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A Convenient Synthesis and Biological Evaluation of Novel Pseudonucleosides Bearing a Thiazolidin-4-one Moiety by Tandem Staudinger/Aza-Wittig/Cyclization

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Novel pseudonucleosides **3** and **4** bearing a thiazolidin-4-one moiety were firstly synthesized by a one-pot, multicomponent, tandem Staudinger/aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization process in good yields of 43.8–88.0 %. Deacetylation of **3** and **4** afforded compounds **5** and **6**, respectively. The structures of the new compounds were determined on the basis of the X-ray crystal structures of **3b** and **3e** and by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The antitumor activity and the inhibitory activities against glycosidases and HIV reverse transcriptase of **5** and **6** were also evaluated.

Introduction

Analogues of natural nucleosides have been a growing research topic in the last decade due to their highly potential value as therapeutic agents for the treatment of many infectious diseases and tumors.[1] In the search for more effective anti-infective and antitumor agents, various chemical modifications of nucleosides have been proposed to improve their biological activities. One of the successful ways is to replace the natural pyrimidine or purine base with heterocycles that can form H-bonds with the natural nucleoside, such as thiazoles, imidazoles, triazoles, triazines, and so on.[2] For instance, the compounds shown in Figure 1 have good antitumor and antiviral activities. These promising biological results demanded to synthesize such potent pseudonucleosides and to meet the ever-growing requirements in the discovery of new drugs.

The thiazolidin-4-one ring is a core substructure in various synthetic pharmaceuticals that are associated with diverse biological activities such as antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, and analgesic, calcium antagonistic, and so on.[3] In the literature, most of the synthetic thiazolidin-4-one derivatives contain aryl and/or alkyl substituents, and only a few examples bear a sugar moiety such as pseudonucleosides have been reported.[4] Considering the strong biological activities of thiazolidin-4-ones, we envisaged to synthesize pseudonucleosides with a thiazolidin-4-one moiety[4c] as a continuation of the synthesis of functionalized glycomimics.[5]

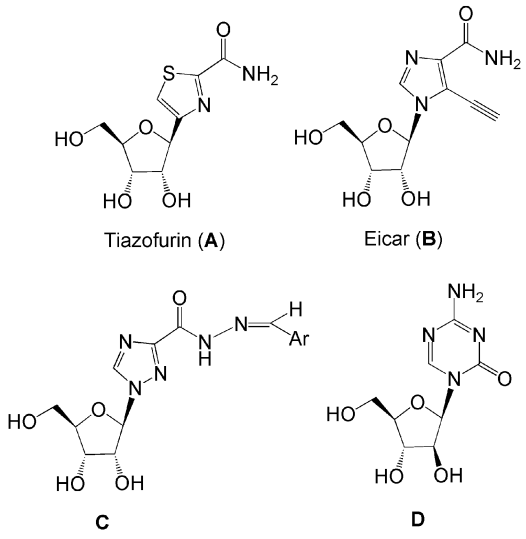

Figure 1. Pseudonucleosides with good biological activities.

Various protocols for preparing thiazolidin-4-one derivatives have been developed.[3,6] Of the most conventional methods, three-component reactions involving an amine, a carbonyl compound, and mercaptoacetic acid have been well documented[3,6] and have been improved by using a condensation agent,[7] microwaves,[8] ion liquids,[8d] and

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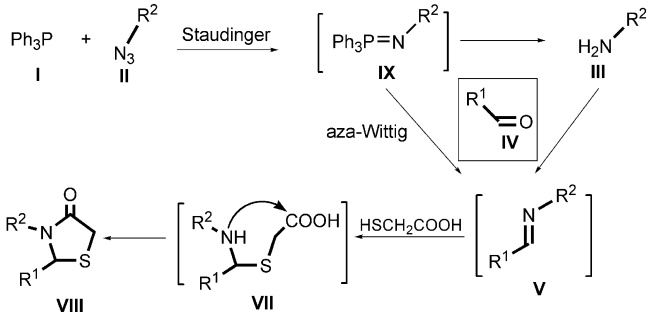
Lewis acids or bases.[6a,8b] The three-component reaction was carried out in a tandem process as shown in Scheme 1, in which aldehyde **IV** was condensed with amine **III** to produce intermediate imine **V**, followed by intermolecular nucleophilic addition with mercaptoacetic acid and then intramolecular cyclization via intermediate **VII** to afford thiazolidin-4-one product **VIII**.



Scheme 1. One-pot tandem Staudinger/aza-Wittig reactions and three-component synthesis of thiazolidin-4-one derivatives.

In our previous paper,[4c] we reported the synthesis of 2-aryl-3-[5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose-5-*C*-yl]thiazolidin-4-ones by the three-component condensation of an amino sugar, an aromatic aldehyde, and mercaptoacetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature. Because intermediate imine **V** (Scheme 1) could be conveniently prepared from azide and aldehyde by a Staudinger/aza-Wittig reaction, which has been successfully used in the constructions of C=N bonds and nitrogenous heterocycles,[9] we conceived that it would be more convenient to utilize the tandem Staudinger/aza-Wittig reaction to generate key intermediate imine **V** directly from azidosugar **I** and aldehyde **IV** to give the thiazolidin-4-one pseudonucleosides after intermolecular nucleophilic addition with mercaptoacetic acid and intramolecular cyclization as depicted in Scheme 1. Herein we would like to report the one-pot tandem Staudinger/aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization process for the synthesis of novel thiazolidin-4-one derivatives as pseudonucleosides starting from an azidosugar and aromatic aldehydes (Scheme 2).

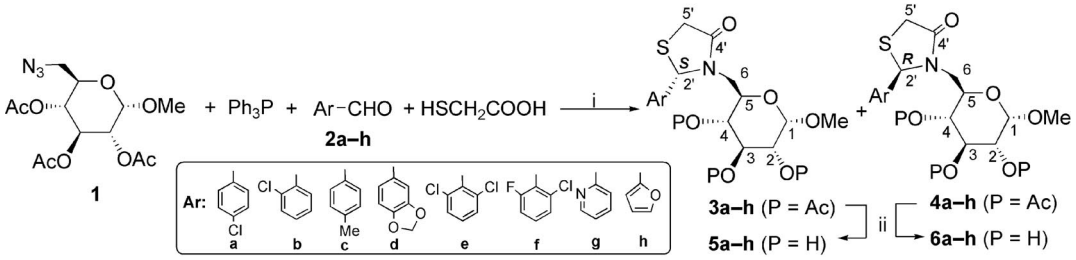
Results and Discussion

Staudinger/aza-Wittig reactions are a powerful tool in organic synthetic strategies toward constructing nitrogen-containing heterocycles.[9] To the best of our knowledge, there is no report of applying such reactions to the synthesis of thiazolidin-4-one derivatives. On the basis of the successful synthesis of the thiazolidin-4-one derivatives containing a sugar moiety,[4c] we firstly investigated the one-pot tandem synthesis by using methyl 6-azido-6-deoxy-2,3,4-*O*-triacetyl-α-D-glucopyranoside (**1**)[10]and aromatic aldehydes **2a**–**h** at room temperature. Our strategy in the one-pot synthesis is in situ Staudinger/aza-Wittig reactions using an azido sugar and aldehydes in the presence of triphenylphosphane, followed by the intermolecular nucleophilic addition of mercaptoacetic acid and then intramolecular cyclization as shown in Scheme 1. Thus, the synthesis was carried out by stirring the mixture of sugar azide **1**, triphenylphosphane (Ph_3P), and aldehyde **2** to generate the imine intermediate via an iminophosphorane, followed by in situ reaction with mercaptoacetic acid to afford the corresponding diastereomeric thiazolidin-4-one derivatives containing a sugar moiety, **3a**–**h** and **4a**–**h**, respectively, in good yields as shown in Scheme 2 and Table 1. The results were similar to those in a previous synthesis starting from an amino sugar by a one-pot, three-component reaction at room temperature in the presence of DCC;[4c] thus, this method provides a convenient one-pot, multicomponent, tandem synthesis of thiazolidin-4-one derivatives directly from azides.

Table 1. Synthesis of novel pseudonucleosides bearing the thiazolidin-4-one moiety.

	Yield [%]			Ratio of	Yield [%]	
	3	**4**	**3** +**4**[a]	**3**/**4**[b]	**5**	**6**
a	31.0	25.7	56.7	1:0.8	88.7	83.6
b	31.2	22.1	53.5	1:0.7	96.6	70.0
c	36.5	26.6	63.1	1:0.7	84.0	74.9
d	27.7	16.1	43.8	1:0.6	99.0	98.1
e	25.5	34.5	60.0	1:1.4	68.8	71.9
f	45.7	27.8	73.5	1:0.6	89.0	81.2
g	43.8	44.2	88.0	1:1.0	90.3	95.3
h	30.2	32.4	62.6	1:1.1	79.3	98.9

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.



Scheme 2. Synthesis of **5** and **6**. Reagents and conditions: (i) (a) **1** (1 equiv.), Ph_3P (1.5 equiv.), **2** (1.5 equiv.), toluene (2 mL), r.t., 1.5 h; (b) $HSCH_2COOH$ (2 equiv.), r.t., 2 h; (two steps); (ii) NaOMe/MeOH, r.t., 30 min.

The deacetylation of diastereomers **3** and **4** was carried out effectively in sodium methoxide in methanol at room temperature, which provided corresponding products **5** and **6** in very good yields (Table 1), respectively.

The structures of **3b** and **3e** were determined by single X-ray crystallographic analysis[11] (Figure 2), which confirmed the new generated chiral carbon centers (C-2′) in both **3b** and **3e** to be of the (*S*) form. Consequently, diastereomers **4b** and **4e** should have the (*R*) form in the corresponding C-2′. On the basis of these crystallographic structures and by comparison of the chemical shifts in the ^{1}H NMR spectra of the protons at C-2′ of compounds **3**–**6** (Table 2), the structures of the other compounds of **3**, **5** and **4**, **6** would be tentatively determined. In the NMR spectra, the H-2′ proton of **4** appeared upfield relative to those of **3**, and the H-2′ proton of its corresponding deacetylated products **6** showed a similar chemical shift change relative to those of **5**, implying that compound **3** would have the same (*S*) configuration at C-2′, and compound **4** would have the (*R*) form. Accordingly, deacetylated products **5** and **6** should possess the (*S*) and (*R*) forms at C-2′, respectively.

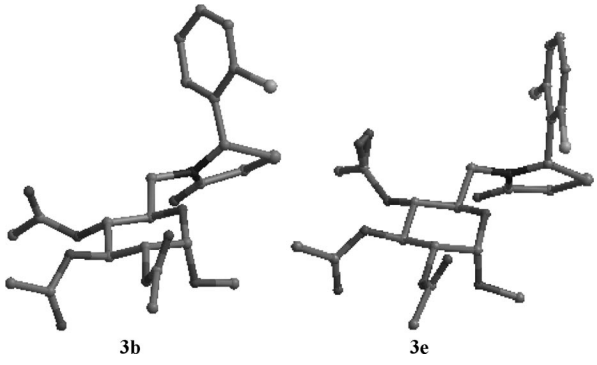


Figure 2. X-ray crystallographic structures of **3b** and **3e**.

Table 2. The chemical shifts of H-2′ of compounds **3**, **4** and **5**, **6**.

	δ of H-2′ [ppm]			
	3(*S*)	**4**(*R*)	**5**(*S*)	**6**(*R*)
a	5.81	5.76	6.08	5.95
b	6.35	6.30	6.44	6.32
c	5.87	5.81	6.03	5.90
d	5.82	5.77	5.98	5.87
e	6.93	6.83	7.02	6.86
f	6.60	6.52	6.74	6.59
g	5.96	5.88	6.12	5.98
h	5.91	5.87	6.04	5.97

Glycosidase inhibitory, HIV reverse transcriptase (RT) inhibitory, and antitumor activities were preliminarily evaluated with some compounds **5** and **6**. The cytotoxicity of compounds **5a**–**d**, **6a**–**d**, **5g**–**h**, and **6g**–**h** against Hela cell lines (human cervical cancer cells) was examined by the modified Mosmann's protocol,[12] the glycosidase inhibitory activities of compounds **5a**–**d**, **6a**–**d**, **5g**–**h**, and **6g**–**h** were measured on hydrolytic reactions of α-amylase, α-glucosidase, and β-glucosidase by comparison with acarbose, respectively, and the RT inhibitory activities of compounds **5a**–**b**, **6a**–**b**, **5e**, and **6e** were evaluated by determining their percentage inhibition of HIV-RT activity in HIV-RT kit by comparison with AZT.[13] However, most of the tested compounds did not show obvious activities. Compounds **5a** and **5h** showed weak inhibitory activity against glycosidases (9.5 and 15.9% in vitro at 25 μg mL^{-1} against α-amylase, respectively; 12.7 and 11.0% in vitro at 25 μg mL^{-1} against β-glucosidase, respectively), and compounds **5e** and **6e** showed certain RT inhibitory activity (39.4 and 55.8% in vitro at 25 μg mL^{-1}, respectively). All tested compounds had no antitumor activities ($IC_{50} > 300$ μM).

Conclusions

In conclusion, we synthesized a series of novel pseudonucleosides bearing a thiazolidin-4-one moiety by a one-pot, multicomponent tandem Staudinger/aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization process starting from azido sugars, aromatic aldehydes, and mercaptoacetic acid at room temperature, providing a convenient method for constructing such thiazolidin-4-one derivatives in good yields under very mild conditions. The configurations of the diastereomers were determined by X-ray crystallographic and NMR spectroscopic analyses. Preliminary biological evaluation of the synthesized compounds against glycosidases, HIV reverse transcriptase (RT), and antitumor were carried out, and no significant activity was observed. Further synthesis and biological study of new pseudonucleosides with the thiazolidin-4-one moiety are underway in this laboratory.

Supporting Information (see footnote on the first page of this article): General procedures and spectroscopic data for compounds **3**, **4**, **5**, and **6**; procedures for glycosidases inhabitation, antitumor activity assay, and in vitro HIV-RT kit assay.

Acknowledgments

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[11] CCDC-733867 (for **3b**) and -733866 (for **3e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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