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SHORT COMMUNICATION

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Regioselective alkylation reaction of purines under microwave irradiation

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Abstract

The alkylation of purines which is generally carried out after anion formation by treatment with a base and alkyl halide is complicated and in the best cases, mixtures of *N*-alkylated compounds are obtained. Purine derivatives can be acquired from alkylation at *N*-7 and *N*-9. In this work, the reaction conditions have been optimized to obtain the alkylation products of *N*-9 regioselectively. Different bases have been tried and tetrabutylammonium hydroxide has led to the best results. The reaction depends on the type of base and solvent used and improves considerably when the aid of microwave irradiation is used, which also considerably reduces the reaction time by reducing the formation of secondary products.

1 | INTRODUCTION

The structure of the purines has an aromatic heterocyclic nucleus consisting of a unit of pyrimidine condensed with an imidazole nucleus which according to IUPAC is recommended to name as imidazo[4,5-*d*]pyrimidines. Purines have a basic character and can exist in two tautomeric forms. Purines, in addition to being part of endogenous ligands, one of the two chemical compounds that cells use to make the basic components of DNA and RNA, are pressent in a large number of compounds that possess therapeutic activity. There are libraries of compounds that contain the purine nucleus that showed antiviral or cytotoxic activities, among others [1].

Due to the biochemical, therapeutic, and chemical interest of purines, it is not surprising that they have been the subject of intensive study using relevant techniques, and that the synthesis and reactions of purines have been examined in great detail.

Despite all this, in recent scientific work, we encountered a major problem in preparing a series of compounds with the purine nucleus. We needed 9-alkylpurines as starting material for the preparation of bioactive compounds and the few ones commercialized present a high price. The vast majority of *N*-alkylpurines are not commercially available, nor have any protocols been found that lead to the desired products in an efficient way. In this study, related to the alkylation of purines and derivatives, it is important to consider the nature of the starting purine and the alkylating agent, the base added and the solvent used. Furthermore, the temperature of the reaction is an important factor in optimizing the yield as well as the p*H* of the medium [2]. One of the serious problems lies in the poor solubility of purine derivatives in organic solvents, this makes the alkylation and of course the purification of these products difficult. The alkylation methods found in the bibliography are compiled in Table 1. Initially, an attempt was made to reproduce the purine synthesis contemplated in Table 1 following the proposed methodology, but in all cases similar or lower yields were obtained.

The presence of bulky substituents at position 6 of the purines allows the regioselective alkylation of *N*-9 using

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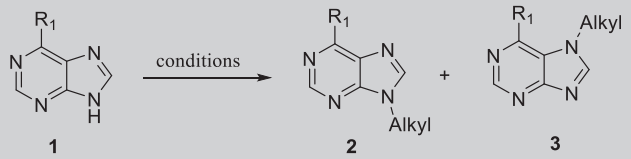
TABLE 1 Results background alkylation of purines



Entry	Conditions	R_1	2 (% yield)	3 (% yield)	Reference
1	CH_3I, K_2CO_3, DMSO, rt, 24 h	Cl	35	6.2	[1e]
2	$(CH_3)_2SO_4$, NaOH, rt, 25 min	Cl	70[a]		[2]
3	CH_3CH_2Br, K_2CO_3, β-CD/H_2O, rt, 1 h	Cl	41	4	[3]
4	CH_3CH_2I, K_2CO_3, DMSO rt, 2 h	Cl	50	5	[4]
5	$C_6H_5CH_2Cl$, K_2CO_3, DMSO rt, 3 h	Cl	38	15	[4]
6	Vinyl acetate, $Hg(CH_3COO)_2$, 40°C, 4 days	H	22	25	[5]
7	$(CH_3)_2SO_4$	NH_2	57	-	[6]
8	$(CH_3)_2SO_4$, diazomethane	H	30	-	[7]
9	Cyclopentyl bromide, K_2CO_3, DMF	Cl	55	-	[8]
10	CH_3I, K_2CO_3, DMSO, rt, 16 h	SCH_3	58	-	[9]

Note: Literature data.
[a]Mixture of **2** and **3**.

NaH as the base and DMF as a solvent [10]. In general, alkylation of purines leads to a mixture of 7- and 9-alkylated purines, but 9-alkyl is often the majority isomer [11].

In addition to the above alkylation methods using alkyl halides in a basic medium, it is worth highlighting the *N*-alkylation with alcohols under Mitsunobu conditions, although in this case very long reaction times are required [12]. Tetrabutylammonium fluoride (TBAF) allows to accelerate the reaction of *N*-alkylation of purine derivatives improving the yield [13].

2 | RESULTS AND DISCUSSION

As previously commented, although different methods and different conditions have been developed for the *N*-alkylation of purines, these methods are not generalizable, they depend on the type of substituents, and most lack regioselectivity. Therefore, the search for an efficient, cheap, and simple route for selective *N*9-purine alkylation is an attractive and challenging work. Given the impossibility of optimizing the reported methods, we have proposed to develop a new route for the alkylation of *N*9 from purines.

When 6-chloropurine was treated with methyl iodide, using DBU as base in acetonitrile, after 48 h of reaction, a mixture of the methylated *N*-7 and *N*-9 products was obtained with yields of 8 and 12% respectively (entry 1, Table 2). The use of KOH as a base still has worse performance (entry 2, Table 2). One of the main causes of these low yields lies in the low solubility of these compounds in organic solvents. Whereas if the alkylation is carried out in more polar solvents such as DMF or DMSO, the yields do not improve due to the difficulties of isolating the alkylated compound.

When tetrabutylammonium hydroxide (40% in water) was used as the base in acetonitrile, mostly *N*-alkylated purine was obtained in a 59% yield (entry 3, Table 2). Increasing the reaction time from 4 to 24 h and keeping the temperature at 50°C, worse results are obtained (entry 4, Table 2). Using these conditions but subjecting the reaction to microwave irradiation, the yield increases but the most remarkable thing is the high regioselectivity, only the *N*9-methylated isomer was detected (entry 6, Table 2). Under these conditions, short reaction times (30 min) offered better yields than longer times (60 min) (entry 6 vs. 7, Table 2).

DBU is a bulky, sterically hindered, and non-nucleophilic organic base which in this case did not lead to good yields or regioselectivity. Changing from base to KOH (an inorganic base), still offered worse results. Instead of these bases, using $(Bu)_4NOH$ (also named TBAOH) led to much better results. Unlike KOH or NaOH, $(Bu)_4NOH$ is a strong base that is more soluble in organic solvents.

The alkylation of 6-chloropurine with cyclopentyl bromide follows practically the same behavior as the methylation indicated above. While the introduction of $(Bu)_4NOH$ improves yields and regioselectivity (Table 2, entries 11 and 12), microwave-assisted irradiation offers

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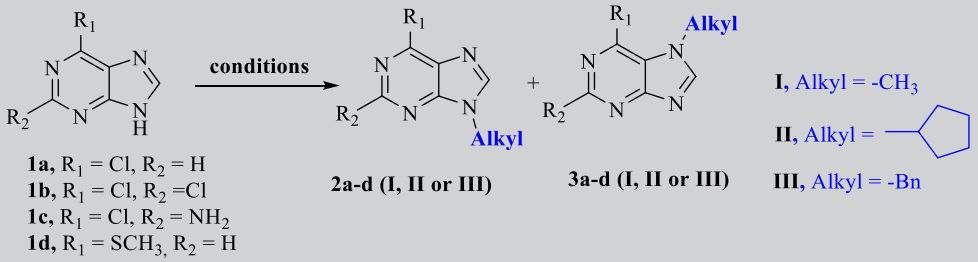
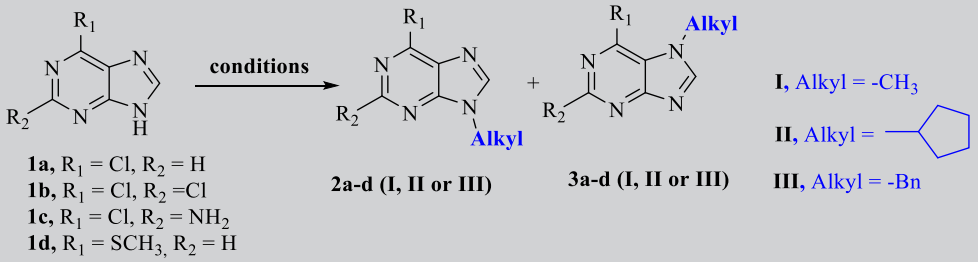
TABLE 2 Alkylation of purines under different conditions



Entry	Conditions	R_1	R_2	Conversion (%)	2 (% yield)[a]	3 (% yield)[a]
1	CH_3I, DBU, rt, 48 h	Cl	H	42	8	12
2	CH_3I, KOH, rt, 40 h	Cl	H	31	6	5
3	CH_3I, $(Bu)_4NOH$, 50°C, 4 h	Cl	H	100	59	31
4	CH_3I, $(Bu)_4NOH$, 50°C, 24 h	Cl	H	100	25	35
5	CH_3I, $(Bu)_4NOH$, rt, 6 h	Cl	H	100	35	11
6	CH_3I, $(Bu)_4NOH$, 60°C, 30 min, MW	Cl	H	100	89	-
7	CH_3I, $(Bu)_4NOH$, 60°C, 60 min, MW	Cl	H	100	75	-
8	CH_3Br, $(Bu)_4NOH$, 60°C, 60 min, MW	Cl	H	100	69	-
9	CH_3Cl, $(Bu)_4NOH$, 60°C, 60 min, MW	Cl	H	90	48	11
10	Cyclopentyl-Br, NaH/DMF, 80°C, 70 h	Cl	H	45	25	8
11	Cyclopentyl-Br, $(Bu)_4NOH$, rt, 6 h	Cl	H	43	36	Trace
12	Cyclopentyl-Br, $(Bu)_4NOH$, 60°C, 48 h	Cl	H	100	60	6
13	Cyclopentyl-Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	H	100	90	-
14	Benzyl-Br, $(Bu)_4NOH$, 50°C, 30 min,	Cl	H	100	68	15
15	MW $(CH_3)_2CHBr$, $(Bu)_4NOH$, 60°C, 60 min, MW	Cl	H	100	88	-
16	CH_3I, $(Bu)_4NH_4OH$, 60°C, 24 h	Cl	Cl	100	62	9
17	CH_3I, $(Bu)_4NH_4OH$, 60°C, 30 min, MW	Cl	Cl	100	89	-
18	CH_3Br, $(Bu)_4NH_4OH$, 60°C, 30 min, MW	Cl	Cl	100	82	-
19	CH_3Cl, $(Bu)_4NH_4OH$, 60°C, 30 min, MW	Cl	Cl	100	56	9
20	Cyclopentyl-Br, $(Bu)_4NOH$, rt, 6 h	Cl	Cl	57	32	-
21	Cyclopentyl-Br, $(Bu)_4NOH$, 60°C, 48 h	Cl	Cl	65	36	7
22	Cyclopentyl-Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	Cl	100	87	-
23	Benzyl-Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	Cl	100	67	14
24	CH_3I, $(Bu)_4NOH$, 60°C, 48 h	Cl	NH_2	<10	Trace	-
25	CH_3I, $(Bu)_4NOH$, rt, 48 h	Cl	NH_2	67	42	-
26	CH_3I, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	NH_2	100	79	-
27	CH_3Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	NH_2	100	74	-
28	CH_3Cl, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	NH_2	90	48	9
29	Cyclopentyl-Br, $(Bu)_4NOH$, rt, 6 h	Cl	NH_2	100	45	16
30	Cyclopentyl-Br, $(Bu)_4NOH$, 60°C, 48 h	Cl	NH_2	<10	Trace	-
31	Cyclopentyl-Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	NH_2	100	78	6
32	Benzyl-Br, $(Bu)_4NOH$, 50°C, 30 min, MW	Cl	NH_2	100	88	-
33	CH_3I, $(Bu)_4NOH$, rt, 48 h	SCH_3	H	100	36	-
34	CH_3I, $(Bu)_4NOH$, 50°C, 30 min, MW	SCH_3	H	100	81	8
35	CH_3Br, $(Bu)_4NOH$, 50 °C, 30 min, MW	SCH_3	H	100	76	-
36	CH_3Cl, $(Bu)_4NOH$, 50 °C, 30 min, MW	SCH_3	H	90	51	9

(Continues)

TABLE 2 (Continued)



Entry	Conditions	R_1	R_2	Conversion (%)	2 (% yield)[a]	3 (% yield)[a]
37	Cyclopentyl-Br, $(Bu)_4NOH$, rt, 6 h	SCH_3	H	75	41	6
38	Cyclopentyl-Br, $(Bu)_4NOH$, 60 °C, 48 h	SCH_3	H	80	23	-
39	Cyclopentyl-Br, $(Bu)_4NOH$, 50 °C, 30 min, MW	SCH_3	H	100	97	Trace
40	Benzyl-Br, $(Bu)_4NOH$, 50 °C, 30 min, MW	SCH_3	H	100	92	0

Note: Results of this work.
[a]Isolated yields after silica gel column chromatography.

even better yields and selectivity (Table 2, entry 13). Treatment of 6-chloropurine with isopropyl bromide under the optimized conditions leads exclusively to *N*9-isopropylpurine with high yields (Table 2, entry 15). The *N*9-alkylation of purines with tert-butyl bromide under the conditions did not allow to obtain the corresponding *N*-alkylpurine and the unaltered starting compound was recovered.

Methylation of 2,6-dichloropurine in the presence of $(Bu)_4NOH$ and assisted by microwaves offer better results than when performed with classical heating (Table 2, entries 16 and 17). At the same time, the introduction of cyclopentyl follows the same strategy, being better when the alkylation is carried out in a microwave oven and for a short time than when it is heated in a conventional way or stirred at room temperature (Table 2, entries 20–22).

The alkylation of 2-amino-6-chloropurine using methyl iodide or cyclopentyl bromide at 60 °C does not lead to the expected products (Table 2, entries 24 and 30). On the other hand, when the alkylation was carried out stirring at room temperature (Table 2, entries 25 and 29) or with the assistance of microwaves (Table 2, entries 26 and 31), the *N*9-alkylated derivative was obtained regioselectively.

*N*9-methyl-6-methylthiopurine was obtained in high yield when 6-methylthiopurine was treated with methyl iodide at 50 °C, 30 min with microwave assistance and in the presence of $(Bu)_4NOH$ (Table 2, entry 34). The introduction of a cyclopentyl group on the *N*9 of the same purine was successfully achieved under the same conditions as the mentioned methylation (Table 2, entry 39). In the other conditions tested, both at room temperature (Table 2, entries 33 and 37) and with classical heating (Table 2, entry 38), lower yields of the alkylated purines were obtained.

The *N*-benzylation was carried out with the benzyl bromide in acetonitrile at 50 °C with the assistance of microwave radiation, and high yields of the respective benzylated products were obtained. However, it is worth highlighting a higher regioselectivity for methylthiopurine and 2-amino-6-chloropurine (92% and 88% yields respectively of alkylated *N*-9, entries 40 and 32, Table 2). While for both 6-chloropurine and 2,6-dichloropurine, the benzylated compound *N*-9 and a small proportion of *N*-7 were obtained (entries 15 and 23, Table 2).

Each of the four different purines alkylated by methyl iodide were also alkylated by treatment with methyl bromide and with methyl chloride using $(Bu)_4NH_4OH$ and heating at 60 °C for 30 min under microwave irradiation. The methyl bromide allows the regioselective preparation of *N*9-methylated derivatives with yields very similar to methyl iodide (Table 2, entries 8, 18, 27, and 35). On the other hand, methyl chloride leads to a mixture of *N*7- and *N*9-methylpurines and with lower yields (Table 2, entries 9, 19, 28, and 36).

Considering that purines are ambident nucleophiles (*N*7 and *N*9) and as it is discovered from the results obtained, in all cases the *N*-alkylations have been formed in a regioselective manner. Reactions that require long time or higher temperatures lead to a mixture of *N*7- and *N*9-alkylpurines, while those carried out with more reactive alkyl halides and consequently the reaction occurs faster lead exclusively to the *N*9-alkylpurines. Thus, this approach constitutes a good procedure for the preparation of *N*-9alkyl purines derivatives.

2.1 | Alkylation of purines: General classical procedure

To a solution of purine derivative (1.0 mmol) in acetonitrile (10–15 mL) tetrabutylammonium hydroxide (1 mmol) was added. Then, the corresponding alkyl halide (2 mmol) was added dropwise and the reaction mixture was stirred at room temperature or heated to 50 °C (see Table 2). The reaction mixture was maintained until no starting material could be detected by thin-layer chromatography. Then, the crude reaction was diluted with a solution of sodium hydroxide 2N (20 ml) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered under vacuum and the solvent was removed under reduced pressure.

The crude reaction obtained was purified by silica gel column chromatography using mixtures of hexane/ethyl acetate 25/75 to 10% methanol as eluent. The alkylated purine or the corresponding regioisomer were isolated.

2.2 | General procedure under microwaves irradiation

To a solution of purine derivative (1 mmol) in acetonitrile (5 mL) was added to the glass tube (special tube for microwave oven) sealed with a special septum under magnetic stirring. Then, the corresponding alkyl halide (2 mmol) and tetrabutylammonium hydroxide (1 mmol) were added dropwise to the tube and the reaction mixture was introduced in a microwave oven and was heated until 50 °C extern temperature (subjected to a variable MW power until 300 W [an IR sensor measured the temperature of glass tube surface]) for 30 min and the progress of the reaction was monitored by TLC. The crude reaction was diluted with water (20 ml) and extracted with ethyl acetate (3 × 20 mL) in a basic p*H* media. The combined organic layers were dried over anhydrous sodium sulfate, filtered under vacuum and the solvent was removed to dryness. The crude reaction obtained was purified by silica gel column chromatography using mixtures of hexane/ethyl acetate 25/75 to 10% methanol as eluent.

2.2.1 | Analytical data

6-Chloro-9-methylpurine

***R*f** (Ethyl acetate/methanol 9:1) = 0.46.

IR: 3327 (=CH); 2923 (C—H); 1562 (C=C); 1325 (C—N); 727 (C—Cl).

Melting point: 142–143 °C (EtOAc). Literature 143–144 °C [14].

^{1}H-NMR (CDCl$_3$, 400 MHz) δ (ppm): 3.95 (s, 3H, -CH$_3$); 8.11 (s, 1H, H-8); 8.78 (s, 1H, H-2).

HRMS (ESI): calculated for $C_6H_5ClN_4Na$ $[M + Na]^+$: 191.5735, obtained: 191,5787.

6-Chloro-7-methylpurine

***R*f** (Ethyl acetate/methanol 9:1) = 0.31.

IR: 3323 (=CH); 2929 (C—H); 1561 (C=C); 1324 (C—N); 729 (C—Cl).

Melting point: 180–182 °C (EtOAc). Literature 178–180 °C [15].

^{1}H-NMR (CDCl$_3$, 400 MHz) δ (ppm): 4.17 (s, 3H, -CH$_3$); 8.18 (s, 1H, H-8); 8.88 (s, 1H, H-2).

^{13}C-NMR (CDCl$_3$, 100 MHz) δ (ppm): 34.4 (CH$_3$, -CH$_3$); 123.0 (C, C-5); 143.4 (C, C-4); 149.6 (CH, C-8); 152.4 (CH, C-2); 161.8 (C, C-6).

HRMS (ESI): calculated for $C_6H_5ClN_4Na$ $[M + Na]^+$: 191.5735, obtained: 191,5734.

3 | CONCLUSION

In summary, the alkylation of the *N*9 of purines has a great interest for the synthesis of a large number of compounds with the potential therapeutic application. In this work, a robust and regioselective method that has been developed under mild conditions, allows the preparation of *N*9-alkylated purine. The use of microwave irradiation assistance makes it possible to significantly reduce the reaction time, providing greater regioselectivity, good yields, and increase the crude purity significantly compared to classical heating. In turn, the use of $(Bu)_4NOH$ as a base, facilitates the solubility of purines and leads to an increase in yields compared to other types of bases previously reported. In summary, this procedure provides advantages over other previously used methods: short reaction time, high regioselectivity, easy manipulation, respect for the environment, and good yields.

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CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Regioselective alkylation of purines at https://doi.org/10.1002/jhet.4407. These data were derived from the following resources available in supporting information.

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