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Synthesis and Reactivity of Michael Adducts of Cyclic β-Ketoesters Enolates with Electrophilic Acetylenes.

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Abstract : *The enolates of cyclic β-ketoesters react with electrophilic acetylenes to give the corresponding Michael adducts in good yields when the reaction is performed in acetone in the presence of catalytic amounts of K_2CO_3. The Michael adducts resulting from ethynylmethylketone, when refluxed in toluene in the presence of catalytic amounts of pTsOH, undergo an intramolecular aldol reaction leading mainly to bicyclo [n. 3. 1]alkadienones besides Robinson annulation products.*

The 1, 4 - addition of enolates of cyclic β-ketoesters to acrylic derivatives is well documented in the litterature[1]. In general Michael adducts are obtained and their reactions were extensively studied[2]. On the contrary, the addition of enolates of cyclic β-ketoesters to electrophilic acetylenes seems to have received little attention. To the best of our knowledge, Michael adducts resulting from the reaction of cyclic β-ketoesters with electrophilic acetylenes are not described. However, it has been reported that the reaction of ethyl propynoate and dimethyl acetylene dicarboxylate with the sodium enolates of cyclic β-ketoesters led to ring expansion products via a [2+2] cycloaddition but not to Michael adducts[3,4].

We observed now that the addition of the β-ketoesters **1** - **6** to ethynylmethylketone **7** and ethyl propynoate **8** led to the corresponding Michael adducts **9Z, 9E - 20Z, 20E** (unseparable mixtures of E and Z isomers except for the adducts **9Z, 9E** and **15Z, 15E**) when the addition was performed at room temperature in acetone in the presence of 0.1 equivalent of potassium carbonate (Scheme I, table I)[5].

Scheme I

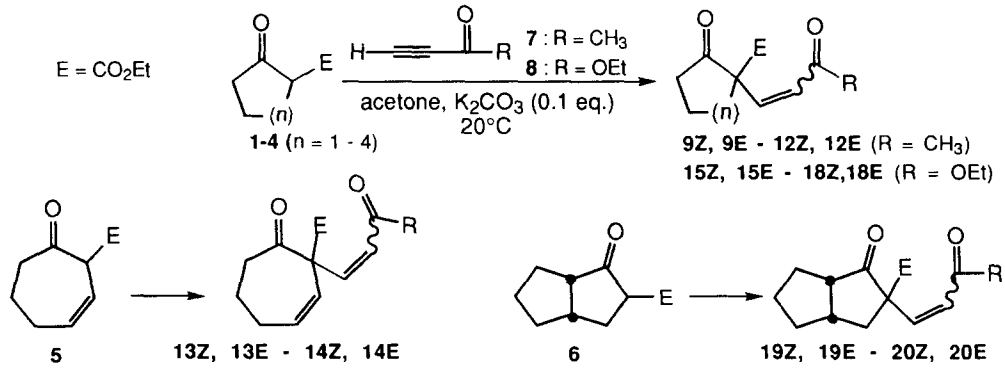

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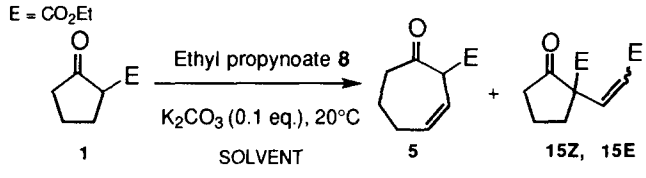
Table I

β - ketoester	Acetylenic derivative	Time[a]	Michael adduct (Yield; ratio E/Z)
1 (n = 1)	**7** (R = CH_3)	30 min.	**9Z, 9E** (79%[b]; 1/3)
2 (n = 2)	**7** (R = CH_3)	40 h	**10Z, 10E** (46%[c]; 2/3)
3 (n = 3)	**7** (R = CH_3)	24 h	**11Z, 11E**(85%[b]; 1/1)
4 (n = 4)	**7** (R = CH_3)	24 h	**12Z, 12E** (97%[b]; 5/3)
5	**7** (R = CH_3)	18 h	**13Z, 13E** (60%[b]; 1/2)
6	**7** (R = CH_3)	24 h	**14Z, 14E** (73%[b]; 2/1)
1 (n = 1)	**8** (R = OEt)	20 min.	**15Z, 15E** (90%[b]; 1/1)
2 (n = 2)	**8** (R = OEt)	18h	**16Z, 16E** (15%[c]; 1/2)
3 (n = 3)	**8** (R = OEt)	72 h	**17Z, 17E** (99%[b]; 4/1)
4 (n = 4)	**8** (R = OEt)	72 h	**18Z, 18E** (83%[b]; 2/1)
5	**8** (R = OEt)	30h	**19Z, 19E** (30%[c]; 3/1)
6	**8** (R = OEt)	15 h	**20Z, 20E** (73%[b]; 1/1)

[a] : for 3-5 mmoles β-ketoester/10 ml solvent [b] : Yields for chromatographed material [c] : Yields for crude material.

The Michael adducts were in general isolated in good yields[6]. We noticed that the ring expansion product **5** was formed in part when the addition of the β-ketoester **1** to ethyl propynoate **8** was carried out in apolar or slightly polar solvents such as benzene, ether or THF. In acetonitrile and acetone, no ring expansion products were obtained and in a polar protic solvent, ethanol, only decomposition occured (Scheme II). We never observed the formation of ring expansion products, whatever solvent was used, when the reaction was performed with ethynylmethylketone **7** as acetylenic reactant.

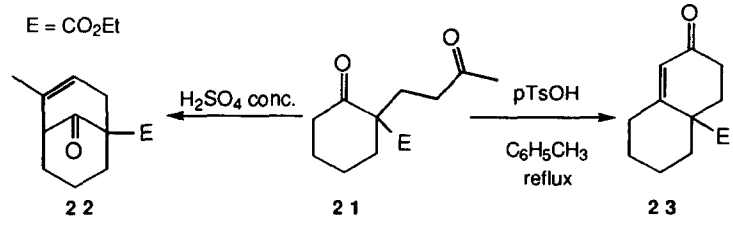
Scheme II



Solvent	5	15Z, 15E (Z/E)
benzene	13%	63% (2/1)
THF	21%	60% (2/1)
Et_2O	10%	51% (2/1)
CH_3CN	0%	90% (3/1)
acetone	0%	90% (1/1)

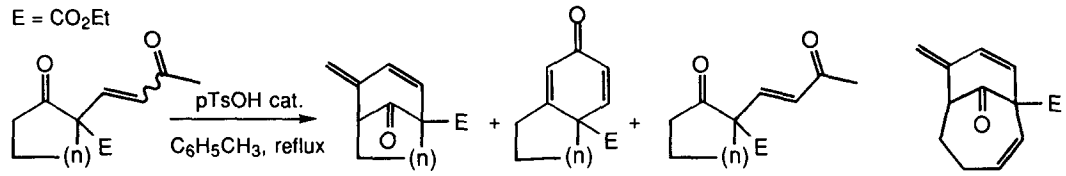
The 1,5-diketones **9Z,9E - 14Z, 14E** were submitted to the action of acids in order to verify if intramolecular cyclisations would occur, for it has been shown that the Michael adduct **21** (resulting from the addition of methyl vinyl ketone to the β-ketoester **2**) led either to the bicyclic[3. 3. 1]nonane derivative **22** or to the Robinson annulation product **23**, depending on whether concentrated sulfuric acid or pTsOH was used[7, 8](Scheme III).

Scheme III



In our case, when the 1,5-diketones **9Z,9E - 14Z, 14E** were treated with concentrated H_2SO_4, only decomposition occured. However, when the Michael adducts **9Z,9E - 11Z, 11E** were refluxed in toluene in the presence of pTsOH, the major products obtained were the bicyclo[n. 3. 1]alkadienone derivatives **24 - 26** along with the Robinson annulation products **27 - 29** and the E isomers **9E - 11E**[10]. These different compounds were easily separable by chromatography on silica gel. The same reaction took place with the diketones **13Z, 13E** with a seven membered ring, giving the bicyclo[4. 3. 1]decane derivative **30** (Scheme IV). When the 1,5-diketones **12Z, 12E** (Z/E: 5/3) were submitted to the same conditions, the sole E isomer **12E** was recovered in 72% yield, indicating that under our reaction conditions an Z -> E isomerization took also place. Under the same conditions, the Michael adducts **15Z, 15E - 20Z, 20E** were quantitatively recovered.

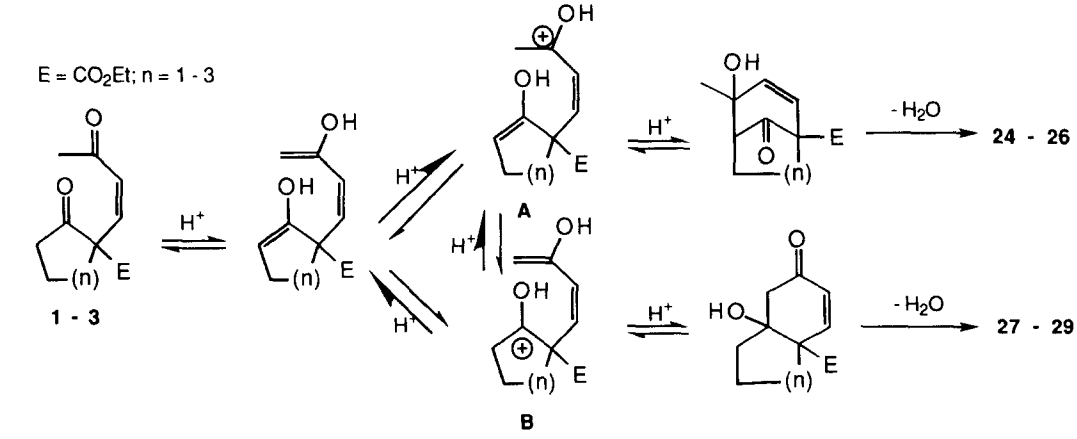
Scheme IV



9Z (n = 1)	**24** (40%)	**27** (8%)	**9E** (14%)	**13Z, 13E** → **30** (41%)
9E (n = 1)	**24** (12%)	**27** (3%)	**9E** (14%)	
10Z, 10E (n = 2)	**25** (50%)	**28** (8%)	**10E** (15%)	
11Z, 11E (n = 3)	**26** (53%)	**29** (6%)	**11E** (35%)	

One could rationalize these results as follows: under our reaction conditions, the protonation of the diketone can generate two carbocationic intermediates **A** and **B**, the equilibrium of which is probably displaced towards **A** (allylic carbocation), so that the formation of the bicyclo [n. 3. 1] alkadienones **24 - 26** (and **30**) is favored (Scheme V).

Scheme V



In summary, we have shown that Michael adducts resulting from the addition of enolates of cyclic β-ketoesters to electrophilic acetylenes are available simply and in good yields by running the reaction in acetone in the presence of catalytic amounts of K_2CO_3. Further, the 1,5-diketones **9Z, 9E - 11Z, 11E** and **13Z, 13E** are easily transformed in refluxing toluene in the presence of catalytic amounts of pTsOH, into bicyclo [n. 3. 1] alkadienones **24 - 26** and **30**[11], which are interesting building blocks for the synthesis of

natural bioactive compounds. Further application of the preparatively easy to run reactions outlined here will be reported in due course.

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5. These reaction conditions (K_2CO_3/acetone) were already used for the Michael addition of β-ketoesters to acrylic derivatives.
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6. Compounds **9E** and **15E** have already been prepared by another route (ketovinylation of the corresponding β-ketoesters **1** and **2**): Kochetkov, N.K., Kudryashov, L.J., Gottich B.P. *Tetrahedron* **1961**, *12*, 63-65.
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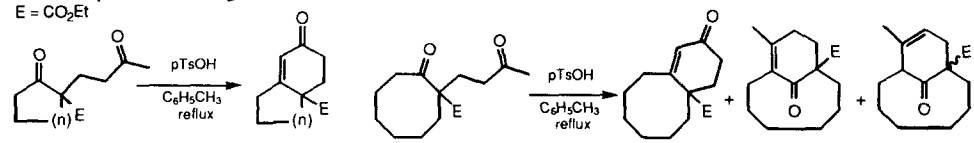
   e) Marshall, J.A.; Partridge, J.J. *Tetrahedron* **1969**, *25*, 2159-2192.
8. We have shown that the formation of Robinson annulation type products was also successful with the 1,5-diketones **31** (n = 1) even when Scanio and Hill reported that no reaction took place under these conditions[9] and **32** (n = 3). However, under the same conditions, the 1,5-diketone **33** led mainly to the bicyclo[7. 3. 1]undecane derivatives **34** and **35**, the Robinson annulation product **36** being minor.



31 (n = 1) **32** (n = 3) — 65% (n = 1) 80% (n = 3) — **33** — **36** (8%) — **34** (27%) — **35** (30%)

9. Scanio, C. J. V.; Hill, L. P. Synthesis **1970**, 651-652.
10. Molecular models indicate clearly that the E isomers **9E** - **11E** cannot undergo an intramolecular aldol cyclisation, the reacting centers being too far away.
11. Selected spectroscopic data :
    27 : colorless oil ; IR (CCl_4) : ν (C=O) : 1716, 1746 cm^{-1} ; ^{1}H-NMR (200 MHz, $CDCl_3$) : 1.13-1.55 (6H, m) ; 1.20 (3H, t, J = 7.1 Hz) ; 2.05 (1H, dd, J = 10.5 Hz and 3.7 Hz) ; 2.14-2.29 (1H, m) ; 3.43 (1H, dd, J = 10.0 Hz and 3.6 Hz) ; 4.14 (2H, dq, J = 7.1 Hz and 2.1 Hz) ; 4.95 (1H, s) ; 5.05 (1H, s) ; 5.65 (1H, dt, J = 9.8 Hz and 0.5 Hz) ; 6.43 (1H, d, J = 9.8Hz) ; ^{13}C-NMR (50 MHz, $CDCl_3$) : 13.0; 24.8; 25.2; 34.2; 34.24; 53.7; 61.5; 61.6; 114.6; 129.1; 129.7; 146.6; 171.1; 206.66