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Knoevenagel condensations of β-hemiacetyl esters

Pilho Kim, Marilyn M. Olmstead, Michael H. Nantz and Mark J. Kurth *

Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616-5295, USA

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Abstract

The intermolecular Knoevenagel condensation of β-hemiacetyl ester proceeds by an in situ unmasking of a reactive ω-hydroxy-β-keto ester giving unsaturated ω-hydroxy-β-keto esters **6**–**12** which accommodate acetal formation.

Keywords: Knoevenagel condensation; acetal formation; eleuthesides.

In the course of studies directed toward total syntheses of eleuthesides (e.g. eleutherobin, Fig. 1), we have undertaken a model study of the Knoevenagel condensation[1] of β-hemiacetyl esters. As outlined below, our total synthesis plan engages two novel Knoevenagel-related questions: (i) will this intramolecular condensation deliver a 10-membered carbocyclic ring in a process which proceeds by an in situ unmasking of a reactive ω-hydroxy-β-keto ester from an unreactive β-hemiacetyl ester; and (ii) will the resulting Knoevenagel product accommodate acetal formation. We point out that the Nicolaou group[2] has successfully employed an intermolecular Knoevenagel condensation as a key step in their recently reported total synthesis of eleutherobin.[3]

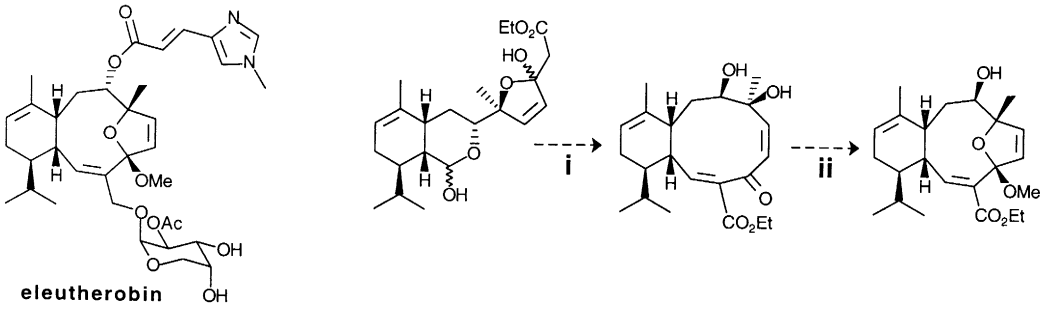

Fig. 1.

Given the central importance of this transformation in our synthetic planning, it seemed prudent to evaluate the potential of this transformation with a model study. As illustrated in Fig. 2, β-hemiacetyl

* Corresponding author.

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esters like **1** do not meet the typical prerequisites for application in the Knoevenagel condensation as the α-methylene is insufficiently activated for deprotonation with an amine base. On the other hand, one might expect that the dynamic equilibrium of the β-hemiacetyl ester to its corresponding ω-hydroxy-β-keto ester (**2**) form will invite amine-based deprotonation and subsequent Knoevenagel condensation to **3**. In the Knoevenagel's 100+ year history,[4] we are aware of only one report of a dynamically masked β-keto ester participating in this transformation (an intramolecular reaction leading to a cyclohexenone).[5]

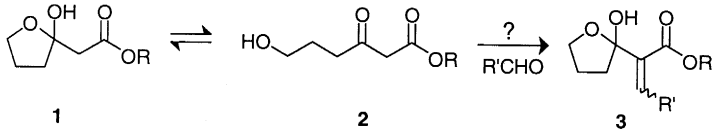
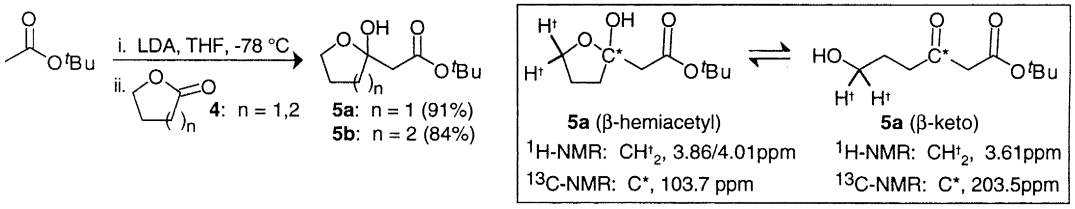


Fig. 2.

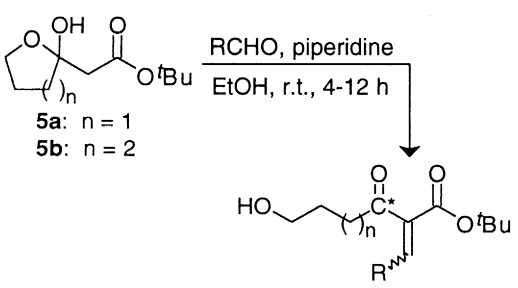
The Claisen condensations of γ-butyrolactone (**4**; *n*=1) and δ-valerolactone (**4**; *n*=2) proceed smoothly (Scheme 1) with the lithium enolate of ^{t}butyl acetate in THF to give ^{t}butyl β-hemiacetyl esters **5** (**5a** and **5b**, *n*=1 and 2 in 91 and 84% yield, respectively).[6] ^{1}H and ^{13}C NMR analyses of these Claisen condensation products indicate that both the hemiacetyl and the keto form are present [cf. **5a** (β-hemiacetyl form) and **5a** (β-keto form) which are present in an ~65:35 ratio].[7]

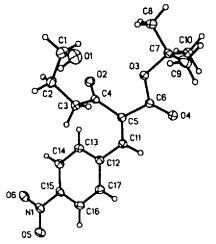


Scheme 1.

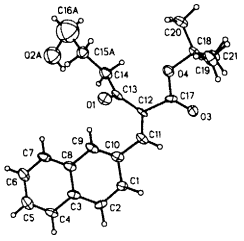
Treating ethanolic **5a** with *p*-nitrobenzaldehyde and piperidine at reflux for 4 h gave the ^{t}butyl ester of *E*-4-nitrocinnamic acid as the sole, isolable product (22% yield). This unexpected result suggested that the desired Knoevenagel reaction had indeed occurred, but the Knoevenagel product suffered an unexpected de-acylation reaction. However, and to our delight, treating an ethanolic solution of β-hemiacetyl ester **5a** or **5b** with aromatic aldehydes and piperidine at room temperature for 4–12 h effected the desired Knoevenagel condensation without the unwanted de-acylation (note: the de-acylation product did begin to appear in the crude reaction mixture at extended reaction times). Under these mild conditions, Knoevenagel products were obtained as an *E*:*Z* mixture of olefin isomers where the *Z*-isomer was always predominant. Yields for these reactions were excellent for the tetrahydrofuranyl hemiacetals (**6**–**9**; 81–91%), but somewhat lower for the tetrahydropyranyl hemiacetals (**10**–**12**; 51–76%; Scheme 2). In all cases, these Knoevenagel products existed in the 'open' form (i.e. ω-hydroxy-β-keto ester) to the near exclusion of the corresponding hemiacetal form. Single crystal X-ray analysis of (*E*)-**7** and (*E*)-**9** confirmed *E*-olefin geometries for these products and, with this information secured, we found that the ^{13}C NMR chemical shift of the ketone carbon in **6**–**12** allowed unambiguous assignment of olefin stereochemistries in this series. Finally, we have found that the isolated *E*- and *Z*-Knoevenagel products interconvert at room temperature when in solution. Thus, isolated *Z*-product (column chromatographic separation: SiO_2/EtOAc:hexanes::1:4, $Z-R_f<E-R_f$) equilibrated rather quickly (~1–2 h) to an *E*/*Z*-mixture, while isolated *E*-product equilibrated more slowly (~24 h).

With the success of this Knoevenagel condensation, we turned to the second question raised in Fig. 1: namely, will these unsaturated ω-hydroxy-β-keto esters accommodate acetal formation? As shown in Scheme 3, treating an *E*/*Z*-mixture of **7** (*n*=1) with acidic methanol at room temperature for 1 h[8] smoothly





x-ray structure of *(E)*-**7**



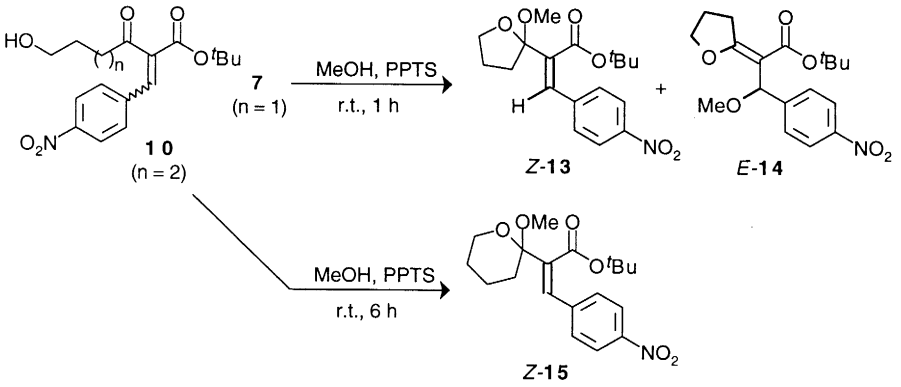
x-ray structure of *(E)*-**9**

	n	R	*E*/*Z*	yield	*E* δ C*=O	*Z* δ C*=O
6	1	C_6H_5	42:58	89%	206.0	197.3
7	1	$^pNO_2C_6H_4$	32:68	88%	204.7	196.7
8	1	$^pBrC_6H_4$	24:76	81%	205.7	197.0
9	1	2-naphthalenyl	35:65	91%	206.2	197.3
10	2	$^pNO_2C_6H_4$	42:58	55%	204.7	196.4
11	2	$^pBrC_6H_4$	47:53	51%	205.6	196.8
12	2	2-naphthalenyl	33:67	76%	206.0	197.0

see indicated C in **6**-**12**

Scheme 2.

delivers the targeted unsaturated β-hemiacetyl ester *Z*-**13**[9] (81%; established by NOESY 1D) together with trace amounts of *E*-**14**[10] (established by NOESY 1D; *E*-**14** becomes a significant product with longer reaction time: 8 h→*Z*-**13**:*E*-**14**::4:6). An isolated solution of pure *Z*-**13** (EtOAc/hexanes) slowly isomerizes to a *Z*-**13**/*E*-**14** mixture upon standing at room temperature. The reaction of Knoevenagel product **10** (*n*=2) with acidic methanol (6 h, room temperture) produces only *Z*-**15** (88%; established by NOESY 1D).[11]



Scheme 3.

In summary, we have demonstrated that the intermolecular Knoevenagel condensation of β-hemiacetyl esters is feasible and that the resulting ω-hydroxy-β-keto esters accommodate acetal formation. Extension of this methodology to a total synthesis of eleutherobin is currently under study and the results will be reported in due course.

Acknowledgements

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9. (*Z*)-**13**: R_f=0.68 (E/H=1/2); FTIR (KBr) 2978, 1719, 1520, 1344, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.90–2.37 (m, 4H), 3.21 (s, 3H), 4.01 (t, J=6.9 Hz, 2H), 6.87 (s, 1H), 7.50 (d, J=8.7 Hz, 2H), 8.16 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 27.8, 39.0, 49.7, 68.5, 82.3, 107.7, 123.4, 127.5, 129.1, 140.2, 141.9, 147.1, 166.6. Anal. calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64: N, 4.01. Found: C, 61.71; H, 6.74; N, 3.94.
10. (*E*)-**14**: R_f=0.50 (E/H=1/2); FTIR (KBr) 2978, 1693, 1519, 1344, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.09 (m, 2H), 3.15 (t, J=7.8 Hz, 2H), 3.41 (s, 3H), 4.15 (m, 1H), 4.30 (m, 1H), 5.60 (s, 1H), 7.52 (d, J=8.8 Hz, 2H), 8.12 (d, J=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 28.3, 31.8, 56.8, 72.2, 77.1, 80.1, 103.7, 122.8, 126.5, 146.3, 151.0, 166.7, 173.6. Anal. calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64: N, 4.01. Found: C, 61.93; H, 6.67; N, 3.94.
11. (*Z*)-**15**: R_f=0.76 (E/H=1/2); FTIR (KBr) 2937, 1720, 1520, 1343, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16–2.07 (m, 6H), 1.42 (s, 9H), 3.23 (s, 3H), 3.60–3.85 (m, 2H), 6.77 (s, 1H), 7.52 (d, J=8.8 Hz, 2H), 8.16 (d, J=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 24.6, 27.8, 35.4, 49.2, 61.8, 82.3, 98.6, 123.5, 127.1, 129.0, 142.1, 142.2, 147.1, 166.6. Anal. calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93: N, 3.85. Found: C 62.92; H, 6.96; N, 3.87.