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Uncatalyzed [2+2] Cycloaddition of Cyclic Ketenetrimethylsilylacetals with Electrophilic Acetylenes.

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Abstract: *Cyclic ketenetrimethylsilylacetals reacted with electrophilic acetylenes (ethyl propynoate, dimethylacetylenedicarboxylate and ethynylmethylketone) to afford the corresponding [2+2] cycloadducts when the reactions were ran at room temperature, without solvent and without a catalyst. α-Alkylidenelactones or substituted furan derivatives proved to be readily available from the [2+2] cycloadduct by treatment either with TBAF in THF solution or with $BF_3.Et_2O$ (8 → 17/19).*

Much attention has been directed to the Lewis acid catalyzed addition of alkenes, silyl enol ethers, ketenealkyltrimethylsilylacetals and allylsilanes to electrophilic acetylenes, which generally leads to cyclobutenes[1-6]. Particularly, Rousseau et al.[4] have reported that cyclobutenes were obtained when ethyl propynoate **1** was treated with acyclic ketenetrimethylsilylacetals in the presence of catalytic amounts of $ZrCl_4$. When the same reaction was performed with dimethylacetylenedicarboxylate (DMAD) **2**, only ring opening products of the [2+2] cycloadduct intermediates were isolated[5]. However, to the best of our knowledge, the reaction of *cyclic* ketenetrimethylsilylacetals with electrophilic acetylenes has not been reported in the literature.

Herein, we wish to report our present results about this particular case of cycloaddition. We observed that the reaction of ethyl propynoate **1** with ketenetrimethylsilylacetal **4**[7] in the presence of 0.1 equivalent of $ZrCl_4$ led to the [2+2] cycloadduct **7**, isolated in 13% yield. In order to improve this yield, various reaction conditions were tried. We finally find out that the best yield was obtained when the reaction was carried out at room temperature, with equimolar quantities of reactants, without solvent and without a catalyst[8]. These reaction conditions also proved to be valuable when DMAD **2** or ethynylmethylketone **3** were used as acetylenic derivatives, leading respectively to the cycloadducts **8**[9] and **9** isolated in high yields. When CCl_4 was employed as solvent, yields were lower, especially with ethyl propynoate **1** and ethynylmethylketone **3** (Scheme I, table I). It should be noted that the cycloadduct **9** could not be obtained when this reaction was carried out in the presence of 0.1 equivalent of $ZrCl_4$. On the other hand, when these reactions were conducted with equimolar quantities of $ZrCl_4$, only decomposition occured[10]. The reactivity of the cyclic ketenetrimethylsilylacetals with acetylenic electrophiles can be compared to the reactivity of enamines with ethyl propynoate or DMAD where no activation (Lewis acid, heat etc..) is necessary to obtain the corresponding cyclobutenic esters[11]. It should also be noted that Mayr et al. have shown that the nucleophilicity of cyclic ketenetrimethylsilylacetals and enamines proved to be in the same order of magnitude[12].

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Scheme I

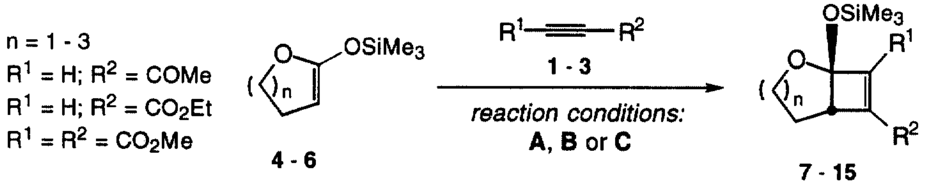


Table I

Acetylenic electrophile	Ketenetrimethylsilyl acetal	Reaction conditions	Product formed [yield%(crude%)]*
1 $(R^1 = H; R^2 = CO_2Et)$	**4** (n = 1)	A	**7** [13% (37%)]
		B	**7** [10% (42%)]
		C	**7** [48% (86%)]
2 $(R^1{=}CO_2Me; R^2{=}CO_2Me)$	**4** (n = 1)	A	**8** [90%]**
		B	**8** [94%]**
		C	**8** [98%]**
3 $(R^1{=}H; R^2{=}COCH_3)$	**4** (n = 1)	A	**9** [0%]
		B	**9** [13% (55%)]
		C	**9** [39% (83%)]
1 $(R^1{=}H; R^2{=}CO_2Et)$	**5** (n = 2)	A	**10** [5% (24%)]
		B	**10** [5% (55%)]
		C	**10** [32% (64%)]
2 $(R^1{=}CO_2Me; R^2{=}CO_2Me)$	**5** (n = 2)	A	**11** [30% (71%)]
		B	**11** [40% (81%)]
		C	**11** [45% (92%)]
3 $(R^1{=}H; R^2{=}COCH_3)$	**5** (n = 2)	A	**12** [0%]
		B	**12** [20% (46%)]
		C	**12** [54% (89%)]
1 $(R^1{=}H; R^2{=}CO_2Et)$	**6** (n = 3)	A	**13** [20% (57%)]
		B	**13** [5% (48%)]
		C	**13** [20% (67%)]
2 $(R^1{=}CO_2Me; R^2{=}CO_2Me)$	**6** (n = 3)	A	**14** [42% (83%)]
		B	**14** [45% (84%)]
		C	**14** [50% (93%)]
3 $(R^1{=}H; R^2{=}COCH_3)$	**6** (n = 3)	A	**15** [0%]
		B	**15** [40% (57%)]
		C	**15** [49% (75%)]

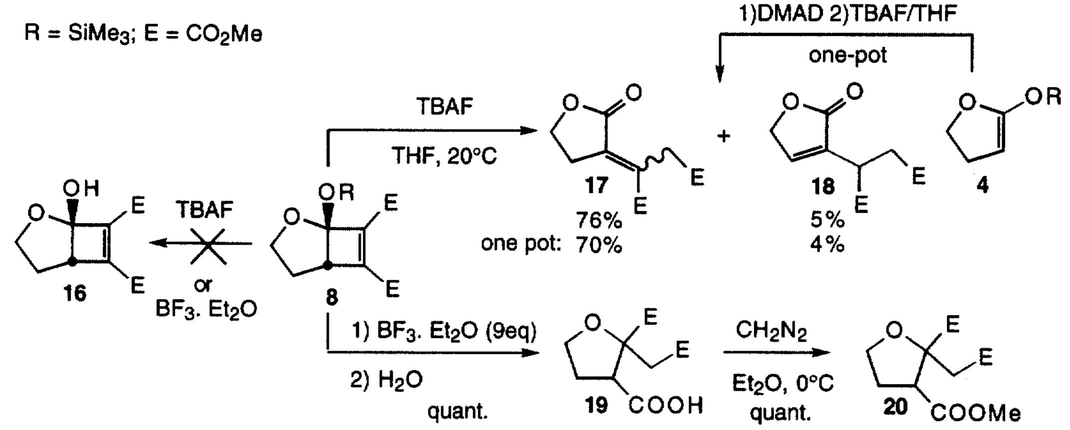
A: 0.1 eq. $ZrCl_4/CCl_4$/20°C; **B**: CCl_4/20°C; **C**: neat. *: yields refer to chromatographed material ; crude yields are indicated when the corresponding cyclobutenes proved to be unstable during the silica gel chromatography; **: chromatography over silica gel was not necessary in this case.

The cyclobutenes **7** - **15** being now readily available, we next turned our attention to their reactivity focusing on the cyclobutenic derivative **8**. When treated with tetra-n-butylammonium fluoride (TBAF), **8** did not give the desired hydroxycyclobutene **16**, but the α-alkylidenebutyrolactone **17**, isolated in 76% yield, along with the α,β -unsaturated lactone **18**, isolated in 5% yield[13]. It was also possible to obtain the lactone **17** in 70% overall yield in a one-pot procedure, starting from the silyl enol ether **4**. In fact, this very efficient and convenient reaction sequence, represents a new method for the synthesis of substituted α-alkylidenelactones.

On the other hand, when the cyclobutenic derivative **8** was treated with an excess $BF_3.Et_2O$, the furan derivative **19** was quantitatively obtained after hydrolysis of the crude reaction mixture. For ease of identification, **19** was subsequently treated with diazomethane to afford the corresponding methyl ester **20**[14] (Scheme II).

Scheme II

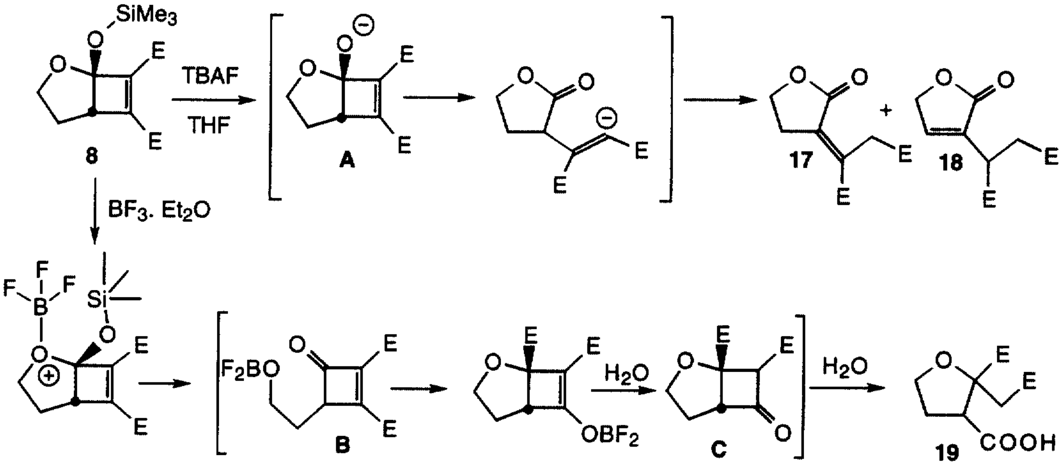
R = $SiMe_3$; E = CO_2Me



These results may be explained as follow: with TBAF as a desilylating reagent, the alkoxide intermediate **A**, formed after removal of the trimethylsilyl group, undergoes a retro-aldol type reaction, leading to lactones **17** and **18** by prototropic isomerizations. On the other hand, with $BF_3.Et_2O$ as a desilylating reagent, the reaction is thought to proceed by a mechanism involving the coordination of the boron atom to the oxygen of the furan **16**, followed by deprotection and ring opening. The intermediate **B** should then undergo an intramolecular 1,4-addition, giving rise to a highly reactive β-ketoester **C** which undergoes an acidic ring opening reaction[15] to afford the furan derivative **19** (Scheme III).

Scheme III

E = CO_2Me



In summary, we have shown that the addition of cyclic ketenetrimethylsilylacetals to electrophilic acetylenes without catalyst and without solvent leads in high yields to the corresponding [2+2] cycloadducts. The cycloadducts, treated with either TBAF or $BF_3.Et_2O$, give access to α-alkylidenelactones or trisubstituted furan derivatives in high yields. Further application of these simple preparative reactions will be reported in due course.

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9) Mitani *et al.*[5] mentionned the synthesis of the electrophilic cyclobutene **8** : however these authors run the reaction with 2 equivalent of silyl enol ether **4** and with 0.1 equivalent of $ZrCl_4$. Furthermore, no yields nor spectroscopic data were reported.
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12) When silyl enol ethers derived from cycloalkanones were added to electrophilic acetylenes, it was absolutely necessary to run the reaction in the presence of 1 eq. $ZrCl_4$ in order to obtain the corresponding [2+2] cycloadducts in good yields : see ref. 3.
13) We also ran the reaction with a 1/1 mixture $TBAF/C_6H_5COOH$ in order to quench the intermediate (potentially formed) alkoxides. However, compounds **17** and **18** were isolated in the same yields.
14) Selected spectroscopic data :
Compound **8** : colorless oil ; $C_{13}H_{20}O_6Si$; IR (CCl_4) : ν (C=O conj.) : 1730 cm^{-1}, υ (C=C) : 1651 cm^{-1} ; ^{1}H-NMR (200 MHz, C_6D_6, ppm) : $\delta = 0.25$ (s, 9H), 1.41-1.63 (m, 2H), 3.16-3.19 (m, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 3.48-3.62 (m), 3.79-3.88 (m, 1H) ; ^{13}C-NMR (50 MHz, $CDCl_3$, ppm) : $\delta = 1.12$, 25.53, 51.88, 52.20, 54.91, 67.07, 106.19, 141.15, 141.37, 160.30, 162.26 ; UV (CH_3CN) : λ max = 219 nm ($\varepsilon = 7530$) ;
Anal.: calc % C : 51.98, H : 6.71 ; found % C : 51.9, H : 6.8.
Compound **20** : colorless oil ; $C_{11}H_{16}O_7$; IR (CCl_4) : ν (C=O) : 1746 cm^{-1} ; ^{1}H-NMR (200 MHz, $CDCl_3$, ppm) : $\delta = 2.15$-2.37 (m, 2H), $\delta_A = 2.76$, $\delta_B = 3.05$ (AB, $J_{AB} = 16$ Hz), 3.33-3.41 (dd, 1H, J = 6.3 and 7.8 Hz), 3.67 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H) 4.01-4.34 (m, 2H) ; ^{13}C-NMR (50 MHz, $CDCl_3$, ppm) : $\delta = 29.28$, 39.39, 50.55, 51.98, 52.27, 52.90, 68.96. 84.72, 170.16, 171.92, 172.88 ; MS (CI, isobutane) : 261 (M+1) ;
Anal.: calc % C : 50.60, H : 6.17 ; found % C : 50.8, H : 6.2.
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