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Mitsunobu Coupling of Nucleobases and Alcohols: An Efficient, Practical Synthesis for Novel Nonsugar Carbon Nucleosides

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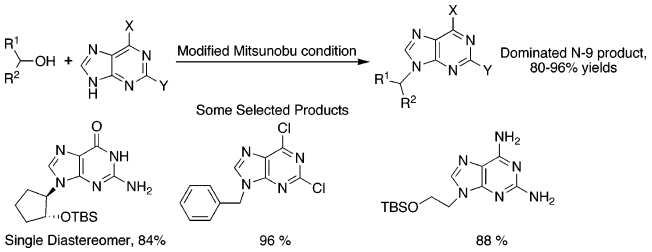

A simple facile synthesis of substituted purine derivatives has been developed by using Mitsunobu conditions for an alcohol and a respective nucleobase. A wide range of alcohols produces good to excellent yield (>90%). The resulting purine analogues show good regioselectivity with N-9 substitution as the dominant products in most of the cases. Application of diastereospecific alcohols reveals a complete inversion of the carbon stereogenic center giving a single diastereomer. More than two dozen novel nucleobase derivatives have been prepared in high yield.

Nucleosides are one of the most important fundamental building blocks in biological systems. Various nucleoside analogues have been used in many different research fields to provide remarkable chemical and biological functions. Some selected examples include peptide nucleic acid (PNA) mimicking helical DNA,[1] carbocyclic nucleosides as antitumor and antiviral agents,[2] and lipophilic nucleosides in the formation of ion channel and ion carriers.[3] The involvement of diverse research efforts and the strong potential of interesting chemical and biological properties produce a great need for the effective synthesis of novel nucleoside analogues. Currently, two approaches are applied for the preparation of nucleoside analogues: direct coupling of a base with a carbon substrate[4] and construction of purines and pyrimidines from respective aminoalkanes.[5] In general, the first route usually involves fewer steps and typically gives higher overall yields. However, all the reported approaches do not work efficiently with electron-enriched purines such as guanine due to side reactions.[6] Three methods have been reported regarding the formation of the carbon−base bond for the synthesis of nucleoside analogues: (a) palladium-catalyzed displacement of an allylic ester or carbonate; (b) direct nucleophilic displacement of halides or activated alcohols; and (c) Mitsunobu coupling. The first two strategies often encounter considerable competition at the N-9 and N-7 positions of the purine base[7] and the reactions give modest yields (usually lower than 60%).[8]

The well-studied Mitsunobu reaction involves two sequential reactions: the activation of primary or secondary alcohols by dialkylazodicarboxylate followed by nucleophilic substitution.[9] It was believed that acidic nucleophiles are necessary, since the dialkylazodicarboxylate must be protonated during the course of the reaction. Therefore, this reaction was usually applied in the synthesis of esters, phenyl ethers, thioethers, and amines (from the nucleophilic addition of phthalimide or hydrogen azide).[10] The Mitsunobu coupling of allylic and benzylic alcohol with adenine and 6-chloro-2-aminopurine has been reported previously with good N-9 selectivity.[11] However, poor to modest yield (20−60%) and limited substrate scope were observed,[12] which significantly limits the application of this method. Currently, there is no detailed study regarding the Mitsunobu coupling between a nucleobase and an alcohol available in the literature. Moreover, in all these methods, direct coupling of guanine with a nonsugar carbon substrate was unsuccessful. The only successful synthesis of guanine nucleosides was achieved by the coupling of 6-chloro-2-aminopurine with carbon substrates followed by nucleophilic aromatic substitution as shown in Scheme 1.[13] The poor overall yields and harsh reaction conditions make the synthesis of nonsugar guanine analogues a big challenge.

Our interest in developing novel self-assembled nucleoside molecular architectures extends our need for facile synthesis of

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(10) (a) Mitsunobu, O. *Synthesis* **1981**, *1*, 1−28. (b) Hughes, D. L. *Organic Reactions*; Wiley: New York, 1992; Vol. 42, pp 335−656.

(11) (a) Kitade, Y.; Ando, T.; Yamaguchi, T.; Hori, A.; Nakanishi, M.; Ueno, Y. *Bioorg. Med. Chem.* **2006**, *14*, 5578−5583. (b) Yang, M.; Schneller, S. W.; Korba, B. B. *J. Med. Chem.* **2005**, *48*, 5043−5046. (c) Yin, X.; Li, W.; Schneller, S. W. *Tetrahedron Lett.* **2006**, *47*, 9187−9189.

(12) (a) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993−3996. (b) Dyatkina, N. B.; Theil, F.; Von Janta-Lipinski, M. *Tetrahedron* **1995**, *51*, 761−772. (c) Iyer, M. S.; Palomo, M.; Schilling, K. M.; Xie, Y.; Formanskii, L.; Zembower, D. E. *J. Chromatogr., A* **2002**, *944*, 263−267.

(13) Besada, P.; Gonzalez-Moa, M. J.; Teran, C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, *16*, 2445−2449.

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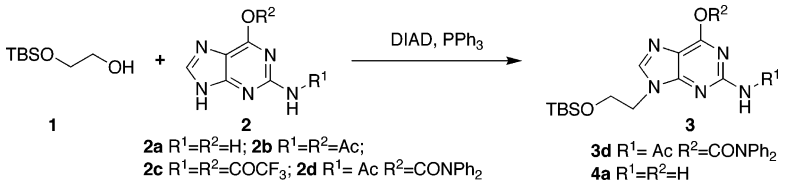
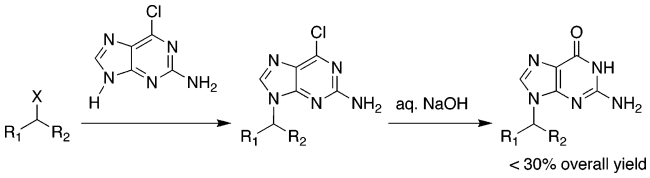
TABLE 1. Screening of Reaction Conditions between Guanine and Primary Alcohol[a]



entry	method	ROH (equiv)	purine base (equiv)	solvent	temp (°C)	yield (%)[b]
1	A	1.0	1.0 equiv, $R^1 = R^2 = H$	THF	70	0
2	A	1.0	1.0 equiv, $R^1 = R^2 = Ac$	THF	70	0
3	A	1.0	1.0 equiv, $R^1 = R^2 = COCF_3$	THF	70	0
4	A	1.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	THF	70	58
5	A	1.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	DMF	70	47
6	A	1.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	CH_3CN	70	38
7	A	1.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	DCE	70	36
8	A	3.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	THF	70	62
9	B	2.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	DMF	70	65
10	B	2.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	CH_3CN	70	57
11	B	2.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	DCE	70	43
12	B	2.0	1.0 equiv, $R^1 = Ac$; $R^2 = CONPh_2$	THF	70	93

[a] Method A: A mixture of guanine or protected guanine (1 equiv), alcohol (1.05 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) was stirred in the designated solvent (0.1 M) at 70 °C for 12 h. Method B: A mixture of **2d** (1.0 equiv), alcohol (1.0 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) in anhydrous THF (0.1 M) with N_2 protection was stirred at 70 °C for 6 h. Then alcohol (1.0 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) were added sequentially and the resulting mixture were heated at 70 °C for another 6 h. [b] Isolated yields.

SCHEME 1. Literature Reported Synthesis of Nonsugar Guanine Analogues



different nonsugar guanine analogues.[14] Herein, we report an efficient and practical synthesis of nonsugar nucleosides using optimized Mitsunobu coupling of guanine and a variety of alcohols with excellent N-9 selectivity and good-to-excellent yield. The reaction between a simple primary alcohol, TBS-protected ethylene glycol, and guanine derivatives was first studied and the results are summarized in Table 1.

It is known that alcohol can be activated by dialkylazodicarboxylate even at low temperature. Both guanine and protected guanine have poor solubility in nonpolar organic solvents such as anhydrous THF, which is usually considered to be the best solvent for the Mitsunobu reaction. Since purines are not great nucleophiles for activated alcohols, dilution of the reaction causes significant increase in the reaction time and leads to a poor yield of the desired coupling product.[15] To increase the purine base solubility, the reaction is carried out at 70 °C, where both guanine and protected guanine are partially soluble. As shown in Table 1, both guanine and diacetyl guanine (entry 2) do not generate the coupling product. To increase the acidity of the nucleophile, trifluoroacetate-protected guanine is used in the coupling reaction (entry 3). However, no coupling product is observed. The *O*-carbamate-*N*-acetate protected guanine, which can be readily prepared from guanine in two steps (>90% overall yield),[16] is found to be the best protecting group, producing the desired coupling product in a moderate yield (entry 4). Notably, only the desired N-9 substituted product is observed in this coupling reaction.

During reflux in anhydrous THF, all of the alcohol is consumed within 4 h while some of the protected guanine remains unreacted. It is reasonable to hypothesize that the activated alcohol undergoes significant decomposition side reactions, which causes the low yield of the coupling product. An increase in the amount of alcohol and DIAD also increases the rate of the side reactions, resulting in only slight improvement of the desired guanine coupling (entry 8). A different reaction condition includes the addition of one more equivalent of the activated alcohol after 6 h of reaction (method B). This modification significantly increases the yield of the guanine product by consuming all the purines. Screening of the solvents reveals that THF is the best solvent for the desired reaction. Compound **3d** can then be readily converted to the desired nonsugar guanine analogue **4a** by treatment with a 1:1 mixture of ammonia and methanol solution at 60 °C with >95% yield.[16] To the best of our knowledge, this method is the first example in the literature that directly couples alcohols with guanine nucleophiles. Compared to the current approach in the literature (Scheme 1), this new strategy will yield the nonsugar carbon−guanine analogue in a more efficient way with much higher overall yield. Therefore, this method provides a very practical synthesis of novel guanine nucleosides. The substrate scope of alcohols is summarized in Table 2.

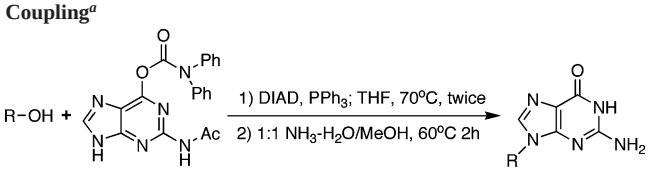
As indicated by Table 2, a large group of different alcohols produce the carbon−guanine products with use of the optimized conditions, including primary alcohols, secondary alcohols, allylic alcohols, propargyl alcohols, benzylic alcohols, etc. *tert*-Butyl alcohol was also reacted with protected guanine, but no coupling product was observed due to steric hindrance on the tertiary carbon. With all these substrates, the carbon−guanine

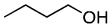
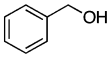
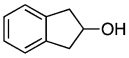
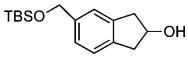
(14) (a) Shi, X.; Fettinger, J. C.; Davis, J. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2827−2831. (b) Shi, X.; Mullaugh, K. M.; Fettinger, J. C.; Jiang, Y.; Hofstadler, S. A.; Davis, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 10830−10841.

(15) When **2d** and **1** were reacted at room temperature under diluted conditions, **3d** was obtained in less than 10% isolated yield even after running the reaction for 16 h.

(16) (a) Zou, R.; Robbins, M. J. *Can. J. Chem.* **1987**, *65*, 1436. (b) Choo, H.; Chong, Y.; Chu, C. K. *Org. Lett.* **2001**, *3*, 1471−1473.

TABLE 2. Reaction Substrate Scope in the Guanine−Alcohol Coupling[a]



Entry	Alcohol	Product	Yield (%)[b]
1		**4a**	86
2		**4b**	85
3		**4c**	83
4		**4d**	85
5		**4e**	76
6		**4f**	81
7		**4g**[c]	72
8		**4h**[c]	78
9		**4i**	74
10		**4j**	84

[a] Reaction condition: A reaction mixture of **2d** (1.0 equiv), alcohol (1.05 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) in anhydrous THF (0.1 M) with N_2 protection was stirred at 70 °C for 6 h, then alcohol (1.05 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) were added sequentially and the resulting mixture was heated at 70 °C for another 6 h. [b] Isolated yields. [c] Structure was confirmed by X-ray crystallography.

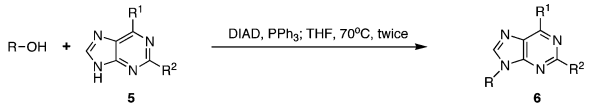
products were prepared in good-to-excellent yields by using this two-step combination.

It is known in the literature that 6-chloropurine, 2,6-dichloropurine, and 6-chloro-2-aminopurine are able to couple with selected alcohols under Mitsunobu conditions. However, the alcohols are limited to allylic and benzylic positions and reaction yields are not satisfactory in all of the cases (20−50%). The chloropurines are much more soluble in THF than guanine derivatives. Therefore, the reaction can take place at room temperature. However, low yields of the coupling products are observed due to the side reactions associated with the poor nucleophilicity of purines. Different purines have been investigated as the nucleophile by using the optimized reaction conditions (Table 3).

As shown in Table 3, the more soluble purines indeed generate the desired coupling products in good yields under the optimized reaction condition. For 6-chloropurine, only N-9 coupled compounds are obtained, while for 2,6-dichloropurine, N-7 compounds are observed as the minor products in some cases. This observation can be attributed to the lower electron density of 2,6-dichloropurine, which results in competition of the nucleophilicity at the N-9 and N-7 positions. These two regioisomers can be separated by column chromatography and the structures are determined by X-ray crystallography (Supporting Information).

Neither adenine nor 2,6-diaminopurine produces the desired coupling product with a simple alcohol, although they were reported as possible purine bases in the Mitsunobu coupling,

TABLE 3. Investigation of Purine Bases[a]



Entry	Alcohol	R^1	R^2	Yield of N-9 Product (%)[b] [Yield of N-7 product (%)[b]]
1		Cl	H	**6a:**89 [0]
2		Cl	Cl	**6b:**90 [**6c:** 5]
3		NH_2	H	0 [0]
4		NH_2	NH_2	0 [0]
5		NHAc	NHAc	0 [0]
6		Cl	H	**6d:**78 [0]
7		Cl	Cl	**6e**[c]**:**88
8		Cl	H	**6f:**87 [0]
9		Cl	Cl	**6g:**88 [0]
10		Cl	H	**6h:**89 [0]
11		Cl	Cl	**6i**[c]**:**86 [0]
12		Cl	H	**6j:**85 [0]
13		Cl	Cl	**6k:**96 [0]
14		NH_2	H	0 [0]
15		NH_2	NH_2	0 [0]
16		NHAc	NHAc	0 [0]
17		Cl	H	**6l:**77 [0]
18		Cl	Cl	**6m**[c]**:**75 [**6n:**17]
19		Cl	H	**6o:**74 [0]
20		Cl	Cl	**6p:**76 [**6q**[c]**:**18]
21		Cl	H	**6r**[c]**:**81 [0]
22		Cl	Cl	**6s**[c]**:**88

[a] Same reaction condition as in Table 2. [b] Isolated yields. [c] Structure was confirmed by X-ray crystallography.

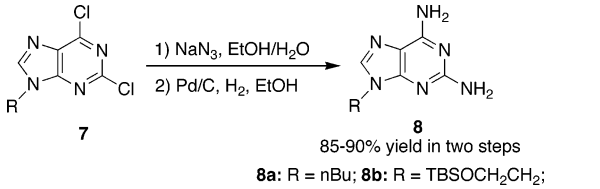


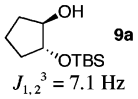
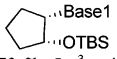
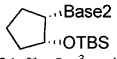
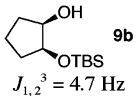
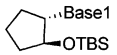
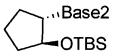
FIGURE 1. Preparation of diaminopurine derivatives from compounds **7**. Reaction condition: the mixture of compound **7** (1.0 equiv) and NaN_3 (2.5 equiv) in EtOH/H_2O (5/1 volume ratio) was refluxed for 2 h, then the solvent was removed under reduced pressure, and the resulting crude product was hydrogenated in EtOH in the presence of Pd/C (10 mol %). Yield: 86% for **8a** and 88% for **8b** in two steps, respectively.

with specific more reactive alcohols. These results may be due to the poor solubility of the bases. An easy conversion of the chloropurine to the respective aminopurine compounds has been developed and the target aminopurine carbon nucleoside is obtained in excellent overall yield.[17] Therefore, the substrate scope of this reaction can be extended even further.

The stereochemistry control of this reaction has also been investigated. In the conventional Mitsunobu reaction, the nucleophiles are believed to undergo an SN2 mechanism. Therefore, a complete conversion of the stereogenic center is expected. Several diastereospecific alcohol derivatives have been employed to evaluate the stereochemistry of this conversion and the results are listed in Table 4.

(17) (a) Sznidman, M. L.; Du, J.; Pesyan, A.; Cleory, D. G.; Hurley, K. P.; Waligora, F.; Almond, M. R. *Nucleoside, Nucleotides & Nucleic Acids*, **2004**, *23*, 1875−1887. (b) Tiwari, K. N.; Messini, L.; Montgomery, J. A.; Secrist, J. A. *Nucleoside, Nucleotides & Nucleic Acids* **2001**, *20*, 743−746.

TABLE 4. Stereochemistry Control of the Nucleobase-Mitsunobu Reaction[a−c]

Starting Materials	Products	
 **9a** $J_{1,2}^3$ = 7.1 Hz	 **10a** 73 %, $J_{1,2}^3$ = 4.4 Hz	 **10b** 81 %, $J_{1,2}^3$ = 4.5 Hz
 **9b** $J_{1,2}^3$ = 4.7 Hz	 **10c** 76 %, $J_{1,2}^3$ = 7.3 Hz	 **10d**[d] 84 %, $J_{1,2}^3$ = 7.8 Hz

[a] Same reaction conditions as shown in Table 2. [b] Isolated yields. [c] Coupling constant between C1−H and C2−H for the determination of relative stereochemistry. [d] Structure was confirmed by X-ray crystallography.

In all the examples, a single diastereomer is obtained. The relative stereochemistry of all the compounds has been determined by NMR and the complete inversion of the alcohol stereogenic center is observed. These results are consistent with the SN2 mechanism and strongly enhance the application of the reported method as a general approach for the stereospecific synthesis of carbon nucleosides.

In summary, a study of the Mitsunobu reaction between simple alcohols and nucleobase has been performed. A large number of nucleobases and alcohols can give the desired coupling products in good-to-excellent yields under the optimized condition. This approach has a very large substrate scope with good stereochemistry control, which makes it a very efficient and practical method for the synthesis of novel carbon nucleosides. Studies of some novel carbon guanine analogues as self-assembly building blocks and potential drug candidates are currently under investigation in our group.

Experimental Section

General Procedure for Mitsunobu Coupling. The substituted purine or protected guanine (1.0 equiv) was added to a solution of alcohol (1.05 equiv) and PPh_3 (1.05 equiv) in anhydrous THF under an N_2 atmosphere. The resulting suspension/solution was treated with diisopropyl azodicarboxylate (DIAD, 1.05 equiv) and the reaction mixture was then stirred at 70 °C for 6 h. Then the second portions of alcohol (1.05 equiv), PPh_3 (1.05 equiv), and DIAD (1.05 equiv) were added to the reaction mixture sequentially. The mixture was stirred for another 6 h at the same temperature. The mixture was cooled, treated with saturated sodium chloride, and extracted with dichloromethane. The combined organic layer was then washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Flash silica gel chromatography gave the pure product.

Deprotection of the Protected Guanine 3. The protected guanine **3** was dissolved in a mixture of ammonia/methanol (1:1). The resulting solution was heated at 60 °C for 2 h. The solvent was removed under reduced pressure and the crude product was purified by flash silica gel chromatography.

Synthesis of Diaminopurine 8. A solution of 2,6-dichloropurine **7** (1.0 equiv) and NaN_3 (2.5 equiv) in EtOH/H_2O (5/1 volume ratio) was refluxed for 2 h. Then solvent was removed under reduced pressure to give the crude product, which was hydrogenated in EtOH in the presence of Pd/C (10 mol %). The resulting mixture was passed through celite, concentrated, and purified by flash silica column chromatography.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, and CIF files for compounds **6e**, **6i**, **6m**, **6q**, **6r**, **6s**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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