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COMMUNICATION

CuBr Catalyzed C–N cross coupling reaction of purines and diaryliodonium salts to 9-arylpurines†

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CuBr was found to be an efficient catalyst for the C–N cross coupling reaction of purine and diaryliodonium salts. 9-Arylpurines were synthesized in excellent yields with short reaction times (2.5 h). The method represents an alternative to the synthesis of 9-arylpurines *via* Cu(II) catalyzed C–N coupling reaction with arylboronic acids as arylating agents.

Purine compounds show a wide range of biological and pharmaceutical activities such as antiviral or anticancer activities.[1] N9-Substituted purines have applications in the treatment of HSV infections,[2] HIV,[3] and hepatitis B.[4] Furthermore, N9-arylpurines are reported to act as enterovirus inhibitors,[5] potential antituberculosis drugs with high antimycobacterial activities,[6] antitumor agents against NCI-H460 (lung), MCF-7 (breast) and SF-268 (CNS) cancer cell lines.[7] Hence, there is considerable interest in the development of more efficient methods for the synthesis of N9-arylpurines due to their unique biological activities.

There are two routes for the synthesis of N9-arylpurines. One route is through heterocyclization from substituted pyrimidine analogues which usually requires multiple steps.[8] Another route is direct N9-arylation of purine *via* a C–N cross-coupling reaction. Aryl iodides and arylboronic acids were widely used as arylating agents in the presence of copper(II) or palladium(II) for the direct N9-arylation of purines to give moderate yields.[9] Gundersen *et al.* reported the synthesis of 9-arylpurines in the presence of copper(II) acetate used arylboronic acids as arylation agents.[9a] And Buchwald and coworkers reported CuI(I) catalyzed N-arylation of nitrogen-containing heterocycles employing aryl iodides as arylating agents in the presence of diamine ligands, and only one purine analogue was obtained in a yield of 66%.[10]

Starting from the early 1990s, the chemistry of polyvalent iodine organic compounds has experienced an explosive development.[11] Diaryliodonium salts,[12] which represent one of the most popular classes of hypervalent iodine compounds,[13] have been widely used as important arylating agents in organic synthesis.[14] During the ongoing course of our study on the synthesis of purine analogues[15] and according to the reports on N9-arylation of purines, we thought that diaryliodonium salts could be utilized as arylating agents for the synthesis of N9-arylpurines, which has never been reported as far as we know.

Initially, we investigated the direct arylation between 2,6-dichloropurine (**1a**) and $Ph_2I^+Cl^-$ (**2a**). Several Cu-catalysts were investigated for this reaction without the protection of nitrogen (Table 1, entries 1–3). The catalytic activity of Cu(I) was better than that of Cu(II) under the same reaction conditions and thus CuBr was chosen as the catalyst for the reaction. We were delighted to find that the yield was improved dramatically when the process was conducted under nitrogen atmosphere (entry 4). The screening of different bases showed that K_2CO_3 was the best choice for the reaction (entries 4–6). Under the same reaction conditions, reducing the amount of **2a** also led to lower yields, so the amount of **2a** was chosen as 1.5 eq (entries 6–7). The solvent effect was also examined and the results showed that CH_2Cl_2 was the best choice (entries 7–10).

Under the optimized reaction conditions, various purines were employed as substrates, and the representative results are listed in Table 2. Various purine derivatives could react with $Ph_2I^+Cl^-$ in excellent yields (entries 1–4). Purine derivatives with nitrogen or oxygen-containing substituents could also afford the desired products in good to excellent yields (entries 5–9). When 2-chloro-6-amino-9*H*-purine (**1j**) was used as the substrate, no desired product was formed, which might be due to the fact that **1j** is difficult to dissolve in CH_2Cl_2 (entry 10).

Some other diaryliodonium salts, including electron-donating and electron-withdrawing substituents, were also investigated under the optimized reaction conditions (Table 3). Good yields were observed when the methyl group was at the *para* position (entry 2), and halogen-substituted diaryliodonium salts could also react smoothly with 2,6-dichloropurine to give the corresponding products in good to excellent yields (entries 3–4). Because of steric hindrance, $(2,4\text{-}Me_2C_6H_3)_2I^+Br^-$ needed more catalyst to improve the reaction and gave a moderate yield (entry 5). When there was no methyl group at the C2 position, the diaryliodonium salts gave excellent yields (entries 6–7). Due to the poor solubility,

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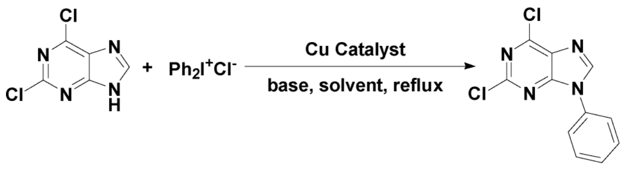
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and the copies of ^1H NMR and ^{13}C NMR spectra. CCDC reference number 825895. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05333g

Table 1 Optimization of the direct N9-arylation catalyzed by Cu compounds[a]

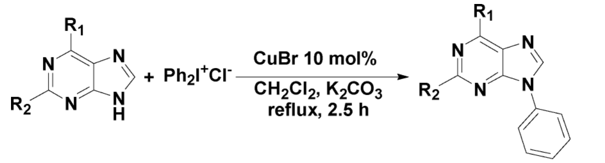


1a 2a 3a

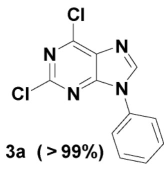
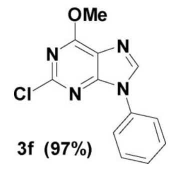
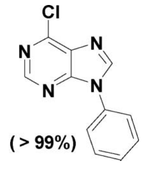
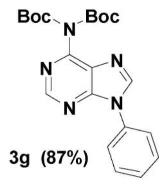
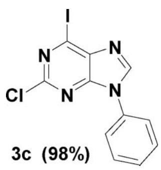
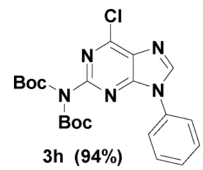
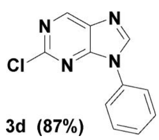
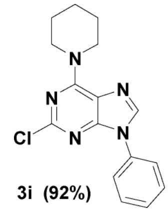
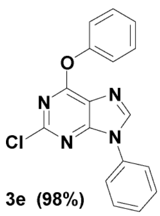
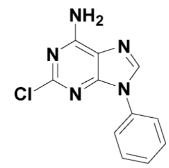
Entry	$Ph_2I^+Cl^-$ (eq)	Cat (mol%)	Solvent	Base	Time (h)	Yield (%)[b]
1[c]	2	$Cu(OAc)_2$ (20)	CH_2Cl_2	Et_3N	24	28
2[c]	2	CuI (20)	CH_2Cl_2	Et_3N	24	54
3[c]	2	CuBr (20)	CH_2Cl_2	Et_3N	24	60
4	1.5	CuBr (10)	CH_2Cl_2	Et_3N	2.5	80
5	1.5	CuBr (10)	CH_2Cl_2	DIPEA	3	50
6	**1.5**	**CuBr (10)**	$\mathbf{CH_2Cl_2}$	$\mathbf{K_2CO_3}$	**2.5**	**>99**
7	1.2	CuBr (10)	CH_2Cl_2	K_2CO_3	2.5	82
8[d]	1.5	CuBr (10)	DMSO	K_2CO_3	2.5	28
9[d]	1.5	CuBr (10)	toluene	K_2CO_3	2.5	30
10[d]	1.5	CuBr (10)	CH_3CN	K_2CO_3	2.5	32

[a] Reaction conditions: 2,6-dichloropurine **1a** (0.5 mmol), solvent (2 mL), 2 equiv base, under nitrogen. [b] Isolated yield based on 2,6-dichloropurine. [c] Without N_2 protection. [d] The reaction temperature was 40 °C.

Table 2 Direct phenylation of various purines at the N9 position with $Ph_2I^+Cl^-$[a]



1a-1j 2a 3a-3j

Entry	Product (yield)[b]	Entry	Product (yield)[b]
1	 3a (>99%)	6	 3f (97%)
2[c]	 3b (>99%)	7[c]	 3g (87%)
3	 3c (98%)	8	 3h (94%)
4[c]	 3d (87%)	9	 3i (92%)
5	 3e (98%)	10	 3j (No Reaction)

[a] Reaction conditions: purines 1 (0.5 mmol), $Ph_2I^+Cl^-$ **2a** (0.75 mmol), CuBr (0.05 mmol), K_2CO_3 (1.0 mmol), DCM (2 mL), reflux for 2.5 h under N_2 protection. [b] Isolated yields based on purines. [c] 50 mol% CuBr was used.

$(3\text{-}NO_2C_6H_4)_2I^+Br^-$ underwent no reaction (entry 8), and $(3\text{-}NO_2\text{-}6\text{-}MeC_6H_3)_2I^+Br^-$ gave a low yield (20%) (entry 9). However $(3\text{-}COOEtC_6H_4)_2I^+Br^-$ gave a moderate yield (60%) (entry 10).

To better understand the product structure, we attempted to grow crystals of 9-arylpurines suitable for X-ray diffraction analysis. The crystal of **3l** proved that the arylation reaction occurred on the N9-position of the purines and gave 2,6-dichloro-9-(4-chlorophenyl)-9*H*-purine (**3l**). (Fig. 1)

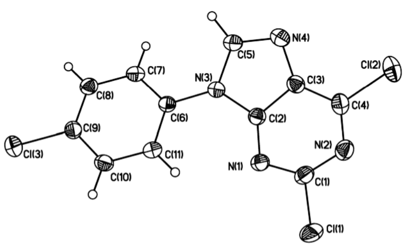


Fig. 1 X-Ray structure of **3l**.

In conclusion, we have developed a novel and efficient CuBr-catalyzed direct N9-arylation of purine bases with diaryliodonium salts. Diaryliodonium salts were firstly used as effective arylation agents for the N9-arylation of purines catalyzed by 10 mol% CuBr to give the products in excellent yields in 2.5 h and thus the catalyst amount and reaction time were greatly reduced while the yields were dramatically enhanced compared to the previously reported methods. The scope of the direct arylation has been shown to tolerate a variety of purine analogues and diaryliodonium salts. The simplicity of this procedure, the absence of expensive catalyst and ligand, the low amount of catalyst, the short reaction time, and excellent yield and regioselectivity make this method more synthetically attractive. The method represents an alternative to the previously available synthesis of 9-arylpurines *via* C–N coupling reaction with arylboronic acids as arylating agents. Investigations into the scope of these Cu-catalyzed direct arylations are in progress.

Acknowledgements

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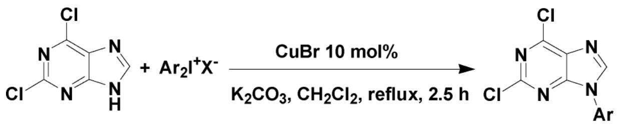
Table 3 Direct arylation of 2,6-dichloropurine at the N9 position with $Ar_2I^+X^-$ [a]



1a 2a-2i 3k-3r

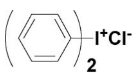
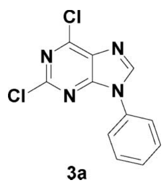
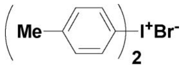
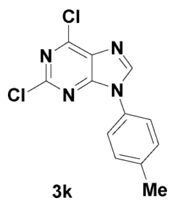
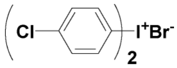
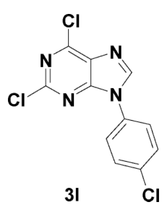
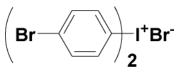
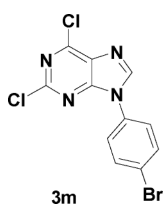
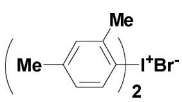
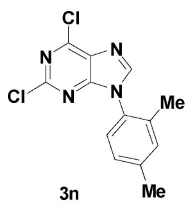
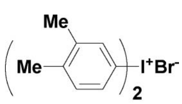
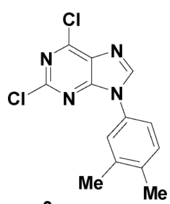
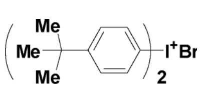
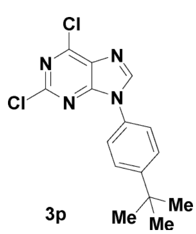
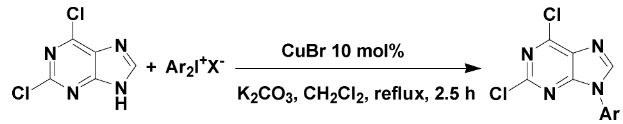
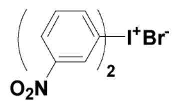
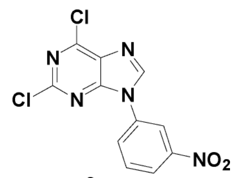
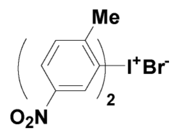
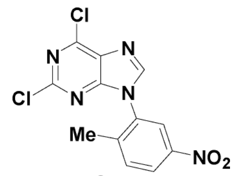
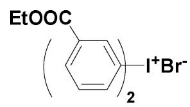
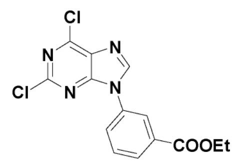
Entry	$Ar_2I^+X^-$	Product	Yield (%)[b]
1	 2a	 3a	> 99
2	 2b	 3k	86
3	 2c	 3l	99
4	 2d	 3m	82
5[c]	 2e	 3n	76
6	 2f	 3o	96
7	 2g	 3p	> 99

Table 3 *(Contd.)*



1a 2a-2i 3k-3r

Entry	$Ar_2I^+X^-$	Product	Yield (%)[b]
8	 2j	 3q	0
9	 2i	 3r	20
10	 2h	 3s	60

[a] Reaction conditions: 2,6-dichloropurine **1a** (0.5 mmol), $Ar_2I^+X^-$ **2** (0.75 mmol), CuBr (0.05 mmol), K_2CO_3 (1.0 mmol), DCM (2 mL), reflux for 2.5 h under N_2 protection. [b] Isolated yield based on 2,6-dichloropurine. [c] 50 mol% CuBr was used.

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