Chinese Chemical Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Communication

N-9 Alkylation of purines *via* light-promoted and metal-free radical relay

Runze Mao[1], Lifeng Sun[1], Yong-Shi Wang, Min-Min Zhou, De-Cai Xiong, Qin Li*, Xin-Shan Ye*

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

ARTICLE INFO

Article history:
Received 4 June 2017
Received in revised form 3 July 2017
Accepted 14 July 2017
Available online xxx

Keywords:
Photochemistry
Alkylation of purines
Regioselectivity
Metal free
CF_3 radical

ABSTRACT

A metal-free and light-promoted approach to the synthesis of *N*-9 alkylated purine nucleoside derivatives, *via* a CF_3 radical triggered radical relay pathway, has been developed. Purine nucleoside derivatives were prepared regioselectively in good to high yields. Photosensitizers and metals are free in this transformation. Visible light or even sunlight can be used as the source of light for the reactions.

Purine nucleoside derivatives play important roles in the field of chemical, biological and medicinal research. Some purine nucleoside analogues have been developed as anti-HIV and anti-cancer drugs [1]. Among them, *N*-9 substituted purine nucleoside analogues are a range of significant heterocyclic compounds involved in biological events [2]. These compounds serve as basic units of nucleic acids and coenzymes, and they are also key constituents in life processes such as metabolism, energy storage and cell signalling [3]. Moreover, there are a number of aminated tetrahydrofuran (THF) derivatives used as therapeutical agents (Fig. 1) [4].

To gain better understanding of these purine nucleoside derivatives, pure and structurally well-defined materials are highly desirable. Alkylation is still a major approach to prepare purine nucleoside derivatives, and the most widely-used donors include halogenated compounds [5], mesylates [6], and tosylates [7]. However, only a handful of studies have been done on the synthesis of purine nucleoside analogues *via* reaction of the sp^3 N—H bond of the purine ring and the sp^3 C—H of alkyl ether. Guo and co-workers developed the metal-free direct alkylation of purines with THF and ethers, but the reaction required high-power-light illumination and high temperature [8]. Hu and co-workers reported an elegant method for the metal-free direct C-H amination of ethers using a hypervalent iodine reagent at room temperature [9]. Liu and co-workers reported the peroxide-promoted coupling of nucleobases with ethers employing copper-catalyzed pathway, whereas requirements of metal, ligand and high excess of peroxide made this method complicated [10]. Besides, other groups also reported interesting work based on reaction of the sp^3 N—H bond and the sp^3 C—H of alkyl ether [11]. However, purines were excluded from the substrates, probably due to their low reactivity when compared with other substrates. Meanwhile, regiospecific alkylation (*N*-9 or *N*-7) of purine is another challenge, thus the site-selective alkylation of purine analogues at the *N*-9 position is in great demand.

To tackle these problems, we therefore hypothesized that an electrophilic CF_3 radical-triggered radical relay would probably lead to an alternative approach to the preparation of *N*-9 alkylated purine nucleoside derivatives. As we know, in recent years, the use of organic photoredox catalysts in a myriad of synthetic transformations has shown a remarkable "renaissance" [12]. We imagined that visible-light-promoted excitation of $[Ru(bpy)_3]^{2+}$ would precede a SET process to Umemoto's reagent to generate an electrophilic CF_3 radical [13] and $[Ru(bpy)_3]^{3+}$ (Scheme 1). On account of the polar effects [14], the *N*-radical **1** was generated through a hydrogen atom transfer (HAT) because of CF_3 radical, which was sequentially followed by another HAT process to form *C*-radical **2**. The *C*-radical **2** could be quickly oxidized by $[Ru(bpy)_3]^{3+}$ to an oxocarbenium ion **3** [15], which was then trapped by the nucleophilic purine *N*-9 position, thus forming the *N*-9 alkylated purine nucleoside derivatives **4**.

* Corresponding authors.
E-mail addresses: liqin@bjmu.edu.cn (Q. Li), xinshan@bjmu.edu.cn (X.-S. Ye).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.cclet.2017.08.005

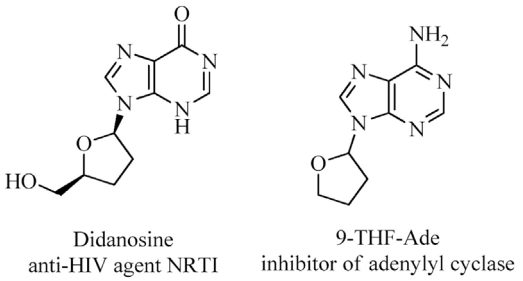
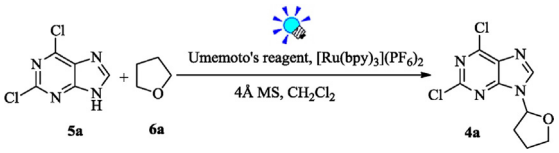


Fig. 1. Selected examples of aminated THF derivatives that exhibit biological activities.

Herein, we report our results inspired by the hypothesis in Scheme 1. Our initial reaction conditions involved irradiation with blue LEDs (λ_{max} = 455 nm) in the presence of 2,6-dichloropurine **5a** (0.030 mmol), tetrahydrofuran (THF) (1.0 mL), Umemoto's reagent (0.078 mmol), photocatalyst $[Ru(bpy)_3](PF_6)_2$ (0.0015 mmol) and 4 Å molecular sieves in CH_2Cl_2 (2.0 mL) (Table 1). When the standard conditions were used, the desired product **4a** was obtained in nearly quantitative yield. The control experiments demonstrated that the irradiation and the use of Umemoto's reagent are essential. The solvent screening experiments showed the insignificant differences or inferior results from those obtained using CH_2Cl_2. However, the irradiation without $[Ru(bpy)_3](PF_6)_2$ provided the similar yield of 99%! This surprising outcome is likely due to the formation of an electron donor-acceptor (EDA) complex [16], in which purine and Umemoto's reagent may serve as the electron donor and electron acceptor, respectively. Thanks to the large conjugated system, the EDA complex could be employed directly as a photon-absorbing EDA that would avoid using photocatalysts.

We next investigated the substrate scope of the reaction under the reaction conditions depicted in entry 7 of Table 1. Under the optimized high-yielding reaction conditions, various purines and several other alkyl ethers were examined. As shown in Table 2, various purines were employed as substrates, and different 6-halopurine derivatives **5a–5c** could react with THF smoothly (entries 1–3). The purine derivatives with nitrogen-containing groups at the C-6 position (**5d–5f**) could also afford the alkylated products in good yields (entries 4-6). Besides, it seemed that when the purine derivatives with C-2 position replaced by halogen atoms (such as Cl and F) were used, the yields of products were increased slightly (entries 1, 2 and 5).

Table 1
Initial screening and optimization.[a]

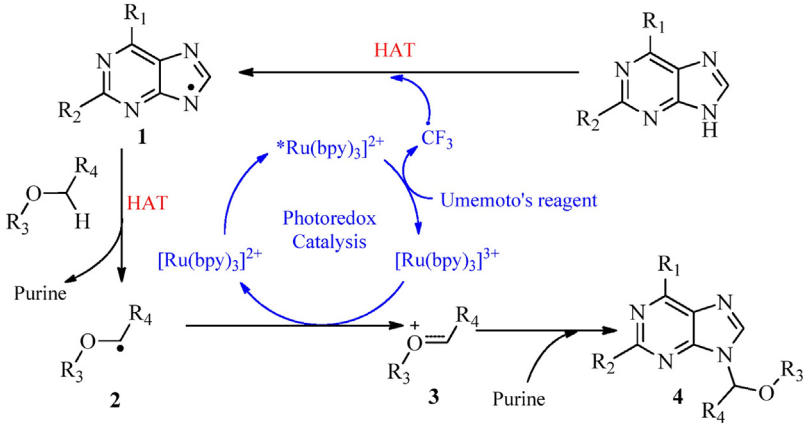


Entry	Change from standard conditions	Yield (%)[b]
1	None	99
2	Reaction run in the dark	0
3	No Umemoto's reagents	0
4	CH_3CN (2.0 mL) as solvent	50
5	DMF (2.0 mL) as solvent	0
6	Toluene (2.0 mL) as solvent	30
7	No photocatalyst	99

[a] Unless specified, a mixture of **5a** (0.030 mmol), THF (1.0 mL), Umemoto's reagent (0.078 mmol), photocatalyst $[Ru(bpy)_3](PF_6)_2$ (0.0015 mmol) and 4 Å molecular sieves (200 mg) in CH_2Cl_2 (2.0 mL) was exposed to blue LEDs irradiation (λ_{max} = 455 nm) at room temperature for 12 h.
[b] Isolated yield.

After surveying various nucleobases, we turned to test the reactions of various ethers with 2,6-di-chloropurine **5a** under the optimized reaction conditions (Table 2, entries 7–10). To our delight, various ethers were proven to be reliable reactants as illustrated in Table 2. Cyclic ether compounds, either five- (**6a**) or six-membered ring (**6b** or **6c**), could afford the desired products in good yields (entries 1, 7 and 8). The sterically hindered compound methyl *tert*-butyl ether (MTBE) (**6d**) also underwent this reaction to yield the product **4i** (entry 9). Interestingly, when the unsymmetrical ether isochroman (**6e**) was used as substrate, a regioselective product **4j** was obtained in good yield (entry 10). The high efficiency of this light-promoted synthesis of *N*-9 alkylated purine nucleoside derivatives was further highlighted by the irradiation of sunlight. The reaction of **5a** and **6a** could also give product **4a** in good yield (71%, Scheme 2).

With the establishment of substrate scope, we also wished to find some evidence to investigate the mechanism of this reaction. It was found that when running the reaction under the optimized reaction conditions depicted (Table 1, entry 7) in the presence of 3.0 equiv. of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), barely no product was obtained even prolonged exposure to light. Besides, the PBN (α-phenyl *N*-tertiary-butyl nitrone) trapped CF_3



Scheme 1. Original hypothesis for the synthesis of *N*-9 alkylated purine nucleoside derivatives.

Please cite this article in press as: R. Mao, et al., *N*-9 Alkylation of purines *via* light-promoted and metal-free radical relay, Chin. Chem. Lett. (2017), http://dx.doi.org/10.1016/j.cclet.2017.08.005