Synthetic Methods

DOI: 10.1002/ange.201208294

Se-Phenyl Prop-2-eneselenoate: An Ethylene Equivalent for Diels–Alder Reactions**

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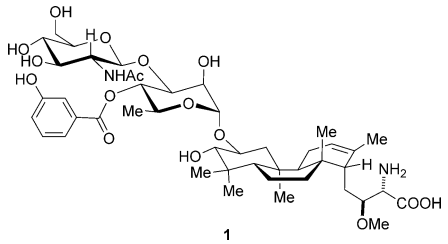
A large number of dienes and dienophiles have been employed in the Diels–Alder reaction[1] to produce cyclohexene products with high facial, regio-, stereo-, and enantioselectivity. The reactions work best when the dienophile is substituted with an electron-withdrawing group. However, often in synthesis, the addition of an ethylene unit to a diene is necessary, and the normal cycloaddition with ethylene requires too forcing conditions to be used easily.[2] Consequently, several "ethylene equivalents" for Diels–Alder reactions have been developed, e.g., vinyl phenyl sulfone,[3] acrolein,[4] nitroethylene,[5] vinyldihaloboranes,[6] among others.[7] In an approach to the total synthesis of brasilicardin A, **1**,[8] we needed an ethylene equivalent for the preparation of the C ring. Since many of the known ethylene equivalents did not work well for various reasons, we decided to develop a new ethylene equivalent for Diels–Alder cycloadditions, *Se*-phenyl prop-2-eneselenoate (phenyl selenoacrylate). Herein we report the successful accomplishment of that goal.



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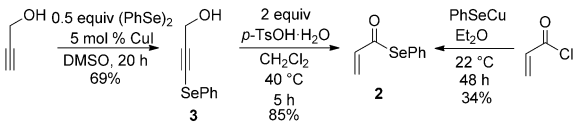
The known[9] *Se*-phenyl prop-2-eneselenoate, **2**, was prepared from propargyl alcohol by copper-catalyzed phenylselenylation[10] of the alkyne to give **3** in 69% yield, followed by a Meyer–Schuster rearrangement to furnish the phenyl selenoacrylate **2** in 85% yield (Scheme 1).[9] An easier preparation of **2** involved an application of the work of Reissig and Scherer,[11] namely reaction of acryloyl chloride

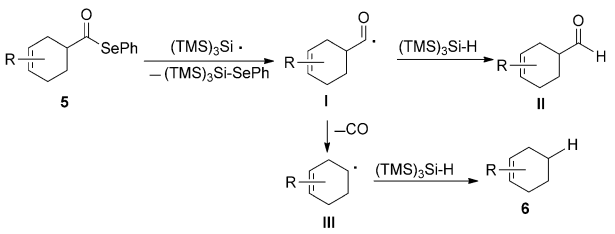


Scheme 1. Synthesis of *Se*-phenyl prop-2-eneselenoate **2**.

with phenylseleno copper which gave the desired selenoacrylate **2** in 34% yield.

We then studied the Diels–Alder reactions of **2**. Hart et al.[12] had shown that selenoacrylates are much more reactive than normal acrylates, presumably owing to poorer overlap between the selenium atom and the carbonyl group, thereby making the carbonyl group more ketone-like rather than ester-like. Thus reaction of **2** with a series of dienes **4 a**–**j** in toluene at reflux for 12 h gave the Diels–Alder adducts **5 a**–**j** in 80–95% yield (Table 1). The regiochemistry of addition was very good, but we usually isolated a mixture of *endo* and *exo* stereoisomers, with the *endo* isomer predominating. For adducts **5 c**, **5 d**, and **5 e** the *endo* stereochemistry was proven by conversion of the seleno ester to the known methyl esters[13] and comparison of the NMR spectra. This mixture did not pose a problem, since that stereocenter is destroyed in the reduction step. Many dienes were used, e.g., substituted butadienes, cyclic dienes, and 2-alkoxyvinyl cyclohexenes. In the case of diene **4j**, we isolated a mixture of four cycloadducts **5j** (as a roughly 1:1 mixture of regioisomers) and showed them to be the expected *endo* and *exo* isomers of the original Diels–Alder reaction (2:1) and the two compounds resulting from an allylic shift, also in a 2:1 *endo*:*exo* ratio. This allylic shift is a process that we have seen before in the presence of Lewis acids.[14] Thus the phenyl selenoacrylate **2** is a reactive dienophile that gives good yields of cycloadducts.

To serve as an ethylene equivalent, the reductive removal of the seleno ester group has to be easy and high-yielding. When we treated the cycloadducts **5** with tris(trimethylsilyl)-silane[15] (2 equiv) and AIBN (0.2 equiv) in either isooctane (method A) or toluene (method B) at reflux for one hour, we obtained generally very good yields of the corresponding



Scheme 2. Radical-promoted reduction of seleno esters with tris(trimethylsilyl)silane.

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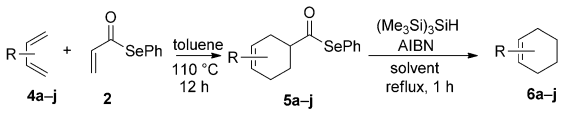
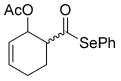
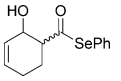
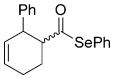
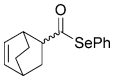
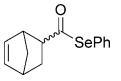
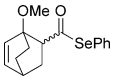
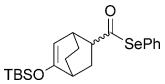
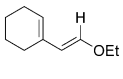
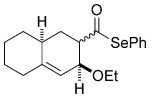
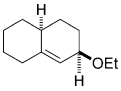
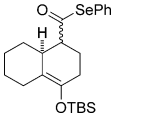
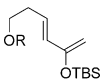
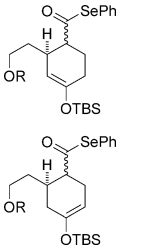
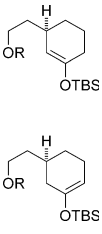
[**] The mass spectrometer used in this project was supported by the National Center for Research Resources under grant number S10RR025631. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The NMR spectrometers were supported by the National Science Foundation under equipment grant no. CHE-1048804.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208294.

Table 1: Diels–Alder cycloadditions of dienes **4 a–j** with **2** and reduction of **5 a–j** to give **6 a–j**.



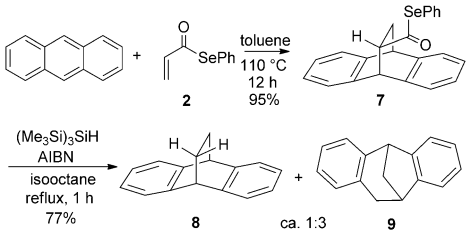
	Diene	Cycloadduct	Yield [%]; *endo/exo*	Reduction product	Yield [%][b]
a			96; >10:1		93 (A)[c] 73 (B)[c]
b			91;[a] 2.2:1		79 (A) 80 (B)
c			88; 3:2		93 (A) 99 (B)
d			97; 8:1		63 (A) 68 (B)
e			91; 9:1		88 (A) 87 (B)
f			87; 5.1:1		67 (A)
g			66; 2.2:1		72 (A) isol.
h			81; 2.8:1		80 (A) 65 (A) isol.
i			85; 2:1		95 (A) 82 (A) isol.
j	 R = TBDPS		86; 2:1		95 (A) 84 (A) isol.

[a] The initial silyl ether Diels–Alder product was hydrolyzed to the alcohol with citric acid. [b] See text for methods A and B. Yield determined by NMR spectroscopy unless otherwise stated. [c] Yield determined by GC–MS. AIBN = azobisisobutyronitrile, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

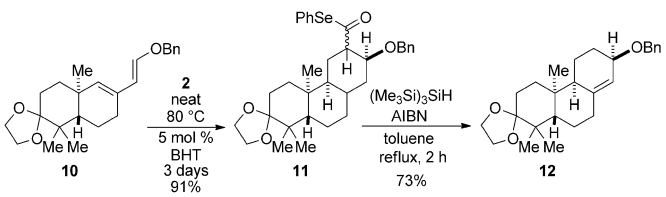
hydrocarbon. The mechanism of reduction (Scheme 2) involves removal[15] of the phenylseleno group of **5** by the silyl radical to generate the acyl radical **I**, which can then either be reduced to the aldehyde **II** or first suffer decarbonylation to give the alkyl radical **III** and thence the hydrocarbon product **6** through reaction with the silane. Since many of the reduction products were volatile, we determined the yield of the reduction by integration of the appropriate peaks in the NMR spectra of the products and compared them to an added standard.[16] In those cases where the products were relatively nonvolatile, yields of isolated products are given. The yields range from 63–99 %. One additional case (Scheme 3) affords information on the lifetime of the alkyl radical **III** formed. Reduction of **7**, which was prepared by cycloaddition of anthracene with **2** in 95 % yield, in isooctane resulted in isolation of the two known products **8**[3a] and **9**[17] in 77 % yield in a 1:3 ratio, which was determined by ^{1}H NMR spectroscopy. Thus the alkyl radical on the bridge of the [2.2.2] bicycle can effectively rearrange[17] to the more stable benzylic radical in the [3.2.1] bicycle before it reacts with the silane.

Finally we investigated the use of this new ethylene equivalent in our approach to the synthesis of brasilicardin A (Scheme 4). The diene **10**[18] was reacted with **2** neat at 80 °C for three days in the presence of 3,5-di(*tert*-butyl)-4-hydroxytoluene (BHT, 5 mol %) to give a 91 % yield of a mixture of the *endo* and *exo* cycloadducts **11**, as only one regioisomer. The key reduction step was carried out using ten equivalents of the silane in toluene at reflux for two hours and led to isolation of the desired allylic ether **12** in 73 % yield. It should be pointed out that the reduction of this substrate **11** is quite sensitive to loss of the allylic benzyloxy group and no other ethylene equivalent worked well to prepare **12**.

In conclusion, we have developed a new ethylene equivalent for Diels–Alder cycloadditions, namely phenyl selenoacrylate **2**. It reacts with a variety of dienes **4** to give high yields of the desired cycloadducts **5**, which can be readily converted to the hydrocarbons **6** by treatment with tris(trimethylsilyl)silane and AIBN. Further use of this process and the synthetic approach to brasilicardin A will be described later.



Scheme 3. Rearrangement of the dibenzobicyclo[2.2.2]octyl radical.



Scheme 4. Transformation of diene **10** into alkene **12**.

Received: October 15, 2012
Published online: January 11, 2013

Keywords: cycloaddition · Diels–Alder reaction · radical reactions · selenium · synthetic methods

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