Chinese Chemical Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

L-ProT catalyzed highly regioselective *N*-alkoxyalkylation of purine rings with vinyl ethers

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ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 24 March 2014
Accepted 8 April 2014
Available online xxx

Keywords:
L-Proline triflate
Regioselectivity
Purine
Vinyl ether
Addition reaction

ABSTRACT

An efficient and regioselective synthesis of N-9 alkoxyalkylated purine nucleoside derivatives was achieved *via* the *N*-alkoxyalkylation of purine rings with vinyl ethers catalyzed by L-ProT. The advantages of this protocol include good to excellent yield, mild reaction condition, and simple manipulation. A plausible mechanism for the transformation was given.

1. Introduction

N-9 substituted purine nucleosides have long been recognized as core structures in biological systems [1,2] and are of great pharmaceutical importance, such as antivirus drugs, Aciclovir and Famciclovir [3–6]. Traditionally, the alkylation of purines with halogenated compounds [7], mesylate [8], or tosylate [9] is an important synthetic route to purine nucleoside derivatives, which usually suffers from poor regioselectivity, resulting in a mixture of N-9 and N-7 isomers. The challenging issue of regioselectivity between two competitive tautomeric forms (N-7-H and N-9-H) makes the development of effective methods for synthesis of N-9 substituted purine derivatives highly desirable [10].

Recently, the addition reaction involves purine rings has been made much progress for its regioselectivity. Lira and Huffman [11] and Wang et al. [12] reported the base-catalyzed Michael addition of purines with α,β-unsaturated compounds. Peel et al. [13] demonstrated the Pd-catalyzed addition reaction of purines with cyclopentadiene monoepoxide to give the N-9 carbocyclic nucleosides exclusively. Moreover, the addition reactions between purines and 3,4-dihydropyran, got high regioselectivity, while it suffered from unsatisfactory yield for extensive use because the product could be decomposed under the acidic conditions [14,15]. Therefore, the further study on the addition reaction involves purine rings is still of great significance for the development of novel and direct access to N-9 substituted purine nucleosides.

Ammonium triflates have emerged as a kind of highly efficient and cost-effective Lewis acid catalyst in various chemical transformations [16–19]. They have many advantages including ease of product separation, recycling of the catalyst and environmental acceptability as compared to traditionally Lewis acid catalysts. In continuation of our interest in the application of novel ammonium triflate organocatalysts [20,21], herein, we report an efficient and environmentally friendly method for the synthesis of N-9-alkoxyalkylated purines *via* highly regioselective *N*-alkoxyalkylation of purines with vinyl ethers catalyzed by L-proline triflate (L-ProT) (Scheme 1).

2. Experimental

Analytical grade solvents and commercially available reagents were used without further purification. The flash column chromatography was carried out over silica gel (200–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were

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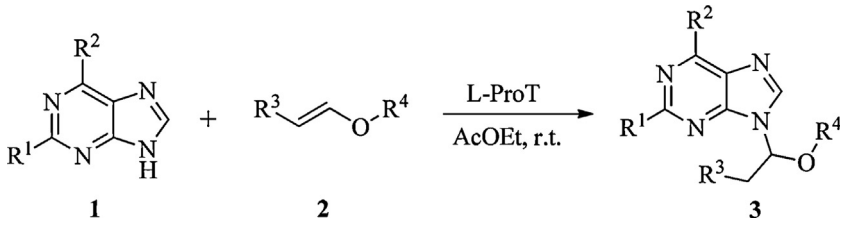
http://dx.doi.org/10.1016/j.cclet.2014.04.023
1001-8417/

Please cite this article in press as: J.-J. Li, X.-X. Gui, L-ProT catalyzed highly regioselective *N*-alkoxyalkylation of purine rings with vinyl ethers, Chin. Chem. Lett. (2014), http://dx.doi.org/10.1016/j.cclet.2014.04.023



1 2 3

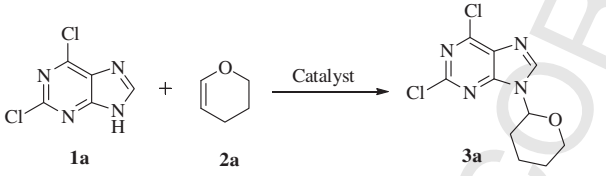
Scheme 1. Selective *N*-alkoxyalkylation of purine rings.

recorded at VARAIN-400 using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hz. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. HRMS analyze were measured on an Agilent 6210 TOF LC/MS using ESI or EI (electrospray ionization) techniques.

General procedures for the synthesis of *N*-9 substituted purine nucleoside derivatives: a mixture of purine (1 mmol), vinyl ether (2 mmol), and L-ProT (0.05 mmol) was stirred in AcOEt (2 mL) at room temperature. After completion of the reaction (monitored by TLC), the mixture was added AcOEt or CH_2Cl_2 (20 mL) and then washed with water (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. Purification by column chromatography on silica gave the product. Physical and chemical data of the chosen product is demonstrated below.

2,6-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (**3a**): white powder; 93% yield; mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 5.77 (dd, J = 10.4, 2.4 Hz, 1H), 4.23–4.14 (m, 1H), 3.79 (td, J = 11.6, 2.8 Hz, 1H), 2.22–1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 152.1, 151.5, 143.7, 130.7, 82.6, 69.0, 32.1, 24.9, 22.7. HRMS-ESI: calcd. for $C_{10}H_{10}Cl_2N_4NaO$: 295.0124; found: 295.0130.

Table 1
The optimization of reaction conditions[a].



1a 2a 3a

Entry	Catalyst	Loading (mol%)	Solvent	Yield (%)[b]
1	PTSA	10	AcOEt	83
2	PAT	10	AcOEt	89
3	MPAT	10	AcOEt	85
4	TFPAT	10	AcOEt	88
5	DPAT	10	AcOEt	87
6	L-ProT	10	AcOEt	91
7	TfOH	10	AcOEt	0
8	L-ProT	5	AcOEt	93
9	L-ProT	2	AcOEt	89
10	L-ProT	5	EtOH	Trace
11	L-ProT	5	DMF	45
12	L-ProT	5	CH_2Cl_2	69
13	L-ProT	5	CH_3CN	76

[a] Reaction conditions: 2,6-dichloropurine (1 mmol), 3,4-dihydropyran (2 mmol), solvent (2 mL), room temperature, 2.5 h.
[b] Isolated yield.

3. Results and discussion

We started our investigation by choosing 2,6-dichloropurine and 3,4-dihydropyran as model substrates for the optimization of reaction conditions. Ammonium triflate catalysts were easily to be removed by washing with water after the completion of reaction and proved more efficient than the traditional catalyst *p*-toluenesulfonic acid (PTSA) (Table 1, entries 1–6). From Table 1, L-ProT proved to be the best catalyst with a 91% yield of **3a**, while others, including aniline triflate (PAT), *N*-methylaniline triflate (MPAT), trifluoromethyl aniline triflate (TFPAT), diphenylammonium triflate (DPAT), gave lower yields of 85%–89% (Table 1, entries 2–6). Product **3a** was not observed when using trifluoromethanesulfonic acid (TfOH) as the catalyst (Table 1, entry 7). And a sufficient amount of 5 mol% L-ProT was necessary for this reaction (Table 1, entries 8 and 9). Then the solvents were examined and the results were summarized in Table 1. Only trace amount of product was obtained in EtOH (Table 1, entry 10). And higher yields were given in DMF, CH_2Cl_2, and CH_3CN, but results were still unsatisfactory (Table 1, entries 11–13). So AcOEt was chosen as the optimum solvent for the reaction. Moreover, the further screening of reaction temperature and time confirmed that reaction could be finished at room temperature within 2.5 h. It should be noted that there was no N-7 isomer [22] or other byproduct in above reactions. The product **3a** was examined as a racemic mixture, which indicated that the catalysis did not influence the enantioselectivity of the reaction.

Under the optimized reaction conditions, various substituted purines were subjected to the reaction as shown in Table 2. The Boc-protected adenine, Boc-protected 6-chloroguanine and chlorinated purines reacted smoothly with 3,4-dihydropyran or 2,3-dihydrofuran in good yields (Table 2, entries 1–7). A variety of groups, such as Cl and Boc were well tolerated, allowing the further conversion of these nucleoside analogues. The purines with different substituents at the C-6 position, including α-methoxy phenyl thiol, phenoxy, piperidyl also gave expected products in moderate to good yields (Table 2, entries 8–11). 2-Chloro-purine and 2-chloro-6-(piperidin-1-yl)-purine, which have poor solubility in AcOEt, were conducted in CH_2Cl_2 with moderate yields (Table 2, entries 7 and 11). From Table 2, the circinal vinyl ethers, including 3,4-dihydropyran and 2,3-dihydrofuran, were proved to be reliable reaction substrates.

After that, various open chain vinyl ethers were also examined to evaluate the general applicability of the method. The chain vinyl ethers with different alkyl groups afforded the corresponding products **3l–3n** in excellent yields of 88%–92% (Table 3, entries 1–3). And the mixtures of *cis*- and *trans*-ethyl propenyl ethers were also proved to be reliable reaction substrates, further illustrating that steric hindrance of the structure has little influence on the reaction except reaction rate (Table 3, entry 4). However, vinyl acetate could not give the desired product **3p** because of the electron-withdrawing effect of acetoxy group on the vinyl group (Table 3, entry 5).

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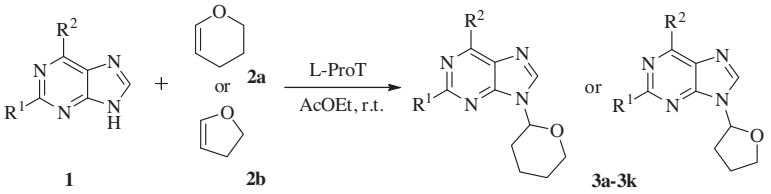
Table 2
The *N*-alkoxyalkylation of various purines[a].



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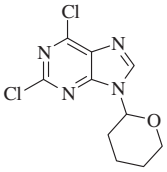
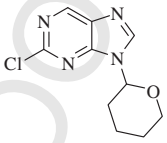
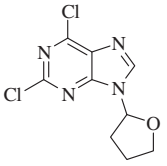
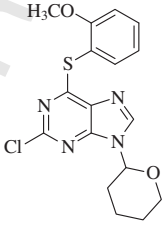
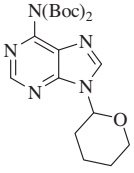
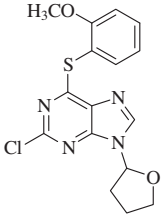
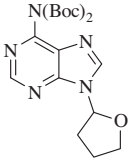
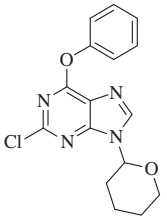
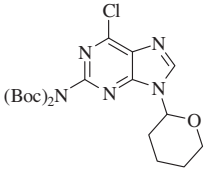
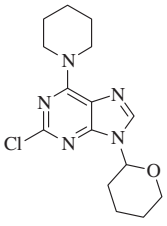
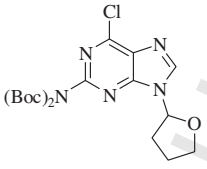
Entry	Product	Reaction time (h)	Yield (%)[b]	Entry	Product	Reaction time (h)	Yield (%)[b]
1	**3a** 	2.5	93	7	**3g** 	24	30, 65[c]
2	**3b** 	2.5	82	8	**3h** 	3	88
3	**3c** 	11	75	9	**3i** 	3	75
4	**3d** 	5	81	10	**3j** 	16	77
5	**3e** 	5	85	11	**3k** 	24	35, 43[c]
6	**3f** 	5	71				

[a] Reaction conditions: purine (1 mmol), 3,4-dihydropyran or 2,3-dihydrofuran (2 mmol), L-ProT (5 mol%), AcOEt (2 mL), room temperature.
[b] Isolated yield.
[c] CH_2Cl_2 as solvent.

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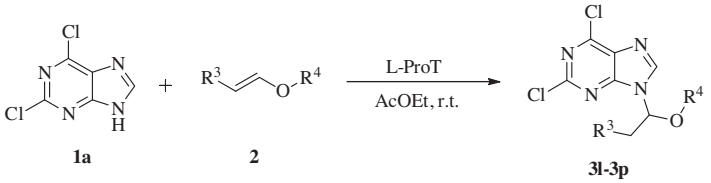
Table 3
The reaction of 2,6-dicholopurine with various vinyl ethers[a].



1a **2** **3l-3p**

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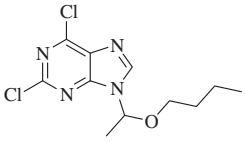
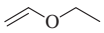
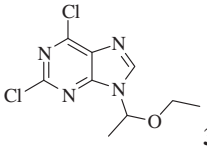
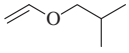
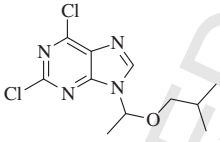
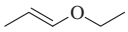
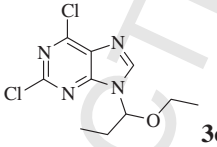
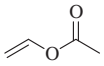
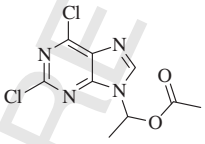
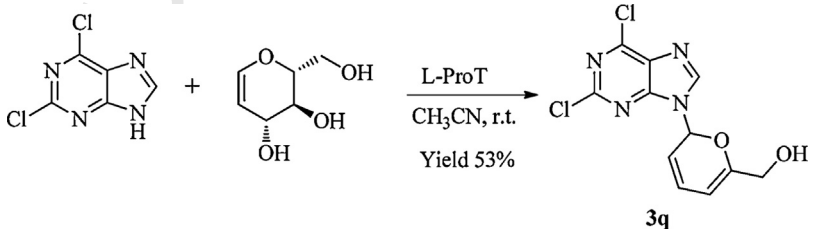
Entry	Vinyl ether	Product	Reaction time	Yield (%)[b]
1		 **3l**	2 min	88
2		 **3m**	30 min	92
3		 **3n**	20 min	88
4		 **3o**	1.5 h	81
5		 **3p**	3 h	NR[c]

[a] Reaction conditions: 2,6-dicholopurine (1 mmol), vinyl ether (2 mmol), L-ProT (5 mol%), AcOEt (2 mL), room temperature.
[b] Isolated yield.
[c] No reaction.

Besides, the reaction of 2,6-dichloropurine and D-(+)-glucal was conducted under the optimized reaction conditions, we surprisingly found that compound **3q** was produced in a 53% yield (Scheme 2).

A plausible mechanism for the N-alkoxyalkylation of various purines in the presence of L-ProT is proposed in Scheme 3. Purine firstly reacted with L-ProT to form intermediates of N-9 isomer and N-7 isomer [21]. The complex of N-9 isomer further reacted with vinyl ether at the N-3 position [23] in the presence of L-ProT to form a complex (**A**), followed by nucleophilic addition reaction to afford the thermodynamically stable N-9 alkoxyalkylated purines exclusively [15].



3q

Scheme 2. Reaction of 2,6-dichloropurine and D-(+)-glucal.

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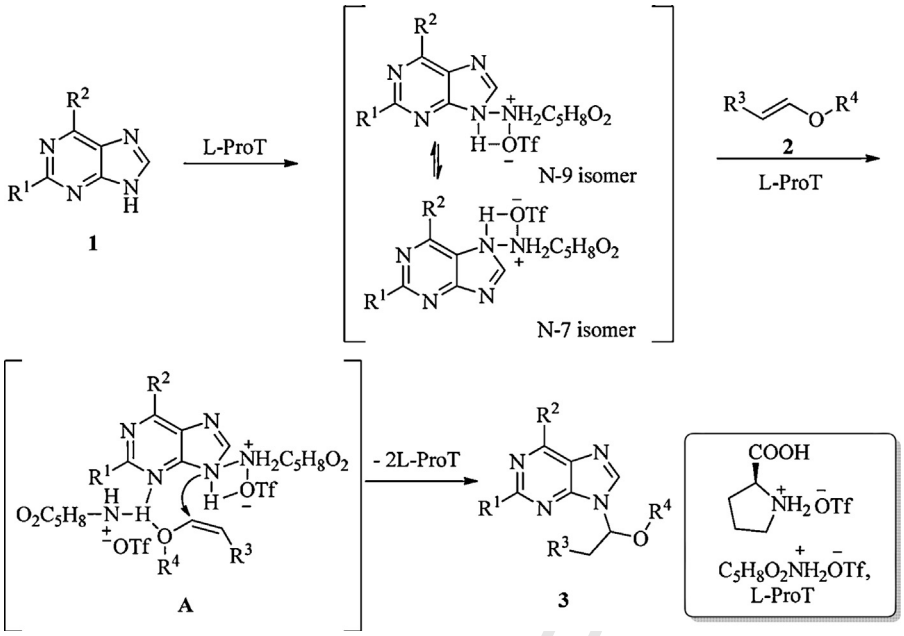

Scheme 3. Proposed mechanism for the reaction of purines and vinyl ethers.

4. Conclusion

In summary, we have developed an alternative route to N-9-alkoxyalkylated nucleobases through highly regioselective alkoxyalkylation of purines with vinyl ethers catalyzed by L-ProT. It is characterized by high regioselectivity, employment of cost-effective catalyst, mild conditions. Besides, the L-ProT catalyzed addition reaction shows general tolerance to a variety of functionalities, such as Cl and Boc, making this method quite attractive. Further application of this methodology to synthesize more promising N-9-alkoxyalkylated purine nucleosides is now underway in our laboratory.

Acknowledgments

Q2 We are grateful to the Natural Science Foundation of Zhejiang Province (No. LY13B020015) and Zhejiang Key Innovation Team of Green Pharmaceutical Technology (No. 2012R10043-07) for financial support.

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Please cite this article in press as: J.-J. Li, X.-X. Gui, L-ProT catalyzed highly regioselective *N*-alkoxyalkylation of purine rings with vinyl ethers, Chin. Chem. Lett. (2014), http://dx.doi.org/10.1016/j.cclet.2014.04.023