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# Towards the synthesis of *C*-glycosylated dihydropyrimidine libraries via the three-component Biginelli reaction. A novel approach to artificial nucleosides

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**Abstract**—The Lewis acid catalyzed ($BF_3{\cdot}Et_2O$, CuCl, AcOH) one-pot three-component cyclocondensation of urea with *C*-glycosylated aldehydes and β-keto esters (Biginelli reaction) in a combinatorial manner afforded three different series of 3,4-dihydropyrimidin-2(1*H*)-ones bearing *C*-glycosyl moieties at C4, C6, and at both C4 and C6. 

The Biginelli reaction is constituted by a one-pot acid-catalyzed condensation of an aldehyde, a β-ketoester and an urea leading to 3,4-dihydropyrimidin-2-(1*H*)-one (DHPM) (Fig. 1). In the last decade, this three-component reaction has become the center of increasing attention[1] since it permits a rapid access to combinatorial libraries of DHPMs as well as their sulphur analogues using both solution and solid-phase reaction techniques.[2] Improved procedures with different types of catalysts[3] and conditions[4] have been reported with the aim of overcoming the main drawback of the Biginelli reaction, which is represented by the modest yields. The considerable interest in DHPM-type products relies on their structural similarity to dihydropyridines (DHP), a class of compounds showing remarkable pharmacological properties as calcium channel antagonists and which are extensively used as therapeutics in the clinical treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina pectoris.[5] Dihydropyrimidinone derivatives (DHPMs) show similar biological activity.[6]

It appeared to us of some interest to explore a route for the creation of a small library of a hitherto scarcely investigated class of dihydropyrimidinones, such as their *C*-glycosyl derivatives.[7] Attractive aspects of these Biginelli compounds lie in an expected increase in bioavailability and water solubility and in the generation of new families of *C*-nucleosides, i.e. carbon-linked glycoside analogues of N-linked natural products.

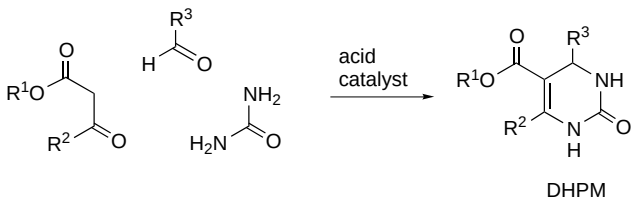
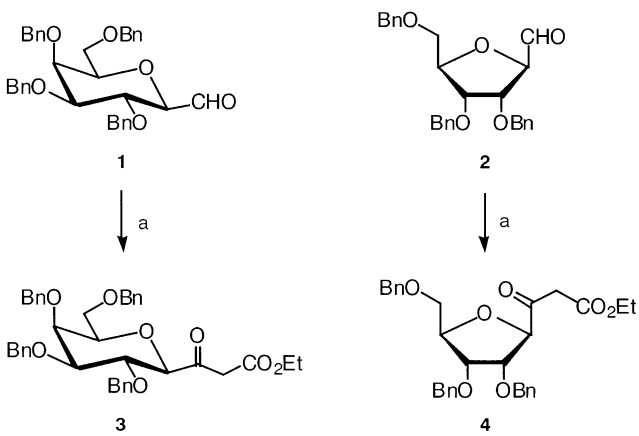



**Figure 1.** The Biginelli cyclocondensation reaction leading to a dihydropyrimidine (DHPM) framework.




**Scheme 1.** Synthesis of *C*-glycosyl β-keto esters **3** and **4**. (a) Ethyl diazoacetate ($HC(N_2)CO_2Et$), $BF_3{\cdot}Et_2O$, 4 Å MS, $CH_2Cl_2$, 0°C, 10 min.

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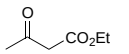
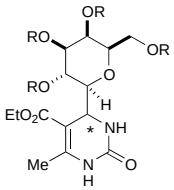
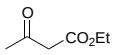
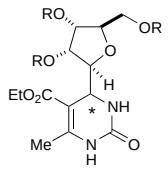
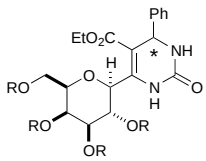
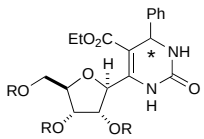
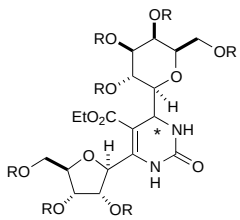
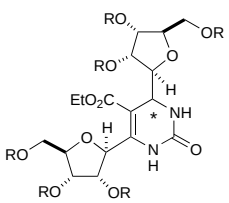
Various anomeric sugar aldehydes (formyl *C*-glycosides) which we need in this program are accessible starting from sugar lactones through our thiazole-based formylation method.[8] The stable β-linked galactopyranoside derivative **1** and ribofuranoside derivative **2** were selected in this initial study.[9] The hitherto unreported *C*-galactopyranosyl and *C*-ribofuranosyl β-keto esters **3** and **4** were obtained in satisfactory yield (60–75%) by $BF_3{\cdot}Et_2O$ promoted coupling of the corresponding aldehydes **1** and **2** with ethyl diazoacetate according to a literature procedure (Scheme 1).[10]

As a model reaction, the cyclocondensation of the sugar aldehyde **1**, ethyl acetoacetate, and urea (1:1:1.5 ratio) in THF at 65°C (molecular sieves) was efficiently promoted by CuCl (1.0 equiv.),[11] $BF_3{\cdot}Et_2O$ (1.3 equiv.) and AcOH (0.2 equiv.) to give after 24 h the *C*-galactosyl DHPM derivatives **5a** as a mixture of diastereomers in a 5:1 ratio and 60% overall yield (Table 1).[12] A similar result was obtained with the use of equimolar ytterbium triflate as a promoter.[3b] After separation by chromatography each individual stereoisomer gave consistent $^1H$, $^{13}C$ NMR, and MS spectral data. The β-linkage at the anomeric carbon of the sugar fragment was confirmed for both compounds by NOE experiments, thus indicating that the stereochemical integrity at C2 of the aldehyde **1** has been retained during the three-component cyclocondensation. On the other hand, the absolute configuration at the newly created C4 stereocenter of the DHPM ring still remains to be established. While this assignment is unimportant in the context of the present study, this goal is actively pursued by attempts to obtain suitable derivatives for X-ray crystal analysis. Nevertheless the removal of the *O*-benzyl groups from the sugar moiety was proven by hydrogenation ($H_2$, $Pd(OH)_2$) of the mixture of the two stereoisomers affording the *C*-galactosyl DHPM derivatives **5b** in almost quantitative yield.[13,14] The above reaction sequence was repeated starting from the ribofuranoside aldehyde **2** to give the *C*-ribofuranosyl derivatives **6a** and **6b** in comparable yields.[12,14] Under the same reaction conditions and the use of the CuCl, $BF_3{\cdot}Et_2O$, AcOH mixture as a promoter, the reactions of the sugar keto esters **3** and **4** with benzaldehyde and urea were carried out resulting in the corresponding C6 glycosylated DHMPs **7a** and **8a** as mixtures of diastereomers in very good overall yields (Table 1).[12] Subsequent catalytic hydrogenation of each mixture afforded the corresponding debenzylated products **7b** and **8b**.[14] Compounds **5**–**8** represent a new class of *C*-nucleosides featuring a C4- or C6-linked DHPM ring. Of course the ribofuranosyl derivatives **6** and **8** are quite attractive as analogues of numerous natural *N*-nucleosides of biological relevance.[15] Finally, cyclocondensation reactions were carried out with two sugar components, i.e. the aldehydes **1** and **2** and the keto ester **4**, giving rise to the bis-*C*-glycosylated Biginelli products **9a** and **10a** as mixtures of diastereomers,[12] which in turn were transformed into the corresponding debenzylated products **9b** and **10b** by hydrogenation.[14] Compounds **9** and **10** constitute another novelty in this work since they can be viewed as bis-*C*-nucleosides. While it is reasonable that the yields of these coupling

**Table 1.** *C*-Glycosylated Biginelli products prepared from various aldehydes, β-keto esters and urea[a]

| aldehyde | β-keto ester | product, **5**-**10** | yield, ratio of diastereomers[b] |
|---|---|---|---|
| **1** |  |  **5a**, R = Bn **5b**, R = H | 60%, 5:1 |
| **2** |  |  **6a**, R = Bn **6b**, R = H | 63%, 3:1 |
| Ph-CHO | **3** |  **7a**, R = Bn **7b**, R = H | 75%, 5:1 |
| Ph-CHO | **4** |  **8a**, R = Bn **8b**, R = H | 92%, 3:1 |
| **1** | **4** |  **9a**, R = Bn **9b**, R = H | 35%, 10:1 |
| **2** | **4** |  **10a**, R = Bn **10b**, R = H | 42%, 9:1 |

[a] Reagents and conditions : Aldehyde, β-Keto Ester, Urea, CuCl, $BF_3.Et_2O$, AcOH, 4-Å MS, 65 °C,12-24h. [b] Overall yield of mixture of isolated perbenzylated diastereomers; ratio of diastereomers determined by $^1H$-NMR analysis.

reactions employing two complex and bulky partners were rather modest (Table 1), it is quite rewarding that the levels of diastereoselectivity were much higher than in the above more simple cases. Evidently the two sugar components match quite well in the creation of the DHPM C4 stereocenter with a preferred configuration. Hence, while the vast majority of examples of Biginelli reaction involves the use of achiral reagents and enantiomerically pure products have been obtained by chemical or enzymatic resolution of racemic mixtures,[16] the results of the present study indicate a viable route toward the asymmetric synthesis of the DHPM ring system, a prerequisite for the development of useful drugs having this structural motif.[17]

In conclusion, it appears to be demonstrated that the three-component Biginelli reaction can be applied to the synthesis of different mono- and bis-*C*-glycosylated DHPMs. Given the availability of various sugar aldehydes and keto esters, the access to a combinatorial library of glycosylated Biginelli products with a wide range of structural and stereochemical elements of diversity for an extensive exploration of biological properties now becomes of interest.

## Acknowledgements

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## References

1. For a recent review, see: Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
2. (a) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49; (b) Kappe, C. O.; Falsone, S. F.; Fabian, W. M. F.; Belaj, F. *Heterocycles* **1999**, *51*, 77; (c) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520.
3. (a) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270; (b) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864; (c) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
4. Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1363.
5. For an updated list of leading references on this topic, see: Jauk, B.; Belaj, F.; Kappe, C. O. *J. Chem. Soc., Perkin Trans 1* **1999**, 307.
6. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806 and references cited therein; (b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629.
7. We are aware of a few reports dealing with the use of rather simple sugar aldehydes (2,3-*O*-isopropylidene-D-glyceraldehyde, 2,4-*O*-ethylidene-D-threose and D-erythrose, 2,5-anhydro-*aldehydo*-D-xylose) in the Biginelli reaction. See: (a) Fernàndez, M. V.; Herrera, F. J. L.; Cobos, T. L. *Heterocycles* **1988**, *27*, 2133; (b) Fernàndez, M. V.; Herrera, F. J. L.; Cobos, T. L. *Heterocycles* **1986**, *24*, 679; (c) Sastre, J. A. L.; Molina, J. M. *An. Quim.* **1978**, *74*, 353.
8. (a) Dondoni, A. *Pure Appl. Chem.* **2000**, *72*, 1577; (b) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404.
9. It has to be noted that the β-D-configured formyl *C*-ribofuranoside **2** was erroneously reported (Ref. 8b) to be the α-isomer. For a revision, see: Dondoni, A.; Formaglio, P.; Marra, A.; Massi, A. *Tetrahedron*, submitted.
10. Dhavale, D. D.; Bhujbal, N. N.; Joshi, P.; Desai, S. G. *Carbohydr. Res.* **1994**, *263*, 303. **3**: $[\alpha]_D^{20}=+22$ ($c=0.9$, $CHCl_3$); **4**: $[\alpha]_D^{20}=+81$ ($c=0.6$, $CHCl_3$).
11. The use of catalytic CuCl as described in Ref. 3c afforded the Biginelli product in much lower yield (ca. 30%). It is likely that the presence of powdered 4 Å molecular sieves, serving as acid sponge, interfered with the action of the heterogeneous promoter.
12. **5a** (major): $[\alpha]_D^{20}=-101$ ($c=1.2$, $CHCl_3$). **5a** (minor): $[\alpha]_D^{20}=+30$ ($c=0.9$, $CHCl_3$). **6a** (major): mp 147–148°C (from isopropyl ether–EtOAc); $[\alpha]_D^{20}=-65$ ($c=0.3$, $CHCl_3$). **6a** (minor): $[\alpha]_D^{20}=+41$ ($c=1.2$, $CHCl_3$). **7a** (major): $[\alpha]_D^{20}=+73$ ($c=0.9$, $CHCl_3$). **7a** (minor): $[\alpha]_D^{20}=-3$ ($c=0.3$, $CHCl_3$). **8a** (major): $[\alpha]_D^{20}=+139$ ($c=1.6$, $CHCl_3$). **8a** (minor): $[\alpha]_D^{20}=+25$ ($c=0.9$, $CHCl_3$). **9a** (major): $[\alpha]_D^{20}=-62$ ($c=1.1$, $CHCl_3$). **9a** (minor): $[\alpha]_D^{20}=-10$ ($c=0.3$, $CHCl_3$). **10a** (major): $[\alpha]_D^{20}=+6$ ($c=1.0$, $CHCl_3$). **10a** (minor): $[\alpha]_D^{20}=+75$ ($c=0.4$, $CHCl_3$).
13. Only the major stereoisomers of *C*-glycosyl DHPMs **5b**–**10b** were isolated and characterized.
14. **5b** (major): $[\alpha]_D^{20}=-117$ ($c=0.9$, MeOH); MALDI-TOF MS: 347.0 ($M^+$+H), 353.5 ($M^+$+Li), 369.5 ($M^+$+Na), 385.8 ($M^+$+K). **6b** (major): mp 264–266°C (from $H_2O$); $[\alpha]_D^{20}=-148$ ($c=0.2$, $H_2O$); MALDI-TOF MS: 340.0 ($M^+$+Na), 356.0 ($M^+$+K). **7b** (major): $[\alpha]_D^{20}=+63$ ($c=0.4$, MeOH); MALDI-TOF MS: 409.6 ($M^+$+H), 415.6 ($M^+$+Li), 431.7 ($M^+$+Na), 448.3 ($M^+$+K). **8b** (major): $[\alpha]_D^{20}=+59$ ($c=1.5$, MeOH); MALDI-TOF MS: 379.8 ($M^+$+H), 386.1 ($M^+$+Li), 402.1 ($M^+$+Na), 418.2 ($M^+$+K). **9b** (major): $[\alpha]_D^{20}=-44$ ($c=0.7$, MeOH); MALDI-TOF MS: 471.8 ($M^+$+Li), 487.7 ($M^+$+Na), 503.9 ($M^+$+K). **10b** (major): $[\alpha]_D^{20}=-73$ ($c=1.3$, MeOH); MALDI-TOF MS: 441.8 ($M^+$+Li), 458.6 ($M^+$+Na).
15. (a) Hunziker, J.; Leumann, C. In *Modern Synthetic Methods* 1995; Ernst, B.; Leumann, C., Eds.; VCH: Basel, 1995; p. 333; (b) Wilson, L. W.; Hager, M. W.; El-Kattan, Y. A.; Liotta, D. C. *Synthesis* **1995**, 1465; (c) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K.; Baker, D. C., Eds.; Plenum Press: New York, 1993; (d) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745; (e) Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903.
16. Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K.; Kappe, C. O. *Tetrahedron: Asymmetry* **2000**, *11*, 1449.
17. Rovnyak, G. C.; Kimbal, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.