Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2231-2234, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00331-6

New Annulation Reactions of Cyclobutenones

John L. Dillon*

Process Exploration Labs, Technical Operations Development, Bristol Myers Squibb Co., P. O. Box 4755, Syracuse, New York 13221-4755

Qi Gao

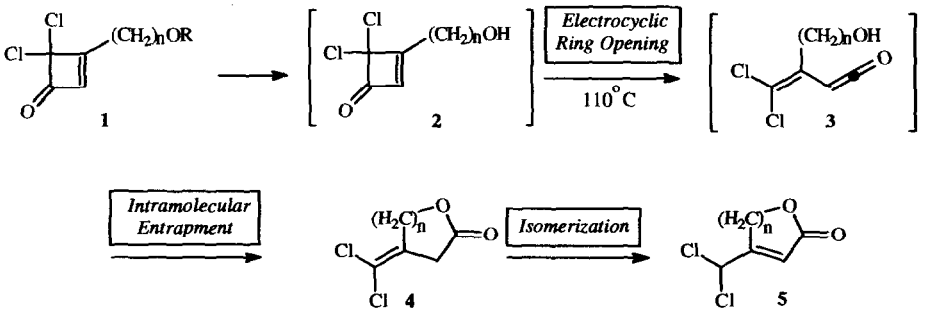
Analytical Research and Development Department, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., 5 Research Parkway, Wallingford, Connecticut 06492

Elizabeth A. Dillon and Nick Adams

Department of Chemistry, LeMoyne College, LeMoyne Heights, Syracuse, New York 13214

Abstract: Dichlorocyclobutenones **1a** and **1c** were exploited in the synthesis of unsaturated lactones **9** and **10** via intramolecular entrapment of a vinylketene with an alcohol. In contrast, thermolysis of dichlorocyclobutenones **1b** or **1d** in methanol led to unsaturated ketone **14** through deprotection, intramolecular Michael addition of the alcohol to the cyclobutenone and torquoselective ring opening.

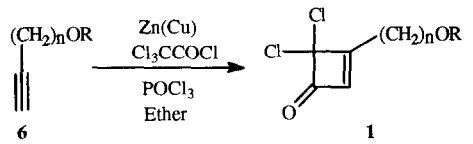
Cyclobutenones have emerged as versatile synthons in recent years as a result of electrocyclic ring opening to vinylketenes and subsequent electrocyclic cascades. These reactions have produced eight-membered carbocycles, phenols, quinones and a variety of heterocycles.[1] Less attention has been directed toward intramolecular entrapment of vinylketenes with heteroatoms such as oxygen to afford unsaturated lactones.[2] In previous studies, we demonstrated that 4,4-dichlorocyclobutenones are stable in refluxing methanol (65°C), but undergo electrocyclic ring opening in refluxing butanol (117°C) to form vinylketenes which can be trapped to produce unsaturated esters.[3a] We envisioned the intramolecular version of this process to proceed by refluxing a solution of **2** in toluene (110°C) to afford vinylketene **3** which would cyclize to **4** (Scheme 1). We anticipated the double bond in **4** would occupy the β,γ-position in accord with our results for acyclic analogues. Isomerization to the α,β-unsaturated isomer **5** could then be effected by treatment with base. In this communication we report the successful implementation of this strategy for synthesis of the isomeric lactones **4** and **5** (n=2) and describe a novel rearrangement of **1** containing a longer chain substituent (n=3).



Scheme 1

The compounds required for this study were readily prepared from commercially available alkynols. Protection of the alcohol as an acetate or TBDMS ether to afford **6** followed by cycloaddition with dichloroketene according to previously established methodology[3] furnished cyclobutenones **1a-d** (Table 1). Satisfactory yields were achieved for the acetates **1a-b**. TBDMS-cyclobutenones **1c-d** could not be obtained in comparable yield due to extensive desilylation under the conditions of the cycloaddition.

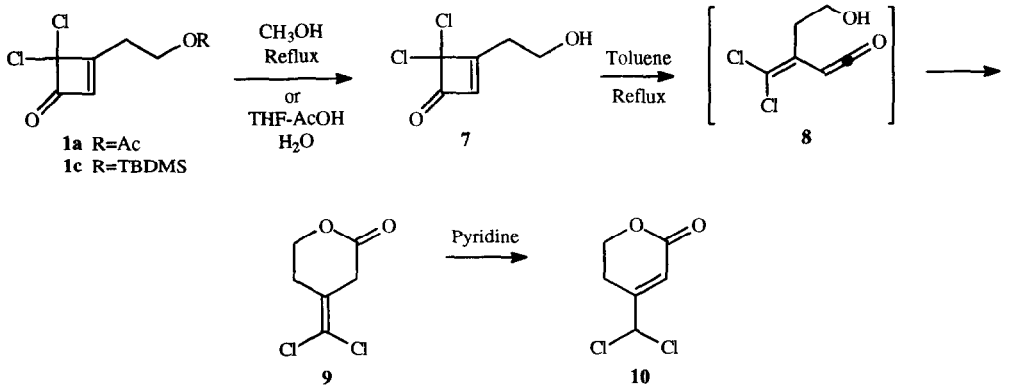
Table 1. Cycloaddition of Dichloroketene to Alkynes, **6**.



6 **1**

	R	n	Yield, %, **1**
a	Ac	2	62
b	Ac	3	69
c	TBDMS	2	23
d	TBDMS	3	38

Deprotection of **1a** (MeOH/reflux/6 h) or **1c** (THF/AcOH/H_2O) produced the alcohol **7** which was obtained in 60% and 76% yield, respectively, after flash chromatography. When a solution of **7** in toluene was refluxed for 16 h, the β,γ-unsaturated lactone **9** was obtained in 67% yield (Scheme 2). The structure of **9** was confirmed by single crystal X-ray analysis.[4] Compound **9** could also be prepared in 54% overall yield without isolation of **7** by refluxing a solution of **1c** in methanol, replacement of the methanol with toluene and refluxing for 16 h. Crystalline **9** recovered by flash chromatography and recrystallization from ether was stable to isomerization. Treatment of **9** with pyridine for 16 h led to nearly complete conversion to **10**.



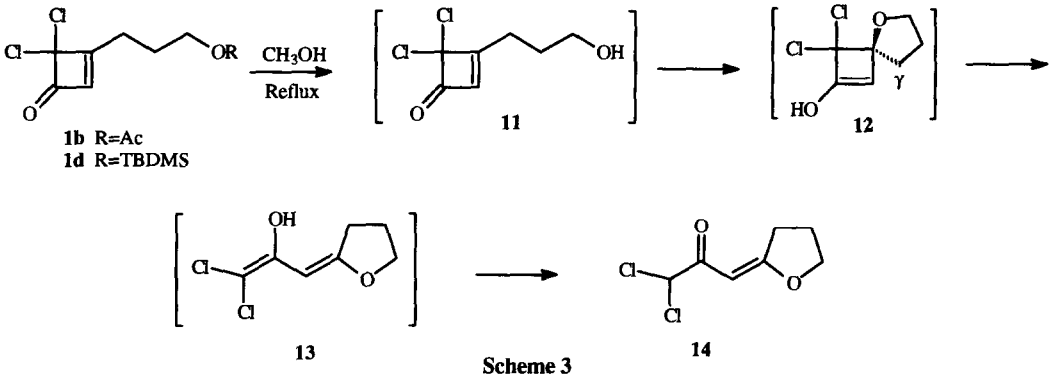
1a R=Ac
1c R=TBDMS

7 **8**

9 **10**

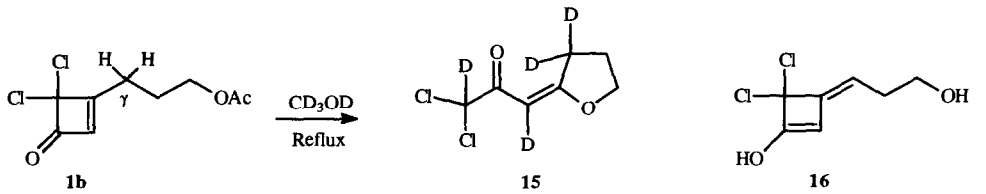
Scheme 2

Attempted extension of this methodology to a cyclobutenone containing one additional carbon in the sidechain resulted in a different reaction pathway. When a solution of **1b** in methanol was refluxed for 8 h, the unsaturated ketone **14** was formed in 78% yield (Scheme 3). The structure of **14** was confirmed by single crystal X-ray analysis.[5-7]



Scheme 3

The formation of **14** can be rationalized by transesterification of the ester **1b** with methanol followed by intramolecular Michael addition of the alcohol moiety in **11** to the strained cyclobutenone. Electrocyclic ring opening of the spirocyclic enol **12** then leads to **14**. Surprisingly, this reaction even proceeded slowly at room temperature. After stirring the silyl analogue **1d** for 10 d in methanol, a 62% yield of **14** was obtained. It was surprising that this reaction proceeded without the addition of an acid catalyst.[8] The *E*-stereochemistry of the olefin is also noteworthy and consistent with *torquoselective*[9] outward rotation of the ring-oxygen away from the chlorine substituents during the ring-opening of **12**. Some evidence for this mechanism was provided by deuterium labeling experiments. Refluxing a solution of **1b** in CD_3OD for 8 h led to nearly complete incorporation of deuterium on both of the carbons α to the ketone to afford **15** (Scheme 4). Surprisingly, deuterium exchange also occurred on the allylic ring-carbon.[10] Deuterium exchange was not observed on the carbons α or γ to the carbonyl group when a solution of **7** or **14** was refluxed in CD_3OD for 8 h. Recovered **1b** from incomplete conversion to **15** also showed little deuterium incorporation. These results suggest that a rapid addition-elimination equilibrium occurs between **11** and **12** via **16** prior to cyclobutene ring opening.



Scheme 4

Further investigations regarding the mechanism and scope of the annulations leading to **9**, **10** and **14** and the isomerization of **9** to **10** are in progress. In particular, chiral compounds analogous to **6** derived from asymmetric epoxidation followed by ethynylation, should allow for the synthesis of a wide array of chiral, unsaturated lactones. The preparation of sulfur and nitrogen-containing heterocycles by these annulation reactions, as well as the potential for these compounds in the synthesis of natural products, is also under investigation in our laboratories.

Acknowledgments: We thank Dr. G. Crull, Dr. H. Y. Lin, K. B. Johns, T. Baker and H. Shuttleworth for their assistance in obtaining spectral data.

References and Notes

1. For reviews in this area see (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (b) Liebeskind, L.S.; *Tetrahedron* **1989**, *45*, 3053. (c) Hyatt, J.; Raynolds, P. W. *Organic Reactions* **1994**, *45*, 159.
2. (a) Moore, H. W.; Perri, S. T. *J. Org. Chem* **1988**, *53*, 996. (b) Dillon, J. L.; Gao, Q. *J. Org. Chem.* **1994**, *59*, 6868. (c) Ohno, M.; Yamamoto, Y.; Eguchi, S. *Tetrahedron Lett.* **1993**, *34*, 4807.
3. (a) Hassner, A.; Dillon, J. L. *J. Org. Chem.* **1983**, *48*, 3382. (b) The preparation of **1b** in 80% yield was reported using a modification of our original procedure, see Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299.
4. A crystal of **9**, obtained as an unstable, colorless plate from ether and measuring 0.25 mm X 0.35 mm X 0.45 mm was used for X-ray diffraction measurements. The six-membered ring of **9** adopts a boat conformation. Crystal data: $C_6H_6Cl_2O_2$; Orthorhombic, space group *Pbca*, a=7.3471(6) Å, b=12.700(1) Å, c=16.0319(6) Å, $\alpha=\beta=\gamma=90.00°$, V=1496.0(2) Å^3, Z=8, d_x=1.607 g cm^{-3}. A total of 1531 independent reflections were measured of which 1190 were observed with $|I| \geq 3\sigma$. Final agreement factors were R(F)=0.060 and *w*R(F)=0.083 for 92 variables.
5. (a) A crystal of **14**, obtained as an unstable, colorless plate from ether-hexane and measuring 0.15 mm X 0.30 mm X 0.40 mm was used for X-ray diffraction measurements. Crystal data: $C_7H_8Cl_2O_2$; Triclinic, space group $P\bar{1}$, a=5.7811(8) Å, b=8.872(1) Å, c=17.440(2) Å, α=85.07(1)°, β=88.08(1)°, γ=82.70(1)°, V=883.7(2) Å^3, Z=4, d_x=1.466 g cm^{-3}. A total of 3684 independent reflections were measured of which 1805 were observed with $|I| \geq 3\sigma$. Final agreement factors were R(F)=0.055 and *w*R(F)=0.067 for 256 variables. (b) The authors have deposited atomic coordinates for compounds **9** and **14** with the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 IEZ, UK.
6. For a synthesis of compounds analogous to **14** by a different route see Detty, M. R. *J. Org. Chem.* **1979**, *44*, 2073.
7. All of the new compounds reported in this paper were characterized by ^{1}H and ^{13}C NMR, FTIR and mass spectrometry.
8. For a review of intramolecular Michael reactions see, Little, R.D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Organic Reactions* **1995**, *47*, 315.
9. Dolbier, W. R. Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Accts. Chem. Res.* **1996**, *29*, 471 and references cited therein.
10. Dreiding has shown that exposure to pyridine-d_5-CD_3COOD results in deuterium exchange for alkyl-substituted dichlorocyclobutenones; see Ammann, A. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1987**, *70*, 321.

(*Received in USA* 12 *December* 1996; *accepted* 11 *February* 1997)