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Synthesis and Reactivity of Dibenzoselenacycloheptynes

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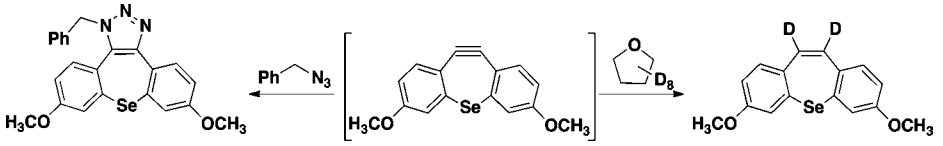
ABSTRACT



Dibenzoselenacycloheptynes were prepared in three steps from commercially available reagents and trapped *in situ* with benzyl azide to form the corresponding triazoles. Surprisingly, the dibenzoselenacycloheptynes also abstracted hydrogen atoms from solvents such as THF or toluene, forming dibenzoselenacycloheptene products. These alkenyl compounds arise from a hydrogen transfer reaction from solvent to the unisolable intermediate, and we postulate that the reaction proceeds via a radical mechanism originating from the strained alkynyl bond that has unusually high radical character.

Angle-strained cycloalkynes have long been a topic of interest to chemists due to their unique physical properties and chemical reactivity.[1] In recent years, these attributes have been exploited for applications in biological labeling.[2] For example, the ring strain associated with cyclooctynes (**1**, Figure 1) enables their facile 1,3-dipolar cycloaddition with azides, a bioorthogonal reaction often termed "copper-free click chemistry" that produces a biologically inert triazole adduct.[3,4] Over the past decade, modifications to the cyclooctyne scaffold have been explored in an effort to increase the rate of cycloaddition. This has been accomplished by modulating the electronics of the cyclooctyne, for example through the addition of propargylic fluorine atoms as in **2**,[5] or by increasing ring strain through the addition of sp^2 centers, as in **3**,[6] or by fusing a cyclopropane ring to the cyclooctyne.[7]

Recently, we explored the utility of cycloheptynes containing an endocyclic heteroatom as reagents for copper-free click chemistry. We showed that tetramethylthiacycloheptyne (TMTH, **4**) is stable under biologically relevant conditions and that the compound undergoes the desired cycloaddition with azides faster than any other isolable cycloalkyne.[8] In principle, one might further increase the ring strain of TMTH through the introduction of two fused aryl rings. However, dibenzothiacycloheptyne **5** is known to be unstable, as is its sulfoxide analog and the all-carbon congoner.[9,10]

Here we explored the chemistry of derivatives of the previously unknown dibenzoselenacycloheptyne **6**. We hypothesized that introduction of a selenium atom, which

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(2) (a) In zebrafish, see: Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. *Science* **2008**, *320*, 664. (b) In *C. elegans*, see: Laughlin, S. T.; Bertozzi, C. R. *ACS Chem. Biol.* **2009**, *4*, 1068. (c) In mice, see: Chang, P. V.; Prescher, J. A.; Sletten, E. M.; Baskin, J. M.; Miller, I. A.; Agard, N. J.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3988. (d) Koo, H.; Lee, S.; Na, H. J.; Kim, S. H.; Hahn, S. K.; Choi, K.; Kwon, I. C.; Jeong, S. Y.; Kim, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11836–11840.

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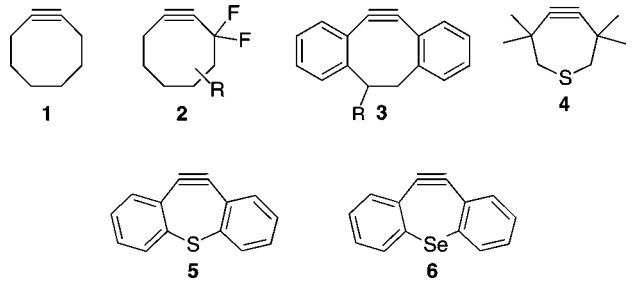
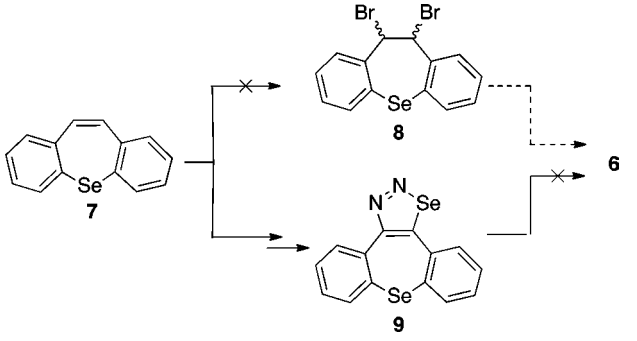


Figure 1. Strained cycloalkynes prepared previously (**1**–**5**) and discussed here (**6**).

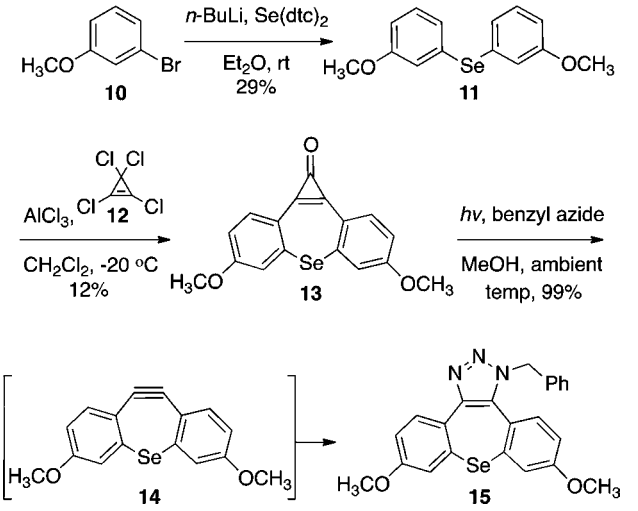
is larger than sulfur, might offset the increased ring strain resulting from fused aryl rings, thereby leading to a stable structure.[11] Our first approach to the synthesis of **6** involved double elimination of the 1,2 dibrominated derivative of alkene **7** (**8**, Scheme 1), an approach that has previously been used in the preparation of the sulfoxide analog of compound **5** as well as the dibenzooxacycloheptyne.[10] Unfortunately, our various attempts to add bromine across the alkene of **7** led to a complex mixture of products.

Scheme 1. Attempted Synthetic Routes to Alkyne **6** via Alkene **7**



We next attempted the synthesis of **6** via selenadiazole **9** (Scheme 1, Scheme S1), a route analogous to the one used to prepare compound **5** and its all-carbon congoner.[9] Selenadiazoles can be thermally disproportionated to reveal alkynes without the use of harsh reagents,[12] and they can be prepared from ketone precursors that are readily accessible from alkenes such as **7**. However, thermolysis of selenadiazole **9** proved challenging, and **6** was never obtained. No identifiable derivatives of **6** were isolated in the presence of traps such as benzyl azide or furan, and attempts to unmask the alkyne via nucleophilic attack of the selenadiazole also proved unsuccessful.[13] Despite these setbacks, we were certain that **6** was not too strained to exist transiently in solution; after all, the sulfur-, oxygen-, and carbon-cycloheptyne analogs have been indirectly observed by trapping *in situ*.[9,10] We suspected that the high temperature and nucleophilic conditions necessary to cleave the selenadiazole of **9** were simply too forcing even for transient persistence of **6**.

Scheme 2. Synthesis and Trapping of Cycloalkyne **14**[a]



[a] $Se(dtc)_2$ = selenium diethyldithiocarbamate.[16]

Our next strategy relied on formation of the strained alkyne by photolysis of a cyclopropenone precursor,[14] a method that has proven to be functional group tolerant and mild enough to produce strained cyclooctynes in good yield (Scheme 2).[15] To make cyclopropenone **13**, we performed a lithium–halogen exchange on commercially available aryl bromide **10** and treated the aryl lithium intermediate with selenium diethyldithiocarbamate ($Se(dtc)_2$)[16] to yield diaryl selenide **11**. Compound **11** underwent a Friedel–Crafts reaction with tetrachlorocyclopropene **12** in the presence of $AlCl_3$, and *in situ* hydrolysis of the dichlorocyclopropene product resulted in **13**. Gratifyingly, when a solution of **13** in methanol was irradiated in the presence of benzyl azide, the desired triazole **15** was obtained in quantitative yield, indicating that the alkyne photodecarbonylation product **14** had formed. But, we could not isolate **14** when the same reaction was performed under ambient conditions without an azide trap.

In a further attempt to isolate **14**, we performed the photolysis reaction at 0 °C in THF in the absence of a trap.[17] Unexpectedly, alkene **16** was the only product formed (Scheme S3). When the reaction was repeated in

(11) DFT calculations indicate that the alkynyl bond angles are approximately 148°, larger (and thus presumably less distorted) than those shown for the stable compound TMTH[1a] (Figure S3).

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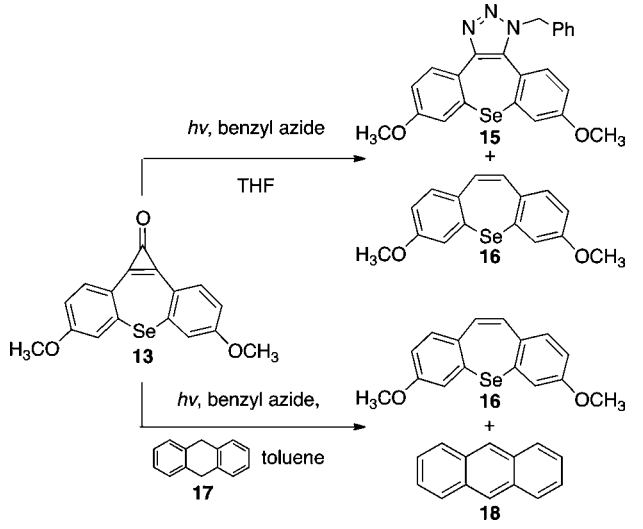
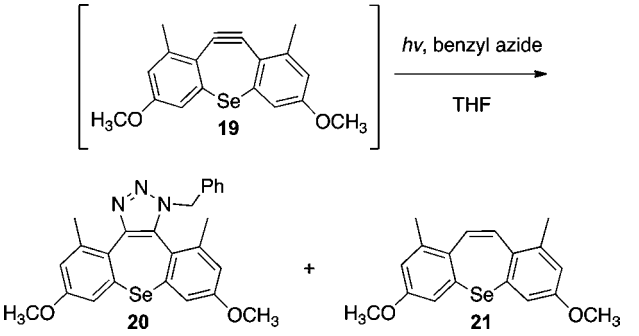
Scheme 3. Photodecarbonylation Products of **13**



Scheme 4. Trapping and Reduction of Alkyne **20**



THF with an excess of benzyl azide, a 2:1 mixture of **15** and **16** was obtained (Scheme 3), indicating that the two products are formed on a similar time scale. Given the exceedingly short lifetimes of the intermediates in the photodecarbonylation reaction,[14] we presume that the alkene results from transfer of two hydrogen atoms from the solvent to the alkyne of **14** or to a photoexcited product thereof. The decreased yield of compound **16** when the reaction was performed in the presence of azide indicates that it originates from the same intermediate alkyne **14** that reacts with benzyl azide to form **15**. To verify that the vinyl hydrogen atoms were in fact originating from the THF solvent, we performed the photodecarbonylation reaction in THF-d_8 and obtained only the dideutero alkene analog of **16** (Scheme S4).[18]

Highly reactive strained cycloalkynes such as TMTH and cyclooctyne have been reported to undergo hydrogen transfer reactions with alcohols, amines, and thiols.[1a] With alcohols, the reaction is thought to proceed via a pericyclic mechanism.[19,20] In this case, however, we thought it more likely that alkyne **14** reacts as a diradical that can abstract hydrogen atoms from the solvent. In accordance with this hypothesis, we performed the photodecarbonylation reaction in toluene, a nonprotic and non-nucleophilic solvent, and again obtained alkene **16** as the major product.

To further explore the possibility that alkyne **14** behaves as a diradical, we added 9,10-dihydroanthracene (DHA, **17**) to the reaction. The weak methylenic C–H bonds of DHA make this compound a good donor of two succesive hydrogen atoms, after which it is converted to anthracene (**18**) (Scheme 3, Figure S1).[21,22] Furthermore, DHA should not initiate radical reactions, so obtaining anthracene as a reaction product would strongly indicate that the radical originates from the dibenzoselenacycloheptyne. In accordance with this hypothesis, photodecarbonylation of **13** in the presence of DHA in toluene did produce anthracene while a control reaction lacking **13** left DHA unaltered (Figure S2). From these experiments, we conclude that the alkynyl bond in **14** has significant diradical character that can dictate some of its reactivity pathways.

Adding ortho methyl groups to diaryl cycloalkynes has been shown to greatly decrease their reactivity via steric blocking of the alkyne.[23] We were curious whether such a modification to **14** might have a differential effect on the rates of its cycloaddition and hydrogen abstraction reactions. Therefore we prepared **19**, the dimethylated analog of **14**, using the same synthetic strategy used in the parent compound's synthesis (Scheme S5). Upon irradiation of the dimethylated cyclopropenone with excess benzyl azide in THF, triazole **20** was indeed obtained, indicating that **19** had formed in the course of the reaction (Scheme 4). However, this was the minor product, obtained in only 7% yield, in a mixture with alkene **21** as the major product. Thus, the bis-orthomethyl groups slowed the rate of the cycloaddition with benyl azide moreso than the rate of hydrogen atom transfer. It is important to note that the mechanism of the cycloaddition with benzyl azide does not necessarily proceed via the radical; most reactions of this type are believed to be concerted pericyclic reactions.[24]

In summary, we developed a short synthetic route to make dibenzoselenacycloheptynes, a new type of strained alkyne with unexpected properties. These compounds are not stable enough to be isolated due to their ability to abstract hydrogen from solvents such as toluene and THF.

(17) We could not perform the reaction at 0 °C in methanol due to the limited solubility of compound **13**.

(18) The analogous reaction in toluene-d_8 also yielded the dideutero alkene. However, in this case the product mixture was much more complex.

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(26) Compound **4** is known to react with triplet oxygen (Turro, N. J.; Ramamurthy, V.; Liu, K.-C.; Krebs, A.; Kemper, R. *J. Am. Chem. Soc.* **1976**, *98*, 6758), but the reaction is 3 orders of magnitude slower than that with singlet oxygen.

Furthermore, this hydrogen abstraction appears to be initiated by a diradical form of the alkyne, an unusual mode of reactivity for strained alkynes.[25,26] Thus, while these compounds have limited use as bioorthogonal reagents, they may find applications in studies of organic radicals.

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Supporting Information Available. Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.