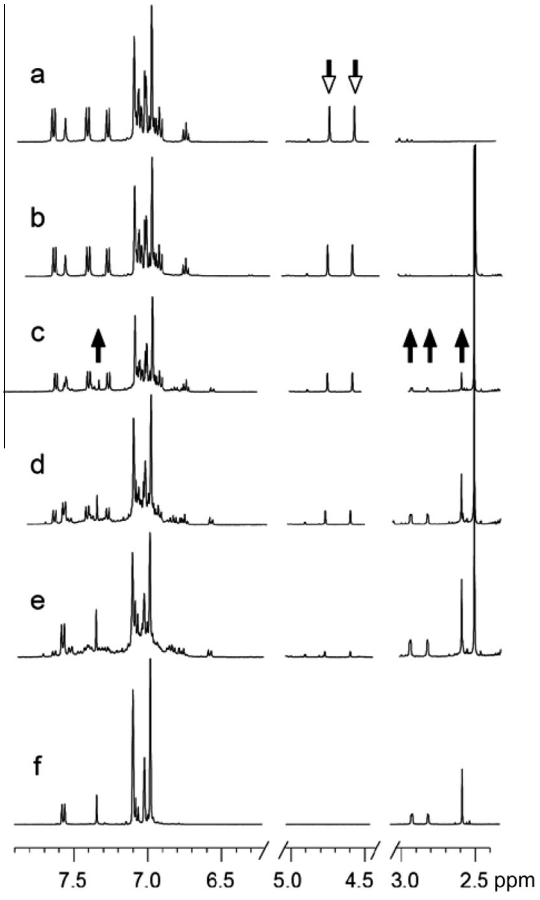


Figure 4. Selected ^{1}H NMR (ppm) in d-toluene showing (a) urea adduct **5o**, (b) **5o** and N-methylmaleimide, (c) **5o** and N-methylmaleimide with new maleimide adduct (**6o**) formation after 24 h of heating at 92 °C, (d) 48 h of heating at 92 °C, (e) 72 h of heating at 92 °C, (f) isolated **6o.**

bridgehead protons of **5o**. The N-methylmaleimide adduct, **6o**, was isolated by prep TLC (20% EtOAc/hexanes) and characterized by ^{1}H, ^{13}C, IR, and HRMS. The steric bulk of the dimethyl group incorporated into the molecular design did not enhance the retro DA reaction rate compared to Kirby's system.

NMR studies in d-DMSO revealed the formation of aniline, most likely the byproduct of the acyl nitroso hydrolysis in the presence of residual water. This suggests nitroxyl may form under such decomposition conditions (Scheme 5). **5c** was stable for six hours at 92 °C in DMSO but began to decompose upon longer heating, and after 24 h the deep red-purple solution was blue-green. To test the possibility of a thermal ring opening reaction, purified **5c** was added to N-methylmaleimide and heated. No maleimide adduct was observed by NMR. Attempts to isolate and characterize the decomposition product are ongoing. Interestingly, the maleimide adducts **6o** and **6c** are stable for greater than 48 h at 90 °C in toluene.

Conclusions

We have presented an example of a photogated reaction in which an 'unlocked' photochromic isomer releases an acyl nitroso compound whereas the 'locked' isomer shows no evidence of release; however, it does decompose at the required temperature. Fine-tuning of the thienyl substituents (as compared to phenyl) can red shift the absorption peak of the closed isomer more substantially, making it useful in biological applications. The high temperature required for the acyl nitroso release represents an opportunity for additional improvement. The photochemical locking of this system can be used to trap reactive acyl nitroso species onto other previously unstudied dienes, such as fulvene, that may ultimately allow for lower temperature release. Such a system may eliminate the complexity of an equilibrium between diene, unstable dienophile, and cycloadduct. In addition to these types of molecular modifications, further work involves using GC/MS and electron paramagnetic resonance spectroscopy to indirectly probe for nitroxyl formation.

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Supplementary data

Supplementary data (UV/Vis Figs. S1 and S2, NMR Fig. S3, Scheme S1, synthetic procedures, and compound characterization including ^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.044.

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