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A D,L-proline catalyzed diastereoselective trimolecular condensation: an approach to the one-pot synthesis of perhydrofuro[3,2-*b*]pyran-5-ones☆

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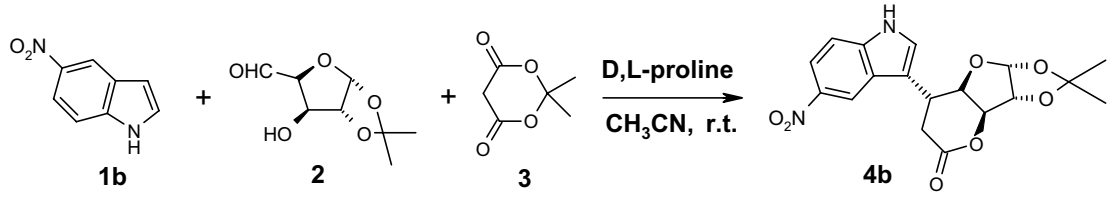
Abstract—D,L-Proline was found to catalyze efficiently the one-pot trimolecular condensation of indoles, a sugar hydroxyaldehyde, and Meldrum's acid followed by intramolecular cyclization with evolution of carbon dioxide and elimination of acetone to afford 7-(1*H*-3-indolyl)-2,3-dimethoxyperhydrofuro[3,2-*b*]pyran-5-ones. The reaction proceeded cleanly at ambient temperature to afford the products in good yields with high diastereoselectivity.

The preparation of substituted tryptophans[1] has been reported using the trimolecular condensation of indoles, with various aldehydes and Meldrum's acid catalyzed by proline under Yonemitsu conditions[2] to give the adducts. Recently we demonstrated the utility of the sugar aldehyde derived from D-glucose for the synthesis of the furopyran core system.[3] To the best of our knowledge, the trimolecular condensation reaction using the chiral sugar aldehyde derived from D-glucose has not been explored, which led us to investigate this reaction. We now report that the organocatalytic trimolecular condensation reaction between indoles **1a**–**g**, the sugar hydroxyaldehyde **2**, and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, **3**) furnishes the 7-(1*H*-3-indolyl)-2,3-dimethoxyperhydrofuro[3,2-*b*]pyran-5-ones **4**[4] as the exclusive products.

The three-component reaction of indole **1b** with sugar hydroxyaldehyde **2** (derived from D-glucose), and Meldrum's acid **3** with a catalytic amount of D,L-proline in acetonitrile at ambient temperature afforded *cis*-fused furo[3,2-*b*]pyranone **4b** as a single isomer in 76% yield (Scheme 1, Table 1, entry 2). We envisioned that proline would catalyze the domino Knoevenagel condensation of the sugar aldehyde **2** with Meldrum's acid **3** to provide the alkylidene derivative of Meldrum's acid, then



Scheme 1.

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Table 1. Trimolecular condensation reactions

Entry	Indoles	Product[a]	Time (days)	Yield[b] (%)
a	Indole	**4a**	2	84
b	5-Nitroindole	**4b**	3	76
c	5-Bromoindole	**4c**	1	81
d	5-Methylindole	**4d**	1	79
e	7-Ethylindole	**4e**	2	75
f	2-Methylindole	**4f**	2	78
g	5-Methoxyindole	**4g**	2	74

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C, and mass spectroscopy.
[b] Isolated yields after column chromatography.

a Michael addition reaction of indole would take place diastereoselectively as a consequence of the adjacent stereocenters to form the adduct. This adduct readily underwent an intramolecular cyclization with evolution of carbon dioxide and elimination of acetone to furnish the furopyranone.

Compound **4** ring system (Scheme 2). The presence of a free hydroxy group on the sugar aldehyde **2** facilitated this extremely facile intramolecular cyclization followed by elimination. The unique 1,3-dioxane-4,6-dione appendage of adducts seemed to help these functional group transformations. This reaction is highly diastereoselective affording exclusively *cis*-fused furo[3,2-*b*]pyranone derivatives with the (*R*) configuration at C-7. The stereochemistry of the product was established by NMR analysis and NOE studies.

The potential of this methodology was extended by demonstrating that the three-component reaction of indoles **1a** and **1c**–**g**, with sugar hydroxyaldehyde **2** and Meldrum's acid **3** catalyzed by D,L-proline in acetonitrile proceeded smoothly to give the corresponding lactones **4a** and **4c**–**g** as single diastereomers in good yields. Noteworthy is the fact that a variety of functional groups were tolerated by these reaction conditions, including nitro and bromo groups. The results are reported in Table 1. All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The structures of the products were further supported by NOE studies (Fig. 1).

The *cis* fusion of the furan ring with the pyran ring in compound **4b** was confirmed by the H3a–7a coupling (J_{3a-7a} = 3.4 Hz) as well as by a strong NOE peak between H3a and H7a. The coupling constants J_{7-7a} =

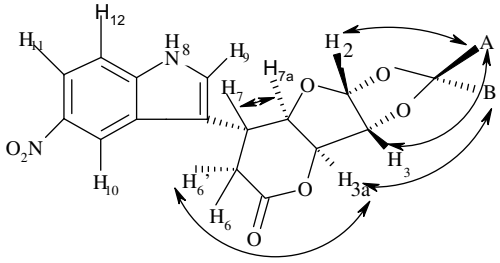
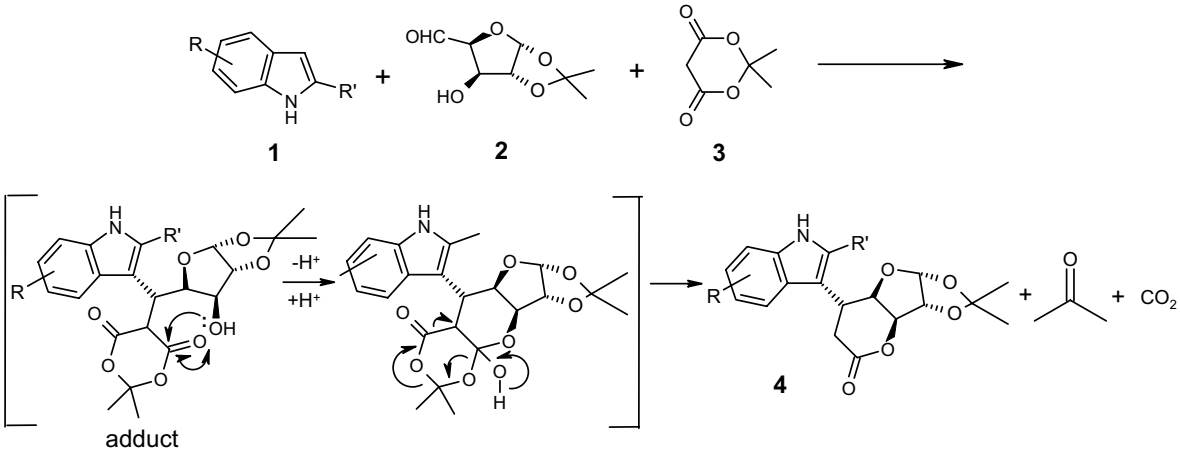
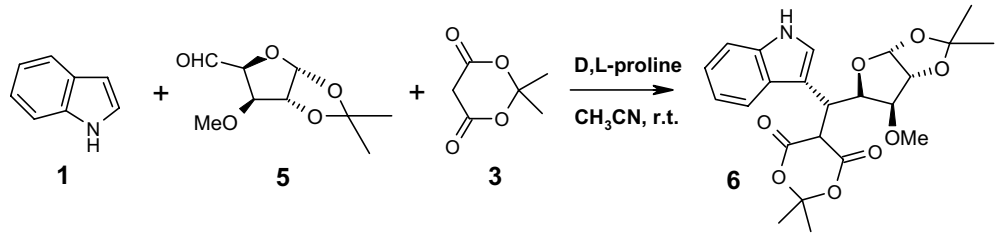


Figure 1. The structure of **4b**, characteristic NOE's.



Scheme 2.



Scheme 3.

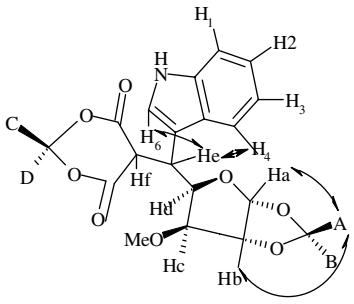


Figure 2. The structure of **6**, characteristic NOE's.

4.6, $J_{6-7} = 4.6$, and $J_{6'-7} = 11.3$ Hz further confirm the (*R*) configuration at C-7. The presence of the NOE cross peak between H3a and H6 supports the boat conformation of the six-membered lactone ring, which is found to be consistent with the couplings.

When the same reaction was carried out using the *O*-protected sugar aldehyde **5** the reaction was found to give the adduct **6** exclusively, as expected (Scheme 3). The structure of the product **6** was confirmed by various 1D and 2D NMR experiments. In the ^{1}H NMR spectrum, the stereocenter at 'C_e' was deduced by using coupling constants and NOE data $J_{d-e} = 10.3$ Hz, $J_{e-f} = 3.0$ Hz, and the NOE cross peaks between H_e and H-4, H_e and H-6 support the configuration at 'C_e' as '*R*' (Fig. 2).

In conclusion, *cis*-fused furo[3,2-*b*]pyranones substituted with indoles have been synthesized in one-pot and in good yields from easily accessible starting materials.

Acknowledgements

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References and notes

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4. *General procedure for the trimolecular condensation of indoles with the sugar hydroxyaldehyde derived from* D-*glucose and Meldrum's acid*: to a solution of indole **1** (0.6 mmol), and Meldrum's acid **3** (0.6 mmol), in CH_3CN (3 mL) freshly prepared sugar hydroxyaldehyde **2** (0.6 mmol) and a catalytic amount of D,L-proline (0.05 equiv) were added. After stirring at room temperature for 1–3 days, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give the corresponding furopyranones **4a**–**g**.
Spectral data for compound **4b**: mp 223–225 °C, $[\alpha]_D^{25}$ −24.3 (*c* 1.25, $CHCl_3$), ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.28 (s, 3H, Me-A), 1.34 (s, 3H, Me-B), 2.78 (dd, $J_{6(pro\text{-}S)-7}$ = 4.6 Hz, $J_{6(pro\text{-}S)-6'(pro\text{-}R)}$ = 15.6 Hz, H-6), 2.98 (dd, $J_{6'(pro\text{-}R)-7}$ = 11.3 Hz, $J_{6'(pro\text{-}R)-6(pro\text{-}S)}$ = 15.6 Hz, H-6′), 3.63 (dt, $J_{6'(pro\text{-}R)-7}$ = 11.3 Hz, $J_{7-6(pro\text{-}S)}$ = 4.6 Hz, J_{7-7a} = 4.6 Hz, H-7), 4.59 (dd, J_{7a-7} = 4.6 Hz, J_{7a-3a} = 3.4 Hz, H-7a), 4.83 (d, J_{2-3} = 4.0 Hz, H-3), 4.98 (d, J_{3a-7a} = 3.4 Hz, H-3a), 5.12 (d, J_{2-3} = 4.0 Hz, H-2), 7.53 (d, J_{9-NH8} = 2.6 Hz, H-9), 7.57 (d, J_{11-12} = 9.0, H-12), 8.02 (dd, J_{11-12} = 9.0 Hz, J_{10-11} = 2.1 Hz, H-11), 8.70 (d, J_{10-11} = 2.1 Hz, H-10), 11.82 (d, J_{NH8-9} = 2.6 Hz, NH-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.4, 140.6, 139.5, 125.9, 125.2, 117.2, 116.9, 115.8, 112.1, 111.3, 104.6, 82.9, 81.6, 79.7, 32.5, 32.3, 26.4, 26.0. IR (KBr): ν_{max} 3442, 2362, 2252, 2126, 1654, 1335, 1027, 824, 762, 626 cm^{-1}. FAB mass: 374 (M^+). Anal. Calcd for $C_{18}H_{17}N_2O_7$: C, 57.75; H, 4.85; N, 7.48%. Found: C, 57.91; H, 4.76; N, 7.57%. *Compound* **6**: gummy material, yield: 86%; $[\alpha]_D^{25}$ −26.8 (*c* 1.5, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 3H, Me-D), 1.24 (s, 3H, Me-A), 1.47 (s, 3H, Me-B), 1.52 (s, 3H, Me-C), 3.44 (s, 3H, –OMe), 3.81 (d, J_{e-f} = 3.0 Hz, 1H, H_f), 3.94 (d, J_{c-d} = 3.3 Hz, 1H, H_c), 4.42 (dd, J_{d-e} = 10.3, J_{e-f} = 3.0 Hz, 1H, H_e), 4.63 (d, J_{b-a} = 3.8 Hz, 1H, H_b), 5.24 (dd, J_{c-d} = 3.3, J_{d-e} = 10.3 Hz, 1H, H_d), 5.79 (d, J_{a-b} = 3.8 Hz, 1H, H_a), 7.01 (t, 1H, J_{3-2} = 7.3 Hz, H-3), 7.04 (t, 1H, J_{2-1} = 7.3 Hz, H-2), 7.08 (br s, 1H, H-6), 7.66 (d, 1H, J_{4-3} = 7.3 Hz, H-4), 8.08 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.3, 135.8, 126.8, 123.4, 122.3, 120.0, 119.9, 112.9, 111.6, 110.9, 105.6, 104.8, 84.2, 81.4, 57.3, 48.8, 36.5, 29.6, 28.3, 28.1, 26.9, 26.5. FAB mass: 445 (M^+). Anal. Calcd for $C_{23}H_{27}NO_8$: C, 59.85; H, 6.46; N, 3.32%. Found: C, 60.01; H, 6.39; N, 3.12%.