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Hetero [4 + 2] Cycloadditions of (Trialkylsilyl)vinylketenes. Synthesis of α,*β*-Unsaturated *δ*-Valerolactones and -Lactams

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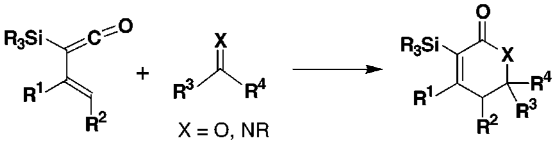
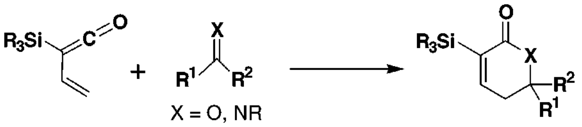
ABSTRACT



Hetero Diels–Alder reactions of (trialkylsilyl)vinylketenes (TAS-vinylketenes) with carbonyl and imino dienophiles are described. TAS-vinylketenes participate as electron-rich dienes in [4 + 2] cycloadditions with diethyl ketomalonate to afford α,*β*-unsaturated *δ*-valerolactones in good yield. Nonenolizable *N*-alkyl- and *N*-(trimethylsilyl)imines combine with TAS-vinylketenes to furnish α,*β*-unsaturated *δ*-valerolactams. In contrast to most Diels–Alder reactions involving unactivated imines, these cycloadditions do not require promotion by Lewis acids and in general proceed with a high degree of stereoselectivity.

The utility of vinylketenes[1] in organic synthesis is well-established. Research in our laboratory has shown that [2 + 2] cycloadditions of vinylketenes can serve as triggering steps in powerful "pericyclic cascade" strategies for the synthesis of six- and eight-membered carbocyclic compounds.[2] In related studies, we have demonstrated that (*trialkylsilyl*)-vinylketenes (TAS-vinylketenes) are remarkably stable ketenes which exhibit reactivity that is complementary to other vinylketenes in many reactions.[3,4] Silyl substitutents[5] suppress the tendency of vinylketenes to undergo dimerization and [2 + 2] cycloaddition, allowing them to express their underlying reactivity as electron-rich conjugated dienes and permitting them to serve as building blocks in novel synthetic routes to five- and six-membered rings.[3,4,6] In this Letter we now report the extension of this chemistry to include hetero Diels−Alder reactions of TAS-vinylketenes with electron-deficient carbonyl compounds and *N*-alkyl- and *N*-(trialkylsilyl)imines (eq 1).



(1)

The TAS-vinylketenes (**1**−**4**) required for this study were prepared by two methods: (1) the photochemical Wolff

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(1) Reviewed in: Tidwell, T. T. *Ketenes*; Wiley: New York, 1991.

(2) (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (b) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (c) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (d) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

(3) (a) Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810. (b) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380.

(4) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690.

(5) For reviews on the chemistry of silylketenes, see ref 1 and the following: (a) Pommier, A.; Kocienski, P.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, *13*, 2105. (b) Schaumann, E.; Scheiblich, S. In *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, E., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1993; Vol. E15, Part 2.

(6) For related reactions involving silylated bisketenes, see: Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 9522.

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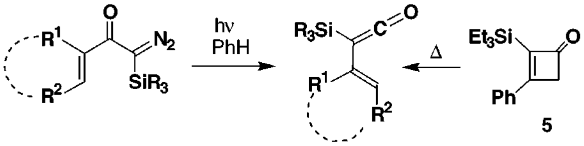
rearrangement of α'-silyl-α'-diazo-α,β-unsaturated ketones[3b] and (2) the 4π-electrocyclic ring opening of 2-silylcyclobutenones[3b,6] (eq 2). The requisite photo Wolff substrates were



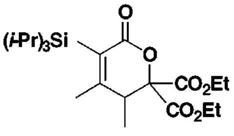
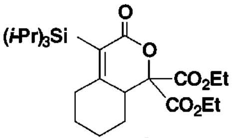
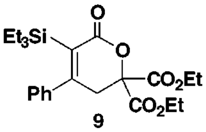
(2)

1 R = *i*-Pr, $R^1 = R^2 = CH_3$
2 R = Et, $R^1 = R^2 = CH_3$
3 R = *i*-Pr, $R^1,R^2 = (CH_2)_4$
4 R = Et, R^1 = Ph, R^2 = H

synthesized by silylation[7] of the corresponding diazo ketones which were obtained by employing our detrifluoroacetylative diazo transfer procedure.[8] Cyclobutenone **5**[3b] was prepared via the [2 + 2] cycloaddition of dichloroketene with (triethylsilyl)phenylacetylene followed by reductive dechlorination.[9]

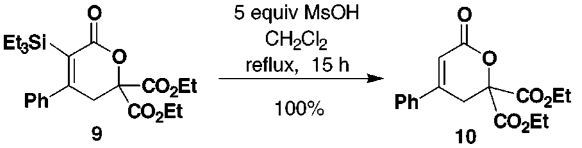
"Oxa Diels−Alder reactions" of carbonyl compounds and conjugated dienes provide valuable synthetic routes to 5,6-dihydropyrans and other six-membered oxygen ring compounds.[10] The most common variants of this cycloaddition process involve reactions of electron-deficient carbonyl groups and cycloadditions of simple aldehydes and ketones activated by coordination with Lewis acids. We tested the feasibility of conducting oxa Diels−Alder reactions with TAS-vinylketenes by first examining their reaction with commercially available diethyl ketomalonate. As summarized in Table 1, heating a solution of TAS-vinylketene **1** in acetonitrile with 1.5 equiv of CO(CO$_2$Et)$_2$ (**6**) for 15 min provided the desired valerolactone **7** in 94% yield after silica gel chromatography.[11] Cycloaddition with the more sterically demanding vinylketene **3** proceeded similarly in 2 h to afford bicyclic lactone **8**. As predicted, in these regiospecific cycloadditions the carbonyl oxygen of the TAS-vinylketene functions as a powerful electron donor substituent to direct the regiochemical course of the reaction.

Table 1. Cycloadditions of TAS-vinylketenes and Diethyl Ketomalonate (**6**)[a]

entry	ketene or precursor	product	% yield[b]
1	**1**	 **7**	94
2	**3**	 **8**	77
3	**5**	 **9**	92

[a] Cycloadditions were effected by heating the ketene or cyclobutenone with 1.5 equiv of CO(CO$_2$Et)$_2$ in acetonitrile at reflux. [b] Isolated yields of products purified by column chromatography.

The oxa Diels−Alder reaction can also be carried out by generating TAS-vinylketenes in situ via electrocyclic ring opening of cyclobutenones. For example, heating cyclobutenone **5** and 1.5 equiv of CO(CO$_2$Et)$_2$ in acetonitrile at reflux for 15 h furnished lactone **9** in 92% yield. Protodesilylation of this cycloadduct was readily achieved in quantitative yield upon exposure to methanesulfonic acid in dichloromethane (eq 3).[12]



(3)

Attempts to extend oxa [4 + 2] cycloadditions of TAS-vinylketenes to include unactivated carbonyl compounds as dienophiles have not been fruitful. Heating vinylketene **1** with pivaldehyde resulted in no detectable reaction, and attempts to promote the cycloaddition using Lewis acids such as Me$_2$AlCl and BF$_3$·OEt$_2$ led only to slow decomposition of the ketene.

We next turned our attention to examining the application of TAS-vinylketenes in hetero [4 + 2] cycloadditions leading to nitrogen heterocycles. Aza Diels−Alder reactions of imino dienophiles have found considerable use in recent years as methods for the synthesis of tetrahydropyridines, 4-piperidones, and other six-membered N-heterocycles.[10] Especially valuable are the reactions of electron-deficient *N*-sulfonyl and *N*-acyl imines and immonium salts. Neutral, unactivated imines fail to engage in hetero [4 + 2] cycloadditions unless paired with electron-deficient dienes (inverse electron demand cycloadditions) or with highly electron-rich dienes in the presence of Lewis acids. We focused our initial studies on unactivated imines which we hoped would combine with TAS-vinylketenes to provide expeditious routes to α,β-unsaturated 2-piperidones (δ-valerolactams).

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[7] (a) Maas, G.; Brückmann, R. *J. Org. Chem.* **1985**, *50*, 2801. (b) Brückmann, R.; Schneider, K.; Maas, G. *Tetrahedron* **1989**, *45*, 5517.

[8] (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959. (b) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Org. Synth.* **1995**, *73*, 134.

[9] (a) Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23. (b) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299. (c) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 82−86.

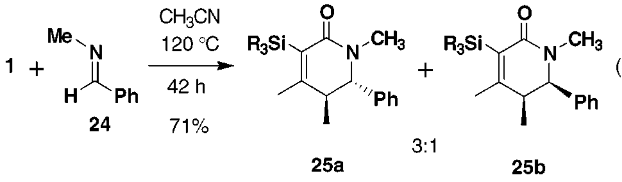
[10] For reviews on the hetero Diels−Alder reaction, see: (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (c) Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 401.

[11] Infrared, ^{1}H NMR, ^{13}C NMR, and elemental analyses were fully consistent with the assigned structures (see Supporting Information).

[12] Attempted desilylation of **9** with *n*-Bu$_4$NF in THF (25 °C, 30 min) led to a complex mixture of products.

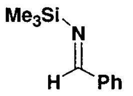
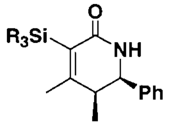
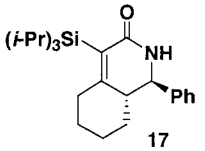
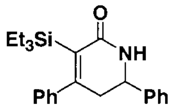
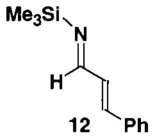
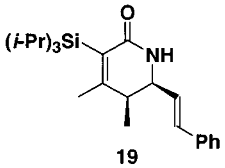
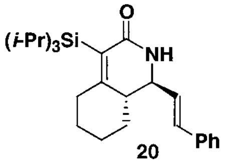
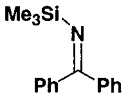
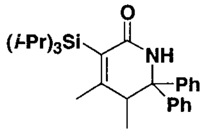
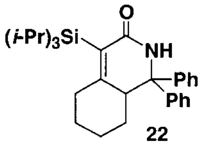
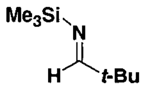
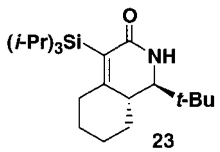
We initially examined reactions involving *N*-(trimethylsilyl)imines[13] in the hope that these derivatives might serve as stable equivalents for imines of the general type $R_2C{=}NH$. Barluenga has shown that *N*-(trimethylsilyl)imines will combine with highly electron-rich 2-aminobutadienes in the presence of the Lewis acid promoter zinc chloride.[14] As summarized in Table 2, we have found that nonenolizable *N*-(trimethylsilyl)imines readily engage in [4 + 2] cycloadditions with TAS-vinylketenes simply upon heating in acetonitrile or at room temperature in the case of reactions conducted without solvent. *No Lewis acid is required to promote these hetero Diels–Alder reactions*. The initial cycloadducts, which are either *N*- or *O*-(trimethylsilyl) derivatives, undergo protodesilylation upon silica gel chromatography to afford the desired lactams **15**–**23** in good to excellent yield.[11] Particularly noteworthy is the stereoselectivity of these cycloadditions. Reactions involving ketenes **1** and **2** (entries 1, 2, and 5) afforded in each case a single cis-substituted product, while reactions of cyclohexenylketene **3** led to the sterically less crowded exo products **17**, **20**, and **23**.[15]

Attempts to extend this chemistry to include *enolizable* *N*-(trimethylsilyl)imines (e.g., $CH_3CH{=}NSiMe_3$) have not been successful, probably due to the instability of these imines at the temperatures necessary for cycloaddition. Efforts to employ TAS-ketenimines ($R_3SiN{=}C{=}CR^1R^2$) as dienophiles also led to complex mixtures of products. On the other hand, simple *N*-alkylimines do function as reactive dienophiles in cycloadditions with TAS-vinylketenes, as illustrated with the reaction of *N*-(methyl)benzaldimine outlined in eq 4. Interestingly, this cycloaddition produced predominantly the trans-substituted cycloadduct, in contrast to the reactions of **1** with *N*-(trimethylsilyl)imines **11** and **12**. Finally, attempts thus far to engage more sterically demanding imines such as *N*-((*S*)-α-methylbenzyl)benzaldimine and 2-phenyl-1-pyrroline in these hetero Diels–Alder reactions have not been successful, and no reaction was observed in attempts to react TAS-vinylketenes with certain amidine, hydrazone, and imidate derivatives.



(4)

Table 2. Cycloadditions of TAS-vinylketenes with *N*-(Trimethylsilyl)imines

entry	dienophile	ketene or precursor	method[a]	product	% yield[b]
					
1	11	1	A	R = *i*-Pr **15**	79-83
2	11	2	B	R = Et **16**	76
3	11	3	A	 **17**	91
4	11	5	A	 **18**	84
5	 **12**	1	B	 **19**	78
6	12	3	B	 **20**	73
7	 **13**	1	A	 **21**	79
8	13	3	A	 **22**	66
9	 **14**	3	C	 **23**	56

[a] Method A: reaction of ketene with 1.5 equiv of imine in refluxing acetonitrile for 1 to 25 h. Method B: reaction of ketene with 1.5 equiv of imine with no solvent for 5 min to 2 h at room temperature. Method C: Reaction of ketene with 3.0 equiv of imine at 110 °C in acetonitrile (sealed tube) for 90 h. Cleavage of the TMS group from the initial cycloadduct occurred during SiO_2 chromatography. [b] Isolated yields of products purified by column chromatography.

Protodesilylation of the aza Diels–Alder cycloadducts was best achieved by treatment with 5 equiv of methanesulfonic acid in dichloromethane at reflux; under these conditions triethylsilyl-substituted cycloadducts undergo clean desilylation in excellent yield (e.g., eq 5). Under similar conditions triisopropylsilyl derivatives also undergo desilyl-

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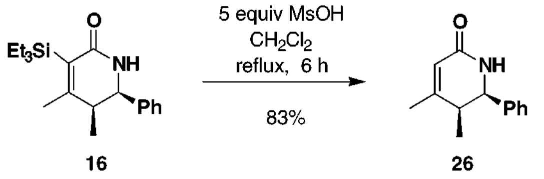
(13) For the synthesis and chemistry of *N*-silyl imines, see: Panunzio, M.; Zarontonello, P. *Org. Process Res. Dev.* **1998**, *1*, 49.

(14) (a) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M.-P. *J. Org. Chem.* **1993**, *58*, 3391. (b) Barleunga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403.

(15) Stereochemical assignments were made on the basis of ^1H NMR difference NOE experiments.

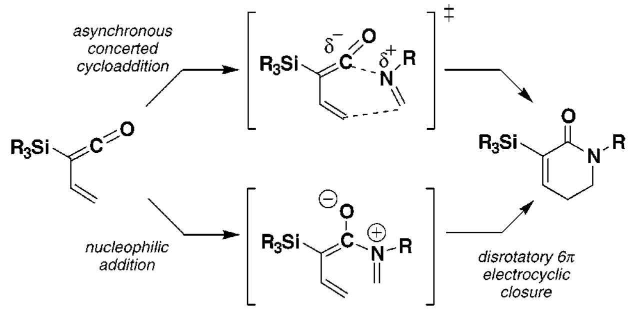
ation; however, in these cases the resulting lactams were found to be difficult to separate from byproducts of the reaction.



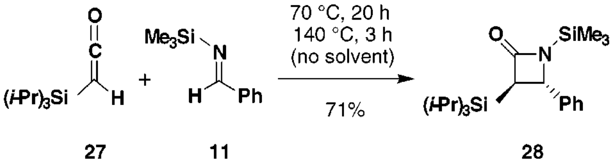
(5)

Further studies will be necessary to develop a full understanding of the mechanistic basis of the stereochemical course of these cycloadditions. The Diels−Alder reactions of TAS-vinylketenes with electron-deficient alkenes studied previously in our laboratory[3] were found to proceed suprafacially with respect to the dienophile and to afford endo cycloadducts, in accord with a concerted [4 + 2] mechanism. We likewise favor a concerted mechanism for the reactions of TAS-vinylketenes with diethyl ketomalonate; however, at this time we do not believe it is possible to distinguish between concerted and stepwise pathways (Scheme 1) in the case of the imine cycloadditions. Note that the indicated stepwise pathway is reminiscent of the mechanism generally accepted for the [2 + 2] cycloadditions of ketenes and imines (the Staudinger reaction).[16] In those [2 + 2] processes, nucleophilic addition of an imine to a ketene produces a zwitterionic intermediate which undergoes conrotatory 4π electrocyclic ring closure to afford a β-lactam.

Scheme 1



Two observations suggest that an analogous stepwise pathway represents a plausible alternative for the reactions of TAS-vinylketenes and imines. First, it is reasonable to expect that nucleophilic addition of imines to TAS-vinylketenes can take place under our cycloaddition conditions since we have observed that Et_2NH adds to vinylketene **2** in acetonitrile at 50 °C in 20 min to afford the expected mixture of isomeric unsaturated amides. Also noteworthy are the results of experiments carried out with *N*-(silyl)imine **11** and TIPS-ketene **27**.[17] Under conditions where [4 + 2] cycloaddition of this imine with TAS-vinylketene **1** is complete, no reaction with **27** occurs, although a good yield of the [2 + 2] cycloadduct **28** is obtained by reaction without solvent at higher temperature (eq 6). This observation can be explained by the operation of different mechanisms for the two types of cycloadditions: stepwise [2 + 2] for **27** and concerted [4 + 2] for the much more facile reaction of vinylketene **1**. Alternatively, both reactions may proceed via stepwise mechanisms in which the rate-determining 6π electrocyclic closure in the [4 + 2] process occurs faster than the 4π electrocyclization involved in the [2 + 2] reaction of **27**. Further studies are planned to resolve this mechanistic issue and to explore the further application of these hetero Diels−Alder reactions in organic synthesis.



(6)

Acknowledgment. We thank the National Institutes of Health (Grant GM 28273) and the Pharmacia & Upjohn Company for generous financial support. D.M.B. was supported in part as a National Science Foundation Predoctoral Fellow, and I.O. was supported as a J.S.P.S. Research Fellow.

Supporting Information Available: Experimental procedures, characterization data, and ^1H NMR spectra for all cycloaddition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] For a review on [2 + 2] cycloadditions of imines and ketenes, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams;* Georg, G. I., Ed.; VCH: New York, 1993; pp 295−368.

[17] The [2 + 2] cycloaddition of *N*-silyl imines with *silyl*ketenes has not been reported previously, although Staudinger reactions of silyl imines with ketenes (generated by dehydrochlorination of acyl chlorides) have been studied extensively by Panunzio and co-workers. See: Bacchi, S.; Bongini, A.; Panunzio, M.; Villa, M. *Synlett* **1998**, 843 and references therein.