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Preparation and Diels−Alder Reactivity of 1-Amino-3-siloxy-1,3-butadienes

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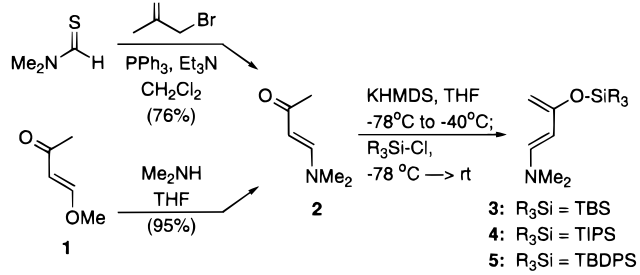
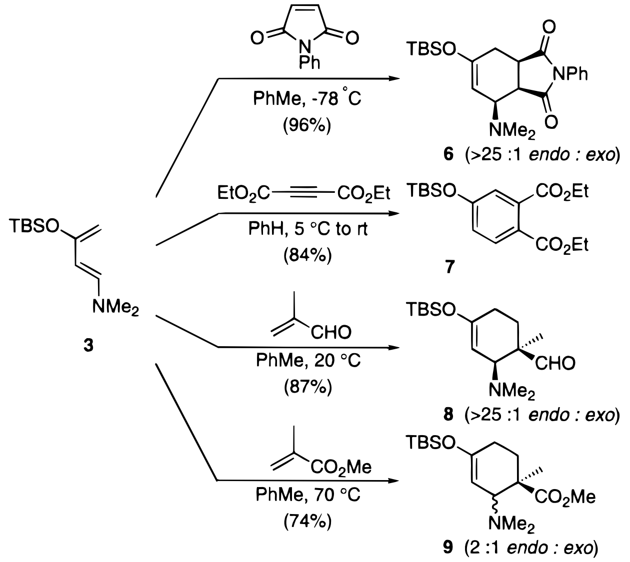
The synthetic potential of the Diels−Alder reaction has been greatly expanded over the years through modification of the diene and dienophile components.[1] Lone pair-containing heteroatom substituents on the diene, for example, render it more reactive to dienophiles and lead to improved regioselectivity in the cycloaddition.[2] As an added benefit, the heteroatom also serves as a handle for further functionalization of the product. Among the most extensively investigated heteroatom-substituted dienes are mono- and dialkoxybutadienes,[3] such as the widely used 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene, known also as Danishefsky's diene.[4] Amino-substituted dienes have also been synthesized and used in the Diels−Alder reaction.[5] By contrast, 1-amino-3-siloxy dienes have received little attention.[6,7] We report here the first preparation of the parent 1-amino-3-siloxy-1,3-butadiene and describe its usefulness in Diels−Alder reactions.

Amino siloxy diene **3** was prepared in high yield from vinylogous amide **1**, which is available via either a one-pot Eschenmoser contraction procedure[8] or an addition elimination reaction of vinylogous ester **2** (Scheme 1).[9] Deprotonation of **1** with potassium bis(trimethylsilyl)amide (KHMDS) and subsequent trapping of the resulting enolate with *tert*-butyldimethylsilyl chloride (TBS-Cl) afforded essentially pure 1-(dimethylamino)-3-siloxy-1,3-butadiene **3** in nearly quantitative yield.[10] Diene **3** is quite stable to normal handling and, if desired, can be further purified by vacuum distillation (85−90% yield). Dienes protected with the bulkier TIPS and TBDPS groups were prepared analogously and exhibit similar reactivity, although offered no particular advantage.[11] Having an enamine unit and an enol ether unit, both in a synergystic arrangement, these dienes were expected to be very reactive in Diels−Alder reactions.

Scheme 1



Scheme 2



The initial studies were designed to evaluate the reactivity of 1-amino 3-siloxy dienes. Diene **3** reacts with doubly-activated dienophiles at or below 0 °C. Indeed, the reaction of **3** with *N*-phenylmaleimide was complete in about 1 h at −78 °C and gave exclusively the *endo*-adduct **6**, in 96% yield after chromatography (Scheme 2). The cycloaddition of **3** with diethyl acetylenedicarboxylate proceeded efficiently at 5 °C and gave directly the aromatized cycloadduct **7**. Slightly higher temperatures were required for cycloadditions with monoactivated dienophiles, such as methacrolein and methyl methacrylate. It is noteworthy that whereas the reaction with the former was highly *endo*-selective, that with the latter gave a significant amount of the *exo* diastereomer. These results suggest that 1-amino-3-siloxybutadienes are considerably more reactive than 1-methoxy-3-siloxy-1,3-butadiene. For comparison, the Diels−Alder reaction between Danishefsky's diene and *N*-phenylmaleimide is reported to require 0 °C to room temperature,[12] and with dimethyl acetylenedicarboxylate and methacrolein, refluxing benzene.[13]

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(1) Oppolzer, W. Intermolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol 5, pp 315−400.

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(3) (a) Shavrygina, O. A., Makin, S. M. *Khim-Farm. Zh.* **1969**, *3*, 17. (b) Cazeau, P., Frainnet, E. *Bull. Soc. Chim. Fr.* **1972**, 1658−1659. (c) Jung, M. E., McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935−2938. (d) Ibuka, T., Mori, Y., Inubushi, Y. *Tetrrahedron Lett.* **1976**, 3169−3172. (e) Obrecht, D. *Helv. Chim. Acta* **1991**, *74*, 27−46.

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(6) (a) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308, and recerences cited therein. (b) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098.

(7) 1-Amino-3-ethoxy-1,3-butadiene was previously prepared but never used in a Diels−Alder reaction: Meerwein, H.; Florian, W.; Schon, N.; Stopp, G. *Liebigs Ann.* **1961**, *641*, 1.

(8) For a recent review, see: (a) Shiosaki, K. Eschenmoser Coupling Reaction. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol 2, pp 865−892. Also, see: (b) Ireland, R. E.; Brown, F. R. *J. Org. Chem.* **1980**, *45*, 1868.

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(10) Other dialkylamino-substituted dienes were similarly prepared. Details of their synthesis and reactivity will be reported in due course.

(11) Dienes **3**−**5** are slowly hydrolyzed in water and in the presence of Lewis acids.

(12) Baldwin, S. W.; Greenspan, P.; Alaimo, C.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 5877.

S0022-3263(97)00438-6 CCC: $14.00

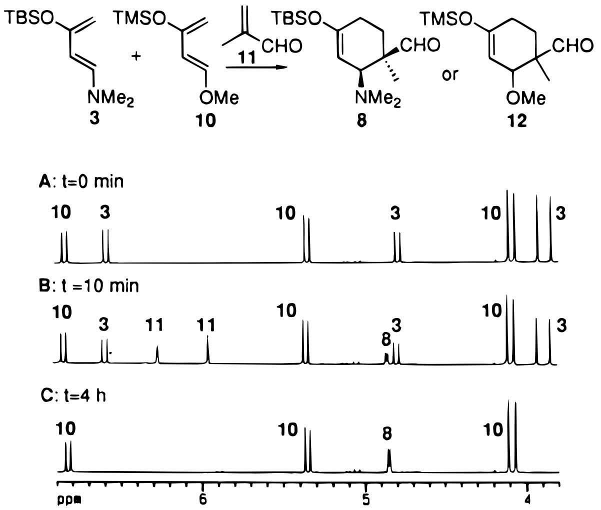
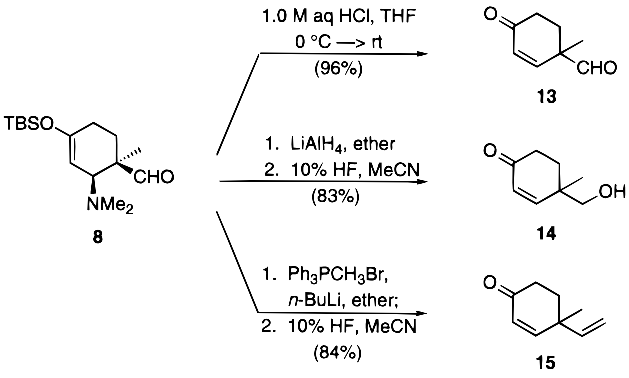


Figure 1. Competition experiment between dienes **3** and **10**. ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 MHz as solutions in CDCl$_3$, using Me$_4$Si (TMS) as an internal standard.

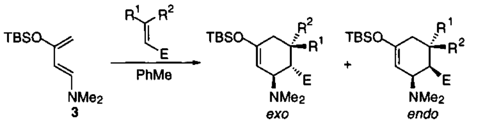
Scheme 3

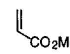
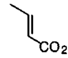
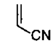
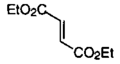
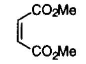


In order to better assess the relative reactivity of amino siloxy diene **3** and Danishefsky's diene **10**, we carried out an experiment which allowed the two dienes to compete directly for a dienophile. A C$_6$D$_6$ solution containing 1 equiv each of dienes **3** and **10** (Figure 1, spectrum A) was treated at room temperature with 1 equiv of methacrolein (**11**). Two adducts, **8** and **12**, can potentially form from the competing Diels–Alder reactions. The NMR spectrum taken soon after addition of the dienophile (t = 10 min, spectrum B) showed appreciable decrease in the relative amount of diene **3**, and the appearance of signals from a single Diels–Alder adduct, independently confirmed to be adduct **8**. After all the dienophile was consumed (t = 4 h, spectrum C), the reaction mixture contained adduct **8** and unreacted diene **10**, with no discernible amount of adduct **12**. On the basis of the assumption that side-products present to the extent of 3–5% should be detectable by NMR, it may be safe to conclude that amino siloxy diene **3** is over 25 times more reactive than 1-methoxy 3-siloxy diene **10**.

Amino siloxy diene **3** undergoes Diels–Alder reactions with various dienophiles (Table I).[14] The cycloaddition reactions proceed under relatively mild conditions and afford the cycloadducts in good yields, with complete regioselectivity. The cycloadducts are stable to flash chromatography, which allowed the separation of the *endo* and *exo* diastereomers. In contrast to the high *endo*-selectivity observed for two of the examples shown above, the reaction of **3** with methyl acrylate, methyl crotonate, and acrylonitrile (entries 1–3) were less selective and gave significant amounts of the *exo* isomers. Remarkably high *exo* selectivity was observed for the cycloaddition with dimethyl maleate (entry 5).

Table 1. Diels–Alder Reactions of Amino Siloxy Diene 3 with Various Dienophiles



entry	dienophile	temp (°C)	yield (%)	*exo* : *endo*
1		20	81	1.5 : 1
2		90	87	3 : 1
3		20	85	4 : 1
4		20	100	1 : 1.4
5		20	92	> 15 : 1

The products of these Diels–Alder reactions are potentially versatile intermediates. As anticipated, the β-amino enol silyl ether portion of the Diels–Alder adducts can be converted to the corresponding enone under acidic conditions, which promote hydrolysis of the silyl enol ether as well as β-elimination of the amino group. For example, subjection of the methacrolein cycloadduct to aqueous HCl in THF afforded 4-formyl-4-methylcyclohexenone **13** in 96% yield. The cycloadducts are sufficiently stable that certain chemical transformations can be carried out on them prior to the hydrolysis step. Thus, the carbonyl group of the methacrolein adduct can either be reduced with lithium aluminum hydride or subjected to Wittig olefination and the resulting products hydrolyzed to afford the corresponding alcohol **14** and alkene **15**, respectively (Scheme 3).

Our studies have shown that 1-amino-3-siloxy-1,3-butadienes can be prepared easily and in high yield and are extremely reactive in Diels–Alder reactions. Diene **3** is appreciably more reactive than a 1-methoxy-3-siloxy-1,3-butadiene and reacts readily with a wide range of dienophiles to afford the cycloadducts in good yield. Further applications of 1-amino 3-siloxy dienes, particularly to the asymmetric Diels–Alder reaction, are in progress and will be reported in due course.[15]

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Supporting Information Available: Experimental procedures and spectral data of all new compounds employed in this study (48 pages).

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(13) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(14) *Typical Diels–Alder procedure*: To a solution of diene **3** (1.2–1.5 mmol) in dry toluene (1–2 mL) was added the dienophile (1 mmol), and the reaction mixture was stirred overnight at the temperature indicated (see Table 1). Concentration in vacuo, followed by flash chromotography on silica gel (the eluent contained 2–5% triethylamine), afforded the cycloadducts shown.

(15) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165.