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Synthesis of Highly Substituted Cyclopentenones via the [4 + 1] Cycloaddition of Nucleophilic Carbenes and Vinyl Ketenes

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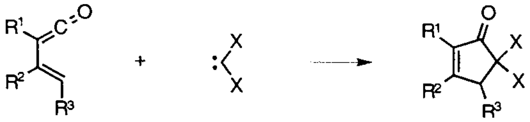
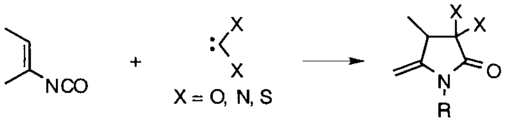
ABSTRACT



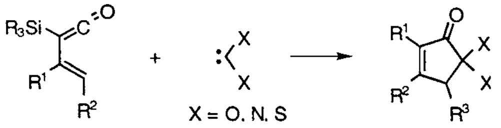
Vinyl ketenes have been shown to undergo [4 + 1] cycloaddition with a variety of nucleophilic carbenes to deliver highly substituted cyclopentenones as products.

Nucleophilic carbenes have been shown to react readily as 1,1-dipole equivalents with vinyl isocyanates to afford a wide range of substituted hydroindolone and pyrrolinone products (Scheme 1).[1−3] On the basis of this precedent, one can easily envision other electrophilic vinyl heterocumulenes behaving in a similar fashion. For example, the cycloaddition of nucleophilic carbenes with vinyl ketenes is particularly intriguing in this regard because *carbocyclic* products exhibiting a substantial level of substitution would result (Scheme 2).

Scheme 1



Scheme 2



The cycloaddition chemistry of (trialkylsilyl)vinyl ketenes[4] has been extensively investigated by Danheiser and coworkers, who have demonstrated that these functions are willing participants in [2 + 2],[5] [4 + 2],[6] and [4 + 1][7] cycloaddition processes, the latter employing *carbene* equivalents such as sulfur ylides and diazomethane as 1,1-dipoles.

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[1] (a) Rigby, J. H. *Synlett* **2000**, 1. (b) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766. (c) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.

[2] Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289−4291.

[3] For leading references to other applications of nucleophilic carbenes, see: (a) Pole, D. L.; Sharma, P. K.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1335. (b) Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214. (c) Arduengo, A. J., III; Dias, H. V. R.; Dixon, D. A.; Harlow, R. L.; Klooster, W. T.; Koetzle, T. F. *J. Am. Chem. Soc.* **1994**, *116*, 6812. (d) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15.

[4] For the preparation of these species, see: Loebach, J. L.; Bennett, Y. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380.

[5] (a) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. (b) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

[6] Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

[7] (a) Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465. (b) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690.

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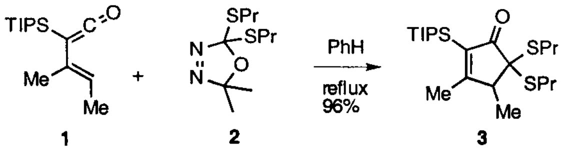
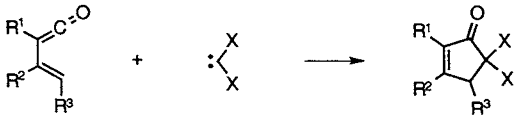
We now disclose that nucleophilic carbenes can indeed undergo efficient [4 + 1] cycloadditions with various (trialkylsilyl)vinyl ketenes to afford highly substituted cyclopentenones.[8] The reaction of vinyl ketene **1** with bis(propylthio)oxadiazoline (**2**)[1b,10] to provide adduct **3** is typical (Scheme 3).

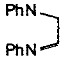
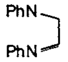
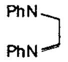
Scheme 3



Other examples of this cycloaddition protocol are compiled in Table 1. This ring-forming process has been shown to be general for oxygen-, nitrogen-, and sulfur-based nucleophilic carbenes. The requisite bis(alkoxy)- and bis(alkylthio)-carbenes were accessed in the usual manner by thermolysis of the corresponding, readily available oxadiazolines.[1a,10,11] The N-heterocyclic carbenes, in contrast, were generated by thermolysis of the 2-trichloromethyl-1,3-imidazolidine (**4**).[2,12]

Table 1. Reactions of Vinyl Ketenes with Nucleophilic Carbenes

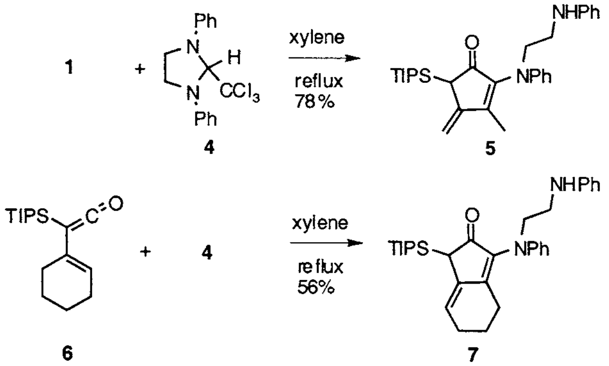


Entry	R1	R2	R3	X	Yield (%)
1	TMS	Ph	H	OMe	63[a,b]
2	TMS	Ph	H	SPr	88[a,b]
3	TIPS	Me	Me	OMe	80[a,b]
4	TIPS	-(CH$_2$)$_4$-		OMe	82[a,b]
5	TIPS	-(CH$_2$)$_4$-		SPr	85[a,b]
6	TMS	Ph	H	 PhN PhN	55[b,c]
7	TIPS	Me	H	 PhN PhN	76[b,c]
8	TIPS	H	Me	 PhN PhN	71[b,c]

[a] A solution of vinylketene (ca. 0.05 M) and excess oxadiazoline (ca. 0.1−0.2 M) in benzene (X = SPr) or xylene (X = OMe) was refluxed for 1−2 h. [b] From ref 9. [c] Reactions run in refluxing xylene (ca. 0.05 M) for 1−2 h.

In most instances the corresponding α-ketoacetal, thioacetal, or aminal was the primary product of these reactions (entries 1−8). However, in a couple of instances more highly unsaturated products were formed. Thus, when vinyl ketenes **1**[9] and **6**[9] were heated with 2-trichloromethyl-1,3-imidazolidine (**4**),[12] methylene-cyclopentenones **5**[9] and **7**[9] were produced in good to very good yields (Scheme 4). Related ring-opened products have been observed previously with N-heterocyclic carbenes in their reactions with vinyl isocyanates.[2] However, the different behavior of structurally related substrates **1** (Scheme 4) and entries 7 and 8 (Table 1) must be attributable to the combination of the extended conjugation available in product **5** and the steric influence of the C3 methyl group in ketene **1** that may help to destabilize the initially formed aminal ring. Only compound **5** satisfies both of these conditions, hence its divergent structure.

Scheme 4



In summary, nucleophilic carbenes have been shown to participate in efficient [4 + 1] cycloaddition reactions with (trialkylsilyl)vinyl ketenes to deliver highly substituted cyclopentenones. These results nicely complement the previous [4 + 1] cycloadditions of these species with ylides and diazoalkanes and provide for a new entry into cyclopentenone targets.

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Supporting Information Available: General procedure and experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] One example of a nucleophilic carbene adding to a bisketene has been reported: Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 9522.

[9] All new compounds exhibit spectral (^{1}HNMR, ^{13}CNMR, IR) and analytical (HRMS and/or elemental analysis) data fully consistent with the assigned structures.

[10] Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D. *Tetrahedron* **2000**, *56*, 10101.

[11] Pole, D. L.; Warkentin, J. *Liebigs Ann. Chem.* **1995**, 1907.

[12] Wanzlick, H. W.; Schrikora, E. *Chem. Ber.* **1961**, *94*, 2389.