Research Article

New 1,2,3-Triazole Iminosugars Derivatives Using Click Chemistry

Chahrazed Benhaoua

Laboratoire Synthèse et Catalyse, LSCT, Université Ibn Khaldoun, Tiaret 14000, Algeria

Correspondence should be addressed to Chahrazed Benhaoua, ch_benhaoua@mail.univ-tiaret.dz

Received 17 March 2012; Accepted 28 April 2012

Academic Editor: R. J. Linhardt

1. Introduction

There are considerable interests in the design of molecules that are able to mimic carbohydrates which play critical roles in various biological events. This is shown by the following example, the 1-deoxynojirimycin (DNJ) family, for which DNJ itself is a competitive inhibitor of α-D-glucosidase (Ki = 8 – 25 μM) [1], while its derivatives Miglustat (N-nBu DNJ, Zavesa) and Miglitol (N-hydroxyethyl DNJ, Glyset, or Diastabol) have already found therapeutic applications in Gaucher’s disease [2] and type 2 (noninsulin-dependant mellitus) diabetes, respectively [3, 4] (Figure 1).

Recently, researches have increasingly accorded to new iminosugars from click chemistry [5].

The term click chemistry was introduced by Sharpless and coworkers and promotes the use of efficient, selective, and versatile chemical reactions in synthetic chemistry [6].

The basic reaction, which is nowadays summed up under the name “Sharpless-type click reaction,” is a variant of the Huisgen 1,3-dipolar cycloaddition reaction between C–C triple bonds and alkyl azides [7, 8] (Scheme 1).

Meldal and coworkers published a paper in 2002 that describes the acceleration of this process by CuI salts that leads to a reaction at 25°C in quantitative yields. It was mentioned that the organic azides and the terminal alkynes are united to afford 1,4-regioisomers of 1,2,3-triazoles as sole products [9].

The source of Cu(I) salts commonly used involves the reduction of copper(II) sulfate by sodium ascorbate [9], although other conditions have been described, such as Cu(I) [10] salts, Cu(I) complexes [11] and stabilized derivatives of Cu(I) [9]. The bases used are mostly triethylamine, 2,6-lutidine and N,N-diisopropylethylamine (DIPEA).

1.1. Click Chemistry and Synthesis of Iminosugars Derivatives. The application of CuAAC-catalysed reactions for the synthesis of new α-glucosidase inhibitors containing a 1-deoxynojirimycin (DNJ) was described by Murphy and coworkers.

These compounds indicate that it is possible to modulate the potency and the selectivity towards different glycosidases [5] (Figure 2).

More recently, Diot et al. reported the synthesis of several iminosugars from a click chemistry reaction between oligoethylene scaffolds and N-substituted DNJ derivative.

Thus, compounds of 4(n = 1) and 5 (n = 4) derivatives of the DNJ-based are good inhibitors of different glycosidases [12] (Figure 3).

Kumar et al. reported the synthesis of various pyrroldine-triazoles, these compounds are achieved by using this intramolecular cycloaddition reaction in water with complete 1,5 regioselectivity [13] (Figure 4).

Researches for new five-membered iminosugars as potential inhibitors of glycosidases reported the synthesis of...
1,2,3-triazole iminosugars from a click chemistry reaction between polyhydroxylated pyrrolidine and different azide.

2. Results and Discussion

2.1. Synthesis of 1,2,3-Triazoles Iminosugars. As illustrated in Scheme 2, a protected triazole-pyrrolidine \( \text{9} \) was obtained by condensation of an appropriate azide and the protected pyrrolidine \( \text{8} \).

From the data presented in Table 1, it was noticed that the compounds \( \text{9} \) are prepared in yields ranging from 60% to 84%.

2.2. Identification of Products. The structure elucidation of compounds \( \text{9} (a-e) \) achieved on the basis of their \( ^{1} \text{H} \) NMR, \( ^{13} \text{C} \) NMR and masse spectra.

The \( ^{1} \text{H} \) and \( ^{13} \text{C} \) NMR spectra showed the formation of the 1,2,3-triazole ring.

For the products \( \text{7} (a-e) \), the signal for the H\(_5\) proton of the pyrrolidine cycle is around 4.11 ppm to 4.71 ppm.

In the \( ^{13} \text{C} \) NMR of the compounds \( \text{9} (a-e) \), characteristic (C=O) appeared at around 169.78 to 173.82. The \( ^{13} \text{C} \) NMR spectrum of all the compounds showed the characteristic signal for the (C(Me)\(_2\)) of isopropylidene at around 112.47 to 115.44 ppm.

The characteristic (C=N=N=N) appeared at around 135.23 to 148.96 ppm and the characteristic (C=N=N=N) is recorded at around 122.98–124.75 ppm.

The yield of compounds \( \text{9d} \) and \( \text{9e} \) is 60%. These results are confirmed to the values of Haridas and coworkers in the synthesis of series of triazolaphanes [14].

3. Conclusion

A series of novel 1,2,3-triazoles iminosugars are synthesized from protected polyhydroxylated pyrrolidine (8). In this work, we have shown that the copper-catalyzed Huisgen cycloaddition of terminal alkyne is a general process affording the 1,4-disubstituted triazole isomer in good yields. This reaction proceeds under mild conditions to afford only one regioisomer.

Work is underway to apply parallel synthesis of triazole-pyrrolidine by condensation of the protected azido-pyrrrolidine and an appropriate alkyne. After the deprotection, we study the biological activities of all triazoles-iminosugars.

4. Experimental

4.1. Materials and Equipments. Chemicals were purchased from Aldrich, Acros, and Fluka and used without further purification. Solvents distilled with appropriate drying agents. All reactions performed under anhydrous conditions employing routine drying techniques unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) performed on E. Merck glass plates silica gel sheets (Silica Gel F\(_{254}\)) and stained with vanillin acid-aqueous H\(_2\)SO\(_4\) solution. Column chromatography carried out on silica gel (E. Merck 230–400 mesh). Nuclear magnetic Resonance (NMR) data \( ^{1} \text{H} \) or \( ^{13} \text{C} \) were obtained on a
1HC and 2D 1H–13C CORR experiments. Optical solvents. Assignments of 1H and 13C were assisted by 2D parts per million relative to tetramethylsilane in deuterated AC-Brucker 300 machine chemical shifts are reported in International Journal of Carbohydrate Chemistry 3

sugars bis (azidomethyl) benzene: 45%. propionitrile: 82%, 1,4 bis (azidomethyl) benzene: 45%, 1,3 MgSO4 and solvent was evaporated to yield pure azide [16]. aqueous layer was extracted with diethyl ether, dried with purified by column (CH2Cl2/MeOH, 95/5). The characterization of each compound obtained by means of NMR and mass spectrometry as reported below.

AC-Brucker 300 machine chemical shifts are reported in parts per million relative to tetramethylsilane in deuterated solvents. Assignments of 1H and 13C were assisted by 2D 1H COSY and 2D 1H–13C CORR experiments. Optical rotations were determined with a Jasco Dip 370 electronic micropolarimeter (10 cm cell). Low resolution electrospray mass spectra (ESI-HRMS) in the positive ion mode were obtained on a Waters-Micromass ZQ quadrupole instrument, equipped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, UK). High-resolution electrospray mass spectra (ESI-HRMS) in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole time-of-flight instrument (Waters-Micromass), equipped with a pneumatically assisted electrospray (Z-spray) ionization source and an additional sprayer (Lock Spray) for the reference compound. The compound (8) is synthesized as described in the literature [15].

4.2. General Procedure for Synthesis of Azide: RN3. The alkyl or benzyl chloride (1.0 equiv) was suspended in water at concentration of 1.5 M. Sodium azide (3.0 equiv) and ammonium chloride (2.0 equiv) were added, and the reaction was heated at 80°C for 48 h with vigorous stirring. The aqueous layer was extracted with diethyl ether, dried with MgSO4 and solvent was evaporated to yield pure azide [16]. Benzylic azide: 97%, 3-azido-propane-1-ol: 92%, 3-azidopropionitrile: 82%, 1,4 bis (azidomethyl) benzene: 45%, 1,3 bis (azidomethyl) benzene: 45%.

4.3. General Procedure for Synthesis of 1,2,3-triazole-iminosugars (9). A mixture of alkyne 11 (0.43 mmol) and the appropriate azide (1.73 mmol) were dissolved in a solution of water and t-BuOH (1:1). To this solution was added DIEA (diisopropyl ethylamine) (0.26 mmol) and CuI (0.17 mmol). The reaction was stirred at room temperature overnight. After the water (20 mL) was added to dilute the solution and the mixture was then extracted with CH2Cl2 (3 × 20 mL). The organic layer was dried over Na2SO4, concentrated and purified by column (CH2Cl2/MeOH, 95/5). The characterization of each compound obtained by means of NMR and mass spectrometry as reported below.

4.3.1. N-{(1-(3-hydroxypropyl)1H-1,2,3-triazol-4-methyl)-3.4-O-isopropylidendioxy-5-(3-hydroxypropyl)1H-1,2,3-triazol-4-yl)methylamino}pyrrolidin-2-one (9a). Colorless syrup. \([\alpha]_D^{20} = +1.33 \quad (C = 0.53, \ MeOH), \ NMR \ 1H \ (300 MHz, CDCl3)_{:} \ [\delta \ 1.14 (s, 3H); \ 1.39 (s, 3H); \ 1.46 (s, 2H); \ 2.75 (m, 4H) \ J = 7.25 Hz); \ 3.78 (m, 4H); \ 4.69 (d, 1H, J = 14.40 Hz); \ 4.70–4.78 (m, 1H, J = 5.19 Hz); \ 7.48 (s, 1H, CH–N–N=N); \ 7.52 (s, 1H, CH–N–N=N). NMR 13C (75 MHz, CDCl3)_{:} \ [\delta \ 15.38; \ 25.95; \ 27.05; \ 32.44; \ 45.33; \ 41.54; \ 47.04; \ 58.38–58.53; \ 71.06; \ 73.01; \ 77.28; \ 112.97; \ 123.15 (C–N–N=N); \ 123.71 (C–N–N=N); \ 143.16 (C–N–N=N); \ 146.49 (C–N–N=N); \ 169.92 (C=O), HRMS (m/z) [M+Na]+ calcd for C19H24N4O5Na = 473.2237, found: 473.2226.

4.3.2. N-1-(2-cyanoeth)1H-1,2,3-triazol-4-methyl)-3.4-O-isopropylidendioxy-5-(2-cyanoethyl)-1H-1,2,3-triazol-4-yl) methylamino)pyrrolidin-2-one (9b). Yellow gum, \([\alpha]_D^{20} = +0.83 \quad (C = 0.22, \ MeOH), \ NMR \ 1H \ (300 MHz, CDCl3)_{:} \ [\delta \ 1.36 (s, 3H); \ 1.40 (s, 3H); \ 1.31–1.39 (m, 2H); \ 2.75 (m, 4H); \ 4.39–4.50 (d, 1H, J = 14.46 Hz); \ 4.29–4.72 (m, 9H), \ 7.78 (s, 1H, CH–N–N=N); \ 7.91 (s, 1H, CH–N–N=N); \ 112.70; \ 116.91–117.00; \ 123.09 (C–N–N=N); \ 147.18 (C–N–N=N); \ 169.78 (C=O). HRMS (m/z) [M+Na]+ calcd for C19H24N4O5Na = 473.2237, found: 473.2226.

4.3.3. N1-(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-3.4-O-isopropylidendioxy-5-(1-benzyl-1H-1,2,3-triazol-4-yl)methylamino}pyrrolidin-2-one (9c). Yellow solid, \([\alpha]_D^{20} = +1.16 \quad (C = 0.22, \ MeOH), \ NMR \ 1H \ (300 MHz, CDCl3)_{:} \ [\delta \ 1.33 (s, 6H); \ 3.92–3.97 (d, \ H, J = 14.32 Hz); \ 3.92–3.97 (d, \ H, J = 14.42 Hz); \ 4.49 (m, 2H), 4.58 (d, 1H, \ J = 5.19 Hz); \ 4.72 (m, 1H), \ 5.79–5.52 (m, 4H); \ 7.24–7.26 (m, \ H-aromatic); \ 7.55–7.56 (2s, \ H–Hyp). NMR 13C (75 MHz, CDCl3)_{:} \ [\delta \ 25.64; \ 26.71; \ 34.61; \ 41.51; \ 71.82; \ 73.41; \ 77.38; \ 112.72; \ 123.53 (C–N–N=N); \ 124.35 (C–N–N=N); \ 129.69 (C–N–N=N); \ 134.77–134.96 (C-aromatic); \ 143.28 (C–N–N=N); \ 147.11
**Table 1**: Result for the preparation of protected 1,2,3-triazole iminosugars (9).

| Entry | Product triazole | Yields 9(a–e) |
|-------|------------------|---------------|
| 1     | ![Diagram 1](image1.png) | 84%           |
| 2     | ![Diagram 2](image2.png) | 70%           |
| 3     | ![Diagram 3](image3.png) | 80%           |
| 4     | ![Diagram 4](image4.png) | 60%           |
4.3.4. N1-(4-(((1H-1,2,3-triazol-1-yl)methyl)benzyl)-3,4-O-isopropylidendioxy-5-((1H-1,2,3-triazol-4-yl)methylamino)pyrrolidin-2-one (9d). Yellow gum, [α]D 19 +1.5 (C = 0.19, MeOH). NMR \( ^1H \) (300 MHz, CDCl₃): \( \delta \) 1.38–1.40 (s, 6H); 4.09–4.09 (d, 1H, \( J_{1H,5} = 156.64 \) (C-aromatic)); 4.70 (m, 2H, –CH₂–); 5.47–5.56 (m, 2H, \( J_{1H,5} = 156.64 \) (C-aromatic)); 7.60 (s, 1H, CH–N); 7.78–7.83 (m, H-aromatic).

NMR \( ^{13}C \) (75 MHz, CDCl₃): \( \delta \) 24.97; 26.09; 34.34; 41.08; 53.24–53.74; 71.90; 73.53; 77.45; 112.47; 122.98 (C–N–N); 123.49 (C–N–N=N); 128.21–128.62 (C-aromatic); 135.23 (C–N–N=N); 136.24 (C–N–N=N); 170.84 (C–O).

HRMS (m/z) [M+Na⁺]⁺ calcld for C₁₃H₁₇N₆O₃Na 271.1065, found 271.1064.

Acknowledgments

C. Benhaoua thanks the Scientific Ministry for Higher Education and Research of Algeria for fellowships and thanks Dr. D. Turk for helping in the English correction of the paper.

References

[1] A. MitraKou, N. Tountas, A. E. Raptis, R. J. Bauer, H. Schulz, and S. A. Raptis, “Long-term effectiveness of a new alpha-glucosidase inhibitor (BAY m1099-miglitol) in insulin-treated type 2 diabetes mellitus,” Diabetic Medicine, vol. 15, no. 8, pp. 657–660, 1998.

[2] L. J. Scott and C. M. Spencer, “Miglitol: a review of its therapeutic potential in type 2 diabetes mellitus,” Drugs, vol. 59, no. 3, pp. 521–549, 2000.

[3] T. M. Block, X. Lu, E. M. Platt et al., “Secretion of human hepatitis B virus is inhibited by the imino sugar N-butyldexnojirimycin,” Proceedings of the National Academy of Sciences of the United States of America, vol. 91, no. 6, pp. 2235–2239, 1994.

[4] A. Mehta, S. Carroee, B. Conyers et al., “Inhibition of hepatitis B virus DNA replication by imino sugars without the inhibition of the DNA polymerase: therapeutic implications,” Hepatology, vol. 33, no. 6, pp. 1488–1495, 2001.

[5] B. Andersen, A. Rassow, N. Westergaard, and K. Lundgren, “Inhibition of glycosylation in primary rat hepatocytes by 1,4-dideoxy-1,4-imino-D-arabinofuranose,” Biochemical Journal, vol. 342, no. 3, pp. 545–550, 1999.

[6] Y. Zhou, Y. Zhao, K. M. O’Boyle, and P. V. Murphy, “Hybrid angiogenesis inhibitors: synthesis and biological evaluation of bifunctional compounds based on 1-deoxynojirimycin and aryl-1,2,3-triazoles,” Bioorganic and Medicinal Chemistry Letters, vol. 18, no. 3, pp. 954–958, 2008.
[7] H. C. Kolb, M. G. Finn, and K. B. Sharpless, “Click chemistry: diverse chemical function from a few good reactions,” Angewandte Chemie International Edition, vol. 40, no. 11, pp. 2004–2021, 2001.

[8] R. Huisgen, G. Szeimies, and L. Mobius, “1,3-Dipolare Cycloaditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen,” Chemische Berichte, vol. 100, no. 8, pp. 2494–2507, 1967.

[9] C. W. Tornoe, C. Christensen, and M. Meldal, “Peptido-triazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(1)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides,” The Journal of Organic Chemistry, vol. 67, no. 9, pp. 3057–3064, 2002.

[10] K. V. Gothelf and K. A. Joergensen, “Asymmetric 1,3-dipolar cycloaddition reactions,” Chemical Reviews, vol. 98, no. 2, pp. 863–910, 1998.

[11] T. R. Chan, R. Hilgraf, K. B. Sharpless, and V. V. Fokin, “Polytriazoles as copper(1)-stabilizing ligands in catalysis,” Organic Letters, vol. 6, no. 17, pp. 2853–2855, 2004.

[12] J. Diot, M. I. Garcoa-Moreno, S. G. Gouin, C. O. Mellet, and K. Kovensky, “Multivalent iminosugars to modulate affinity and selectivity for glycosidases,” Organic and Biomolecular Chemistry, vol. 7, no. 2, pp. 357–363, 2009.

[13] I. Kumar, N. A. Mir, C. V. Rode, and B. P. Wakhloo, “Intramolecular Huisgen [3+2] cycloaddition in water: synthesis of fused pyrrolidine-triazoles,” Tetrahedron, vol. 23, no. 3-4, pp. 225–229, 2012.

[14] V. Haridas, K. Lal, Y. K. Sharma, and S. Upreti, “Design, synthesis, and self-assembling properties of novel triazolophanes,” Organic Letters, vol. 10, no. 8, pp. 1645–1647, 2008.

[15] C. Benhaoua, “One-pot synthesis of pyrrolidine-2-ones from erythronolactone and amine,” Organic Chemistry International, vol. 2012, Article ID 482952, 6 pages, 2012.

[16] A. Maisomial, P. Serafin, M. Traikia et al., “Click chelators for platinum-based anticancer drugs,” European Journal of Inorganic Chemistry, vol. 2008, no. 2, pp. 298–305, 2008.
Submit your manuscripts at http://www.hindawi.com