Pergamon

Tetrahedron Letters, Vol. 36, No. 31, pp. 5499-5502, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01115-3

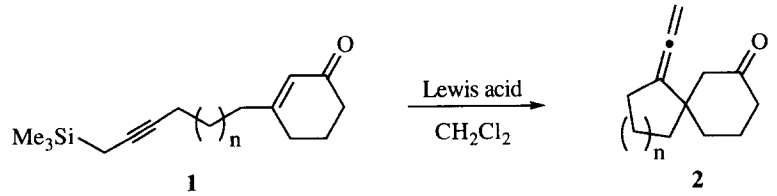
Cyclobutene Formation Accompanying an Intramolecular Lewis Acid-Promoted Spirocyclization of a Propargylic Silane

John D. Spence, Lee E. Lowrie, and Michael H. Nantz*

Department of Chemistry
University of California, Davis, CA 95616

Abstract: An intramolecular Lewis acid-promoted conjugate addition of a propargylic silane to a functionalized cyclohex-2-en-1-one resulted in part in the remarkable formation of a highly fused cyclobutene. The reaction was found to be dependent on the stoichiometry and selection of Lewis acid.

The addition of allylic and propargylic silanes to acceptor groups is a well established process in organic synthesis.[1] For example, the intermolecular addition of allylic silanes to α,β-unsaturated ketones (the Sakurai reaction) is accomplished by fluoride ion or Lewis acid catalysis.[2] In a similar manner, the intramolecular addition of allylic and propargylic silanes to cyclic enones is also promoted by treatment with Lewis acid catalysts.[3] Schinzer *et al.* noted, however, in contrast to the intermolecular Sakurai reaction in which a wide variety of Lewis acids may be used, that only $EtAlCl_2$ and $TiCl_4$ were effective in promoting the intramolecular cyclization reactions. Treatment of propargylic silanes containing appended cyclohexenones (e.g. **1**) with $EtAlCl_2$ was shown to be an effective method for the preparation of spirobicyclic systems with concomitant formation of a terminal allene moiety, as shown by **2**.[4] The utility of terminal allenes[5] in synthesis led us to investigate the preparation of highly functionalized spirocyclic allenes using the Schinzer approach. During the course of these studies, a previously unobserved Lewis acid-promoted reaction of a propargylic silane was uncovered which provides a highly fused cyclobutene.

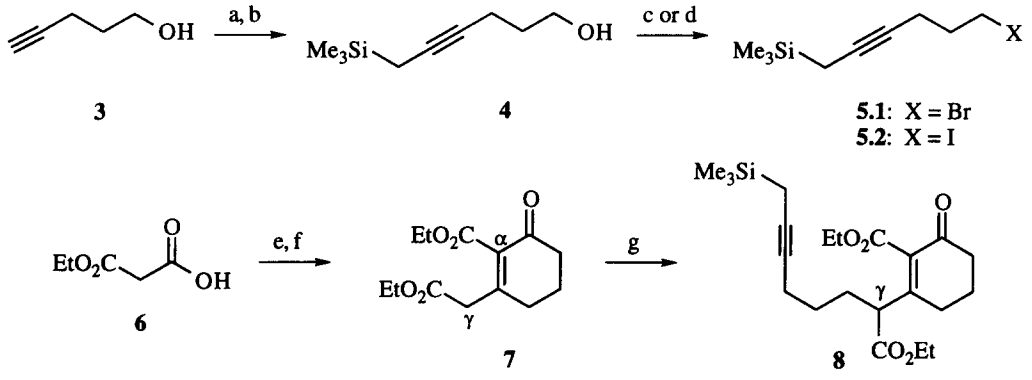


1 **2**

The synthesis of a cyclizable substrate which is structurally analogous to enone **1** but is more highly functionalized was performed as outlined in Scheme 1. Protection of the primary alcohol in **3** as a tetrahydropyranyl ether was followed by acetylide anion alkylation using (iodomethyl)trimethylsilane.[6] Subsequent acid-catalyzed methanolysis of the tetrahydropyranyl protection group afforded alcohol **4** in 79% overall yield. The corresponding bromide **5.1** and iodide **5.2** were obtained from alcohol **4** according to literature procedures.[7] Alkylation reactions of keto-diester **7** using these propargylic silane-containing halides were investigated following its preparation as follows (Scheme 1).

Keto-diester **7** was synthesized by condensation of glutaryl dichloride with 4.0 equivalents of the dianion derived on treatment of monoethyl malonate (**6**) with 2.0 equivalents of nBuLi.[8] Subsequent aqueous acid work-up resulted in spontaneous decarboxylation to give an acyclic bis(β-ketoester) as a mixture of enol and keto tautomers. The crude product was cyclized using a procedure analogous to one developed by Heathcock[9] by treatment of the tautomeric mixture with $MeSO_3H$ in benzene at room temperature. Keto-diester **7** was obtained in 67% yield following silica gel chromatography. Several acid catalysts were examined in the cyclization reaction and all were found to be inferior to $MeSO_3H$ in promoting the formation of **7**.

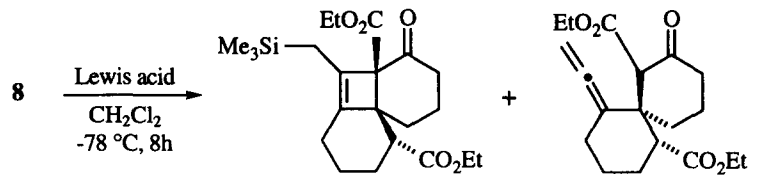
Scheme 1



Reagents and Conditions: (a) dihydropyran (excess), PPTS (cat), CH_2Cl_2, 25 °C, 12 h, 94%; (b) i. nBuLi, THF, 0 °C; ii. $(CH_3)_3SiCH_2I$, 60 °C, 20 h; iii. H_2SO_4 (cat), MeOH, 25 °C, 12 h, 84%; (c) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 3 h, 94%; (d) PPh_3, I_2, imidazole, Et_2O/CH_3CN, 25 °C, 1 h, 89%; (e) i. nBuLi (2 eq.), THF, -65 °C; ii. $ClC(O)(CH_2)_3C(O)Cl$ (0.25 eq.), THF, -65 °C, 1 h; (f) $MeSO_3H$ (3.0 eq.), C_6H_6, 25 °C, 20 min, 67% (2 steps); (g) i. NaH (1.05 eq.), DMF, 0 °C; ii. **5.2** (1.0 eq.), 25 °C, 12 h, 73%.

Having prepared **7**, it was γ-deprotonated by treatment with NaH to give an extended enolate with multiple sites for alkylation. Reaction of this extended enolate with iodide **5.2** in DMF at room temperature provided good C- vs. O-alkylation regioselectivity, and predominant alkylation of the γ-position was achieved to give **8** in 73% yield. Under these conditions, no α-alkylated product was detected, and only a minor amount (*ca.* 11%) of a corresponding dienyl ether O-alkylated product was isolated. In comparison, treatment of the extended enolate of **7** with bromide **5.1** in DMF required heating for reaction to ensue and resulted in significant O-alkylation (C vs. O, 1:1.4).

The results of the Lewis acid-promoted spirocyclization of **8** are given in Table 1. Treatment of **8** according to Schinzer's reaction conditions[4] (1.0 equivalent $EtAlCl_2$, CH_2Cl_2, -78 °C) yielded a single isolable product which, unexpectedly, still possessed the trimethylsilyl group. Under these conditions, the reaction failed to go to completion and 58% of the starting material was recovered. The product was assigned the cyclobutene structure **9** based on spectral analyses.[10] The formation of the highly fused cyclobutene ring in **9** is remarkable in that there have been no previous reports of a cyclobutene synthesis from propargylic silanes under Lewis acid catalysis.[11,12] An increase in the equivalents of $EtAlCl_2$ was found to increase the consumption of **8** and give a second product, the initially anticipated terminal allene **10**. The terminal allene functionality was readily identified



9 **10**

Table 1. Lewis acid-promoted spirocyclization of **8**.[a]

Lewis Acid	Equivalents	Cyclobutene **9** (%)	Allene **10** (%)	Recovered **8** (%)
$EtAlCl_2$	1.0	30	0	58
	2.0	39	14	27
	5.0	13	→ 72	10
Et_2AlCl	2.0	52	17	40
	5.0	→ 55	16	23
$AlCl_3$	2.0	12	58	17
	5.0	2	50	11
$TiCl_4$	2.0	14	21	36

[a] All reactions were conducted in CH_2Cl_2 at -78 °C and quenched (H_2O) after 8h; yields of **9** and **10** correspond to isolated chromatographed material relative to reacted **8**.

by characteristic signals in the ^1H NMR (δ 4.42 (m, 2H)), ^{13}C NMR (δ 206.7, 104.9, 74.4) and IR (1958 cm^{-1}) spectra.[10] An optimal, 72% conversion of **8** to allene **10** was obtained when a large excess (5.0 equivalents) of $EtAlCl_2$ was used; additional equivalents of $EtAlCl_2$ did not improve the overall transformation. Higher reaction temperatures resulted in significant desilylation of **8** to yield the corresponding uncyclized terminal allene.

The dependence of Lewis acid stoichiometry on the product distribution may be attributed to the reactivity of the incipient enolate formed on conjugate addition.[13] Under conditions in which the α-ester and ketone carbonyl moieties in **8** are fully coordinated to Lewis acid, the enolate species formed on conjugate addition of the propargylic silane is expected to be less effective in trapping the putative vinyl carbenium intermediate,[1] thereby increasing the likelihood of trimethylsilyl group elimination to form allene. If the extent of β-keto ester complexation is reduced, a more reactive enolate species is formed and, consequently, interception of the carbenium intermediate may proceed to form a cyclobutene. With this rationale, attenuation of enolate reactivity by changing the Lewis acid would also be expected to influence the product distribution. Indeed, as shown in Table 1, the use of a weaker Lewis acid, Et_2AlCl, resulted in a greater formation of the cyclobutene product relative to the allene product when compared with $EtAlCl_2$ under identical stoichiometry. Similarly, the use of stronger Lewis acids (e.g. $AlCl_3$ or $TiCl_4$) resulted in predominant allene formation, although in lower overall yields in comparison to $EtAlCl_2$.

The possibility that cyclobutene **9** may also serve as a precursor to allene **10** was examined. Thus, treatment of **9** with $EtAlCl_2$ (5.0 equivalents) in CH_2Cl_2 at -78 °C was found to provide allene **10** in 80% yield. This observation may also account for the improved allene to cyclobutene ratios when using excess Lewis acid to promote the spirocyclization. Interestingly, while treatment of **9** with fluoride ion may also be envisioned to result

in desilylation and subsequent β-keto ester enolate elimination to ultimately yield allene **10**, the reaction of **9** with CsF in DMSO at room temperature resulted only in desilylation.

In conclusion, we have observed the first example of cyclobutene formation from a propargylic silane under Sakurai reaction conditions. This new annulation reaction may provide a useful and alternative[14] route to highly fused cyclobutenes.

Acknowledgments: We thank the University of California, Davis, committee on research, and the University of California Cancer Research Coordinating Committee (3-504030) for financial support.

References and Notes:

1. (a) Schinzer, D. *Synthesis* **1988**, 263. (b) Majetich, G. in *Organic Synthesis. Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, **1989**; Vol. 1, pp 173-240.
2. Hosomi, A.; Sakurai, H. *J. Amer. Chem. Soc.* **1977**, *99*, 1673.
3. (a) Schinzer, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 308. (b) Schinzer, D.; Allagiannis, C.; Wichmann, S. *Tetrahedron* **1988**, *44*, 3851.
4. (a) Schinzer, D; Sólyom, S.; Becker, M. *Tetrahedron Lett.* **1985**, *26*, 1831. (b) Schinzer, D.; Steffen, J.; Sólyom, S. *J. Chem. Soc. Chem. Commun.* **1986**, 829.
5. (a) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (b) Montury, M.; Goré, J. *Tetrahedron Lett* **1980**, 51. (c) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 2966. (d) Schuster, H. F., Copolla, G. M. *Allenes in Organic Synthesis*, John Wiley & Sons, New York, 1984.
6. Heimstra, M.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.
7. (a) alcohol to bromide: Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353. (b) alcohol to iodide: Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883.
8. Skulnick, H. I.; Wierenga, W. *J. Org. Chem.* **1979**, *44*, 310.
9. Heathcock, C. H.; Thompson, S. K. *J. Org. Chem.* **1992**, *57*, 5979.
10. All new compounds gave satisfactory spectroscopic and analytical data. Data for selected compounds: **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (m, 1H), 4.05 (q, 2H, J = 7.1 Hz), 3.95 (m, 1H), 2.71 (dd, 1H, J = 12.3, 3.3 Hz), 2.34 (m, 1H), 2.21 (m, 2H), 2.05 (m, 1H), 1.85 - 1.32 (m, 10H), 1.22 (t, 6H, J = 7.1 Hz), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 172.8, 169.3, 145.0, 133.5, 70.2, 60.3, 59.5, 49.8, 47.9, 40.6, 25.1, 24.5, 24.0, 22.3, 17.8, 15.4, 13.8, 13.4, -1.3; IR (neat) 2942, 1731, 1699, 1646 cm^{-1}; HRMS $C_{22}H_{35}O_5Si$ (M^+ + H) calc'd 407.2254, found 407.2265. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.2 (s, 1H), 4.43 (m, 2H), 4.23 (q, 2H, J = 7.1 Hz), 4.07 (m, 1H), 3.84 (m, 1H), 3.68 (dd, 1H, J = 13.1, 4.2 Hz), 2.31 - 2.02 (m, 6H), 1.89 - 1.35 (m, 6H), 1.26 (t, 3H, J = 7.1 Hz), 1.11(t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 174.1, 173.9, 173.1, 104.8, 103.0, 74.2, 60.0, 59.6, 47.8, 42.1, 30.4, 27.4, 27.1, 24.7, 23.7, 16.6, 14.1, 13.9; IR (neat) 3480, 3072, 1958, 1725, 1708, 1632, 1601 cm^{-1}; HRMS $C_{19}H_{27}O_5$ (M^+ + H) calc'd 335.1859, found 335.1873.
11. The intermolecular addition of an allylsilane to enones has been reported to give cyclobutanes; see: Pardo, R.; Zahra, J.-P.; Santelli, M. *Tetrahedron Lett.* **1979**, 4557.
12. Lewis acid-promoted addition of alkenes to acetylenic esters have been reported to give cyclobutene products; see: (a) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283. (b) Halweg, K. M.; Jung, M. E. *Tetrahedron Lett.* **1981**, *22*, 2735.
13. Enolate reactivity is not necessarily the principal operative effect in cyclobutene formation; for example, the $AlCl_3$ catalyzed dimerization of an unactivated alkyne has been shown to yield cyclobutenyl complexes, see: Hogeveen, H.; Jorritsma, H.; Wade, P. A.; van Rantwijk, F.; Koster, J. B.; Prooi, J. J.; Sinnema, A.; van Bekkum, H. *Tetrahedron Lett.* **1974**, 3915.
14. For a photochemical 2+2 cycloaddition approach to cyclobutenes, see: Crimmons, M. J. *Chem. Rev.* **1988**, *88*, 1453.

(*Received in USA* 9 *May* 1995; *revised* 8 *June* 1995; *accepted* 15 *June* 1995)