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Direct Synthesis of 6-Arylpurines by Reaction of 6-Chloropurines with Activated Aromatics

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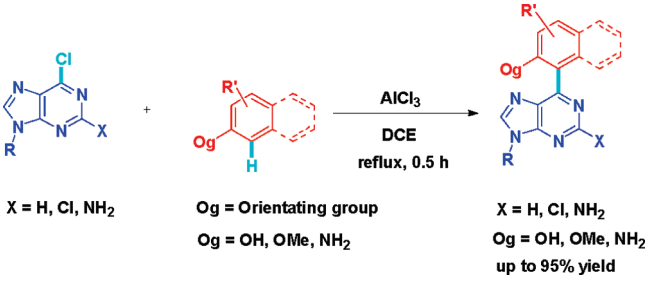

Highly functionalized C6-aryl-substituted purine analogues were synthesized through direct arylation of 6-chloropurine with aromatics promoted by anhydrous $AlCl_3$ in a single step. The reactions, which were conducted using a 3-fold excess of $AlCl_3$ in refluxing 1,2-dichloroethane, gave moderate to excellent product yields in 0.5 h. This work is complementary to the classical coupling reactions for the synthesis of C6-aryl-substituted purine analogues.

Purine bases and purine nucleoside derivatives play prominent roles in biology, biochemistry, and pharmaceutical areas.[1] Purine analogues with various substituents at C6 have received great attention due to their high cytotoxicity, antitumor activity, and broad spectrum of biological activities.[2] 6-Arylpurine bases and their nucleosides are of particular importance due to *anti*-HCV, cytostatic, and antimycobacterial activities.[3] The studies on biological activities of 6-arylpurines have been limited to easily available purines bearing simple aryl groups, while those bearing highly substituted and/or functionalized aryl moieties remain to be explored.[4]

The classical methods for the synthesis of 6-arylpurines involve the cross-coupling reactions of aryl organometallics (Ar-M) and 6-halopurines (Scheme 1, eq 1) or aryl halides (Ar-X) and 6-metalpurines[5] (Scheme 1, eq 2). For example, Suzuki−Miyaura,[3a,6] Stille,[7] Negishi,[7a,8] and Kumada coupling reactions[9] have been commonly applied to the preparation of 6-arylpurines. Though significant attention has been received over the last several years, these cross-coupling reactions usually involve the following aspects: (a) expensive palladium, nickel, and complex ligands are employed as catalysis systems; (b) the preparation of organometallic reagents is usually conducted under rigorous reaction conditions (anhydrous, nitrogen atmosphere); (c) the reaction with metallic reagents usually requires multistep including protection of the sensitive functional groups (such as hydroxyl, amino, or imino group) in the substrates if necessary. This generates byproducts and wastes from reagents, solvents, and purification. Therefore, it is still of great importance to develop alternative methods for the preparation of 6-arylpurines. Herein, we will report direct arylation of 6-chloropurine with arenes promoted by anhydrous $AlCl_3$ for the synthesis of highly functionalized C6-aryl-substituted purine analogues.

During the ongoing course of our study on the development of new methods for the synthesis of nucleoside analogues[10] and according to reports on arylation and heteroarylation of heterocyclic systems,[11] we had predicted that C6-aryl-substituted purine analogues could be synthesized

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SCHEME 1. Different Routes for the Synthesis of 6-Arylpurines

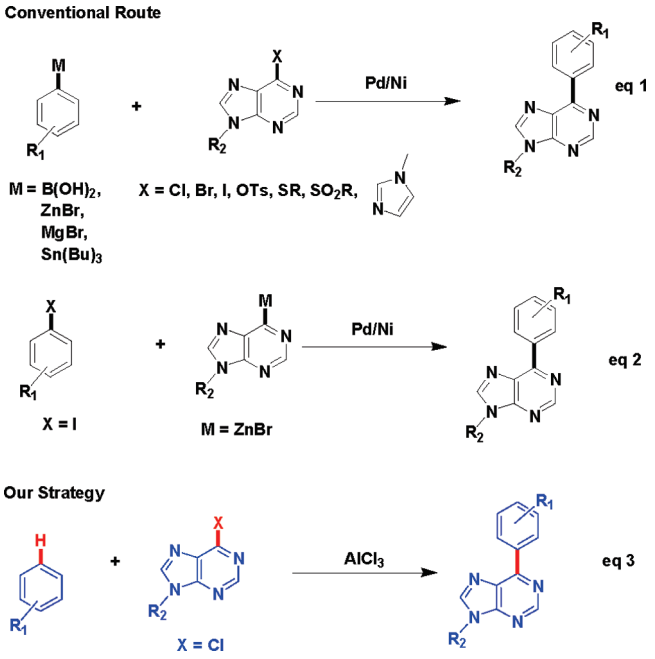
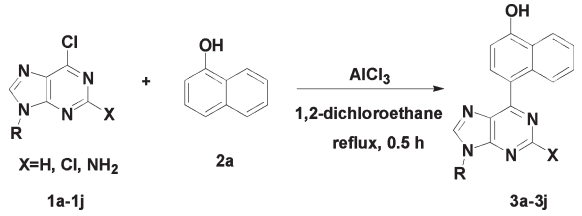
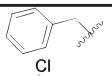
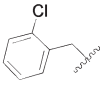
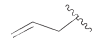
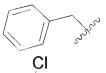
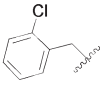
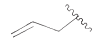
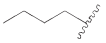
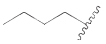


TABLE 1. Reaction of 1-Naphthol with Various 6-Chloropurines Derivatives[a]



entry	product	X	R	yield (%)[b]
1	**3a**	H		75
2	**3b**	H		76
3	**3c**	H		70
4	**3d**	H	H	53
5	**3e**	Cl		85
6	**3f**	Cl		87
7	**3g**	Cl		74
8	**3h**	Cl		75
9	**3i**	Cl	H	75
10	**3j**	NH_2		92

[a]Reaction condition: 6-chloropurine derivatives (0.5 mmol), 1-naphthol (1 mmol), $AlCl_3$ (1.5 mmol), 1,2-dichloroethane (5 mL). [b]Isolated yields based on nucleobases.

through direct arylation of 6-chloropurine with electron-rich aromatics or heteroaromatics promoted by anhydrous $AlCl_3$ (Scheme 1, eq 3). Thus, when the reaction of 9-Bn-6-chloropurine with 1-naphthol was conducted in 1,2-dichloroethane at room temperature, the direct arylation proceeded successfully to produce the desired product **3a**.

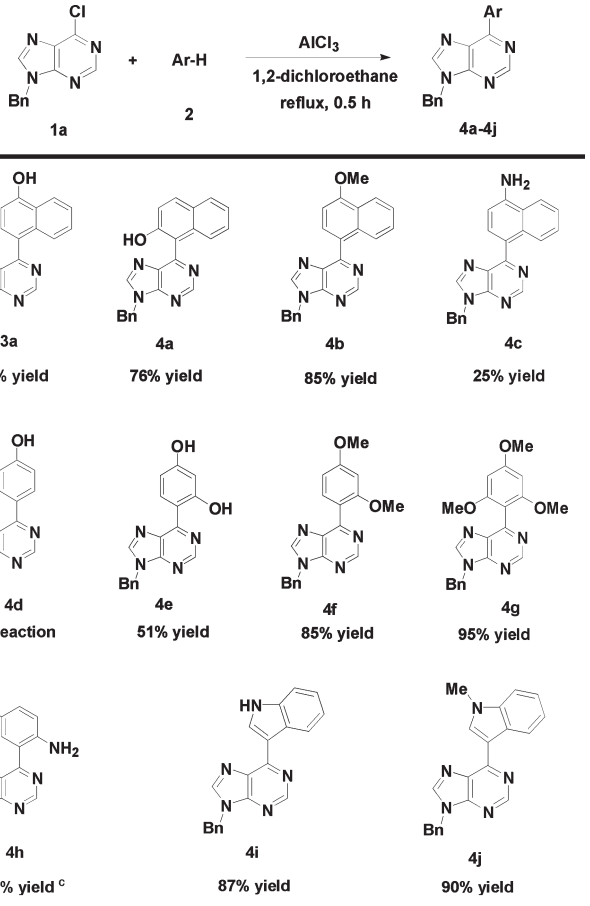
During optimization of reactions conditions, we found that when the reaction of 9-Bn-6-chloropurine with 1-naphthol was carried out in 1,2-dichloroethane at reflux temperature in the presence of 300 mol % of $AlCl_3$, the product was isolated in 75% yield in 0.5 h (see the Supporting Information for details).

To evaluate the generality of the reaction, a number of 6-chloropurine derivatives with various substituents at N9 were subjected to the optimized conditions (Table 1, entries 1−4), affording the desired products in moderate to good isolated yields (53−76%). It was found that the kind of substituents at N9 had little impact on the yields of the products.

To study the influence of substituent groups at C2, a series of 2,6-dichloropurines and 2-amino-6-chloropurines were employed as the substrates under the optimized reaction conditions (Table 1, entries 5−10). In most cases, the replacement of hydrogen with Cl or NH_2 led to better yields when the same functional group presents at N9.

The substrate scope of aryl compounds under the optimized conditions was also examined (Table 2). First, the naphthol derivatives were explored. Whether 1-naphthol, 2-naphthol, or 1-naphthol methyl ether (**3a**, **4a**, and **4b**) was used as starting material, good to high yields were obtained. While 1-naphthylamine (**4c**) gave a low yield of 25% even in a

TABLE 2. Reaction of Ar-H with 9-Bn-6-chloropurine[a,b]



[a]Reaction conditions: 9-Bn-6-chloropurine (0.5 mmol), **2** (1 mmol), $AlCl_3$ (1.5 mmol), 1,2-dichloroethane (5 mL). [b]Isolated yields based on nucleobases. [c]Reaction time: 10 h.

prolonged time (10 h). Subsequently, various phenol derivatives were also investigated (**4d**−**g**). It is noteworthy that no product was observed when phenol was used as starting material under the optimized conditions (**4d**). But other substrates gave moderate to high yields (**4e**−**g**). It was also found that the reaction could proceed using *p*-toluidine as a substrate with prolonged reaction time (**4h**). The use of heteroarenes such as indole and *N*-methylindole also afforded the corresponding products in good yields (**4i** and **4j**).

To better understand the product structure, we attempted to grow crystals of 6-arylpurines suitable for X-ray diffraction analysis. The crystal of **3b** proved that the substitution reaction occurred on the para position of the hydroxyl group of 1-naphthol to give 4-[9-(2-chlorobenzyl)-9*H*-purin-6-yl]-naphthalen-1-ol (**3b**) (see the Supporting Information)

In conclusion, we have developed an unprecedented method for the synthesis of highly functionalized C6-aryl substituted purine analogues by direct arylation of purine with electron-rich aromatics or heteroaromatics promoted by anhydrous $AlCl_3$. Application of $AlCl_3$-promoted coupling reactions between purine bases and aryls allows the synthesis of biologically important 6-aryl-substituted purine analogues to be carried out under mild condition in one step without protection of sensitive functional groups. This method avoids the use of transition-metal catalysts, organometallic reagents, complex ligands, rigorous reaction conditions, multiple steps, or the formation of byproducts and represents an important complement to the classical coupling reactions for synthesis of C6-aryl-substituted purine analogues when substrates and products are stable toward $AlCl_3$.

Experimental Section

Typical Experimental Procedure for the Reaction of Purines with 1-Naphthol. Purine base **1a** (122 mg, 0.5 mmol) and 1,2-dichloroethane (5 mL) were put into a 25 mL glass vial equipped with a small magnetic stirring bar. To this were added 1-naphthol **2a** (144 mg, 1 mmol) and anhydrous $AlCl_3$ (200 mg, 1.5 mmol). The reaction mixture was stirred in a boiling heating bath at reflux temperature for 0.5 h. The vial was cooled to room temperature, and the mixture was poured into water (20 mL), stirred for 15 min, and then extracted with ethyl acetate (3 × 10 mL). The organic layers were collected, combined, washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The resulting residue was purified by column chromatography over silica gel (dichloroethane/ethyl acetate) to give the desired product **3a**.

Compound **3a**: light yellow powder; mp 282−284 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.76 (s, 1H), 9.03 (s, 1H), 8.71 (s, 1H), 8.45 (t, J = 5.6 Hz, 1H), 8.26 (t, J = 2.8 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 4.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 4.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 5.55 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.3, 154.9, 151.3, 151.2, 145.5, 136.1, 131.6, 131.5, 131.2, 128.3, 127.5, 127.3, 126.3, 125.3, 124.3, 124.2, 122.4, 121.8, 106.9, 46.0; HRMS calcd for $C_{22}H_{17}N_4O$ [M + H$^+$] 353.1402, found 353.1403.

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Supporting Information Available: Optimization of reaction conditions, X-ray structure of **3b**, and experimental procedures, including spectroscopic information. This material is available free of charge via the Internet at http://pubs.acs.org.