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The Mitsunobu reaction in preparing 3-deazapurine carbocyclic nucleosides

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Abstract—The coupling reaction of 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (6-chloro-3-deazapurine, **3**) with several cyclopentyl derivatives under Mitsunubo reaction conditions provides an efficient entry into N-7 and N-9 substituted 3-deazapurine carbocyclic nucleosides of antiviral potential. The versatility of this procedure is illustrated with a new and efficient synthesis of (−)-3-deazaaristeromycin, a formal preparation of 3-deazaneplanocin A, and a route to 3-deaza-5′-homoaristeromycin.

1. Introduction

Nucleoside analogs based on the 3-deazapurine (1*H*-imidazo[4,5-*c*]pyridine) framework have found significant usefulness in antiviral agent design and biochemical investigations.[1,2] The carbocyclic nucleosides[3] 3-deazaristeromycin (**1**)[4] and 3-deazaneplanocin (**2**)[5] have been central to these studies (Fig. 1). In our efforts to further exploit the 3-deazapurine carbocyclic nucleoside platform as a source for new antiviral candidates, it was necessary to seek a more versatile synthetic means to this series that would give access to a number of structural variations. In this regard it was surprising to find that the Mitsunobu reaction,[6] which has been successfully employed to produce traditional carbocyclic nucleosides, had not been investigated in the 3-deazapurine genera. This paper describes the use of the Mitsunobu reaction in the preparation of such derivatives.[7]

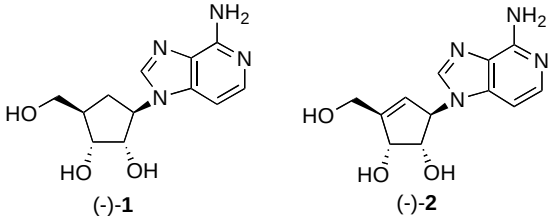
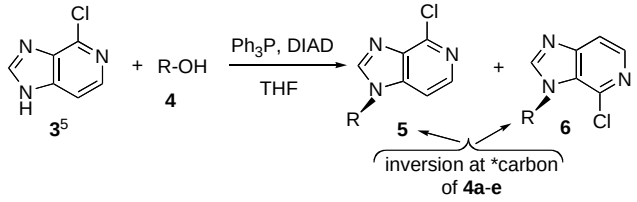
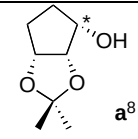
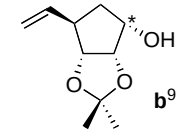
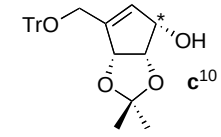
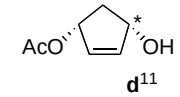
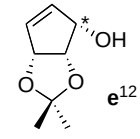


Figure 1.

Table 1. Mitsunubo reaction of 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (3-deaza-6-chloropurine) with substituted cyclopentanols



Entry	R-OH	Products (%)	
		5	**6**
1	 **a**[8]	86	0
2	 **b**[9]	70	0
3	 **c**[10]	42	53
4	 **d**[11]	38	57
5	 **e**[12]	32	43

Keywords: 4-Amino-1*H*-imidazo[4,5-*c*]pyridine; Carbocyclic nucleosides; Aristeromycin; Neplanocin.
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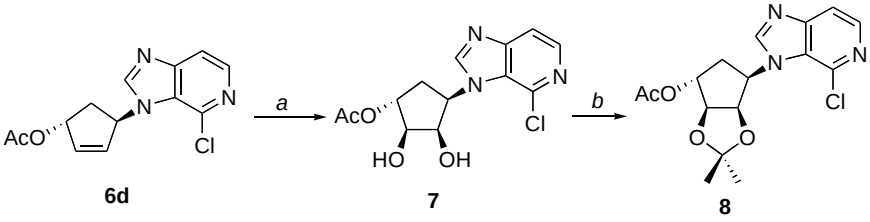


Scheme 1. Reagents: a, OsO_4, NMO, CH_2Cl_2; b, $(MeO)_2CMe_2$, acetone, *p*TSA, 83% (two steps).

2. Chemistry

Following standard Mitsunobu conditions (that is, triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran), the reaction of 4-chloro-1*H*-imidazo-[4,5-*c*]pyridine (**3**)[5] with various cyclopentanols gave the results presented in the Table 1. Thus, reacting **4a** with **3** cleanly gave **5a** as the only isomer. Likewise, compound **4b** provided **5b** as the only regioisomer. The more reactive allylic alcohols **4c–e**, however, yielded the N-1 (purine N-9) products **5c–e** along with the N-3 (purine N-7) isomers **6c–e**, which were the major products.

Structural assignments for the N-1 (N-9) and N-3 (N-7) isomers were possible because the proton on the cyclopentyl carbon bearing the heterocyclic ring in the N-3 product is downfield in the proton NMR spectrum compared to the N-1 product (by correlating the data of Ref. 5 with the data found in this study that is supported by the X-ray structural confirmation of **8**, vide infra). A characteristic carbon-13 NMR peak ($\delta = \sim 106$ ppm) was observed for the carbon (possibly C-2) in the heterocyclic ring of all N-1 products (**5**) while the peak moves to ($\delta = 115$ ppm) in all N-3 products (**6**). Supporting these NMR assignments for N-3 products was the conversion of **6d** to **8** (Scheme 1), whose structure was confirmed by X-ray crystallography (Fig. 2) and whose NMR spectrum fit the diagnostic peaks used for isomer distinction.

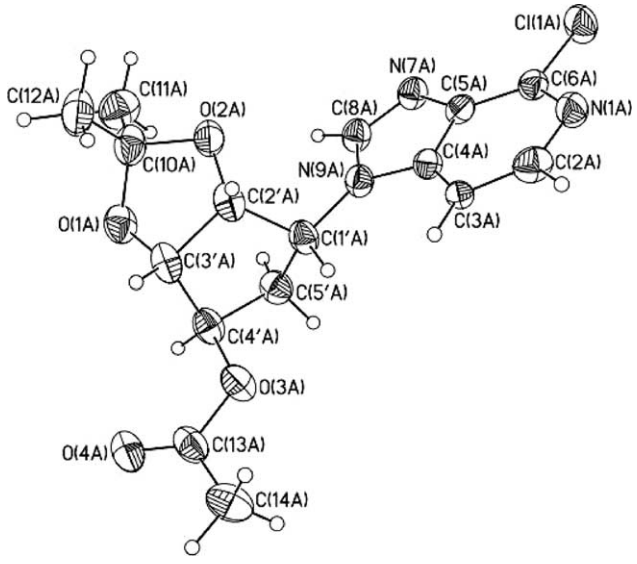
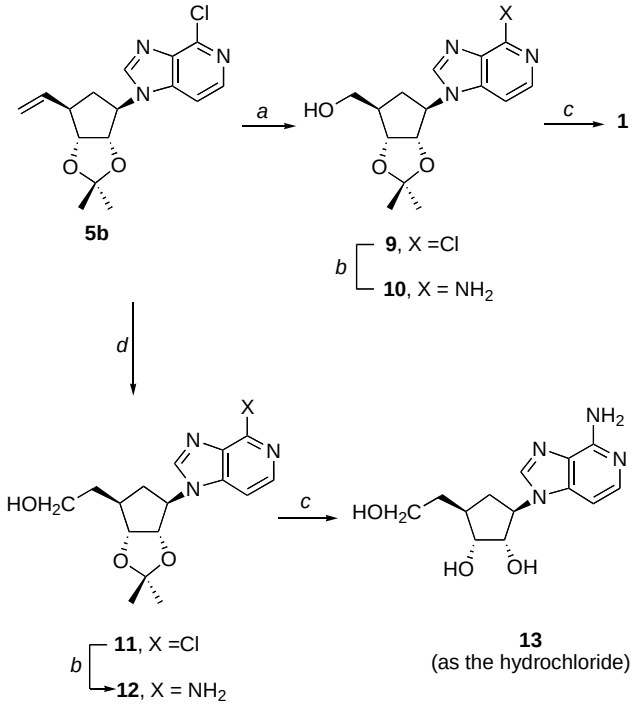


Figure 2. X-ray structure for compound **8**.

Further transformations of the coupled products **5b** and **5c** were sought for additional structural confirmation and to demonstrate extended synthetic versatility by their conversion into two important 3-deazapurine carbocyclic nucleosides, 3-deazaaristeromycin (**1**) and 3-deazaneplanocin (**2**). Whereas compound **2** was obtained from **5c** by modifying a known procedure,[5] manipulation of the vinyl group in **5b** to a hydroxymethyl moiety following our recently reported procedure[9a] furnished (−)-**1** in good overall yield (Scheme 2).[13] Compound **5b** also provided access to 3-deaza-5′-homoaristeromycin (**13**), which is a compound of potentially significant activity toward the orthopox viruses.[14]



Scheme 2. Reagents: a, (i) OsO_4, $NaIO_4$, MeOH; (ii) $NaBH_4$, MeOH, 81%; b, (i) NH_2NH_2, THF; (ii) Ra-Ni, MeOH/H_2O, 75% (two steps for **9**); 80% (two steps) for **12**; c, HCl/MeOH, 89% for **1**; 78% for **13**; d, (i) 9-BBN, THF; (ii) NaOH, H_2O_2, 80% (two steps).

3. Experimental

3.1. General

Melting points were recorded on a Meltemp II melting point apparatus and the values are uncorrected. The combustion analyses were performed at Atlantic Microlab, Norcross, GA. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AC 250 spectrometer (250 MHz for proton and 62.9 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The X-ray