



A novel tandem transesterification — intramolecular hetero Diels–Alder reactions for construction of fused heterocycles

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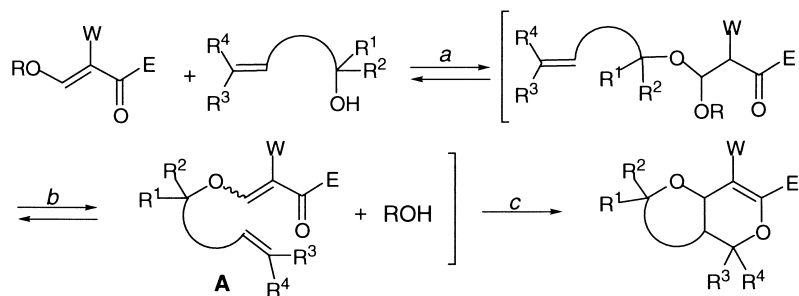
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Abstract

β -Alkoxy-substituted α,β -unsaturated carbonyl compounds activated with an additional electron-withdrawing substituent undergo a facile tandem transesterification/intramolecular hetero Diels–Alder reactions when reacted with δ,ϵ -unsaturated alcohols under thermal conditions. These reactions are stereoselective producing the corresponding functionalized hydropyranopyran derivatives in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

Tandem reactions have emerged as a powerful method for the efficient and stereoselective construction of polyheterocyclic and polycarbocyclic skeletons.² One of the most remarkable examples is the tandem Knoevenagel/intramolecular hetero Diels–Alder reaction, which is useful for the construction of polyheterocycles.¹ Recently a new type of tandem reaction providing pyranobenzopyrans via intramolecular hetero Diels–Alder reaction of *o*-quinonemethides generated from salicylaldehyde dimethyl acetals and unsaturated alcohols has also been reported.³



Scheme 1. (a, b) transesterification, (c) intramolecular hetero Diels–Alder reaction

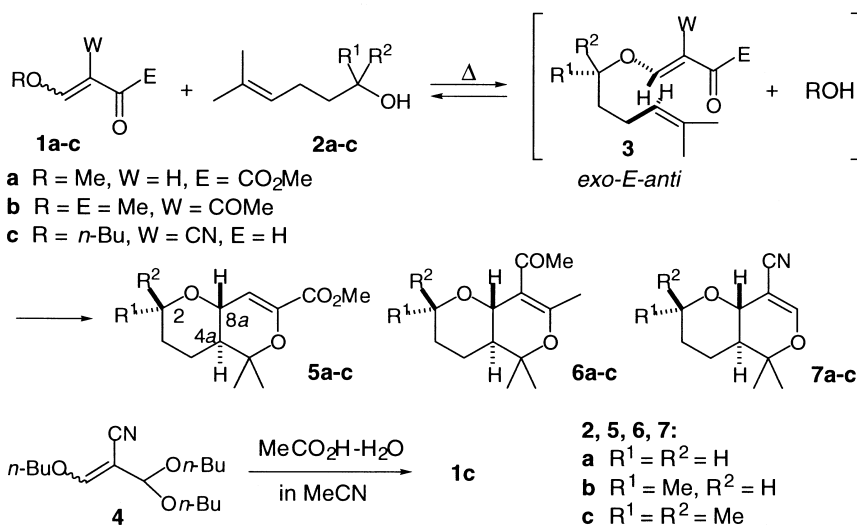
During our investigation concerning the development of intermolecular hetero Diels–Alder reaction with 1-oxa-1,3-butadienes,⁴ a transesterification reaction⁵ of ethyl (*E*)-4-methoxy-2-oxo-3-butenate

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leading to ethyl (*E*)-4-isopropoxy-2-oxo-3-butenolate was observed on treatment with $\text{Ti}(i\text{-PrO})_2\text{Br}_2$ at -78°C . With this result, our attention has been directed to the design of a new type of synthetic process, tandem transesterification/intramolecular hetero Diels–Alder reaction, for the convenient construction of fused heterocycles. This process involves the conjugated addition of unsaturated alcohols to β -alkoxy-substituted α,β -unsaturated carbonyls and the reversible elimination of alcohols (ROH), followed in tandem by a new type of intramolecular hetero Diels–Alder reaction^{1,3} of the resulting transesterified compounds **A** leading to the fused heterocycles as outlined in Scheme 1. These three sequential reactions are expected to proceed in one flask and the intramolecular cycloaddition process would secure high stereoselectivity.

In this communication, we present the preliminary results which have been observed in the one-pot tandem reaction by the use of methyl (*E*)-4-methoxy-2-oxo-3-butenolate **1a**,^{6a,b} 3-methoxymethylene-2,4-pentanedione **1b**,^{6c,d} and β -butoxy- α -cyanoacrolein **1c** with *prim*-, *sec*-, and *tert*- δ,ϵ -unsaturated alcohols **2a–c** having two methyl substituents at the terminal position.⁷

To evaluate the reactivity and stereoselectivity in these thermal tandem reactions, enones **1a–c** were allowed to react with an excess amount of alcohols **2a–c** (2 equivalents) under reflux in an appropriate solvent (Scheme 2 and Table 1) under nitrogen atmosphere.⁸



Scheme 2.

At first enone **1a** and primary alcohol **2a** were refluxed in *o*-dichlorobenzene for 6 h to afford 4a,8a-*trans*-hydropyranopyran **5a** as a single isomer in 70% yield (entry 1). The stereochemistry at the junction of **5a** was estimated to be *trans* based on the large vicinal coupling constant for J_{8a-4a} (9.9 Hz) by ¹H NMR spectrum analysis. Further, the stereostructure of **5a** has been established by X-ray diffraction analysis.⁹ The *trans* structure arises from the *exo-E-anti* transition state of the transesterified intermediate **3** (R¹=R²=W=H, E=CO₂Me), which is well documented.^{1,10} A similar tandem reaction took place using enone **1b** and **2a** under reflux in *o*-dichlorobenzene (12 h) to afford selectively a single stereoisomer 4a,8a-*trans*-**6a** (J_{8a-4a} =9.5 Hz) in 76% yield (entry 2). Next, the reaction of enal **1c**, which was prepared from acetal **4** by hydrolysis, **2a** was carried out under milder conditions (reflux in toluene for 20 h) to give a single stereoisomer 4a,8a-*trans*-**7a** (J_{8a-4a} =9.5 Hz) in 82% yield (from **4**, entry 3).

The generality of the present tandem reaction was examined by using secondary and tertiary alcohols **2b** and **2c** as nucleophilic dienophiles, respectively. The tandem reactions of unsaturated carbonyl

Table 1
Tandem transesterification/intramolecular hetero Diels–Alder reactions of unsaturated carbonyls **1a–c**
with unsaturated alcohols **2a–c**^{a)}

Entry	Substrate 1	Alcohol 2	Solvent ^{b)}	Time (h)	Product 5-7	Yield ^{c)} (%)
1	1a	2a	DCBZ	6	5a	70
2	1b	2a	DCBZ	12	6a	76
3	1c	2a	TL	20	7a	82 ^{d)}
4	1a	2b	DCBZ	6	5b	68
5	1b	2b	DCBZ	12	6b	72
6	1c	2b	TL	20	7b	90 ^{d)}
7	1a	2c	DCBZ	6	5c	63
8	1b	2c	DCBZ	12	6c ^{e)}	75
9	1b	2c	XL	48	6c	65
10	1b	2c	XL	72	6c	76
11	1c	2c	TL	20	7c	85 ^{d)}

a) All reactions were performed with two equivalents of alcohols **2** under reflux in the solvent shown. b) DCBZ: *o*-dichlorobenzene, XL: xylene, TL: toluene. c) Yield of isolated product. d) Overall yields from acetal **4**. e) Cycloadduct **6c** was obtained as a mixture of *4a,8a-cis* isomer (*4a,8a-trans-6c*:*4a,8a-cis* isomer = 19:1).

compounds **1a–c** with secondary alcohol **2b** proceeded stereoselectively under reflux in appropriate solvents to afford the corresponding cycloadducts **5b** (68%), **6b** (72%), and **7b** (90%) each as single stereoisomers in good yields, respectively (entries 4–6). The stereostructure of cycloadduct **6b** was determined on the basis of the ¹H NMR spectrum: based on the large vicinal couplings for J_{8a-4a} (10.0 Hz) as well as the notable NOEs between H-2/H-8a, the stereoisomer **6b** was confirmed to be the *2,8a-cis-8a,4a-trans* structure. Additionally, the large vicinal coupling for J_{2-3ax} (10.1 Hz) indicates the axial position of H-2. Similar structural analysis by ¹H NMR spectra was applied to **5b** ($J_{8a-4a}=10.0$ and $J_{2ax-3ax}=11.0$ Hz) and **7b** ($J_{8a-4a}=9.7$ and $J_{2ax-3ax}=10.0$ Hz). Thus, each stereoisomer **5b** and **7b** has been determined to have *2,8a-cis-8a,4a-trans* structure.

The reactions of both **1a** in *o*-dichlorobenzene and **1c** in toluene with the bulky tertiary alcohol **2c** under reflux also took place to afford *4a,8a-trans-5c* (63%, $J_{8a-4a}=9.7$ Hz) and **7c** (85%, $J_{8a-4a}=9.5$ Hz), respectively (entries 7 and 11). On the other hand, the reaction of **1b** with **2c** under reflux for 12 h in *o*-dichlorobenzene afforded a 19:1 mixture of *4a,8a-trans-6c* ($J_{8a-4a}=9.5$ Hz) and *4a,8a-cis-cycloadduct* ($J_{8a-4a}=3.4$ Hz) in 75% yield (entry 8). The stereoselectivity of this reaction was improved by refluxing in xylene to provide *4a,8a-trans-6c* as a single stereoisomer in 65 and 76% yields (entries 9 and 10).

In summary, the tandem transesterification/intramolecular hetero Diels–Alder reaction leading to stereochemically defined hydroxyranopyrans has been achieved by using activated β -alkoxy-substituted α,β -unsaturated carbonyl compounds and δ,ϵ -unsaturated alcohols. This new methodology of intramolecular hetero Diels–Alder reaction offers an effective synthetic route for the construction of fused heterocycles. To explore the scope of this process further investigation is now in progress.

Acknowledgements

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8. Characterization of the new compounds discussed in this work was based on the spectral and analytical data. Some typical spectral data are shown as follows: 4a,8a-*trans*-**5a**: colorless prisms (hexane); mp 75°C; IR (KBr): 1720 and 1651 cm^{-1} ; ^1H NMR (C_6D_6) δ =1.15, 1.40 (each 3H, each s, 2 \times 5-Me), 1.25 (1H, m), 1.54 (1H, m), 1.65–1.78 (2H, m), 1.85 (1H, m), 3.51 (1H, dt, $J_{\text{gem}}=J_{2\text{ax}-3\text{ax}}=11.5$ and $J_{2\text{ax}-3\text{eq}}=3.5$ Hz, H-2ax), 3.75 (1H, dd, $J_{8\text{a}-4\text{a}}=9.9$ and $J_{8\text{a}-8}=2.0$ Hz, H-8a), 4.03 (1H, m, H-2eq), and 5.96 (1H, d, $J_{8-8\text{a}}=2.0$ Hz, H-8). ^{13}C NMR (C_6D_6) δ =19.51 (5-Me), 24.73 (5-Me), 26.33 (C-3), 26.91 (C-4), 44.86 (C-4a), 52.21 (7-OMe), 68.41 (C-2), 72.67 (C-8a), 80.20 (C-5), 109.51 (C-8), 142.78 (C-7), and 163.46 (7-CO); MS (70 eV) (relative intensity, %) m/z 226 (M^+ , 41), 211 (base peak), 167 (54), 151 (36), 149 (23), 125 (47), 97 (47), and 58 (34). Anal. calcd for $\text{C}_{12}\text{H}_{18}\text{O}_4$: C, 63.70; H, 8.02%. Found: C, 63.90; H, 8.09%.
9. A single crystal of **5a** was monoclinic having a space group $P 2_1/n$, $a=15.861(2)$ Å, $b=9.505(3)$ Å, $c=8.0660(10)$ Å, $\beta=100.160(10)^\circ$, $V=1197.0(4)$ Å³, $Z=4$. The final R factor was 0.0472 for 4532 measured reflections.
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