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Unexpected Reactivity of Acetylenic ω-Ketoesters toward TBAF and *t*-BuOK; New Cascade Reactions Affording Allene and Oxetane Derivatives†

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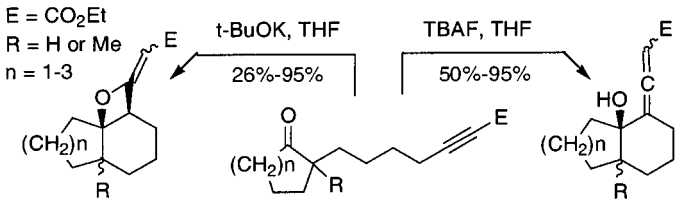
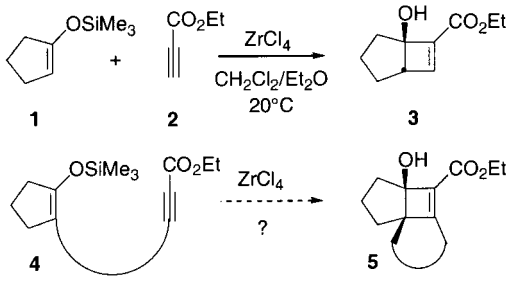
ABSTRACT



The reactivity of acetylenic ω-ketoesters toward tetra-*n*-butylammonium fluoride and potassium *tert*-butoxide was studied. These cascade reactions proceeded smoothly and afforded either electrophilic allene derivatives or highly functionalized oxetane derivatives in moderate to high yields.

Strained molecules play an important role as synthetic intermediates. Therefore the development of new reaction pathways toward small ring assembly is still of considerable interest.[1,2] More specifically, unsaturated four-membered rings fused to other cycles correspond to that type of compound. Among the possibilities for their synthesis, the nonphotochemical [2 + 2] cycloaddition reaction of electrophilic alkynes to alkene derivatives remains one of the most powerful methodologies.[3] Previously, we have shown that the *intermolecular* $ZrCl_4$-catalyzed [2 + 2] cycloaddition reaction of silyl enol ether **1** with ethyl propynoate **2** afforded in high yield the corresponding cycloadduct **3** (Scheme 1),[4]

Scheme 1. $ZrCl_4$-Catalyzed [2 + 2] Cycloaddition Reaction



the latter being a valuable intermediate for the total synthesis of natural products.[5] Interestingly, the *intramolecular* version of that type of reaction has attracted little attention. Thus, in continuation of our interest into the synthesis and the

† This Letter is dedicated to the memory of Prof. Donald J. Cram, deceased June 17, 2001.

(1) De Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20−32.

(2) Wong, H. J. C.; Lau, K. L.; Tam, K. F. *Top. Curr. Chem.* **1986**, *133*, 83−157.

(3) (a) Miesch, M.; Franck-Neumann, M; Wendling, F. *Tetrahedron Lett.* **1999**, *40*, 839−842. (b) Miesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, *20*, 3381−3392 and references therein.

(4) Franck-Neumann, M.; Miesch, M.; Miesch-Gross, L. *Tetrahedron Lett.* **1990**, *31*, 5027−5030.

(5) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett*, **1991**, *32*, 2135−2136. Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1992**, *33*, 3879−3882. Miesch, M.; Cotté, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1993**, *34*, 8085−8086. Miesch, M.; Cotté, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1994**, *35*, 7031−7032. Miesch, M.; Miesch-Gross, L.; Franck-Neumann, M. *Tetrahedron* **1997**, *53*, 2103−2110. Miesch, M.; Miesch-Gross, L.; Franck-Neumann, M. *Tetrahedron* **1997**, *53*, 2111−2118.

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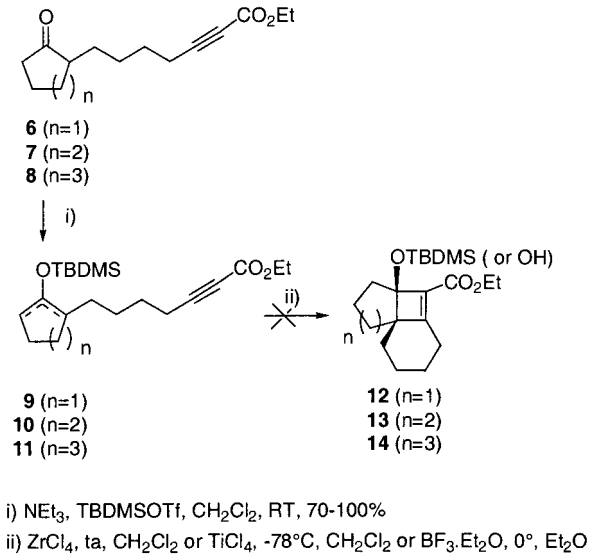
reactivity of strained molecules, we investigated the possibility of preparing unsaturated four-membered rings fused to polycyclic ring systems **5** by means of an *intramolecular* [2 + 2] cycloaddition reaction of electrophilic acetylenes linked to keto-derivatives of type **4** (Scheme 1). Herein, we describe our preliminary results concerning the *intramolecular* reactivity of acetylenic ω-ketoester derivatives **4** (Scheme 1).[6]

Our studies began with the synthesis of the silyl enol ethers **9**−**11** starting from the corresponding acetylenic ω-ketoesters **6**−**8**[7] and using conventional methods (TBDMSOTf, NEt_3, CH_2Cl_2, 20 °C). To promote an intramolecular [2 + 2] cycloaddition reaction, the latter were added to a suspension of $ZrCl_4$ in CH_2Cl_2 at room temperature. No cycloadducts were observed, and the sole products recovered quantitatively were the acetylenic ω-ketoesters **6**−**8**. The same results were obtained with other Lewis acids such as $TiCl_4$ and $BF_3{\cdot}Et_2O$ (Scheme 2).

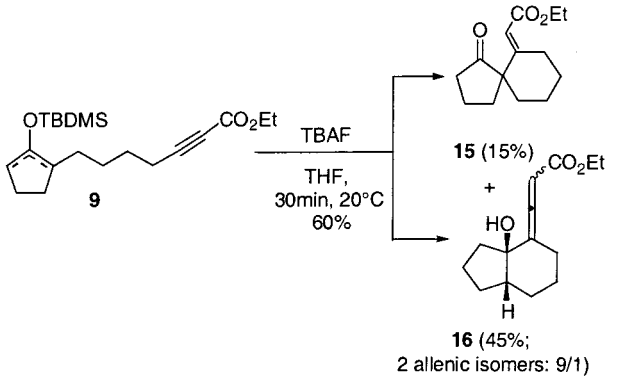
Scheme 2. Reactivity of Acetylenic ω-Ketoester Derivatives toward $ZrCl_4$



To develop other reaction conditions that could lead to the cyclobutenic derivatives **12**−**14** starting from the acetylenic ω-ketoesters **6**−**8**, we attempted to deprotect the silyl enol ethers **9**−**11**. For practical reasons, we decided to use tetra-*n*-butylammonium fluoride (TBAF) as deprotecting reagent.

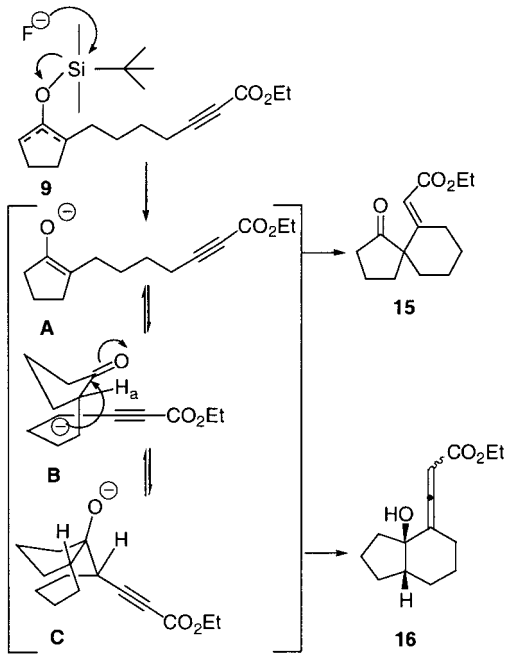
Surprisingly, the treatment of the silyl enol ether **9** with TBAF did not afford the desired acetylenic ω-ketoester **6** but led to a mixture of two easily separable products: the spiroketone derivative **15** isolated in 15% yield and the allene derivative **16** isolated in 45% yield (mixture of two separable allene isomers, 9/1 most polar/less polar) (Scheme 3).

Scheme 3. TBAF Treatment of the Silyl Enol Ether **9**



The formation of these two compounds could be explained as follows. After deprotection of the silyl enol ether **9**, the resulting enolate **A** could evolve according to two different pathways: (a) an intramolecular Michael addition takes place giving the spiroketone derivative **15**, or (b) the enolate **A** is in equilibrium with the propargylic carbanion **B**; an intramolecular cyclization then takes place onto the carbonyl function, giving rise to the alcoolate **C**, which evolves to give the allene derivative **16** (Scheme 4).

Scheme 4. Proposed Mechanism for the Formation of **15** and **16**



Compound **16** possesses a *cis* ring junction, this being in good accordance with the fact that the approach path of

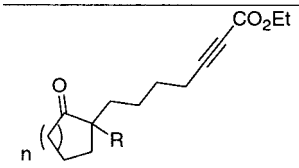
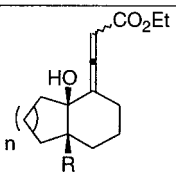
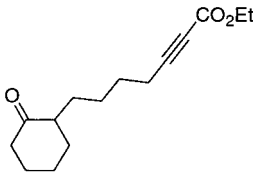
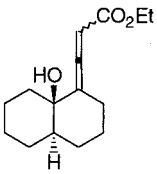
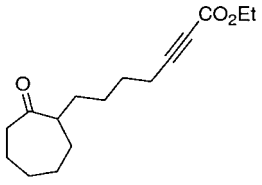
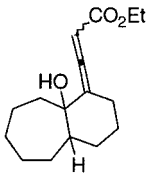
(6) It has to be noted that Fukumoto et al. studied the *intramolecular* reactivity of olefinic ω-ketoesters in order to obtain polycyclic ring systems fused to cyclobutanes: (a) Ihara, M.; Taniguchi, T.; Makita, K.; Tanako, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K. *J. Am. Chem. Soc.* **1993**, *115*, 8107−8115. (b) Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Synthesis* **1995**, 1405−1410. If we applied the reaction conditions developed by Fukumoto et al. to our acetylenic ω-ketoesters, the corresponding silyl enol ethers were quantitatively recovered. The length of the carbon chain between the carbonyl group and the acetylenic moiety was chosen after molecular models examination so that the intramolecular cyclization could take place. The influence of the chain's length is actually under investigation: Miesch, M.; Wendling, F. *J. Org. Chem.* submitted for publication.

(7) Barbier, M.; Hügel, M.-F. *Bull. Chem. Soc. Fr.* **1961**, 1324−1326. (b) Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1995**, *60*, 4595−4601.

carbanion **B** should take place in an *anti* manner compared to the hydrogen atom located in the α position (H_a) and also with the Bürgi−Dunitz[8] way and angle (∼109°) of approach.

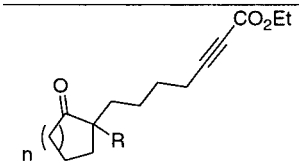
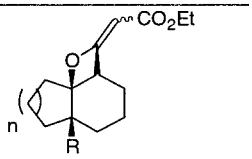
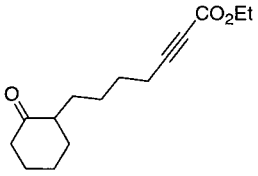
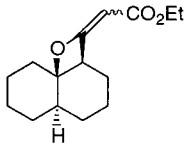
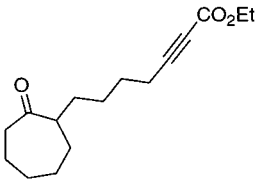
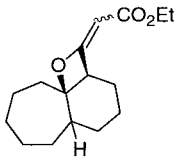
Intrigued by these findings, we have further investigated the possibility of preparing these compounds directly from the acetylenic *ω*-ketoester **6**. Indeed, according to our mechanism proposal, acetylenic *ω*-ketoester **6** should afford directly compounds **15** and **16** upon treatment under basic conditions. Thus, when compound **6** was treated with TBAF,[9,10] compounds **15** and **16** were also obtained in 25% and 50% yield, respectively. This easy to run reaction was also applied to the acetylenic *ω*-ketoesters **7**, **8**, **17**, and **18**. In each case the allene derivatives **19**, **20**, **21**, and **22** were isolated as major products (50−95% yield). It has to be noted that no Michael adducts (spiro compounds) were isolated starting from the acetylenic *ω*-ketoesters **7**, **8**, and **18**. The ring junction for compounds **16**, **19**, and **20** proved to be *cis*, and for compound **21** it was *trans*. However, we were not able to determine the stereochemistry of the ring junction for compound **22**.

Table 1. Synthesis of Allene Derivatives by Treatment of Acetylenic *ω*-Ketoesters **6**−**8**, **17**, and **18** with TBAF

acetylenic ω-ketoesters	allene derivatives (2 allene isomers : ratio; overall yield %)
 **6** (n = 1; R = H) **17** (n = 1 ; R = CH_3) **18** (n = 2 ; R = CH_3)	 **16** (n=1; R=H : 9/1; 50%) **19** (n=1; R=CH_3 : 1.6/1; 57%) **20** (n=2; R=CH_3 : 5/1; 95%)
 **7**	 **21** (1.5/1; 87%)
 **8**	 **22** (1/1; 80%)

To determine the influence of the base, the acetylenic *ω*-ketoesters were submitted to other bases such as K_2CO_3 in acetone; NaH in THF; and NaOEt in EtOH. In all of these cases, the starting material was recovered. However, when the reaction was carried out with *t*-BuOK in THF, the oxetanes **23**−**27**[11] were obtained in moderate to good yields (26−83%). The stereochemistry of the ring junction indicated for each compound was determined by NMR experiments (NOESY), and therefore the *cis* or *trans* stereochemistry of the ring junction was also secured for the allene derivatives.

Table 2. Synthesis of Oxetane Derivatives by Treatment of Acetylenic *ω*-Ketoesters **6**−**8**, **17**, and **18** with *t*-BuOK

acetylenic ω-ketoesters	oxetane derivatives (2 oxetane isomers : ratio; overall yield %)
 **6** (n = 1; R = H) **17** (n = 1 ; R = CH_3) **18** (n = 2 ; R = CH_3)	 **23** (n=1; R=H : 26%) **24** (n=1; R=CH_3 : 2/1; 31%) **25** (n=2; R=CH_3 : 1/2; 83%)
 **7**	 **26** (57%)
 **8**	 **27** (34%)

These results could be explained as follows. The carbanion **C** is probably the same intermediate involved in the allene and oxetane derivatives formation. So, **C** evolves either as a base or as a nucleophile, depending on whether the ion pair is associated or dissociated.[12]

In summary, we have succeeded in developing a new easily performed cascade reaction providing allene and oxetane derivatives. This strategy is currently being extended to the preparation of other allene and oxetane derivatives, especially in the acyclic series.

Acknowledgment. This work was supported by the Centre National de la Recherche Scientifique (CNRS).

Supporting Information Available: General experimental procedures and characterization data for allene derivatives **16** and **19**−**22** and oxetane derivatives **24**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. -M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956−1957. (b) Bürgi, H. B.; Lehn, J. M. *Tetrahedron*. **1974**, *30*, 1563−1572.

(9) (a) Clark, J. H. *Chem. Rev*. **1980**, 429−452. (b) Furin, G. G.; *Tetrahedron* **1988**, *44*, 2675−2749.

(10) We observed that a similar reaction takes place when the acetylenic *ω*-ketoester **6** was treated with Triton B ($Bn(CH_3)_3N^+OH^-$). The spiro compound **15** and the allene derivative **16** were also obtained in the same ratio (1/9), but the reaction was more sluggish and the overall yield lower (50%).

(11) For data concerning another alkylideneoxetane, see: Sakai, T., Katayama, T., Takeda, A. *J. Org. Chem*. **1981**, *46*, 2924−2931.

(12) Guibe, F.; Bram, G. *Bull. Chem. Soc. Fr*. **1975**, *3*, 933−948.