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Hetero Diels–Alder Reactions of 1-Amino-3-siloxy-1,3-butadienes under Strictly Thermal Conditions

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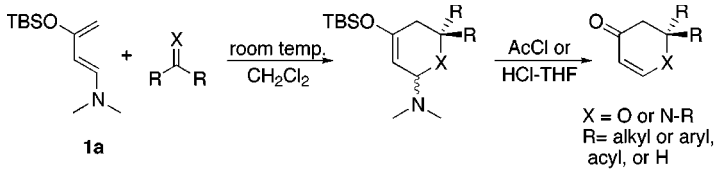
ABSTRACT



The hetero Diels–Alder reaction of 1-amino-3-siloxy-1,3-butadiene (1a) with a range of unactivated aldehydes proceeds readily under remarkably mild conditions: at room temperature and in the absence of Lewis acid catalysts. The cycloadducts are formed in good yields and can be converted directly to the corresponding dihydro-4-pyrones using acetyl chloride. Ketones and imines are also reactive in hetero Diels–Alder reactions with this diene.

The hetero Diels−Alder reaction has emerged as the method of choice for the stereocontrolled synthesis of six-membered heterocycles such as dihydropyrones and dihydropyridones, building blocks to a wide range of natural products of interest.[1] The cycloaddition of electron-rich dienes with aldehydes and ketones, for example, provides de novo syntheses of biologically significant carbohydrates.[2] Its clear importance to organic synthesis notwithstanding, the hetero Diels−Alder is a sluggish reaction. Only highly reactive carbonyls, such as that in formaldehyde or in aldehydes bearing electron-withdrawing groups (e.g., glyoxylates), are reported to react with dienes.[3] The hetero Diels−Alder reactions of less reactive carbonyl groups necessitate either very high pressure (15−25 kbar)[4] or the use of Lewis acid catalysts.[5,6] We report here the first hetero Diels−Alder reactions between a stable diene and an unactivated carbonyl group under atmospheric pressure and in the absence of Lewis acids.[7] The cycloadditions are carried out at room temperature or lower and afford upon workup dihydro-4-pyrones in good yields.

We recently reported on the synthesis and Diels−Alder reactivity of a new family of highly reactive dienes possess-

(1) For excellent general reviews, see: (a) Tietze, L. F.; Kettschau, G. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer-Verlag: Berlin, 1997; Vol. 189, pp 1−120, and references therein. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed; Academic Press: San Diego, CA, 1987; Vol. 47.

(2) Reviews: (a) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250−259. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *15*, 5−23. (c) Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, *42*, 245−333. (d) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. *2*, pp 661−706.

(3) (a) Gresham, T. L.; Steadman, T. R. *J. Am. Chem. Soc.* **1949**, *71*, 737−738. (b) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81−82. (c) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron. Lett.* **1981**, *22*, 4607−4610.

(4) Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41−42.

(5) Reviews: (a) Santelli, M.; Pons, J, -M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996. See also refs 1 and 2.

(6) (a) Molander, G. A.; Rzasa, R. M. *J. Org. Chem.* **2000**, *65*, 1215−1217 and references therein. For recent examples of chiral Lewis acid-catalyzed hetero Diels−Alder reactions, see: (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38*, 2427−2430. (c) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−406. (d) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605, and references therein.

(7) This work was presented at the 219th National Meeting of the American Chemical Society: Huang, Y.; Rawal, V. H. *Abstr. Pap. Am. Chem. Soc.* **2000**, *219*, 527-ORGN. After this manuscript was completed and being readied for submission, a paper appeared describing the thermal hetero Diels−Alder reactions of in situ generated *ortho*-quinodimethanes with carbonyl and imino hetero dienophiles: Hentemann, M. F.; Allen, J. G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1937−1940.

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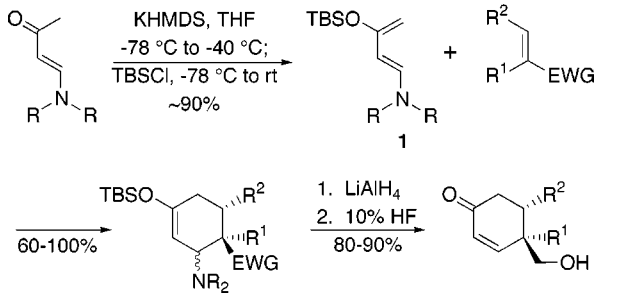
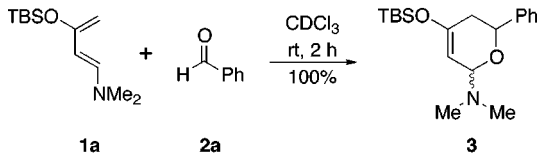
ing an amine at the 1-position and a siloxy substituent at the 3-position (**1**).[8−12] Such amino-siloxy dienes are conveniently prepared on a large scale (up to 20 g)[12] and are highly reactive in conventional Diels−Alder reactions, providing quick access to a wide range of 4- and 4,5-disubstituted cyclohexenones,[8,9] even in enantiomerically enriched[10] form (Scheme 1).

Scheme 1



The exceptional reactivity[11] of amino-siloxy dienes was clearly evident from its hetero Diels−Alder reaction with benzaldehyde (Scheme 2). Upon addition of benzaldehyde

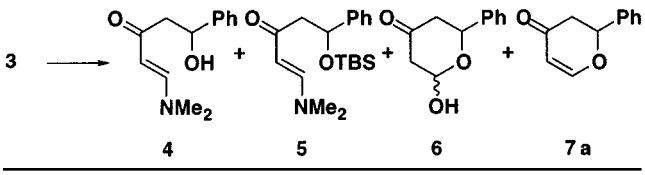
Scheme 2



to a solution of diene **1a** in $CDCl_3$, a rapid cycloaddition ensued, as monitored by NMR. The reaction was complete in only ca. 30 min, resulting in clean, quantitative formation of the expected cycloadducts (**3**, ca. 3:1 ratio). The high rate of the reaction cannot simply be explained by invoking catalysis by the trace amounts of HCl present in chloroform, since comparable results were obtained even when *i*Pr_2NEt or K_2CO_3 was added to the reaction mixture. The facility of this cycloaddition is noteworthy in light of the high-pressure conditions reportedly required for an analogous uncatalyzed reaction of **2a** and 1-methoxy-1,3-butadiene (19.5 kbar, 50 °C).[4]

The presence of the labile amino-glycoside linkage in cycloadduct **3** precluded the use of standard workup and purification procedures. However, the adduct could easily be transformed to a stable product. Interestingly, depending on the workup conditions, it was possible to obtain alcohol **4**, TBS-ether **5**, or dihydro-4-pyrone **7a** as the major product (Table 1). Thus, direct subjection of the reaction mixture to

Table 1. Direct Transformations of Cycloadduct **3**



entry	hydrolysis conditions	time	**4**[a,b]	**5**	**6**	**7a**
1	silica gel or alumina		78%			
2	TFA−THF	24 h		72%		
3	HF−CH_3CN	20 h			42%	17%
4	HCl−THF	24 h			19%	40%
5	$ClCO_2Me$, −78 °C	30 min				66%
6	acetyl chloride, −78 °C	30 min				86%

[a] Yields refer to isolated, chromatographically purified products. [b] Products constituting <10% of the product mixture were not isolated.

either silica gel or alumina column chromatography afforded primarily alcohol **4** (entry 1). TBS-ether **5**, the Mukaiyama-aldol type product,[13] was the major product using trifluoroacetic acid in THF (entry 2). Aqueous acidic conditions did afford the desired dihydro-4-pyrone (**7**), but it was accompanied by appreciable quantities of the hydrolysis product, lactol **6**. To circumvent the concomitant hydrolysis to **6**, nonaqueous eliminative workup conditions were explored. After completion of the cycloaddition, the reaction solution was chilled (−78 °C) and then treated with a slight excess of an acylating agent (entries 5 and 6). Presumably, under these conditions the amino group is acylated, making it a good leaving group, followed by attack of the silyl group by the chloride ion, triggering a β-elimination to reveal the dihydroprone product.

We have examined the hetero Diels−Alder/hydrolysis sequence using a variety of aldehydes as hetero dienophiles and have found this methodology to be quite general and reliable. The reactions proceed at room temperature and afford, after quenching with acetyl chloride, the dihydro-4-pyrone products in good to high yields (Table 2). The cycloadditions between diene **1a** and aromatic aldehydes were quite fast, and the reaction rates appeared to correlate with the electrophilicities of the respective carbonyl groups (entries 1−4). The cycloadditions with primary aliphatic aldehydes were complete within ∼2−3 h (entries 5 and 6) and required 6−8 h with secondary aldehydes (entries 7 and 8). Even less reactive was the tertiary aldehyde, pivaldehyde,

(8) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252−5253. (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039−3052.

(9) Application to tabersonine synthesis: Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524.

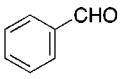
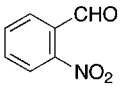
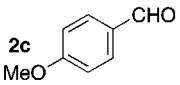
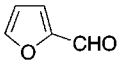
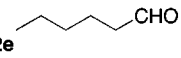
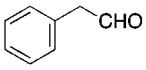
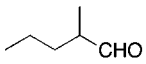
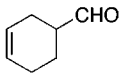
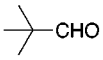
(10) (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562−9573.

(11) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045−8047.

(12) Two preparative procedures have been accepted for publication in *Organic Syntheses*, one for the synthesis of amino-siloxy diene **1a**, and the other for the use of this diene in a Diels−Alder reaction: Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, in press.

(13) Cf.: (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron. Lett.* **1992**, *46*, 6907−6910. (b) Keck, G. E.; Li, X.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999.

Table 2. Hetero Diels−Alder Reactions of Various Aldehydes

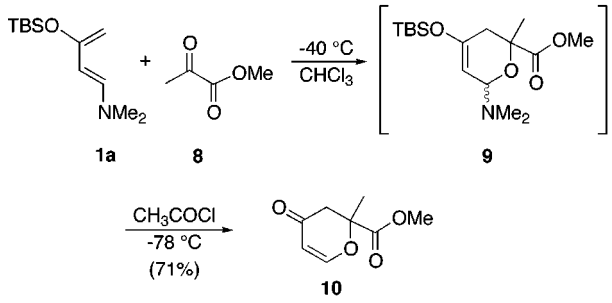
entry	aldehyde (**2**)	rxn time	product **4**	yield[a]
1	**2a** 	1.5 h	**7a**	86%
2	**2b** 	45 min	**7b**	81%
3	**2c** 	15 h	**7c**	71%
4	**2d** 	2.5 h	**7d**	72%
5	**2e** 	2 h	**7e**	73%
6	**2f** 	2.5 h	**7f**	82%
7	**2g** 	8 h	**7g**	83%[b]
8	**2h** 	6 h	**7h**	92%[b]
9	**2i** 	2 d	**7i**	54%

[a] Yield of chromatographically purified product. [b] Obtained as an inseparable mixture of diastereomers.

the cycloaddition with which required over 1 day to go to completion (entry 9). Aldehydes with a chiral center adjacent to the carbonyl group afforded a mixture of diastereomers, with only moderate diastereoselectivity (entries 7 and 8, ratios of 1.3/1 and 1.2/1, respectively).

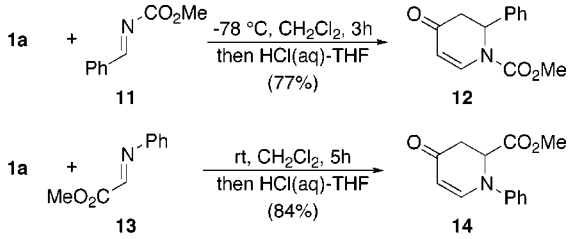
Initial examination showed that diene **1a** was considerably less reactive with simple ketones (e.g., cyclohexanone) than aldehydes. On the other hand, the hetero Diels−Alder reaction with methyl pyruvate (**8**) proceeded nicely even at −40 °C and gave, after acetyl chloride workup, the carboxylated dihydroprone **10** in 77% yield (Scheme 3). The cycloaddition of **1a** with activated imines also proceeded well.[14] The reaction of **1a** and the *N*-carbomethoxy imine of benzaldehyde (**11**) went to completion in 3 h at −78 °C and gave, upon aqueous acidic hydrolysis of the intermediate cycloadduct, dihydro-4-pyridone **12** in 77% yield (Scheme 4). The corresponding reaction of *N*-phenyl imine of methyl

Scheme 3



glyoxylate (**13**) was equally effective and afforded the expected dihydropyridone (**14**) in good yield.

Scheme 4



In summary, the present work demonstrates another facet of the remarkable utility of 1-amino-3-siloxy-1,3-butadienes. These dienes are easily prepared and stable, and yet are so reactive that they readily undergo hetero Diels−Alder reactions with a wide range of heterodienophiles, including various aldehydes and activated ketones and imines. The cycloadditions proceed under mild, strictly thermal conditions (i.e., without the assistance of Lewis acid catalysis) and the adducts can be hydrolyzed in the same flask. The one-pot sequence proceeds in good yields and provides a simple synthesis of many useful dihydro-4-pyrone and dihydro-4-pyridone derivatives.

Acknowledgment. This work was supported by the National Institutes of Health (R01-GM-55998). Pfizer Inc. and Merck Research Laboratories are also thanked for generous financial assistance.

Supporting Information Available: General experimental procedures for the cycloadditions shown and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Thermal hetero Diels−Alder reactions of doubly activated imines have been reported: (a) Birkinshaw, T. N.; Tabor, A. B.; Holmes, A. B.; Kaye, P.; Mayne, P. M.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1988**, 1599−1601. (b) Birkinshaw, T. N.; Tabor, A. B.; Holmes, A. B.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1988**, 1601−1602.