ORGANIC LETTERS

2012
Vol. 14, No. 13
3388–3391

Synthesis of Tetrazole-Fused Glycosides by a Tandem Fragmentation–Cyclization Reaction

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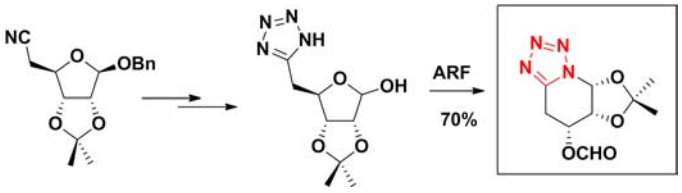
Received May 17, 2012

ABSTRACT



The fragmentation of anomeric alkoxyl radicals (ARF) and the subsequent intramolecular cyclization promoted by hypervalent iodine reagents provide an excellent method for the synthesis of tetrazolo-sugars. This new reaction offers additional advantages for the synthesis of these compounds, including the ready availability of the starting materials, experimental simplicity, mild conditions, and good yields.

The numerous therapeutic applications of iminosugars have helped maintain synthetic interest in this type of substrates at its highest level. This has led to a continuous search for new and more efficient approaches for accessing new structures and original synthetic methodologies.[1]

However, the synthesis of hybrid structures, which are both carbohydrates and aromatic heterocycles (Figure 1), has been comparatively less studied as a source of potential glycosidase inhibitors.[2]

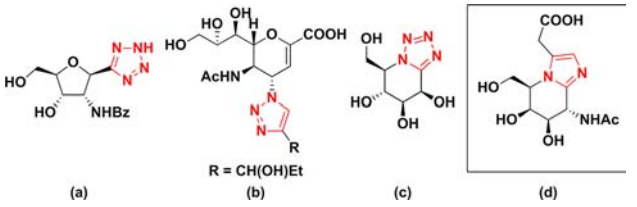


Figure 1. Examples of bioactive compounds with hybrid structures: (a) Nucleoside mimic (ref 2h) ; (b) Zanamivir analog (ref 2e); (c) Vasella's tetrazolo-sugar (ref 5a, d); (d) Nagstatine (ref 3).

Within this group, nagstatine,[3] a polyhydroxylated tetrahydropyrimidine-imidazole (Figure 1d), is the only naturally occurring product that contains an aromatic nitrogenated heterocycle attached to the pseudoanomeric position of a carbohydrate analog, and it shows strong inhibitory effects against several hexosaminidases. From the study of different

(1) (a) *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; Wiley: Chichester, 2007. (b) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999. (c) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615–1637.

(2) (a) Zhong, M.; Meng, X.-B.; Li, Z.-J. *Carbohydr. Res.* **2010**, *345*, 1099–1106. (b) Worch, M.; Wittmann, V. *Carbohydr. Res.* **2008**, *343*, 2118–2129. (c) Anegundi, R. I.; Puranik, V. G.; Hotha, S. *Org. Biomol. Chem.* **2008**, *6*, 779–786. (d) Couri, M. R.; Luduvico, I.; Santos, L.; Alves, R.; Prado, M. A.; Gil, R. F. *Carbohydr. Res.* **2007**, *342*, 1096–1100. (e) Li, J.; Zheng, M.; Zhu, W.; Li, T.; Zuo, J.-P.; Liu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5009–5013. (f) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 771–797. (h) Popsavin, M.; Torovic, L.; Spaic, L.; Stankov, S.; Kapor, A.; Tomic, Z.; Popsavin, V. *Tetrahedron* **2002**, *58*, 569–580. (i) Esperón, M. F. M.; Fascio, M. L.; D'Accorso, N. B. *J. Heterocycl. Chem.* **2002**, *39*, 221–224.

(3) Isolation of nagstatine: (a) Aoyama, T.; Naganawa, H.; Suda, H.; Uotami, K.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1404–1408. Total synthesis: (b) Tatsuka, K.; Miura, S. *Tetrahedron Lett.* **1995**, *36*, 6721–6724. Analogue synthesis: (c) Gessier, F.; Tschamber, T.; Tarmus, C.; Neuburger, M.; Huber, W.; Streith, J. *Eur. J. Org. Chem.* **2001**, 4111–4125. (d) Frankowski, A.; Deredas, D.; Streith, J.; Tschamber, T. *Tetrahedron* **1998**, *54*, 9033–9042. (e) Tatsuka, K.; Miura, S.; Ohta, S.; Gunji, H. *Tetrahedron Lett.* **1995**, *36*, 1085–1088. (f) Hua, D. H.; Zhang, F.; Chen., J. *J. Org. Chem.* **1994**, *59*, 5084–5087.

10.1021/ol3013638
Published on Web 06/13/2012

analogs and regioisomers of nagstatine, it was concluded that the presence of an sp^2–hybridized nitrogen atom in the anomeric position was necessary for inhibitory activity.[4]

Therefore, novel compounds similar to nagstatine were designed, in which the imidazole ring was replaced by a tetrazole ring,[5] whose structure is similar, yet presents enhanced metabolic stability. Tetrazoles can also be used as precursors of other heterocycles and can be considered as bioisosteres of carboxylic acids and *cis*-amide bonds.[6]

Previous approaches to these compounds by Vasella and Fleet[5] centered on the intramolecular [3 + 2] dipolar cycloaddition between an azide and a nitrile, as shown in Figure 2a. Herein we present a new strategy for the synthesis of tetrazole-fused glycosides where the key step is a tandem fragmentation–cyclization process (Figure 2b).

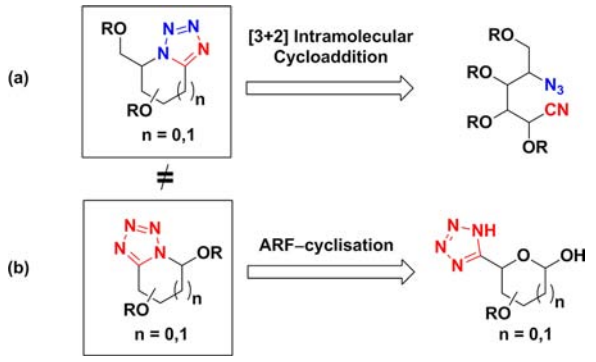
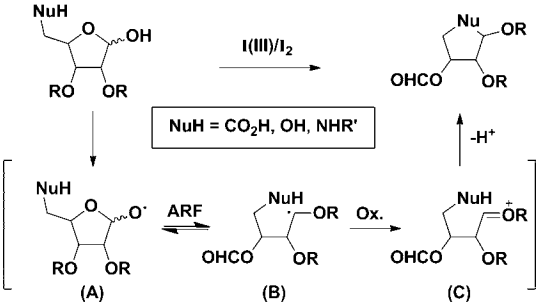


Figure 2. Synthesis of tetrazolo-sugars: comparison between dipolar cycloaddition and ARF-cyclization.

The study of the fragmentation reaction of anomeric alkoxyl radicals (ARF) has been one of our main topics of research in recent years.[7] The application of this protocol allowed us to transform aldoses into ketoses and has been very useful for the preparation of chiral synthons. This methodology relies on the initial formation of an alkoxyl anomeric radical (**A**) originated by the action of a hypervalent iodine reagent in the presence of iodine and presumably proceeds through an alkyl hypoiodite intermediate. Subsequently, the alkoxyl radical undergoes a fragmentation of the C1–C2 bond, giving rise to a C2 radical (**B**) that is afterward oxidized by an excess of reagent to the oxycarbenium ion (**C**). Finally, intramolecular nucleophilic cyclization affords the required sugar derivatives (Scheme 1).

Scheme 1. Mechanism of the ARF–Cyclization Reaction



Recently, we have been interested in applying this reaction to synthesize new compounds that may behave as glycosidase inhibitors.[8] Taking these results as a starting point, we decided to carry out the synthesis of tetrazolo-sugars via tandem ARF and subsequent intramolecular cyclization.

In Scheme 2, our retrosynthetic analysis of these tetrazolo-sugars is depicted. These would come from the corresponding carbohydrates tethered with a 1*H*-tetrazol-5-yl substituent, easily obtainable from a nitrile group. The synthesis of nitrile derivatives from sugars is well documented in the literature, as well as the cycloaddition reaction with different azides to generate tetrazole rings.[9]

The novelty of this project would stem from its first use of the β-fragmentation reaction to provide this type of aromatic heterocycle for use as an internal nucleophile. In addition, the cyclization products would present a pseudoanomeric alcohol unlike other tetrazolo-sugars

(4) (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553. (b) See ref 1.

(5) (a) Heightman, T. D.; Ermert, P.; Klein, D.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 514–532. (b) Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7507–7510. (c) Davis, B.; Brandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7511–7514. (d) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043–2053.

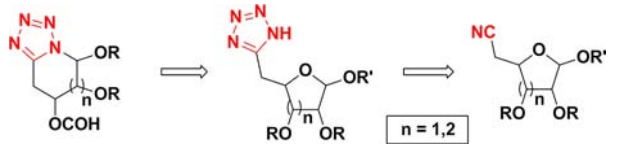
(6) Chen, F.; Qin, C.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11487–11491.

(7) β-Fragmentation of alkoxyl radicals: (a) Francisco, C. G; González, C. C.; Kennedy, A. R; Paz, N. R; Suárez, E. *Chem.—Eur. J.* **2008**, *14*, 6907–6912. (b) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 4116–4122. (c) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **2007**, *48*, 7207–7210. (d) Francisco, C. G.; González, C. C.; Kennedy, A. R.; Paz, N. R.; Suárez, E. *Tetrahedron Lett.* **2006**, *47*, 35–38. (e) Alonso-Cruz, C. R.; León, E. I.; Ortiz-López, F. J.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **2005**, *46*, 5265–5268. (f) Francisco, C. G.; González, C. C.; Kennedy, A. R.; Paz, N. R.; Suárez, E. *Tetrahedron: Asymmetry* **2004**, *15*, 11–14. (g) González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Chem.—Eur. J.* **2003**, *9*, 5800–5809. (h) González, C. C.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Tetrahedron Lett.* **2003**, *44*, 6347–6350. (i) Francisco, C. G.; Martín, C. G.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099–2109. (j) de Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865–8866. (k) de Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772–774. For a review, see: Suárez, E.; Rodríguez, M. S. β-Fragmentation of Alkoxyl Radicals: Synthetic Applications. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley–VCH: Weinheim, 2001; Vol. 2, pp 440–454.

(8) (a) Francisco, C. G.; Freire, R.; González, C. C.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 1861–1866. (b) Francisco, C. G.; Freire, R.; González, C. C.; Suárez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971–1974.

(9) (a) Rama, V.; Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2011**, *76*, 9090–9095. (b) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7101–7105. (c) Das, B.; Reddy, C. R; Kumar, D. N.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 391–394. (d) Hanessian, S.; Simard, D.; Deschênes-Simard, B.; Chenel, C.; Haak, E. *Org. Lett.* **2008**, *10*, 1381–1384. (e) Bräse, E.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240. (f) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110–2113. (g) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139–4141.

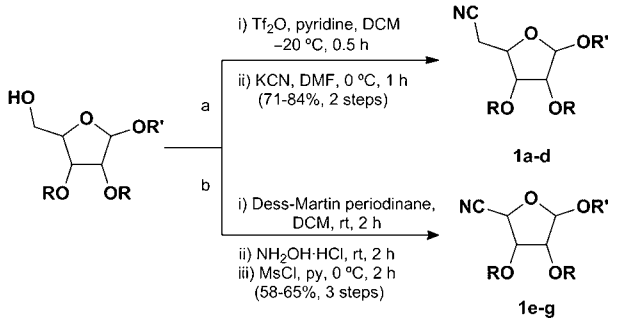
Scheme 2. Retrosynthetic Analysis



already published. From our experience, the tetrazole ring meets the characteristics needed for the reaction to proceed.

The syntheses of the different nitriles that were used in this study were carried out by two different procedures. Nitriles **1a**–**d** were synthesized by the activation of the corresponding alcohol, in the form of triflate, and its substitution with KCN (Scheme 3, path a), while nitriles **1e**–**g** were obtained by oxidation of the alcohol to the corresponding aldehyde,[10] oxime formation, and subsequent dehydration with MsCl (Scheme 3, path b).[11] All nitriles were obtained in very good yields.

Scheme 3. Synthesis of Nitriles **1a**–**g**

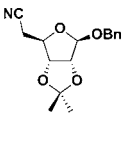
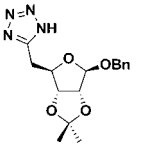
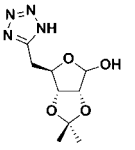
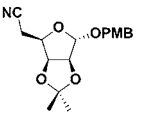
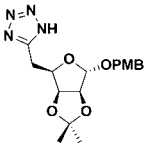
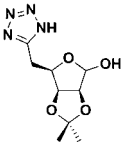
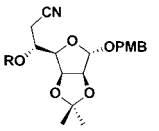
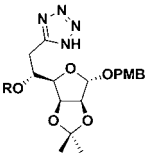
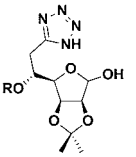
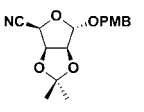
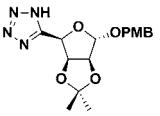
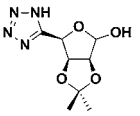
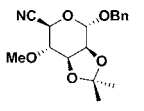
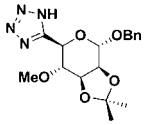
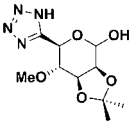
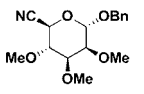
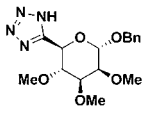
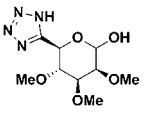


In initial attempts to synthesize the tetrazole ring, NaN_3 in DMF at 115 °C was used, providing the desired tetrazoles in very low yield. However, when $TMSN_3$ and catalytic dibutyltin oxide were used at 120 °C in a sealed tube, compounds **2a**–**g** were obtained in good to excellent yields, as stated in Table 1. The deprotection of the anomeric position was carried out either by hydrogenolysis at 6 atm to remove the benzyl group (entries 1, 5, and 6) or by reaction with CAN in aqueous acetonitrile (entries 2–4), providing the corresponding hemiacetals **3a**–**g** in good yields.

To perform the ARF reaction, we had to modify our classical reaction conditions (PhIO, I_2, DCM)[8] due to the high polarity of the hemiacetals **3a**–**g**. After trying various solvents and conditions, we found that dry ethyl acetate was the most suitable solvent for effecting this reaction. Thus, compounds **3a**–**g** were dissolved in dry ethyl acetate and treated with iodosylbenzene and iodine at reflux under the irradiation of two tungsten lamps. The different tetrazolo-sugars thus obtained are summarized in Table 2.

The reaction of the hemiacetal **3a** afforded, under the conditions described above, the corresponding tetrazole- derivative **4a** in 70% yield as a white solid. The change of ribose for lyxose (**3b**) produced no significant change, and the product **4b** was now obtained in 66% yield.

Table 1. Synthesis of the Intermediate Compounds

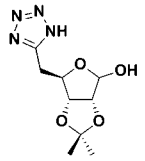
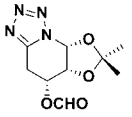
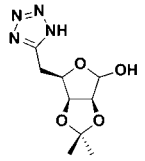
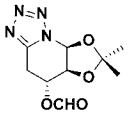
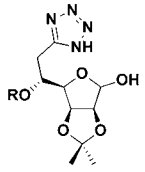
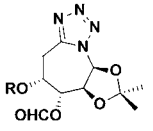
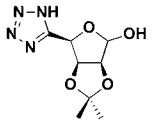
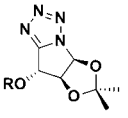
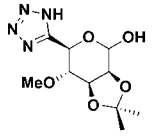
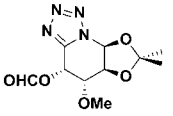
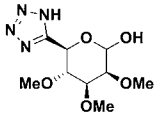
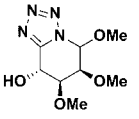
entry	nitriles	tetrazoles[a] (yield)[c]	hemiacetals[b] (yield)[c]
1	 **1a**	 **2a** (88%)	 **3a** (85%)
2	 **1b**	 **2b** (86%)	 **3b** (95%)
3	 **1c** R = Me **1d** R = Bn	 **2c** R = Me (93%) **2d** R = Bn (97%)	 **3c** R = Me (90%) **3d** R = Bn (98%)
4	 **1e**	 **2e** (81%)	 **3e** (81%)
5	 **1f**	 **2f** (90%)	 **3f** (83%)
6	 **1g**	 **2g** (91%)	 **3g** (95%)

[a] $TMSN_3$ (3 equiv), Bu_2SnO (0.2 equiv), dry toluene (5 mL/mmol), 120 °C, 16 h. [b] H_2 (6 atm), $Pd(OH)_2/C$, EtOAc/HOAc or CAN (3 equiv), $MeCN/H_2O$ (10 mL/mmol, 10:1), 0 °C, 2 h. [c] Isolated yield.

(10) For the synthesis of compound **1e**, the aldehyde was synthesized from 4-methoxybenzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside by fragmentation of the diol with sodium periodate; for further details, see Supporting Information.

(11) (a) Frederickson, M.; Grigg, R.; Redpath, J.; Thorthon-Pett, M. *Tetrahedron* **1994**, *50*, 5495–5502. (b) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Plantier-Royon, R. *Eur. J. Org. Chem.* **2005**, 5084–5088.

Table 2. Synthesis of Tetrazolo-sugars[a]

entry	starting material	products	yield[b]
1			
	3a	**4a**	70%
2			
	3b	**4b**	66%
3			
	3c R = Me **3d** R = Bn	**4c** R = Me **4d** R = Bn	68% 55%
4			
	3e	**4e** R = CHO **5e** R = H	56% 9%
5			
	3f	**4f**	68%
6			
	3g	**4g**	80% (1:1)

[a] Reaction conditions: All reactions were performed in dry EtOAc (20 mL) under irradiation with two 80 W tungsten-filament lamps at reflux temperature for 1 h containing PhIO (2.2 mmol) and I_2 (1.2 mmol) per mmol of substrate. [b] Isolated yield.

In order to study the scope of the reaction, the fragmentation of **3c** or **3d** generated the corresponding tetrazole-azepane derivatives **4c** or **4d** in satisfactory yield (entry 3). When **3e** was reacted the tricyclic pyrrolidine **4e** was obtained in 56% yield. It should be noted that the fragmentation of this compound provided another minor product (**5e**, 9%) that came from hydrolysis of the sensitive formate group during the purification step.

The ARF reaction of the models discussed so far has led to the synthesis of several tetrazole-fused heterocycles with ring sizes ranging from five- to seven-membered, where all of them incorporated a dioxolane moiety and their respective precursors were in furanose form.

In the last two models, sugars in pyranose form were used in order to check whether the size of the hemiacetal ring affected the reaction. The fragmentation of compound **3f** led to **4f** in 68% yield, while the fragmentation of **3g** afforded two isomers in an equimolecular ratio. It is worth mentioning that the products resulting from the photolysis of **3g** were not stable under the purification conditions. For that reason, the formate group was previously hydrolyzed, obtaining compounds **4g** in 80% yield after two steps. Unlike the precedent models, which contained an isopropylidene group and yielded only a single product, the fragmentation of **3g** afforded two epimers, as expected from the cyclization onto a planar oxycarbenium ion.

In summary, the methodology described herein represents, to our knowledge, the only general method presently available for the formation of tetrazolo-sugars that are oxidized in the pseudoanomeric position. The reaction takes place under mild conditions and in good yields. It should be emphasized that the efficiency of the reaction sequence, and the possibility of using different monosaccharides as starting materials, makes this approach suitable for structure–activity relationship studies, which will be reported in due course.

Acknowledgment. This work was supported by the Gobierno de Canarias (Research Program ProID20100088) and the investigation program no. CTQ2007-67492/BQU of the Ministerio de Educación y Ciencia (Spain) cofinanced with the Fondo Europeo de Desarrollo Regional (FEDER). A.G.S. thanks the I3P-CSIC Program for a fellowship.

Supporting Information Available. Experimental procedure, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.