ORGANIC LETTERS

2009
Vol. 11, No. 17
3822−3825

Tin(IV) Chloride Catalyzed Cycloaddition Reactions between 3-Ethoxycyclobutanones and Allylsilanes

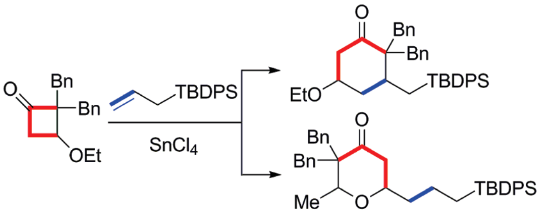
Jun-ichi Matsuo,* Shun Sasaki, Takaya Hoshikawa, and Hiroyuki Ishibashi

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

jimatsuo@p.kanazawa-u.ac.jp

Received June 13, 2009

ABSTRACT



Formal [4 + 2] cycloaddition between various 3-ethoxycyclobutanones and allyltrialkylsilanes proceeded to give 3-ethoxy-5-[(trialkylsilyl)methyl]cyclohexan-1-ones by catalysis with tin(VI) chloride. The use of allyl-*tert*-butyldiphenylsilane induced 1,5-hydride transfer, which gave 2-[3-(*tert*-butyldiphenylsilyl)propyl]-6-methyltetrahydro-4-pyrones.

Substituted cyclohexenones are valuable compounds in organic synthesis, and various methods for preparation of these compounds have been developed. Reported methods include a Diels−Alder reaction of siloxy diene with a dienophile followed by acid treatment,[1] Robinson annulation,[2] Birch reduction of *o*-methoxy-substituted benzoic acid derivatives followed by alkylation and hydrolysis,[3] and alkylation of 3-alkoxycyclohex-2-en-1-ones followed by acid hydrolysis.[4,5] A highly substituted cyclohexane ring, which is often seen in natural products and biologically active compounds, can be constructed by using substituted cyclohexenones, and efficient construction of multifunctionalizable cyclohexenones remains an important task.

Recently, we found that 3-ethoxycyclobutanones reacted with aldehydes or ketones to afford 2-ethoxytetrahydro-4-pyrone derivatives in high yields by catalysis with boron trifluoride etherate.[6] Since the C−O double bond of aldehydes and ketones was efficiently inserted into the more substituted C2−C3 bond of the cyclobutanone ring, we next planned insertion of the C−C double bond into the cyclobutanone ring. Allylsilanes[7] have been employed as good dipolarophiles for construction of four- and five-membered carbocyclic compounds,[8] and it was thought that 1,4-

---

(1) For leading references: (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (c) Danishefsky, S. *Chemtracts-Org. Chem.* **1989**, *2*, 273. (d) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252. (e) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039. (f) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (g) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562.

(2) Reviews:(a) Gawley, R. E. *Synthesis* **1976**, 777. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(3) (a) Taber, D. F. *J. Org. Chem.* **1976**, *41*, 2649. (b) Taber, D. F.; Gunn, B. P.; Chiu, I.-C. *Org. Synth.* **1983**, *61*, 59, and references therein.

(4) (a) Woods, G. F.; Griswold, P. H.; Armbrecht, B. H.; Blumenthal, D. I.; Plapinger, R. *J. Am. Chem. Soc.* **1949**, *71*, 2028. (b) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775. (c) Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414.

(5) Another method:Stork, G.; Ponaras, A. A. *J. Org. Chem.* **1976**, *41*, 2939.

(6) Matsuo, J.; Sasaki, S.; Tanaka, H.; Ishibashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 11600.

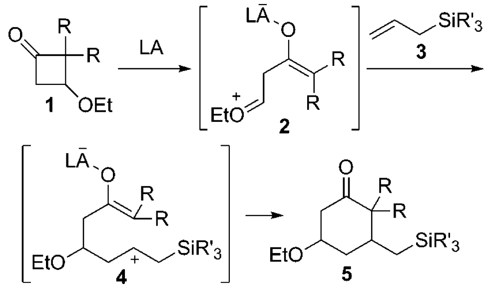
(7) General reviews for the use of allylsilanes in organic synthesis: (a) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. (b) Parnes, Z. N.; Bolestova, G. I. *Synthesis* **1984**, 991. (c) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (d) Schinzer, D. *Synthesis* **1988**, 263. (e) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *31*, 57. (f) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

(8) Review:(a) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

10.1021/ol901329c CCC: $40.75

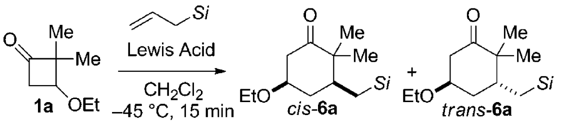
zwitterionic species **2**, generated by Lewis acid mediated ring-opening of 3-ethoxycyclobutanones **1**, would react with allylsilanes **3** to give a formal [4 + 2] cycloadduct **5** via a β-silyl cation[9] intermediate **4** (Scheme 1). The product **5** has a silyl group that can tolerate many organic reactions and can be transformed to a hydroxyl group by Tamao oxidation.[10] [4 + 2] Cycloaddition to give six-membered *carbocyclic compounds by using allylsilanes as a C2 unit have not been reported to date.*[11−14] We report herein formal [4 + 2] cycloadditions between 3-ethoxycyclobutanones and allylsilanes and also report a unique cyclization via 1,5-hydride transfer.

Scheme 1. Plan for Synthesis of Cyclohexanone Derivatives **5** by Lewis Acid (LA) Catalyzed Formal [4 + 2] Cycloaddition between 3-Ethoxycyclobutanones **1** and Allylsilanes **3**



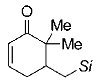
First, we explored a suitable Lewis acid for the planned [4 + 2] cycloaddition between cyclobutanone **1a** and allyltriisopropylsilane (Table 1). Allyltriisopropylsilane was employed first because its sterically demanding silyl group has been reported to suppress allylation reactions (Hosomi−Sakurai reaction[15]).[16] It was found that the desired [4 + 2] cycloaddition did not proceed by catalysis with trimethylsilyl triflate, but dimerization of the starting material **1a** to **9** took place (entry 1). Only a trace amount (1%) of the desired product **6a** was obtained by the use of boron trifluoride etherate (entry 2), whereas activation with ethylaluminum dichloride gave **6a** in 53% yield (entry 3). Catalysis with titanium(IV) chloride gave product **8**, which was formed by allylation of the initial product **6a**, in 23% yield along with cyclohexanone derivative **6a** (57%) and enone **7a**, which was formed by one-pot elimination of ethanol from **6a** (entry 4). Enone **7a** was obtained as the major product when titanium(IV) bromide was employed (entry 5). Tin(IV) chloride was found to catalyze the desired [4 + 2] cycloaddtion most effectively among Lewis acids we tested, and **6a** was obtained in 80% yield as a mixture of diastreomers (*cis*-**6a**/*trans*-**6a** = 71:29, entry 6). The present cycloaddition proceeded smoothly also in toluene (entry 7), and a catalytic amount (20 mol %) of tin(IV) chloride efficiently catalyzed the desired cycloaddition to give **6a** in 85% yield (entry 8). It was found that the *cis*/*trans* ratio of **6a** (*cis*/*trans* = ca. 70:30) did not depend significantly on the Lewis acid employed.

Table 1. Optimization of Reaction Conditions[a]

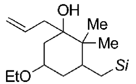


entry	Lewis acid	% yield[b] **6a** (*cis*/*trans*)
1[c]	Me_3SiOTf	0
2	$BF_3{\cdot}OEt_2$	1 (75:25)
3	$EtAlCl_2$	53 (79:21)
4[d]	$TiCl_4$	57 (89:11)
5[e]	$TiBr_4$	6 (83:17)
6	$SnCl_4$	80 (71:29)
7[f]	$SnCl_4$	78 (71:29)
8[g]	$SnCl_4$	85 (73:27)
9	$SnBr_4$	16 (69:31)

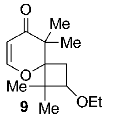
[a] Cyclobutanone **1a** (1.0 equiv), allyltriiropropylsilane (1.5 equiv), and Lewis acid (1.2 equiv) were employed. Si = Si(i-Pr$_3$). [b] Combined yield of *cis*- and *trans*-**6a** and *cis*/*trans* ratio of **6a** were determined by ^{1}H NMR analysis. [c] Compound **9** was obtained in 50% isolated yield. [d] Compound **7a** (2%) and **8** (23%) were obtained. [e] Compound **7a** (57%) and **8** (16%) were obtained. [f] Toluene was used as a solvent. [g] A catalytic amount of $SnCl_4$ (20 mol %) was used.



7a



8



9

The scope and limitations of the present cycloaddition reaction were then investigated by employing tin(IV) chloride, various 3-ethoxycyclobutanones **1a**−**f** and allyltriisopropylsilane in dichloromethane (Table 2). Several 2,2-dialkyl-3-ethoxycyclobutanones **1a**−**c** readily reacted with

---

(9) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(10) (a) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. (b) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (c) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.

(11) Synthesis of tetahydropyrans: (a) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 10211. (b) Angle, S. R.; Belanger, D. S.; El-Said, N. A. *J. Org. Chem.* **2002**, *67*, 7699. See also: (c) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608.

(12) Synthesis of piperidine and tetrahydropyridine derivatives: (a) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958. (b) Horino, Y.; Kimura, M.; Naito, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3427.

(13) Synthesis of tetrahydroqunolines and tetrahydroquinoxalines: (a) Akiyama, T.; Suzuki, M.; Kagoshima, H. *Heterocycles* **2000**, *52*, 529. (b) Shindoh, N.; Tokuyama, H.; Takasu, K. *Tetrahedron Lett.* **2007**, *48*, 4749. (c) Nair, V.; Vidya, R. D. N.; Devipriya, S. *Synthesis* **2006**, 107.

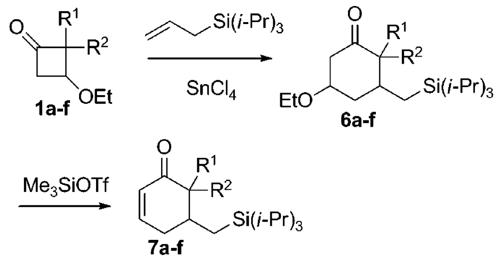
(14) Allylsilanes as C4 units: Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254.

(15) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354. (c) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (d) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. (e) Fleming, I.; Dunogues, I.; Smithers, R. *Org. React.* **1989**, *37*, 57.

(16) (a) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094. (b) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081. (c) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627. (d) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401. (e) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem.−Eur. J.* **1997**, *3*, 538. (f) Akiyama, T.; Hoshi, E.; Fujiyoshi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2121. (g) Akiyama, T.; Ishida, Y. *Synlett* **1998**, 1150. (h) Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, *49*, 657.

allyltriisopropylsilane at −45 °C to afford [4 + 2] cycloadducts **6a−c** in 79−96% yields (entries 1−3). Elimination of ethanol from the initial product **6** proceeded by treatment with trimethylsilyl triflate, and enones **7** were obtained in good to high yields in two steps from cyclobutanone **1**. Spirocyclobutanones such as **1d,e** also reacted smoothly to afford **6d,e** in 74% and 88% yields (entries 4 and 5). 3-Ethoxy-2-methylcyclobutanone **1f**, which has a monomethyl substituent at the 2-position, also reacted readily with allyltriisopropylsilane, and subsequent elimination gave enone **7f** in 61% yield (entry 6). In all examples described above, allyltriisopropylsilane was regioselectively inserted into the more substituted C2−C3 bond of cyclobutanones, and other products formed by regioisomeric insertion of allyltriiropropylsilane or noncyclized products were not detected.

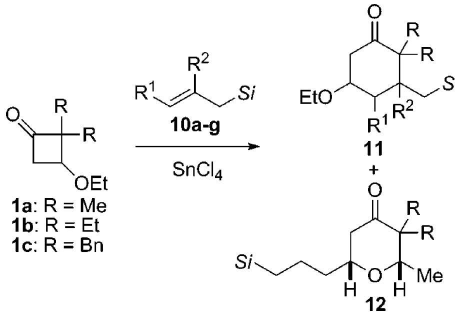
Table 2. Tin(IV) Chloride Catalyzed [4 + 2] Cycloaddition of Various 3-Ethoxycyclobutanones **1a−f** to Allyltriisopropylsilane



entry	cyclobutanone 1 R^1, R^2	6	% yield[a] of 6 (*cis*/*trans*)	7	% yield[b] of 7
1	**1a** R^1, R^2 = Me	**6a**	80 (71:29)	**7a**	78
2	**1b** R^1, R^2 = Et	**6b**	96 (72:28)	**7b**	94
3	**1c** R^1, R^2 = Bn	**6c**	79 (70:30)	**7c**	77
4	**1d** R^1, R^2 = $(CH_2)_4$	**6d**	74 (68:32)	**7d**	69
5	**1e** R^1, R^2 = $(CH_2)_5$	**6e**	88 (70:30)	**7e**	82
6	**1f**[c] R^1, R^2 = Me, H	**6f**	nd[d]	**7f**	61 (54:46)[e]

[a] Yield and *cis*/*trans* ratios were determined by ^1H NMR analysis. [b] Isolated yield for two steps from **1**. [c] *cis*/*trans* = 23:77. [d] Not determined. [e] Diastereomer ratio.

Table 3. Tin(IV) Chloride Catalyzed [4 + 2] Cycloaddition of 2-Diethyl-3-ethoxycyclobutanones to Various Allylsilanes



entry	1	allylsilane 10	% yield[a] of 11 (*cis*/*trans*)[b]	% yield[a] of 12
1	**1b**	R^1, R^2 = H, Si = $SiMe_3$ (**10a**)	**11ba** 80 (70:30)	0
2	**1b**	R^1, R^2 = H, Si = $SiMe_2Ph$ (**10b**)	**11bb** 72 (70:30)	0
3	**1b**	R^1, R^2 = H, Si = $SiMe_2CHPh_2$ (**10c**)	**11bc** 75 (63:37)	0
4	**1b**	R^1, R^2 = H, Si = $SiPh_2$*t*-Bu (**10d**)	**11bd** 55 (72:28)	**12bd** 22
5	**1a**	**10d**	**11ad** 53 (79:21)	**12ad** 16
6	**1c**	**10d**	**11cd** 50 (80:20)	**12 cd** 39
7	**1a**	R^1 = H, R^2 = Me, Si = $SiMe_3$ (**10e**)	**11ae** 78 (52:48)[c]	0
8	**1a**	R^1, R^2 = $(CH_2)_4$, Si = $SiMe_3$ (**10f**)	**11af** 64 (55:45)[c]	0
9	**1a**	R^1, R^2 = $(CH_2)_3$, Si = $SiMe_3$ (**10g**)	**11ag** 70 (57:43)[c]	0

[a] Isolated yield. [b] Determined by ^1H NMR analysis. [c] Stereochemistry was not determined.

Next, various allylsilanes **10a−d** were employed instead of allyltriisopropylsilane (Table 3). It is interesting that cycloaddition between cyclobutanone **1b** and allyltrimethylsilane **10a** proceeded to afford the desired compound **11ba** in 80% yield (entry 1). This result suggests that formation of a six-membered ring proceeds smoothly rather than elimination of the trimethylsilyl group from intermediate **4**, and it is in contrast to the usual tendency of Lewis acid catalyzed reaction of allyltrimethylsilane with carbonyl compounds to give an allylation product (Sakurai product). The reaction with allyldimethylphenylsilane **10b** and allylbenzhydryldimethylsilane[17] **10c** also gave the desired [4 + 2] cycloadducts **11bb** and **11bc** in 72% and 75% yields, respectively (entries 2 and 3). It was found that the *cis*/*trans* ratios of cyclohexanone derivative **11** did not depend on the steric hindrance of silyl groups.

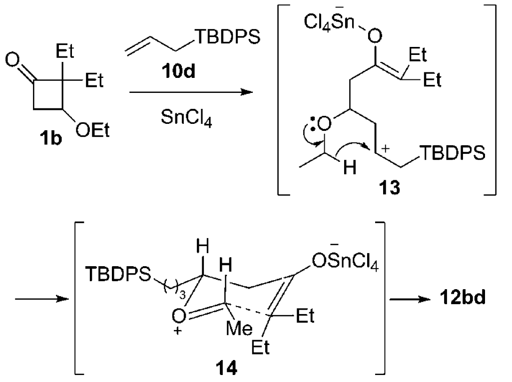
Allyl-*tert*-butyldiphenylsilane **10d** reacted with cyclobutanone **1b** to afford [4 + 2] cycloadduct **11bd** in 55% yield along with an unexpected product **12bd** in 22% yield (entry 4). It is notable that only one distereomer (*cis*-product, **12**) was obtained. A possible mechanism for formation of **12bd** is shown in Scheme 2. 1,5-Hydride transfer[18] of β-silyl cation **13**, which is generated by tin(IV) chloride catalyzed addition of **10d** to **1b**, gives a more stable zwitterionic intermediate **14** in which steric hindrance between two reaction sites is reduced compared to that in the case of **13**. Tetrahydro-4-pyrone derivative **12bd** is formed by cyclization of the intermediate **14** with the six-membered chair transition state.[19]

---

(17) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379.

(18) 1,5-Hydride transfer: (a) Akiyama, T.; Nakano, M.; Kanatani, J.; Ozaki, S. *Chem. Lett.* **1997**, 385. (b) Choi, G. M.; Yoo, B. R.; Lee, H.-J.; Lee, K.-B.; Jung, I. N. *Organometallics* **1998**, *17*, 2409.

Scheme 2. Possible Mechanism for Formation of **12bd**



To investigate the steric factors involved in inducing 1,5-hydride transfer, cycloaddition of two cyclobutanones **1a,c** bearing dimethyl and dibenzyl groups at the 2-position of 3-ethoxycyclobutanone was examined (entries 5 and 6). It was found that the yields of tetrahydro-4-pyrone derivatives **12** increased as the steric size of 2-alkyl groups became larger. This suggests that steric hindrance between the *tert*-butyldiphenylsilyl group[20] and enolate moiety of the intermediate **13** accelerates the 1,5-hydride transfer. The fact that allyltriisopropylsilane did not induce 1,5-hydride transfer suggests that the cation-stabilizing effect of the silyl group may also play an important role in controlling the reaction pathway (compare Table 2, entry 2 and Table 3, entry 4).[21]

Some substituted allyltrimethylsilanes **10e−g** were employed in the present cycloaddition reaction with cyclobutanone **1a** (entries 7−9). The formal [4 + 2] cycloaddition reaction proceeded to afford cycloadducts in good yields.

In summary, we have developed a formal [4 + 2] cycloaddition between 3-ethoxycyclobutanones and allylsilanes by catalysis with tin(IV) chloride. We have also found the use of allyl-*tert*-butyldiphenylsilane induced 1,5-hydride transfer, which gave a tetrahydro-γ-pyrone derivative. This new method for the synthesis of cyclohexanones by employing a cycloaddition reaction between two easily accessible small components, 3-ethoxycyclobutanone and allylsilane, will have unique applicability in organic synthesis.

Acknowledgment. This study was supported by a SUMBOR grant and a Grant-in-Aid for Scientific Research from MEXT, Japan.

Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901329C

---

[19] 1,5-Hydride transfer/cyclization: (a) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (b) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (c) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90. (d) Mátyus, P.; Éás, O.; Tapolcsányi, P.; Polonka-Bálint, Á.; Halász-Dajka, B. *Synthesis* **2006**, 2625. (e) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (f) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (g) Barluenga, J.; Fañanás-Mastral, M.; Aznar, F.; Valdes, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594.

[20] Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599.

[21] Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.