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Synthesis of fused triazole-piperidinoses: a free radical cyclization approach

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Abstract

A new strategy has been reported for the synthesis of fused triazole-piperidinoses featuring an unprecedented 6-*exo–trig* free radical cyclization onto conveniently functionalized 1,2,3-triazoles contained in sugar templates. These compounds are potential key intermediates for the synthesis of azole-glycosidase inhibitors. Radical precursors have been prepared by standard methodologies from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. The key 6-*exo–trig* free radical cyclizations using tris(trimethylsilyl)silane/AIBN in toluene, yielded the desired aza-annulated sugars in moderate yields.

Keywords: glycosidase inhibitors; free radicals; azole-piperidinoses; triazoles.

Several tetrazoles,[1] triazoles[2] and imidazoles[3] fused to furanoses or pyranoses have been identified as good, selective and potent glycosidase inhibitors.[4] This is the case with synthetic compounds **1**[2] (Scheme 1). Most of the synthesis of these azasugars[5] have relied either on the intramolecular 1,3-dipolar cycloaddition (1,3-DC) of δ-azidonitriles[1] or δ-azido α,β-unsaturated esters[2] derived from sugars, intramolecular S_N2 reactions on tethered azole triflate sugar derivatives,[6] or from gluconolactams by annulation of hydrazinecarbaldehyde and aminoacetaldehyde dimethyl acetal.[7] In spite of these efforts, new synthetic alternatives are sought due to the potential biological activity and therapeutic profile of these molecules.[4]

In this communication we report a new and efficient synthetic approach for the preparation of fused azole-piperidinoses, a series of key intermediates for the synthesis of the above cited and related glycosidase inhibitors. The main aspects of this strategy are shown in Scheme 1 and consist of: (i) the introduction of an *N*-azole at C3 on a hexofuranose starting material (**A**); and (ii) an unprecedented 6-*exo–trig* cyclization of a radical species at C6′ onto a heterocyclic ring system in intermediates (**B**), leading to the aza-annulated sugar[8] (**C**). It is expected that further standard synthetic manipulations would afford piperidinoses of type (**1**).

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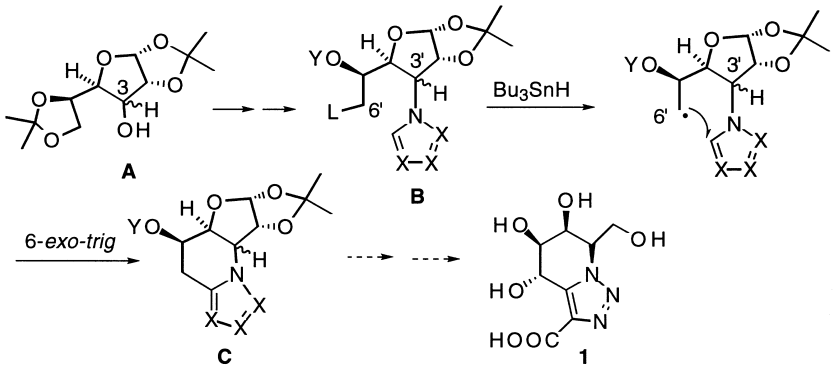
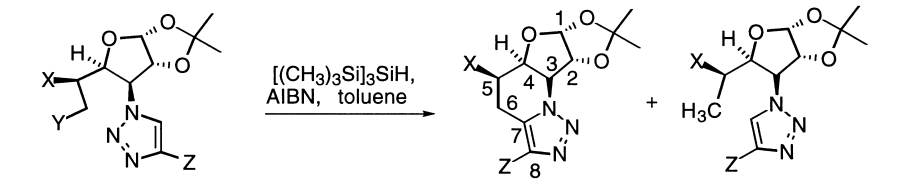


Scheme 1. Y=protecting groups; L=radical precursor groups (Br, I); X=C, O, N, S

This approach seems to be new, attractive, flexible and versatile, due to the following facts: (i) we can modulate the absolute stereochemistry at C3 during incorporation of the *N*-azole; (ii) differently substituted azole nucleus (X=O, N, S) can be placed at C3 by Mitsunobu reaction and/or S_N2 displacement of good leaving groups; and (iii) free radical cyclizations onto heterocycles are known,[9] but these protocols have been seldom used with sugar templates.[10]

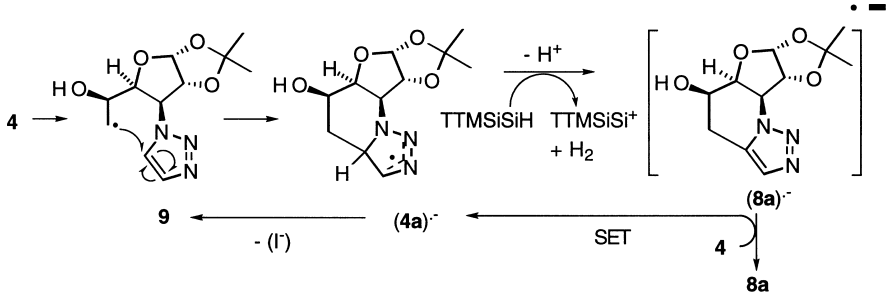
In this communication we report our first results on this subject. We have concentrated our efforts on the synthesis and free radical cyclization of 1,2,3-triazole derivatives of type **B**, positioned at C3′ in β-orientation (Scheme 1). The radical precursors **2**–**4** (Scheme 2) have been prepared by standard methodologies from the starting material 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**).[11] These compounds are 1,2,3-triazoles monosubstituted at carbon C4 with a trimethylsilyl group (**2** and **3**) or unsubstituted (**4**), with different leaving groups at C6′ or protecting groups at C5′. To our satisfaction, free radical cyclization[12] of compound **2** under the usual conditions,[13] using tris(trimethylsilyl)silane, gave the fused azole-piperidinose **6a**[13] (Scheme 2) in 36% yield (61% taking into account the recovered starting material).[14] The analytical and spectroscopic data of this compound clearly supported this structure, showing that the 6-*exo–trig* cyclization has occurred onto carbon C5 of the 4-trimethylsilyl substituted 1,2,3-triazole, followed by aromatization. The acetylated precursor **3**, submitted to the same experimental conditions, gave the aza-annulated sugar **7** (Scheme 2) in a 32% yield (78% taking into account the recovered starting material). The 6-*exo* free radical cyclization of compound **4** proceeded as expected giving the fused triazole **8a**[13] (Scheme 2) in 17% yield.[14] Note that, in spite of the excess of the reagent used or the prolonged reaction times, the reaction was not complete. This is probably due to the sterically demanding trimethylsilyl group at C4 during the free radical cyclization. In the case of compound **4** the low yield is possibly due to the low chemical stability of the compound. In general, these heterocyclic ring systems showed low reactivity. In any case, it is important to note that this is the first example described in the literature showing a free radical cyclization onto a 1,2,3-triazole heterocyclic system and the first example of a free radical cyclization onto an heterocycle contained in a strictly carbohydrate template.[10] The chemicals' yield have not been optimized, and work is still in progress to improve these results.

The formation of aromatic products during this type of cyclization has been explained by disproportionation, oxidation of an intermediate radical by AIBN[15] or by a pseudo $S_{RN}1$[9] mechanism. In our case, the series of events observed in the free radical cyclization of products **2**–**4** can be explained as shown in Scheme 3. Based on Bowman's proposal,[9d] a probable mechanism involving single electron transfer (SET) could be operating. In order to confirm a radical mechanism for these transformations, a



Scheme 2.

blank experiment (in the same experimental conditions without AIBN/TTMSiSiH) was carried out. No cyclization took place, excluding a possible nucleophile+electrophile route.[16]



Scheme 3.

In summary, a new strategy has been reported for the synthesis of fused triazole-piperidinoses featuring an unprecedented 6-*exo–trig* free radical cyclization onto 1,2,3-triazole nucleus installed at C3′, in conveniently functionalized furanose templates.

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slowly added (9 h) at reflux, under argon, via a syringe pump. After heating for 12 h more, the process was repeated, adding similar quantities of the reagents. The flask was cooled, the solvent was evaporated and the residue submitted to flash chromatography, eluting with hexane/ethyl acetate mixtures to give the final product (**6**–**8**). Selected spectroscopic data. Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (d, $J_{1,2}$=3.6 Hz, 1H, H1), 5.26 (d, $J_{1,2}$=3.6 Hz, 1H, H2), 4.95 (d, $J_{3,4}$=3.6 Hz, 1H, H3), 4.88 (br s, 1H, H4), 4.18 (m, 1H, H5), 3.24 (dd, $J_{6,6'}$=15.6 Hz, $J_{5,6}$=5.7 Hz, 1H, H6), 2.90 (dd, $J_{5,6'}$=11.0 Hz, 1H, H6′), 2.69 (d, J=9.2 Hz, 1H, OH), 1.60 and 1.36 [s, s, 3H, 3H, $OC(CH_3)_2O$], 0.34 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (C8)*, 137.7 (C7)*, 112.9 [$OC(CH_3)_2O$], 105.0 (C1), 84.7 (C2), 77.3 (C4), 65.9 (C5), 63.1 (C3), 26.6 and 26.3 [$OC(CH_3)_2O$], 25.4 (C6), −1.1 [$Si(CH_3)_3$]; (*these values can be interchanged). Compound **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1 H, H8), 5.74 (d, $J_{1,2}$=3.5 Hz, 1H, H1), 5.20 (d, $J_{1,2}$=3.5 Hz, 1H, H2), 4.88 (d, $J_{3,4}$=3.9 Hz, 1H, H3), 4.82 (m, 1H, H4), 4.11 (ddd, $J_{5,6}$=5.6 Hz, $J_{5,6'}$=10.9 Hz, $J_{5,OH}$=1.8 Hz, 1H, H5), 3.15 (dd, $J_{6,6'}$=15.6 Hz, $J_{5,6}$=5.6 Hz, 1H, H6), 2.83 (dd, $J_{6,6'}$=15.6 Hz, $J_{5,6'}$=10.9 Hz, 1H, H6′), 2.29 (br s, 1 H, OH), 1.54 and 1.29 [s, s, 3H, 3H, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2 (C7), 130.7 (C8), 112.9 [$OC(CH_3)_2O$], 104.9 (C1), 84.5 (C2), 77.3 (C4), 65.7 (C5), 63.2 (C3), 26.6 and 26.2 [$OC(CH_3)_2O$], 24.2 (C6).

14. In these cases, traces of the reduced, uncyclized derivatives **6b** and **8b** (Scheme 2) were detected.
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16. The authors thank the referee for this suggestion.