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Microwave promoted palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of 6-chloropurines with sodium tetraarylborate in water

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ABSTRACT

An efficient method for the synthesis of 6-arylpurines (nucleosides) was developed via Suzuki–Miyaura cross-coupling reactions of 6-chloropurines (nucleosides) and sodium tetraarylborate in neat water (ethanol). The process gave good to high isolated yields within a short reaction time under microwave irradiated conditions.

1. Introduction

Purine bases and nucleosides have broad application in biological and pharmaceutical chemistry.[1] Especially, purine derivatives with various substituents (such as *C*-, *N*-, *O*-, *S*-substituents) at C6 have attracted much more attention in heterocyclic compounds because of their unique bioactivities.[2] Recently, many reports show that the 6-arylpurine derivatives possess anti-HCV, cytostatic, and antimycobacterial activities.[3] Up to now, several methodologies were described for the preparation of 6-arylpurine analogues and nucleosides, such as C–OH bond activation,[4] Kumada coupling reaction,[5] Negishi coupling reaction,[6] Stille coupling reaction,[7] and Suzuki–Miyaura cross-coupling reaction as another methodology was also developed by several groups, especially by Hocek's group[8] and Lakshman's group.[9] For example, Hocek and co-workers reported the synthesis of 6-aryl and heteroarylpurine analogues in good yields via cross-coupling reactions of 6-chloropurines with diverse aryltrifluoroborates using H_2O and MeCN as cosolvent.[10]

Based on the review of related literatures, we found that there are few reports on using sodium tetraarylborate as an arylation agent for the synthesis of 6-arylpurine derivatives except that Villemin et al. reported the synthesis of 9-benzyl-6-phenylpuruine in monomethylformamide.[11] Compared with arylboronic acid and aryltrifluoroborates, sodium tetraarylborate have better atom economy and good solubility in water, which allow the reaction to be conducted in neat water under mild reaction conditions.

Over the past few decades, water have been reported to be a perfect solvent because of its safe, environmentally benign and cheap properties.[12] To the best of our knowledge, no successful Suzuki–Miyaura cross-coupling reaction of 6-chloropurines (nucleosides) with arylation reagents in neat water has been described. The use of both water as solvent and sodium tetraarylborate as arylation reagent makes the reaction process more attractive. Based on our preliminary work on the synthesis of various nucleoside analogues,[13] herein, a green and efficient protocol for the synthesis of 6-arylpurine nucleosides was described via the Suzuki–Miyaura cross-coupling reactions of 6-chloropurine nucleosides and sodium tetraarylborate in neat water.

Initially, we tried to optimize the catalytic system and reaction conditions on the model reaction of 9-benzyl-6-chloro-9*H*-purine with sodium tetraphenylborate. Several classic palladium catalysts for the Suzuki–Miyaura reaction were used in this experiment. As

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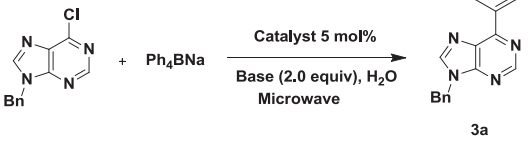
shown in Table 1, $Pd(PPh_3)_4$ did not give any product (entry 1), and $PdCl_2$ gave a trace yield of **3a** (entry 2). When we used $Pd(OAc)_2$ or $Pd(dppf)Cl_2$ as catalyst, a small amount of **3a** was obtained (entries 3 and 4). On the other hand, the reaction in the presence of $Pd(PPh_3)_2Cl_2$ gave **3a** in moderate yield (entry 5), so we chose $Pd(PPh_3)_2Cl_2$ as the suitable catalyst. Next, we investigated the effect of bases. Unfortunately, K_2CO_3, Cs_2CO_3, and K_2HPO_4 did not give acceptable amount of **3a** (entries 6–8), and Na_2CO_3 only gave 47% yield (entry 5). Because the yield was not satisfied, we decided to prolong the reaction time. When the reaction time was 20 min, the yield was low (entry 9, 61%). By increasing the reaction time to 30 min, the yield reached 85% (entry 10). When the reaction time was 40 min, no significant change in the yield was observed (entry 11, 87%). Reducing the amount of **2a** also led to lower yield (entry 12, 65%). Therefore, Pd $(PPh_3)_2Cl_2$ as the catalyst, Na_2CO_3 as base and the reaction time 30 min were the optimized reaction conditions.

Table 1
Optimization of reaction conditions[a]



3a

Entry	Catalyst	Base	Time (min)	Yield[b] (%)
1	$Pd(PPh_3)_4$	Na_2CO_3	10	0
2	$PdCl_2$	Na_2CO_3	10	Trace
3	$Pd(OAc)_2$	Na_2CO_3	10	10
4	$Pd(dppf)Cl_2$	Na_2CO_3	10	23
5	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	10	47
6	$Pd(PPh_3)_2Cl_2$	K_2CO_3	10	Trace
7	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	10	0
8	$Pd(PPh_3)_2Cl_2$	K_2HPO_4	10	0
9	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	20	61
10	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	30	85
11	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	40	87
12[c]	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	30	65

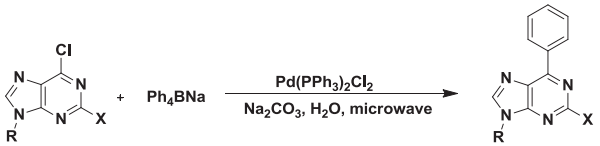
[a] Reaction conditions: 9-benzyl-6-chloro-9*H*-purine (0.25 mmol), sodium tetraphenylborate (0.0938 mmol), catalyst 5 mol % based on 9-benzyl-6-chloro-9*H*-purine, base (0.5 mmol), MWI 400 W 100 °C.
[b] Isolated yields based on 9-benzyl-6-chloro-9*H*-purine.
[c] Sodium tetraphenylborate (0.08 mmol) was used.

2. Results and discussion

To evaluate the generality of the reaction, a number of 6-chloropurine derivatives with various substituents, including a sugar carbon substituent at N9, were subjected to the optimized reaction conditions, affording the desired 6-phenylpurine derivatives in good to excellent isolated yields (61–98%) (Table 2). The type of substituent at N9 had a little impact on the yield of the products: the alkyl-substituted substrates gave higher yields, while the sugar-substituted substrates gave lower yields. When acetylated nucleosides (**1g**) was subjected to the reaction in water, the C–N glycosidic bond breaking product was obtained. So we used ethanol as solvent, and then 6-arylpurine nucleoside (**3g**) was obtained in an acceptable yield (entry 7). Unfortunately, unprotected 6-chloropurine nucleoside gave the C–N glycosidic bond breaking product both in water and in ethanol.

Intrigued by the results described above, a series of sodium tetraarylborate were chosen as aryl agents to probe whether the Suzuki–Miyaura reactions could be easily accessed. The results are shown in Table 3. As expected, when we used 9-benzyl-6-chloro-9*H*-purine as the starting material, the reactions proceeded smoothly to give the corresponding products in good to high yields

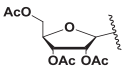
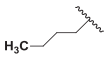
Table 2
The reaction of Ph_4BNa with various 6-chloropurines[a]



1a-1g: X=H
1h: X=NH_2

2a

3a-3g: X=H
3h: X=NH_2

Entry	Product	R	Yield[b] (%)
1	3a		85
2	3b		73
3	3c		88
4	3d		98
5	3e		93
6	3f		90
7[c]	3g		61
8	3h		92

[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.0938 mmol), $Pd(PPh_3)_2Cl_2$ 5 mol % based on **1**, Na_2CO_3 (0.5 mmol), solvent: H_2O (2 mL), MWI 400 W 100 °C for 30 min.
[b] Isolated yields based on **1**.
[c] Solvent: EtOH (2 mL), MWI 400 W 90 °C for 30 min.

(entries 1–6). When we used protected 6-chloropurine nucleoside as the substrate, the reactions proceeded to give the desired product in a moderate yields in ethanol (entries 7–10). This might be due to the relatively poor solubility of sodium carbonate in ethanol.

3. Conclusion

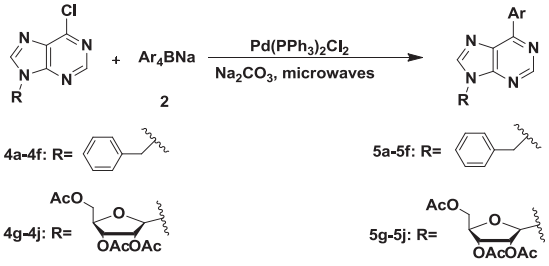
We have developed a general, rapid, and eco-friendly protocol for the synthesis of 6-arylpurines between 6-chloropurine analogues and sodium tetraarylborate under microwave irradiation in neat water, which avoids the use of toxic solvents, such as acetonitrile, toluene, tetrahydrofuran, 1,4-dioxane or tetrahydropyran. Furthermore, most of the reactions involved are efficient, giving the desired compounds in higher yields within short reaction time. This environmentally friendly procedure represents a promising green route for the synthesis of these important 6-arylpurine (nucleoside) compounds.

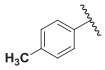
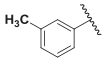
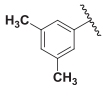
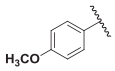
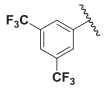
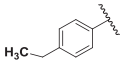
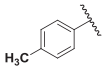
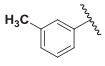
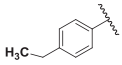
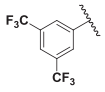
4. Experimental section

4.1. General information

Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for ^1H NMR, 100 MHz for ^{13}C NMR. Proton

Table 3
The reaction of 6-chloropurines with various sodium tetraarylborate[a]



Entry	Ar	Product	Yield[b] (%)
1		5a	96
2		5b	97
3		5c	92
4		5d	83
5		5e	78
6		5f	94
7[c]		5g	72
8[c]		5h	70
9[c]		5i	63
10[c]		5j	54

[a] Reaction conditions: **4** (0.25 mmol), **2** (0.0938 mmol), $Pd(PPh_3)_2Cl_2$ 5 mol % based on **4**, Na_2CO_3 (0.5 mmol), solvent: H_2O (2 mL), MWI 400 W 100 °C for 30 min.
[b] Isolated yields based on **4**.
[c] Solvent: EtOH (2 mL), MWI 400 W 90 °C for 30 min.

chemical shifts δ were given in parts per million relative to tetramethylsilane (0.00 ppm) in $CDCl_3$ or to the residual proton signals of the deuterated solvent CD_3OD (3.31 ppm). High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TofMS/MS system. For column chromatography 200–300 mesh silica gel (GF_{254}) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used. All microwave irradiation experiments were carried out in the cavity of a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity infrared sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, PR China) with continuous irradiation power from 0 to 600 W. The reactions were carried out in glass vials. The temperature was measured with an IR sensor on the outer surface of the reaction vials.

4.2. General procedure for the synthesis of $NaBAr_4$

Slow addition of a solution of (60 mmol) of aryl bromides in THF (20 mL) to Mg turnings (0.60 mol) in THF (5 mL), followed by refluxing for 1 h, gave a dark gray solution of the aryl Grignard reagent. After the vial was cooled to room temperature, and then $B(OCH_3)_3$ (0.125 mol) was slowly added to the mixture. The reaction mixture was stirred until the vial was cooled to room temperature. Then the reaction mixture was added to Na_2CO_3 (6.25 g) in water (50 mL), stirred for 30 min. The resulted mixture was extracted with ethyl acetate (4×50 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from petroleum ether.

4.3. General procedure for the Suzuki–Miyaura cross-coupling reaction

9-Benzyl-6-chloro-9*H*-purine (0.25 mmol) and sodium tetraphenylborate (0.0938 mmol) were put in a 10 mL glass vial, and then Na_2CO_3 (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.0125 mmol), and water (2 mL) was added. Then the resulted turbid solution was put into the cavity of the microwave synthesis apparatus and irradiated at 400 W at 100 °C for 30 min under nitrogen atmosphere. After completion of the reaction, the vial was cooled to room temperature. The reaction mixture was extracted with ethyl acetate (3×5 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulted residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate) to give the desired products **3a**.

*4.3.1. 9-Benzyl-6-phenyl-9H-purine (**3a**).* White solid, mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.79 (q, J=3.2 Hz, 2H), 8.08 (s, 1H), 7.58–7.52 (m, 3H), 7.36–7.30 (m, 5H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 152.5, 144.2, 135.6, 135.2, 131.0, 130.9, 129.8, 129.1, 128.7, 128.6, 127.8, 47.2. HRMS: calcd for $C_{18}H_{15}N_4$ $[M+H]^+$ 287.1291, found 287.1296.

*4.3.2. 9-(2-Chlorobenzyl)-6-phenyl-9H-purine (**3b**).* White solid, mp 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.79–8.77 (m, 2H), 8.20 (s, 1H), 7.59–7.52 (m, 3H), 7.43 (t, J=7.6 Hz, 1H), 7.31–7.24 (m, 3H), 5.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.6, 152.5, 144.3, 135.6, 133.5, 132.7, 131.0, 130.8, 130.3, 130.1, 130.0, 129.8, 128.7, 127.5, 44.9. HRMS: calcd for $C_{18}H_{14}ClN_4$ $[M+H]^+$ 321.0902, found 321.0906.

*4.3.3. 6,9-Diphenyl-9H-purine (**3c**).* White solid, mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.82 (q, J=3.3 Hz, 2H), 8.41 (s, 1H), 7.76 (q, J=3.2 Hz, 2H), 7.65–7.53 (m, 5H), 7.51 (t, J=7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 155.5, 153.1, 143.3, 135.5, 131.5, 131.1, 130.0, 129.8, 128.7, 128.6, 123.8. HRMS: calcd for $C_{17}H_{13}N_4$ $[M+H]^+$ 273.1135, found 273.1142.

*4.3.4. 9-Methyl-6-phenyl-9H-purine (**3d**).* White solid, mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.67 (d, J=7.2 Hz, 2H), 7.87 (s, 1H), 7.47–7.41 (m, 3H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 152.6, 152.2, 144.7, 135.6, 130.8, 129.6, 128.5, 29.6. HRMS: calcd for $C_{12}H_{11}N_4$ $[M+H]^+$ 211.0978, found 211.0986.

*4.3.5. 9-Ethyl-6-phenyl-9H-purine (**3e**).* White solid, mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.72 (d, J=7.6 Hz, 2H), 7.99 (s, 1H), 7.49–7.42 (m, 3H), 4.19 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 152.2, 152.1, 143.8, 135.7,

131.1, 130.8, 129.7, 128.5, 38.8, 15.2. HRMS: calcd for $C_{13}H_{13}N_4$ $[M+H]^+$ 225.1135, found 225.1142.

*4.3.6. 6-Phenyl-9-propyl-9H-purine (**3f**).* Light yellow powder, mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.73 (d, J=7.2 Hz, 2H), 8.02 (s, 1H), 7.52–7.45 (m, 3H), 4.16 (t, J=7.2 Hz, 2H), 1.88 (q, J=7.3 Hz, 2H), 0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 152.4, 152.2, 144.3, 135.7, 131.0, 130.9, 129.7, 128.6, 45.5, 23.2, 11.2. HRMS: calcd for $C_{14}H_{15}N_4$ $[M+H]^+$ 239.1291, found 239.1295.

*4.3.7. 2-(Acetoxymethyl)-5-(6-phenyl-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**3g**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.73 (q, J=3 Hz, 2H), 8.28 (s, 1H), 7.58–7.52 (m, 3H), 6.29 (d, J=5.2 Hz, 1H), 6.01 (t, J=5.2 Hz, 1H), 5.70 (t, J=4.8 Hz, 1H), 4.48–4.45 (m, 2H), 4.39 (q, J=6 Hz, 1H), 2.14 (d, J=10.4 Hz, 6H), 2.07 (d, J=6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 155.5, 152.7, 152.0, 142.6, 135.3, 131.6, 131.2, 129.8, 128.7, 86.4, 80.3, 73.1, 70.6, 63.1, 20.8, 20.6, 20.4. HRMS: calcd for $C_{22}H_{23}N_4O_7$ $[M+H]^+$ 455.1561, found 455.1564.

*4.3.8. 9-Butyl-6-phenyl-9H-purin-2-amine (**3h**).* White solid, mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (q, J=3.2 Hz, 2H), 7.80 (s, 1H), 7.54–7.49 (m, 3H), 5.21 (s, 2H), 4.11 (t, J=7.2 Hz, 2H), 1.89–1.81 (m, 2H), 1.43–1.33 (m, 2H), 0.97 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 155.5, 154.4, 142.0, 135.6, 132.6, 130.7, 129.5, 128.5, 128.0, 125.6, 43.2, 31.8, 19.9, 13.6. HRMS: calcd for $C_{15}H_{18}N_5$ $[M+H]^+$ 268.1557, found 268.1560.

*4.3.9. 9-Benzyl-6-p-tolyl-9H-purine (**5a**).* White solid, mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.70 (d, J=8.4 Hz, 2H), 8.07 (s, 1H), 7.37–7.30 (m, 7H), 5.45 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 152.6, 152.4, 143.9, 141.4, 135.2, 132.9, 130.7, 129.7, 129.4, 129.1, 128.5, 127.8, 47.2, 21.7. HRMS: calcd for $C_{19}H_{17}N_4$ $[M+H]^+$ 301.1448, found 301.1450.

*4.3.10. 9-Benzyl-6-m-tolyl-9H-purine (**5b**).* White solid, mp 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.61 (d, J=7.6 Hz, 2H), 8.55 (s, 1H), 8.09 (s, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.36–7.30 (m, 6H), 5.46 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.6, 152.5, 144.1, 138.3, 135.5, 135.2, 131.9, 131.0, 130.0, 129.1, 128.6, 128.5, 127.8, 127.2, 47.2, 21.6. HRMS: calcd for $C_{19}H_{17}N_4$ $[M+H]^+$ 301.1448, found 301.1451.

*4.3.11. 9-Benzyl-6-(3,5-dimethylphenyl)-9H-purine (**5c**).* Light yellow powder, mp 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.41 (s, 2H), 8.08 (s, 1H), 7.37–7.26 (m, 5H), 7.17 (s, 1H), 5.44 (s, 2H), 2.45 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 152.5, 144.0, 138.2, 135.5, 135.2, 132.8, 130.9, 129.1, 128.5, 127.85, 127.5, 47.2, 21.5. HRMS: calcd for $C_{20}H_{19}N_4$ $[M+H]^+$ 315.1604, found 315.1613.

*4.3.12. 9-Benzyl-6-(4-methoxyphenyl)-9H-purine (**5d**).* White solid, mp 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.81 (q, J=3 Hz, 2H), 8.60 (s, 1H), 7.36–7.30 (m, 5H), 7.07 (q, J=7.3 Hz, 2H), 5.46 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.6, 152.6, 152.3, 143.6, 135.3, 131.5, 130.4, 129.1, 128.5, 128.3, 127.8, 114.1, 55.4, 47.2. HRMS: calcd for $C_{19}H_{17}N_4O$ $[M+H]^+$ 317.1397, found 317.1400.

*4.3.13. 9-Benzyl-6-(3,5-bis(trifluoromethyl)phenyl)-9H-purine (**5e**).* White solid, mp 125–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 2H), 9.10 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.39–7.33 (m, 5H), 5.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 152.5, 150.9, 145.1, 137.7, 134.8, 132.1, 131.8, 131.2, 129.8, 129.2, 128.8, 127.9, 124.7, 124.1, 122.0, 47.5. HRMS: calcd for $C_{20}H_{13}F_6N_4$ $[M+H]^+$ 423.1039, found 423.1041.

*4.3.14. 9-Benzyl-6-(4-ethylphenyl)-9H-purine (**5f**).* White solid, mp 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.72 (d, J=8 Hz, 2H), 8.05 (s, 1H), 7.38 (d, J=8.4 Hz, 2H), 7.33–7.27 (m, 5H), 5.41 (s, 2H), 2.72 (q, J=7.6 Hz, 2H), 1.27 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 152.6, 152.4, 147.7, 143.9, 135.3, 133.1, 130.7, 129.8, 129.1, 128.5, 128.3, 127.8, 47.2, 29.0, 15.5. HRMS: calcd for $C_{20}H_{19}N_4$ $[M+H]^+$ 315.1604, found 315.1608.

*4.3.15. 2-(Acetoxymethyl)-5-(6-p-tolyl-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**5g**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.73 (q, J=3 Hz, 2H), 8.28 (s, 1H), 7.58–7.52 (m, 3H), 6.29 (d, J=5.2 Hz, 1H), 6.01 (t, J=5.2 Hz, 1H), 5.70 (t, J=4.8 Hz, 1H), 4.48–4.45 (m, 2H), 4.39 (q, J=6 Hz, 1H), 2.14 (d, J=10.4 Hz, 6H), 2.07 (d, J=6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.6, 169.4, 155.5, 152.6, 142.9, 142.3, 135.7, 132.6, 131.4, 129.8, 129.5, 128.7, 86.3, 80.3, 73.1, 70.7, 63.1, 21.9, 20.8, 20.6, 20.4. HRMS: calcd for $C_{23}H_{24}N_4NaO_7$ $[M+Na]^+$ 491.1537, found 491.1545.

*4.3.16. 2-(Acetoxymethyl)-5-(6-m-tolyl-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**5h**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.54 (d, J=7.6 Hz, 2H), 8.48 (s, 1H), 8.26 (s, 1H), 7.41 (t, J=7.6 Hz, 1H), 7.30 (d, J=7.6 Hz, 1H), 6.26 (d, J=5.2 Hz, 1H), 5.99 (t, J=5.6 Hz, 1H), 5.68 (t, J=5.2 Hz, 1H), 4.45–4.41 (m, 2H), 4.36 (q, J=6 Hz, 1H), 2.44 (s, 3H), 2.10 (d, J=10 Hz, 6H), 2.04 (d, J=5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 155.6, 152.6, 151.9, 142.6, 138.3, 135.2, 132.0, 131.6, 130.0, 128.6, 127.2, 86.3, 80.3, 73.0, 70.6, 63.0, 21.6, 20.8, 20.5, 20.4. HRMS: calcd for $C_{23}H_{24}N_4NaO_7$ $[M+Na]^+$ 491.1537, found 491.1541.

*4.3.17. 2-(Acetoxymethyl)-5-(6-(4-ethylphenyl)-9H-purin-9-yl)-tetrahydrofuran-3,4-diyl diacetate (**5i**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.67 (d, J=8 Hz, 2H), 8.26 (s, 1H), 7.39 (d, J=8 Hz, 2H), 6.29 (d, J=5.2 Hz, 1H), 6.01 (t, J=5.6 Hz, 1H), 5.71 (t, J=5.2 Hz, 1H), 4.46 (q, J=4.1 Hz, 2H), 4.39 (q, J=5.9 Hz, 1H), 2.73 (q, J=7.6 Hz, 2H), 2.14 (d, J=10 Hz, 6H), 2.08 (d, J=6.8 Hz, 3H), 1.28 (t, J=7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 155.6, 152.7, 151.9, 147.9, 142.3, 132.8, 131.4, 129.8, 128.3, 86.3, 80.3, 73.1, 70.6, 63.1, 29.0, 20.8, 20.6, 20.4, 15.4. HRMS: calcd for $C_{24}H_{26}N_4NaO_7$ $[M+Na]^+$ 505.1694, found 505.1697.

*4.3.18. 2-(Acetoxymethyl)-5-(6-(3,5-bis(trifluoromethyl)phenyl)-9H-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**5j**).* Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 2H), 9.05 (s, 1H), 8.36 (s, 1H), 8.01 (s, 1H), 6.31 (d, J=5.2 Hz, 1H), 6.02 (t, J=5.2 Hz, 1H), 5.71 (t, J=4.8 Hz, 1H), 4.51–4.46 (m, 2H), 4.41 (q, J=5.4 Hz, 1H), 2.16 (d, J=9.2 Hz, 6H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.7, 169.5, 152.6, 152.5, 151.3, 143.7, 137.3, 132.1, 131.8, 129.8, 124.6, 121.9, 86.6, 80.4, 73.1, 70.6, 63.0, 20.8, 20.5, 20.4. HRMS: calcd for $C_{24}H_{20}F_6N_4NaO_7$ $[M+Na]^+$ 613.1128, found 613.1136.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.082.

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