ORGANIC LETTERS

2007
Vol. 9, No. 19
3757−3760

Synthesis and Ring Expansions of Functionalized Spirocyclobutanones

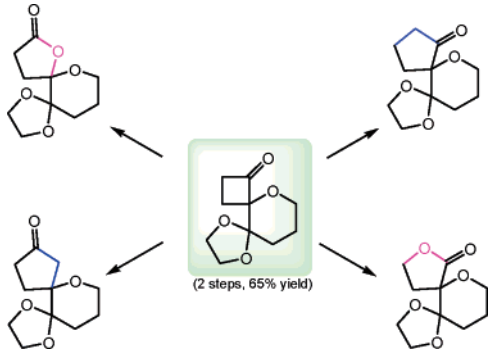
Nuno Maulide and István E. Markó*

Département de Chimie, Université catholique de Louvain, 1 Place Louis Pasteur, 1348 Louvain-la-Neuve, Belgium

marko@chim.ucl.ac.be

Received July 5, 2007

ABSTRACT



The first condensations between bis(trimethylsilyloxy)cyclobutene derivatives and functionalized orthoesters are reported. The resulting adducts are readily converted into spirocycloethers, which undergo a variety of –CH_2– and –O– insertions with excellent regioselectivity.

Cyclobutanes are important building blocks in synthesis and chemists have long been fascinated by these strained cyclic structures, which readily undergo a number of interesting rearrangements, including ring expansion and contraction.[1]

Accordingly, the preparation of cyclobutanone derivatives has been the subject of much synthetic work. Among the most popular methods developed over the years, the [2 + 2]-cycloaddition methodology still occupies a prominent position.[1c]

On the other hand, it would be of considerable interest to use simple, readily accessible cyclobutane starting materials as scaffolds onto which functionalities can be gradually appended. Bis-trimethylsilyloxy cyclobutenes such as **1** (n = 1), which are commercially available and easily obtained in large scale by acyloin condensation of succinate diesters, appear to be excellent candidates to participate in such an endeavor.[2]

Previous synthetic applications of silylated acyloins of the general structure **1** have largely derived from the work of Burnell and others.[3] In particular, the Burnell group has developed a broadly applicable geminal acylation procedure, which converts bis-siloxyalkenes to functionalized 1,3-diketones, by Lewis acid mediated reaction with either aldehydes, ketones, or acetals (Scheme 1).[3] Following an initial Mukaiyama−aldol reaction between the silylated acyloins **1** and a suitable electrophilic partner, intermediates **2** undergo an in situ rearrangement to the 1,3-diketones **3**, in the presence of an excess of Lewis acid. The adducts thus produced have been employed in various synthetic ventures.

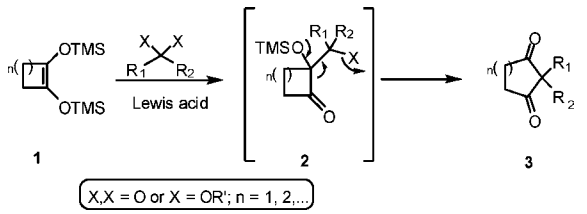
(1) (a) Namyslo, J. C.; Kaufman, D. E. *Chem. Rev.* **2003**, *103*, 1485. (b) Fu, N.-Y.; Chan, S.-H. In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; J. Wiley & Sons: Chichester, New York, 2005; p 357. (c) Lee-Ruff, E. In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; J. Wiley & Sons: Chichester, New York, 2005; p 281.

(2) Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1977**, *57*, 1. Compound **1** (n = 1) is commercially available from Acros Organics.

(3) (a) Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356. (b) Crane, S N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352. (c) Wu, Y.-J.; Zhu, Y.-Y. *J. Org. Chem.* **1994**, *59*, 104. (d) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485. (e) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P. Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311 and references therein. See also: (f) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

10.1021/ol7015753 CCC: $37.00
Published on Web 08/23/2007

Scheme 1. Geminal Acylation Procedure Reported by Burnell et al.

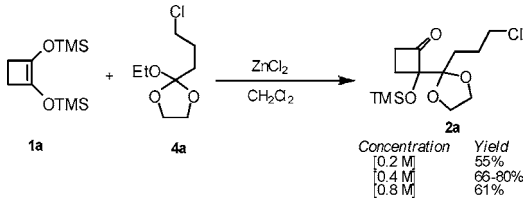


However, applications of the Mukaiyama adducts **2** in reactions other than pinacol-type rearrangements are somewhat scarce,[4] and the geminal acylation procedure seemed to be ineffective as far as orthoesters are concerned.[5]

Our laboratory has been interested in the use of readily available functionalized orthoesters, of which **4** are representative members (Figure 1).[6] During these studies, we have observed that a dioxolane substituent in the orthoester usually conferred increased robustness to both the orthoesters and their condensation adducts. Thus, it was hoped that its presence would enable the preparation of cyclobutanone adducts akin to **2**, by slowing down or inhibiting the subsequent pinacol rearrangement. In this paper, we wish to disclose some of our preliminary results on the preparation of such functionalized four-membered ring compounds and highlight their synthetic versatility.

Initial experiments focused upon the Lewis acid mediated condensation of bis(trimethylsilyloxy)cyclobutene **1a** with orthoester **4a** (Scheme 2). After extensive screening, it was

Scheme 2. Optimization of the Condensation Reaction



found that the use of zinc chloride in dichloromethane, in the presence of a 1.5-fold excess of orthoester, provided the best results. Under these conditions, no rearrangement of **2a** occurred. Concentration was also an important parameter (Scheme 2) and performing the reaction at an optimal [0.4 M] consistently afforded **2a** in 66−80% yields. It is noteworthy that, to the best of our knowledge, this reaction constitutes the first example of successfully merging an orthoester and a silylated acyloin. Furthermore, in this process a quaternary center is created.

Compound **2a** possesses an interesting concatenation of functional groups, and we became intrigued by the possibility of directly connecting the silylated alcohol and the halogenated terminus to form a spirocyclic ether.

To this end, we have developed a sequence involving a desilylation followed by a Williamson-like ring closure (Figure 1, Table 1). While desilylation could be readily

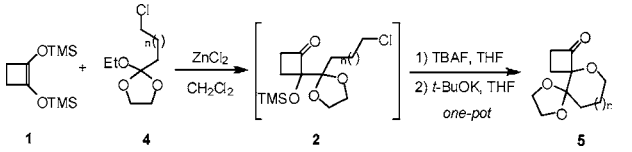
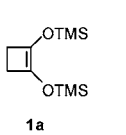
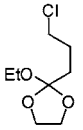
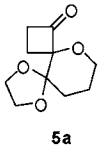
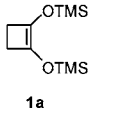
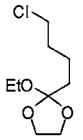
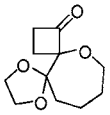
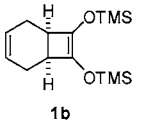
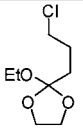
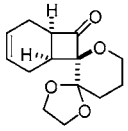
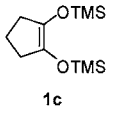
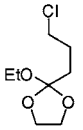
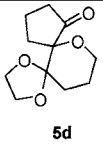


Figure 1

Table 1. Sequential Condensation/annelation to Spirocyclic Ethers

Silylated acyloin	Orthoester	Adduct **5**	Yield of **5**[a,b]
 **1a**	 **4a**	 **5a**	*63%*
 **1a**	 **4b**	 **5b**	*36%*
 **1b**	 **4a**	 **5c**[c]	*35%*
 **1c**	 **4a**	 **5d**	--[d]

[a] All yields refer to pure, isolated products. [b] Overall yield for the condensation/cyclization sequence. [c] Compound **5c** was obtained as a single diastereomer upon stirring crude **2c** with TBAF in THF. [d] No condensation adduct could be detected in the reaction.

accomplished with TBAF in THF, the desired cyclization was best performed with *t*-BuOK. Interestingly, both reactions could be performed in the same vessel, thus leading to a simple one-pot procedure which delivered the cyclobutanone−spiroether **5a** in good overall yields.

(4) For an isolated example, see: Li, W.-D. Z.; Zhang, X.-X. *Org. Lett.* **2002**, *4*, 3485.

(5) In a full account on the scope of the reaction, Burnell and co-workers mention that "orthoesters do not give geminally acylated products in synthetically useful yields" (see ref. 3e). It appears that a host of competitive pathways severely hamper the usefulness of this reaction.

(6) (a) Markó, I. E.; Ates, A. *Synlett* **1999**, 1033. (b) Markó, I. E.; Vanherck, J.-C.; Ates, A.; Tinant, B.; Leclercq, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3333. (c) Maulide, N.; Markó, I. E. *Chem.Commun.* **2006**, 1200. (d) Maulide, N.; Markó, I. E. *Org. Lett.* **2006**, *8*, 3705. (e) Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962.

The scope of this condensation-cyclization sequence was then examined (Table 1), revealing some unique features. For example, although only a few examples of direct oxepane annelation by the Williamson reaction have been reported in the literature, this process allows the creation of a spiro-oxepane moiety in reasonable overall yield (entry 2).[7] When the *cis*-fused bicyclic acyloin derivative **1b** is employed, complete diastereocontrol is exercised as a result of the face-selective approach of the oxonium cation onto the silylenol ether (entry 3).[8] Cyclization occurs readily upon simple exposure of the crude condensation product to TBAF in THF.

With easy access to gram-quantities of spiroannulated compounds **5a**−**c** in hand, their subsequent transformations via the rich chemistry of cyclobutanones were examined.[1] For instance, Baeyer−Villiger oxidation of **5a** with *m*-CPBA smoothly provided spiroketal-lactone **6a** in quantitative yield. A similar ring-expansion took place in the case of **5b** (Figure 2, Table 2, entries 1 and 2).[9] This constitutes a simple three-step procedure for the preparation of functionalized spiroketal-like fragments.[10]

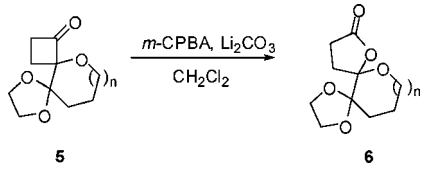
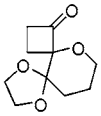
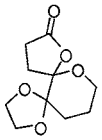
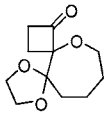
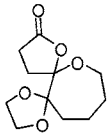
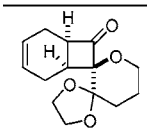
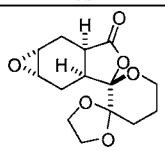


Figure 2

Table 2. Baeyer−Villiger Oxidation of Spirocyclobutanones **5**

Cyclobutanone **5**	Baeyer-Villiger product **6**	Yield[a]
 **5a**	 **6a**	*96%*
 **5b**	 **6b**	*97%*
 **5c**	 **6c**	*60%*

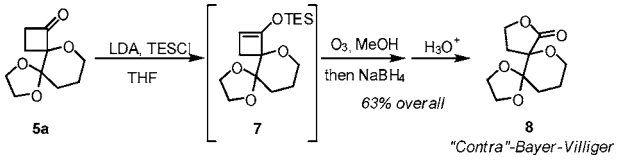
[a] All yields refer to diastereomerically pure, isolated substances.

In the case of **5c**, the key Baeyer−Villiger homologation was accompanied by a simultaneous, diastereoselective epoxide formation (Table 2, entry 3). Remarkably, the lactone **6c**, thus prepared, possesses five stereogenic centers of fixed relative configuration, built in three operations from achiral substances and with complete diastereocontrol.

In addition to these Baeyer−Villiger products, we were also interested in accessing other spirolactones, particularly those derived from what could be considered as a "reverse-Baeyer−Villiger" oxygen insertion.

Although this is not possible through a direct oxygen insertion reaction, a simple two-step procedure can accomplish the same result (Scheme 3).[11] Therefore, formation

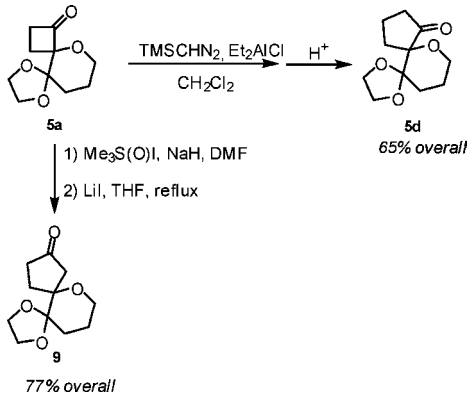
Scheme 3. Access to the "Reverse-Baeyer−Villiger" Lactone **8**



of silyl enol ether **7**, followed by ozonolysis and acidic workup, provided the regioisomeric Baeyer−Villiger lactone **8** in an unoptimized 63% overall yield.

While all of these oxygen-insertion reactions proceeded smoothly and offered an easy access to a variety of spiro-bicyclolactones, the ring expansion of spirocyclobutanone **5a**, using carbon-based reagents, led to interesting observations.[12] A selection of some of our results is presented in Scheme 4.

Scheme 4. Regioselective Ring Expansions of Spirocyclobutanone **5a**



Interestingly, all methylene insertion reactions using diazomethane failed to provide the desired adducts. However,

(7) For a rare example, see: (a) Lai, Y.-S.; Stamper, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2147.

(8) Stereochemistry assigned by NOE experiments: see the Supporting Information.

(9) (a) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (b) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 684.

(10) For reviews on spiroketals, see: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

when (trimethylsilyl)diazomethane was employed in the presence of diethylaluminum chloride, chemoselective ring-expansion to a mixture of silylated cyclopentanones ensued. Following acidic workup, a single product **5d** was isolated in 65% yield. In contrast to the Baeyer−Villiger oxidation, this $-CH_2-$ insertion implied the migration of the less substituted carbon−carbon bond of cyclobutanone **5a**. Pleasingly, this ring-expansion allowed the indirect preparation of the product that should have been formed by the direct condensation−annelation of bis(silyloxy)cyclopentene **1c** (Table 1).

The high regioselectivity observed can be reconciled with the work of Hegedus, who observed that migration of the less substituted carbon center usually dominated (albeit with many exceptions) in the diazo-mediated ring expansions of cyclobutanone derivatives.[13]

Complete reversal of regioselectivity was observed when an alternative sequence was investigated. In the event, Corey−Chaykovsky epoxidation of cyclobutanone **5a**, followed by direct lithium iodide induced rearrangement of the crude epoxide, provided β-spiroether **9** in high yield.[12a,14] This transformation, which generates the regiocomplementary cyclopentane, clearly illustrates the versatility of adducts **5**, since it now becomes evident that the regiochemistry of both carbon and oxygen insertions can be controlled at will, enabling the efficient preparation of at least four different products from a single precursor. The fact that spiroethers **5** are readily accessible from the simplest of precursors on a gram scale further emphasizes their synthetic potential.

In summary, the first successful condensations between bis(silyloxy)cyclobutenes and orthoesters are reported. These reactions proceed under mild conditions, and the Mukaiyama−aldol adducts can be isolated in high yields. The resulting cyclobutanone derivatives can then be easily elaborated into spirocycloethers **5** by a novel, one-pot deprotection/cyclization sequence. Direct oxygen insertion through Baeyer−Villiger ring expansion of these cyclobutanones leads to a simple synthesis of functionalized spiroketal frameworks. However, the way in which the cyclobutanone ring can be induced to regioselectively undergo all possible carbon and oxygen insertions simply by the judicious choice of reaction conditions is arguably the most impressive feature of these adducts. We are currently investigating other ring-expansion reactions as well as broadening the scope of the methodologies reported, with the aim of applying them to the synthesis of relevant natural products. The results of these investigations will be reported in due course.

Acknowledgment. Financial support of this work by the Université catholique de Louvain, the Fond National de la Recherche Scientifique (N.M., Aspirant F.N.R.S.), Merck, Sharp, and Dohme (Merck Academic Development Award to I.E.M.), and SHIMADZU Benelux (financial support for the acquisition of a FTIR-8400S spectrometer) is gratefully acknowledged. Dr. Grégori Binot (Team Leader, Syngenta AG) is acknowledged for useful discussions on this project.

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

OL7015753

(11) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785.

(12) For examples, see: (a) Ghosez, L.; Yang, G.; Cagnon, J. R.; Le Bideau, F.; Marchand-Brynaert, J. *Tetrahedron* **2004**, *60*, 7591. (b) Mahuteau-Betzer, F.; Ghosez, L. *Tetrahedron* **2002**, *58*, 6991 and references therein.

(13) (a) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **2000**, *65*, 1865. (b) Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306.

(14) Halazi, S.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1200.