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Synthesis and biological activity of novel 5′-arylamino-nucleosides by microwave-assisted one-pot tandem Staudinger/aza-Wittig/reduction

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ABSTRACT

Novel pseudonucleosides with benzylamino group on 5′-position (**4**) were synthesized by using the microwave-assisted one-pot tandem Staudinger/aza-Wittig/reduction reaction in good yields of 55.2–71.7%. The deacetylation of **4** afforded compounds **5**. HIV-1 reverse transcriptase (RT) inhibitory and antitumor activities were preliminarily evaluated with **5**. The results showed that the new pseudonucleosides (**5**) could effectively inhibit HIV-1 RT activity, but no antitumor activity.

The analogs of natural nucleoside have been a growing research topic in the past decades due to their high potential as therapeutic agents for the treatment of many infectious diseases and tumors.[1] To develop novel anti-infective and antitumor drugs, various chemically modified nucleosides have been proposed to improve their biological activities. The typical modifications mainly focused on the bases and sugars of the nucleosides. Some structurally modified analogs included heterocyclic-sugar nucleosides,[2] unnatural bases nucleosides,[3] spirocyclic nucleosides,[4] two-headed nucleosides,[5] and nucleotide analogs in which the phosphonate linkage was replaced by amide,[6] phosphoramidate,[7] or sulphonamide.[8] Moreover, it has been reported that in physiological condition, the anion nucleoside, for example, nucleoside 5′-monophosphate could be hindered to cross the negatively charged cell membranes.[9] It would be imaged that the introduction of neutral lipophilic or positively charged moieties to the nucleoside might facilitate the compound to penetrate the cell membrane and increase its concentration inside of the cell.[10] In light of this, we conceived to synthesize a series of novel 5′-arylamino nucleoside derivatives for investigating their antitumor and antivirus activities.

The tandem Staudinger/aza-Wittig reaction is one of very important protocol for constructing C=N bond and has been successfully used in the synthesis of nitrogenous heterocycle[11] and amine derivatives[12] via the key imine intermediate. Based on the tandem reaction, we have recently developed a convenient access to synthesize novel thiazolidinone glycosides.[13] Herein, we would like to report a simple and efficient method to synthesize novel 5′-arylamino nucleoside derivatives by the microwave-assisted one-pot tandem Staudinger/aza-Wittig/reduction from 5′-azido nucleosides and aromatic aldehydes (Scheme 1) and the biological activities of antitumor and HIV-RT inhibition.

5-Deoxy-5-azido-2,3-diacetyl-ribose (**1**) was prepared according to the reported procedure from D-ribose.[14] Then, N-glycosylation reaction of **1** with trimethylsilylated uracil or 5-F-uracil which was in situ generated in the presence of N,O-bis(trimethylsilyl)acetamide (BSA) afforded the corresponding 5′-deoxy-5′-azido-2′,3′-diaceto-ribonucleosides (**2**) in good yield.[15]

Based on our previous works,[13] the one-pot tandem Staudinger/aza-Wittig/reduction reaction was explorated with azidonucleoside (**2a**) and 4-chlorobenzaldehyde (**3a**) under microwave irradiation as shown in Scheme 2 and Table 1. It was found that the addition of Molecular Sieves could dramatically improve the reaction efficiency. Thus, as described in Table 1 entry 7, the one-pot tandem synthesis were firstly performed at 60 °C by stirring the mixture of the azidonucleoside (**2a**), triphenylphosphine (Ph_3P, 1.2 equiv) and 4 Å MS (2 equiv) in anhydrous THF under microwave irradiation for 5 min, then, 4-chlorobenzaldehyde (**3a**, 1.2 equiv) was added and the solution was stirred at 90 °C under microwave irradiation for another 5 min to generate the imine intermediate via an iminophosphorane, and followed by the reduc-

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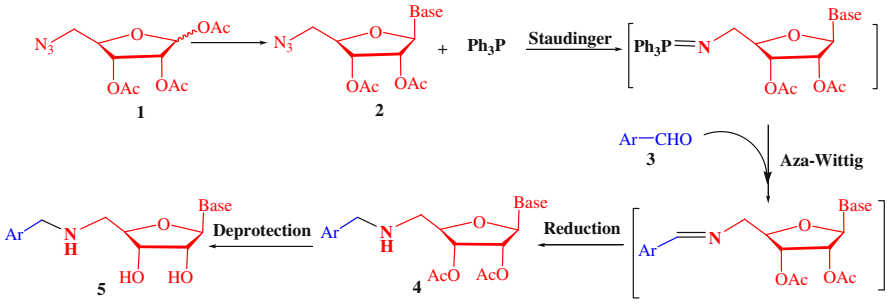
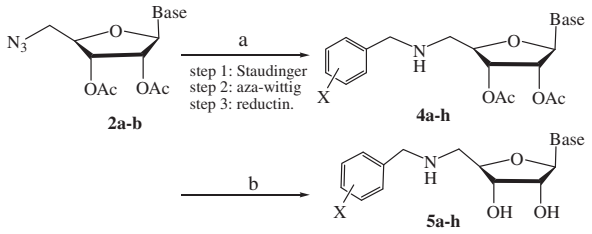


Scheme 1. One-pot tandem Staudinger/aza-Wittig/Reduction reaction for synthesizing 5′-arylamino-nucleosides.



2a: Base= uridine
2b: Base= 5-F-uridine
4, 5a-d: Base= uridine, X= 4-Cl; 2-Cl-6-F; 2, 6-di-Cl; 2-Cl.
4, 5e-h: Base= 5-F-uridine, X= 4-Cl; 2-Cl- 6-F; 2, 6-di-Cl; 2-Cl.

Scheme 2. Reagents and condition: (a) step (1) PPh_3, 4 Å MS, THF, MW, 60 °C, 5 min; step (2) compound **3**, MW, 90 °C, 5 min; step (3) $NaBH_3CN$–AcOH, 0 °C, 10 min; (b) MeONa, MeOH, 50 °C.

tive reaction with $NaBH_3CN$–AcOH (2 equiv) at 0 °C for 10 min to afford the corresponding 5′-(4-chlorobenzylamino)-2′,3′-diacetyl-uridine (**4a**). The total yield for the three steps was 70.7%. Under the same conditions, the one-pot tandem reactions of 5′-azido nucleosides (**2**) and aromatic aldehydes (**3**) produced the corresponding 5′-arylamino-2′,3′-diacetyl-nucleosides **4a–h** in good yields as shown in Scheme 2 and Table 2, providing a convenient one-pot multi-component tandem synthesis of 5′-amino-nucleoside derivatives.

The deacetylation of **4a–h** was carried out effectively in sodium methoxide in methanolic solution at room temperature, afforded the corresponding target products **5a–h** in high yields (Table 2), respectively.

HIV-1 reverse transcriptase (RT) inhibitory and antitumor activities were preliminarily evaluated with pseudonucleosides **5**. The RT inhibitory activities of **5** were evaluated by determining their percentage inhibition of HIV-RT activity in HIV-1-RT kit by comparison with AZT,[16] and the results were shown in Table 3. It could be seen from the table that compounds **5** showed significant HIV-RT inhibitory activity, better than that of positive control AZT, implying that compound **5** with benzylamino group at 5′-position on nucleosides may be better accommodated into the HIV-1 RT active binding site. It is also suggested that the compounds with a N-linked neutral lipophilic groups at 5′-position would be better for the HIV-RT inhibitory activity. Although compound **5a** where chlorine existed at 4-position on the aromatic ring showed a more significant HIV-RT inhibitory activity and its IC_{50} values was 2.82 ± 0.81 μM, the position or the number of halo atoms on the phenyl ring led to no obvious influence on the anti-HIV-RT activity. The cytotoxicity of the compounds **5** against Hela cell lines (human cervical cancer cells) was examined by the modified Mosmann's protocol,[17] but showed no inhibition against the Hela-tumor cell (IC_{50} >200 μM).

In conclusion, we have designed and synthesized a series of novel pseudonucleosides with benzylamino group on 5′-position by using the microwave-assisted one-pot tandem Staudinger/aza-Wittig/reduction reaction starting from 5′-azido nucleosides and aromatic aldehydes, providing a convenient protocol for constructing such 5′-N-linked nucleoside analogs in good yields. The aimed

Table 2
The yields of compounds **4** and **5**

Yield[a] (%)	a	b	c	d	e	f	g	h
4	70.7	71.7	67.6	69	66.3	63.4	55.2	58.1
5	82.3	71.6	84.6	84.1	84.3	80.3	72	85.5

[a] Isolated yield.

Table 3
In vitro HIV-1-RT kit assay for compounds **5**

Compounds	IC_{50} (μM) (HIV-RT kit assay)	Compounds	IC_{50} (μM) (HIV-RT kit assay)
5a	2.82 ± 0.81	**5e**	3.75 ± 1.19
5b	4.99 ± 2.35	**5f**	3.90 ± 1.65
5c	4.72 ± 1.41	**5g**	4.84 ± 1.82
5d	6.13 ± 2.54	**5h**	3.53 ± 1.42
AZT	21.43 ± 1.93		

Table 1
Conditions optimization of the one-pot Staudinger/aza-Wittig/reduction

Entry	Ph_3P (equiv)	Aldehyde (equiv)	Conditions of step 2 (M. W.)	Reduction reagent (equiv)	Conditions of step 3	Yield[a] (%)
1	1.5	1.2	80 °C, 10 min	$NaBH_4$ (4.0)	rt	–
2	1.5	1.2	90 °C, 5 min	$NaBH_4$–AcOH (2.0)	0 °C, 3 min	31.2
3	1.5	1.2	80 °C, 10 min	$NaBH_3CN$ (4.0)	0 °C, 30 min	42.9
4	1.5	1.2	90 °C, 5 min	$NaBH_3CN$–AcOH (4.0)	0 °C, 10 min	46.8
5	1.2	1.2	90 °C, 5 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 10 min	45.2
6	1.2	2.0	90 °C, 5 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 10 min	45.3
7[b]	1.2	1.2	90 °C, 5 min	$NaBH_3CN$–AcOH (2.0)	0 °C, 10 min	70.7

[a] Isolated yield.
[b] 2.0 of 4 Å molecular sieves (MS) was added.

compounds (**5**) showed notable in vitro anti-HIV-1 RT activity, higher than that of AZT. The further synthesis and biological activity evaluation are underway in this laboratory.

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Supplementary data

Supplementary data associated (experimental procedures and characterization data for compounds **2**, **4**, and **5**) with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.054.

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