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One-Pot Synthesis of 7,9-Dialkylpurin-8-one Analogues: Broad Substrate Scope

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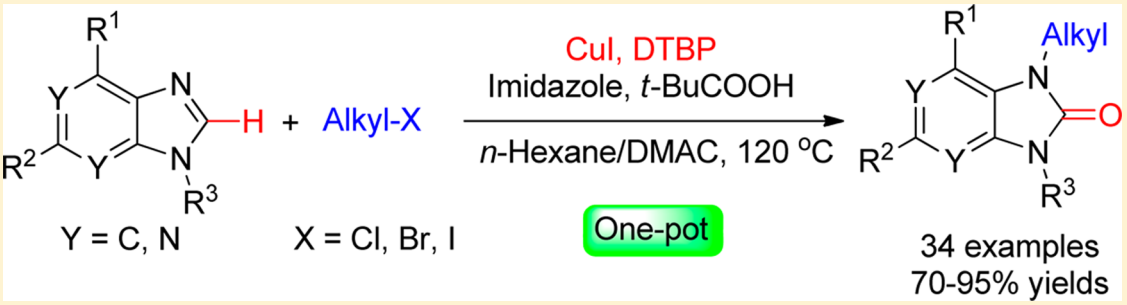
Supporting Information



ABSTRACT: The one-pot and direct synthesis of 7,9-dialkylpurin-8-one analogues with broad substrate scope has been developed. This copper-catalyzed C−H oxidation reaction could avoid multistep synthesis of quaternary ammonium salts and expand the scope of halogenated alkanes. Moreover, benzimidazole derivatives are also applicable in the catalytic system.

INTRODUCTION

Purin-8-one analogues are key components in many natural products, advanced intermediates, and biologically active compounds (Figure 1),[1] and they are commonly used as potential anxiolytics and/or antidepressants (e.g., **A**),[1a] potent interferon inducers (e.g., **B** and **C**),[1b,c] small-molecule immunostimulants,[2] and physiological antioxidants.[3] Due to their unique properties, the synthesis of such compounds has been of increasing interest.[4,5]

A photoinduced oxidation reaction of quaternary ammonium salts to afford purin-8-one derivatives has been developed.[6a] However, the application of this method is limited to iodine salts (Scheme 1, route a).[6b] Alternatively, H_2O_2 was employed as an oxidant for the C−H oxidation reaction of the same iodine salts as substrates (Scheme 1, route b).[6a,c] These methods suffered from narrow substrate scope and multiple steps because quaternary ammonium salts of N-aromatic heterocyclic derivatives needed to be synthesized beforehand. Considering the biological importance of purin-8-one derivatives, a more efficient and direct method with broad substrate scope for the synthesis of purin-8-one analogues is highly desirable. In the context of ongoing projects for the synthesis of purine analogues,[7] we report here a copper-catalyzed one-pot synthesis of 7,9-dialkylpurin-8-one analogues via a direct sp^2 C−H oxidation reaction.[8]

RESULTS AND DISCUSSION

Initially, we started the study with the optimization of the reaction conditions by using 9-benzyl-6-methoxy-9*H*-purine (**1a**) and benzyl chloride (**2a**) as substrates. Due to the low cost and ready availability, several copper sources were chosen as catalysts, and the results showed that CuI was the best one for the reaction, with 49% yield obtained (Table 1, entries 1−3). Encouraged by the result, we screened some oxidants for the reaction, and di-*tert*-butyl peroxide (DTBP) gave a better yield (68% yield) than any other oxidant, such as *N*-chlorosuccinimide (NCS), $K_2S_2O_8$, *N*-bromosuccinimide (NBS), or $PhI(OAc)_2$ (entries 3−7). Next, we also examined the effect of various solvents including dimethylacetamide (DMAC), *N*-methyl-2-pyrrolidone (NMP), CH_3CN, cyclohexane, and dioxane. The yield of the product was not satisfactory when the reaction was conducted in a single solvent (entries 8−12). Considering that most of the reagents and substrate used in the reaction were not soluble in *n*-hexane, a mixed solvent was attempted. To our delight, a high yield (87% yield) was observed when a 15:1 mixture of *n*-hexane and DMAC was used as solvent (entry 14). Both pivalic acid (t-$BuCO_2H$) and imidazole were essential for the reaction because the yield was poor without either of them (entries 16 and 17). No product was detected in the absence of the catalyst (entry 18). Therefore, the optimal reaction conditions were CuI (20 mol

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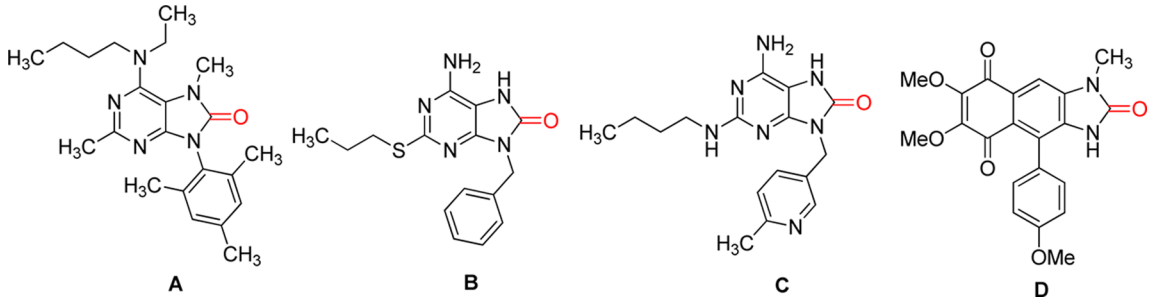
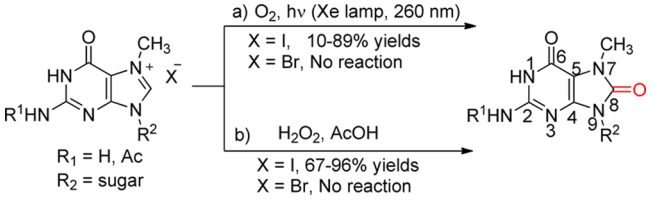


Figure 1. Selected examples of purin-8-one analogues with biological activities.

Scheme 1. Strategies for the Synthesis of Purin-8-one Derivatives from N7 Quaternary Ammonium Salts

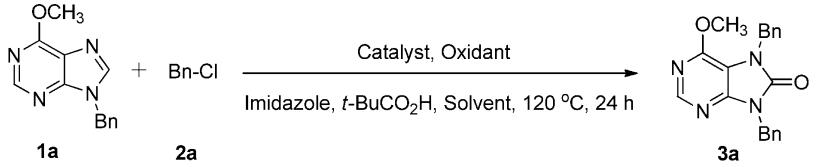


%) as catalyst, 2.0 equiv of DTBP as oxidant, 1.0 equiv of imidazole and 1.2 equiv of *t*-$BuCO_2H$ as additives in a mixed solvent (*n*-hexane/DMAC = 15:1, v/v) at 120 °C for 24 h.

To examine the generality of the reaction, a number of purine derivatives were explored as substrates under the improved reaction conditions, and the results are shown in Scheme 2. The reaction of a series of 6-phenoxy-9-alkyl-substituted purine derivatives with benzyl chloride proceeded efficiently, and the corresponding products were obtained in high yields (**3b**−**3g**, 81−95%). When the substitutions of purine at N9 were cycloalkyl, allyl, ester, or phenyl, the reactions could proceed smoothly and provide high yields (**3h**−**3k**, 84−91%). Purine derivatives with different substitutes at C6 including chlorine, oxygen, sulfur, and nitrogen could also afford the expected purin-8-one products in satisfactory yields (**3l**−**3o**, 70−82%).

The reaction of a variety of halogenated alkanes (including Cl, Br, and I) was further explored under the optimized conditions (Scheme 3). We were pleased to find that the reaction with various halogenated alkanes all proceeded smoothly and gave good to high yields (Scheme 3, **3p**−**3x**, 71−87%). Longer length of the alkyl chain led to a little decrease of the yield, which might be caused by the reduced activity of the halogenated alkanes with the growth of the carbon chain (**3p**−**3t**). Particularly, double bond, bromo, and ester moieties were all well tolerated in this direct C−H oxidation reaction (**3v**−**3x**), making further elaborations of the corresponding 7,9-dialkylpurin-8-one analogues possible. Thus, this strategy indeed expanded the scope of halogenated alkanes.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant	solvent	additive	yield (%)[b]
1	CuCl	NCS	*n*-hexane	imidazole, *t*-$BuCO_2H$	25
2	CuBr	NCS	*n*-hexane	imidazole, *t*-$BuCO_2H$	10
3	CuI	NCS	*n*-hexane	imidazole, *t*-$BuCO_2H$	49
4	CuI	$K_2S_2O_8$	*n*-hexane	imidazole, *t*-$BuCO_2H$	36
5	CuI	DTBP	*n*-hexane	imidazole, *t*-$BuCO_2H$	68
6	CuI	NBS	*n*-hexane	imidazole, *t*-$BuCO_2H$	31
7	CuI	$PhI(OAc)_2$	*n*-hexane	imidazole, *t*-$BuCO_2H$	23
8	CuI	DTBP	DMAC	imidazole, *t*-$BuCO_2H$	62
9	CuI	DTBP	NMP	imidazole, *t*-$BuCO_2H$	46
10	CuI	DTBP	CH_3CN	imidazole, *t*-$BuCO_2H$	13
11	CuI	DTBP	cyclohexane	imidazole, *t*-$BuCO_2H$	51
12	CuI	DTBP	dioxane	imidazole, *t*-$BuCO_2H$	26
13	CuI	DTBP	*n*-hexane/DMAC (10/1)	imidazole, *t*-$BuCO_2H$	76
14	CuI	DTBP	*n*-hexane/DMAC (15/1)	imidazole, *t*-$BuCO_2H$	87
15	CuI	DTBP	*n*-hexane/DMAC (20/1)	imidazole, *t*-$BuCO_2H$	72
16	CuI	DTBP	*n*-hexane/DMAC (15/1)	imidazole	43
17	CuI	DTBP	*n*-hexane/DMAC (15/1)	*t*-$BuCO_2H$	trace
18		DTBP	*n*-hexane/DMAC (15/1)	imidazole, *t*-$BuCO_2H$	NR[c]

[a]Unless otherwise stated, all of the reactions were carried out with **1a** (0.2 mmol), **2a** (0.5 mmol), catalyst (20 mol %), oxidant (2.0 equiv), additive (1.0 equiv of imidazole, 1.2 equiv of *t*-$BuCO_2H$), solvent (1.0 mL), 120 °C, 24 h. [b]Isolated yield. [c]No reaction.

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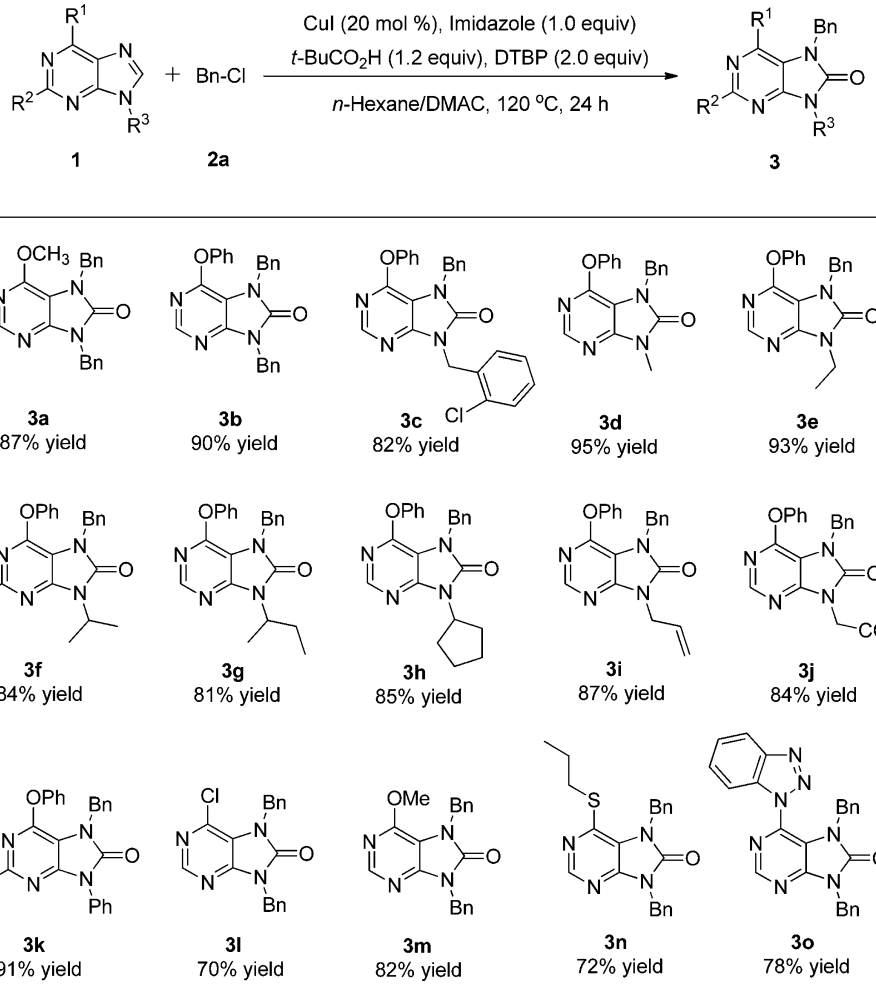
Scheme 2. Reaction of Various Purine Derivatives with Benzyl Chloride[a,b]



[a]Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2a** (0.5 mmol), CuI (20 mol %), DTBP (2.0 equiv), imidazole (1.0 equiv), *t*-$BuCO_2H$ (1.2 equiv), *n*-hexane/DMAC (v/v = 15/1, 1.0 mL), 120 °C, 24 h. [b]Isolated yield.

Encouraged by the above results, we used 1-benzyl-1*H*-benzo[*d*]imidazole[9] instead of purines as starting material to react with various halogenated alkanes under the standard reaction conditions, and the results are listed in Scheme 4. Different alkyl chains of halogenated alkanes could afford the desired product with good yields (**5b**−**5f**). More importantly, some functional groups, including double bond, bromo, and ester moieties, were also tolerated in this catalytic system, and satisfactory yields of the products were obtained (**5g**−**5j**).

To further understand the structure of the product, we tried to grow crystals of the products suitable for X-ray diffraction analysis. The crystal of compound **5a** confirmed that the oxidation reaction occurred on the C2 position, and the alkylation reaction occurred on the N3 position of 1-benzyl-1*H*-benzo[*d*]imidazole (Figure 2), so the product was established as 1,3-dibenzyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (**5a**).[10]

As for the reaction pathway, we speculated that the targeted product might be produced by direct C−H oxidation from a quaternary ammonium salt of purine analogues, which was first generated from the substrates. To probe the nature of reaction, in the absence of the catalyst, oxidant, and additives, we performed the reaction of **4** and **2a** in the solvent at 120 °C for 24 h, and intermediate **6a** was obtained in a 51% isolated yield (Scheme 5, **A1**), consistent with our speculation. When compound **4** was reacted under the standard conditions in the absence of BnCl, no reaction occurred (Scheme 5, **B1**). In the second step, intermediate **6a** was used as starting material under the standard conditions, and the target product **5a** was obtained in 89% yield (Scheme 5, **C1**). To further verify the reaction pathway, this one-pot reaction was monitored by TLC and we found the presence of intermediate **6a** (Scheme 5, **D1**). Therefore, the reaction involved the formation of a quaternary ammonium salt which gave the targeted product by direct C−H oxidation under the standard reaction conditions. A detailed mechanism investigation about how the C−H oxidation reaction occurs is underway.

In conclusion, we have developed an efficient and direct method for the synthesis of the 7,9-dialkylpurin-8-one analogues via copper-catalyzed direct sp^2 C−H oxidation. This strategy could avoid multiple steps for the synthesis of quaternary ammonium salts and expand the scope of halogenated alkanes. A series of substrates involving purine derivatives, benzimidazole derivatives, and halogenated alkanes are applicable in this protocol at a 0.2 mmol scale. The relatively inexpensive catalyst and the generally high yields make this method very promising for the synthesis of many biologically important C8 oxidated purines/imidazoles. The

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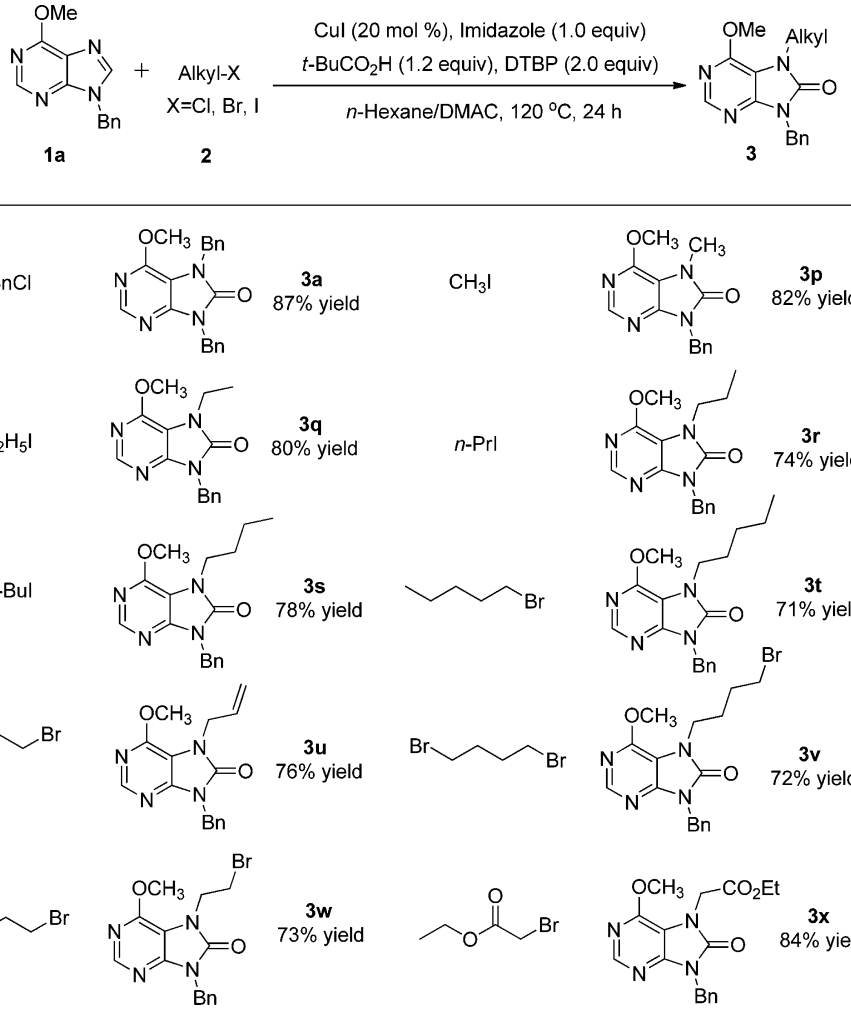
Scheme 3. Reaction of 9-Benzyl-6-methoxy-9*H*-purine with Various Halogenated Alkanes[a,b]



[a]All reactions were carried out with **1a** (0.2 mmol), **2** (0.5 mmol), CuI (20 mol %), DTBP (2.0 equiv), imidazole (1.0 equiv), *t*-$BuCO_2H$ (1.2 equiv), *n*-hexane/DMAC (v/v = 15/1, 1.0 mL), 120 °C, 24 h. [b]Isolated yield.

further expansion of the reaction and further investigation of the reaction mechanism are in progress in our laboratory.

EXPERIMENTAL SECTION

General. Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for ^1H NMR and 100 MHz for ^{13}C NMR. Chemical shifts δ were given in parts per million relative to tetramethylsilane in $CDCl_3$ for ^1H and ^{13}C NMR. High-resolution mass spectra are taken using Q-TOF system, with electrospray ionization (ESI) as the ionization method used for the HRMS measurement. For column chromatography, 200−300 mesh silica gel (GF254) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All reactions were set up in air (with no use of a glovebox) and carried out in a sealed pressure tube. All reagents (including CuI) and solvents were purchased from commercial sources and used as received.

Typical Procedure. A dried pressure tube containing a stirbar was charged with N-aromatic heterocycles (0.2 mmol), CuI (8.0 mg, 20 mol %), imidazole (14.0 mg, 1.0 equiv), and *t*-BuCOOH (25.0 mg, 1.2 equiv). Then halogenated alkanes (2.5 equiv), di-*tert*-butylperoxide (DTBP, 0.075 mL, 2.0 equiv) and a mixed solvent of *n*-hexane and DMAC (v/v = 15/1, 1.0 mL), were successively added to the pressure tube. Then the pressure tube was fitted with a threaded sealing cap, and the reaction mixture was stirred in an oil bath at 120 °C for 24 h. After the completion of the reaction monitored by TLC, the resulting mixture was cooled to room temperature, filtered through a plug of Celite, and the Celite was rinsed with copious amounts ethyl acetate. The solvent of the filtrate was removed under reduced pressure. The residue was purified on a silica gel column (eluting with petroleum ether/ethyl acetate), affording the corresponding product.

7,9-Dibenzyl-6-methoxy-7*H*-purin-8(9*H*)-one (3a): White solid, 60.2 mg, 87% yield; mp 80−82 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.50−7.48 (m, 2H), 7.42−7.39 (m, 2H), 7.33−7.25 (m, 6H), 5.17 (s, 2H), 5.13 (s, 2H), 4.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.4, 150.4, 149.1, 137.2, 136.1, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 107.5, 53.9, 46.3, 44.1; HRMS calcd for $C_{20}H_{19}N_4O_2$ [M + H^+] 347.1508, found 347.1503.

7,9-Dibenzyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3b): White solid, 73.5 mg, 90% yield; mp 120−123 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (s, 1H), 7.56−7.54 (m, 2H), 7.46−7.42 (m, 4H), 7.38−7.27 (m, 7H), 7.07−7.05 (m, 2H), 5.30 (s, 2H), 5.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 152.1, 151.2, 150.6, 150.3, 137.1, 136.0, 129.8, 128.8, 128.6, 128.2, 128.1, 125.9, 121.6, 108.2, 46.5, 44.4; HRMS calcd for $C_{25}H_{20}N_4NaO_2$ [M + Na^+] 431.1473, found 431.1478.

7-Benzyl-9-(2-chlorobenzyl)-6-phenoxy-7*H*-purin-8(9*H*)-one (3c): White solid, 72.6 mg, 82% yield; mp 116−118 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 7.47−7.40 (m, 5H), 7.36−7.28 (m, 4H), 7.24−7.18 (m, 2H), 7.12−7.06 (m, 3H), 5.33 (d, J = 1.2 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 152.0, 151.3, 150.7, 150.4, 137.0, 133.0, 129.8, 129.1, 128.8, 128.3, 128.2, 128.1, 127.0,

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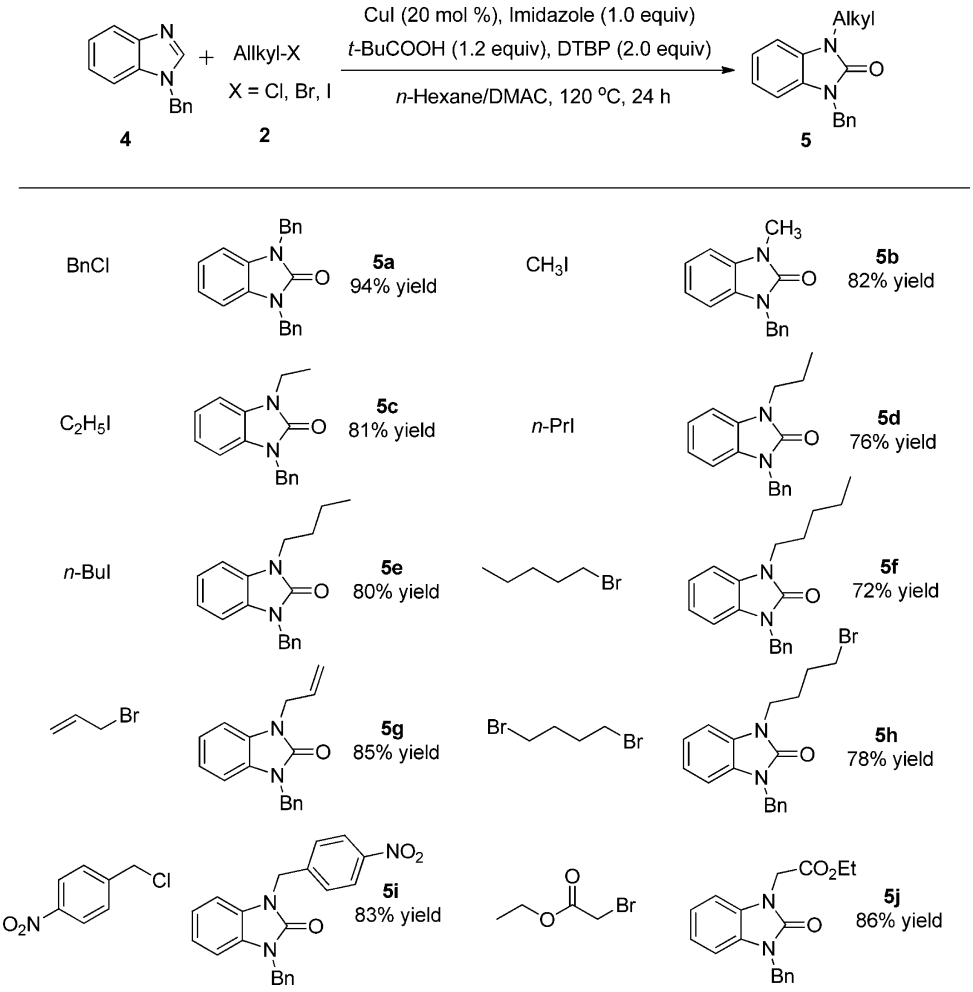
Scheme 4. Reaction of 1-Benzyl-1*H*-benzo[*d*]imidazole with Various Halogenated Alkanes[a,b]



[a]All reactions were carried out with **4** (0.2 mmol), **2** (0.5 mmol), CuI (20 mol %), DTBP (2.0 equiv), imidazole (1.0 equiv), *t*-BuCO$_2$H (1.2 equiv), *n*-hexane/DMAC (v/v = 15/1, 1.0 mL), 120 °C, 24 h. [b]Isolated yield.

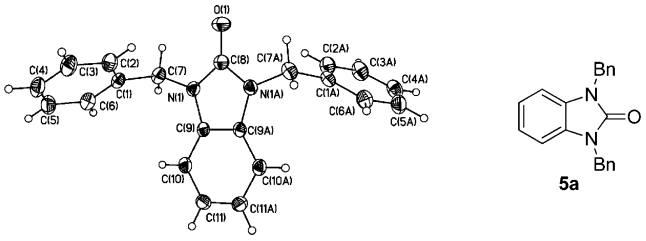


Figure 2. X-ray structure of **5a**.

125.9, 121.6, 108.2, 46.6, 42.0; HRMS calcd for $C_{25}H_{19}ClN_4NaO_2$ [M + Na$^+$] 465.1096, found 465.1089.

7-Benzyl-9-methyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3d): White solid, 63.1 mg, 95% yield; mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.45−7.41 (m, 4H), 7.33−7.28 (m, 4H), 7.07−7.05 (m, 2H), 5.28 (s, 2H), 3.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 152.1, 151.0, 150.7, 150.4, 137.0, 129.8, 128.7, 128.2, 128.0, 125.8, 121.5, 108.2, 46.4, 26.8; HRMS calcd for $C_{19}H_{17}N_4O_2$ [M + H$^+$] 333.1339, found 333.1346.

7-Benzyl-9-ethyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3e): White solid, 64.4 mg, 93% yield; mp 101−103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (s, 1H), 7.45−7.41 (m, 4H), 7.34−7.28 (m, 4H), 7.07 (d, J = 8.0 Hz, 2H), 5.30 (s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 152.2, 151.0, 150.4, 137.2, 129.8, 128.7, 128.1, 128.0, 125.8, 121.5, 108.2, 46.3, 36.0, 13.9; HRMS calcd for $C_{20}H_{18}N_4NaO_2$ [M + Na$^+$] 369.1326, found 369.1322.

7-Benzyl-2-chloro-9-isopropyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3f): White solid, 66.4 mg, 84% yield; mp 137−139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.39 (m, 4H), 7.34−7.25 (m, 4H), 7.04 (d, J = 7.6 Hz, 2H), 5.24 (s, 2H), 4.86−4.79 (m, 1H), 1.61 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 151.8, 151.6, 151.0, 150.3, 136.9, 129.7, 128.8, 128.1, 125.8, 121.2, 106.9, 46.3, 20.2; HRMS calcd for $C_{21}H_{19}ClN_4NaO_2$ [M + Na$^+$] 417.1097, found 417.1089.

7-Benzyl-9-(*sec*-butyl)-6-phenoxy-7*H*-purin-8(9*H*)-one (3g): Colorless oil, 60.7 mg, 81% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (s, 1H), 7.44−7.41 (m, 4H), 7.32−7.28 (m, 4H), 7.05 (d, J = 7.6 Hz, 2H), 5.30 (s, 2H), 4.62−4.57 (m, 1H), 2.30−2.21 (m, 1H), 1.98−1.90 (m, 1H), 1.62 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 152.1, 151.1, 150.6, 150.1, 137.3, 129.7, 128.7, 128.0, 127.9, 125.7, 121.5, 108.0, 52.0, 46.3, 27.0, 18.4, 11.3; HRMS calcd for $C_{22}H_{22}N_4NaO_2$ [M + Na$^+$] 397.1636, found 397.1635.

7-Benzyl-9-cyclopentyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3h): Yellow oil, 65.7 mg, 85% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 7.46−7.40 (m, 4H), 7.34−7.27 (m, 4H), 7.07−7.05 (m, 2H), 5.28 (s, 2H), 4.98−4.89 (m, 1H), 2.36−2.28 (m, 2H), 2.08−1.99 (m, 4H), 1.75−1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.2, 151.1, 150.5, 150.0, 137.2, 129.7, 128.7, 128.2, 127.9, 125.7, 121.5, 108.2, 54.0, 46.3, 29.5, 24.8; HRMS calcd for $C_{23}H_{23}N_4O_2$ [M + H$^+$] 387.1814, found 387.1816.

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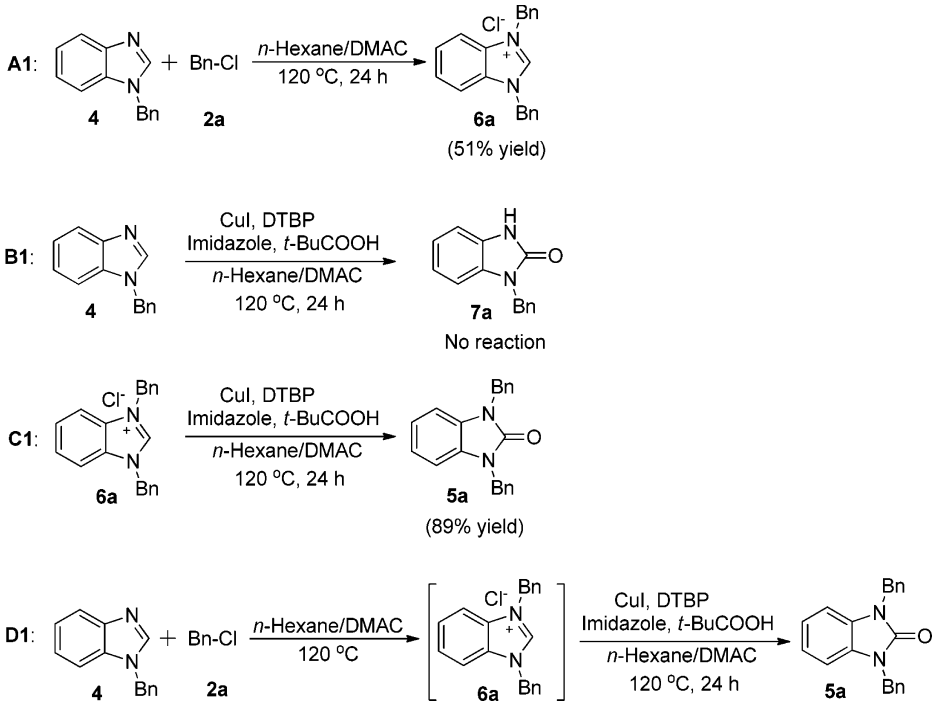
Scheme 5. Possible Reaction Pathway



9-Allyl-7-benzyl-6-phenoxy-7*H*-purin-8(9*H*)-one (3i): White solid, 62.4 mg, 87% yield; mp 97−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (s, 1H), 7.44−7.41 (m, 4H), 7.31−7.28 (m, 4H), 7.05 (d, J = 8.0 Hz, 2H), 6.06−6.00 (m, 1H), 5.29−5.25 (m, 4H), 4.63 (d, J = 5.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.1, 151.2, 150.5, 150.3, 137.1, 131.2, 129.8, 128.7, 128.1, 128.0, 125.8, 121.5, 118.2, 108.2, 46.4, 42.8; HRMS calcd for $C_{21}H_{18}N_4NaO_2$ [M + Na^+] 381.1327, found 381.1322.

Ethyl 2-(7-benzyl-8-oxo-6-phenoxy-7*H*-purin-9(8*H*)-yl)-acetate (3j): White solid, 67.9 mg, 84% yield; mp 89−91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (s, 1H), 7.42−7.41 (m, 4H), 7.34−7.28 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 5.31 (s, 2H), 4.77 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 152.9, 152.0, 151.3, 150.6, 150.2, 136.9, 129.8, 128.7, 128.0, 125.9, 121.5, 108.4, 62.1, 46.5, 41.4, 14.2; HRMS calcd for $C_{22}H_{21}N_4O_4$ [M + H^+] 405.1548, found 405.1557.

7-Benzyl-2-chloro-6-phenoxy-9-phenyl-7*H*-purin-8(9*H*)-one (3k): White solid, 78.1 mg, 91% yield; mp 231−233 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68−7.66 (m, 2H), 7.56−7.42 (m, 7H), 7.36−7.28 (m, 4H), 7.09−7.07 (m, 2H) 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 151.7, 151.6, 151.2, 151.0, 136.6, 132.3, 129.8, 129.3, 128.8, 128.4, 128.3, 128.2, 126.0, 125.7, 121.2, 107.1, 46.7; HRMS calcd for $C_{24}H_{17}ClN_4NaO_2$ [M + Na^+] 451.0926, found 451.0932.

7,9-Dibenzyl-6-chloro-7*H*-purin-8(9*H*)-one (3l): Colorless oil, 49.1 mg, 70% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.46 (s, 1H), 7.51−7.48 (m, 2H), 7.38−7.28 (m, 8H), 5.34 (s, 2H), 5.17 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 150.8, 150.2, 136.3, 136.0, 135.3, 128.9, 128.7, 128.3, 128.1, 127.4, 119.3, 45.4, 44.5; HRMS calcd for $C_{19}H_{15}ClN_4NaO$ [M + Na^+] 373.0820, found 373.0827.

7,9-Dibenzyl-2,6-dimethoxy-7*H*-purin-8(9*H*)-one (3m): Colorless oil, 56.8 mg, 82% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49−7.47 (m, 2H), 7.37−7.27 (m, 8H), 5.10 (s, 2H), 5.06 (s, 2H), 4.01 (s, 3H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 153.7, 153.2, 150.8, 137.4, 136.3, 128.7, 128.6, 128.0, 127.9, 127.7, 102.2, 55.0, 53.9, 46.2, 44.1; HRMS calcd for $C_{21}H_{21}N_4O_3$ [M + H^+] 377.1600, found 377.1608.

7,9-Dibenzyl-6-(propylthio)-7*H*-purin-8(9*H*)-one (3n): White solid, 56.3 mg, 72% yield; mp 79−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 7.48 (d, J = 6.8 Hz, 2H), 7.35−7.28 (m, 8H), 5.34 (s, 2H), 5.13 (s, 2H), 3.25 (t, J = 7.2 Hz, 2H), 1.73−1.63 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 150.8, 146.9, 145.8, 136.9, 135.9, 128.7, 128.5, 128.0, 127.8, 127.4, 119.4, 46.1, 44.0, 31.7, 22.9, 13.4; HRMS calcd for $C_{22}H_{22}N_4NaOS$ [M + Na^+] 413.1399, found 413.1407.

6-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-7,9-dibenzyl-7*H*-purin-8(9*H*)-one (3o): White solid, 67.6 mg, 78% yield; mp 163−165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (s, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.63−7.58 (m, 3H), 7.48−7.33 (m, 5H), 6.81−6.73 (m, 3H), 6.46 (d, J = 7.2 Hz, 2H), 5.40 (s, 2H), 5.32 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 152.7, 150.6, 146.0, 135.6, 135.4, 135.0, 132.4, 129.0, 128.9, 128.6, 128.4, 128.1, 127.3, 125.9, 125.2, 119.8, 114.9, 111.9, 46.0, 44.7; HRMS calcd for $C_{25}H_{20}N_7O$ [M + H^+] 434.1716, found 434.1724.

9-Benzyl-6-methoxy-7-methyl-7*H*-purin-8(9*H*)-one (3p): White crystals, 44.3 mg, 82% yield; mp 111−113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H), 7.48−7.46 (m, 2H), 7.32−7.23 (m, 3H), 5.10 (s, 2H), 4.06 (s, 3H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.6, 150.1, 148.8, 136.2, 128.6, 128.5, 127.9, 108.1, 53.9, 44.0, 29.4; HRMS calcd for $C_{14}H_{15}N_4O_2$ [M + H^+] 271.1198, found 271.1190.

9-Benzyl-7-ethyl-6-methoxy-7*H*-purin-8(9*H*)-one (3q): White solid, 45.5 mg, 80% yield; mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H), 7.48−7.46 (m, 2H), 7.32−7.23 (m, 3H), 5.10 (s, 2H), 4.07 (s, 3H), 4.03 (t, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 152.3, 150.1, 149.0, 136.2, 128.6, 128.4, 127.8, 107.4, 53.9, 44.0, 37.9, 15.3; HRMS calcd for $C_{15}H_{16}N_4NaO_2$ [M + Na^+] 307.1173, found 307.1165.

9-Benzyl-6-methoxy-7-propyl-7*H*-purin-8(9*H*)-one (3r): White solid, 44.2 mg, 74% yield; mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (s, 1H), 7.46−7.44 (m, 2H), 7.31−7.22 (m, 3H), 5.10 (s, 2H), 4.06 (s, 3H), 3.94 (t, J = 7.2 Hz, 2H), 1.80−1.70 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 152.2, 150.1, 148.9, 136.2, 128.6, 128.4, 127.8, 107.7, 53.9, 44.4, 43.9, 23.2, 10.9; HRMS calcd for $C_{16}H_{18}N_4NaO_2$ [M + Na^+] 321.1317, found 321.1322.

9-Benzyl-7-butyl-6-methoxy-7*H*-purin-8(9*H*)-one (3s): White solid, 48.7 mg, 78% yield; mp 69−70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H), 7.47−7.45 (m, 2H), 7.32−7.23 (m, 3H), 5.10 (s, 2H), 4.06 (s, 3H), 3.98 (t, J = 7.2 Hz, 2H), 1.74−1.67 (m, 2H), 1.40−

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1.31 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 152.2, 150.1, 148.9, 136.2, 128.6, 128.4, 127.8, 107.7, 53.9, 44.0, 42.6, 32.0, 19.7, 13.6; HRMS calcd for $C_{17}H_{20}N_4NaO_2$ [M + Na^+] 335.1478, found 335.1478.

9-Benzyl-6-methoxy-7-pentyl-7*H*-purin-8(9*H*)-one (3t): Light yellow solid, 46.3 mg, 71% yield; mp 42−43 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.48−7.46 (m, 2H), 7.33−7.27 (m, 3H), 5.12 (s, 2H), 4.07 (s, 3H), 3.98 (t, J = 6.4 Hz, 2H), 1.73 (t, J = 6.2 Hz, 2H), 1.33 (s, 4H), 0.89 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 152.2, 150.1, 149.0, 136.2, 128.6, 128.4, 127.8, 107.7, 53.9, 43.9, 42.8, 29.6, 28.6, 22.2, 13.9; HRMS calcd for $C_{18}H_{22}N_4NaO_2$ [M + Na^+] 349.1643, found 349.1635.

7-Allyl-9-benzyl-6-methoxy-7*H*-purin-8(9*H*)-one (3u): Light yellow solid, 45.0 mg, 76% yield; mp 70−71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (s, 1H), 7.47−7.45 (m, 2H), 7.32−7.23 (m, 3H), 5.98−5.89 (m, 1H), 5.18−5.13 (m, 2H), 5.11 (s, 2H), 4.60−4.58 (m, 2H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 152.4, 150.3, 149.0, 136.1, 132.7, 128.6, 128.4, 127.9, 117.6, 107.5, 53.9, 44.9, 44.0; HRMS calcd for $C_{16}H_{16}N_4NaO_2$ [M + Na^+] 319.1173, found 319.1165.

9-Benzyl-7-(4-bromobutyl)-6-methoxy-7*H*-purin-8(9*H*)-one (3v): Light yellow oil, 56.3 mg, 72% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (s, 1H), 7.45 (d, J = 6.8 Hz, 2H), 7.32−7.23 (m, 3H), 5.10 (s, 2H), 4.08 (s, 3H), 4.02 (t, J = 6.4 Hz, 2H), 3.44 (t, J = 5.8 Hz, 2H), 1.91−1.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 152.3, 150.3, 149.0, 136.1, 128.6, 128.4, 127.9, 107.5, 54.0, 44.0, 41.8, 32.9, 29.5, 28.4; HRMS calcd for $C_{17}H_{19}BrN_4NaO_2$ [M + Na^+] 413.0584, found 413.0584.

9-Benzyl-7-(2-bromoethyl)-6-methoxy-7*H*-purin-8(9*H*)-one (3w): White solid, 53.0 mg, 73% yield; mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.34−7.29 (m, 3H), 5.13 (s, 2H), 4.39 (t, J = 7.0 Hz, 2H), 4.10 (s, 3H), 3.65 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 152.3, 150.7, 149.1, 136. 0, 128.7, 128.4, 128.0, 107.3, 54.2, 44.1, 43.9, 29.2; HRMS calcd for $C_{15}H_{15}BrN_4NaO_2$ [M + Na^+] 385.0270, found 385.0271.

Ethyl 2-(9-benzyl-6-methoxy-8-oxo-8,9-dihydro-7*H*-purin-7-yl)acetate (3x): White solid, 57.5 mg, 84% yield; mp 81−83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.32−7.23 (m, 3H), 5.13 (s, 2H), 4.74 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.02 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 152.7, 152.5, 150. 7, 149.1, 135.9, 128.6, 128.2, 127.9, 107.6, 61.7, 54.0, 44.1, 43.8, 14.1; HRMS calcd for $C_{17}H_{18}N_4NaO_4$ [M + Na^+] 365.1222, found 365.1220.

1,3-Dibenzyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5a): White solid, 59.1 mg, 94% yield; mp 106−108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.26 (m, 10H), 6.99−6.96 (m, 2H), 6.90−6.86 (m, 2H), 5.13 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 136.4, 129.3, 128.8, 127.7, 127.5, 121.4, 108.4, 45.0; HRMS calcd for $C_{21}H_{19}N_2O$ [M + H^+] 315.1499, found 315.1492.

1-Benzyl-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5b): White solid, 39.1 mg, 82% yield; mp 85−87 °C ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.23 (m, 5H), 7.10−6.97 (m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 5.08 (s, 2H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 136.4, 130.1, 129.2, 128.7, 127.6, 127.5, 121.3, 121.2, 108.2, 107.4, 44.9, 27.2; HRMS calcd for $C_{15}H_{14}N_2NaO$ [M + Na^+] 261.0992, found 261.0998.

1-Benzyl-3-ethyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5c): Light yellow solid, 40.9 mg, 81% yield; mp 81−83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.24 (m, 5H), 7.09−6.98(m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 5.09 (s, 2H), 4.00 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.1, 136.4, 129.3, 129.2, 128.7, 127.6, 127.5, 121.2, 121.0, 108.3, 107.5, 44.8, 36.0, 13.7; HRMS calcd for $C_{16}H_{16}N_2NaO$ [M + Na^+] 275.1158, found 275.1155.

1-Benzyl-3-propyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5d): Yellow oil, 40.5 mg, 76% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.24 (m, 5H), 7.09−6.98 (m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 5.09 (s, 2H), 3.91 (t, J = 7.2 Hz, 2H), 1.88−1.79 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 136.5, 129.6, 129.2, 128.7, 127.6, 127.4, 121.2, 121.0, 108.3, 107.7, 44.8, 42.8, 21.8, 11.4; HRMS calcd for $C_{17}H_{18}N_2NaO$ [M + Na^+] 289.1319, found 289.1311.

1-Benzyl-3-butyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5e): Light yellow oil, 44.9 mg, 80% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (m, 5H), 7.09−6.98 (m, 3H), 6.88 (d, J = 7.2 Hz, 1H), 5.09 (s, 2H), 3.94 (t, J = 7.2 Hz, 2H), 1.82−1.75 (m, 2H), 1.43−1.39 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 136.4, 129.5, 129.3, 128.7, 127.6, 127.5, 121.2, 121.0, 108.3, 107.7, 44.8, 41.0, 30.5, 20.1, 13.8; HRMS calcd for $C_{18}H_{20}N_2NaO$ [M + Na^+] 303.1462, found 303.1468.

1-Benzyl-3-pentyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5f): Colorless oil, 42.4 mg, 72% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.23 (m, 5H), 7.08−6.97 (m, 3H), 6.87 (d, J = 7.2 Hz, 1H), 5.08 (s, 2H), 3.92 (t, J = 7.4 Hz, 2H), 1.82−1.75 (m, 2H), 1.39−1.35 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 136.4, 129.5, 129.2, 128.7, 127.6, 127.4, 121.2, 121.0, 108.3, 107.7, 44.8, 41. 3, 29.0, 28.1, 22.4, 14.0; HRMS calcd for $C_{19}H_{22}N_2NaO$ [M + Na^+] 317.1628, found 317.1624.

1-Allyl-3-benzyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5g): Dark yellow oil, 44.9 mg, 85% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.25 (m, 5H), 7.08−6.99 (m, 3H), 6.90 (d, J = 7.2 Hz, 1H), 6.00−5.90 (m, 1H), 5.27(s, 1H), 5.24 (d, J = 4.8 Hz, 1H), 5.10 (s, 2H), 4.57 (d, J = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 136.4, 132.1, 129.4, 129.2, 128.7, 127.7, 127.5, 121.3, 117.6, 108.3, 44.9, 43.6; HRMS calcd for $C_{17}H_{16}N_2NaO$ [M + Na^+] 287.1162, found 287.1155.

1-Benzyl-3-(4-bromobutyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5h): Yellow oil, 56.0 mg, 78% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 −7.24 (m, 5H), 7.10−6.99 (m, 3H), 6.89−6.87 (m, 1H), 5.08 (s, 2H), 3.98 (t, J = 6.6 Hz, 2H), 3.48 (t, J = 5.6 Hz, 2H), 1.97−1.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154. 4, 136.3, 129.2, 128.8, 127.7, 127.4, 121.4, 121.3, 108.4, 107.6, 44.9, 40.2, 33.0, 29.7, 26.9; HRMS calcd for $C_{18}H_{19}BrN_2NaO$ [M + Na^+] 381.0579, found 381.0573.

1-Benzyl-3-(4-nitrobenzyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5i): Yellow solid, 59.7 mg, 83% yield;mp 159−161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.35−7.27 (m, 5H), 7.05−6.98 (m, 2H), 6.94−6.92 (m, 1H), 6.83−6.81 (m, 1H), 5.21 (s, 2H), 5.13 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 147.6, 143.6, 136.0, 129.3, 128.8, 128.1, 127.8, 127.5, 124.1, 121.9, 121.6, 108.7, 107.9, 45.1, 44.3; HRMS calcd for $C_{21}H_{17}N_3NaO_3$ [M + Na^+] 382.1169, found 382.1162.

Ethyl-2-(3-benzyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)acetate (5j): White solid, 34.2 mg, 51% yield; mp 126−128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.24 (m, 5H), 7.07−6.99 (m, 2H), 6.91−6.87 (m, 2H), 5.09 (s, 2H), 4.67 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 154.3, 136.1, 129.3, 129.2, 128.7, 127.7, 127.4, 121.8, 121.6, 108.6, 107.7, 61.8, 44.9, 42.4, 14.1; HRMS calcd for $C_{18}H_{18}N_2NaO_3$ [M + Na^+] 333.1218, found 333.1210.

1,3-Dibenzyl-1*H*-benzo[*d*]imidazol-3-ium Chloride (6a): White solid, mp 207−209 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.73 (s, 1H), 8.01−8.00 (m, 2H), 7.59−7.58 (m, 6H), 7.40−7.33 (m, 6H), 5.88 (s, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 143.4, 134.6, 131.5, 129.5, 129.2, 128.8, 127.2, 114.5, 50.5.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of compounds **3a−3x**, **5a−5j**, and **6a**. 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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(10) CCDC-943544 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif.