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Organic Reactions at High Pressure.
Conjugate Additions of O-Silylated Ketene Acetals to Activated Enones

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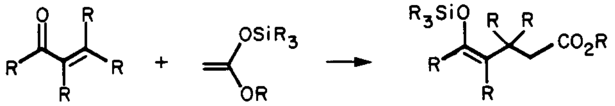
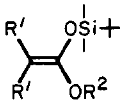
Abstract: O-Silylated ketene acetals have been added to activated enones possessing varying degrees of β-substitution under 15 kbar (1.5 GPa) pressure in acetonitrile at 20 °C to afford good to excellent yields of 1,4-adducts. The additions at elevated pressures are compared with analogous thermal and Lewis acid promoted reactions.

Conjugate addition of O-silylated ketene acetals to α,β-unsaturated carbonyl systems constitutes a useful and efficient method for introducing an acetic acid residue β to a carbonyl group (see equation 1).[3] To date these transformations have been accomplished thermally in acetonitrile and through the agency of Lewis acids ($TiCl_4$, $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$) in methylene chloride for more sterically demanding acceptors.[4] The thermal reaction is useful for relatively unhindered cases but is limited in that addition occurs only in acetonitrile while the Lewis acid promoted reactions are restricted to substrates possessing functionality compatible with the catalyst employed. In view of recent work on high pressure Michael reactions,[5] it was expected that increased pressures might accelerate such addition processes. The present study demonstrates that elevated pressures do provide an alternate means of inducing ketene acetal additions to sensitive enones having steric and conformational constraints.



(1)

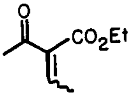
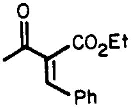
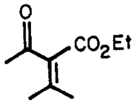
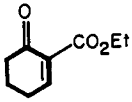
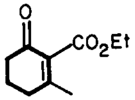
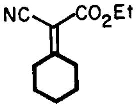
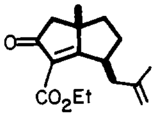
A summary of additions by increasingly hindered ketene acetals (**1**-**3**) to a variety of activated enones is given in Table 1.[6] The high pressure reactions were performed on a 0.5 mmol scale in sealed Teflon® tubes containing a 3:1 molar ratio of ketene acetal and enone in acetonitrile at concentrations of 0.45 *M* and 0.15 *M*, respectively. The tubes were pressurized[7] at 15 kbar (1.5 GPa) hydrostatic pressure at 20° for 24 h. The reactions were depressurized and each reaction mixture concentrated under reduced pressure at 20° to give good to excellent yields of 1,4-adducts which were readily purified by preparative thin layer chromatography.



1 $R' = H,H$; $R^2 = Me$ **3** $R' = Me, Me$; $R^2 = Me$
2 $R' = H,Me$; $R^2 = Me$ **4** $R' = H,H$; $R^2 = t\text{-}Bu$

It is evident from 1 bar control runs that the thermally-induced Michael-type addition is highly sensitive to the steric environment at the enone terminus. However, at 15 kbar these steric factors proved to be less of a problem, and the reactions afford nearly quantitative yields of the adducts. Lastly, 1-methoxy-1-(*t*-butyldimethylsiloxy)-2-methyl-1-propene (**3**) is unreactive at 15 kbar, both at room temperature and at 40-50 °C.

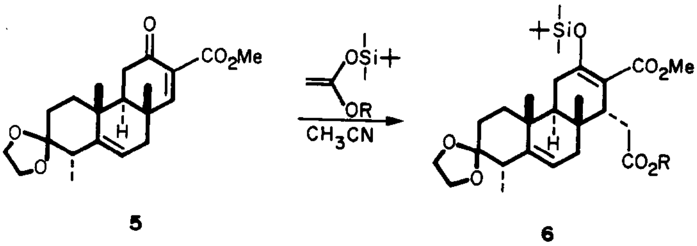
Table 1. Addition of O-Silylated Ketene Acetals to Activated α,β-Unsaturated Carbonyl Systems.

		Ketene Acetal			
		1		2	
Entry	Enone	15 kbar[a]	1 bar[b]	15 kbar[a]	1 bar[b]
1		95%	93%	93%	93%
2		97%	95%	96%	89%
3		89%	89%	90%	48%
4		96%	91%	95%	83%
5		87%	43%	81%	<5%
6		97%	45%	88%	13%
7		88%	20%	-	-

(a) 0.15 M enone, 0.45 M ketene acetal, 24 h, 20 °C, isolated yield; (b) 0.15 M enone, 0.45 M ketene acetal, 24 h, 60-80 °C, isolated yield.

Several features are critical to the success of the reaction. Even at elevated pressures, acetonitrile is the preferred solvent; methylene chloride and tetrahydrofuran give only sporadic success with the less hindered cases. Secondly, the high pressure variant of the ketene acetal Michael addition can be utilized only on doubly activated systems; simple enones generally afford less than 20% yield of product. Furthermore, the enolsilane form of one of the activating groups must be of lower energy than the enolsilane of the reactant ketene acetal. If the latter conditions are not met, silyl transfer, an important driving force for the reaction, is unfavorable. Thus, efficient reaction occurs only when at least one of the activating groups on the acceptor is a ketone or a nitrile.[9] The silyl transfer process could conceivably be inter- or intramolecular but the requirement of a three-fold excess of ketene acetal suggests an intermolecular process.

The full potential of high pressure in overcoming steric and conformational requirements while maintaining conditions compatible with sensitive functionality was realized in the conversion of **5** to **6**, a key step in a projected total synthesis of the antitumor diterpenoid bruceantin.[10] As shown in Table 2, the transformation is



5 **6** (2)

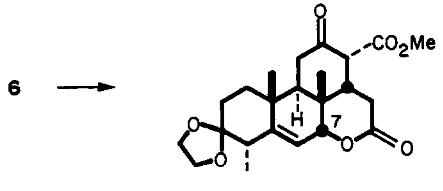
unsuccessful at 1 bar, even at elevated temperature. Lewis acid catalysis leads to extensive decomposition of the starting material, partially as a result of reaction of the acid-sensitive dioxolane moiety. In contrast, the addition is readily effected at 15 kbar. With enolsilane **1**, the addition provides two diastereomeric adducts in a ratio of 5:1. With the more sterically-demanding enolsilane 1-*t*-butoxy-1-(*t*-butyl-dimethylsiloxy)ethylene (**4**) in acetonitrile (20 °C, 24 h, 0.15 *M* in **5**, 0.45 *M* in **4**) the diastereoselectivity is 12:1. The reaction occurs equally as well at 8 kbar. At 6 kbar, the yield of adduct is also high, but longer reaction time is required. More importantly, however, under these conditions the stereoselectivity is enhanced, the two diastereomers being obtained in a ratio of >30:1. By comparison, the use of forcing thermal conditions (21 h, 155 °C) failed to provide the adduct in significant yield. Attempts at Lewis acid catalysis with $TiCl_4$ and $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$ resulted in extensive ketal cleavage.

Table 2. Evaluation of Conditions for O-Silylated Ketene Acetal Additions to an Acid-Labile Bruceantin Precursor (Eq 2).

R	Pressure	T(° C)	Time	Isolated Yield (%)
Me	15 kbar	20	24 h	95[a]
Me	8 kbar	20	24 h	75
t-Bu	15 kbar	20	24 h	91[b]
t-Bu	6 kbar	20	8 d	95[c]
t-Bu	1 bar	155	21 h	10[d]
t-Bu	1 bar	80	7 d	trace
t-Bu	1 bar	-78	-	-[e]

(a) 5:1 ratio of α:β product, 3% of starting enone recovered; (b) 12:1 ratio of α:β product, 9% of starting enone recovered; (c) This 11.6 mmol run was kindly performed by Professor W.H. Pirkle of the University of Illinois; (d) 10% of starting enone recovered; (e) $TiCl_4$-mediated addition gives a complex mixture of starting enone and adduct accompanied by products resulting from ketal cleavage. Use of $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$ gives complete addition but also results in considerable ketal cleavage.

The stereostructure of adduct **6** was elucidated by its conversion to the crystalline tetracyclic lactone **7**. The X-ray structure of this substance clearly shows that the C-7 oxygen occupies the axial position. Thus, the addition of enolsilanes **1** and **4** to **5** occurs from the axial direction, as expected on stereoelectronic grounds.



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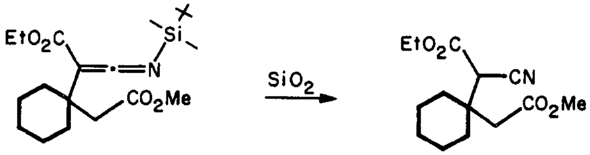
References and Notes

1. Current address: Department of Chemistry, Oklahoma State University, Stillwater, OK 74078.
2. Current address: Department of Chemistry, Polytechnic Institute of New York, Brooklyn, NY 11201.
3. (a) Kita, Y.; Segawa, J.; Haruta, J.; Fujii, T.; Tamura, Y. *Tetrahedron Lett.*, **1980**, *21*, 3779-3782. (b) This reference contains general procedures for the preparation of the ketene acetals.
4. Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163-164.
5. (a) Matsumoto, K. *Angew. Chem. Int. Ed. Eng.* **1980**, *19*, 1013-1014. (b) Matsumoto, K. *ibid.* **1981**, *20*, 770-771; (c) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673-1676; (d) Dauben, W.G.; Bunce, R.A. *J. Org. Chem.*, in press; (e) Dauben, W.G.; Gerdes, J.M. *Tetrahedron Lett.*, in press.
6. All new compounds gave satisfactory spectral and analytical data.
7. A description of the high pressure equipment employed in this study has been given previously in Dauben, W.G.; Krabbenkoft, H.O. *J. Org. Chem.* **1977**, *42*, 282-287 as supplementary material.
8. The transenolization process involving silyl transfer from ketene acetals has been previously observed in the presence of fluoride ion; see Kita, Y.; Yasuda, H.; Haruta, J.; Segawa, J.; Tamura, Y. *Synthesis*, **1982**, 1089-1091.
9. The initial product formed in the case of the nitrile is the silyl-protected ketenimine which was detected by infrared spectroscopy (ν 2075, 1590 cm^{-1}). Upon TLC purification this species is reconverted to the nitrile.



10. (a) Kupchan, S.M.; Britton, R.B.; Ziegler, M.F.; Sigel, C.W. *J. Org. Chem.* **1973**, *38*, 178-179. (b) Kupchan, S.M.; Britton, R.B.; Lacadie, J.A.; Ziegler, M.F.; Sigel, C.W. *ibid.* **1975**, *40*, 648-654.

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