Chinese Chemical Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Original article

Synthesis of C8-alkyl-substituted purine analogues by direct alkylation of 8-*H* purines with tetrahydrofuran catalyzed by $CoCl_2 \cdot 6H_2O$

Hong-Ying Niu [a,*], Ling-Yun Su [b], Shi-Xia Bai [b], Jian-Ping Li [b], Xi-Lan Feng [a], Hai-Ming Guo [b]

[a] School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China
[b] School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China

ARTICLE INFO

Article history:
Received 1 April 2016
Received in revised form 25 May 2016
Accepted 26 May 2016
Available online xxx

Keywords:
Purine
C–H activation
Alkylation
Tetrahydrofuran
Co-catalyzed

ABSTRACT

C8-Alkyl-substituted purine analogues were synthesized through direct alkylation of 8-*H* purine with tetrahydrofuran in the presence of Co catalyst in one step. The reactions gave a series of novel C8-oxygen heterocyclic alkyl purine compounds in good yields under mild reaction conditions by the readily available alkylating reagents, providing a complementary route to the classical coupling reactions for the synthesis of C8-alkyl-substituted purine analogues.

1. Introduction

Purine bases and nucleosides show a wide range of biological and pharmaceutical activity such as antiviral or anticancer activity [1–9]. Especially, purine derivatives with alkyl group at C8 have played much more important role in heterocyclic compounds because of their unique bioactivities. For example, 8-metyladenosine is highly selective inhibitor of vaccinia virus, and 8-ethyladenosine shows special biochemistry activity against respiratory syncytial virus [10]. 8-Vinyladenosine has a high bioactivity against herpes simplex virus (type 1) [11], and 8-cyclopentyl-2,6-diphenylpurine has been shown to be very promising with an affinity of 0.29 nmol/L at the human adenosine A_1 receptor [12].

The classical methods for the synthesis of 8-alkylpurines are transition-metal catalyzed cross-coupling reactions of 8-halogenopurines with various alkylating reagents including tetraorganotin [13–15], tetraorganozinc [16], alkylaluminium [17,18], alkylboronic acids [19], grignard reagents [20–22], *etc.* (Scheme 1). Though the coupling reactions have received significant attention due to their generality over the last several years, they do involve the following disadvantage aspects: the reactions often demand expensive metal catalysts, complex ligands, organometallic reagents which usually need to be prepared by multi-step processes, the pre-activation of C–H bond to C–X (X = Cl, Br, I, OTf, *etc.*) bond, the anhydrous and anaerobic conditions. Therefore, it is still of great importance to develop alternative methods for the preparation of 8-alkylpurines.

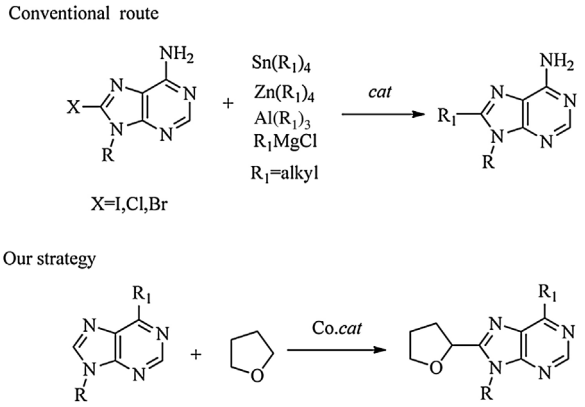
Double C–H activation was successfully developed by using transition-metal as catalyst for the efficient construction of carbon–carbon bond formation as a highly atom-economical and direct approach [23–34]. However, only one example of such direct double C–H activation process was used for the alkylation of C-6 of purines up to now. In 2002, Ellman *et al.* successfully synthesized C-6 alkylated purine *via* rhodium-catalyzed C–H bond activation using alkene as alkylating reagent at 150 °C in THF [35]. However, alkyl esters are seldom used as alkylating reagents though they are cheaper and more readily available than their corresponding alkyl halides [36]. On our continued interest on the modification of purines [37–41], herein, we report our discovery for the synthesis of C8 alkylated purine by direct C–H bond activation of purines in the presence of cheap and readily available Co catalyst from 8-H purines and tetrahydrofuran.

2. Experimental

All reagents and solvents were purchased from commercial sources and purified commonly before used. For column

* Corresponding author.
E-mail address: niu_hy@163.com (H.-Y. Niu).

http://dx.doi.org/10.1016/j.cclet.2016.06.009



Scheme 1. Different routes for the synthesis of 8-alkylpurines.

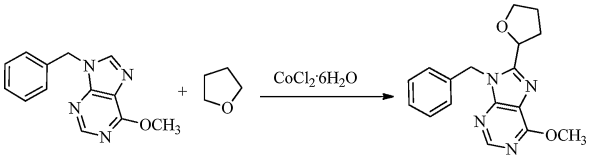
chromatography silica gel (200–300 mesh) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H NMR and ^{13}C NMR. Chemical shifts δ are given in ppm relative to tetramethylsilane as internal standard, residual $CDCl_3$/DMSO-d_6 for ^{1}H NMR or $CDCl_3$ in ^{13}C NMR spectroscopy. High-resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TOF MS/MS system. Melting points were recorded with a micro melting point apparatus and uncorrected.

Synthesis of 9-benzyl-6-methoxy-8-(tetrahydrofuran-2-yl)-9*H*-purin by direct alkylation of 8-*H* purine with tetrahydrofuran catalyzed by $CoCl_2{\cdot}6H_2O$: A mixture of 9-benzyl-6-methoxy-9*H*-purine (0.125 mmol), $CoCl_2{\cdot}6H_2O$ (20 mol%), $MgSO_4$ (0.625 mmol), and THF (2 mL) in a 25 mL of reaction tube was stirred at 70 °C for 48 h under O_2 atmosphere and monitored by TLC. After cooling, the reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the desired product **3a**. The characterization data of the products are summarized in the Supporting information.

3. Results and discussion

We initially carried out our experiments by employing 9-benzyl-6-methoxyl-9*H*-purine and tetrahydrofuran as model substrates (Table 1). First, the reaction was conducted by using air as oxidant in the presence of 20 mol% catalytic amount of $CoCl_2{\cdot}6H_2O$, and the corresponding 8-alkylated product was given in poor yield (35%, entry 1). Since the reaction is a kind of dehydrogenation reaction between the substrates, we tried to use oxygen as the oxidant instead of air, and got a higher yield (50%, entry 2). Then different cobalt catalysts were tested and $CoCl_2{\cdot}6H_2O$ was proved to be the best choice (entries 2–4). Adding some oxidants such as oxone and AgOAc did not enhance the yield (entries 5–6), and no target product was obtained when CuI was added (entry 7). However, a higher yield was obtained when anhydrous magnesium sulfate or molecular sieves was used as an additive (entries 8–9), and 5 equiv. of anhydrous magnesium sulfate led to a best yield (85%, entry 10). In order to verify whether $MgSO_4$ acted as a desiccant, we used anhydrous cobalt dichloride as catalyst in redistilled THF, the yield of the target product was only 50% (entry 11), proving that the role of magnesium sulfate or molecular sieves was more than a desiccant. When the reaction time was reduced to 24 h, no product was obtained (entry 12). And when the reaction time was prolonged from 48 h to 72 h, the yield of the product was almost the same (entry 10 *vs.* 13). The reaction solvent was subsequently screened. When 1 equivalent of THF as the reaction raw material was added to dichloromethane, ethanol, benzene, acetonitrile, no product was obtained, which indicated that excess THF was essential for the reaction (entries 14–17). And

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1[c]	$CoCl_2{\cdot}6H_2O$	—	THF	50	48	35
2	$CoCl_2{\cdot}6H_2O$	—	THF	70	48	50
3	$Co(NO_3)_2{\cdot}6H_2O$	—	THF	70	48	30
4	$Co(acac)_2{\cdot}6H_2O$	—	THF	70	48	30
5	$CoCl_2{\cdot}6H_2O$	0.5 eq. oxone	THF	70	48	50
6	$CoCl_2{\cdot}6H_2O$	0.5 eq. AgOAc	THF	70	48	40
7	$CoCl_2{\cdot}6H_2O$	0.5 eq. CuI	THF	70	48	0
8	$CoCl_2{\cdot}6H_2O$	1 eq. $MgSO_4$	THF	70	48	80
9	$CoCl_2{\cdot}6H_2O$	0.6 g molecular sieves (4Å)	THF	70	48	80
10	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	THF	70	48	85
11	$CoCl_2$	—	THF	70	48	50[d]
12	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	THF	70	24	0
13	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	THF	70	72	86
14[e]	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	DCM	70	48	0
15[e]	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	Ethanol	70	48	0
16[e]	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	Benzene	70	48	0
17[e]	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	CH_3CN	70	48	0
18	$CoCl_2{\cdot}6H_2O$	5 eq. $MgSO_4$	THF	120	48	35

[a] Reaction conditions: **1a** (0.125 mmol), additive (0.625 mmol), catalyst (20 mol%), THF (2 mL), O_2, 70 °C.
[b] Isolated yield based on **1a**.
[c] Using air as oxidant.
[d] Redistilled THF, dehydrated $CoCl_2$.
[e] 1 equiv. THF, 2 mL of solvent.

Please cite this article in press as: H.-Y. Niu, et al., Synthesis of C8-alkyl-substituted purine analogues by direct alkylation of 8-*H* purines with tetrahydrofuran catalyzed by $CoCl_2{\cdot}6H_2O$, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.06.009