



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



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ARTICLE INFO

Article history:

Received 13 January 2016

Revised 10 February 2016

Accepted 11 February 2016

Available online 12 February 2016

Keywords:

Gated photochromism

Acyl nitroso

Diels–Alder

Nitroxyl

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.

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Introduction

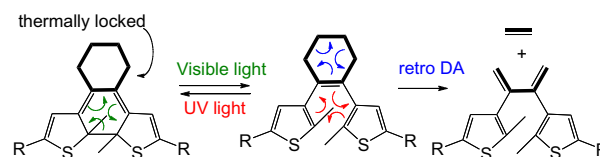
The one-electron reduced and protonated cousin of NO, nitroxyl (HNO), has been rapidly emerging as a novel pharmacological agent.¹ Recent studies demonstrating HNO production in vitro have ignited interest due to its possible endogenous production.^{2,3} Furthermore, HNO has many beneficial pharmacological 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).

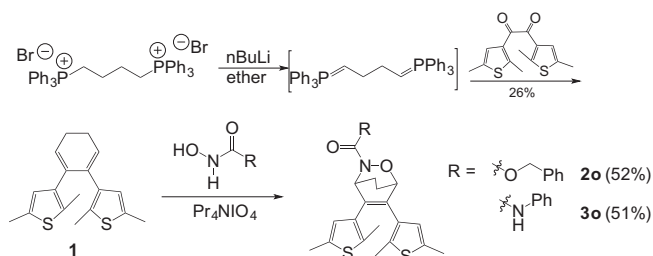
Dithienylethene photochromic molecules are ideal molecular switches for biological applications because they are extraordinarily stable against thermal opening/closing reactions, and the HNO release should be promoted by >450 nm irradiation.¹⁶ This is desirable in order to prevent unwanted release of 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**.

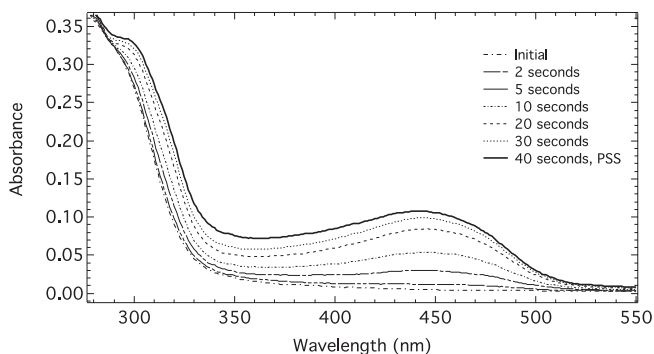
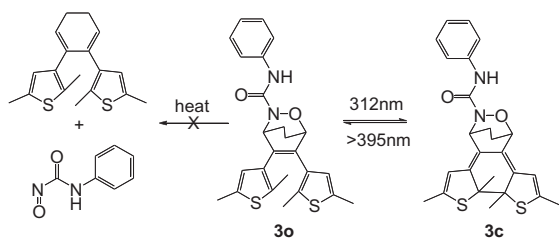


Figure 1. Changes in UV/Vis absorption spectra for **3o** (6.8×10^{-5} M) in acetonitrile solution upon irradiation with 312 nm light.



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 *n*BuLi 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

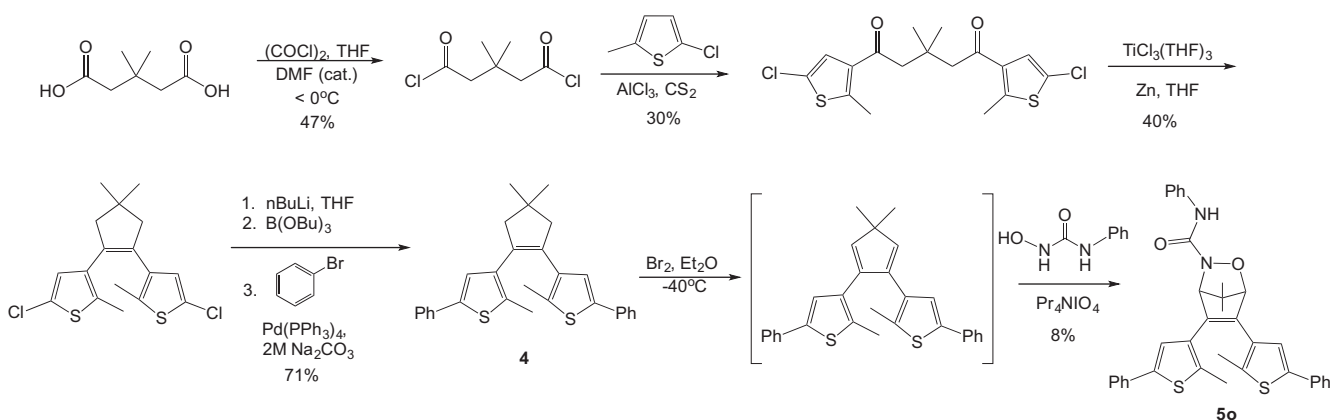
The DA cycloadducts have the appropriate 6π -electron backbone to undergo the characteristic conrotatory electrocyclic ring closing reaction. We studied the cycloadducts derived from both *N*-hydroxybenzylcarbamate, **2**, and *N*-hydroxyphenylurea, **3**. Previous work by [Feringa](#) and co-workers¹⁹ 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*-hydroxyurea, 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**.

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