First Examples of Proline-Catalyzed Domino Knoevenagel/Hetero-Diels–Alder/Elimination Reactions†

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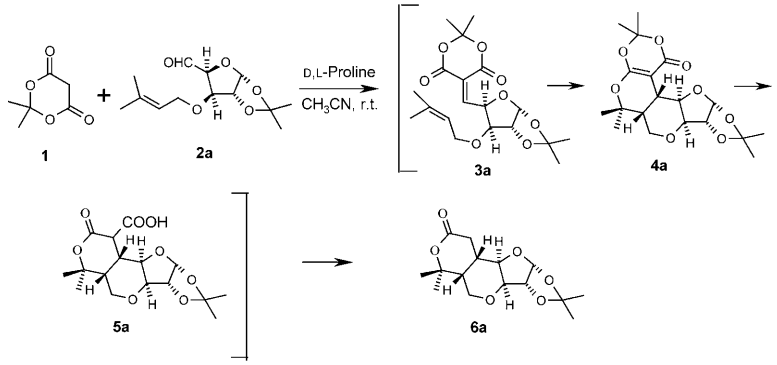
Abstract: A novel and efficient one-pot synthesis of lactones (pyranones) has been achieved by domino Knoevenagel/hetero-Diels–Alder/elimination reactions of *O*- and *N*-prenyl aldehyde derivatives with Meldrum's acid in the presence of L- or D,L-proline. The reaction proceeds cleanly at room temperature to afford *cis*- or *trans*-fused products in good yields with high diastereoselectivity.

Keywords: domino reaction; lactones; Meldrum's acid; organocatalysis

Domino reactions[1] are considered to be versatile tools and are used for the synthesis of structurally diverse compounds, biologically active natural products and drugs.[2–4] Among these, the domino Knoevenagel/hetero-Diels–Alder approach[5] has been studied extensively by Tietze[6] and other groups[7] to construct fused heterocycles, usually in a stereoselective manner. Recently we have reported[8] a domino Knoevenagel/hetero-Diels–Alder reactions of D-glucose-derived *O*-prenyl aldehyde with Meldrum's acid for the synthesis of perhydrofuro[3,2-*b*]pyran-5-ones using EDDA catalyst. In connection to our observation[9] with the D,L-proline-catalyzed Yonemitsu reaction, we were delighted to see domino Knoevenagel/hetero-Diels–Alder/elimination reactions of *O*- and *N*-prenyl aldehydes with Meldrum's acid in one-pot catalyzed by L- or D,L-proline. Therefore, we report here a new and highly efficient synthesis of lactones by domino Knoevenagel/hetero-Diels–Alder/elimination reactions of *O*- and *N*-prenyl aldehyde derivatives with Meldrum's acid using L- or D,L-proline as a catalyst. However, this is the first finding for the loss of acetone and decarboxylation in one-pot in domino Knoevenagel/hetero-Diels–Alder reactions. The unique 1,3-dioxane-4,6-dione appendage of the adducts seemed to be convenient for these functional group transformations. Thus a furo-pyrano-pyranone ring system **6a** could be obtained applying Knoevenagel condensation of D-glucose derived *O*-prenylated sugar aldehyde **2a** with Meldrum's acid **1** to form an intermediate **3a**, followed by an intramolecular hetero-Diels–Alder cycloaddition and elimination reactions in one-pot (Scheme 1). The reaction proceeded smoothly in the presence of a catalytic amount of L-proline at room temperature in acetonitrile and proved to be highly stereoselective since only the *cis*-fused isomer, **6a** is formed exclusively in 95% yield. The structure of the product was assigned on the basis of ^{1}H NMR, ^{13}C NMR, IR and mass spectra. The presence of the lactone C=O is supported by the observation of a peak in the IR spectrum at 1720 cm^{-1} and ^{1}H NMR spectral data of the compounds were compared with the products obtained in EDDA-catalyzed domino reactions.[8]



Scheme 1.

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Table 1. Domino Knoevenagel/hetero-Diels–Alder/elimination reactions.

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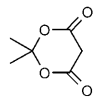
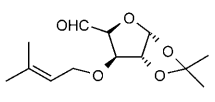
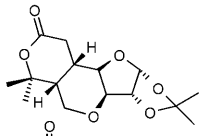
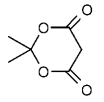
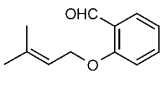
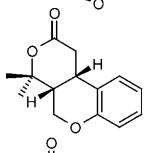
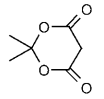
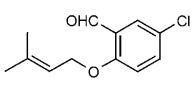
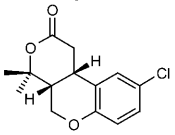
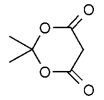
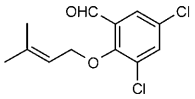
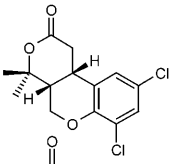
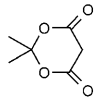
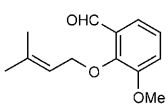
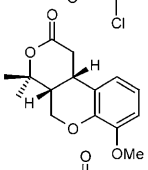
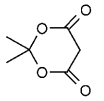
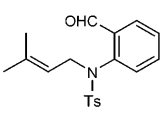
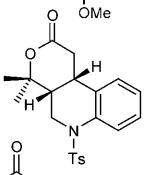
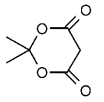
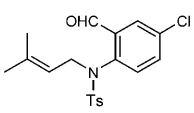
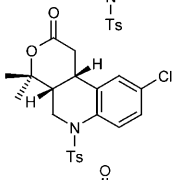
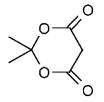
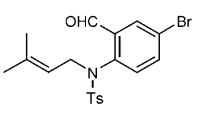
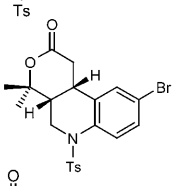
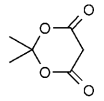
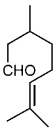
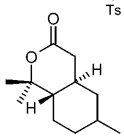
a				3/1	95
b				3/1	96
c				3/1.5	92
d				3/1.5	89
e				3/1	88
f				3/1	95
g				3/1.5	92
h				3/1.5	90
i				3/1	95

[a] Products are confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectra.
[b] Yields obtained after column chromatography.
[c] 10 mol % of L-proline was used in each reaction.

In the domino reaction, aromatic, heteroaromatic and aliphatic aldehydes are successfully employed, which clearly shows the scope of the reaction (Table 1). Under similar conditions, *O*-prenyl and *N*-prenyl aldehydes **2b, 2f** derived from salicylaldehyde and anthranilic acid reacted with Meldrum's acid to afford the corresponding *cis*-fused lactones **6b** and **6f** in excellent yields. In addition, other substituted aromatic aldehydes **2c**–**2e**, **2g**, **2h** were also used to give the corresponding lactones **6c**–**6e**, **6g**, **6h** in 88–92% yields *via* cycloadducts with *cis* selectivity.

Aliphatic aldehyde, such as citral (**2i**) can also be employed in this domino reaction. As before, the reaction is highly selective, however, the main product is the *trans*-

annulated pyranone. In all cases, the reactions proceeded smoothly at room temperature and were complete within 3 h. It is worthy of note to mention that all the reactions were also performed at reflux temperature and found to proceed in 1–1.5 h to give the lactones. All products are new and characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. In the absence of catalyst the domino reaction did not proceed at all even after a prolonged reaction time. This domino reaction is also run using D,L-proline and found to give the same results. The spectral data of the products exactly match with the product data derived from the L-proline-catalyzed reactions. When the domino reaction is carried out using other secondary amines such as pyrrolidine, piperidine or morpholine, the lactones are not formed, instead it gave unidentified products. This clearly shows the role of the proline catalyst. To understand the mechanism, under similar conditions in addition to proline we have run the reaction by adding molecular sieves powder to quench the water molecules formed by the Knoevenagel reaction, since the presence of water molecules is believed to be responsible for the opening of Meldrum's acid. But, to our surprise, the reaction did not proceed at all and the starting materials were recovered unchanged. Therefore, the present method is complimentary to the domino Knoevenagel/hetero-Diels–Alder reactions reported in the literature, where only adducts are reported as products.

In summary, We have described a proline-catalyzed reactions of *O*- and *N*-prenyl aldehydes with Meldrum's acid in a domino fashion by Knoevenagel/hetero-Diels–Alder/elimination reactions in a stereoselective way. This domino reaction is a ecologically and economically favorable synthetic entry into a new fused pyranones.

Experimental Section

General Procedure for the Domino Knoevenagel/Hetero-Diels–Alder/Elimination Reactions to form Fused Lactones 6

O- or *N*-prenylated aldehyde **2** (0.64 mmol) and Meldrum's acid (**1**; 0.092 mg, 0.64 mmol) were dissolved in 2 mL of dry acetonitrile. A catalytic amount (10 mol %) of L-proline was added to the reaction mixture and stirred at room temperature for 3 h or refluxed for 1–1.5 h. After complete conversion as monitored by TLC, the solvent was removed and the residue was purified by column chromatography using silica gel (EtOAc:hexane) to give the lactone **6** in good yields.

Characterization data for 6a: yellow solid, mp 139 °C; $[\alpha]_D$: −0.67 (*c* 1, $CHCl_3$); IR: $\nu = 1720\ cm^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.29$ (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 2.12 (td, 1H, $J = 11.3$, 4.5 Hz), 2.34 (dd, 1H, $J = 18.8$ Hz, 11.3 Hz), 2.71 (dd, 1H, $J = 18.8$ Hz, 8.3 Hz), 2.86 (br m, 1H), 3.37 (t, 1H, $J = 11.3$ Hz), 3.84 (s, 1H), 3.87 (d, 1H, $J = 3.77$ Hz), 3.92 (s, 1H), 4.39 (d, 1H, $J = 3.7$ HZ), 5.82 (d, 1H, $J = 3.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 25.9$, 26.0, 26.5, 27.5, 27.6, 28.2, 35.1, 61.3, 75.1, 76.6, 81.9, 83.3, 104.8, 111.7, 169.1; FAB mass: $m/z = 298$ [M^+].

Acknowledgements

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† IICT Communication No: 041022.

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