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Domino Knoevenagel–hetero-Diels–Alder reactions: a stereoselective synthesis of sugar-annulated furo[3,2-*b*] pyrano[4,3-*d*]pyran derivatives

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ABSTRACT

The *O*-propargyl derivative of a sugar aldehyde derived from D-glucose undergoes smooth intramolecular domino Knoevenagel–hetero-Diels–Alder reactions with 1,3-diketones in the presence of CuI/Et_3N system in refluxing methanol to afford a novel class of carbohydrate analogues, furopyranopyrans in good yields. 1-Aryl-pyrazol-5-ones also undergo smooth coupling with *O*-propargyl tethered sugar aldehyde under similar conditions to furnish pyrazole-annulated furopyranopyrans. The stereochemistry of the products was assigned by various NMR experiments.

The pyrazole moiety is frequently found in various biologically active compounds.[1] Pyrazole derivatives are known to exhibit a wide spectrum of biological activities such as anti-hyperglycemic, analgesic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemics, and sedative-hypnotic activity.[2] Recently, some arylpyrazole derivatives are reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[3] The domino Knoevenagel intramolecular hetero-Diels–Alder reaction is one of the most powerful synthetic routes for the synthesis of various heterocycles and natural products.[4,5] Recently, there have been some reports on domino Knoevenagel–hetero-Diels–Alder reactions to produce annulated polycyclic heterocycles.[6,7] However, to the best of our knowledge, there are no reports on domino Knoevenagel intramolecular hetero-Diels–Alder reactions using an *O*-propargyl tethered sugar aldehyde derived from D-glucose.

In this Letter, we describe a novel protocol for the synthesis of sugar-fused pyrano[4,3-*d*]pyrans via domino Knoevenagel–hetero-Diels–Alder reaction between propargyl ether tethered sugar aldehyde and 1,3-diketones. Thus, the treatment of 4-hydroxycoumarin (**1**) with *O*-propargyl tethered sugar aldehyde (**2**) in the presence of 0.3 equiv of CuI and a stoichiometric amount of triethylamine in methanol at 70 °C resulted in the formation of coumarin-annulated furo[3,2-*b*]pyrano[4,3-*d*]pyran **3a** in 75% yield (Scheme 1).

The reaction proceeds via a tandem Knoevenagel- and hetero-Diels–Alder pathway. The structure of product **3a** was characterized by NMR experiments including 2-D nuclear Overhauser effect spectroscopy (NOESY) and double quantum filtered correlation spectroscopy (DQFCOSY) (Fig. 1). From the one dimensional ^{1}H NMR experiments, $^3J_{H1\text{-}H2}$ = 3.9 Hz, $^3J_{H3\text{-}H4}$ = 2.6 Hz, $^3J_{H4\text{-}H5}$ = 4.8 Hz, and $^3J_{H6\text{-}H7(pro\text{-}R)}$ = 1.6 Hz were determined. The twist boat conformation of the oxygen-containing six-membered ring is supported by the NOESY cross peak H5/H7(*pro-S*), H6/H7(*pro-S*), and H3/H7(*pro-R*). In addition, the small values of $^3J_{H3\text{-}H4}$ and $^3J_{H4\text{-}H5}$ provide further evidence for the structure.[8]

In case of 4-hydroxycoumarin, no other regioisomer was observed (entry a, Table 1) by ^{1}H NMR. Encouraged by the results obtained with 4-hydroxycoumarin, we turned our attention to various 1,3-diketones (Table 1, entries b–d). The cyclic 1,3-diketones such as cyclohexa-1,3-dione, dimedone, and 1,3-dimethylbarbituric acid participated effectively in this reaction. In all cases, the corresponding furo[3,2-*b*]pyrano[4,3-*d*]pyrans were isolated in good yields. However, acyclic 1,3-ketones such as acetyl acetone and ethyl acetoacetate did not participate in the reaction. Similarly, cyclic ketones such as cyclohexanone, cyclopentanone, and tetralone also failed to give the desired products under similar conditions. Furthermore, substituted propargyl ether tethered sugar aldehyde did not undergo the hetero-Diels–Alder reaction with 1,3-diones. The reaction was successful only with unsubstituted propargyl ether tethered sugar aldehyde. Next, we have attempted

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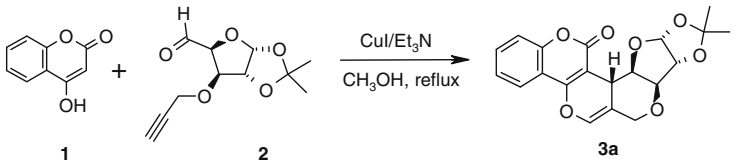


Scheme 1. Reaction of sugar aldehyde with 4-hydroxycoumarin.

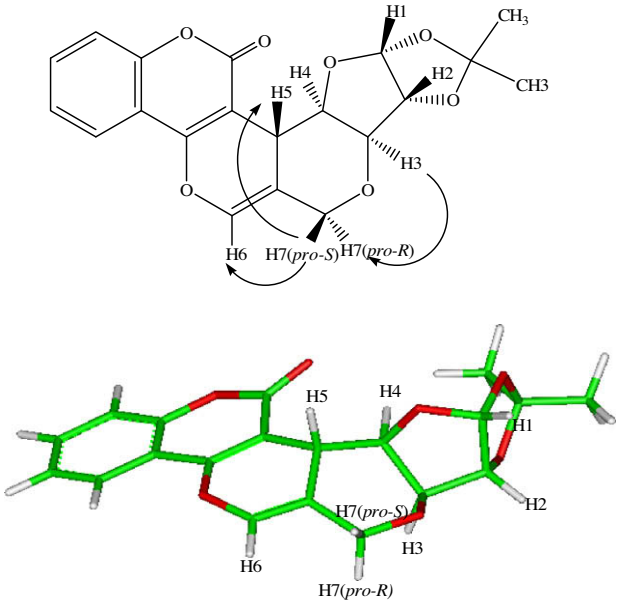


Figure 1. Characteristic NOE's and energy-minimized structure of **3a**.

the condensation of propargyl ether tethered sugar aldehyde with 1-aryl-pyrazol-5-ones. Interestingly, various pyrazol-5-ones underwent smooth coupling with sugar aldehyde to afford pyrazole-annulated furo[3,2-*b*]pyrano[4,3-*d*]pyrans in good yields (Scheme 2, entries e–h).

Next, we attempted the domino-Knoevenagel–hetero-Diels–Alder reaction with *O*-propargyl tethered sugar aldehyde derived from D-ribose. The reaction proceeded well under similar conditions to give the desired product in 80% yield (entry i, Table 1). As a solvent, methanol appeared to give the best results. In all cases, the reactions proceeded rapidly in refluxing methanol. The reactions were clean and the desired products were obtained in good yields. Only a single product was obtained from each reaction, the structure of which was confirmed by ^{1}H NMR.

We assume that the cycloaddition proceeds in a concerted way via *endo-E-syn* transition state. Mechanistically, a 1-oxa-1,3-butadiene may be formed from 1,3-diketone and propargyl ether tethered sugar aldehyde which may undergo subsequently an intramolecular hetero-Diels–Alder reaction leading to tetracyclic heterocycle (Scheme 3).

The scope and generality of the reaction are illustrated with respect to various cyclic 1,3-diketones and pyrazolin-5-ones and the results are presented in Table 1.[9]

In summary, we have developed a novel method for the synthesis of poly-oxygenated ring heterocycles via a domino Knoevenagel–hetero-Diels–Alder reaction between propargyl ether tethered sugar aldehyde and cyclic 1,3-diketones. This method also works well with pyrazolin-5-ones. It is entirely a new strategy to construct sugar annulated tetracyclic- and pentacyclic-heterocycles in a single-step operation.

Table 1
Domino Knoevenagel–hetero-Diels–Alder reaction

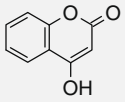
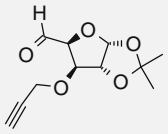
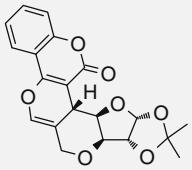
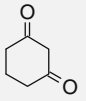
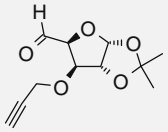
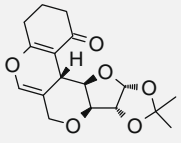
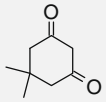
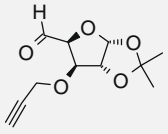
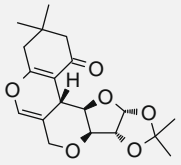
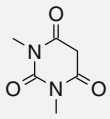
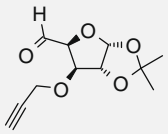
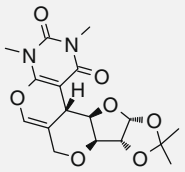
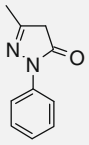
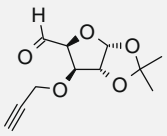
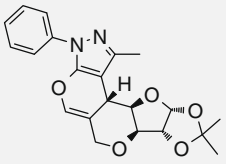
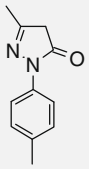
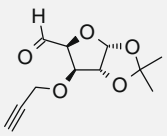
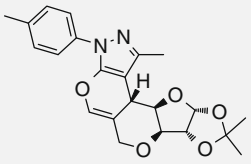
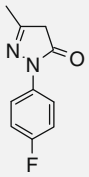
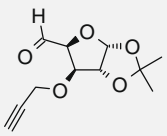
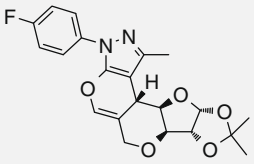
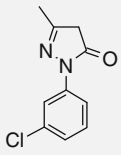
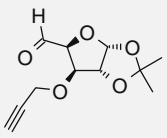
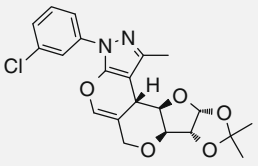
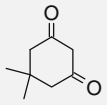
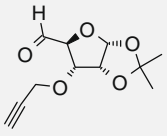
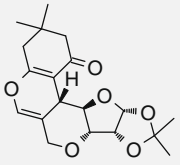
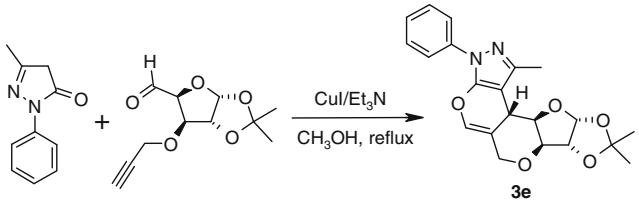
Entry	Substrate	Aldehyde	Product[a]	Time (h)	Yield[b] (%)
a				4.0	75
b				4.0	90
c				3.5	84
d				4.5	85

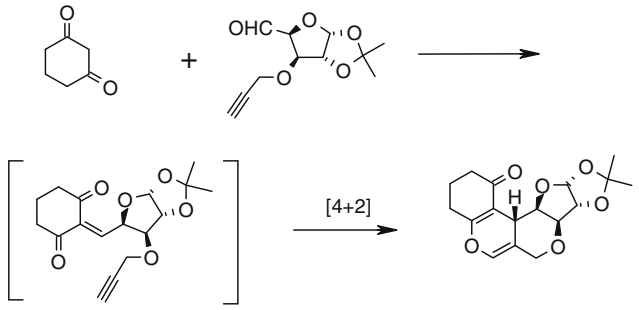
Table 1 (*continued*)

Entry	Substrate	Aldehyde	Product[a]	Time (h)	Yield[b] (%)
e				5.0	76
f				4.5	80
g				5.0	75
h				5.5	78
i				4.5	80

[a] The products were characterized by NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2. Reaction of sugar aldehyde with 3-methyl-pyrazol-5-one.



Scheme 3. A plausible reaction mechanism.

Acknowledgment

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8. Molecular mechanics calculations were carried out using Insight-II (97.0/Discover 1) programme on a silicon graphics O2 workstation.
9. *Typical procedure*: A mixture of ketone **1** (1 mmol), *O*-propargylated sugar aldehyde **2** (1.2 mmol) and triethyl amine (1 mmol) was stirred in methanol solution for 30 min. Then CuI (0.3 mmol) was added and the resulting mixture was allowed to stir under reflux for specified time (Table 1). After complete conversion, as monitored by TLC, the mixture was filtered and washed with methanol. The filtrate was concentrated in vacuo

and purified by column chromatography using ethyl acetate/hexane (1:9) as an eluent to afford pure product. *Spectral data for the selected compounds* **3b**: IR (KBr): ν 3421, 2925, 2854, 1726, 1658, 1457, 1214, 1078 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.42 (s, 1H), 5.97 (d, J = 3.6 Hz, 1H), 4.39 (d, J = 3.6 Hz, 1H), 4.37 (s, 1H), 4.16 (d, J = 12.6 Hz, 1H), 4.04 (dd, J = 2.7, 4.5 Hz, 1H), 3.95 (d, J = 2.7 Hz, 1H), 3.38 (d, J = 5.4 Hz, 1H), 2.57–2.32 (m, 6H), 1.40 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 165.8, 134.2, 113.5, 111.2, 105.8, 87.3, 82.7, 79.0, 66.4, 37.0, 30.0, 29.6, 27.4, 26.8, 26.2, 20.0. LC–MS: m/z: 321 (M+H). HRMS calcd for $C_{17}H_{21}O_6$ (M+H): 321.1338. Found: 321.1349. Compound **3c**: IR(KBr): ν 3436, 2954, 1729, 1620, 1448, 1382, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.42 (s, 1H), 5.97 (d, J = 3.7 Hz, 1H), 4.42–4.36 (m, 2H), 4.16 (d, J = 12.3 Hz,1H), 4.03 (dd, J = 2.8, 4.7 Hz, 1H), 3.96 (d, J = 2.6 Hz, 1 Hz), 3.37 (d, J = 4.7 Hz, 1H), 2.41–2.19 (m, 4H), 1.39 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.0, 183.2, 153.5, 132.5, 130.5, 125.0, 106.2, 101.8, 97.9, 85.54, 70.17, 60.32, 51.0, 49.3, 47.5, 47.3, 46.0, 45.4, 20.1. LC–MS: m/z: 349 (M+H). HRMS calcd for $C_{19}H_{25}O_6$ (M+H): 349.1651. Found: 349.1649. Compound **3d**: IR(KBr): ν 3436, 2926, 1704, 1640, 1453, 1378, 1162, 1073 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.51 (s, 1H), 5.98 (d, J = 2.9 Hz, 1H), 4.48–4.40 (m, 2H), 4.24–4.20 (m, 2H), 3.95 (d, J = 2.9 Hz, 1H), 3.55 (d, J = 3.9 Hz, 1H), 3.35 (s, 6H), 1.41 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 133.0, 114.4, 111.4, 105.8, 87.4, 86.7, 82.6, 79.1, 65.7, 31.7, 29.6, 28.9, 28.2, 26.8, 26.3. LC–MS: m/z: 365 (M+H). HRMS calcd for $C_{17}H_{20}N_2O_7Na$ (M+Na): 387.1168. Found: 387.1153. Compound **3f**: White yellow solid, mp 145–148 °C, IR (KBr): ν 3435, 2924, 2854, 1743, 1674, 1607, 1521, 1521, 1457, 1220, 1076, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, 2H), 7.16 (d, 2H), 6.51 (m, 1H), 5.97 (d, J = 3.7 Hz, 1H), 4.54–4.52 (m, 1H), 4.50–4.47 (m, 1H), 4.36–4.27 (m, 2H), 3.93 (d, J = 3.7 Hz, 1H), 3.58 (d, J = 5.2 Hz, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 135.5, 134.3, 129.5, 120.7, 111.6, 110.8, 105.8, 97.1, 97.0, 86.6, 83.4, 79.5, 66.2, 32.8, 29.6, 27.0, 26.5, 20.9, 21.0. LC–MS: m/z: 397 (M+H). HRMS calcd for $C_{22}H_{25}N_2O_5$ (M+H): 397.1763. Found: 397.1768. Compound **3i**: ^1H NMR (600 MHz, $CDCl_3$): δ 6.52 (t, J_4 = 0.9 Hz, 1H), 5.85 (d, J_3 = 4.0 Hz, 1H), 4.60 (t, J_3 = 4.0 Hz, 1H), 4.19 (d, J_2 = 12.2 Hz, 1H), 4.02 (dt, J_4 = 1.8, 12.2 Hz, 1H), 3.64 (dd, J_3 = 9.9, J_3 = 8.6 Hz,1H), 3.57 (d, J_3 = 9.9 Hz, 1H) 3.44 (dd, J_3 = 4.0, 8.6 Hz,1H), 2.44 (d, J_2 = 15.6 Hz, 1H), 2.41 (d, J_2 = 17.2 Hz, 1H), 2.24 (d, J_2 = 15.6 Hz, 1H), 2.19 (d, J_2 = 17.2 Hz, 1H), 1.55 (s, 3H), 1.31 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 164.2, 138.2, 112.9, 112.4, 104.1, 82.4, 78.4, 76.1, 69.4, 50.9, 41.2, 35.0, 32.1, 29.6, 28.8, 27.8, 26.1, 25.9. LC–MS: m/z: 349 (M+H).