A Facile Synthesis of (Imidazo[1,2-*a*]pyrimidin-2-yl)sugars by a Modified Maillard Reaction

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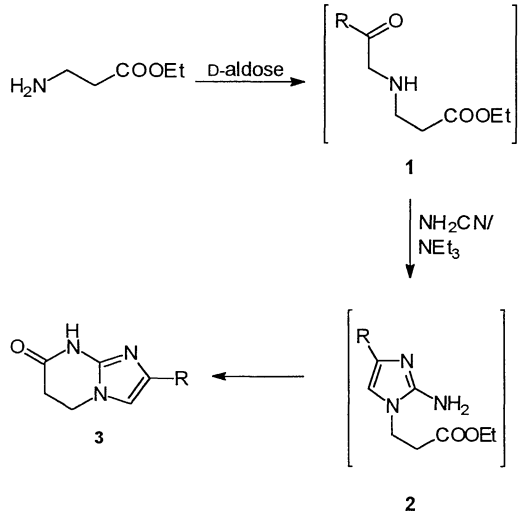
(5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-on-2-yl)-sugars are easily prepared in a one-pot synthesis in basic ethanolic solutions from ethyl β-alaninate, D-aldoses and cyanamide in 21-48% yield.

C-2 and C-4 linked imidazolosugars[1] are important building blocks for the preparation of imidazole *C*-nucleosides[2] and some glycosidase inhibiting imidazosugars like Nagstatin and its analogs.[3] In addition, a recently isolated natural antibiotic CV-1 produced by a strain of *Streptomyces* sp. was also found to possess an imidazole ring substituted with a glucose-derived polyolic side chain.[4]

Several synthetic approaches have been developed during the last decades for the preparation of monocyclic imidazolosugars[3,5,6] but to the best of our knowledge no simple syntheses of their bicyclic analogs suitable for the preparation of polycyclic azasugars have been described so far.

In this communication we would like to report a simple, one-pot synthesis of (imidazo[1,2-*a*]pyrimidin-7(8*H*)-on-2-yl)sugars[7] **3** from ethyl β-alaninate, D-aldoses and cyanamide applying the modified conditions of the Maillard reaction.[8] The formation of **3** can be explained by a two-step cyclization process of the primarily formed 1-amino-1-deoxy-2-ketoses (Amadori compounds) **1**, with cyanamide; the initial formation of the aminoimidazole[9] **2** being followed by formation of a lactam (pyrimidinone) ring as shown below.



R = $(CHOH)_nCH_2OH$
n = 2 (from D-aldopentoses)
n = 3 (from D-aldohexoses)

In a typical experiment a mixture of ethyl β-alaninate hydrochloride (10 mmol) and equimolar amounts of D-aldose and triethylamine were heated under reflux in absolute ethanol (20-25 ml) for one hour. Cyanamide (14 mmol) and additional triethylamine (2-3 ml) were added to the reaction mixture and heating was continued for the time indicated in Table 1. The resulting (5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-on-2-yl)sugars **3** were precipitated as TLC pure products after cooling the reaction mixtures to the room temperature.

Table 1. Synthesis of (5,6,7,8-tetrahydroimidazo[1,2-*a*]-pyrimidin-7(8*H*)-on-2-yl)sugars under modified Maillard conditions

starting aldose	reaction time (h)[a]	relative configuration of R in **3**	yield (%)[b]
D-glucose			48
	0.75	D-*arabinotetritol-1-yl* (**3a**)	
D-mannose			43
D-galactose	4	D-*lyxotetritol-1-yl* (**3b**)	40
D-arabinose			22
	2	D-*erythrotriitol-1-yl* (**3c**)	
D-ribose			21

[a] After addition of cyanamide. [b] Unoptimized isolated yields of TLC pure products.

The products **3** prepared by this reaction sequence are summarized in Table 1. All new compounds gave satisfactory analytical and spectroscopic data for the proposed bicyclic structures **3** .[10] The observed chemical shifts and coupling constants of protons and carbon atoms from the sugar-derived polyolic side chains in imidazo[1,2-*a*]pyrimidin-7(8*H*)-ones **3** are in good agreement with those reported for monocyclic imidazolosugars.[3,6] The ^1H and ^{13}C NMR spectra of the compound **3c** were assigned on the basis of 2D $^1H/^{13}C$ HMQC and HMBC NMR experiments. As it could be expected from the structure of the intermediate Amadori compounds **1**, the same products[11] were obtained from the C-2 epimeric D-aldoses.

Although a variety of heterocyclic compounds were characterized as degradation products of Amadori compounds during the Maillard reaction, almost none of these reactions are synthetically applicable because of very low yields (< 5%) and a variety of different products obtained.[12] However, when the reaction of ethyl β-alaninate with D-aldoses was monitored by TLC it was found that aldoses were almost quantitatively consumed giving predominantly one product (pressumably the Amadori compounds **1**) before addition of cyanamide. Further reaction with cyanamide resulted in the formation of imidazo[1,2-*a*]pyrimidin-7(8*H*)-ones **3** as main products; the TLC of the reaction mixture after precipitation of **3** indicated the presence of several browning products which were not isolated but could be attributed to the complex degradation pathways of the Amadori compounds during late stages of the Maillard reaction.[12]

In conclusion, the present modification of the Maillard reaction in basic ethanolic solution gives (imidazo[1,2-*a*]-pyrimidin-7(8*H*)-on-2-yl)sugars **3** with preparatively useful yields from inexpensive starting materials in a simple reaction sequence.

Further studies of the syntheses of tricyclic azasugars by

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cyclizations of the polyolic side chain in compounds **3** onto the imidazole ring as well as the extensions of the methodology described herein to esters of α-amino acids are in progress.

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References and Notes

1 A term "imidazolosugar" refers to imidazoles substituted with a sugar-derived polyolic chain (see Ref. 6), and a term "imidazosugar" refers to bicyclic or polycyclic azasugars containing a fused imidazole ring according to the nomenclature of fused heterocyclic systems.

2 S. Harusawa, Y. Murai, H. Moriyama, H. Ohishi, R. Yoneda, and T. Kurihara, *Tetrahedron Lett.*, **36**, 3165 (1995) and references cited therein.

3 K. Tatsuta, S. Miura, S. Ohta, and H. Gunji, *Tetrahedron Lett.*, **36**, 1085 (1995).

4 T. Yasuzawa, M. Yoshida, M. Ichimura, K. Shirahata, and H. Sano, *J. Antibiot.*, **40**, 727 (1987).

5 See, for example: J. P. Ferris, S. S. Badesha, W. Y. Ren, H. C. Huang, and R. J. Sorcek, *J. Chem. Soc., Chem. Commun.*, **1981**, 110.

6 J. Streith, A. Boiron, A. Frankowsky, D. Le Nouen, H. Rudyk, and T. Tschamber, *Synthesis*, **1995**, 944, and references cited therein.

7 According to the recommended IUPAC nomenclature compounds **3** should be named as 2-(triitol-1-yl)- and 2-(tetritol-1-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrimidin-7(8*H*)-ones.

8 As a "Maillard reaction" are usually regarded non-enzymatic sugar-amine transformations in aqueous media at physiological *p*H.

9 A similar cyclization between aminoacetaldehyde diethyl acetal and cyanamide resulted in the formation of 2-amino-imidazole; see : A. Lawson, *J. Chem. Soc.*, **1956**, 307.

10 Characterized by ^{1}H and ^{13}C NMR, IR, FABMS or EIMS and elemental analyses. **3a**: mp 249-251 ^{0}C (dec.) (from EtOH/H_2O), $[\alpha]_D^{24}$ -19.8 (± 0.5) (*c* 2.09 in 0.25M HCl), ^{1}H NMR (300 MHz, DMSO-d_6) δ/TMS 2.68 (t, *J*= 7.2 Hz, 2H), 3.40 (ddd, *J*= 10.6, 5.7, 2.4 Hz, 1H), 3.50 (m, 2H), 3.59 (ddd, *J*= 10.6, 5.7, 4.2 Hz, 1H), 4.00 (t, *J*= 7.2 Hz, 2H), 4.26 (t, *J*= 5.7 Hz, 1H), 4.31 (d, *J* = 6.0 Hz, 1H), 4.53 (d and m, *J*= 6.6 Hz, 2H), 4.60 (d, *J*= 6.5 Hz, 1H), 6.70 (s, 1H), 10.88 (br. s, 1H); br. singlet at 10.88 ppm (NH), dublets at 4.31, 4.53, 4.60 ppm and triplet at 4.26 are excheangable with D_2O (protons from the OH groups). ^{13}C NMR δ 30.6, 39.0, 63.5, 66.8, 71.3, 73.9, 112.2, 140.6, 141.3, 167.6. IR (KBr)/cm^{-1}: 3500-3000, 2900, 1670, 1540, 1310, 1080, 1020. EIMS (*m/e*, %): 257 (M^+, 2). Anal.: Calcd. for $C_{10}H_{15}N_3O_5$: 46.69 %C, 5.88 %H, 16.34 %N. Found: 46.55 %C, 5.76 %H, 16.38 %N. **3b**: mp 181-3 ^{0}C (from EtOH/H_2O), $[\alpha]_D^{24}$ -3.0 (± 0.5) (*c* 1.71 in H_2O), ^{1}H NMR (300 MHz, D_2O) δ/TSPD_4 2.57 (t, *J*= 7.4 Hz, 2H), 3.57 (m, 2H), 3.74 (dd, *J*= 7.9, 2.3 Hz, 1H), 3.85 (ddd, *J*= 9.5, 7.3, 2.3 Hz, 1H), 3.91 (t, *J*= 7.4 Hz, 2H), 4.47 (d, *J*= 7.9 Hz, 1H), 6.69 (s, 1H). ^{13}C NMR δ 29.7, 39.8, 63.3, 67.6, 70.5, 72.3, 114.3, 136.8, 146.3, 174.6. IR (KBr)/cm^{-1}: 3600-3000, 2940, 1700, 1600, 1580, 1550, 1050. EIMS (*m/e*, %): 257 (M^+, 2). Anal.: Calcd. for $C_{10}H_{15}N_3O_5$: 46.69 %C, 5.88 %H, 16.34 %N. Found: 46.52 %C, 5.93 %H, 16.43 %N. **3c**: mp 201-2 ^{0}C, (from EtOH/H_2O) $[\alpha]_D^{24}$ +3.8 (± 0.5) (*c* 2.12 in H_2O), ^{1}H NMR (300 MHz, D_2O) δ/TSPD_4 2.46 (t, *J*= 7.4 Hz, 2H, both H_6), 3.50 (dd, *J*= 11.9, 6.8 Hz, 1H, one $H_{3'}$), 3.68 (dd, *J*= 11.9, 3.2 Hz, 1H, one $H_{3'}$), 3.82 (m, 1H, $H_{2'}$), 3.84 (t, *J*= 7.4 Hz, 2H, both H_5), 4.40 (d, *J*= 6.8 Hz, 1H, $H_{1'}$), 6.61 (s, 1H, H_3). ^{13}C NMR δ 29.7(C-6), 39.8(C-5), 62.7(C-3'), 68.5(C-1'), 73.6(C-2'), 114.0(C-3), 136.4(C-2), 147.0(C-8a), 174.9 (C-7). IR (KBr)/cm^{-1}: 3500-3000, 2920, 1680, 1590, 1570, 1540, 1110, 1030. FABMS (*m/e*, %): 228 (MH^+, 28), Anal.: Calcd. for $C_9H_{13}N_3O_4$: 47.57 %C, 5.77 %H, 18.49 %N. Found: 47.82 %C, 5.80 %H, 18.84 %N.

11 Identical in all respects (mp, mixed mp, optical rotation and NMR).

12 For recent reviews on the chemistry of the Maillard reaction, see: R. Ikan (Ed.), "*The Maillard Reaction*", J. Wiley, New York (1996); F. Ledl and E. Schleicher, *Angew. Chem.*, **102**, 597 (1990); F. Ledl, J. Beck, M. Sengl, H. Osiander, S. Estendorfer, T. Severin, and B. Huber, *Prog. Clin. Biol. Res.*, **304**, 23 (1989).