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One-Pot Etherification of Purine Nucleosides and Pyrimidines

Hari Prasad Kokatla and Mahesh K. Lakshman*

Department of Chemistry, The City College and The City University of New York, 160 Convent Avenue, New York, New York 10031-9198

lakshman@sci.ccny.cuny.edu

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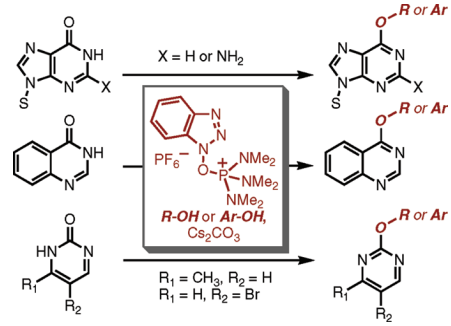
ABSTRACT



A one-pot synthesis of ethers derived from inosine, guanosine, 2′-deoxyguanosine, and pyrimidinones is described. Exposure of the heterocycle to 1*H*-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and Cs_2CO_3 produces a reactive intermediate, which is converted to the desired ether by subsequent addition of an appropriate alcohol or phenol and Cs_2CO_3. Although rapid formation of HMPA from BOP can occur in the presence of an alcohol and base, as demonstrated by the reaction with methanol, under appropriate conditions these heteroaryl ethers can be efficiently synthesized.

Modification of the natural nucleoside scaffold offers convenient access to unnatural or modified nucleosides.[1] In this context, modified nucleosides are highly important in biochemistry, in biology, and as pharmaceutical agents. Natural nucleosides contain a pyrimidine motif, and pyrimidines themselves are privileged structures in medicinal chemistry.[2]

Halogenation of nucleoside derivatives via in situ activation of their amide linkages with PPh_3/CCl_4[3,4] or combinations of HMPT with CCl_4 or CBr_4 or NBS[5,6] are known. A similar principle has been used for the *N*6 modification of adenine as well as 2,6-diaminopurine nucleosides by PPh_3/I_2[7,8] and the C-2 modification of 3,4-dihydropyrimidin-2(1*H*)-ones by PyBroP.[9] Recently, we[10−16] and others[17−23] have been interested in the in situ activation of nucleosides, purines, and other heterocycles that contain an amide linkage as part of the cyclic system. In these cases, the heterocycle is converted to a reactive phosphonium salt using an appropriate reagent, and the phosphonium salt subsequently reacts with a suitable nucleophile. Amines have been classically used as nucleophiles in these transformations. Although phenols have also been used as nucleophiles, only

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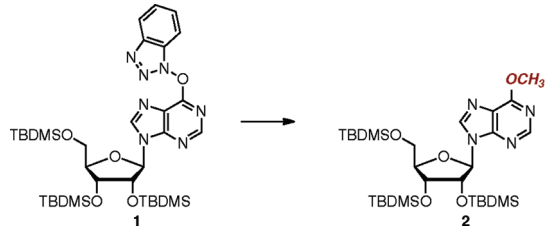
a single one-pot reaction of quinazolin-4(3*H*)-one and phenol has been reported.[20] Other such etherifications were conducted on preformed benzotriazol-1-yloxy and 7-azabenzotriazol-1-yloxy derivatives, obtained by reactions of pyrimidinones with BOP and PyAOP, respectively.[20,24−26] The serendipitous formation of such triazolyl derivatives was first reported in the reaction of thymidine with a hydroxybenzotriazole-derived phosphorylating agent.[27] Despite recent interest in the in situ activation protocols for nucleosides and pyrimidines, there are no examples of a general procedure for the synthesis of alkyl ethers from these heterocycles. Notably, our previous attempts at one-pot etherification of nucleosides with alcohols were unsuccessful, although reactions of preformed O^6-(benzotriazol-1-yl) nucleoside derivatives with both alcohols and phenols were eminently feasible.[10,16] This led us to consider a general approach for accomplishing etherification by in situ activation, thereby augmenting the methodological palette for one-pot transformations of nucleosides and pyrimidines.

Our work commenced with analysis of conditions that would provide efficient conversion of O^6-(benzotriazol-1-yl)inosine **1**[10] to the O^6-methyl ether **2**. These data are shown in Table 1. Consistent with our previous observations, in the *absence* of base, no methanolysis was observed even after 24 h at room temperature, and $(i\text{-Pr})_2$NEt was ineffective for this transformation (entries 1 and 2).[10,11] DBU and Cs_2CO_3 proved to be effective for the rapid conversion of **1** to ether **2** (entries 3 and 4).

Table 1. Analysis of the Reaction of **1** with MeOH under Various Conditions



entry	conditions[a]	time[b]	% yield[c]
1	MeOH (20 molar equiv)	24 h	NR[d]
2	MeOH (20 molar equiv), $(i\text{-Pr})_2$NEt (2 molar equiv)	24 h	NR[d]
3	MeOH (20 molar equiv), DBU (2 molar equiv)	45 min	75
4	MeOH (20 molar equiv), Cs_2CO_3 (2 molar equiv)	45 min	77

[a] Reactions were conducted using 70 μmol of **1** in MeOH. [b] Reactions were monitored by TLC. [c] Yields reported are of isolated and purified product. [d] No reaction was observed, and only **1** was observed by TLC.

Once this understanding was gained, the next step in the development of a one-pot method was to determine whether any reaction occurred between alcohol and BOP. Exposure of a THF solution of BOP to excess MeOH led to no discernible change in the $^{31}P\{^1H\}$ NMR (singlet at $\delta = 46$ ppm and septet at $\delta = 143$ ppm) over 1 h, indicating that BOP does not directly react with the alcohol. However, when this experiment was repeated in the presence of Cs_2CO_3, rapid formation of HMPA was observed by $^{31}P\{^1H\}$ NMR (singlet at $\delta = 25$ ppm) within 1 h. This reaction led to the isolation of 1-methoxy-1*H*-benzotriazole[28] in >70% yield. On its own, in comparison to existing methods,[29−32] this reaction represents facile, general entry to hydroxybenzotriazole ethers, and our results on such a direct etherification are forthcoming. In the context of the present work, these results demonstrated that combining BOP, alcohol, and base could lead to a competing reaction.

The next stage in the development was a consolidation of the two steps, i.e., formation of the (benzotriazol-1-yl) derivative **1** and etherification, into a *one-pot* operation. For this evaluation, we were presented with several options involving DBU or Cs_2CO_3 as bases and THF as solvent. Table 2 shows the results of our analysis.

Table 2 presents several notable observations. When all components were present at the start of the reaction, a mixture of products was observed (entries 1 and 5), consistent with the fact that a reaction between MeOH and BOP occurs in the presence of base. For reasons presently unknown, when 4 molar equiv of base was present at the beginning of the reaction, O^6-(benzotriazol-1-yl) derivative **1** was seen to form but it did not undergo further reaction when MeOH alone was added subsequently (entries 2 and 6). On the other hand,

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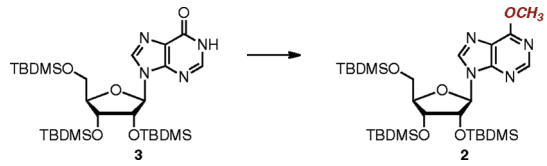
Table 2. Evaluation of Conditions for a One-Pot Conversion of Trisilyl Inosine **3** to the O^6-Methyl Ether **2**



3 **2**

entry	conditions[a]	time[b]	% yield[c]
1	DBU (4 molar equiv), BOP (2 molar equiv), MeOH (20 molar equiv), THF, rt	24 h	—[d]
2	DBU (4 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 2 h	
	then *evaporate solvent and add* MeOH (20 molar equiv), rt	step 2: 24 h	—[e]
3	DBU (2 molar equiv), BOP (2 molar equiv), THF, rt	step1: 2 h	
	then add DBU (2 molar equiv) and MeOH (20 molar equiv), rt	step 2: 8 h	74
4	DBU (2 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 2 h	
	then *evaporate solvent and add* DBU (2 molar equiv) and MeOH (20 molar equiv), rt	step 2: 4 h	76
5	Cs_2CO_3 (4 molar equiv), BOP (2 molar equiv), MeOH (20 molar equiv), THF, rt	48 h	—[d]
6	Cs_2CO_3 (4 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 20 min	
	then add MeOH (20 molar equiv), rt	step 2: 24 h	—[e]
7	DBU (2 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 2 h	
	then *evaporate solvent and add* Cs_2CO_3 (2 molar equiv) and MeOH (20 molar equiv), rt	step 2: 1 h	77
8	Cs_2CO_3 (2 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 10 min	
	then add Cs_2CO_3 (2 molar equiv) and MeOH (20 molar equiv), rt	step 2: 2 h	94
9	Cs_2CO_3 (2 molar equiv), BOP (2 molar equiv), THF, rt	step 1: 10 min	
	then *evaporate solvent and add* Cs_2CO_3 (2 molar equiv) and MeOH (20 molar equiv), rt	step 2: 10 min	94

[a] Reactions were conducted using 0.16 mmol of **3** in THF (2 mL). [b] Reactions were monitored by TLC. [c] Yields reported are of isolated and purified product. [d] Mixture of products. [e] Formation of the O^6-(benzotriazol-1-yl) derivative **1** was complete as observed by TLC.

addition of base and MeOH as a separate operation, after the formation of **1**, gave the desired result. Here, base and MeOH can be added either directly to the reaction mixture (entries 3 and 8) or after evaporation of the reaction mixture (entries 4, 7, and 9). As can be expected, reactions were faster when MeOH and base were added after evaporation of the solvent (compare entries 3 and 4, as well as entries 8 and 9). From these data, the best protocol that emerges is entry 9, where a high product yield was attained within an overall reaction time of 20 min. A variety of nucleoside alkyl ethers were generated via this procedure (Figure 1). Aryl ethers **8**, **10**, and **12** were synthesized by adding 2 molar equiv each of the phenol and

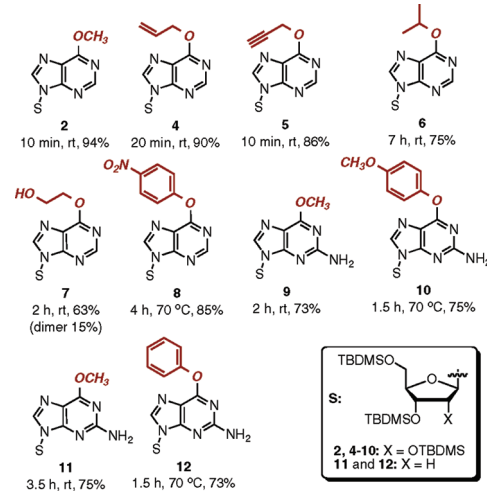


Figure 1. Nucleoside O^6-ethers synthesized. (Step 1: 10 min for inosine and 1 h for guanosine as well as 2′-deoxyguanosine, at room temperature. Step 2: reaction temperatures and times are shown above.)

Cs_2CO_3 to the reaction mixture after formation of the O^6-(benzotriazol-1-yl) ether (step 1) *without* evaporation of the mixture, and the displacement (step 2) was conducted at 70 °C.

As seen from Figure 1, reactions proceeded with *tert*-butyldimethylsilyl protected ribo and 2′-deoxyribonucleosides. Reactions with alcohols proceeded at room temperature. In the reaction of ethylene glycol and **3**, a small amount (15%) of the bisetherification product of ethylene glycol by **3** was isolated. Notably, the electron-deficient *p*-nitrophenol reacted well, leading to **8**. Yields of products obtained were generally comparable to our previously reported two-step procedures.[10,16] Reactions of silylated guanosine and 2′-deoxyguanosine in MeCN were superior to those in THF (yields were 10−15% lower in THF). This is consistent with our previous observation on the superiority of MeCN for the reactions of guanine nucleosides with BOP.[16]

We next considered the application of this method for a general synthesis of ethers derived from pyrimidines. Typically, such ethers are prepared by an S_NAr displacement reaction between chloropyrimidines and alkoxides[33] or alternatively by more complex procedures such as oxidation of a hydrazone,[34] displacement of a trichloromethyl group,[35] or a direct alkylation where *N*- and *O*-alkyl products are formed.[36,37] By comparison, the present method would offer significant operational simplicity. Therefore, for evaluation we selected three representative substrates shown in Figure 2: quinazolin-4(3*H*)-one (**13**), 4-methylpyrimidin-2(1*H*)-one hydrochloride (**14**·HCl), and 5-bromopyrimidin-2(1*H*)-one (**15**).

With the pyrimidinone substrates, the reaction with 2 molar equiv each of BOP and Cs_2CO_3 was performed in THF, at room temperature. This step was typically complete within 50 min. The second step, leading to the formation of the pyrimidine ethers, was conducted with a variety of alcohols (20 molar equiv) or 4-methoxyphenol (2 molar equiv) and Cs_2CO_3 (2

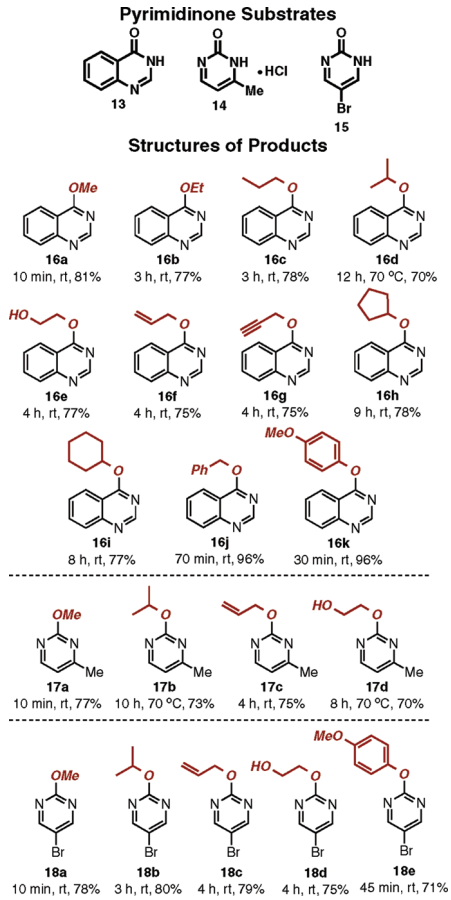


Figure 2. Pyrimidine ethers synthesized. (Step 1: 50 min at room temperature. Step 2: reaction temperatures and times are shown above.)

molar equiv). Structures of the 20 compounds synthesized via this route are displayed in Figure 2. Reaction times (when reactions were observed to be complete by TLC analysis but which were not further optimized), reaction temperatures, and product yields are shown under each compound.

As evidenced by Figure 2, etherification can be achieved by the in situ activation of the amide group in all three substrates (**13**−**15**), followed by reaction with a range of hydroxyl nucleophiles. Although these reactions proceeded with 1° and 2° alcohols, we did not obtain successful reactions with *t*-BuOH. This contrasts with the successful reaction of **13** with *t*-$BuNH_2$.[18] Some reactivity differences between the pyrimidinones were observed. For example, 4-methylpyrimidin-2(1*H*)-one (**14**) required elevated temperature for complete reaction with ethylene glycol, whereas quinazolin-4(3*H*)-one (**13**) and 5-bromopyrimidin-2(1*H*)-one (**15**) underwent reaction with this alcohol at room temperature, within 4 h. In comparison to the reaction of nucleoside **3** with ethylene glycol, there was no discernible formation of a dimeric product with the pyrimidines. Despite the intrinsic reactivity differences of the various pyrimidines toward S_NAr displacement, the method appears general.

Finally, we evaluated whether the etherification could be accomplished via in situ formation of a phosphonium salt from the tautomerizable heterocycle rather than the benzotriazolyl ether. Thus, in one unoptimized experiment, **13** was exposed to PyBroP and Cs_2CO_3 (2 molar equiv each) in THF at room temperature for 12 h. Although **13** was not fully consumed, the mixure was evaporated and exposed to 20 molar equiv of MeOH and 2 molar equiv of Cs_2CO_3. In addition to the expected **16a**, the less than clean product contained another inseparable, presently uncharacterized impurity.

In summary, we have developed a simple, one-pot method for the etherification of hypoxanthine as well as guanine nucleosides and pyrimidinones. Reaction of these heterocyclic amides with BOP produces reactive intermediates in situ, which can be made to undergo reactions with alcohols and phenols by appropriate control of reaction conditions.

For nucleoside modification, this direct route obviates separate syntheses of electrophilic nucleoside precursors such as halo nucleosides and nucleoside sulfonates or the Mitsunobu reaction. Similarly, etherification of pyrimidinones can be accomplished without additional steps or application of other types of chemistry. We believe that the method described herein will find broad applicability in the development of pharmacologically important entities from precursors containing cyclic amides, such as those used in this study.

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Supporting Information Available: General experimental considerations, general procedure for the etherification using alcohols and phenols, characterization data, and copies of ^1H NMR spectra of **2**, **4**−**12**, the dimeric byproduct from the reaction of **3** with ethylene glycol, **16a**−**16k**, **17a**−**17d**, **18a**−**18e**, and ^1H−^1H COSY spectra of **8**, **9**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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