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Tetrahedron Letters 44 (2003) 2125–2128

TETRAHEDRON LETTERS

Unusual *O*-conjugate addition reactions of β-ketoesters and 1,3-diketones to ethyl propynoate: applications to the synthesis of furans

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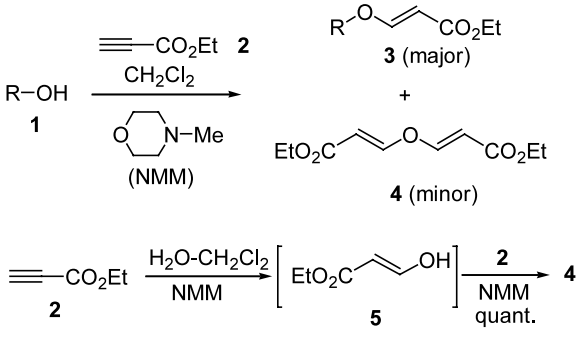
Received 5 December 2002; revised 11 January 2003; accepted 16 January 2003

Abstract—Divinyl ethers were synthesized from 1,3-dicarbonyl compounds. Reactions of β-ketoesters and 1,3-diketones with ethyl propynoate in the presence of *N*-methylmorpholine produced unusual *O*-conjugate addition products in good yields. The divinyl ethers derived from 1,3-diketones were utilized for the synthesis of 2,3,5-trisubstituted furans under the standard radical cyclization conditions.

Conjugate addition reactions[1] of enolates have been studied extensively and applied towards numerous syntheses. The carbon centers of enolates normally add to α,β-unsaturated carbonyl systems to give *C*-conjugate addition products. *O*-conjugate addition does not generally occur for most enolate conjugate addition reactions. However, during enolate alkylation reactions, *O*-alkylation can compete with *C*-alkylation especially for stabilized enolates with electrophiles possessing hard leaving groups.[2] Herein we report unusual *O*-conjugate addition reactions of β-ketoesters and 1,3-diketones to ethyl propynoate.



Scheme 1.

The reaction of alcohols with ethyl propynoate (**2**) in the presence of *N*-methylmorpholine (NMM) yields β-alkoxyacrylate **3** (predominantly *trans*) as a major product with a minor side product **4**[3] (Scheme 1). The origin of the oxygen atom in **4** appears to arise from a water molecule from the reaction mixture. In order to investigate this hypothesis, we added water to the reaction mixture in the absence of alcohol and obtained compound **4** exclusively in quantitative yield. Therefore, the initially formed compound **5** participates in another conjugate addition reaction under the reaction conditions to generate divinyl ether **4**. This observation clearly depicts the synthetic potential of *O*-conjugate addition reactions of stabilized 1,3-dicarbonyl compounds to reactive acetylenic esters.

In order to determine the generality of this reaction, we first tested ethyl acetoacetate (**6**) under the same reaction conditions. Ethyl acetoacetate (**6**) was treated with 1.2 equiv. of ethyl propynoate (**2**) in the presence of 1.2 equiv. of *N*-methylmorpholine in dichloromethane at 25°C for 17 h to obtain divinyl ethers **7** and **8** in 69% and 22% yields respectively in addition to 6% of **4** (Scheme 2).[4] Both **7** and **8** proved to be *O*-conjugate addition products and possess the same (*E*)-alkene geometries at the β-alkoxyacrylate terminus, which is typically seen in analogous alcohol addition reactions.[5] However, a mixture of alkene geometries was observed for the enolate portion of **7** and **8**.[6] The product ratio (**7**:**8**) appears to be independent of the solvent system employed, and solvent-free conditions gave similar product ratios. Furthermore, the replacement NMM with DABCO (1,4-diazabicyclo[2.2.2]octane) had no affect on the product distribution.

Keywords: *O*-conjugate addition; 1,3-dicarbonyl compounds; divinyl ethers; electrophilic alkynes; furans.

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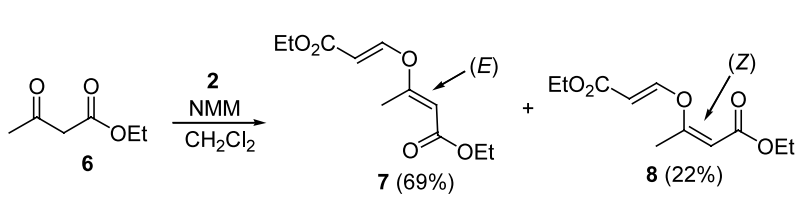
doi:10.1016/S0040-4039(03)00151-5



conditions	ratio (**7** : **8**)
NMM, CH_2Cl_2	76 : 24
NMM, THF	74 : 26
NMM, benzene	71 : 29
NMM, acetone	83 : 17
NMM, Et_2O	67 : 33
NMM, neat	76 : 24
DABCO, CH_2Cl_2	79 : 21

Scheme 2.

As shown in Table 1, a number of other β-ketoesters and 1,3-diketones were also suitable for the *O*-conjugate addition reaction. Methyl substituted substrate **9** (Table 1, entry 2) produced both isomers **9a** and **9b** in 32% and 35% respectively. Introduction of *n*-propyl and allyl groups (Table 1, entries 3, 4) yielded only (*E*)-alkene products (**10a** and **11a**). Substrate **12** (entry 5) was transformed quantitatively into the desired divinyl ether compounds **12a** (55%) and **12b** (45%). Benzyl substituted β-ketoesters were also evaluated as shown in entries 6 and 7 in Table 1. Compound **13** (Table 1, entry 6) produced two divinyl ether products **13a** and **13b** in good yields (57% and 27% respectively) and **14** gave exclusively **14a** (98%). Therefore, we found that β-ketoesters are generally good substrates for *O*-conjugate additions to ethyl propynoate (**2**).

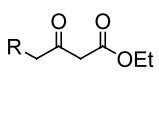
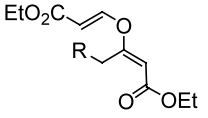
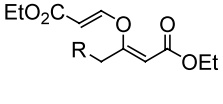
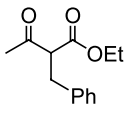
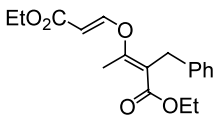
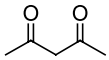
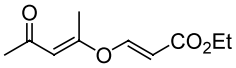
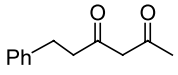
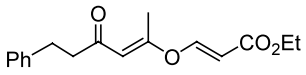
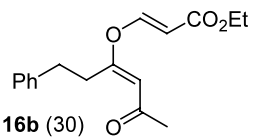
We then investigated the *O*-conjugate addition reaction using 1,3-diketones. The symmetrical 2,4-pentanedione (**15**) reacted with ethyl propynoate to afford **15a** in 63% (Table 1, entry 8). When the unsymmetrical benzyl substituted 1,3-diketone **16** was subjected to the same reaction conditions (Table 1, entry 9), two compounds (**16a** and **16b** in 63% and 30% respectively) were isolated after purification by flash column chromatography from four possible isomers.[7]

Cyclic β-ketoesters were reported to react with electrophilic acetylenes in the presence of K_2CO_3 (0.1 equiv.) to give mainly *C*-conjugate addition adducts.[8] However, when the cyclic β-ketoester **17** was submitted to the standard *O*-conjugate addition conditions (**2**, NMM, CH_2Cl_2), *O*-conjugate addition product **17a** (27%) was obtained as the major product with *C*-conjugate addition product **17b** (15%) as the minor component (Table 2, entry 1). Water addition product **4** (20%) was also isolated. Moreover, 2-acetylcyclohexanone (**18**) gave only *C*-conjugate addition product **18a** (45%) with no *O*-conjugate addition product (Table 2, entry 2) while 1,3-cyclohexanedione (**19**) exclusively gave rise to *O*-conjugate addition products **19a** (86%) and **19b** (12%) (Table 2, entry 3).

A reasonable mechanism[3] for this addition reaction is described in Scheme 3. Addition of *N*-methylmorpholine to **2** produces adduct **20** which deprotonates **21** to give **22** and **23**. Subsequent addition of **23** to **22** in a 1,4-fashion followed by elimination of *N*-methylmorpholine affords **24**. According to this mechanism, the nucleophile **21** should have acidic C–H bond(s), which could be deprotonated by **20**, for the reaction to occur. As a result, acetophenone, with slightly less acidic C–H bonds than **21**, produced no addition product. Furthermore, diethyl malonate was also unreactive under the addition reaction conditions.

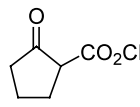
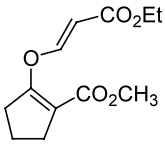
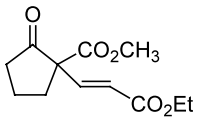
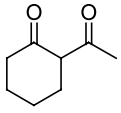
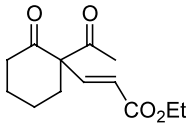
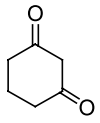
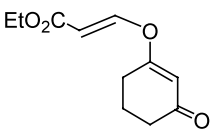
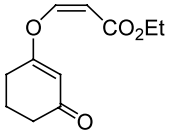
The synthetic utilities of the unique divinyl ethers were exemplified by the synthesis of furans via free radical cyclizations.[9] The divinyl ethers, derived from the corresponding 1,3-diketones, were treated with tributyltin

Table 1. *O*-Conjugate addition of β-ketoesters and 1,3-diketones to ethyl propynoate (**2**)[a]

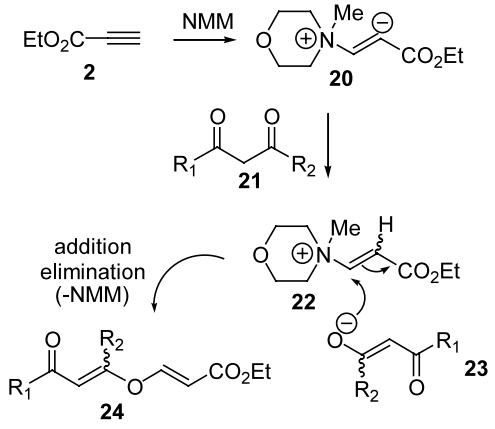
entry	substrate	products (% yield)[b]	
			
1	**6**, R= H	**7** (69)	**8** (22)
2	**9**, R= Me	**9a** (32)	**9b** (35)
3	**10**, R= *n*-Pr	**10a** (85)	**10b** (-)
4	**11**, R= 	**11a** (43)	**11b** (-)
5	**12**, R= 	**12a** (55)	**12b** (45)
6	**13**, R= $PhCH_2$	**13a** (57)	**13b** (27)
7	 **14**	 **14a** (98)	
8	 **15**	 **15a** (63)	
9	 **16**	 **16a** (63)	
		 **16b** (30)	

[a] Reaction conditions: **2** (1.2 equiv.), NMM (1.2 equiv.), CH_2Cl_2, 25°C, 17 h.
[b] Isolated yields.

Table 2. *O*-Conjugate addition of cyclic β-ketoesters and 1,3-diketones to ethyl propynoate (**2**)[a]

entry	substrate	products (% yield)[b]	
1		 **17a** (27 %)	 **17b** (15 %)
	17		
2		 **18a** (45 %)	
	18		
3		 **19a** (86 %)	 **19b** (12 %)
	19		

[a] Reaction conditions: **2** (1.2 equiv.), NMM (1.2 equiv.), CH_2Cl_2, 25°C.
[b] Isolated yields.

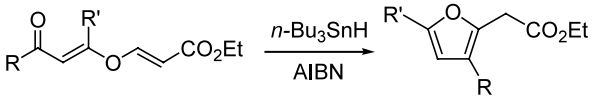


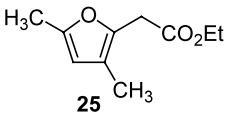
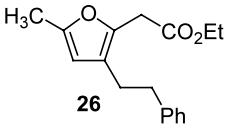
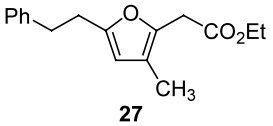
Scheme 3.

hydride under standard radical cyclization conditions (Table 3). 2,3,5-Trisubstituted furans were formed directly from the divinyl ethers in moderate yields after flash column chromatography. A possible mechanism is illustrated in Scheme 4. The addition of tin radical to β-alkoxyenone generates allylic radical **28** which isomerizes to **29**. Subsequent intramolecular cyclization onto the β-alkoxyacrylate followed by protonation furnishes **31**. The allylic tertiary alcohol eliminates to give the stable furan **25** during column chromatography.

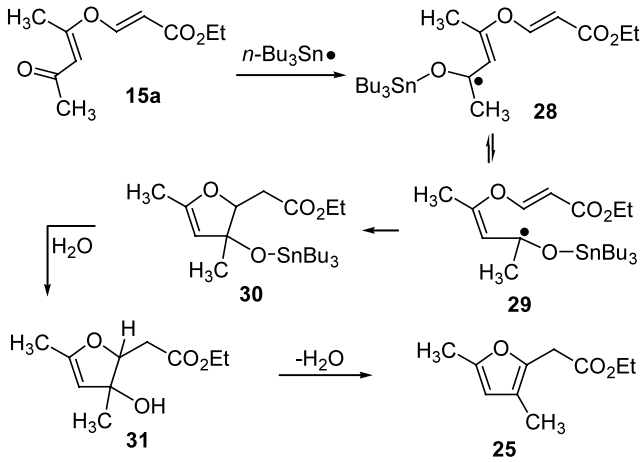
In summary, we have shown that stabilized enolates from β-ketoesters and 1,3-diketones can be added to ethyl propynoate (**2**) in an unusual *O*-conjugate addition fashion.[10] The divinyl ether compounds obtained by this method are interesting building blocks for the

Table 3. Synthesis of 2,3,5-trisubstituted furans from divinyl ethers[a]



entry	substrate	product	% yield[b]
1	**15a**	 **25**	63
2	**16a**	 **26**	36
3	**16b**	 **27**	53

[a] Reaction conditions: *n*-Bu_3SnH (1.2 equiv.), AIBN (cat.), benzene, 80°C.
[b] Isolated yields.



Scheme 4.

synthesis of related natural and unnatural compounds as exemplified through the transformation of a number of 1,3-diketones to furans under radical cyclization conditions. Thus, 2,3,5-trisubstituted furans were efficiently synthesized from 1,3-diketones in two steps.[11]

Acknowledgements

This work was supported by Korea Research Foundation Grant (KRF-2002-003-C00080).

References

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3. (a) Acheson, R. M.; Woollard, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 740–743; (b) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 3569–3576; (c) Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1972**, *1*, 904–908.
4. The water addition product **4** was observed for most of the conjugate addition reactions.
5. The (*E*)-stereochemistries of alkoxyacrylate were readily confirmed by comparison of coupling constants. See reference 3.
6. The alkene stereochemistries were confirmed by NOE experiments. In general, the (*E*)-isomers were formed favorably over the (*Z*)-isomers (see Table 1) because of the dipole and steric repulsions between two ester groups. The 1,3-diketones produced (*E*)-isomers (**15a**, **16a**, and **16b**) exclusively (see Table 1, entry 8 and 9). In these cases, the (*Z*)-isomers that were detected by the TLC analysis isomerized completely to (*E*)-isomers under the column chromatographic conditions. This implies that β-alkoxyenones are easily isomerized but β-alkoxyacrylates are relatively stable under the typical isolation conditions.
7. The relative bond attachments of **16a** and **16b** were determined by HMBC NMR experiments.
8. Miesch, M.; Mislin, G.; Frank-Neumann, M. *Tetrahedron Lett.* **1998**, *39*, 6873–6876.
9. For the radical cyclizations of β-alkoxyacrylates, see: (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831–4834; (b) Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129–132.
10. **General procedure of *O*-conjugate addition reaction**: To a dry CH_2Cl_2 (2 mL) solution of β-keto ester **13** (220 mg, 1.00 mmol) and *N*-methylmorpholine (0.13 mL, 1.2 mmol), ethyl propynoate (**2**) (0.12 mL, 1.2 mmol) was added at 25°C under nitrogen atmosphere. The reaction mixture was stirred at this temperature for 17 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica-gel (elution with 10% ethyl acetate in hexanes) to give 183 mg of **13a** (57%) and 86 mg of **13b** (27%).
11. Selected data for **13a**, **13b**, and **27**:
    For **13a**: colorless oil; $R_f = 0.5$ (Hex/CH_2Cl_2/EtOAc = 10/5/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 12.1$ Hz, 1H), 7.38–7.25 (m, 5H), 5.73 (d, $J = 12.1$ Hz, 1H), 5.38 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.22–3.15 (m, 2H), 2.97–2.91 (m, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 171.3$, 166.3, 166.0, 154.3, 140.5, 128.6, 128.5, 126.3, 106.3, 99.5, 60.5, 60.2, 33.2, 32.8, 14.4 (2 C); IR (film, cm^{-1}) 2981, 2936, 1717, 1635, 1125; MS: *m*/*z* (rel. intensity): 91 (100), 115 (60), 157 (40), 226 (50), 244 (25), 272 (M^+–EtOH, 20).
    For **13b**: colorless oil; $R_f = 0.4$ (Hex/CH_2Cl_2/EtOAc = 10/5/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 12.2$ Hz, 1H), 7.40–7.21 (m, 5H), 5.58 (d, $J = 12.2$ Hz, 1H), 5.46 (s, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.94–2.88 (m, 2H), 2.68–2.62 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 167.1$, 165.9, 163.7, 159.0, 139.7, 128.8, 128.4, 126.7, 105.2, 101.3, 60.5, 60.2, 36.5, 32.6, 14.4, 14.3; IR (film, cm^{-1}) 2981, 2935, 1716, 1634, 1124); MS: *m*/*z* (rel. intensity): 91 (100), 115 (50), 157 (40), 226 (45), 244 (20), 272 (M^+–EtOH, 10).
    For **27**: colorless oil; $R_f = 0.6$ (Hex/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$ (m, 5H), 5.83 (s, 1H), 4.2(q, $J = 7.0$ Hz, 2H), 3.60 (s, 2H), 2.95 (m, 2H), 2.88 (m, 2H), 1.96 (s, 3H), 1.30 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 170.1$, 153.9, 141.6, 141.5, 128.5(2C), 126.1, 117.5, 108.9, 61.1, 34.4, 32.5, 30.1, 14.3, 10.0; IR (film, cm^{-1}) 2925, 2853, 1744, 1174.