Chelation and Nonchelation Control in the [3 + 4] and [3 + 5] Annulation Reactions of Benzyloxy-Substituted Dicarbonyl Electrophiles with Bis(trimethylsilyl) Enol Ethers

Gary A. Molander* and Paul R. Eastwood

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

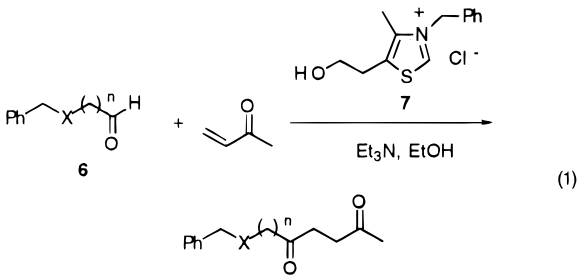
Received January 4, 1996

The Lewis acid-mediated annulation of 1,4- and 1,5-dicarbonyl compounds with bis(trimethylsilyl) enol ethers represents an increasingly versatile means to access seven- and eight-membered carbocycles as well as bicyclic ethers.[1] The regiochemical outcome of such reactions relies predominantly on the Lewis acid utilized. For instance, in the reaction of keto aldehydes **1** with **2** promoted by TMSOTf, the exclusive regioisomer isolated is **3** (Scheme 1). This regiochemistry can be explained by a process which involves the cyclic oxocarbenium ion **4**.

By contrast, the use of $TiCl_4$ as the Lewis acid partner leads predominantly to products of type **5**, which possess the opposite regiochemistry (Scheme 2).[1e] Presumably, in this case the reaction pathway does not involve intermediates of type **4**.

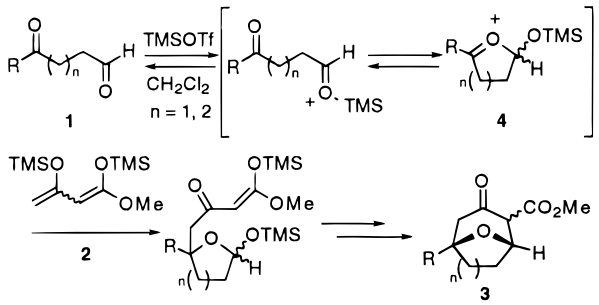
The high regioselectivity obtained in either protocol depends upon initial complexation of the Lewis acid to the least sterically hindered carbonyl center. We were intrigued by the possibility of incorporating chelating alkoxy substituents into the dicarbonyl compounds which could direct the course of the annulation without reliance upon this steric factor. Herein we report our findings of this study.

The 1,4- and 1,5-dicarbonyl substrates required for the studies were readily prepared by straightforward routes. For example, reaction of the aldehydes **6** with methyl vinyl ketone catalyzed by 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**7**) afforded the 1,4-dicarbonyl compounds **8a**−**8d** in modest to good yield (eq 1).[2] Compound **8a** was prepared as a control substrate

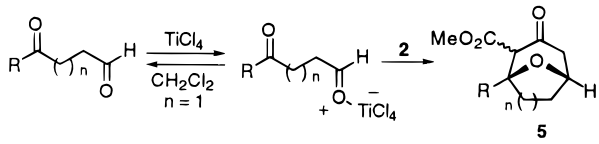


(1)

Scheme 1

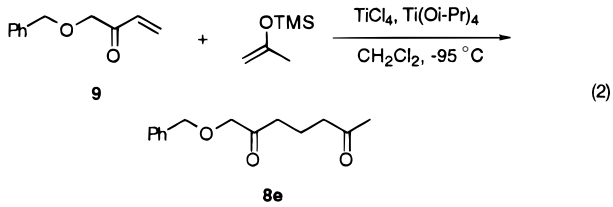


Scheme 2



in order to determine annulation regioselectivity without the presence of the chelating heterosubstituent in the chain.

The 1,5-dicarbonyl compound **8e** was prepared by the Lewis acid-promoted[3] addition of acetone trimethylsilyl enol ether[4] onto the known α,β-unsaturated ketone **9** (eq 2).



(2)

Upon annulation the bicyclic ethers were converted to the corresponding enol acetates (**12** and/or **13**) to simplify structural assignments made difficult by the initial formation of two epimers. In the $TiCl_4$-mediated annulations endo epimers were obtained, whereas in the TMSOTf-promoted reactions the exo isomers were favored. The reactivity of the epimers was reflected in the ease of formation of the enol acetates—the endo isomers were easily acetylated under normal conditions (Ac_2O, pyridine, DMAP) whereas for the exo isomers the use of an alternative procedure (NaH/Ac_2O) was usually necessary for efficient conversion. Structural assignments of the regioisomeric bicyclic ethers were established by NOE studies on the enol acetates.

Results of the Lewis acid-mediated annulations of **8a**−**8e** with **2** (Scheme 3) are presented in Table 1. When no directing oxygen was present (entries 1 and 6, Table 1) moderate regioselectivity was observed. In this case the major isomer isolated was dependent on the Lewis acid utilized. These results can be rationalized on the basis of the mechanistic discussion presented above.[1]

Entries 2 and 3 of Table 1 demonstrate that when a heterosubstituent was suitably placed for five- or six-membered ring chelation with $TiCl_4$, complete regioselectivity was obtained with initial attack of **2** occurring

(1) (a) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1991**, *56*, 2617. (b) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931. (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830. (d) Molander, G. A.; Siedem, C. S. *J. Org. Chem.* **1995**, *60*, 130. (c) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559. (d) Molander, G. A.; Carey, J. C. *J. Org. Chem.* **1995**, *60*, 4845. (e) Molander, G. A.; Andrews, S. W. *Tetrahedron Lett.* **1989**, *30*, 2351. (f) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 8382.

(2) Stetter, H.; Mohrmann, K.-H.; Schlenker, W. *Chem. Ber.* **1981**, *114*, 581.

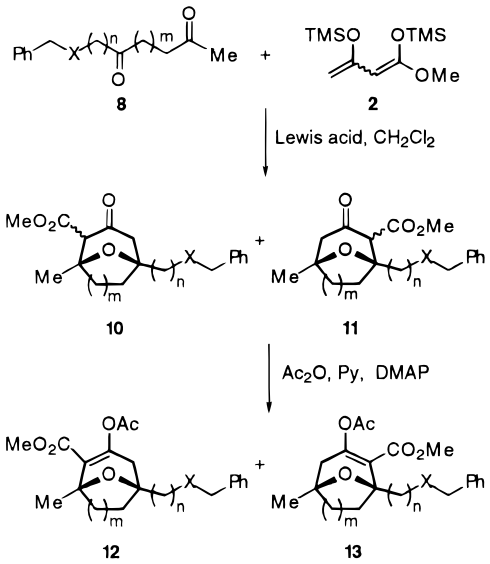
(3) Huffman, J. W.; Potnis, S. M.; Satish, A. V. *J. Org. Chem.* **1985**, *50*, 4266.

(4) Walshe, N. D. A.; Goodwin, G. B. T.; Smith, G. C.; Woodward, F. E. *Organic Syntheses;* Wiley: New York, 1993; Coll. Vol. III, p 1.

(5) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

0022-3263/96/1961-1910$12.00/0

Scheme 3



at the chelated, more electrophilic carbonyl center. Formation of an unfavorable seven-membered chelate accounts for the poor selectivity obtained with substrate **8d** (entry 4, Table 1). Chelation must also account for the excellent regioselectivity obtained in the [3 + 5] annulation (entry 5, Table 1).

As TMSOTf is a nonchelating Lewis acid it was expected that the oxygen substituent would have much less influence upon the relative selectivities. However, upon annulation of the 1,4-dicarbonyl compound **8b** or the 1,5-dicarbonyl compound **8e** (entries 7 and 9, Table 1) only single regioisomers were obtained. The compounds isolated were isomeric to those generated using the $TiCl_4$-mediated process. This suggests that the heterosubstituent is directing the complexation of TMSOTf to the carbonyl center. Participation by the remaining carbonyl group then ensues, followed by attack of **2**. This directing effect is considerably diminished when the heterosubstituent is further away from the carbonyl (entry 8, Table 1) in which case the regioselectivity is poor. The precise manner by which this Lewis acid activation occurs is under current investigation.

Table 1. Lewis Acid-Promoted Annulations of Diketone Substrates 8 with 2

entry	substrate	*m*	Lewis acid	% isoltd yield (**10** + **11**)[a]	% isoltd yield (**12** + **13**)[a]	regioselectivity (**12**:**13**)[b]
1	**8a**	1	$TiCl_4$	89	96	1:6
2	**8b**	1	$TiCl_4$	76	83	>100:1
3	**8c**	1	$TiCl_4$	83	98	>100:1
4	**8d**	1	$TiCl_4$	51	90	2:1
5	**8e**	2	$TiCl_4$	65	88	>100:1
6	**8a**	1	TMSOTf	72	90	4:1
7	**8b**	1	TMSOTf	70	89	1:>100
8	**8c**	1	TMSOTf	37 (46)[c]	77	1.2:1
9	**8e**	2	TMSOTf	70	54	1:>100

[a] Refers to yields of purified products. All of these compounds have been fully characterized spectroscopically (^{1}H NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or high-resolution mass spectrometry. [b] Regioselectivities were determined either by NMR or fused silica capillary GC analysis. [c] Based on recovered starting material.

In conclusion, the incorporation of chelating heterosubstituents, combined with complementary Lewis acids, provides yet another means to control the regiochemistry in these [3 + 4] and [3 + 5] annulation reactions.[1] Further studies concerning mechanistic and stereochemical aspects of these reactions are underway, as well as applications of the method to natural product total synthesis.

Acknowledgment. This work was carried out with generous support from the National Institutes of Health. We thank Paul J. Nichols for his assistance with the NOE studies.

Supporting Information Available: ^{1}H and ^{13}C for spectra of compounds for which no elemental analysis was obtained (56 pages).

JO9600060