Synthesis and biological activity of bi/tricyclic azasugars fused thiazolidin-4-one and thiazinan-4-one by microwave-assisted tandem Staudinger/aza-Wittig/cyclization

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Article history:
Received 16 January 2012
Revised 26 February 2012
Accepted 29 February 2012
Available online 6 March 2012

Keywords:
Bi/tricyclic azasugars
Staudinger/aza-Wittig/cyclization
Microwave-assisted
Thiazolidin-4-one
Thiazinan-4-one
Biological activity

Azasugars or iminosugars, which exhibit effective inhibition against carbohydrate-processing enzymes, have attracted great interest for their potential clinical applications as anti-HIV, anti-diabetic, and anti-cancer agents and immunomodulators in past decade. The bicyclic azasugars such as the naturally occurring compounds A–D (Fig. 1) have attracted special attention by virtue of their increased possibility leading to discovering new biologically active therapeutic agents. It has been suggested that the rigid bicyclic structures are responsible for their potent activities by mimicking the flattened-chair transition state of the enzymatic reaction. Therefore, the design of non-natural bicyclic azasugars containing a glycosidic heteroatom (O, N, S) has led to the synthesis of numerous innovative analogs (Fig. 1, compounds E–H), such as azole-azasugar hybrids, lactam-azasugar hybrids, and so on. Generally, there are two common strategies to construct such bicyclic azasugars: one is via the intramolecular aminocyclization from the preformed N-heterocycle or monocyclic azasugar; the other is based on the intramolecular 1,3-dipolar cycloaddition of sugar-derived δ-azidonitriles or δ-azidoalkynes. However, both synthetic strategies suffered from the complex multi-step reactions and the introduction of the special functional groups like C=O, C=N, etc. In addition, the tricyclic azasugars were so far scarcely reported for their synthesis and biological activity study. Hence, it is still of great interest to explore the convenient synthesis of novel bioactive bi/tricyclic azasugar analogs to further investigate the structure–activity relationship (SAR) and develop iminosugar-based drugs.

Figure 1. Naturally occurring bicyclic azasugars A–D and some examples of the non-natural ones E–H.
Recently,\textsuperscript{10} by using one-pot tandem Staudinger/aza-Wittig\textsuperscript{11}/
condensation reaction, we have synthesized a series of novel glycomimics bearing a thiazolidin-4-one moiety\textsuperscript{10} as potential immunostimulating agents. The key step for the synthesis is the Schiff base C–N formation via the intermolecular Staudinger/aza-Wittig between sugar azide and sugar/aromatic aldehyde, which has been well applied in the preparation of both monocyclic azasugars\textsuperscript{13} and nitrogenous heterocyclic compounds.\textsuperscript{12,14} Inspired by this, we conceived that the novel bicyclic azasugars fused thiazolidin-4-one (Fig. 2) would be easily prepared by the one-pot intramolecular Staudinger/aza-Wittig/cyclization from the readily available azidosugar 1 and mercaptoacetic acid as depicted in Scheme 1. The intramolecular Staudinger/aza-Wittig reaction was firstly carried out by stirring the mixture of the azidosugar and triphenylphosphine (Ph3P) to generate the imine intermediate (II) via an iminophosphorane (I), followed by in situ reaction with mercaptoacetic acid to afford the thiazolidin-4-one fused bicyclic azasugar derivatives (2) and (3). Herein, we would like to report this simple protocol and its extensive applications in the synthesis of the bicyclic azasugars fused thiazinan-4-one (Fig. 2) under microwave radiation. As the continuation on our research for immunomodulators,\textsuperscript{15} the biological activities, such as immunological activities, and glycosidases inhibitory activities of the azasugars were also preliminary evaluated.

The requisite azidosugars 1a and 1b (Table 2) were prepared according to the literatures\textsuperscript{10} starting from α-ribose, and α-mannose, respectively. The one-pot Staudinger/aza-Wittig/cyclization reaction was firstly carried out using azidosugar 1a as the starting material at room temperature following the reported procedure for glycomimics bearing a thiazolidin-4-one moiety\textsuperscript{10} (Scheme 2). The tandem reaction could proceed effectively at room temperature and afforded the diastereomeric mixture of 2a and 3a in yield of 80.3% with a good stereoselectivity in ratio of 9.5:1 after standard workup and flash silica column chromatography (Table 1, entry 1). The good results showed that the method could be successful in constructing the new bicyclic azasugars fused thiazolidin-4-one based on Schiff base, which promoted us to explore its applications extensively. In order to shorten the reaction time and consider the great achievements of microwave-assisted organic synthesis,\textsuperscript{17} we then studied the tandem reaction under microwave radiation (entries 2–7).

As expected, the reaction could be dramatically accelerated under microwave radiation and gave good yield and stereoselectivity in very short time (Table 1, entries 2 and 3). Furthermore, the reaction in nonpolar solvent like toluene showed higher stereoselectivity than that in polar solvent such as 1,4-dioxane, THF, and acetone (entries 3 vs 5–7). Thus, as described in Table 1 entry 3, the 4-thiazolidinone-azasugar hybrids (2a and 3a) were obtained in total yield of 92.6% with the diastereomeric ratio of 9.2:1. Under the same conditions, the one-pot tandem reaction of other azidosugars 1b and mercaptoacetic acid generated the thiazolidin-4-one fused bicyclic azasugars 2b and 3b in good yields, respectively. The results are shown in Table 2.

To obtain the thiazinan-4-one fused bicyclic azasugars 4a and 5a by the tandem reaction of 1a and 3-mercaptopropionic acid, the reaction temperature was optimized (Table 1, entries 8–10).
The results showed that the tandem reaction could be carried out effectively in 15 min at M.W. 100 °C to afford the diastereomeric mixture of 4a and 5a in a good yield of 83.3% (Table 1, entry 9). Using the same conditions, the reaction of azidosugars (1) and 3-mercaptopropionic acid or 2-mercaptobenzoic acid produced bicyclic azasugars fused thiazinan-4-one 4b and 5b, and tricyclic azasugars fused 2,3-dihydrobenzo[e][1,3]thiazin-4-ones 6a,b and 7a,b as shown in Table 2. The moderate yields for compounds 6a,b and 7a,b might be due to the low nucleophilicity of the mercapto caused by the conjugation with benzene and the carboxyl group.

Following the procedure as described in Table 1 entry 9, the tricyclic azasugars fused 2,3-dihydropyrido[3,2-e][1,3]thiazin-4-one 8a and 9a were synthesized from 1a and 2-mercaptopropionic acid (Scheme 3) in a very low yield of 10.8%, owing to the low nucleophilic reactivity of 2-mercaptonicotinic acid. To improve the reaction efficiency, the condensation reagent DCC which has been found to be able to remarkably improve the three component synthesis of thiazolidin-4-one derivatives was used for promoting the intramolecular cycloamidation process with 2-mercaptonicotinic acid. Thus, the procedure for preparing 8a and 9a was modified to be: 1a and Ph3P were firstly stirred for 5 min at M.W. 100 °C in a sealed tube, then 1.2 equiv DCC was added accompanied with 2-mercaptonicotinic acid for another 10 min stirring under microwave radiation at 100 °C to produced 8a and 9a in total yields of 46.8%. By using the modified method, the tricyclic azasugars fused 2,3-dihydropyrido[3,2-e][1,3]thiazin-4-one 8b and 9b were synthesized in satisfied yields as shown in Table 2.
be mentioned that in the cases of 6a,b and 7a,b the yields were not improved when DCC was used.

After deprotection in 1 N HCl–dioxane solution at 45 °C, the corresponding bi/tricyclic azasugars fused thiazolidin-4-one or thiazinan-4-one 10a,b to 17a,b were obtained in high yields, respectively.

The structures of all the synthesized new bi/tricyclic azasugars were determined by their 1H, 13C NMR, 1H–1H COSY, and HRESIMS spectra (see Supplementary data). The typical coupling constants of H-1 and H-2 (Table 3) indicated that compounds 10a, 11a, 12a, 13a, 14a, 15a, 16a, 17a, 11b, 12b, 13b, 15b, and 17b had significant immunopotentiating activity. The convenience, good yield, and stereoselectivity make this new strategy very attractive for the design and synthesis of a wide variety of lactam-azasugar hybrids with promising pharmacological profiles for drug discovery.

Acknowledgments

The financial supports from the National Natural Science Foundation of China (NSFC) (20972039, 21172051), the Natural Science Foundation of Hebei (B2011201169), the Program of Science and Technology (S&T) of Hebei (09276418D-13), the Natural Science Foundations of Education Department of Hebei (2009309, ZH2011110, Y2011119), and Open Research Fund of the State Key Laboratory of Natural and Biomimetic Drugs, Peking University (20082005).

Supplementary data

Supplementary data (experimental procedures and characterization data for compounds 2–17) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.02.103.

References and notes


19. CCDC-799983 (for 2a), and -837110 (for 13a) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.