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Highly efficient protocol for one-pot *N*-alkylation of nucleobases using alcohols in bmim[Br]: a rapid route to access acyclic nucleosides

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Abstract Highly efficient protocol for one-pot *N*-alkylation of nucleobases using alcohol in ionic liquid media as a straightforward route to access acyclic nucleoside was described. In this protocol purine, pyrimidine as well as azole derivatives underwent the *N*-alkylation reaction with primary or secondary alcohols using TsCl/TEA/K_2CO_3 in bmim[Br] to afford the products in good-to-excellent yields. The influence of factors in this method including the type of ionic liquid, base and sulfonating agents was discussed. The current method showed an appropriate selectivity in reaction with primary alcohols in comparison with secondary alcohols. This protocol is mild, safe and easy to apply; moreover, it is quite compatible with eco-friendly and green chemistry protocols, since the exploitation of toxic and hazardous materials such as DMF and alkyl halides has been prevented.

Keywords Acyclic nucleoside · Alcohol · Ionic liquids · Nucleobase · One-pot *N*-alkylation

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Introduction

The *N*-alkylation reactions of nucleobases are of great significance, since these reactions are rapid and straightforward route to access the acyclic nucleosides as the most known and used pharmaceutical agents for viral and cancer chemotherapy [1–9]. However, the *N*-alkylation of nucleobases is a difficult reaction as the nucleobases including purines and pyrimidines are known as ambident nucleophiles that traditionally react to produce a mixture of isometric products [10–13]. This often causes a complicated mixture of products that mostly led to cumbersome separation process. Additionally, the nucleobases have marginal solubility in normal organic solvents. This lack of solubility usually results in decline in nucleobase reactivity and hence lowers the yield of products [14, 15].

For increasing the nucleobases solubility in organic media, solvents with high dielectric constants, comprising DMF, NMP and DMSO are normally employed. However, despite these solvents' abilities to accelerate the nucleophilic displacements [16], the relatively high boiling points, thermal instability, remarkable odour problems and miscibility with both aqueous and organic phases can make product isolation tedious and solvent recovery in most cases is impossible [17].

Therefore, for solvent recovery, high temperature even at reduced pressure is often required to remove the aforementioned solvents from the products. Recovery of the solvent at a high temperature can damage sensitive molecules such as nucleosides. Furthermore, the use of highly toxic DMF as a solvent has a serious environmental cost and hence its application ineluctably should be limited [18, 19].

Traditionally, the *N*-alkylation reaction of nucleobases via alkyl halides is a rapid synthetic route to get access

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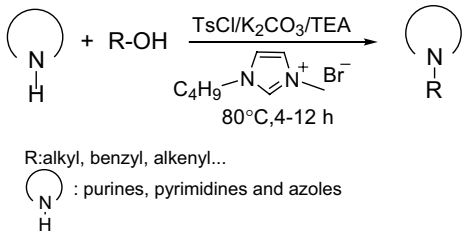
to acyclic nucleosides [20–23]; however, alkyl halides are known today as harmful reagents with proven carcinogenic properties [24]. Therefore, employing carbon electrophile with a lower toxic effect is critically essential. To overcome this problem, the direct *N*-alkylation of nucleobases with alcohols would be a highly advantageous and attractive strategy, since alcohols are known as versatile reagents that are less toxic, easily handled and wildly available in comparison with related alkyl halides [25]. In general, the most established procedures developed for *N*-alkylation of nucleobases with alcohols are based on Mitsunobu conditions [26–31]. However, these protocols, suffer from many disadvantages. For example, the use of diethyl azodicarboxylate (DEAD) and its related esters limited the applicability of Mitsunobu reactions in large-scale synthesis of *N*-alkylated nucleobase since these reagents are not only expensive but are also potentially explosive. In addition, the generated triphenyl phosphine oxide ($O{=}PPh_3$) often interferes with other products during the purification process. These defects largely annihilate the applicability of Mitsunobu conditions in *N*-alkylation of nucleobases.

One of the most significant aspects of green chemistry is the elimination of hazardous and toxic solvents in chemical synthesis to avoid the generation of waste. In this regard, ionic liquids have proved to be an alternative green reaction media, catalysts, and reagents owing to their unique properties such as extreme of polarity, non-flammability, less volatility, high thermal stability, recyclability, negligible vapour pressure and ability to dissolve a wide range of materials [32–38]. During the past decade, there has been a dramatic increase in employing the recyclable room-temperature ionic liquids (RTILs) as solvent for organic synthesis [32–35, 39–41]. Up to now, many ionic liquids have been synthesized and their applications in several organic transformations and synthesis have been extensively examined and reviewed [32, 33, 42–44]. Among RTILs, imidazolium ionic liquids are typical, since they are easily synthesized and their physical and chemical properties can be tuned by considering the different alkyl side chains on imidazolium ring and also appropriate counter ions [45–49].

Recently, we established two different protocols for one-pot *N*-alkylation of nucleobases via alcohols [50, 51]. However, in both protocols, DMF ineluctably was used as a solvent to dissolve all reactants and reagents. As part of our continual research on one-pot *N*-alkylation of nucleobases using alcohols and exploiting the utilities of ionic liquids in organic transformation, we hereby disclose the first example of one-pot *N*-alkylation of nucleobases via alcohols using $TsCl/K_2CO_3$/TEA in bmim[Br] as RTILs (Scheme 1).



Scheme 1 One-pot *N*-alkylation of nucleobases via alcohols using $TsCl/K_2CO_3$/TEA in bmim[Br]

Experimental

General remarks

All chemical reagents were purchased from Fluka or Merck. Solvents were purified by standard procedures, and stored over 3 Å molecular sieves. Reactions were followed 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). Melting points were measured using a Büchi-510 melting point apparatus in open capillary tubes and they are uncorrected. IR spectra were obtained using a Shimadzu FT-IR-8300 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Brüker Avance-DPX-250 spectrometer operating at 250/62.5 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, etc. 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 micro-analyzer.

General procedure for the one-pot *N*-alkylation of nucleobases via alcohols in ionic liquids

In a double-necked round-bottom flask (100 mL) was added a mixture consisting of nucleobase (0.01 mol), alcohol (0.012 mol), TsCl (2.86 g, 0.015), TEA (1.01 g, 0.01 mol) and K_2CO_3 (1.38 g, 0.010 mol) in bmim[Br] (10 mL). The flask was immersed in an oil bath, kept at 80 °C and stirred for the time when TLC indicated no further progress in the conversion (Tables 4, 5, 6). The mixture was then diluted with water (200 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford the crude product which was purified by traditional column chromatography on silica gel eluting with proper solvents.

Recovery of bmim[Br]

The aqueous layer obtained from work-up procedure was evaporated in vacuo on an oil bath to remain the crude bmim[Br] in which was diluted and extracted from the dissolved salts using anhydrous DCM (30 mL). The solution was filtered and evaporated to obtain the pure bmim[Br] which was subsequently used for further reactions.

Characterization data of new compounds

*9-((Tetrahydrofuran-2-yl)methyl)-9H-purin-6-amine (**1 g**)*

Column chromatography purification on silica gel with MeOH/EtOAc (1:7) afforded pale yellow foam (1.75 g, 80 %); R_f (MeOH/EtOAc, 1:7) 0.12; ^{1}H NMR (400 MHz, DMSO-d6, 25 °C): δ = 1.30–1.54 (complex, 4 H, 2 CH_2), 3.34–3.52 (m, 2 H, NCH_2), 3.87–3.99 (m, 3 H, OCH_2, OCH), 7.01 (s, 2 H, NH_2, exchangeable with D_2O), 7.83 (s, 1 H, C(2)-H, adenine), 7.91 (s, 1 H, C(8)-H, adenine) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 25.1, 29.1, 57.8, 67.9, 80.6, 117.2, 144.7, 149.2, 152.9, 156.6 ppm; IR (liquid film) ν cm^{-1}: 3417, 3100, 2958, 1649, 1464, 1168; MS [m/z (%)]: 219 (20.5); Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.70; H, 5.87; N, 32.05.

*1-(2-(1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)ethyl) pyrimidine-2,4 (1H,3H)-dione (**2c**)*

Column chromatography purification on silica gel with *n*-hexane/EtOAc (1:3) afforded yellow foam (2.57 g, 80 %); R_f (EtOAc) 0.19; ^{1}H NMR (400 MHz, DMSO-d6, 25 °C): δ = 3.67 (t, J = 7.6 Hz, 2 H, NCH2), 3.73 (t, J = 7.6 Hz, 2 H, NCH2), 5.22 (d, J = 7.9 Hz, 1 H, C(5)-H, uracil), 6.97–7.31 (m, 4 H, aryl) 7.54 (d, J = 7.9 Hz, 1 H, C(6)-H, uracil), 11.08 (s, 1 H, NH, exchangeable with D_2O) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 40.1, 56.1, 102.5, 122.2, 123.3, 128.6, 135.8, 137.8, 140.8, 146.9, 150.8, 163.9, 171.4 ppm; IR (liquid film) ν cm^{-1}: 3420, 3110, 2958, 1732, 1615, 1459, 1164; MS [m/z (%)]: 321 (26.2); Anal. Calcd for $C_{13}H_{11}N_3O_5S$: C, 48.59; H, 3.45; N, 13.08; S, 9.98. Found: C, 48.50; H, 3.54; N, 13.17; S, 10.03.

*1-(2-Cyclohexylethyl) pyrimidine-2, 4(1H, 3H)-dione (**2d**)*

Column chromatography purification on silica gel with MeOH/EtOAc (1:7) afforded creamy solid (1.73 g, 78 %); mp = 153–154 °C; R_f (MeOH/EtOAc, 1:7) 0.31; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 0.88–1.12 (complex, 5 H, 2 CH_2, CH), 1.63–1.70 (m, 6 H, 3 CH_2), 2.39–2.40 (m, 2 H, NCH_2CH_2), 4.15 (t, J = 6.8 Hz, 2 H, NCH_2) 5.45 (d, J = 7.2 Hz, 1 H, C(5)-H, uracil), 8.14 (d, J = 7.2 Hz, 1 H, C(6)-H, uracil), 11.10 (s, 1 H, NH exchangeable with D_2O) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 25 °C): δ = 25.4, 26.1, 32.3, 33.4, 38.8, 48.9, 101.7, 147.5, 151.1, 164.2 ppm; IR (KBr) ν cm^{-1}: 3276, 3117, 2921, 2849, 1679, 1716, 1478; MS [m/z (%)]: 222 (25.8); Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.92; H, 8.21; N, 12.67.

*5-(2-(1H-Benzo[d]imidazol-1-yl)ethyl)-4-methylthiazole (**3c**)*

Column chromatography purification on silica gel with MeOH/EtOAc (1:14) afforded bright brown foam (1.60 g, 66 %); R_f (MeOH/EtOAc, 1:7) 0.36; ^{1}H NMR (400 MHz, CDCl3, 25 °C): δ = 1.97 (s, 3 H, CH3), 3.15 (t, J = 6.4 Hz, 2 H, NCH_2CH_2), 4.22 (t, J = 6.4 Hz, 2 H, NCH2), 7.17–7.22 (m, 3 H, aryl) 7.55 (s, 1 H, C(2)-H, benzimidazole), 7.68–7.70 (m, 1 H, aryl), 8.44 (s, 1 H, C(2)-H, thiazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 15.5, 27.8, 53.0, 108.9, 120.3, 122.5, 123.9, 128.3, 133.9, 144.2, 144.4, 148.0, 151.9 ppm; IR (liquid film) ν cm^{-1}: 3076, 2984, 1698, 1459, 1282; MS [m/z (%)]: 243 (18.4); Anal. Calcd for $C_{13}H_{13}N_3S$: C, 64.17; H, 5.39; N, 17.27; S, 13.18. Found: C, 64.25; H, 5.47; N, 17.19; S, 13.32.

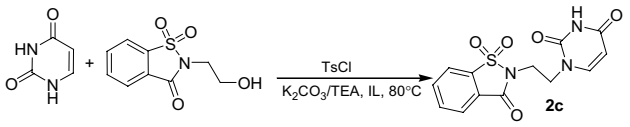
Results and discussion

To optimize the reaction condition, we examined the reaction of uracil with 2-hydroxyethyl saccharine as a sample reaction. First, we focused our attention on the choice of an appropriate ionic liquid as a reaction media. For this purpose, we investigated some representative examples among the main classes of ILs that have been established so far. The results are shown in Table 1.

As can be seen in Table 1, the influence of certain ionic liquids including 1-alkyl-3-methylimidazolium ($C_n$mim) and tetrabutyl ammonium ILs was examined on a sample reaction. In general, among the examined ILs, 1-alkyl-3-methyl-imidazolium ILs (Table 1, entries 1–12) demonstrated to be more appropriate media for conducting the experiment in comparison with tetrabutyl ammonium ILs (Table 1, entries 13–15). Concerning the ionic liquids, we found that the nature of the cation played the predominant role. From 1-alkyl-3-methyl-imidazolium [$C_n$mim] ILs, it is well demonstrated that the length of alkyl side chains on imidazolium core evidently affects the progress of reaction [45–49] and in this context the best result was obtained when C_4mim salts, in particular [bmim][Br] were used.

Interestingly, increasing the length of 1-alkyl residue from ethyl to butyl enhanced the progress of reaction, whereas more increase in alkyl length from butyl up to octyl resulted in lower yields for **2c** (Table 1, entries 1–7).

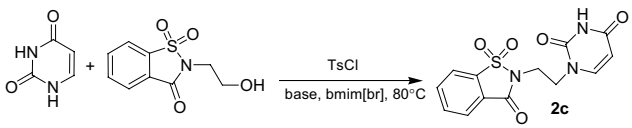
Table 1 The influence of ILs type on one-pot *N*-alkylation of nucleobases via alcohol



Entry	IL	Time (h)	Yield (%)[a]
1	emim[Br]	11	51
2	C_3mim[Br]	9	55
3	bmim[Br]	7	80
4	C_5mim[Br]	9	73
5	C_6mim[Br]	9	73
6	C_7mim[Br]	10	68
7	omim[Br]	12	48
8	bmim[Cl]	8	76
9	bmim[I]	8	78
10	bmim[BF_4]	9	77
11	bmim[PF_6]	9	77
12	bmim [OTf]	8	79
13	TBAB[b]	12	34
14	TBAC	10	46
15	TBAF	10	52

[a] Isolated yield, [b] The reaction was conducted at 100 °C

Table 2 The influence of various bases on one-pot *N*-alkylation of nucleobases via alcohol



Entry	Base	Time (h)	Yield (%)[d]
1	–	72	0
2	DBU	9	69
3	DBN	10	60
4	DABCO	14	58
5	DMAP	12	53
6	NMM[a]	9	60
7	K_2CO_3	9	62
8	MgO	24	32
9	TEA	10	57
10	K_2CO_3/TEA[b]	7	80
11	KOH	8	42
12	NaOH	8	36
13	Al_2O_3[c]	24	20

All bases were tested at 80 °C

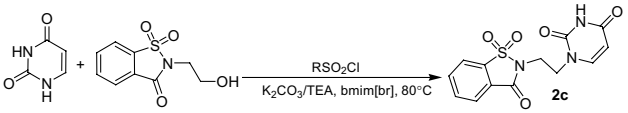
[a] *N*-Methyl morpholine, [b] 1:1 ratio was used, [c] basic alumina, [d] isolated yield

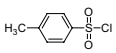
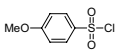
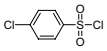
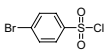
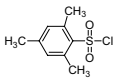
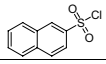
It was well reviewed that the physicochemical properties of ionic liquids can be altered by choosing the different alkyl residues and anions [45–49]. In this regard, the effects of various anion conjugates with [bmim] cation were tested (Table 1, entries 3, 8–12). Changing the bromide anion to chloride and also iodide had a marginal effect in promoting the sample reaction. In the same circumstances, the use of [bmim] ILs bearing the fluorine anions including bmim[BF_4], bmim[PF_6] and bmim[OTf] (Table 1, entries 10–12) showed undistinguishable effects in rise of reaction compare to bmim[Br]. Although PF_6^- and BF_4^- are the two anion types that were utilized majorly in most of IL applications [39–44]; nevertheless, they are suffering from several defects: these two anions may decompose when heated in the presence of water and liberate HF [52, 53]. Furthermore, they are too expensive to be employed in a large-scale organic synthesis. In addition, bmim[PF_6] is water immiscible and extremely hydrophobic which causes a technical problem through the workup procedure. Tetrabutylammonium halides including tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC) and tetrabutylammonium fluoride (TBAF) were proved to be mediocre ILs media for conducting the *N*-alkylation of uracil using the current procedure (Table 1, entries 13–15). The insufficiencies of tetrabutylammonium halides in the current protocol are attributed to side reactions like Hoffmann elimination and *N*-butylation reaction of nucleobases that normally happened through the course of reaction. The *N*-butylation was often observed when the reaction was prolonged and remained at high temperature. Therefore, TBAB was proved to have the weakest performance and *N*-butyl uracil adducts are considerably produced when TBAB was employed.

The nucleobases and alcohols are weak nucleophiles. To activate the nucleobase and alcohol, the use of an appropriate base is critically essential for progress of the reaction. To this end, some organic and inorganic bases were applied to evaluate their impacts in progress of sample reaction (Table 2).

As can be seen in Table 2, in the absence of base, the reaction was not achieved at all even if the reaction time was prolonged up to 72 h. The best result was obtained when an equimolar ratio of K_2CO_3/TEA was applied. The combination of K_2CO_3/TEA (Table 2, entry 10) was previously experienced by our research group and found to be an appropriate basic mixture for one-pot *N*-akylation of nucleobases in DMF [50]. Similarly, this basic mixture also works well in an ionic liquid media and it was used for one-pot *N*-akylation of nucleobases in the current method. It is worth mentioning that when K_2CO_3 or TEA was used alone, moderate yield of product was obtained. The use of heterocyclic bases including, DBU, DBN, DABCO, DMAP, and NMM resulted in average-to-good yields of

Table 3 The influence of various sulfonating agents on one-pot *N*-alkylation of nucleobases via alcohol



Entry	RSO_2Cl	Time (h)	Yield (%)[a]
1		9	59
2		6	79
3		10	64
4		7	80
5		7	74
6		10	61
7		10	73
8		14	38
9		12	54

All experiments were achieved at 80 °C

[a] Isolated yield

product; whereas, the use of strong bases such as KOH and NaOH unexpectedly led to faint yields of product as these bases expedite the decomposition of bmim[Br] through the Hoffmann-like elimination.

In another experiment, the influence of some sulfonyl chloride derivatives was surveyed (Table 3). As can be seen in Table 3, in addition to TsCl, TfCl also showed a satisfactory result; however, because of its expensiveness, TsCl was preferred. Other sulfonating agents also underwent the reaction to display the moderate-to-good yields of **2c** which vary in range of 54–74 %, while 2,4,6-trimethybenzene-sulfonyl chloride (Table 3, entry 8) was reluctant to react efficiently and afforded a low yield of **2c** (38 %).

To assess the scope of this protocol, three significant classes of *N*-heterocyclic compounds that often display the remarkable propensity to interact with biomolecules, encompass purines, pyrimidines and azoles were applied for this purpose. In this context, the purines, pyrimidines as well as azoles were successfully *N*-alkylated using the current protocol with a set of structurally diverse alcohols (Tables 4, 5, 6).

For purine nucleobases (Table 4), adenine, *N6*-benzyladenine, theophylline and theobromine were regioselectively alkylated with primary and secondary alcohols; whereas, tertiary alcohols were ineffectual in this protocol. Simple aliphatic, aliphatic bearing various functionalities, allylic and benzylic alcohols were used for *N*-alkylation of purine nucleobases. Using the current protocol, good regioselectivity was also observed for purine nucleobases as ambident nucleophiles. While theophylline and theobromine were merely *N*-alkylated from N7 and N1 sites, respectively; nevertheless, *N6*-benzyladenine and adenine majorly afforded the *N9*-alkyl adducts. To assess the scope of this protocol, three significant classes of *N*-heterocyclic compounds that often display the remarkable propensity to interact with biomolecules, encompass purines, pyrimidines and azoles were applied for this purpose. In this context, the purines, pyrimidines as well as azoles were successfully *N*-alkylated using the current protocol with a set of structurally diverse alcohols (Tables 4, 5, 6).

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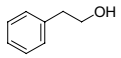
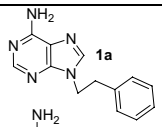
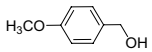
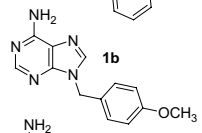
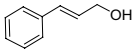
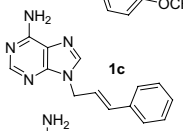
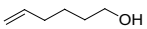
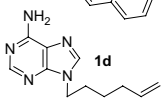
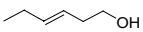
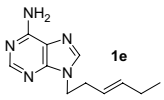
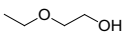
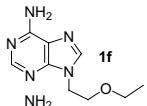
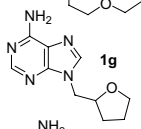
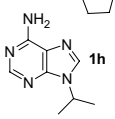
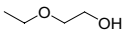
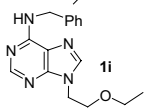
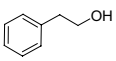
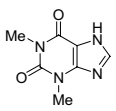
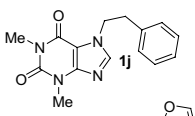
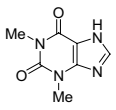
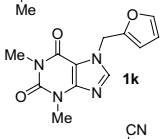
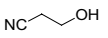
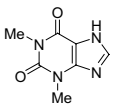
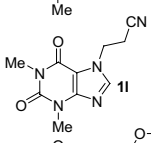
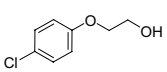
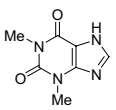
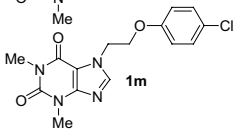
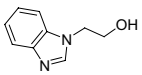
A marginal amount of *N7*-alkyl adducts for *N6*-benzyladenine and adenine were also produced which are <8 % for *N6*-benzyladenine and <10–15 % for adenine, accordingly. These ratios of isomers were assigned by GC analysis. Alkylation from other nucleophilic sites of used purines was not detected.

Likewise purines, pyrimidines and also azole analogues were *N*-alkylated with different types of alcohols (Tables 5, 6). In spite of the ready *N*-alkylation of pyrimidine and azoles with primary and secondary alcohols; these nucleobases failed to couple with tertiary alcohols using this method. Uracil and 6-azauracil showed considerable regioselectivity for alkylation from N1-site; nevertheless, a few *N1*,*N3*-dialkyl derivatives were still produced in negligible yields (10–15 %) which were assigned by GC analysis.

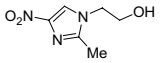
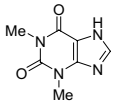
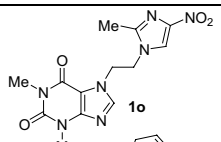
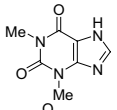
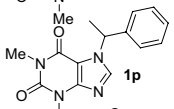
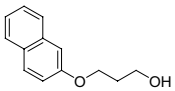
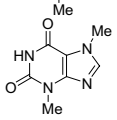
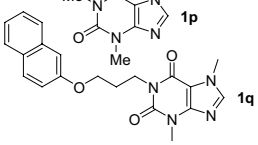
To understand the selectivity of this protocol for type of alcohol, we performed a competitive reaction between a mixture consisting of primary and secondary alcohols under optimized condition. To this end, a mixture of two isomeric alcohols including 1-phenylethanol (1 equiv.) and 2-phenylethanol (1 equiv.) was introduced to react with theophylline (1 equiv.) in the presence of TsCl (1 equiv.). As can be seen in Scheme 2, a good selectivity for the reaction with primary alcohol in comparison with secondary alcohol was observed in which **1j** was mainly obtained, whereas **1p** was generated in a trace amount.

Table 4 One-pot *N*-alkylation of purines via alcohols

Compound	Alcohol	Nucleobase	Product	Time (h)	Yield (%) [a]
1				7	84
2				6	79
3				11	74
4				6	85
5				8	79
6				7	81
7				8	80
8				12	36
9				7	64
10				4	91
11				8	88
12				6	83
13				7	81
14				8	88

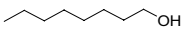
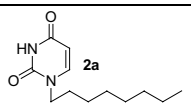
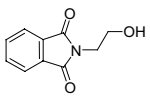
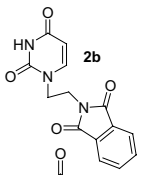
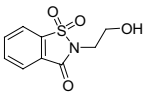
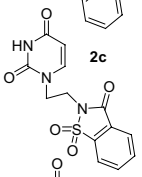
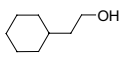
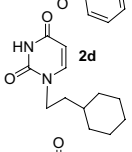
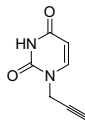
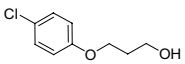
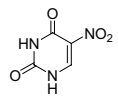
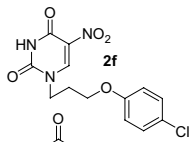
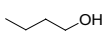
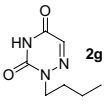
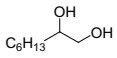
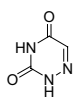
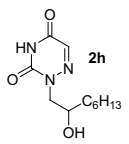
To assess the selectivity of nucleobase in reaction with different types of hydroxyl groups in a diol, we extended the optimized reaction condition to reaction of 6-azauracil with 1,2-octandiol (Scheme 3). As shown in Scheme 3, in the presence of secondary hydroxyl moiety, the primary hydroxyl group was exclusively replaced and no

Table 4 continued

Compound	Alcohol	Nucleobase	Product	Time (h)	Yield (%) [a]
15				6	90
16				11	61
17				12	68

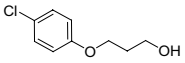
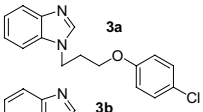
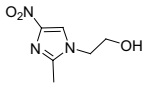
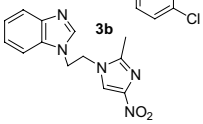
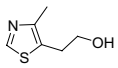
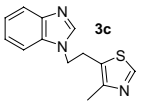
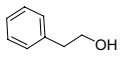
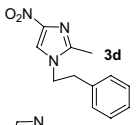
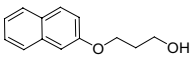
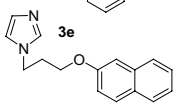
[a] Isolated yield

Table 5 One-pot *N*-alkylation of pyrimidines via alcohols

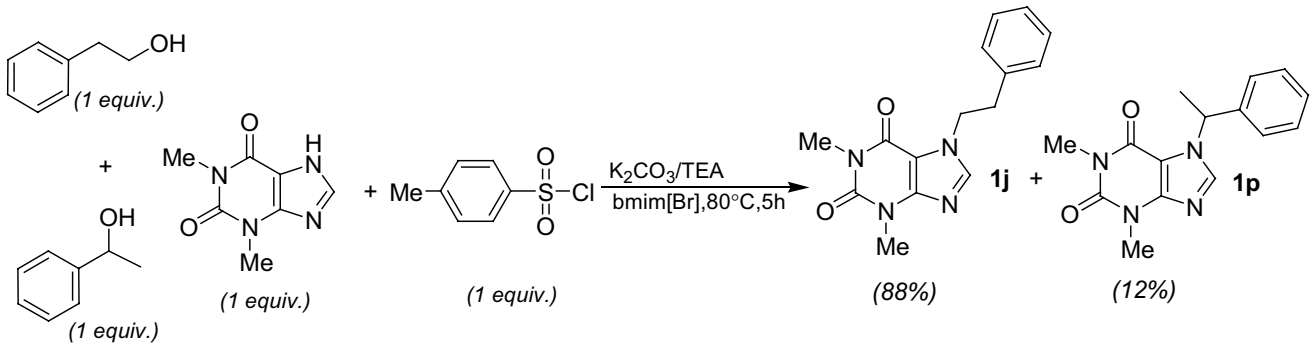
Compound	Alcohol	Nucleobase	Product	Time (h)	Yield (%) [a]
1				8	73
2				7	81
3				7	80
4				6	78
5				8	75
6				11	71
7				9	65
8				12	60

[a] Isolated yield

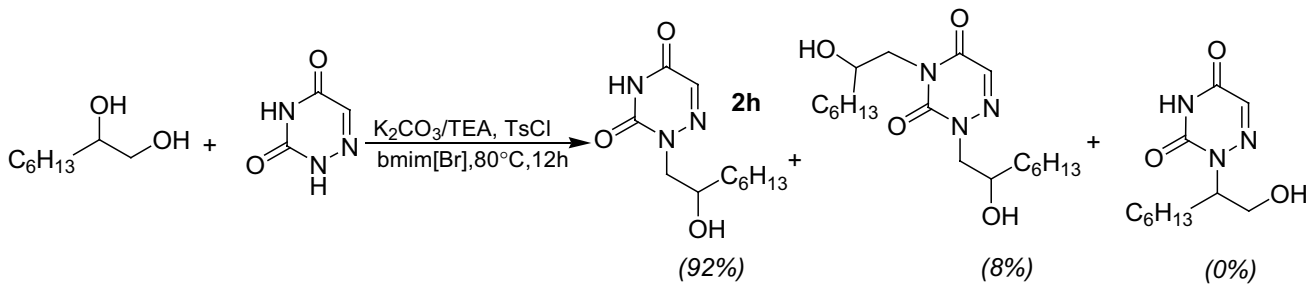
Table 6 One-pot *N*-alkylation of azole derivatives via alcohols

Compound	Alcohol	Nucleobase	Product	Time (h)	Yield (%) [a]
1				7	76
2				10	67
3				10	66
4				7	71
5				6	79

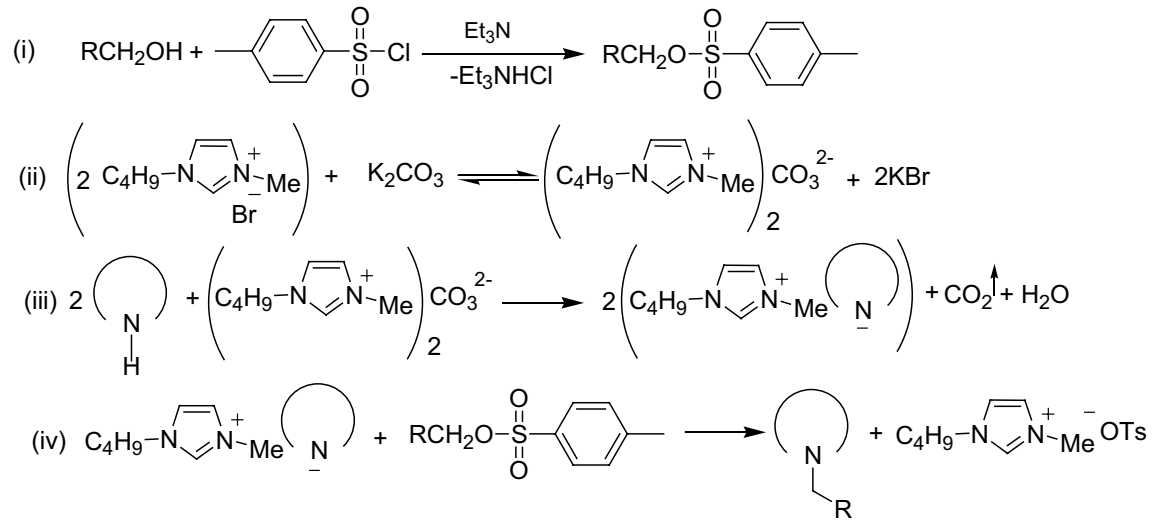
[a] Isolated yield



Scheme 2 The competitive one-pot *N*-alkylation reaction of theophylline via primary vs. secondary alcohols using TsCl/K_2CO_3/TEA in bmim[Br]



Scheme 3 The selectivity between primary vs. secondary hydroxyl groups in a one-pot *N*-alkylation reaction of 6-azauracil via using TsCl/K_2CO_3/TEA in bmim[Br]



Scheme 4 A plausible mechanism for one-pot *N*-alkylation of nucleobases via alcohol in bmim[Br] using TSCl/TEA/K_2CO_3

N-alkylation was observed at site of secondary hydroxyl group.

A plausible mechanism for one-pot *N*-alkylation of nucleobases via alcohols in bmim[Br] using TsCl and K_2CO_3/TEA is suggested (Scheme 4). In this mechanism, TEA as a homogeneous base, first scavenges a proton from alcohol, and then activated alcohol (alkoxide ion) attacks TsCl to attain the corresponding alkyltosylate. To endorse this, the generation of alkyltosylate was readily observed during the early stage of reaction process and the in situ generation of alkyltosylate was confirmed by comparing the reaction contaminants with authentic samples using GC analysis. Bmim[Br] as a highly polar reaction media assists the solvation of heterogeneous K_2CO_3 through cation–anion exchange reaction which results in formation of butyl methyl imidazolium carbonate $[Bmim]_2[CO_3]$ [54]. $[Bmim]_2[CO_3]$ scavenges a proton from the corresponding nucleobase through acid–base reaction and generates butyl methyl imidazolium-nucleobase ion-pair. Afterward, the nucleobase anion attacks the electrophilic carbon at produced alkyltosylate to afford the corresponding *N*-alkyl nucleobase.

Conclusions

In summary, an efficient protocol for one-pot *N*-alkylation of nucleobases via alcohol in Bmim[Br] as a rapid and straightforward route for synthesis of acyclic nucleoside was described. In this protocol nucleobases or *N*-heterocyclics encompass purine, pyrimidine as well as azole derivatives were regioselectively *N*-alkylated via primary or secondary alcohols using TsCl/TEA/K_2CO_3 in bmim[Br] to afford the products in good-to-excellent yields. The influence of factors on this method including ionic liquid, base and sulfonating agent types was studied. The current method showed an appropriate selectivity to react with primary alcohols in comparison with secondary alcohols, while tertiary alcohols were inert. Good versatility was observed from the reaction of structurally diverse alcohols and nucleobases using the current protocol. This method is mild, safe and environmentally compatible, since the exploitation of toxic and hazardous materials such as DMF and alkyl halides has been prevented. Bmim[Br] as a green solvent is highly sustainable in that it can be recycled and reused for multiple reaction runs.

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