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A Copper-Catalyzed Domino Route toward Purine-Fused Tricyclic Derivatives

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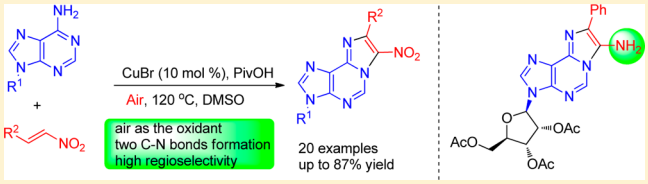
Supporting Information

ABSTRACT: Purine-fused tricyclic derivatives have been synthesized via a copper-catalyzed domino Michael/oxidative cross-coupling reaction between adenines and nitroolefins for the first time. With air as the oxidant, this method has high regioselectivity, which provides a new route for constructing purine-nucleoside-conjugated systems with two newly formed C−N bonds. Meanwhile, purine nucleosides with an exocyclic amino group could be obtained easily by simple reduction, which may lead to potential applications in fluorescence recognition of various bases in vivo.



INTRODUCTION

The valuable biological and medicinal activities of purine analogues have made the modification of purines among the hot topics in the chemical and pharmaceutical fields.[1] In particular, purine-fused tricyclic and polycyclic derivatives have attracted considerable attention because of their unique properties and special conjugated structures.[2] For example, purine-fused tricyclic 1,N^6-ethenoadenine 3′,5′-monophosphate (Figure 1) is a strongly fluorescent probe[3] and 9-hydroxy-1,N^6-benzetheno-2′-deoxyadenosine (Figure 1) exhibits binding activity toward HeLa cells.[4] It is well-known that the exocyclic hydroxyl or amino group in the nucleoside derivatives has a vital function in base pairing. If a hydroxyl or amino group is introduced into purine-fused polycyclics, they may work as fluorescent probes to recognize various bases in vivo. Thus, searching for a useful and efficient approach for the synthesis of purine-fused polycyclic derivatives with exocyclic hydroxyl or amino groups is highly desirable.

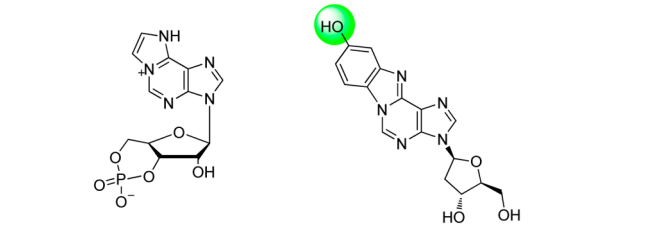


Figure 1. Selected examples of purine-fused polycyclic derivatives exhibiting strong fluorescence or biological activity.

The classical approach for the synthesis of purine-fused polycyclic derivatives is via the reaction of haloacetaldehyde with adenine or adenosine (Scheme 1a).[5] Later, Singer's group developed the reaction of *p*-benzoquinone with deoxyadenosine to afford purine-fused polycyclic derivatives with an exocyclic hydroxyl group (Scheme 1b).[4] However, the limitation of previous methods is the lack of structural diversity in the products. Very recently, our group reported the

Scheme 1. Strategies for the Synthesis of Purine-Fused Polycyclic Derivatives

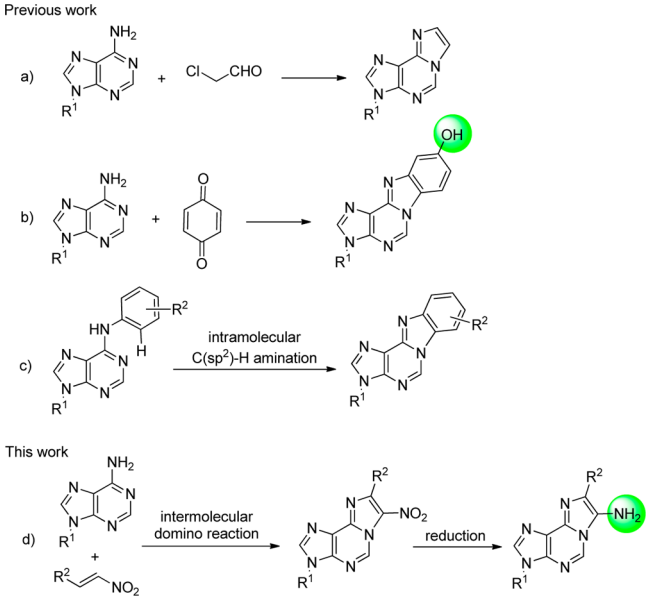


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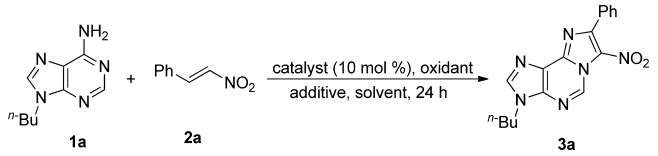
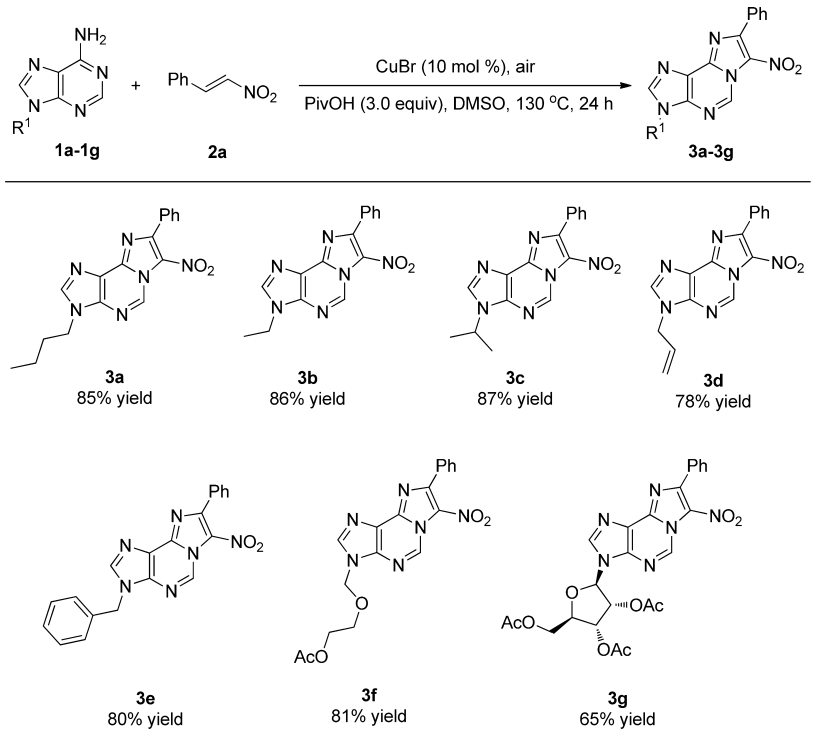
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant[b]	solvent	additive	T (°C)	yield (%)[c]
1	$Cu(OAc)_2$	$PhI(OAc)_2$	DMF	–	120	41
2	$Cu(OAc)_2$	O_2	DMF	–	120	46
3	CuCl	O_2	DMF	–	120	50
4	CuBr	O_2	DMF	–	120	61
5	CuI	O_2	DMF	–	120	43
6	CuBr	air	DMF	–	120	62
7	CuBr	30% H_2O_2	DMF	–	120	<5
8	CuBr	$K_2S_2O_8$	DMF	–	120	<5
9	CuBr	air	DMF	Cs_2CO_3	120	0
10	CuBr	air	DMF	HOAc	120	51
11	CuBr	air	DMF	TFA	120	46
12	CuBr	air	DMF	PivOH	120	75
13	CuBr	air	DCE	PivOH	70	43
14	CuBr	air	CH_3CN	PivOH	70	37
15	CuBr	air	DMSO	PivOH	130	85
16	CuBr	air	xylene	PivOH	100	52
17	CuBr	air	EG	PivOH	120	0
18[d]	CuBr	air	DMSO	PivOH	70	trace

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 equiv), catalyst (10 mol %), additive (3.0 equiv), solvent (2.0 mL), 24 h. [b]Oxidant (3.0 equiv); O_2 or air (1.0 atm). [c]Isolated yields. [d]Reaction time: 48 h.

Scheme 2. Reaction with Various Adenines[a,b]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 equiv), CuBr (10 mol %), PivOH (3.0 equiv), DMSO (2.0 mL), 130 °C, 24 h. [b]Isolated yields are shown.

intramolecular C(sp^2)–H amination reaction of 6-anilinopurine nucleosides to construct purine-fused polycyclic derivatives, in which the starting material should be preprepared beforehand (Scheme 1c).[6] Although great endeavors have been devoted to the synthesis of purine-fused polycyclic derivatives, the structural diversity of these derivatives is still very limited. Thus, developing an efficient method to obtain structurally diverse purine-fused polycyclic derivatives without preprepara-

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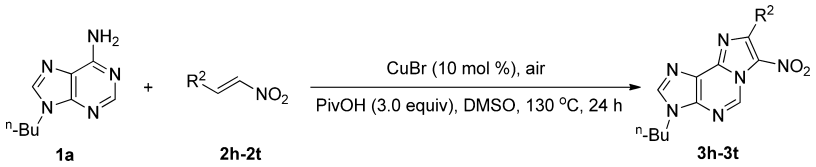
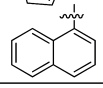
Table 2. Reaction with Various Nitroolefins[a]



entry	R_2	product	yield (%)[b]
1	C_6H_5	**3a**	85
2	2-ClC_6H_4	**3h**	60
3	3-ClC_6H_4	**3i**	64
4	4-ClC_6H_4	**3j**	76
5	4-FC_6H_4	**3k**	78
6	4-BrC_6H_4	**3l**	80
7	3-BrC_6H_4	**3m**	66
8	4-$NO_2C_6H_4$	**3n**	60
9	2-$MeOC_6H_4$	**3o**	63
10	4-$MeOC_6H_4$	**3p**	80
11	4-MeC_6H_4	**3q**	82
12		**3r**	41
13		**3s**	31
14		**3t**	25

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 equiv), catalyst (10 mol %), PivOH (3.0 equiv), DMSO (2.0 mL), 130 °C, 24 h. [b]Isolated yields.

tion of the starting material is still of great interest. In the context of ongoing projects on the modification of purine analogues,[7] herein we report the domino intermolecular Michael/oxidative cross-coupling reaction of adenines and nitroolefins to afford purine-fused polycyclic derivatives, which can be further transformed to purine-fused polycyclic derivatives with an exocyclic amino group by simple reduction.

RESULTS AND DISCUSSION

Initially, 9-butylpurin-6-amine (**1a**) and (*E*)-(2-nitrovinyl)-benzene (**2a**) were chosen as model substrates to explore the domino reaction conditions (Table 1). Gratifyingly, when $Cu(OAc)_2$ was used as a catalyst and $PhI(OAc)_2$ was employed as an oxidant, the desired purine-fused tricyclic product **3a** was obtained in 41% yield (Table 1, entry 1). Subsequently, O_2 was used as the oxidant, and the product **3a** was still obtained in 46% yield (Table 1, entry 2). Then several copper salts were examined with O_2 as the oxidant, and CuBr was the best one (Table 1, entries 2−5). With CuBr as the catalyst, a series of oxidants including air, H_2O_2, and $K_2S_2O_8$ were tested, and air was found to give the highest yield (62%; Table 1, entries 6−8). To further increase the yield of the product, some additives were tested, and PivOH emerged as the best one (75% yield; Table 1, entries 9−12). Switching the reaction solvent from DMF to 1,2-dichloroethane (DCE), CH_3CN, DMSO, xylene, or ethane-1,2-diol (EG) proved that aprotic solvents were much better than protic solvents, and DMSO gave the highest yield (85%) with almost complete consumption of the starting material **1a** (Table 1, entries 12−17). When the reaction was performed at a lower temperature such as 70 °C, only a trace amount of product **3a** was detected even when the reaction time was prolonged to 48 h (Table 1, entry 18). Therefore, the optimal reaction conditions were found to be CuBr (10 mol %) as the catalyst, air as the oxidant, and PivOH as an additive in DMSO at 130 °C for 24 h (Table 1, entry 15).

To evaluate the generality of the adenine component in this domino reaction, a number of adenines with different substituents at N9 were examined. As shown in Scheme 2, the corresponding purine-fused polycyclic derivatives were obtained in good yields (65−87%). Purine rings bearing different N9 substituents such as *n*-butyl, ethyl, isopropyl, allyl, and benzyl groups all furnished the target purine-fused polycyclic products **3a−e** well (78−87% yield). It is noteworthy that 2′,3′,5′-tri-*O*-acetyladenosine (**1g**) also gave the corresponding product **3g** in 65% yield, providing a useful route for the preparation of polycyclic nucleoside analogues.

To further evaluate the generality of the domino reaction, the series of nitroolefins **2h−t** were investigated under the optimized reaction conditions (Table 2). The steric hindrance of the substituent groups was examined, and the substrate with a substituent group at the *para* position afforded a higher yield than those substituted at the *ortho* and *meta* positions (Table 2, entries 2−4). Next, several nitroolefins with different electron-withdrawing groups on the phenyl ring were examined, and the corresponding purine-fused tricyclic derivatives were obtained in moderate to good yields (Table 2, entries 5−8). To our delight, when nitroolefins with electron-donating groups on the phenyl ring were tested, the desired tricyclic adducts **3o−q** were obtained with good results (Table 2, entries 9−11, 63−82% yields). On the basis of the above results (Table 2, entries 1−11), we found that electron-rich nitroolefins show higher yields than electron-deficient ones (Table 2, entries 10 and 11

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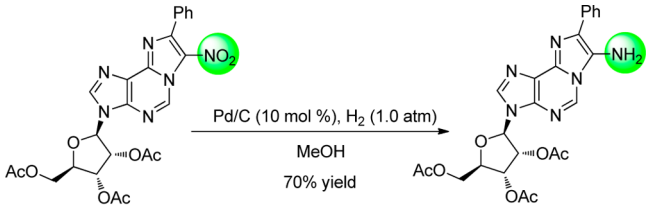
vs entries 4–6 and 8 and entry 9 vs entry 2). In addition, heteroaryl species, including 2-furanyl and 2-thienyl nitroolefins, also underwent the domino reaction to afford the purine-fused tricyclic products, although the yields were somewhat low (Table 2, entries 12 and 13). In the case of the 1-naphthaldehyde-derived nitroolefin, the corresponding product **3t** was obtained in 25% yield (Table 2, entry 14). However, when aliphatic nitroolefins such as cyclohexyl and *n*-butyl nitroolefins were tested, trace amounts of products were observed. Finally, other Michael acceptors including methyl acrylate and acrylonitrile were also tested, and no reactions occurred.

To verify the structure of the products, we tried to grow crystals of the products suitable for X-ray diffraction analysis. The structure of purine-fused tricyclic derivative **3j** was unambiguously determined by single-crystal X-ray diffraction analysis.[8] The crystal structure of compound **3j** confirmed the nitro group to be connected to the N1 position of the purine derivative, indicating that the domino reaction proceeds with high regioselectivity.

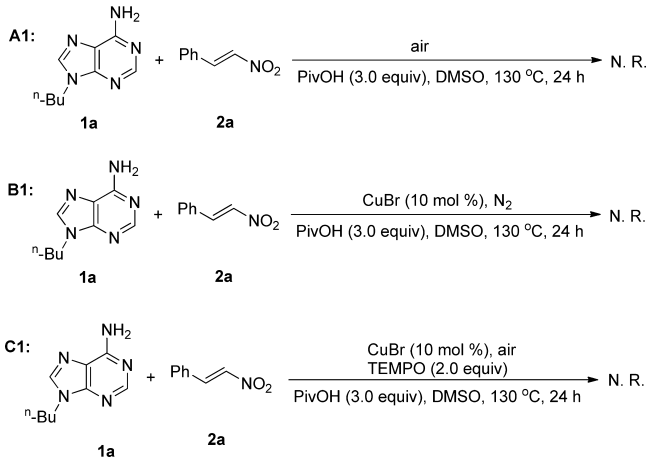
In view of the importance of exocyclic amino groups in purine-fused polycyclic derivatives, the reduction of the nitro group in product **3g** was tried. As shown in Scheme 3, with the help of Pd/C, the polycyclic nucleoside **3g** was hydrogenated smoothly, and the desired polycyclic nucleoside **4g** with an exocyclic amino group was obtained in 70% yield.

Scheme 3. Reduction of 3g To Afford the Polycyclic Nucleoside with an Exocyclic Amino Group



Next, some control experiments were designed to evaluate the mechanism of this domino reaction. First, the role of the copper catalyst was tested. When the reaction was performed in the absence of CuBr, no product was observed (Scheme 4, A1), indicating that the CuBr catalyst plays a critical role in the reaction. Next, when air was replaced by N_2, the reaction also did not occur (Scheme 4, B1), proving that air functions as an oxidant and that the oxidant is essential for the reaction to happen. In addition, the reaction did not proceed in the presence of the radical scavenger TEMPO, and the starting material nitroolefin **2a** was recovered (Scheme 4, C1). Thus, a radical intermediate may be included in the reaction.

Scheme 4. Control Experiments



On the basis of the above control experiments, the X-ray structure of **3g**, and previous work,[9,10] a proposed mechanism of the reaction is illustrated in Scheme 5. In the first step, the Michael addition reaction between adenine **1** and nitroolefin **2** takes place, forming intermediate **5**. With the Cu(II) catalyst as an oxidant, radical cation **6** is generated from intermediate **5** by a one-electron oxidation. Next, with the help of CuBr and air, the oxidative cross-coupling reaction forms imine intermediate **7**, which subsequently equilibrates to enamine intermediate **8**. Similarly, radical cation **9** is generated by hydride abstraction with the Cu(II) catalyst. Finally, the oxidative cross-coupling reaction of intermediate **9** generates the cyclization product **3**. In the case of aliphatic nitroolefins and acrylonitrile, it may be hard to form the corresponding Michael adduct intermediates, and the reaction does not occur.

CONCLUSION

We have developed a copper-catalyzed domino Michael/oxidative cross-coupling reaction of adenines and nitroolefins. With CuBr as a catalyst and air as an oxidant, a series of purine-fused polycyclic derivatives with structural diversity were obtained in good yields. Meanwhile, this method proceeds with high regioselectivity, and two new C–N bonds are generated in this domino reaction. Moreover, purine nucleosides with an exocyclic amino group can be easily obtained, which may lead to potential applications in fluorescence recognition of various bases in vivo.

EXPERIMENTAL SECTION

General. All of the reagents and solvents were purchased from commercial sources and purified commonly before use. DMSO used in reactions was reagent grade and distilled from CaH_2. All of the reactions were monitored by thin-layer chromatography (TLC). NMR spectra were recorded at 400 MHz for ^{1}H NMR or 100 MHz for ^{13}C NMR. Chemical shifts (δ) are given in parts per million relative to the residual proton signals of the deuterated solvent $CDCl_3$ or DMSO for ^{1}H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). High-resolution mass spectra were recorded using a Q-TOF system, and electrospray ionization (ESI) was used as the ionization method for the HRMS measurements. For column chromatography, silica gel (200–300 mesh) was used as the stationary phase. Melting points were recorded with a micro melting point apparatus and are uncorrected.

Typical Procedure for the Domino Reaction. A mixture of CuBr (10 mol %), PivOH (3.0 equiv), 9-butylpurin-6-amine (**1a**) (0.3 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (1.2 equiv), and dry DMSO (2.0 mL) in a dry round-bottom flask were stirred at 130 °C for 24 h under a N_2 atmosphere, and the reaction was monitored by TLC. After cooling, the reaction mixture was extracted with ethyl acetate and water. Then the organic phase was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to give the desired product **3a** in 85% yield.

*3-Butyl-7-nitro-8-phenyl-3H-imidazo[2,1-i]purine (**3a**).* Yellow solid (85.6 mg, 85% yield). Mp 223–225 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.11 (s, 1H), 8.14 (s, 1H), 8.06 (d, J = 4.8 Hz, 2H), 7.53 (d, J = 3.6 Hz, 3H), 4.40 (t, 2H), 1.98 (m, 2H), 1.41 (m, 2H),

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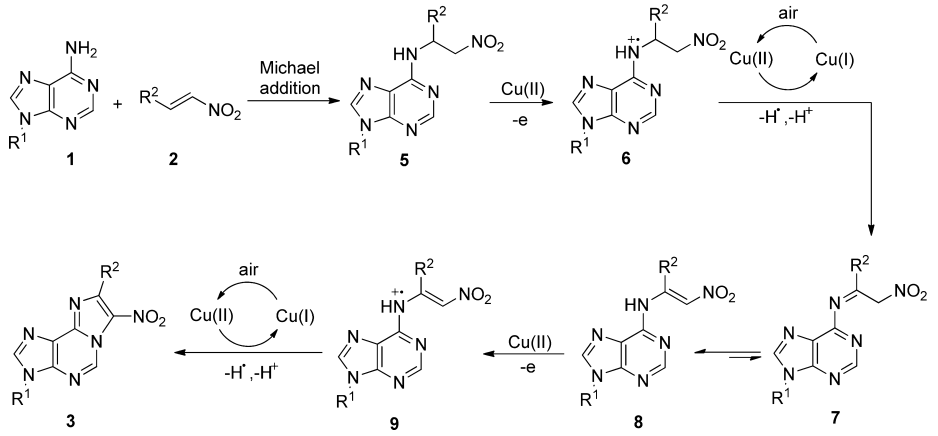
Scheme 5. Proposed Mechanism of the Reaction



1.00 (t, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 149.9, 145.1, 142.9, 141.7, 136.8, 132.0, 130.7, 130.5, 129.1, 128.4, 122.4, 44.1, 31.9, 19.6, 13.8. HRMS: calcd for $C_{17}H_{16}N_6O_2$ [M + Na]$^+$ 359.1227, found 359.1229.

3-Ethyl-7-nitro-8-phenyl-3H-imidazo[2,1-i]purine (**3b**). Yellow solid (79.5 mg, 86% yield). Mp 215−217 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.09 (s, 1H), 8.15 (s, 1H), 8.05 (t, 2H), 5.51 (d, J = 5.2 Hz, 3H), 4.45 (q, 2H), 1.64 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.0, 142.9, 141.7, 136.2, 131.1, 130.8, 130.7, 128.1, 123.1, 39.9, 15.6. HRMS: calcd for $C_{15}H_{12}N_6O_2$ [M + Na]$^+$ 311.0914, found 331.0911.

3-Isopropyl-7-nitro-8-phenyl-3H-imidazo[2,1-i]purine (**3c**). Yellow solid (84.0 mg, 87% yield). Mp 205−207 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.01 (s, 1H), 8.19 (s, 1H), 7.97 (q, 2H), 7.46 (m, 3H), 4.97 (m, 1H), 1.67 (s, 3H), 1.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 141.6, 141.3, 135.9, 131.0, 130.7, 130.6, 128.5, 128.0, 123.2, 48.6, 22.7. HRMS: calcd for $C_{16}H_{14}N_6O_2$ [M + Na]$^+$ 345.1070, found 345.1069.

3-Allyl-7-nitro-8-phenyl-3H-imidazo[2,1-i]purine (**3d**). Yellow solid (74.9 mg, 78% yield). Mp 202−204 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.10 (s, 1H), 8.15 (s, 1H), 8.05 (d, J = 5.6 Hz, 2H), 7.53 (s, 3H), 6.11 (m, 1H), 5.40 (d, J = 10.4 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.01 (d, J = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.0, 143.2, 141.6, 136.4, 131.1, 131.0, 130.8, 130.7, 128.1, 122.9, 119.9, 46.7. HRMS: calcd for $C_{16}H_{12}N_6O_2$ [M + Na]$^+$ 343.0914, found 343.0906.

3-Benzyl-7-nitro-8-phenyl-3H-imidazo[2,1-i]purine (**3e**). Yellow solid (88.8 mg, 80% yield). Mp 229−231 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.12 (s, 1H), 8.14 (s, 1H), 8.05 (d, J = 5.2 Hz, 2H), 7.53 (s, 3H), 7.36 (t, 5H), 5.56 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.1, 143.2, 142.6, 141.6, 136.5, 134.7, 131.0, 130.8, 130.7, 129.3, 128.9, 128.1, 127.9, 123.0, 48.3. HRMS: calcd for $C_{20}H_{14}N_6O_2$ [M + H]$^+$ 371.1251, found 371.1243.

2-((7-Nitro-8-phenyl-3H-imidazo[2,1-i]purin-3-yl)methoxy)ethyl Acetate (**3f**). Yellow solid (96.2 mg, 81% yield). Mp 145−147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.14 (s, 1H), 8.30 (s, 1H), 8.05 (m, 2H), 7.53 (m, 3H), 5.83 (s, 2H), 4.22 (t, 2H), 3.82 (t, 2H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 150.9, 143.7, 142.5, 141.3, 136.9, 130.8, 130.8, 130.6, 128.6, 128.1, 122.8, 73.5, 68.0, 62.7, 20.8. HRMS: calcd for $C_{18}H_{16}N_6O_5$ [M + H]$^+$ 397.1255, found 397.1247.

(2R,3R,4R,5R)-2-(Acetoxymethyl)-5-(7-nitro-8-phenyl-3H-imidazo[2,1-i]purin-3-yl)tetrahydrofuran-3,4-diyl Diacetate (**3g**). Yellow oil (104.9 mg, 65% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.13 (s, 1H), 8.34 (s, 1H), 8.04 (t, 2H), 7.53 (d, J = 7.2 Hz, 3H), 6.32 (d, J = 5.2 Hz, 1H), 5.97 (t, 1H), 5.64 (t, 1H), 4.56−4.51 (q, 1H), 4.51−4.40 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 169.7, 169.4, 150.9, 142.1, 141.7, 141.2, 136.8, 130.9, 130.8, 130.6, 128.6, 128.1, 123.8, 87.1, 80.5, 73.5, 70.4, 63.0, 20.8, 20.6, 20.4. HRMS: calcd for $C_{24}H_{22}N_6O_9$ [M + Na]$^+$ 561.1340, found 561.1333.

3-Butyl-8-(2-chlorophenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3h**). Yellow solid (66.8 mg, 60% yield). Mp 220−222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.10 (s, 1H), 8.16 (s, 1H), 7.61 (d, J = 5.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.47−7.39 (m, 2H), 4.41 (t, 2H), 1.95 (m, 2H), 1.38 (m, 2H), 0.95 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.1, 143.6, 142.6, 141.6, 135.7, 134.1, 131.4, 131.3, 131.1, 129.5, 126.8, 123.1, 44.6, 32.2, 19.8, 13.5. HRMS: calcd for $C_{17}H_{15}ClN_6O_2$ [M + Na]$^+$ 393.0837, found 393.0830.

3-Butyl-8-(3-chlorophenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3i**). Yellow solid (71.2 mg, 64% yield). Mp 180−182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.99 (s, 1H), 8.12 (s, 1H), 7.96 (s, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.44−7.36 (m, 2H), 4.35 (t, 2H), 1.91 (m, 2H), 1.34 (m, 2H), 0.93 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1, 143.6, 141.5, 136.0, 133.9, 132.8, 130.6, 130.5, 129.3, 128.8, 128.5, 122.8, 44.6, 32.1, 19.8, 13.5. HRMS: calcd for $C_{17}H_{15}ClN_6O_2$ [M + H]$^+$ 371.1018, found 371.1023.

3-Butyl-8-(4-chlorophenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3j**). Yellow solid (84.6 mg, 76% yield). Mp 209−210 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.06 (s, 1H), 8.14 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.2 Hz, 2H), 4.39 (t, 2H), 1.96 (m, 2H), 1.39 (m, 2H), 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.7, 143.4, 142.7, 141.6, 136.9, 136.1, 132.1, 129.5, 128.3, 122.9, 44.5, 32.1, 19.8, 13.4. HRMS: calcd for $C_{17}H_{15}ClN_6O_2$ [M + H]$^+$ 371.1018, found 371.1011.

3-Butyl-8-(4-fluorophenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3k**). Yellow solid (82.8 mg, 78% yield). Mp 193−195 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.02 (s, 1H), 8.13 (s, 1H), 8.03 (q, 2H), 7.14 (t, 2H), 4.36 (t, 2H), 1.92 (m, 2H), 1.36 (m, 2H), 0.95 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4, 162.9, 157.9, 149.9, 143.5, 141.6, 136.2, 133.1, 133.0, 128.4, 127.1, 127.1, 115.3, 115.1, 44.6, 32.2, 19.8, 13.5. HRMS: calcd for $C_{17}H_{15}FN_6O_2$ [M + H]$^+$ 355.1313, found 355.1319.

8-(4-Bromophenyl)-3-butyl-7-nitro-3H-imidazo[2,1-i]purine (**3l**). Yellow solid (99.6 mg, 80% yield). Mp 225−227 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.07 (s, 1H), 8.15 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 4.39 (t, 2H), 1.95 (m, 2H), 1.38 (m, 2H), 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.8, 143.5, 141.7, 136.2, 132.3, 131.4, 129.9, 125.6, 44.6, 32.2, 19.8, 13.5. HRMS: calcd for $C_{17}H_{15}BrN_6O_2$ [M + H]$^+$ 415.0513, found 415.0513.

8-(3-Bromophenyl)-3-butyl-7-nitro-3H-imidazo[2,1-i]purine (**3m**). Yellow solid (82.2 mg, 66% yield). Mp 170−172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.01 (s, 1H), 8.13 (d, J = 1.6 Hz, 2H), 7.92 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 9.2 Hz, 1H), 7.34 (t, 1H), 4.36 (t, 2H), 1.92 (m, 2H), 1.35 (m, 2H), 0.94 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1, 143.6, 142.8, 141.6, 136.1, 133.6, 133.4, 133.0, 129.6, 129.3, 128.5, 122.9, 121.9, 44.6, 32.2, 19.8, 13.5. HRMS: calcd for $C_{17}H_{15}BrN_6O_2$ [M + H]$^+$ 415.0513, found 415.0518.

3-Butyl-7-nitro-8-(4-nitrophenyl)-3H-imidazo[2,1-i]purine (**3n**). Yellow solid (68.6 mg, 60% yield). Mp 230−232 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.09 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 8.8 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 8.18 (s, 1H), 4.43 (t, 2H), 1.99 (m,

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2H), 1.41 (m, 2H), 1.00 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.8, 148.1, 143.6, 142.8, 141.7, 137.3, 135.9, 131.7, 123.2, 44.6, 32.2, 19.8, 13.4. HRMS: calcd for $C_{17}H_{15}N_7O_4$ $[M + Na]^+$ 404.1078, found 404.1069.

*3-Butyl-8-(2-methoxyphenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3o**).* Yellow oil (69.2 mg, 63% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.07 (s, 1H), 8.12 (s, 1H), 7.71 (q, 1H), 7.50 (m, 1H), 7.11 (t, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.39 (t, 2H), 3.82 (s, 3H), 1.96 (m, 2H), 1.38 (m, 2H), 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 147.6, 143.0, 142.3, 141.5, 135.8, 131.8, 131.2, 123.0, 121.2, 120.6, 110.8, 55.6, 44.5, 32.2, 19.8, 13.4. HRMS: calcd for $C_{18}H_{18}N_6O_3$ $[M + Na]^+$ 389.1333, found 389.1328.

*3-Butyl-8-(4-methoxyphenyl)-7-nitro-3H-imidazo[2,1-i]purine (**3p**).* Yellow solid (87.8 mg, 80% yield). Mp 209−211 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.07 (s, 1H), 8.11 (s, 1H), 8.09 (t, 2H), 7.01 (d, J = 6.8 Hz, 2H), 4.37 (t, 2H), 3.88 (s, 3H), 1.95 (m, 2H), 1.38 (m, 2H), 0.97 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8, 151.2, 143.2, 142.8, 141.7, 136.4, 132.7, 123.2, 122.8, 113.5, 77.4, 77.3, 77.1, 76.8, 55.5, 44.5, 32.2, 19.8, 13.5. HRMS: calcd for $C_{18}H_{18}N_6O_3$ $[M + H]^+$ 367.1513, found 367.1514.

*3-Butyl-7-nitro-8-(p-tolyl)-3H-imidazo[2,1-i]purine (**3q**).* Yellow solid (86.1 mg, 82% yield). Mp 206−208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.88 (s, 1H), 8.58 (s, 1H), 7.81 (d, J = 3.6 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 4.36 (t, 2H), 2.39 (s, 3H), 1.87 (t, 2H), 1.29 (m, 2H), 0.90 (t, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 150.1, 145.1, 142.9, 141.7, 140.8, 136.9, 130.6, 129.1, 129.0, 128.9, 122.3, 44.1, 31.9, 21.5, 19.6, 13.7. HRMS: calcd for $C_{18}H_{18}N_6O_2$ $[M + H]^+$ 351.1564, found 351.1556.

*3-Butyl-8-(furan-2-yl)-7-nitro-3H-imidazo[2,1-i]purine (**3r**).* Yellow solid (40.1 mg, 41% yield). Mp 220−222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.11 (s, 1H), 8.15 (s, 1H), 8.00 (d, J = 3.2 Hz, 1H), 7.79 (s, 1H), 6.69 (d, J = 1.6 Hz, 1H), 4.38 (t, 2H), 1.96 (m, 2H), 1.39 (m, 2H), 0.98 (t, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.8, 145.4, 143.3, 142.3, 140.5, 136.2, 120.0, 112.8, 44.5, 32.2, 19.8, 13.5. HRMS: calcd for $C_{15}H_{14}N_6O_3$ $[M + Na]^+$ 349.1020, found 349.1015.

*3-Butyl-7-nitro-8-(thiophen-2-yl)-3H-imidazo[2,1-i]purine (**3s**).* Yellow solid (31.8 mg, 31% yield). Mp 239−241 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.10 (s, 1H), 8.65 (dd, J = 3.6, 0.8 Hz, 1H), 8.11 (s, 1H), 7.74−7.70 (m, 1H), 7.29−7.24 (m, 1H), 4.38 (t, J = 7.2 Hz, 2H), 2.04−1.93 (m, 2H), 1.43−1.38 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.0, 143.1, 136.4, 134.5, 133.7, 133.2, 128.2, 44.5, 32.2, 19.8, 13.4. HRMS: calcd for $C_{15}H_{14}N_6O_2S$ $[M + Na]^+$ 365.0791, found 365.0792.

*3-Butyl-8-(naphthalen-1-yl)-7-nitro-3H-imidazo[2,1-i]purine (**3t**).* Yellow solid (28.9 mg, 25% yield). Mp 217−218 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.18 (s, 1H), 8.16 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 7.8, 0.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 8.4, 7.2 Hz, 1H), 7.54−7.50 (m, 1H), 7.47−7.42 (m, 1H), 4.42 (t, J = 7.2 Hz, 2H), 2.00−1.96 (m, 2H), 1.44−1.38 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.3, 143.4, 141.8, 136.0, 133.4, 131.1, 130.7, 129.3, 128.9, 128.6, 127.0, 126.2, 125.0, 44.6, 32.2, 19.8, 13.4. HRMS: calcd for $C_{21}H_{18}N_6O_2$ $[M + Na]^+$ 409.1383, found 409.1380.

Reduction Reaction of 3g To Give (2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(7-amino-8-phenyl-3*H*-imidazo[2,1-*i*]purin-3-yl)-tetrahydrofuran-3,4-diyl Diacetate (4g). A solution of compound **3g** (0.2 mmol, 100.2 mg) in MeOH (10.0 mL) was treated with Pd/C (10 mol %, 2.12 mg) under H_2 (1.0 atm) and stirred for 24 h at room temperature. After completion of the reaction, the reaction mixture was filtered through a Celite pad and washed with MeOH. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH = 100:1−50:1) to give the desired product **4g** as a pale-yellow solid in 70% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.81 (s, 1H), 8.09 (s, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.48 (t, 2H), 7.34 (t, 1H), 6.23 (d, J = 5.2 Hz, 1H), 6.06 (t, 1H), 5.71 (t, 1H), 4.50 (d, J = 9.2 Hz, 2H), 4.42−4.38 (q, 1H), 4.56−3.49 (m, 2H), 2.17 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H). HRMS: calcd for $C_{24}H_{24}N_6O_7$ $[M + Na]^+$ 531.1599, found 531.1599.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **3a**−**t** and **4g** and the X-ray crystal structure of **3j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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