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Short Note

Ethyl (*1R*,10S*,12R*,15S**)-4-Hydroxy-2-oxo-15-(2-oxo-1-pyrrolidinyl)-9-oxatetracyclo[10.2.2.0^{1,10}.0^{3,8}] hexadeca-3,5,7,13-tetraene-13-carboxylate

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Abstract: *N*-Vinylpirrolidinone reacts with (*E*)-ethyl 5-hydroxy-3-(4-oxo-4*H*-chromen-3-yl) acrylate (**1**) through a domino reaction similar to that reported reaction for ethyl vinyl ether. Inverse electron demand Diels–Alder (IEDDA)–elimination-IEDDA generates isomeric tetracycles **5** and **6**. The assignment of the relative stereochemistry of the products was made by comparing the proton couplings with those obtained by reaction with ethyl vinyl ether.

Keywords: domino-reaction; inverse electron demand Diels–Alder; *N*-vinylpyrrolidinone; chromone derivatives

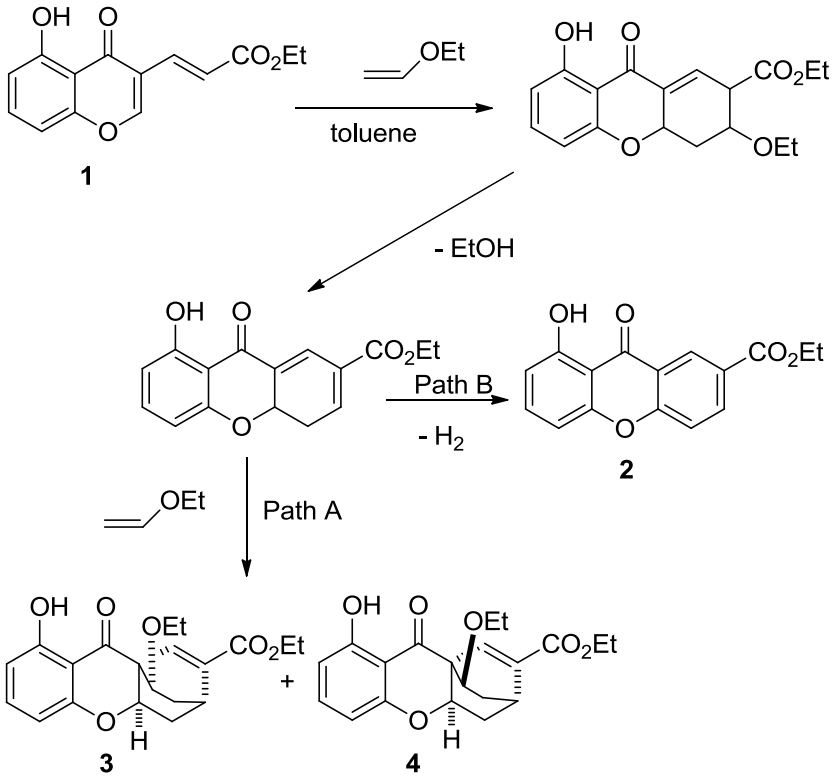
1. Introduction

Domino reactions, also known as cascade or tandem reactions, are an important type of chemical transformation in organic synthesis. These reactions have several benefits that are well established: high atom economy, shorter reaction time, and reduced waste generation, among others. Thus, they can be considered to fall under the banner of green chemistry. These reactions take advantage of the formation of several bonds in sequence without the workup and isolation of intermediates, changing the reaction conditions or adding reagents. This increases the structural complexity of the products obtained effectively in one step since each reaction that makes up the sequence occurs spontaneously [1–3].

The classification of domino reactions is sometimes difficult because of the diverse nature of the many steps involved in the transformation; however, it is generally done considering the major theme of the sequence. Most of these reactions consist of two or more nucleophilic, electrophilic, radical, pericyclic, or transition metal-catalyzed transformations [2,4]. The combination of reactions can be of the same (homo-domino) or different type (hetero-domino), for example, Knoevenagel-hetero-Diels–Alder [5], Knoevenagel-ene [6], or Sakurai-ene [7–10] reactions. Some examples showing inverse electron demand Diels–Alder reactions have also been reported, especially with dienes containing two electron-withdrawing groups at positions 1 and 3. These dienes react with enamines or enol ethers to provide functionalized 1-tetralones, benzocoumarines, 2-hydroxybenzophenones, bicyclic lactams, and xanthones [11–14].

In this field, we have described the reactions of (*E*)-ethyl-3-(4-oxo-4*H*-chromen-3-yl)acrylate (**1**), (*E*)-3-(4-oxo-4*H*-chromen-3-yl)-2-acrylonitrile, and their 5-hydroxy-derivatives with ethyl vinyl ether. For example, **1** undergoes competitive, solvent-dependent, domino reactions. In toluene, inverse electron demand Diels–Alder (IEDDA)–elimination-IEDDA generates isomeric tetracycles **3** and **4**.

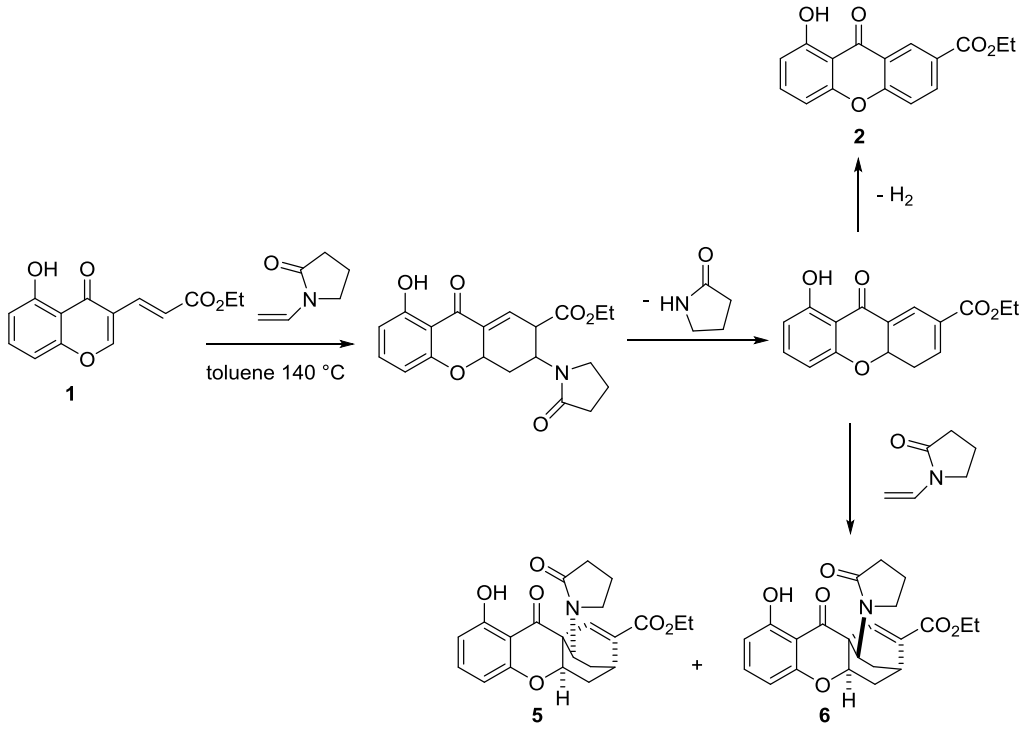
Alternatively, IEDDA followed by elimination and oxidation provide xanthone **2** [15] (Scheme 1). 2D NMR experiments along with X-ray crystal crystallography, allowed for the unequivocal assignment of these structures. In this communication, we describe the use of *N*-vinylpyrrolidinone as a useful dienophile for obtaining highly functionalized tetracyclic compounds analogues to **3** and **4**.



Scheme 1. Alternative domino reactions of chromone derivatives with ethyl vinyl ether in toluene.

2. Results

The starting chromone derivative **1** was obtained by Wittig reaction of 5-hydroxy-3-formylchromone with carboethoxymethylenetriphenylphosphorane in toluene under reflux. The *E*/*Z* product mixture has a 55/40 *E*/*Z* ratio and an overall yield of 95% [16]. When *N*-vinylpyrrolidinone, a dienophile already used in inverse electron demand Diels–Alder reactions [17], reacted with **1** in toluene at 140 °C in a sealed tube, a mixture of isomeric tetracyclic compounds **5** and **6**, along with the xanthone **2**, were obtained in yields of 35%, 15% and 2%, respectively (Scheme 2). NMR spectra are provided as supplementary materials.



Scheme 2. Domino reaction of chromone **1** with *N*-vinylpyrrolidinone.

3. Discussion

The analysis of 1D and 2D NMR spectra (^{1}H, ^{13}C, HMBC and HSQC) of **5** and **6** allowed unequivocal structure assignments. The relative stereochemistry of these cycloadducts was made analyzing the *cis* and *trans* coupling constants between H-10 and H-15 with H-11 and H-16, respectively, and by comparing them with analogs **3** and **4** obtained in the reaction with ethyl vinyl ether [15]. The spectra of **5** and **6** show a very similar coupling pattern in the bicyclic moiety compared to that of **3** and **4** respectively, including a similar $^{4}J_{H,H}$ coupling through a W coupling path between the H-16 and H-11 protons in **5**. Selected coupling constants are shown in Table 1.

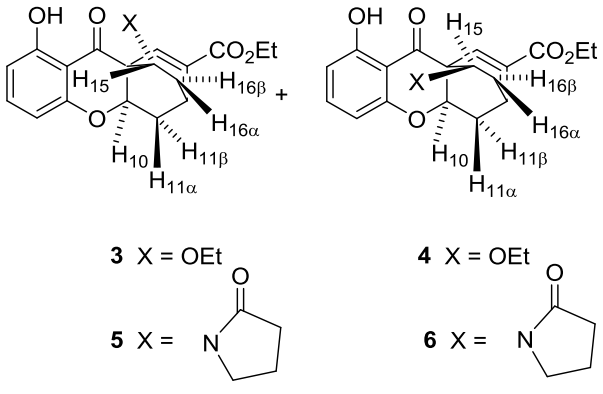


Table 1. Selected H,H coupling constants of tetracycles **3**–**6** [a].

$J_{H,H}$	3	4	5	6
10-11β	10	8.6	10.3	8.3
10-11α	3.4	2.8	3.8	2.4
11α-11β	13.8	13.7	13.9	14.2

Table 1. *Cont.*

$J_{H,H}$	3	4	5	6
11β-16β	3.1	—	2.9	—
11α-16α	—	3.7	—	—
15-16β	3.1	7.8	5.6	9.6
15-16α	8.1	2.4	9.8	5.6
16α-16β	13	13.3	13.3	13.5

[a] values in Hz.

4. Materials and Methods

The ^{1}H and ^{13}C-NMR spectra were recorded at 300.13 MHz and 75.47 MHz, respectively, on a AVANCE DRX 300 Spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) using $CDCl_3$ as a solvent. The chemical shifts are reported in ppm downfield from TMS for ^{1}H-NMR and relative to the central $CDCl_3$ resonance (77.0 ppm) for ^{13}C-NMR. Melting points are uncorrected and were taken with a Gallenkamp melting point apparatus. Infrared spectra were recorded with a NICOLET 510P FT-IR spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). High resolution mass spectrum was obtained on a MAT 95XP, Thermo Finnigan spectrometer(Thermo Fisher Scientific, Waltham, MA, USA). Commercial *N*-vinylpyrrolidinone was used without purification. The domino reactions were done in an Ace pressure tube (Aldrich catalogue number: Z564605-1EA). The separations and purifications were performed by column chromatography on silica gel 60 (Merck, Darmstadt, Germany, 70-230 mesh). The reported yields of the cycloadducts were calculated based on the integration of the ^{1}H-NMR spectrum.

4.1. Domino Reaction

The reaction was performed in a pressure tube by adding 0.9 mL of *N*-vinylpyrrolidinone (0.9 g, 8.3 mmol) to a solution of 107 mg of 5-hydroxy-(*E*)-ethyl-3-(4-oxo-4*H*-chromen-3-yl)acrylate (**1**) (0.41 mmol) in toluene (5.0 mL). The mixture was stirred for 3 days at 140 °C, the solvent was removed at reduced pressure, and the crude product was dissolved in 5.0 mL of EtOAc. The solution was washed with a large excess of water to remove the unreacted *N*-vinylpyrrolidinone, dried over $MgSO_4$ and evaporated to dryness in vacuum. The crude product was purified by column chromatography on silica gel using hexane/EtOAc 4:1 as an eluent to afforded fractions with almost pure products. Recrystallizations in EtOAC/hexane afford pure compound **5** in a 13.4% yield and **6** as an analytical sample.

Ethyl (1R,10S*,12R*,15S*)-4-hydroxy-2-oxo-15-(2-oxo-1-pyrrolidinyl)-9-oxatetracyclo[10.2.2.0^{1,10}.0^{3,8}] hexadeca-3,5,7,13-tetraene-13-carboxylate* (**5**). Crystallized from EtOAc/hexane as colorless crystals; ^{1}H-NMR ($CDCl_3$) δ: 1.30 (dddd, 1H, J_1 = 13.4 Hz, J_2 = 5.6 Hz, J_3 = 2.9 Hz, J_4 = 2.9 Hz, H-16β), 1.35 (t, 3H, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$), 1.75 (ddd, 1H, J_1 = 13.9 Hz, J_2 = 3.8 Hz, J_3 = 2.2 Hz, H-11α), 1.80–1.88 (m, 1H, H-4′), 1.90–2.01 (m, 1H. H-4′), 2.09 (dddd, 1H, J_1 = 13.9 Hz, J_2 = 10.3 Hz, J_3 = 3.3 Hz, J_4 = 2.9 Hz, H-11β), 2.16–2.26 (m, 2H, H-3′), 2.25 (ddd, 1H, J_1 = 13.4 Hz, J_2 = 9.8 Hz, J_3 = 2.9 Hz, H-16α), 3.00 (ddd, 1H, J_1 = 9.0 Hz, J_2 = 8.6 Hz, J_3 = 4.5 Hz, H-5′), 3.16 (dt, 1H, J_1 = 9.0 Hz, J_2 = 7.5 Hz, H-5′), 3.40 (m, 1H, H-12), 4.22–4.33 (m, 3H, H-10 and $CO_2\underline{CH_2}CH_3$), 5.44 (dd, 1H, J_1 = 9.7 Hz, J_2 = 5.6 Hz, H-15), 6.49 (dd, 1H, J_1 = 8.3 Hz, J_2 = 0.8 Hz, H-7), 6.54 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.8 Hz, H-5), 7.38 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.3 Hz, H-6), 7.39 (m, 1H, H-14), 11.55 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ: 14.2 ($CO_2CH_2\underline{CH_3}$), 18.2 (C-4′), 29.7 (C-12), 30.6 (C-16), 30.8 (C-3′), 31.1 (C-11), 44.6 (C-5′), 45.7 (C-15), 53.3 (C-1), 61.1 ($CO_2\underline{CH_2}CH_3$), 77.33 (C-10), 107.6 (C-7), 107.7 (C-3), 110.3 (C-5), 134.9 (C-14), 138.4 (C-6), 139.6 (C-13), 160.9 (C-8), 162.5 (C-4), 163.9 ($\underline{C}O_2Et$), 175.2 (C-2), 198.1 (C-2); mp 181.5−183 °C; IR (KBr) 2971, 1714, 1690, 1642, 1221 cm^{-1}; HREIMS [M]$^{+}$ m/z calcd. for $C_{22}H_{23}NO_6$ 397.1525: found 397.1524.

Ethyl (1R,10S*,12R*,15R*)-4-hydroxy-2-oxo-15-(2-oxo-1-pyrrolidinyl)-9-oxatetracyclo[10.2.2.0^{1,10}.0^{3,8}] hexadeca-3,5,7,13-tetraene-13-carboxylate* (**6**). Crystallized from EtOAc/hexane as colorless crystals; ^{1}H-NMR ($CDCl_3$) δ 1.13 (ddt, 1H, J_1 = 13.5 Hz, J_2 = 5.6 Hz, J_3 = 3.0 Hz, H-16α), 1.31 (t, 3H, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$), 1.65 (dddd, 1H, J_1 = 14.2 Hz, J_2 = 3.5 Hz, J_3 = 3.5 Hz, J_4 = 2.4 Hz, H-11α), 1.82–1.95 (m, 1H, H-4′), 2.04–2.11 (m, 1H, H-16β), 2.08–2.16 (m, 1H, H-4′), 2.24 (ddd, 1H, J_1 = 14.2 Hz, J_2 = 8.3 Hz, J_3 = 2.4 Hz, H-11β), 2.37 (ddd, 1H, J_1 = 16.6 Hz, J_2 = 9.5 Hz, J_3 = 3.6 Hz, H-3′), 2.53 (dt, 1H, J_1 = 16.8 Hz, J_2 = 9.5 Hz, H-3′), 3.06 (ddd, 1H, J_1 = 9.2 Hz, J_2 = 8.8 Hz, J_3 = 3.0 Hz, H-5′), 3.08–3.16 (m, 1H, H-5′), 3.42 (m, 1H, H-12), 4.24 (q, 2H, J_1 = 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 4.68 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 2.4 Hz, J_3 = 1.2 Hz, H-10), 4.82 (dd, 1H, J_1 = 9.6 Hz, J_2 = 5.6 Hz, H-15), 6.34 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz, H-7), 6.54 (d, 1H, J = 8.3 Hz, H-5), 6.77 (m, 1H, H-14), 7.35 (t, 1H, J = 8.3 Hz, H-6), 11.72 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$) δ 14.2 ($CO_2CH_2\underline{CH_3}$), 18.3 (C-4′), 28.1 (C-12), 31.0 (C-16), 31.2 (C-3′), 33.5 (C-11), 45.5 (C-5′), 48.1 (C-15), 49.3 (C-1), 61.2 ($CO_2\underline{CH_2}CH_3$), 78.2 (C-10), 107.2 (C-7), 108.2 (C-3), 110.1 (C-5), 134.5 (C-14), 138.4 (C-6), 139.5 (C-13), 160.3 (C-8), 162.7 (C-4), 163.5 ($\underline{C}O_2Et$), 176.0 (C-2), 198.8 (C-2); mp 217–219 °C.

Supplementary Materials: The following are available online at www.mdpi.com/1422-8599/2017/1/M928, Figure S1: ^{1}H-NMR spectrum of compound **5**, Figure S2: ^{13}C-NMR spectrum of compound **5**, Figure S3: HSQC spectrum of compound **5**, Figure S4: HMBC spectrum of compound **5**, Figure S5: ^{1}H-NMR spectrum of compound **6**, Figure S6: ^{13}C-NMR spectrum of compound **6**, Figure S7: HSQC spectrum of compound **6**, Figure S8: HMBC spectrum of compound **6**.

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Author Contributions: J.H-M. and R.A-M. conceived and designed the experiments; J.H-M performed the experiments; J.H-M and R.A-M analyzed the data; R.A-M contributed reagents/materials/analysis tools; R. A-M and J.H-M wrote the paper.

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