Microwave-Assisted Rapid Synthesis of 2,6,9-Substituted Purines

He Huang,[†] Hong Liu,*[,†,§] Kaixian Chen,[†] and Hualiang Jiang[†,‡,§]

Drug Discovery and Design Centre, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institute for Biological Sciences, and Graduate School, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China, and School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

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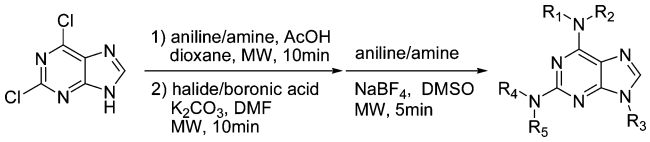
Purine analogues represent an excellent scaffold for targeting many biosynthetic, regulatory, and signal transduction proteins including cellular kinases, G proteins, and polymerases.[1] Purine core compounds, especially the 2,6,9-substituted purines, act as potent inhibitors of Hsp90, Src kinase, P38α MAP kinase, sulfotransferases, phosphodiesterases, and Cdks.[2] Accordingly, the developement of more efficient, convenient, and environmentally friendly methods for the synthesis of 2,6,9-substituted purines is important. 2,6,9-Substituted purines were synthesized previously by Fiorini et al. using solution-phase synthetic approaches with 2,6-dichloropurine as the starting material.[3] However, this synthetic process needs a long heating time and complicated reaction conditions. Subsequently, several solid-phase synthesis methods were developed,[4] but the substitution at the C2 position was difficult. To expand the diversity of the N9 position of purine, Ding et al. employed a copper(II)-mediated coupling reaction to prepare 9-arylpurines with yields of 43−47%.[5] The coupling reaction has emerged as a valuable method for the preparation of 9-arylpurines, but long reaction times are required.

Microwave-assisted organic reactions have been applied to a wide range of reaction types, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions.[6] It accelerates a variety of synthetic transformations via time- and energy-saving protocols.[6] Herein, we report on an expeditious and efficient method to prepare 2,6,9-substituted purines in a two-pot reaction using microwave-assisted reactions. First, 2-chloro-6, 9-substituted purines were prepared via a one-pot two-step reaction, which involves a sequential S_NAr displacement of the C6 chloro substituent with various anilines and amines, followed by N-alkylation and N-arylation at the N9 position with different organic halides and boronic acids. Second, $NaBF_4$ catalysis supports a S_NAr substition of the C2 chloro displacement with high product conversion (Scheme 1).

Scheme 1



A one-pot two-step derivative process was carried out by microwave irradiating the sample in a sealed tube to afford the desired products (**2a**−**o**) using commercially available 2,6-dichloropurine **1** as the starting material. Initially, it was found that the C6 chloro substituent is the most efficient under acidic conditions. Compound **1** was treated with 1.0 equiv of aniline and 1.0 equiv of acetic acid in dioxane for 10 min at 150 °C using microwave irradiation. After the reaction was cooled to ambient temperature, organic halides (2.0 equiv), NaOH (2.0 equiv), and an equal volume of DMF were added to the crude reaction mixture. The reaction was heated to 150 °C for another 10 min using microwave irradiation, which afforded the desired product (**2**). To explore the generality and scope of this reaction, a wide range of structurally varied substituents were investigated for this one-pot two-step reaction (Table 1).

The results indicated that the anilines bearing bromo-, methyl-, and methoxyl-substitutions were well tolerated (entries 2, 3, and 6−9, Table 1), although those containing an electron-withdrawing group typically gave lower yields (entries 4 and 5, Table 1). No significant electronic effects were observed for the ortho-, meta-, and para-substituted anilines (entries 6, 7, and 8, Table 1). Amines underwent reaction with yields relatively lower than those of the anilines; for example, 2-aminopropane, diethylamine, and morpholine afford 72.3, 80.3, and 82.8% of **2j**−**l**, respectively (entries 10−12, Table 1). In addition, the ethyl bromide substitution at the N9 position of purine also reacted efficiently (entries 9 and 13, Table 1); compounds **2i** and **2m** were isolated in 83.2 and 81.4% yields, respectively. A phenyl group can be directly introduced at the N9 position of purine with a copper(II)-mediated coupling reaction in 20 min under microwave irradiation. Compounds **2n** and **2o** were rapidly synthesized with corresponding yields of 16.9 (entry 14, Table 1) and 19.2% (entry 15, Table 1).

The S_N2Ar substitution of 2-chloropurine with amines usually required higher temperatures and extended reaction time.[2,3,4] We found that $NaBF_4$ could facilitate the rapid construction of 2-substituted purine (entry 2, Table 2). To date, the application of $NaBF_4$ to catalyze the S_N2Ar substitution of the 2-chloropurine has not been reported.

Using 2-chloro-6-morpholino-9-benzylpurine **3** and morpholine **4** as model substrates, we optimized the reaction conditions by testing several parameters, such as different bases, various solvents, and different amounts of $NaBF_4$. The results are summarized in Table 2. The optimum condition of this procedure is 0.1 M of the starting material with 5 equiv of amines and 1.0 equiv of $NaBF_4$ crystals in DMSO at 180 °C for 5 min.

* To whom correspondence should be addressed. Phone: +86-21-50807042. Fax: +86-21-50807088. E-mail: hliu@mail.shcnc.ac.cn.

† Chinese Academy of Sciences.

‡ School of Pharmacy.

§ Co-Principal Investigator.

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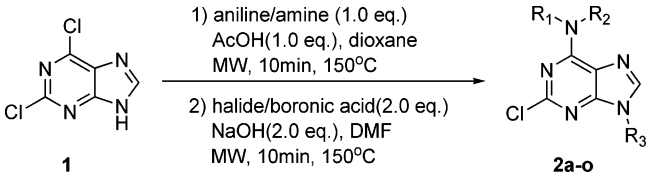
Table 1. One-Pot Two-Step Microwave-Assisted Reaction

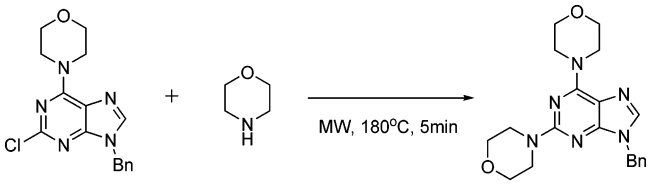


1 **2a-o**

entry	aniline/ amine	aryl halide/ boronic acid	product	crude purity	yield
1	$C_6H_5NH_2$	benzyl bromide	**2a**	85.4%	80.1%
2	4-$MeC_6H_4NH_2$	benzyl bromide	**2b**	97.1%	94.1%
3	4-$BrC_6H_4NH_2$	benzyl bromide	**2c**	92.3%	87.8%
4	3-$F_3CC_6H_4NH_2$	benzyl bromide	**2d**	51.0%	47.3%
5[a]	4-$NO_2C_6H_4NH_2$	benzyl bromide	**2e**	29.7%	21.0%
6	2-$MeOC_6H_4NH_2$	benzyl bromide	**2f**	92.9%	91.7%
7	3-$MeOC_6H_4NH_2$	benzyl bromide	**2g**	87.3%	83.0%
8	4-$MeOC_6H_4NH_2$	benzyl bromide	**2h**	97.0%	94.2%
9	4-$MeOC_6H_4NH_2$	ethyl bromide	**2i**	86.8%	83.2%
10	2-aminopropane	benzyl bromide	**2j**	78.9%	72.3%
11	diethylamine	benzyl bromide	**2k**	83.7%	80.3%
12	morpholine	benzyl bromide	**2l**	88.6%	82.8%
13	morpholine	ethyl bromide	**2m**	84.5%	81.4%
14[b]	4-$MeOC_6H_4NH_2$	phenylboronic acid	**2n**	20.0%	16.9%
15[b]	morpholine	phenylboronic acid	**2o**	22.8%	19.2%

[a] Reaction conditions: 180 °C, 20 min in each step. [b] Reaction conditions: 0.265 mmol of 2,6-dichloropurine, 1.0 equiv of aniline/amine, and 1.0 equiv of AcOH in 2 mL of dry DMF for 10 min in the microwave. Then 2.0 equiv of boronic acid, 2.0 equiv of anhydrous cupric acetate, 0.5 g of activated molecular sieves (4 Å), and 3.0 equiv of triethylamine were added for 20 min in the microwave.

Table 2. Procedure Optimization of the S_N2Ar Substitution at the C2 Position of 6,9-Substituted Purines



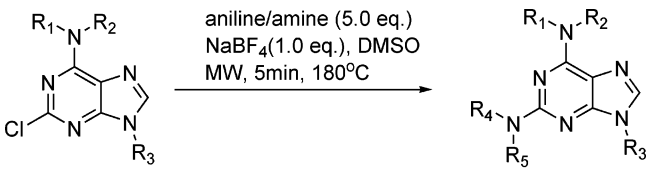
3 **4** **5**

entry	solvent (base)	$NaBF_4$ (equiv)	yield
1	DMF	0	51.3%
2	DMF	0.2	78.0%
3[a]	DMF(K_2CO_3)	0.2	67.1%
4[b]	DMF(NaOH)	0.2	66.0%
5[c]	DMF(NaOEt)	0.2	61.2%
6	NMP	0.2	61.8%
7	CH_3CN	0.2	17.4%
8[d]	CH_3CN/NMP	0.2	50.8%
9	dioxane	0.2	17.4%
10	DMSO	0.2	82.1%
11	DMSO	0.5	88.7%
12	DMSO	1.0	96.0%
13	DMSO	2.0	86.5%
14	DMSO	5.0	62.7%

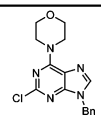
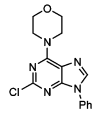
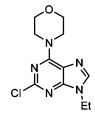
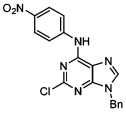
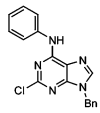
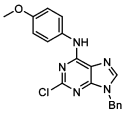
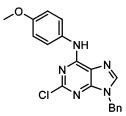
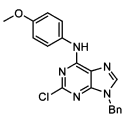
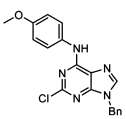
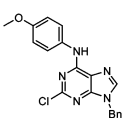
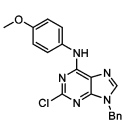
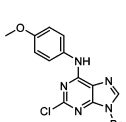
[a] One equivalent of K_2CO_3 was used as the base. [b] One equivalent of NaOH was used as the base. [c] One equivalent of NaOEt was used as the base. [d] A 1:1 mixture of CH_3CN and NMP was used as the solvent.

The effect of aniline/amine substitutions at the 2-position of the purine ring was also investigated (Table 3). Six diverse 6,9-disubstituted purines reacted smoothly with morpholine

Table 3. Examples of $NaBF_4$-Catalyzed S_N2Ar Substitution at the C2 Position of 6,9-Substituted Purines



2 **6a-l**

entry	reactant	aniline/ amine	product	crude purity	yield
1			**6a**	**97.8%**	96.0%
2			**6b**	**96.7%**	94.7%
3			**6c**	**98.1%**	93.2%
4			**6d**	**92.1%**	88.3%
5			**6e**	**99.7%**	99.1%
6			**6f**	**99.7%**	99.3%
7			**6g**	**86.8%**	81.0%
8			**6h**	**85.9%**	83.4%
9			**6i**	**99.4%**	98.9%
10			**6j**	**91.2%**	87.0%
11			**6k**	**82.9%**	81.2%
12			**6l**	**18.3%**	13.1%

to produce a range of 2,6,9-substituted derivatives (entries 1−6, Table 3) in good to excellent yields (88.3−99.3%). Using compound **2h** as a model substrate, we further tested the $NaBF_4$-catalyzed S_N2Ar substitution with various amines (entries 7−11, Table 3). The isolated yields ranged from 81.0 to 98.9%. However, 4-methylaniline (entry 12, Table 3) reacted with compound **2h** with a very low yield (13.1%) under the same reaction conditions used for the amines.

All of the microwave-assisted reactions were performed in an Initiator EXP microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation.

In summary, we have described a simple, rapid, efficient, and convenient protocol for the preparation of 2,6,9-substituted purines. A one-pot two-step reaction was developed to rapidly construct 6,9-disubstituted 2-chloropurines. Subsequently, we investigated the novel $NaBF_4$-catalyzed S_N2Ar substitution at the C2 position of these purines. All these reactions were carried out under microwave irradiation. Furthermore, the procedure used commercially available reagents and equipment, and most of the reactions involved are efficient, giving the desired compounds in higher purity and yield. The versatility of this methodology is suitable for library synthesis in drug discovery efforts.

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Supporting Information Available. Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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