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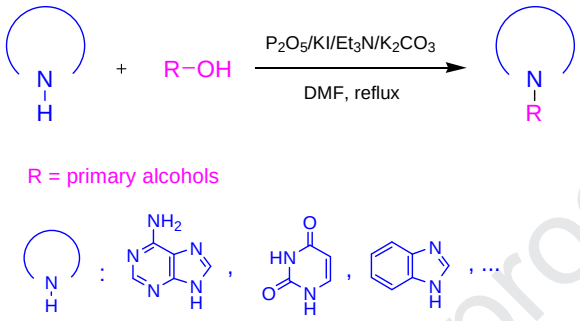
Graphical Abstract



Triphenylphosphine-free approach for one-pot N-alkylation of purine, pyrimidine, and azole derivatives with alcohols using P_2O_5/KI: A facile and selective route to access carboacyclic nucleosides

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Abstract: A facile, selective, and mild synthetic approach for one-pot N-alkylation of nucleobases and other related N-heterocycles via alcohols, using a mixture of P_2O_5 and KI is described. The reaction of structurally diverse purines, pyrimidines, and/or azoles with primary alcohols with the use of P_2O_5/KI and basic mixture of Et_3N/K_2CO_3 in refluxing DMF affords the corresponding N-alkyl derivatives (carboacyclic nucleosides) in good to reasonable yields. The influence of different parameters comprising solvent, base, temperature, and substrate/reagent ratios was assessed on the reaction progress. The secondary and tertiary alcohols were failed to react with nucleobases. The main advantageous of current protocol is formation of water soluble side products in which provides simple work-up and purification processes.

Keywords: *alcohol, N-alkyl nucleobase, nucleoside, P_2O_5/KI, selective N-alkylation, triphenylphosphine-free*

1. Introduction

Over the years, natural and synthetic *N*-heterocyclic derivatives have gained a special attention in different area of sciences and industries due to their broad spectrum of applications. Purine and pyrimidine nucleobases are among the most abundant *N*-heterocycles which mainly found as a component in DNA and RNA structures. Carboacyclic nucleosides are known as an important class of N-alkylnucleobase derivatives that have received enormous research interests owing to their abundant applications in medicinal chemistry. In particular, they have been known for their chemotherapeutic properties against numerous types of cancer, viral, and microbial diseases [1]. Penciclovir, famciclovir, adefovir, and cidofovir are well-identified carboacyclic nucleoside drugs having potent anti-viral activity (Figure 1). In addition, nucleosides are used as molecular tools and probes for studying the biological systems [2].

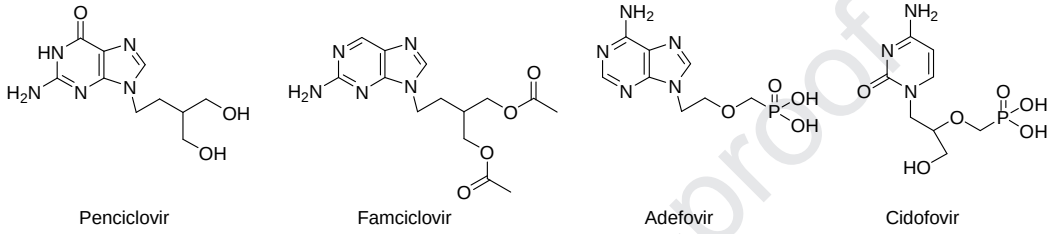
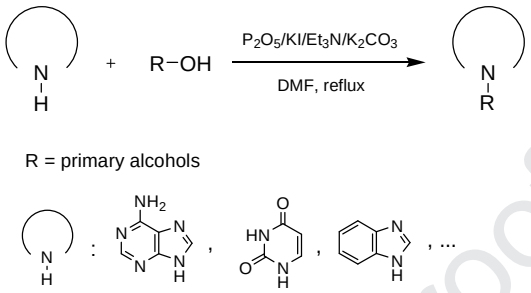


Figure 1. The structure of some carboacyclic nucleosides as anti-viral drugs

Regarding to the unique therapeutic activity of nucleosides, there has been the massive interests to synthesize the numerous carboacyclic nucleoside derivatives via N-alkylation of nucleobases using different carbon electrophiles. To gain the N-alkylated nucleobases, the most common used carbon electrophiles are comprising alkyl halides [3], alkyl sulfonates [4], epoxides [5], α, β-unsaturated carbonyl compounds [6], and ethers [7]. Despite the fact that these carbon electrophiles are strong alkylating agents; however, most of them were recognized to be toxic and carcinogenic [8]. Thus, because of toxicity, the applicability of the aforementioned alkylating agents particularly in scale-up synthesis is restricted. Therefore, there is an enormous interest to apply the other sources of carbon electrophiles with more safety. To this end, alcohols would be a suitable and worthwhile candidate regarding to their wide structural diversity, accessibility, lower toxicity, ease of handling and more safety in comparison with other structurally related alkylating agents. In this context, the first report by Mitsunobu on use of alcohols as the alkylating agent had initiated a massive upheaval in organic transformations [9,10]. Particularly, the use of Mitsunobu conditions for the direct synthesis of N-alkylated nucleobases from alcohols affords the remarkable achievements and provides the N-alkyl nucleobases in good yields [11-16]. However, the application of this reaction is restricted by two main drawbacks; first, the use of diethyl azodicarboxylate (DEAD), and second, the formation of triphenylphosphine oxide. While the former is an explosive and expensive reagent, the latter is tediously separated from the reaction mixture. To overcome these problems, our group has reported N-(*p*-toluenesulfonyl)imidazole (TsIm) [17] and TsCl/bmim[Br] [18] as efficient, inexpensive, and safe reagents for one-pot synthesis of N-alkyl nucleobases from alcohols. Up to now, a few TPP-free protocols for efficient conversion of alcohols into N-alkyl nucleobases have been established, hence there is a

great deal of endeavors to discover and improve the simple, convenient and efficient protocols to acquire the N-alkyl nucleobases from alcohols.

Phosphorus pentoxide is a commercially available, non-toxic, and low-cost reagent which is used in many organic transformations [19]. In continuation of our ongoing interest on discovering simple, mild, and efficient process for synthesis of N-alkyl nucleobases from alcohols [17, 18]; hereby, we report the simple and convenient method for the direct N-alkylation of nucleobases and other related N-heterocycles via alcohols using P_2O_5/KI in the presence of Et_3N/K_2CO_3 in DMF at reflux condition (Scheme 1).



Scheme 1. The N-alkylation of nucleobases via alcohols using P_2O_5/KI

2. Results and discussion

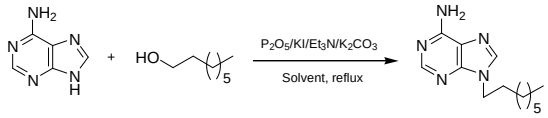
The initial effort for N-alkylation of nucleobases and other N-heterocycles via alcohols was begun by recognizing the optimized condition. In this connection, the N-alkylation reaction of adenine with 1-octanol using P_2O_5/KI was selected as a sample reaction. Afterward, the influence of parameters like solvent, base, temperature, and molar ratio of ROH/P_2O_5/KI was investigated on sample reaction.

As the solvent displays an undeniable role in the reaction progress, primarily our attempt was focused on studying the effect of different solvents on synthesis of 9-octyl-9H-purin-6-amine as a sample product (Table 1). The results in Table 1 demonstrate that among the different types of examined solvents, anhydrous DMF affords the best results in terms of reaction rate and yield (entry 5). The progress of sample reaction was also explored in normal DMF to determine whether the contained moisture in DMF could affect the reaction path (Table 1, entry 4). However, a negligible difference was observed. Thus, the normal DMF was selected as a choose solvent for all reactions. Among tested solvents, HMPA and DMSO result in 65% and 71% yields of product, respectively (Table 1, entries 2 and 3). Furthermore, using polar protic solvents such as H_2O, EtOH, and PEG-400 failed to acquire the satisfactory result even though the reaction time was prolonged up to 24 h (entries 7-9). Moreover, when [bmim]Br was employed as a typical room temperature ionic liquid, only 27% of product was obtained after 18 h (Table 1, entry 10). Other solvents such as MeCN, acetone, toluene and THF provide no further improvement in the reaction progress (entries 1, 6, 11, and 12).

In the next step, the effect of diverse bases on progress of sample reaction was examined (Table 2). In the absence of base, no product was gained even after 48 h (Table 2, entry 1). Apparently, the presence of an efficient base has undeniable role for activation of N-H bond in nucleobases to enhance their nucleophilic power. Regarding to obtained results in Table 2, the examined heterogeneous inorganic bases lead to less satisfactory

results compare to assessed organic bases (Table 2, entries 2-5 vs 7-10). As depicted, the highest yield of the product and shortest reaction time were obtained when the combination of Et_3N/K_2CO_3 in a 1:1 molar ratio was employed (Table 2, entry 6). Also, the separate use of each one of K_2CO_3 (entry 5) or Et_3N (entry 7) were not as efficient as the combination of Et_3N/K_2CO_3 (1:1 ratio).

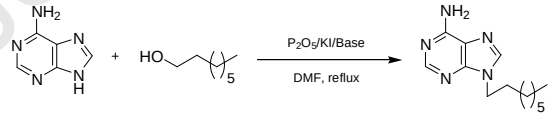
Table 1 Effect of different solvents on synthesis of 9-octyl-9H-purin-6-amine [a]



Entry	Solvent	Time (h)	Yield [d] (%)
1	MeCN	12	24
2	HMPA	10	65
3	DMSO	7	71
4	DMF	7	79
5	DMF [b]	7	80
6	Acetone	18	20
7	H_2O	24	15
8	EtOH	24	17
9	PEG-400 [c]	24	27
10	[bmim]Br [c]	18	22
11	Toluene	24	Trace
12	THF	18	Trace

[a] Reaction conditions: adenine (1 mmol), 1-octanol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), Solvent (5 mL). [b] Anhydrous DMF. [c] The reaction temperature was raised up to 100 °C. [d] Isolated yield.

Table 2 Effect of different bases on synthesis of 9-octyl-9H-purin-6-amine [a]

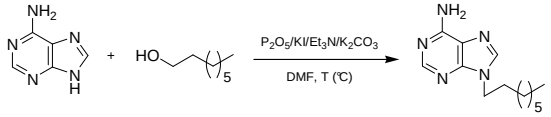


Entry	Base	Time (h)	Yield [c] (%)
1	-	48	NR [d]
2	Al_2O_3	36	29
3	KOH	14	45
4	MgO	36	21
5	K_2CO_3	12	58
6	Et_3N/K_2CO_3 [b]	7	79
7	Et_3N	10	65
8	DBU	9	73
9	DABCO	12	60
10	DMAP	63	63

[a] Reaction conditions: adenine (1 mmol), 1-octanol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Base (1 mmol), DMF (5 mL). [b] 1:1 ratio was employed. [c] Isolated yield. [d] No reaction.

In further assessment, we also investigated the effect of temperature variations on the reaction progress. Thus, the reaction of adenine with 1-octanol was achieved at different temperatures (Table 3). Firstly, it was attempted to perform the reaction at ambient temperature. Practically, no reaction was carried out even if the reaction time was prolonged from 24 h up to 36 h (entries 1 and 2). However, increasing the reaction temperature from room temperature up to reflux condition remarkably increased the reaction efficiency (Table 3, entries 3-9). The best result was attained when the sample reaction was achieved at reflux condition for 7 h (Table 3, entry 10). Further increase in reaction time at reflux condition did not result in more satisfactory result (entry 11).

Table 3 Effect of different temperatures on synthesis of 9-octyl-9H-purin-6-amine [a]



Entry	Temperature (°C)	Time (h)	Yield [b] (%)
1	r.t.	24	NR [c]
2	r.t.	36	NR
3	80	18	10
4	80	24	15
5	100	12	23
6	100	18	35
7	120	9	45
8	120	12	57
9	Reflux	5	65
10	Reflux	7	79
11	Reflux	12	79

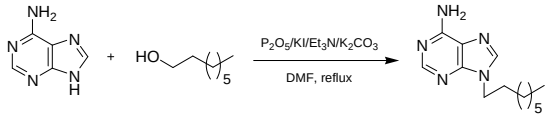
[a] Reaction conditions: adenine (1 mmol), 1-octanol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yield. [c] No reaction.

In another attempt to improve the reaction efficiency, the effect of different molar ratios of ROH/P_2O_5/KI for synthesis of 9-octyl-9H-purin-6-amine was examined (Table 4). When the reaction was carried out in the absence of KI, no desired product was obtained after reflux for 48 h (entry 1). It is also worth mentioning that the corresponding alkene is generated through the course of reaction in the absence of KI as detected by GC analysis. Practically, using KI increased the reaction yield and rate. As shown in Table 4, no reaction was conducted in the absence of P_2O_5 even though the reaction was prolonged up to 24 h (entry 2). Clearly, this experience confirms that P_2O_5 has undeniable role on reaction progress. The optimized molar ratio of ROH/P_2O_5/KI for conversion of 1-octanol into 9-octyl-9H-purin-6-amine was found to be 1.0:1.5:1.5 (Table 4, entry 6). Furthermore, raising the amount of P_2O_5-KI relative to alcohol has no distinguishable improvement on the reaction efficacy (Table 4, entries 7-9).

After discovering the optimized reaction conditions, the general applicability, scope and limitations of the present protocol were assessed by examining varities of structurally diverse alcohols, nucleobases and other N-

heterocycles (Tables 5-7). Thus, several primary and secondary alcohols involving various functionalities underwent the reaction with purine and pyrimidine nucleobases as well as several bioactive N-heterocycles including, benzimidazole, imidazole, 2-phenylimidazole, 2-methyl-4(5)-nitroimidazole, and indole.

Table 4 Effect of different molar ratios of ROH/P_2O_5/KI (X:Y:Z) on synthesis of 9-octyl-9H-purin-6-amine [a]



Entry	molar ratios of ROH/P_2O_5/KI	Time (h)	Yield [b] (%)
1	1:1:0	48	NR [c]
2	1:0:1	24	NR [c]
3	1:0.5:1	12	41
4	1:1:1	10	65
5	1:1.3:1.3	9	73
6	1:1.5:1.5	7	79
7	1:1.7:1.7	7	80
8	1:2:2	7	80
9	1:2.5:2.5	7	79

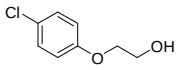
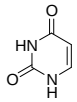
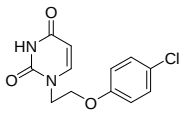
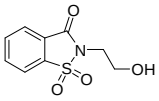
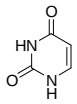
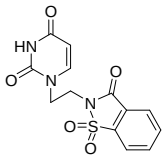
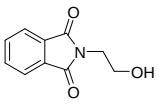
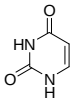
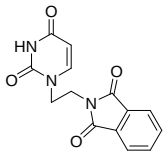
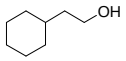
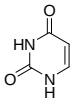
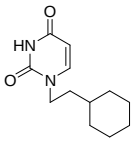
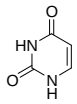
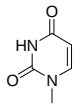
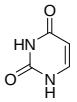
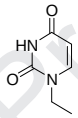
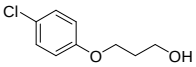
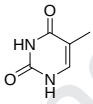
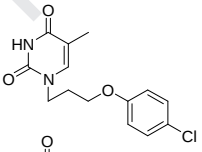
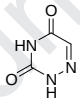
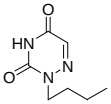
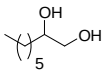
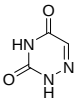
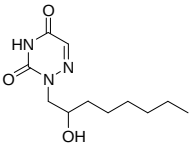
[a] Reaction conditions: adenine (1 mmol), 1-octanol (X mmol), P_2O_5 (Y mmol), KI (Z mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yield. [c] No reaction.

Pyrimidine type nucleobases like uracil, thymine, and 6-azauracil were converted to the corresponding *N*-alkyl derivatives in good yields (Table 5, entries 1-9). Despite the fact that nucleobases are known for their ambident behavior for their nucleophilicity; however, the notable regioselectivity was observed for *N*-alkylation site of applied pyrimidines. Thus, the *N*1-alkylated adducts were almost obtained as the major products. Due to GC analysis, the *N*1,*N*3-dialkyl adducts were also identified less than 8% [25]. Furthermore, no *O*-alkylated adducts of pyrimidine nucleobases were detected using the present protocol.

Purines like adenine, 6-chloropurine, theophylline and theobromine were also readily *N*-alkylated with primary alcohols (Table 6, entries 1-9). Like pyrimidines, purines also exhibited the satisfactory regioselectivity toward the site of N-alkylation. In the case of adenine and 6-chloropurine, the *N*9-isomers were mainly produced and the *N*7-isomers were obtained in trace amounts (less than 6% based on GC analysis) [26]. The *N*-alkylation of theophylline was regioselectively led to synthesize of *N*7-alkylated adducts.

We also examined the generality of this method for *N*-alkylation of several *N*-heterocyclic derivatives. In this context, benzimidazole, imidazole, 2-phenylimidazole, 2-methyl-4(5)-nitroimidazole, and indole were selected to undergo the *N*-alkylation reaction exploiting the current protocol (Table 7, entries 1-6). As can be seen in Table 7, the related *N*-alkyl adducts were obtained in good yields; however, the use of 2-phenylimidazole resulted in 70% yield (entry 4). This lower yield can be attributed to the steric hindrance of the starting *N*-heterocycle.

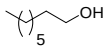
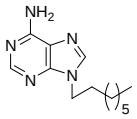
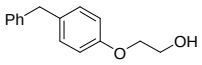
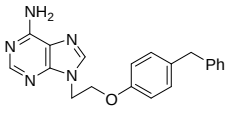
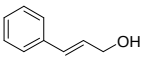
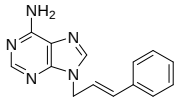
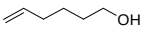
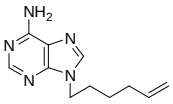
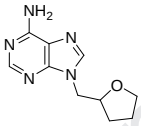
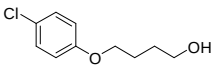
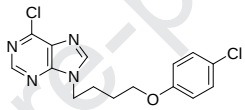
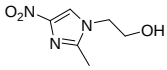
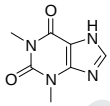
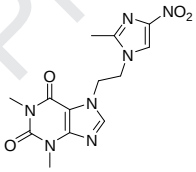
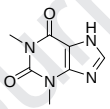
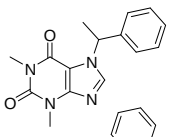
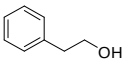
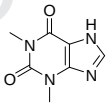
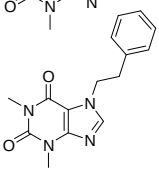
Table 5 Synthesized N-alkyl pyrimidines using P_2O_5/KI [a]

Entry [Ref.]	alcohol	pyrimidine	Product	Time (h)	Yield [b]
1				7	82
2 [18]				8	80
3 [20]				8	81
4 [18]				7	78
5 [21]				9	50
6 [21]				9	53
7				7	76
8 [20]				9	69
9 [18]				9	66

[a] Reaction conditions: pyrimidine (1 mmol), alcohol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yield.

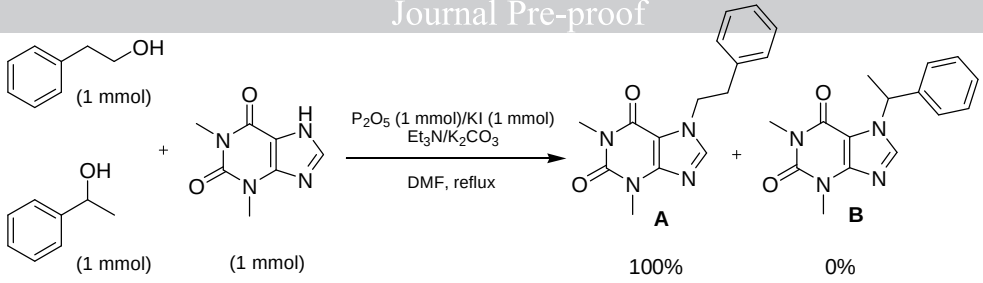
Fortunately, the obtained results demonstrated the selectivity of the present protocol for the primary alcohols compare to other types of alcohols. Different primary alcohols having a simple aliphatic side chain or aliphatic side chain bearing different functional groups like allylic, benzylic, aryl, ether, and several heterocyclic cores were efficiently applied for *N*-alkylation of purines, pyrimidines, and other related N-heterocycles (Tables 5-7). When 1-phenylethanol was used as a typical secondary alcohol for N-alkylation of theophylline, only 12% of the corresponding product was obtained (Table 6, entry 8). Attempts were failed to achieve the N-alkylation reaction of theophylline via tertiary alcohols like t-butyl alcohol and no product was obtained even in trace amount.

Table 6 Synthesized N-alkyl purines using P_2O_5/KI [a]

Entry [Ref.]	alcohol	purine	Product	Time (h)	Yield [b]
1				7	79
2				9	74
3 [20]				8	78
4 [20]				9	75
5 [18]				9	72
6				8	82
7 [22]				7	90
8 [22]				10	12
9 [22]				7	91

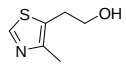
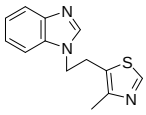
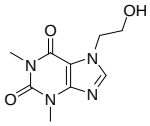
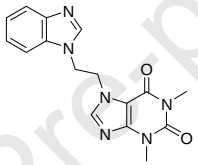
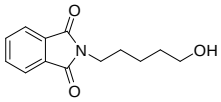
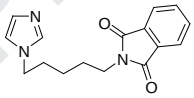
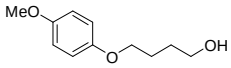
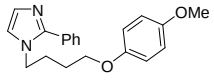
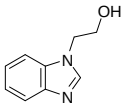
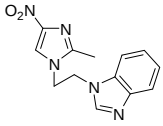
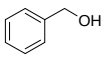
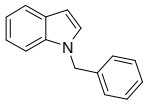
[a] Reaction conditions: purine (1 mmol), alcohol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yield.

The selectivity of the present protocol for primary alcohol was confirmed through performing a competitive reaction between two isomeric alcohols comprising 2-phenylethanol (1 mmol) and 1-phenylethanol (1 mmol) as the representative for primary and secondary alcohols, respectively. The reaction was carried out using theophylline and P_2O_5/KI under optimized reaction conditions (Scheme 2). Based on the GC analysis, product (**A**) was exclusively produced from the reaction of theophylline with 2-phenylethanol. Practically, there is no chance for the reaction of 1-phenylethanol with theophylline against 2-phenylethanol.



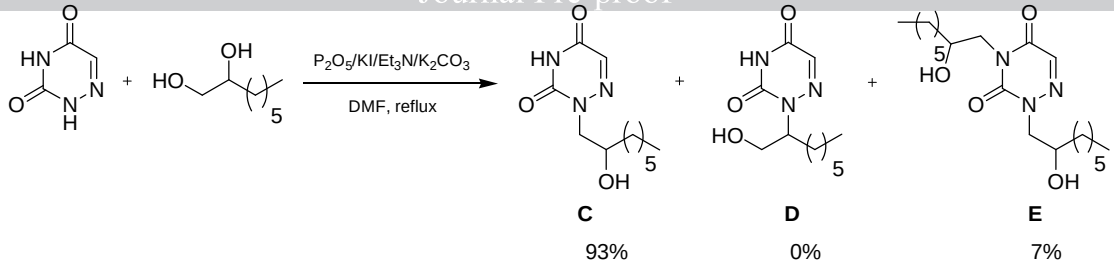
Scheme 2. Competitive one-pot N-alkylation of theophylline with 2-phenylethanol and 1-phenylethanol using P_2O_5/KI (yields based on GC analysis)

Table 7 Synthesized N-alkyl azole derivatives using P_2O_5/KI [a]

Entry [Ref.]	alcohol	azole	Product	Time (h)	Yield [b]
1 [18]				8	86
2 [23]				8	89
3				8	90
4				7	70
5 [23]				11	83
6 [24]				10	41

[a] Reaction conditions: azole (1 mmol), alcohol (1 mmol), P_2O_5 (1.5 mmol), KI (1.5 mmol), Et_3N (1 mmol), K_2CO_3 (1 mmol), DMF (5 mL). [b] Isolated yield.

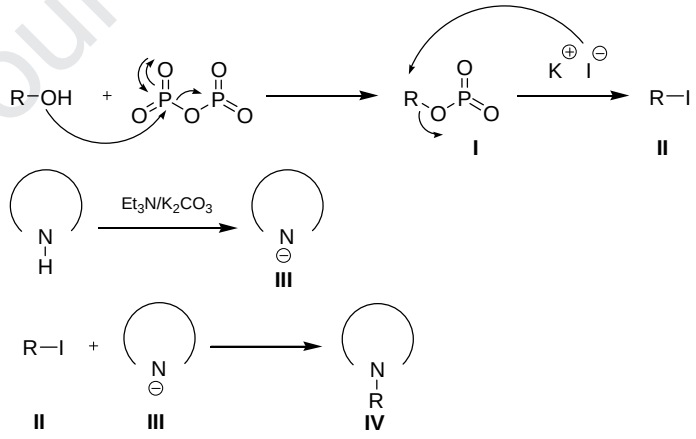
The selectivity of the present protocol was evaluated via conducting the reaction between a nucleobase and a diol consisting both primary and secondary hydroxyl groups, simultaneously. Thus, the reaction of 6-azauracil with 1,2-octandiol was achieved under optimized reaction conditions (Scheme 3). As expected, the result showed the excellent selectivity between two types of hydroxyl groups. Thus, 6-azauracil reacted readily with primary hydroxyl group of 1,2-octandiol to afford compound **C** as the major product. In addition, N,N-dialkyl adduct of 6-azauracil (**E**) was obtained in a trace amount. However, no **D** adduct which may be resulted from the reaction at a secondary hydroxyl of 1,2-octandiol with 6-azauracil was observed.



Scheme 3. Competitive reaction between primary and secondary hydroxyl groups of 1,2-octandiol with 6-azauracil (yields based on GC analysis)

A plausible mechanism for one-pot *N*-alkylation of nucleobases and other N-heterocycles via alcohols in the presence of P_2O_5/KI is suggested (Scheme 4). We proposed that mechanism should be progressed through the synthesis of alkyl iodide **II** as the main reactive intermediate via the reaction of adduct (**I**) with KI. As matter of fact, the formation of alkyl iodide (**II**) was confirmed by TLC monitoring and GC analysis at the early stage of the reaction. Afterward, the activated nucleobase (**III**) by Et_3N/K_2CO_3 reacts with *in situ* generated alkyl iodide (**II**) to afford the desired *N*-alkyl adduct (**IV**).

It is worth mentioning that the use of triphenylphosphine for *N*-alkylation of nucleobases with alcohols leads to synthesize of triphenylphosphine oxide (TPPO) as the main by-product. Practically, TPPO separation from the desired N-alkyl nucleobases is cumbersome which is a main problem in most cases. However, the use of P_2O_5/KI results in phosphorus oxoacid as a main side-product which is readily soluble in water and can be easily discarded by a simple washing. Therefore, the work-up and purification processes are much easier and cleaner compare to other TPP-based protocols.



Scheme 4. A tentative mechanism for one-pot N-alkylation of nucleobases with alcohols using P_2O_5/KI

3. Conclusions

In summary, we have developed a mild, selective, and one-pot procedure for *N*-alkylation of nucleobases and its derivatives using alcohols. In this protocol, treatment of primary alcohols with P_2O_5/KI in the presence of Et_3N/K_2CO_3 in refluxing DMF, regioselectively affords the corresponding *N*-alkyl nucleobases in good yields. The influence of different parameters on the progress of reaction was investigated. Using this method, primary

alcohols were selectively underwent the reaction with nucleobases while secondary and tertiary alcohols were inactive towards nucleobases. Furthermore, this protocol is TPP-free and the main by-product is readily soluble in water which provides the simple work-up and purification processes.

4. Experimental

4.1. General

All chemicals were purchased from Merck. Solvents were purified using standard procedures and stored over 3Å molecular sieves. Reactions were monitored by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). ^{1}H- and ^{13}C-NMR spectra were recorded on Brüker Avance-DPX-250 and Brüker Avance-DPX-400 spectrometers operating at 250/62.5, 300/75 and 400/100 MHz, respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard, coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are *s* singlet, *d* doublet, *t* triplet, *q* quartet, *m* multiplet, *b* broad, *dd* doublet of doublet. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (m/z; rel.%). Elemental analyses were performed on a Perkin–Elmer 240-B microanalyzer. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. Melting points were measured using Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected.

4.2. General procedure for synthesis of N-alkyl nucleobases via alcohols using P_2O_5/KI

To a double-necked round bottom flask (100 mL), equipped with a condenser, it was added a mixture of KI (1.5 mmol), P_2O_5 (1.5 mmol) and the desired alcohol (1 mmol) in DMF (5 mL). The reaction mixture was stirred at r.t. for 30 min. Next, the considered nucleobase (1 mmol), K_2CO_3 (1 mmol) and Et_3N (1 mmol) were added and the reaction mixture was heated to reflux for a further 6.5-10.5 h (until TLC indicated no further progress in reaction, Table 5). The solvent was then evaporated at reduced pressure, and the remaining foam was dissolved in chloroform (150 mL) and washed with water (2 × 150 mL). The organic layer was dried on Na_2SO_4 (1 g) and evaporated. The product was purified using short column chromatography on silica gel eluting with proper solvents.

4.3. Data for new compounds

4.3.1. 1-(2-(4-chlorophenoxy)ethyl)pyrimidine-2,4(1H,3H)-dione (Table 5, entry **1**)

Column Chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (218 mg, 82%); m.p. 216-217 °C. IR (KBr): 3200, 3041, 2949, 1725, 1712, 1492, 1039 cm^{-1}. ^{1}H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 4.08 (t, *J* = 4.8 Hz, 2H, NCH_2), 4.20 (t, *J* = 4.8 Hz, 2H, OCH_2), 5.57 (d, *J* = 7.8 Hz, 1H, C(5)-H of uracil), 6.96 (d, *J* = 8.9 Hz, 2H, aryl), 7.32 (d, *J* = 8.9 Hz, 2H, aryl), 7.71 (d, *J* = 7.8 Hz, 1H, C(6)-H of uracil), 11.34 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 46.8, 65.5, 100.6, 116.2, 124.6, 129.2, 146.2, 150.9, 156.8, 163.7. MS (EI): m/z (%) = 266 (27.2) [M^{+}]. Anal. Calc. for $C_{12}H_{11}ClN_2O_3$: C, 54.05; H, 4.16; N, 10.50; found: C, 53.84; H, 4.28; N, 10.31.

4.3.2. 1-(3-(4-chlorophenoxy)propyl)-5-methylpyrimidine-2,4(1H,3H)-dione (Table 5, entry **7**)

Column Chromatography on silica gel eluted with hexane/EtOAc (1:1) afforded pure product as white solid (223 mg, 76%); m.p. 169-170 °C. IR (KBr): 3151, 3075, 2867, 1730, 1718, 1456, 1052 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 1.73 (s, 3H, CH_3), 2.03-2.10 (m, 2H, OCH_2CH_2), 3.82 (t, *J* = 6.7 Hz, 2H, NCH_2), 4.00 (t, *J* = 5.8 Hz, 2H, OCH_2), 6.94 (d, *J* = 8.9 Hz, 2H, aryl), 7.33 (d, *J* = 8.9 Hz, 2H, aryl), 7.62 (s, 1H, C(6)-H of thymine), 11.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 11.8, 27.8, 44.9, 65.4, 108.3, 116.0, 124.2, 129.1, 141.5, 150.9, 157.1, 164.3. MS (EI): m/z (%) = 294 (29.4) [M^+]. Anal. Calc. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50; found: C, 57.18; H, 5.29; N, 9.71.

4.3.3. *9-octyl-9H-purin-6-amine* (Table 6, entry **1**)

Column Chromatography on silica gel eluted with hexane/EtOAc (1:10) afforded pure product as yellow solid (195 mg, 79%); m.p. 233-234 °C. IR (KBr): 3320, 3100, 2943, 1640, 1453 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 0.81 (s, 3H, CH_3), 1.19 (br s, 10H, $5CH_2$), 1.78 (br s, 2H, NCH_2CH_2), 4.10 (t, *J* = 5.2 Hz, 2H, NCH_2), 7.16 (s, 2H, NH_2), 8.13-8.14 (complex, 2H, C(2)-H , C(8)-H of adenine); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 14.6, 23.3, 29.3, 30.5, 31.3, 33.4, 56.8, 120.9, 141.7, 150.6, 153.7, 158.3. MS (EI): m/z (%) = 247 (17.2) [M^+]. Anal. Calc. for $C_{13}H_{21}N_5$: C, 63.13; H, 8.56; N, 28.31; found: C, 63.25; H, 8.39; N, 28.45.

4.3.4. *9-(2-(4-benzylphenoxy)ethyl)-9H-purin-6-amine* (Table 6, entry **2**)

Column Chromatography on silica gel eluted with EtOAc afforded pure product as yellow solid (255 mg, 74%); m.p. 201-202 °C. IR (KBr): 3332, 3076, 2929, 1595, 1487, 1045 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 3.81 (s, 2H, NH_2), 4.29 (t, *J* = 4.9 Hz, 2H, NCH_2), 4.49 (t, *J* = 4.9 Hz, 2H, OCH_2), 6.82 (s, 2H, $PhCH_2$), 7.05-7.25 (complex, 10 H, aryl, C(2)-H of adenine), 8.14 (s, 1H, C(8)-H of adenine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 40.1, 42.5, 65.6, 114.4, 118.6, 125.8, 128.3, 128.5, 129.6, 133.7, 141.1, 141.6, 149.5, 152.4, 155.9, 156.2. MS (EI): m/z (%) = 345 (15.3) [M^+]. Anal. Calc. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28; found: C, 69.38; H, 5.70; N, 20.07.

4.3.5. *6-chloro-9-(4-(4-chlorophenoxy)butyl)-9H-purine* (Table 6, entry **6**)

Column Chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as white solid (276 mg, 82%); m.p. 110-111 °C. IR (KBr): 3095, 2947, 1591, 1473, 1045 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ_{ppm} = 1.61-1.72 (m, 2H, NCH_2CH_2), 1.94-2.05 (m, 2H, OCH_2CH_2), 3.91 (t, *J* = 6.3 Hz, 2H, NCH_2), 4.34 (t, *J* = 7.0 Hz, 2H, OCH_2), 6.83-6.89 (complex, 3H, aryl, C(2)-H of purine), 7.21-7.27 (m, 2H, aryl), 8.69 (s, 1H, C(8)-H of purine). ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ_{ppm} = 25.6, 25.8, 43.5, 67.1, 116.0, 124.1, 129.1, 130.8, 147.4, 148.9, 151.3, 151.9, 157.2. MS (EI): m/z (%) = 336 (30.8) [M^+]. Anal. Calc. for $C_{15}H_{14}Cl_2N_4O$: C, 53.43; H, 4.18; N, 16.62; found: C, 53.28; H, 4.34; N, 16.53.

4.3.6. *2-(5-(1H-imidazol-1-yl)pentyl)isoindoline-1,3-dione* (Table 7, entry **3**)

Column Chromatography on silica gel eluted with hexane/EtOAc (1:10) afforded pure product as creamy foam (254 mg, 90%). IR (liquid film): 3100, 2952, 1701, 1590, 1532, 1448 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ_{ppm} = 1.19-

1.29 (m, 2H, CH_2), 1.55-1.66 (m, 2H, CH_2), 1.71-1.79 (m, 2H, CH_2), 3.55 (t, *J* = 6.0 Hz, 2H, NCH_2), 3.81 (t, *J* = 6.0 Hz, 2H, NCH_2), 6.81 (s, 1H, C(5)-H of imidazole), 6.92 (s, 1H, C(4)-H of imidazole), 7.36 (s, 1H, C(2)-H of imidazole), 7.60-7.63 (m, 2H, aryl), 7.71-7.74 (m, 2H, aryl). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ_{ppm} = 25.1, 28.6, 31.4, 42.4, 54.6, 121.2, 127.4, 128.4, 132.9, 133.4, 137.6, 169.1. MS (EI): m/z (%) = 283 (19.8) [M^+]. Anal. Calc. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83; found: C, 67.70; H, 5.91; N, 14.92.

4.3.7. *1-(4-(4-methoxyphenoxy)butyl)-2-phenyl-1H-imidazole* (Table 7, entry **4**)

Column Chromatography on silica gel eluted with hexane/EtOAc (2:1) afforded pure product as colorless foam (225 mg, 70%). IR (liquid film): 3065, 2949, 1594, 1471, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} = 1.63-1.70 (m, 2H, NCH_2CH_2), 1.85-1.95 (m, 2H, OCH_2CH_2), 3.72 (s, 3H, CH_3), 3.76 (t, *J* = 6.0 Hz, 2H, NCH_2), 4.02 (t, *J* = 7.2 Hz, 2H, OCH_2), 6.70-6.80 (m, 4H, aryl), 7.02 (s, 1H, C(5)-H of imidazole), 7.12 (s, 1H, C(4)-H of imidazole), 7.37-7.39 (m, 3H, aryl), 7.53-7.56 (m, 2H, aryl). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} = 28.1, 29.1, 46.6, 55.9, 69.3, 115.3, 116.2, 121.5, 127.7, 128.4, 128.9, 129.3, 131.0, 150.4, 154.0, 155.7. MS (EI): m/z (%) = 322 (16.5) [M^+]. Anal. Calc. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.67; H, 6.96; N, 8.58.

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Conflicts of interest

The authors declare that they have no conflict of interest.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/

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Highlights in this current research:

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