Intramolecular Ring Opening Reactions of 2-Oxetanones Leading to Tetrahydrofuran Ring Formation: A Lewis Acid Study

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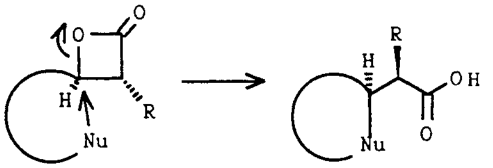
Received October 31, 1989

Summary: A study of Lewis acid mediated intramolecular ring opening reactions of 2-oxetanones has been undertaken. Using α-substituted 4-(3-(benzyloxy)propyl) analogues as substrates, we have found the reaction outcome to be highly Lewis acid dependent.

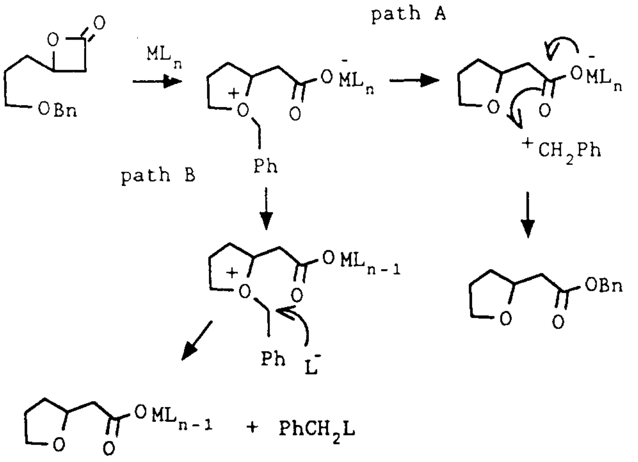
For years intermolecular *β-cleavage* reactions of 2-oxetanones have been usefully applied in synthesis as a means of establishing both carbon-carbon and carbon-heteroatom bond formation highly regio-[1] and stereoselectively.[2] By contrast, intramolecular versions of this reaction (see eq 1) have not been reported until recently.[3,4]



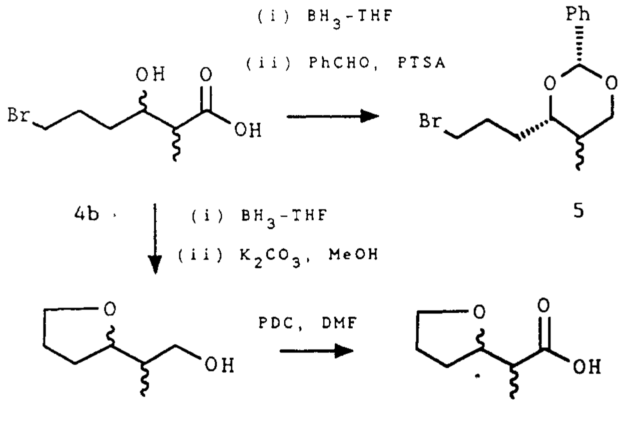
(1)

As part of an on-going program aimed at developing new synthetic methods based on the 2-oxetanone framework, we decided to investigate the synthetic possibilities of this process. In our initial work, we were able to demonstrate the viability of intramolecular β-cleavage as a method for preparing five- and six-membered cyclic ethers.[3] Specifically, we showed that treatment of the 2-oxetanone **1a** with boron trifluoride etherate provided the benzyl ester **2** as the major product (see Table I, entry 1). In a later paper, we provided proof that ring opening proceeds with inversion of configuration[4] (see eq 1). Here, we report on an intriguing facet of these reactions: the role of the Lewis acid in determining reaction outcome.

Scheme I



Scheme II



3b

As shown (see Table I), a variety of 2-oxetanones[5,6] and Lewis acids were chosen for study. Each reaction was taken to completion simply by adding a 1 M solution of the Lewis acid dropwise to the lactone under the conditions indicated, with reaction workup generally involving an aqueous quench followed by ether extraction. The only diversion from this procedure was required when zinc bromide was used as the Lewis acid (entry 4). In this case, following the addition of water to the reaction mixture on workup, the aqueous phase had to be acidified with mineral acid prior to ether extraction, presumably in order to effect complete hydrolysis of the initially formed zinc

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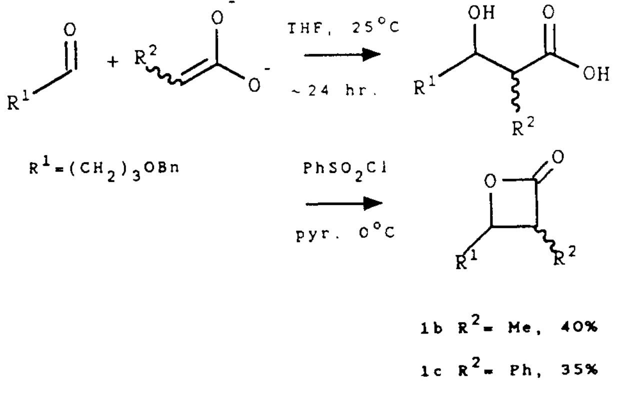
[1] Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4649. Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.

[2] Sato, T.; Kawara, T.; Nishizawa, A.; Fujisawa, T. *Tetrahedron Lett.* **1980**, *21*, 3377.

[3] Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573.

[4] Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829.

[5] The 2-oxetanones **1b** and **1c** were prepared as shown below. Derivative **1b** was isolated as a mixture of trans and cis stereoisomers, in which the trans:cis ratio varied from 3:1 to 2:1, depending upon the precise reaction time of the aldol step. The lactone **1c** was prepared as a single compound, identified as the trans stereoisomer by the coupling constant between the C-α and C-β protons of the lactone ring (4.2 Hz). For a review on reactions of carboxylic acid dianions, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521. For other examples of trans-selective 2-oxetanone syntheses by this route, see: Mulzer, J.; Pointner, A.; Chucholowski, A.; Bruntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52. For the preparation of **1a**, see ref 3.



[6] The 2-oxetanone **1d** was prepared (see below) from **1c** by low-temperature alkylation. See: Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620.

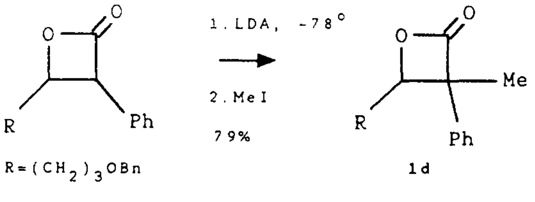
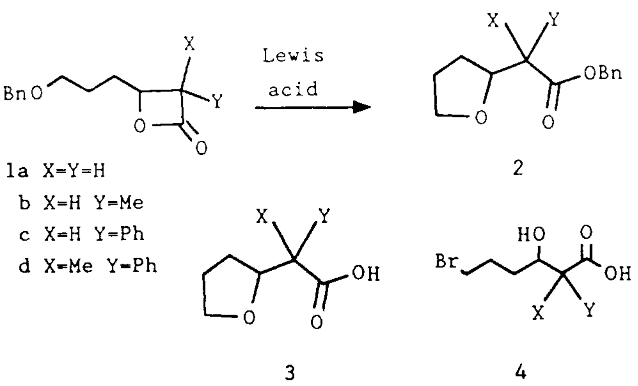


Table I. Reactions of 2-Oxetanones 1a–d with Lewis Acids



1a X=Y=H
b X=H Y=Me
c X=H Y=Ph
d X=Me Y=Ph

2

3

4

entry	lactone[a]	Lewis acid	product(s)[b]
1	1a	$BF_3·OEt_2$[c]	2 (69), 3a (9)
2	1a	$TiCl_4$[d]	3a (75)
3	1a	$SnCl_4$[d]	3a (52)
4	1a	$ZnBr_2$[e]	3a (71)
5	1b	$TiCl_4$[d]	3b (76)
6	1c	$TiCl_4$[d]	3c[f] (87)
7	1d	$TiCl_4$[d]	3d (72)
8	1a	BBr_3[g]	4a[h] (62)
9	1b	BBr_3[g]	4b[i] (71)

[a] Each of the substrates 1a–d was characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b] All products were characterized by their spectral data (IR, 300-MHz ^{1}H NMR, and 75.6-MHz ^{13}C NMR) and by comparison, where appropriate, with authentic samples. Values in parentheses refer to isolated yields of materials. [c] 2 molar equivalents, −20 °C, CH_2Cl_2, 30 min. [d] 1.1 molar equivalents, −78 °C, CH_2Cl_2, 30 min. [e] 5 molar equivalents, 25 °C, Et_2O, 3 h. [f] Isolated as a single stereoisomer.[8] [g] 1.1 molar equivalents, 0 °C, CH_2Cl_2, 5 min. [h] Further characterized by its conversion to acid 3a (see Scheme II). [i] Further characterized by its conversion to acid 3b (see Scheme II).

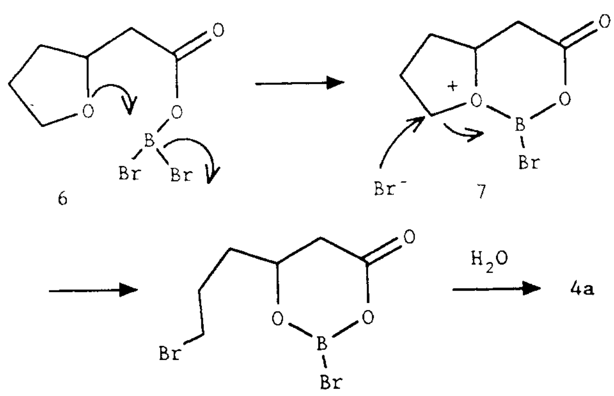
carboxylate. The isolated yield of the acid **3a** was significantly reduced when this procedure was not followed.[7]

Noteworthy from our study is that internal β-attack appears to be unimpeded by α-substituents on the 2-oxetanone ring (see, for example, entry 7). More important, we have found that three different types of product (**2**–**4**) can be formed, depending on the nature of the Lewis acid chosen to initiate rearrangement.

We believe that each reaction proceeds, via intramolecular β-cleavage, with the formation of a cyclic oxonium species (see Scheme I). From this intermediate, we contend, based on our results, that reaction outcome is then determined by the ligand-donating preference of the Lewis acid (ML_n). For example, in the case of boron trifluoride etherate, it would appear that the release of a fluoride ion from boron is slow, and carboxylate ion transfer to a benzyl carbocation (path A, $ML_n = BF_3$) is the preferred course, providing a benzyl ester as the major product. This result contrasts sharply with the titanium tetrachloride mediated reaction, in which no benzyl ester product was detected. Our interpretation of this is that the loss of a chloride ion and titanium–oxygen bond retention (path B, $ML_n = TiCl_4$) are now favored in this case. Following the addition of water, a carboxylic acid product results. Analogous pathways (i.e. path B) are assumed to be followed for zinc bromide and tin tetrachloride mediated reactions (see entries 3 and 4).

Quite unexpectedly, brominated acyclic products **4a** and **4b** (**4b** as a mixture of stereoisomers[8]) were formed when the lactones **1a** and **1b**, respectively, were treated with boron tribromide (see entries 8 and 9). When the behavior of this Lewis acid toward isolated 2-oxetanones[9] and benzyl ethers[10] is considered, different regioisomeric products might have been predicted. Independent conversions of the mixture of acids **4b** to their benzylidene acetals **5** (40%), and tetrahydrofuran derivatives **3b** (51%) (see Scheme II) helped to confirm our structural assignments.

Scheme III



To explain this particular reaction outcome, we propose that following intramolecular cleavage of the lactone ring to give the tetrahydrofuran intermediate **6** (see Scheme III) the loss of a second halide ligand takes place with concomitant six-membered ring formation. From the bicyclic complex **7**[11] thus generated, tetrahydrofuran ring opening then proceeds regioselectively as shown.

Recently, new methods which employ the 2 + 2 cycloaddition reaction have been developed for preparing α,β-disubstituted 2-oxetanones stereoselectively.[4,12] With the aid of these methods, we are currently exploring synthetic applications of the chemistry demonstrated herein.

Acknowledgment. The research upon which this material is based was supported in part by the National Science Foundation through Grant No. RII-8902064, the state of Mississippi, and Mississippi State University. Mention of trade names or commercial products used in research does not necessarily constitute their endorsement by the funding agencies. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available: Representative experimental procedures and spectral peak listings for **1a–d**, **2**, **3b–d**, and **4a,b** (5 pages). Ordering information is given on any current masthead page.

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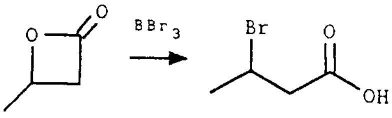
(7) Variable amounts of highly polar (perhaps polymeric) material accompanied each of the reaction products shown in Table I, which undoubtedly accounts for the low yield in some of the examples.

(8) This follows from the stereospecific nature of the ring opening process (see eq 1) and the stereochemistry of the starting material (see ref 5).

(9) Olah has reported the following reaction:



See: Olah, G. A.; Karpeles, R.; Narang, S. C. *Synthesis* **1982**, 963.

(10) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656.

(11) Six-membered ring complexes similar to **7** have been proposed to explain the regiocontrolled opening of a number of 2-substituted tetrahydrofurans by dimethylboron bromide. For details, see: Guindon, Y.; Therien, M.; Girard, Y.; Yoakim, C. *J. Org. Chem.* **1987**, *52*, 1680.

(12) Pons, J.-M.; Kocieński, P. *Tetrahedron Lett.* **1989**, *30*, 1833.