Microwave irradiated C6-functionalization of 6-chloropurine nucleosides with various mild nucleophiles under solvent-free conditions†

Hai-Ming Guo,*[a] Peng-Yang Xin,[a] Hong-Ying Niu,[b] Dong-Chao Wang,[a] Yi Jiang[a] and Gui-Rong Qu*[a]

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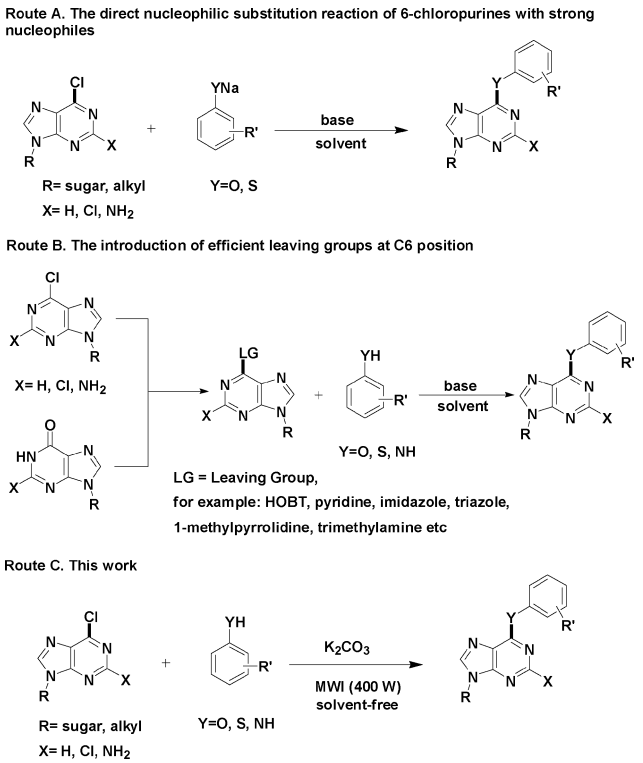
An efficient method for the synthesis of C6-functionalized purine nucleosides was developed *via* the direct nucleophilic substitution reaction of 6-chloropurine derivatives with various mild nucleophiles. The eco-friendly solvent-free process gave good to high isolated yields within a short reaction time (5 min) under microwave irradiated conditions.

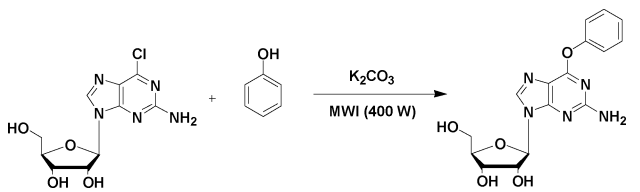
Over the past few decades, purine bases and nucleosides have been reported to possess a wide scope of bioactivities.[1] Purine derivatives with various substituents (such as C-, N-, O-, S-substituents) at C6 constitute one of the largest classes of these bioactive compounds.[2] The method commonly used for the construction of theses C6-substituted purine bases and nucleosides is based on the classical nucleophilic substitution reaction. One route is through the direct nucleophilic substitution reaction of 6-halopurine analogues and strong nucleophilic agents such as MeONa, PhONa, MeSNa, and PhSNa *etc.* (route A, Scheme 1).[3] Another route proceeds *via* the introduction of an efficient leaving group[4] (such as 1-hydroxybenzotriazole (HOBT),[4a,4b,4c] pyridine,[4d] imidazole,[4e] 1,4-diazabicyclo-[2.2.2]octane (DABCO),[4f] triazole,[4g] 1-methylpyrrolidine,[4h] trimethylamine[4i]) at C6 position, followed by the nucleophilic displacement (route B, Scheme 1). In both routes, either strong alkaline nucleophiles or efficient leaving groups are needed with long reaction times.[4] It is known that the S_N (nucleophilic substitution) reaction depends on the activities of nucleophiles and leaving groups. Chlorine is a relatively poor leaving group compared to HOBT, pyridine, *etc.* At the same time, the nucleophilic abilities of PhOH, PhSH or $PhNH_2$ are much poorer than their corresponding alkaline compounds. Up to now, however, there is no report on the process between 6-chloropurine analogues and mild nucleophilic agents such as PhOH, PhSH, $PhNH_2$ and naphthol.

Reactions under solvent-free conditions are especially appealing as they provide the opportunity to avoid the use of toxic solvents.[5] Based on our preliminary work on the synthesis of various nucleoside analogues,[6] herein a green and efficient protocol for the synthesis of C6-functionalized purine



Scheme 1 Different routes for the synthesis of C6-functionalized purine analogues.

Table 1 Optimization of the reaction conditions[a]



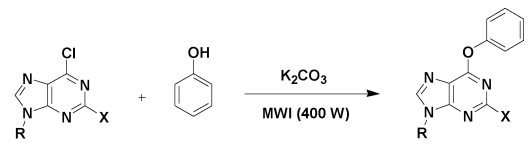
Entry	*T*/°C	Time/min	Yield[b](%)
1	50	10	54
2	70	10	76
3	90	10	85
4	110	10	87
5	90	3	62
6	**90**	**5**	**83**

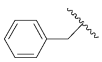
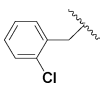
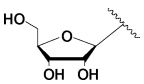
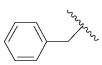
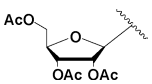
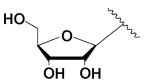
[a] Reaction conditions: 6-chloroguanosine (1 mmol), phenol (1.5 mmol), K_2CO_3 (2 mmol), MWI 400 W. [b] Isolated yields based on 6-chloroguanosine.

[a]*College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang, 453007, China. E-mail: guohm518@hotmail.com, guguir@sina.com; Fax: +86-3733329276*
[b]*School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang, 453003, China*

† Electronic supplementary information (ESI) available: Experimental details, NMR data of all compounds and full characterization of novel compounds. See DOI: 10.1039/c0gc00517g

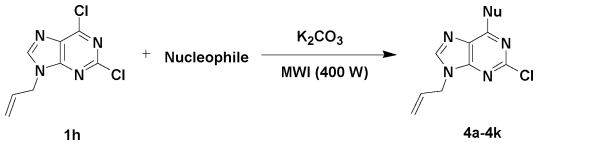
Table 2 Reaction of phenol with various 6-chloropurines[a]

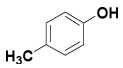
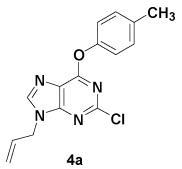
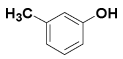
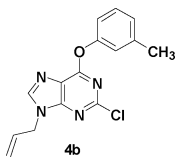
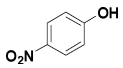
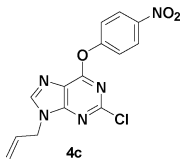
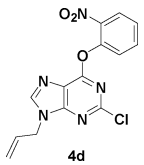
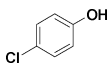
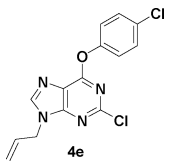
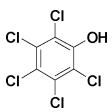
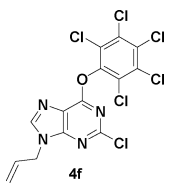
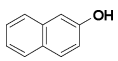
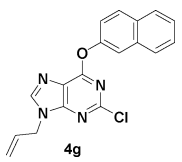
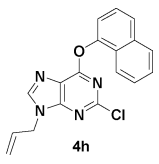


Entry	Product	*R*	Yield[b](%)
1	**3a**	H	87
2	**3b**	CH_3	95
3	**3c**		84
4	**3d**		89
5	**3e**		91
6	**3f**		79
7	**3g**	H	86
8	**3h**		87
9	**3i**		91
10	**3j**		75
11	**3k**		81

[a] Reaction conditions: 6-chloropurines (1 mmol), phenol (1.5 mmol), K_2CO_3 (2 mmol), MWI 400 W (90 °C). [b] Isolated yields based on nucleobases.

Table 3 Reaction of 9-allyl-2,6-dichloro-9*H*-purine with various mild nucleophiles[a]

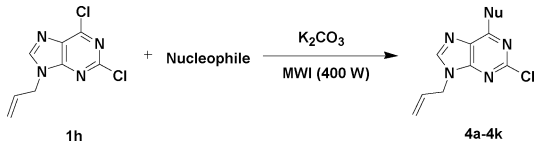


Entry	Nucleophile	Product	Yield[b](%)
1		 **4a**	95
2		 **4b**	89
3		 **4c**	89
4		 **4d**	87
5		 **4e**	90
6		 **4f**	81
7		 **4g**	93
8		 **4h**	97

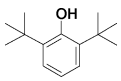
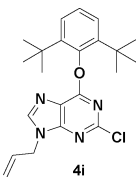
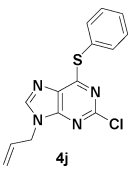
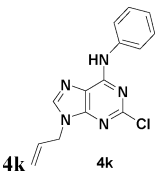
nucleosides was described *via* the direct nucleophilic substitution reaction of 6-chloropurine derivatives and mild nucleophiles like PhOH, PhSH, $PhNH_2$ under microwave irradiated conditions without solvent (route C, Scheme 1).

To initiate our study, we examined the microwave promoted nucleophilic substitution reaction between 6-chloroguanosine and phenol. As shown in Table 1, at 50 °C the yield was low (entry 1, 54%). With the increase of the reaction temperature, the yields were improved. When the reaction temperature was at 90 °C, the yield reached up to 85% (entry 3). By increasing the reaction temperature to 110 °C, no significant change in the yield was observed (entry 4, 87%). Next, we investigated the effect of reaction time. When the reaction time was 3 min, the yield was low (entry 5, 62%). By increasing the reaction time to 5 min, the yield reached 83% (entry 6). When the reaction time was 10 min, no significant change in the yield was observed (entry 3, 85%). Therefore, 90 °C and 5 min were the optimized reaction

Table 3 *(Contd.)*



1h 4a-4k

Entry	Nucleophile	Product	Yield[b](%)
9		 4i	0
10		 4j	91
11		 4k	78[c]

[a] Reaction conditions: 9-allyl-2,6-dichloro-9*H*-purine (1 mmol), nucleophile (1.5 mmol), K_2CO_3 (2 mmol), MWI 400 W (90 °C). [b] Isolated yields based on nucleobases. [c] Reaction time, 10 min.

conditions. Further screening of irradiation power showed that 400 W was the best choice.

To evaluate the generality of the reaction, a number of 6-chloropurine derivatives with various substituents, including a sugar carbon substituent at N9, were subjected to the optimized reaction conditions, affording the desired 6-phenoxypurine derivatives in good to excellent isolated yields (75–95%) (Table 2). The type of substituent at N9 had a slight impact on the yield of the products: the alkyl-substituted substrates gave higher yields, while the sugar-substituted substrates gave slightly lower yields.

Intrigued by the results described above, other substrates, such as phenol, naphthol, thiophenol and aniline derivatives, were chosen as mild nucleophiles to probe whether the nucleophilic substitution reactions could be easily accessed. The results are shown in Table 3. As expected, these reactions also proceeded smoothly to give the corresponding 6-substituted purines in good to high yields (78–97%) except that the desired product **4i** could not be obtained even after 0.5 h, which might be due to the strong steric hindrance of *tert*-butyl.

In order to compare the efficiency of microwave irradiation with conventional heating, the formation of **4c** was carried out in an oil bath under the same conditions. It turned out that the reaction afforded only 45% yield even after 24 h, far less than the yield of 89% afforded under microwave irradiation within 5 min. This clearly indicated that the microwave-assisted reaction exhibited significant advantages over the conventional heating by not only reducing the reaction time, but also improving the reaction yield.

In conclusion, we have developed a general, rapid and solvent-free protocol for the synthesis of C6-funtionalized purine nucleosides between 6-halopurine analogues and mild nucleophiles, which avoids the use of strong alkaline nucleophiles or the introduction of efficient leaving groups. This method also has several advantages such as mild reaction conditions, ease of manipulation and a short reaction time. Furthermore, most of the reactions involved are efficient, giving the desired compound in higher purity and yield. Moreover, our eco-friendly solvent-free method avoids the use of toxic solvents such as DMF, DMSO, CH_3CN and toluene. This environmentally friendly procedure represents a promising green route for the synthesis of these important C6-functionalized purine nucleoside compounds.

Acknowledgements

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