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Reactions of (Trialkylsilyl)vinylketenes with Lithium Ynolates: A New Benzannulation Strategy

Wesley F. Austin, Yongjun Zhang, and Rick L. Danheiser*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

danheisr@mit.edu

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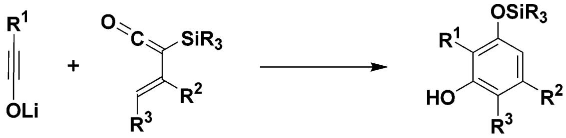
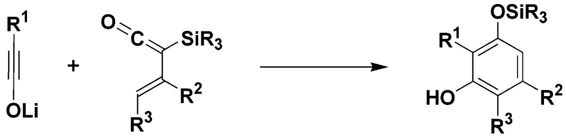
ABSTRACT



1 2 3

(Trialkylsilyl)vinylketenes react with lithium ynolates to produce highly substituted phenols in a new benzannulation strategy that proceeds via the 6π electrocyclization of an intermediate 3-(oxido)dienylketene.

Vinylketenes[1] function as versatile four-carbon building blocks in a variety of useful methods for the synthesis of carbocyclic and heterocyclic compounds. For example, research in our laboratory has shown that [2 + 2] cycloadditions of vinylketenes can serve as triggering steps in several "pericyclic cascade" strategies for the synthesis of six- and eight-membered carbocyclic compounds.[2] Like most ketenes, however, vinylketenes are rarely isolable species and generally must be generated as transient intermediates for in situ trapping with ketenophilic π bonds. In previous studies, we have demonstrated that (*trialkylsilyl*)vinylketenes ("TAS-vinylketenes") are remarkably stable ketenes and exhibit reactivity complementary to other vinylketenes in many useful synthetic reactions. In these transformations, the silyl substituent[3] suppresses the tendency of vinylketenes to undergo dimerization and [2 + 2] cycloaddition, allowing them to express their underlying reactivity as electron-rich dienes in Diels−Alder cycloadditions[4] and as reactive carbonyl compounds in [4 + 1] annulation reactions.[5,6] In this Letter we now report a new transformation of these versatile synthons: the reaction of TAS-vinylketenes with lithium ynolates in a new benzannulation strategy for the synthesis of substituted phenols (eq 1).



(1)

1 2 3

The TAS-vinylketenes **6a−6d** required for this investigation were prepared via the photochemical Wolff rearrange-

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(1)) Reviewed in: Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(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) For reviews of the chemistry of silylketenes, see ref 1 and (a) Pommier, A.; Kocienski, P.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2105. (b) Schaumann, E.; Scheiblich, S. In *Methoden der Organischen Chemie (Houben Weyl)*; Kropf, E., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1993; Vol. E15, parts 2 and 3. (c) Pons, J.-M.; Kocienski, P. J. In *Science of Synthesis: Houben Weyl Methods of Molecular Transformations*; Fleming, I., Ed.; Thieme: Stuttgart, Germany; Vol. 4; section 4.31.

(4) (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. (c) Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

(5) (a) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690. (b) Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465. (c) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263. (d) Davie, C. P.; Danheiser, R. L. *Angew. Chem., Int. Ed.* In press.

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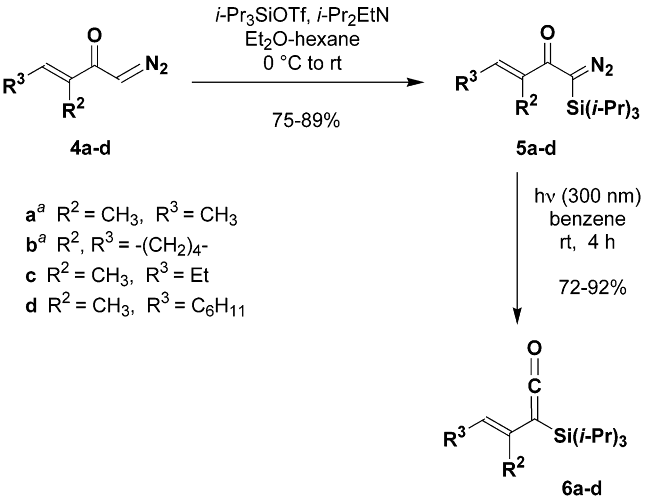
ment of α′-silyl-α′-diazo-α,β-unsaturated ketones[4b] (Scheme 1). The requisite photo-Wolff substrates (**5a**−**5d**) were synthesized by silylation[7] of the corresponding diazo ketones (**4a**−**4d**), which were obtained employing our detrifluoroacetylative diazo transfer procedure.[8] As noted previously, TAS-vinylketenes are remarkably robust ketenes, stable at 25 °C and at mildly elevated temperatures, and amenable to purification using conventional silica gel chromatography.

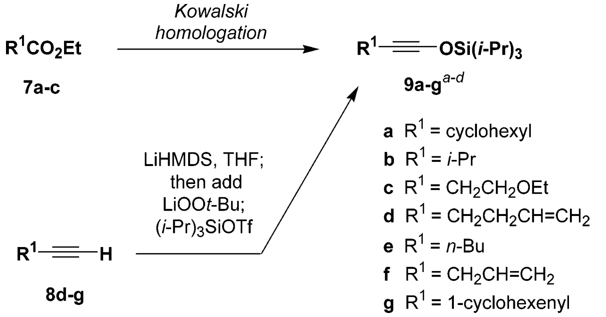
Scheme 1



[a] For the prior preparation of **4a,b**, **5a,b**, and **6a,b**, see ref **4b**.

As shown in eq 1, lithium ynolates (**1**) serve as the second reaction partner in the proposed benzannulation. Recent studies have demonstrated that “ynolate anions” function as valuable synthetic intermediates in a number of useful transformations, and several reliable methods are now available for their preparation.[9] For our initial studies, we focused our attention on the generation of lithium ynolates via the cleavage of siloxy alkynes (“silyl ynol ethers”) with methyllithium. This method, first described by Kowalski,[10] is a variant of the well-known strategy for the regiospecific generation of enolates introduced by Stork and Hudrlik.[11] For our purposes, this process offered the attraction that it takes place under mild conditions and produces only inert tetraalkylsilanes as byproducts. In addition, the siloxy alkynes that serve as ynolate precursors can be conveniently prepared in one step from readily available acetylenes or esters. As shown in Scheme 2, siloxy alkynes **9d**−**9g** were thus prepared in 69−90% yield employing the method of Julia,[12] and alkynes **9a**−**9c** were obtained via the Kowalski homologation of esters **7a**−**7c**.[10,13] As noted previously, these TIPS ynol ethers can be purified by distillation or careful chromatography and are stable to extended storage in solution at 0 °C.

Scheme 2



[a] **9a**: ref 10. [b] **9b**: Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471. [c] **9d**: Zang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. [d] **9e**: Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442.

Scheme 3 outlines the mechanistic pathway envisaged for the proposed ynolate benzannulation as well as several of the possible side reactions that we anticipated might compete with the desired reaction. C-Acylation of the ynolate by the TAS-vinylketene was expected to produce intermediate **10**, with addition to the ketene occurring anti to the bulky trialkylsilyl group to afford the indicated (*Z*)-enolate. Several modes of cyclization for this densely functionalized intermediate are then conceivable. The addition of ynolates to aldehydes and ketones leads to the formation of β-lactone enolates,[9] and an analogous reaction in this case would give rise to products of type **12**. An alternative mode of ring closure would generate the four-membered carbocycle **13**, an enolate derivative of a substituted 1,3-cyclobutanedione. Our expectation, however, was that intermediate **10** would most likely undergo facile 6π electrocyclic ring closure to afford the desired cyclohexadienone **11**.[14−16] Favoring this mode of cyclization is the (*Z*)-enolate geometry of **10**, which enforces close proximity between the C-1 and C-6 carbon atoms at which bond formation is desired to occur. Also

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[6] For related reactions involving silylated bisketenes, see: (a) Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 9522. (b) Huang, W.; Tidwell, T. T. *Synthesis* **2000**, 457. (c) Allen, A. D.; Huang, W.-W.; Moore, P. A.; Far, A. R.; Tidwell, T. T. *J. Org. Chem.* **2000**, *65*, 5676.

[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. *Organic Syntheses;* Wiley: New York, 1998; Collect. Vol. IX, p 197.

[9] For reviews of the chemistry of ynolates, see: (a) Shindo, M. *Synthesis* **2003**, 2275. (b) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367.

[10] Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127.

[11] Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

[12] Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993**, 233.

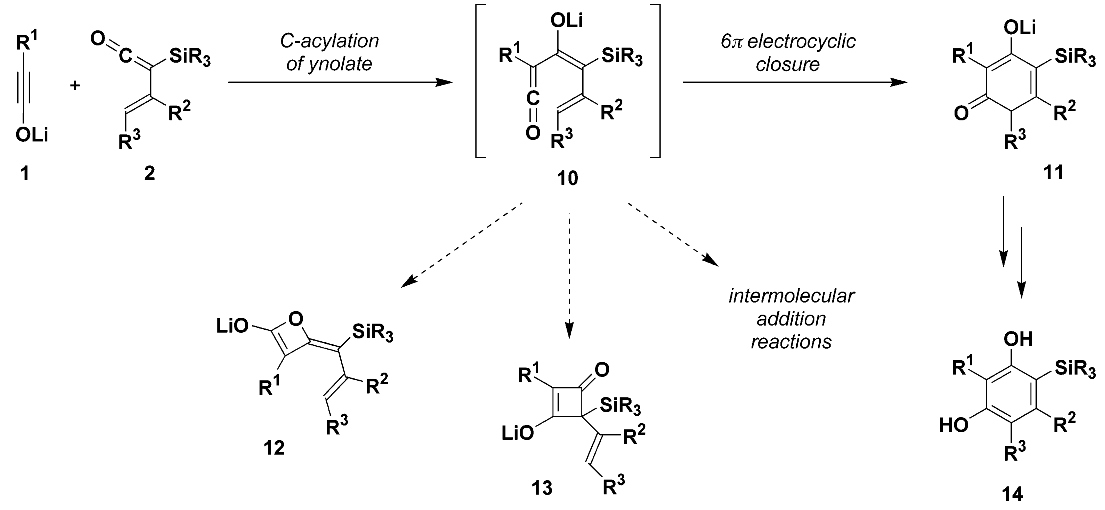
[13] Siloxy alkyne **9c** (see Supporting Information) was prepared using a two-step variant of the Kowalski reaction; see: (a) Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 321. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

[14] The possibility that intermediate **11** might form via a concerted [4 + 2] cycloaddition of **1** and TAS-vinylketene **2** cannot be excluded.

[15] For a discussion of the 6π electrocyclization of 3-oxido-1,3,5-hexatrienes, see: Magnus, P. *Nouv. J. Chem.* **1978**, *2*, 555.

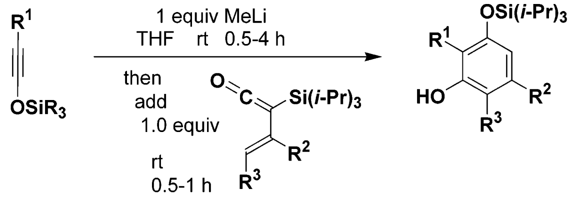
[16] For prior examples of 6π electrocyclization reactions involving enolate derivatives, see: (a) White, J. D.; Skeean, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 6296. (b) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939. (c) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624. (d) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *Org. Lett.* **2004**, *6*, 3373 and references therein.

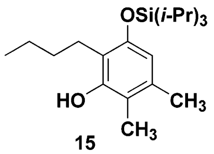
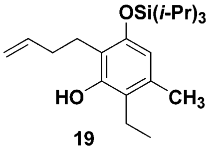
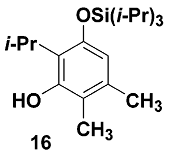
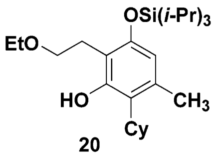
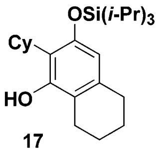
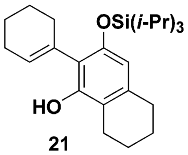
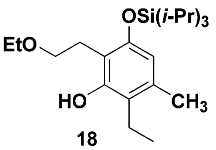
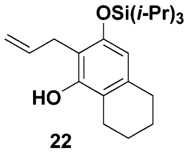
Scheme 3



important is the significant increase in charge stabilization that should develop in the transition state leading to the 1,3-dicarbonyl enolate system in **11**. It was our expectation that these factors would suffice to favor the desired mode of ring

Table 1. Benzannulation via Reaction of TAS-Vinylketenes with Lithium Ynolates



entry	alkyne	ketene	product	yield (%)[a]	entry	alkyne	ketene	product	yield (%)[a]
1	**9e**	**6a**	 **15**	62	5	**9d**	**6c**	 **19**	68-70
2	**9b**	**6a**	 **16**	65	6	**9c**	**6d**	 **20**	44-46
3	**9a**	**6b**	 **17**	67-71	7	**9g**	**6b**	 **21**	43
4	**9c**	**6c**	 **18**	46	8	**23**	**6b**	 **22**	44-48

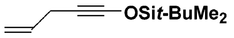
[a] Isolated yield of products purified by column chromatography.

closure over alternative cyclization pathways and intermolecular condensation reactions.

The feasibility of the benzannulation was initially investigated using TAS-vinylketene **6a** and the ynolate derived from the siloxy hexyne **9e**. Exposure of **9e** to 1 equiv of methyllithium in THF at room temperature led to complete consumption of the siloxy alkyne within 3 h as monitored by TLC analysis. Upon addition of TAS-vinylketene **6a**, a new aromatic product rapidly appeared that was isolated in 62% yield after purification by silica gel chromatography. Interestingly, this benzannulation product was identified as the silyl ether **15** (Table 1) rather than the originally expected resorcinol of type **14**. We speculate that the initially formed electrocyclization product **11** isomerizes under the conditions of the benzannulation to produce a 6-silyl-2,4-cyclohexadienone intermediate that aromatizes via a 1,3 carbon → oxygen silyl shift. 1,3-Silyl shifts in α-silyl ketones to form silyl enol ethers are well-known processes,[17] and related rearrangements involving silylcyclohexadienones have been observed in our laboratory[4b] and others.[18]

Previous studies in our laboratory have demonstrated that TAS-vinylketenes behave as electron-rich dienes in Diels–Alder reactions and react best with electron-deficient dienophiles.[4b,c] In view of these prior observations, we were not surprised to find that no reaction occurs upon heating TAS-vinylketene **6a** and siloxy alkyne **9e** in refluxing toluene, and attempted reaction in the presence of Lewis and Bronsted acids (e.g., ZnI_2, $TiCl_4$, $AgNTf_2$, $HNTf_2$) resulted only in complex mixtures of products.

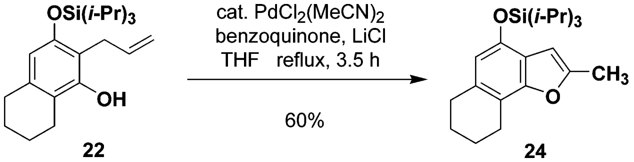
Table 1 delineates the scope of the ynolate benzannulation reaction. Optimization studies revealed methyllithium to be the most effective agent for the generation of ynolates from siloxy alkynes **9a**–**9g**, and low yields of the desired benzannulation products were obtained when TBAF, TBAT, or KOEt[19] were substituted for MeLi in the reaction. A variety of siloxy alkynes and vinylketenes participate in the benzannulation, and branching is accommodated on either annulation component. Unfortunately, attempts thus far to extend the reaction to include TAS-*aryl*ketenes have not been successful. In addition, low yields of the desired product were obtained upon attempted benzannulation with the allyl-substituted acetylene **9f**, apparently as a result of competitive metalation at the methylene carbon by MeLi during the ynolate generation step.[20] This problem was easily circumvented, however, by substituting the TBDMS ynol ether **23**[21] for the TIPS derivative **9f** as the ynolate precursor (entry 8). Cleavage of this siloxy alkyne with MeLi is complete within minutes, and upon reaction with TAS-vinylketene **6b** the desired benzannulation product **22** is obtained in good yield.



23

In summary, TAS-vinylketenes react with lithium ynolates in a regiocontrolled benzannulation process that provides efficient access to highly substituted aromatic compounds. We anticipate that these annulation products should serve as useful intermediates in a variety of further synthetic transformations. Phenols such as **21** and **22** are of particular interest, as the unsaturated ortho substitutents can provide the basis for subsequent cyclization reactions to form a variety of oxygen heterocycles including benzofurans and benzopyrans.[22] For example, as illustrated in Scheme 4, treatment of **22** with catalytic $PdCl_2(MeCN)_2$ in the presence of benzoquinone and LiCl[23] furnished the tetrahydronaphthofuran **24** in good yield.

Scheme 4



22 **24**

Acknowledgment. We thank the National Institutes of Health (GM 28273) and Merck Research Laboratories for generous financial support. Y.Z. was supported by a Po Ting Ip Fellowship.

Supporting Information Available: Experimental procedures and characterization data for **4c,d**, **5c,d**, **6c,d**, **9c,f,g**, and **15**–**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a recent theoretical study and leading references, see: Takahashi, M.; Kira, M. *J. Am. Chem. Soc.* **1999**, *121*, 8597.

(18) (a) Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389. (b) Chamberlin, S.; Wulff, W. D. *J. Org. Chem.* **1994**, *59*, 3047. (c) Fogel, L.; Hsung, R. P.; Wulff, W. D.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5580.

(19) Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369.

(20) The metalation of 1-phenyl-4-penten-1-yne with MeLi has previously been reported: Klein, J.; Brenner, S.; Medlik, A. *Isr. J. Chem.* **1971**, *9*, 177.

(21) The TBDMS siloxy alkyne **23** was prepared from allylacetylene by employing the method of Julia (see Supporting Information). In general, however, the use of TIPS derivatives is preferred because of their increased stability to purification and storage.

(22) Reviewed in: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

(23) These conditions have been employed by Hegedus for the cyclization of 2-allylanilines to indoles. See: Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.