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Ugi-type four-component reaction for a novel synthesis of 5-oxo-perhydrofuro[3,2-*b*]pyran carboxylate derivatives

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ABSTRACT

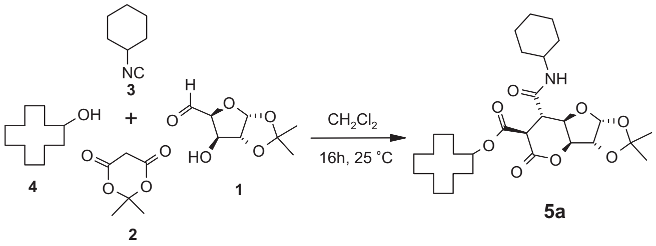
The four-component coupling (4CC) of sugar hydroxyaldehyde, Meldrum's acid, isocyanide, and a secondary alcohol in dichloromethane has been accomplished at room temperature in a highly stereoselective manner to produce a novel class of carbohydrate derivatives, 5-oxo-perhydrofuro[3,2-*b*]pyrans in good yields with *trans*-selectivity. The stereochemistry of the products was assigned by various NMR experiments.

The multi-component reactions are highly important because of their wide range of applications in pharmaceutical chemistry for production of the diversified structural scaffolds and combinatorial libraries for drug discovery.[1] Multi component reactions (MCRs) are extremely convergent, producing a remarkably high increase of molecular complexity in just one step.[2] Among MCRs, those based on the peculiar reactivity of isocyanides, such as the Ugi[3] and the Passerini reactions,[4] have been among the most widely used, also in an industrial context.[5] The ability of isonitriles to undergo facile addition with a nucleophile and an electrophile under mild conditions makes them useful reactants for the development of novel MCRs.[6,7] Recently, a highly functionalized dihydrocoumarin derivatives have been synthesized via a four-component reaction.[8] However, to the best of our knowledge, there are no reports on four-component coupling (4CC) reaction between sugar hydroxyaldehyde, 2,2-dimethyl-1,3-dioxane-4,6-dione, isocyanide, and a secondary alcohol to produce sugar annulated 5-oxo-pyran derivatives.

Following our interest on the synthesis of sugar annulated heterocycles[9] we herein describe a novel multi-component reaction for the synthesis of 5-oxo-perhydrofuro[3,2-*b*]pyran derivatives. Thus, treatment of sugar hydroxyaldehyde (**1**) with Meldrum's acid (**2**), isocyanide (**3**), and cyclododecanol (**4**) in dichloromethane at room temperature gave the product **5a** as a single isomer in 72% yield (Scheme 1).

The structure of **5a** was characterized thoroughly with the help of 2-D rotating frame nuclear Overhauser effect spectroscopy (ROESY) and double quantum filter correlation spectroscopy experiments. $J_{H5-H6} = 12.2$ Hz suggests that the two protons are diaxially disposed with respect to each other, which is further confirmed by exclusive NOE cross-peaks between H6/H3 and H6/H4. Hence C5 and C6 have *S*- and *R*-configuration, respectively. The proximity to H3 and H6 is consistent with the flagpole interaction in the boat conformation of six-membered ring (Figure 1).[10]

Encouraged by the results obtained with cyclohexyl isocyanide and cyclododecanol, we turned our attention to various alcohols and isocyanides. Other isocyanides including 1,1,3,3-tetramethylbutyl isocyanide and *t*-butyl isocyanide participated well in this reaction (Table 1, entries g–i). Similarly, secondary alcohols such as cyclohexanol, tetrahydropyran-4-ol, menthol, cyclopentanol, and isopropanol also gave the desired products in good yields under identical conditions (Table 1, entries b–i). However, in case



Scheme 1. Selective formation of **5a** via four-component reaction.

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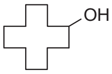
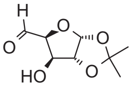
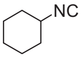
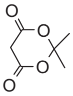
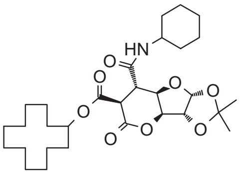
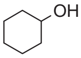
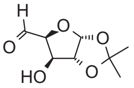
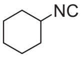
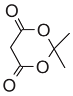
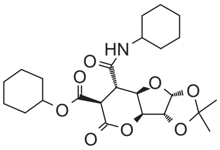
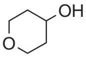
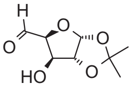
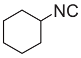
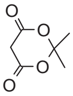
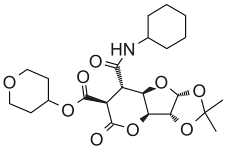
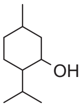
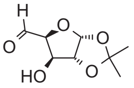
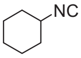
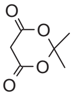
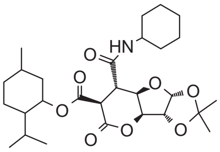
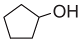
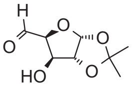
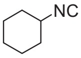
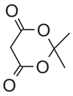
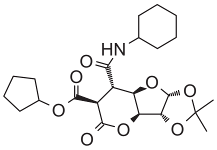
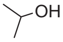
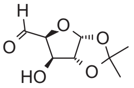
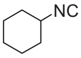
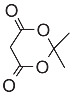
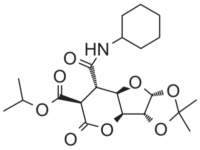
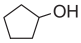
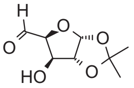
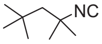
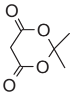
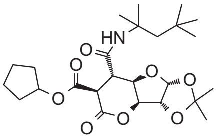
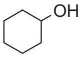
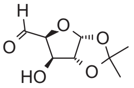
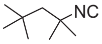
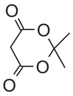
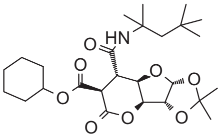
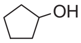
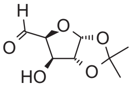
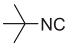
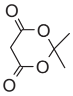
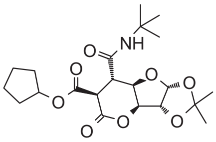
Table 1
Four-component reaction for the synthesis of sugar fused pyrone derivatives

Entry	Alcohol	Aldehyde	Isonitrile	Medium's acid	Product[a] (**5**/**6**)	Time	Yield[b] (%)
a						16.0	72[c]
b						17.0	76 (7:3)[d]
c						20.0	75 (7:3)[d]
d						18.0	70 (1:1)[d]
e						19.0	80 (7:3)[d]
f						17.0	65 (6:4)[d]
g						23.0	77 (6:4)[d]
h						24.0	75 (6:4)[d]
i						18.0	79 (6:4)[d]

[a] The products were characterized by NMR, IR and mass spectroscopy.

[b] Yield refers to pure products after chromatography.

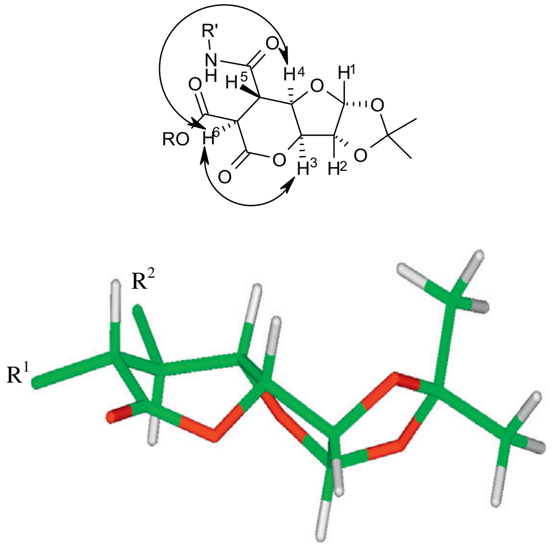
[c] 100% monoester with *trans*-stereochemistry.

[d] Monoester was obtained as a major product.

of secondary alcohols, except cyclododecanol, the products were obtained as a mixture of mono- and diesters **5e** and **6e**, respectively, as depicted in Scheme 2. The structures of mono and diesters were established and confirmed by ^{1}H NMR and HRMS.

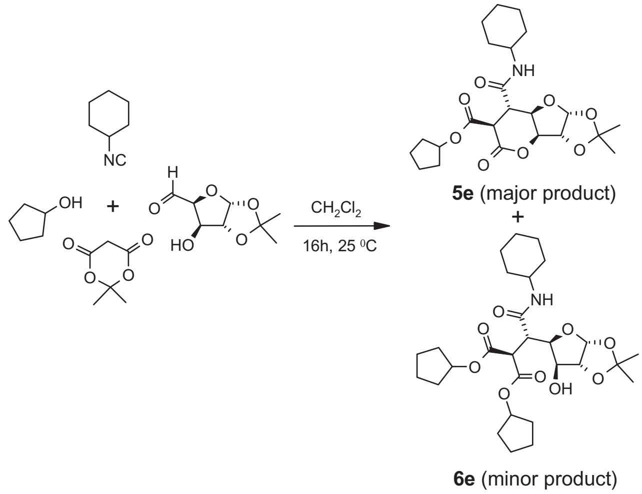
In addition to **5a**, the structure of **5e** was also established by NOE experiments. The chemical shifts in the coumarin ring of **5e** were very similar to those of **5a**, suggesting small perturbation due to change of the side chain. $^3J_{H5-H6} = 12.0$ Hz suggests that H5 and H6 are oriented diaxially with respect to each other, which is further supported by NOE cross-peaks between H6/H3 and H6/H4, similarly to **5a**. Hence C5 and C6 have same configuration as in **5a**.

The mono- and diesters could easily be separated by column chromatography. It is noteworthy to mention that the ratio of mono- and diesters was decreased as increasing the steric hindrance of the alcohol (Table 1). Notably, secondary alcohols are



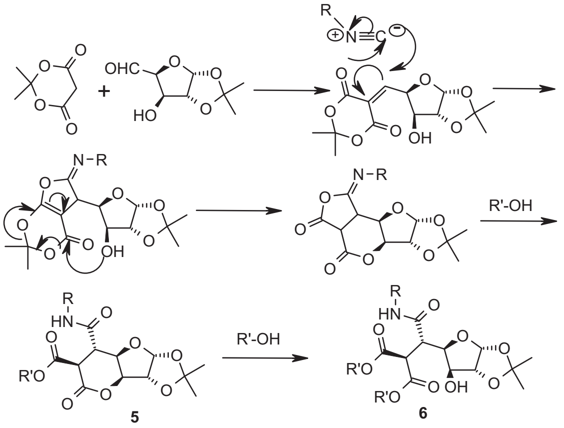
$R^1 = C_{13}H_{23}O_2$; $R^2 = C_7H_{12}NO$

Figure 1. Charteristic NOE's and energy minimized structure of **5a**.



Scheme 2. Formation of both mono-**5e** and diesters **6e** via four-component reaction.

more effective than primary ones for this reaction. The reactions are so sluggish with primary alcohols such as methanol, ethanol, and benzyl alcohol. Furthermore, phenols also failed to give the desired product under these conditions. As a solvent, dichloromethane appeared to give the best results. In all cases, the reactions proceeded at room temperature in dichloromethane and the corresponding products were obtained in good yields. A variety of functional groups such as cyclic acetal, ester, amide, and lactone are well-tolerated. Mechanistically, we assume that a conjugated electron-deficient alkylidene derivative may be formed from sugar hydroxyaldehyde and Meldrum's acid by means of Knoevenagel reaction. Then a Michael addition of isocyanide would take place diastereoselectively as a result of the adjacent stereogenic centers to give iminolactone. This adduct simultaneously undergo intramolecular cyclization with hydroxyl group of sugar to give bis-lactone with concomitant loss of acetone. Eventual alcoholysis of iminolactone with a secondary alcohol gave the desired product **5** as depicted in Scheme 3.



Scheme 3. A plausible reaction mechanism.

In case of sterically less hindered alcohols, the product **5** underwent further alcoholysis to give the diester **6** as a minor product (Scheme 2). This method doesn't require any activators or promoters. The scope and generality of the reaction are illustrated with respect to various alcohols and isocyanides and the results are presented in Table 1.[11]

In summary, we have developed a novel four-component reaction for the synthesis of highly functionalized perhydrofuro[3,2-*b*]pyran-5-one derivatives from readily available precursors under neutral conditions. It is entirely a new strategy to produce ester, amide, and lactone ring system in a single-step operation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.083.

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11. *Typical procedure*: A mixture of sugar hydroxyaldehyde (188 mg, 1 mmol) and Meldrums' acid (144 mg, 1 mmol) was stirred in dichloromethane (5 mL) for

30 min at room temperature and then cyclohexylisocyanide (109 mg, 1 mmol) followed by cyclopentanol (86 mg, 1 mmol) was added at room temperature. After complete conversion, as monitored by TLC, the mixture was concentrated in vacuo and purified by column chromatography using ethyl acetate–hexane (1:9) as eluent to afford pure product. *Spectral data for the selected compounds*: **5a**: solid, mp 184–190 °C. IR (KBr): ν_{max} 3342, 2932, 2858, 1769, 1668, 1542, 1329, 1290, 1164, 1078, 1011 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (d, J = 3.7 Hz, 1H), 5.71 (d, J = 8.3 Hz, NH), 5.12–5.07 (m, 1H), 4.77 (d, J = 3.7 Hz, 1H), 4.67 (d, J = 3.3 Hz, 1H), 4.63 (t, J = 3.4 Hz, 1H), 3.75–3.68 (m, 1H), 3.63 (d, J = 12.2 Hz, 1H), 3.04 (dd, J = 3.4, 12.2 Hz, 1H), 2.00–1.00 (m, 32H), 1.54 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 167.1, 166.7, 112.7, 104.6, 96.0, 82.7, 81.8, 76.1, 74.7, 48.8, 47.5, 45.3, 32.6, 32.5, 29.7, 28.7, 26.6, 26.1 25.3, 24.6, 23.8, 23.6, 23.2, 23.1, 23.0, 22.9, 20.6, 20.6. LC–MS: *m/z*: 550 (M+H). HRMS calcd for $C_{30}H_{47}NO_8Na$ (M+Na): 572.3199. Found: 572.3223. **5c**: liquid, IR (KBr): ν_{max} 3340, 2925, 2855, 1767, 1667, 1542, 1454, 1376, 1207, 1029, 891 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (d, J = 3.7 Hz, 1H), 5.81 (d, J = 7.5 Hz, NH), 5.08–4.97 (m, 1H), 4.74 (d, J = 3.7 Hz, 1H), 4.65 (d, J = 3.0 Hz, 1H), 4.58 (t, J = 3.7 Hz, 1H), 3.95–3.82 (m, 1H), 3.68 (d, J = 12.0 Hz, 1H), 3.04 (dd, J = 4.5, 12.8 Hz, 1H), 2.00–1.50 (m, 18H), 1.49 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 167.1, 166.8, 112.7, 104.7, 82.7, 81.8, 76.1, 48.8, 47.2, 45.3, 32.6, 32.4, 32.4, 31.9, 29.7, 29.3, 26.6, 26.1, 25.3, 24.6, 23.6, 22.7. LC–MS: *m/z*: 490 (M+Na). HRMS calcd for $C_{23}H_{33}NO_9Na$ (M+Na): 490.2053. Found: 490.2068. **5e**: liquid, IR (KBr): ν_{max} 3329, 2928, 2855, 1739, 1660, 1542, 1454, 1378, 1225, 1163, 1025, 865 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (d, J = 8.3 Hz, NH), 5.91 (d, J = 3.8 Hz, 1H), 5.27–5.23 (m, 1H), 4.75 (d, J = 3.7 Hz, 1H), 4.68 (d, J = 3.0 Hz, 1H), 4.56 (t, J = 3.0 Hz, 1H), 3.77–3.70 (m, 1H), 3.68 (d, J = 12.0 Hz, 1H), 3.04 (dd, J = 3.8, 12.0 Hz, 1H), 2.00–1.58 (m, 18H), 1.49 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 167.1, 166.4, 112.7, 104.7, 82.7, 81.8, 76.3, 64.9, 48.8, 47.1, 45.2, 32.7, 32.6, 31.9, 31.2, 31.1, 29.6, 29.3, 26.6, 26.1, 25.2, 24.6. LC–MS: *m/z*: (M+H) 452. HRMS calcd for $C_{23}H_{33}NO_8$ (M+H): 452.2284. Found: 452.2296. **6e**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.30 (d, J = 8.1 Hz, NH), 5.90 (d, 1H, J = 3.7 Hz, C_1H), 5.23–5.15 (m, 2H), 4.49 (d, 1H, J = 3.7 Hz, C_2H), 4.30 (dd, 1H, J = 2.3, 8.3 Hz, C_4H), 4.21 (d, 1H, J = 8.3 Hz, C_6H), 3.90 (d, 1H, J = 2.3 Hz, C_3H), 3.75–3.65 (m, 1H, OH), 3.35 (t, 1H, J = 8.3 Hz, C_5H), 2.00–1.00 (m, 26H), 1.45 (s, 3H, CH_3), 1.35 (s, 3H, CH_3'). HRMS calcd for $C_{28}H_{43}NO_9$ (M+H): 538.2998. Found: 538.3086.