Benzimidazoles from D-glucose derivatives

M. Soledad Pino-Gonzalez *, Inmaculada Martín-Torres

Departamento de Quimica Orgánica, Universidad de Málaga, 29071, Málaga, Spain
pino@uma.es

Abstract

Benzimidazole derivatives are compounds of great interest by their applications as pharmaceuticals, exhibiting a variety of biological applications. However, few samples of benzimidazoles linked to monosaccharides are described. Herein, we report the synthesis of benzimidazoles from D-glucose derivatives.

Keywords

benzimidazole, D-glucose

Introduction

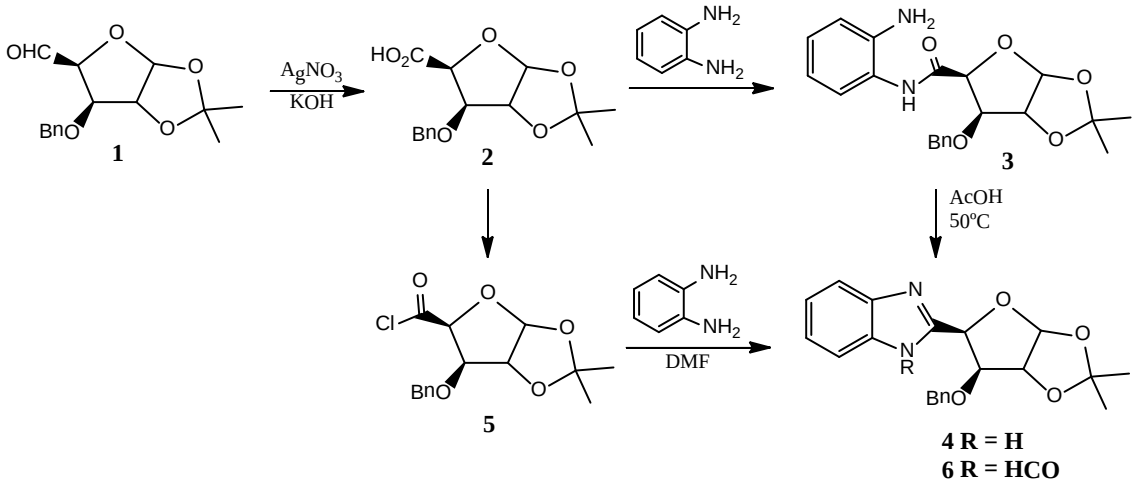
Heterocycles coupled with a carbohydrate moiety show a high chemotherapeutic potential, with biological properties such as antitumor and antiviral activities, and have been studied as building blocks in syntheses of products with great medicinal value.
The most of the syntheses of benzimidazoles are carried out from aromatic aldehydes and *o*-phenylenediamine and its derivatives. Only a limited number of works are referred to monosaccharide derivatives as the aldehydic product.

An O-propargylated aldehyde derived from diacetone glucose was chosen for a general synthesis of triazole linked chiral benzimidazoles.[1] When 2,3-naftalendiamine is reacted with aldoses in AcOH, with iodine as oxidant, aldo-naftimidazoles were obtained in good yields and used to form fluorescent markers.[2] Iminosugars linked to benzimidazole rings have been described as glycosidase inhibitors.[3] Thus, pyrrolidines linked to benzimidazole showed inhibitory activities against α-L-Fucosidases.

When a deprotected monosaccharide reacts with *o*-fenilendiamine in oxidative conditions, the free hydroxyl groups can be affected. In fact, when we tested the oxidative condensation of D-glucose with I_2 in AcOH or $Cu(NO_3)_2 \cdot 3\ H_2O$, mixtures of compounds were obtained.

With the aim of obtaining good results of monosaccharide derivatives linked to benzimidazoles we planned to start with the aldehyde **1**[4] obtained from D-glucose. Direct condensation of aldehyde **1** with *o*-phenylenediamine and $Cu(NO_3)_2 \cdot 3\ H_2O$ did not give the expected results. Therefore we transformed the aldehyde to carboxylic acid **2** and then two alternatives were carried out. (Scheme 1) Firstly, the reaction of the acid **2** with *o*-phenylenediamine was carried out using BOP (*terc*-butyloxy carbonyl) as coupling agent. This reaction let us the isolation and characterization of the amide intermediate **3**. Heating the amide **3** in AcOH the cyclization was complete to give the benzimidazole **4** which was characterized in basis to its NMR data.

An alternative was the conversion of the acid **2** into the acid chloride **5**, but not only the benzimidazole **4** was formed and a new compound was isolated from the mixture of the reaction. Its structure could be elucidated by NMR spectroscopy corresponding to the formyl derivative **6**.



Scheme 1. Synthesis of benzimidazole **4** and of its formyl derivative **6**.

Experimental

Synthesis of amide 3.- To a stirred solution of acid **2** (350 mg, 1.0 eq, 1.19 mmol) and *o*-phenylenediamine (140 mg, 1.1 eq, 1.31 mmol) in 10 mL de CH_2Cl_2 were added BOP (580 mg, 1.1 eq, 1.31 mmol) and triethylamine (1.2 eq,), under an argon atmosphere. After 2 d the mixture is dissolved in AcOEt, filtered by a pack of silicagel and purified by column chromatography to give **4** as golden foam. Rf: 0.8 (1:3 Hex/AcOEt). ^{1}H-RMN ($CDCl_3$, 400MHz, δ ppm): 8.02 (s, 1H), 7.32 – 7.26 (m, 5H), 7.15 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.04 (m, *J* = 7.8, 1H), 6.73 (m, 1H), 6.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.10 (d, *J* = 3.5 Hz, H-1), 4.94 (d, *J* = 3.5 Hz, H-2), 4.69 (s, *J* = 3.4 Hz, C*H*$_2$-Ph), 4.62 (d, H-4), 4.45 (d, *J* = 3.4 Hz, H-3), 1.52 y 1.36 (2s, 2x3H, C*Me*$_2$).

Cyclization to benzimidazole 4: The amide obtained from the column was dissolved in 5 mL of glacial AcOH and heated at 50 ºC overnight. The crude product was dissolved in CH_2Cl_2 and purified by column chromatography (Hex/AcOEt/CH_2Cl_2 4:1:1), giving **4** in 53% yield.^{1}H-RMN ($CDCl_3$, 400MHz, δ ppm): 7.60 (sa, N*H*), 7.32 – 7.26 (m, 3H), 7.22 – 7.12 (m, 3H), 6.88 (d, *J* = 6.6 Hz, 2H), 6.10 (d, $J_{1,2}$ = 3.6 Hz, H-1), 5.63 (d, H-2), 4.72 (d, *J* = 3.6 Hz, H-4), 4.35 (2d, 2H, CH_2-Ph y H-3), 4.15 (d, *J* = 11.2 Hz, CH_2-Ph), 1.56 and 1.36 (2x3H, CMe_2). ^{13}C-RMN ($CDCl_3$, 100MHz, δ ppm): 149.6, 136.8, 128.4, 128.0, 127.8, 122.7, 112.7, 105.3, 83.7, 83.2, 77.8, 77.4, 77.1, 76.8, 73.0 (*CH*$_2$Ph), 26.9 and 26.4 (CMe_2).

Reaction with the acid chloride 5: The acid chloride **5** (380 mg, 1.0 eq, 1.22 mmol) and *o*-phenylenediamine (132 mg, 1.0 eq, 1.22 mmol) were dissolved in 5 mL of DMF in ice bath with stirrer and NEt_3 (0.2 mL, 1.0 eq, 1.22 mmol) was added. The reaction was left at r.t. overnight under argon atmosphere. Then, 126 mg of Na_2CO_3 were added. The mixture was refluxed for 5 h. After filtered, solution was concentrated under reduced pressure, the residue dissolved in AcOEt and the solution eluted with aq. NH_4Cl (15 ml). After extraction with AcOEt (2 x 15 mL) the organic extracts were dried ($MgSO_4$), filtered and concentrated to give 420 mg of residue. Purification by column chromatography gave 35 mg of benzimidazole **4** and 157 mg of its formyl derivative **6**

^{1}H-RMN ($CDCl_3$, 400MHz, δ ppm): 8.50 (s, 1H), 7.55 – 7.49 y 7.38 - 7.15 (m, aromáticos), 6.07 (d, $J_{1,2}$ = 3.4 Hz, H-1), 4.87 (d, $J_{1,2}$ = 3.4 Hz, H-2), 4.63 (m, CH_2-Ph), 4.61 (d, $J_{3,4}$ = 3.4 Hz, H-4), 4.41 (d, $J_{3,4}$ = 3.4 Hz, H-3), 1.51 y 1.35 (2s, 2x3H, CMe_2).^{13}C-RMN ($CDCl_3$, 100MHz, δ ppm): 167.04, 137.06, 129.52, 128.43, 127.98, 127.88, 126.27, 125.21, 112.86, 105.92, 82.76, 82.53, 81.45, 77.36, 77.05, 76.73, 73.26 (*CH*$_2$Ph), 27.07 y 26.46 (CMe_2).

Acknowledgements

This work was financially supported by the Spanish Ministerio de Economía y Competitividad (MINECO) (CTQ2014-60223-R) and Consejería de Educación y Ciencia of Junta de Andalucía (FQM-0158).

References

[1] S. Dutta, S. Sarkar, A. K. Sen, *J. Heterocyclic Chem*.. **2013***, 50*, 689.

[2] C. Lin, P.-T. Lai, S. K.-S. Liao, W.-T. Hung, W.-B. Yang, J.-M. Fang, *J. Org. Chem*., **2008**, *73*, 3848.

[3] A. J. Moreno-Vargas, A. T. Carmona, F. Mora, P. Vogel, I. Robina, *Chem. Commun*., **2005**, *39*, 4949.

[4] N. Oña, A. Romero-Carrasco and M. S. Pino-González, *Tetrahedron: Asymmetry* **2013**, *24*, 156.