Efficient Synthesis of Purines and Purine Nucleosides via an Inverse Electron Demand Diels−Alder Reaction

Qun Dang,* Yan Liu, and Mark D. Erion

Department of Medicinal Chemistry, Metabasis Therapeutics, Inc., 9390 Towne Centre Drive, San Diego, California 92121

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Purine nucleosides represent an important class of therapeutically active agents and consequently a central focus of many drug discovery efforts.[1] Recently we became interested in the synthesis of 2- and 6-substituted purine nucleosides on the basis of theoretical calculations suggesting that certain substituents at these positions might promote hydration of the 1,6-double bond and consequently enable inhibition of adenosine deaminase with high potency via transition state mimicry.[2] Synthesis of these compounds and purine nucleosides, in general, is frequently achieved by synthesis of the base and sugar units separately, followed by a coupling reaction. Unfortunately, the coupling reaction can produce complex diastereomeric mixtures and proceed in poor overall yields, especially when applied to the synthesis of 2′-deoxynucleoside analogues. Accordingly, efforts to develop new synthetic methodologies that circumvent these limitations continue to be important. For example, Trost and Shi recently reported a chemoselective glycosylation reaction that enables enantioselective alkylation of 6-chloropurine at the 9-position with 2,5-dibenzoyloxy-2,5-dihydrofuran under palladium-catalyzed reaction conditions in the presence of chiral ligands.[3] Alternatively, the coupling reaction is avoided in the synthesis of inosine analogues by using ribosylated imidazoles such as 5-amino-1-(β-D-ribofuranosyl)-4-imidazolecarboxamide and various reagents that result in pyrimidine ring closure.[4] These strategies, however, are not readily adapted to the synthesis of purine nucleosides containing electron-withdrawing carbon substituents at the 6-position. Compounds such as 6-cyano-9-β-D-ribofuranosylpurine and 6-carbamoyl-9-β-D-ribofuranosylpurine are prepared from 6-thioinosine and 6-cyanopurine in low yield,[5a,5b] and 6-formylpurine is prepared from 6-methylpurine in five steps.[5c]

In an effort to find a more efficient synthesis of purine analogues, we explored the inverse electron demand Diels−Alder reaction between 5-aminoimidazoles and 1,3,5-triazines. Previously, Boger and co-workers showed that 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1**) is a useful diene for the synthesis of pyrimidines,[6] and we reported that reaction of **1** with 5-aminopyrazoles yields pyrazolopyrimidines.[7] In contrast to these reactions, synthesis of purine analogues using the analogous Diels−Alder reaction is complicated by the instability of the dienophile, i.e., the electron-rich 5-aminoimidazole analogue.[8] Since 5-amino-4-imidazolecarboxylic acids are known to undergo decarboxylation under relatively mild conditions,[9] we chose to study the propensity of 5-aminoimidazoles, generated in situ via decarboxylation, to be trapped by 1,3,5-triazines via a [4 + 2] cycloaddition reaction.

Table 1. Tandem Decarboxylation/Diels−Alder Reactions of **2a**−**c**

entry	dienophile	condition[a]	product	yield (%)
1	**2a**	80 °C/2 h/DMF	**3a**	83
2		25 °C/7 days/DMF	**3a**	50
3		80 °C/2 h tBuOH/buffer (pH = 4.8)	**3a**	49
4		80 °C/30 h tBuOH/buffer (pH = 7)	**3a**	10
5		80 °C/30 h tBuOH/1N HCl	**3a**	0[b]
6		80 °C/42 h tBuOH/(sat) $NaHCO_3$	**3a**	0[c]
7	**2b**[d]	110 °C/16 h/DMF-AcOH	**3b**	45
8		100 °C/20 h/DMF-AcOH	**3b**	70
9		90 °C/20 h/DMF-AcOH	**3b**	75[e]
10		80 °C/24 h/DMF-AcOH	**3b**	81
11	**2c**	90 °C/6 h/DMSO	**3c**	75

[a] Reactions were conducted with 1 equiv of **1** and 2 equiv of **2a**−**c**. [b] Decomposition of **1** was observed. [c] Compound **1** was recovered. [d] The potassium salt of **2b** was used. [e] Three equivalents of **2b** were used.

Reaction of 5-amino-1-benzyl-4-imidazolecarboxylic acid (**2a**)[10] with **1** at 80 °C in DMF led to 9-benzyl-2,6-bis(ethoxycarbonyl)-purine (**3a**) in 83% yield (Table 1). Failure of the reaction to produce **3a** under basic conditions suggests that the decarboxylation of **2a** precedes the [4 + 2] cycloaddition reaction and that **2a** itself is not reactive enough to participate in the [4 + 2] reaction with **1** (Table 1, entry 6). In contrast, under conditions known to induce decarboxyaltion, e.g., slightly acidic conditions, the reaction is quite facile. The results also suggest that 5-amino-1-benzylimidazole, generated in situ from **2a**, is a more reactive dienophile compared with 5-aminopyrazole[7] on the basis of the shorter reaction times at similar temperatures. For example, previously reported 1,3,5-triazine Diels−Alder reactions[6] required extensive heating, whereas the current reaction is capable of generating **3a** at room temperature (Table 1, entry 2). Overall, the results support the reaction sequence shown in Scheme 1 wherein decarboxylation of **2a** produces the highly reactive 5-aminoimidazole which in the presence of **1** is rapidly trapped as the [4 + 2] cycloadduct. This cycloadduct then spontaneously undergoes a retro Diels−Alder reaction with the loss of ethyl cyanoformate followed by the loss of ammonia and aromatization to produce **3a** in a regioselective manner.

Purines prepared using **1** have ester functionalities at the 2- and 6-positions which can be modified in a regiospecific manner to produce various 6-substituted and 2,6-disubstituted purine analogues (Scheme 2). The 2,6-unsubstituted analogue of **3a**, i.e.,

* Corresponding author. (tel.) 619-622-5517; (fax) 619-622-5573; (e-mail) dang@mbasis.com.

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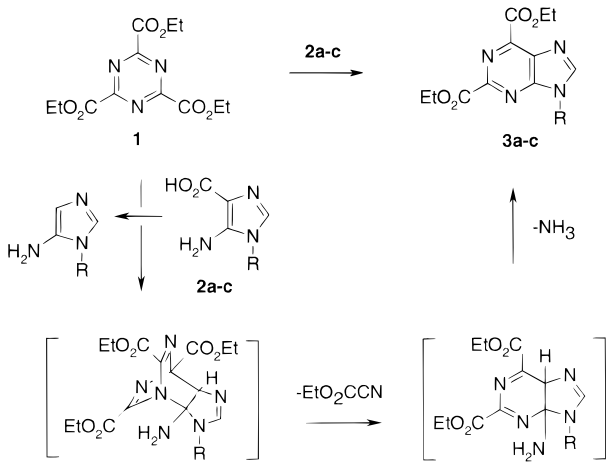
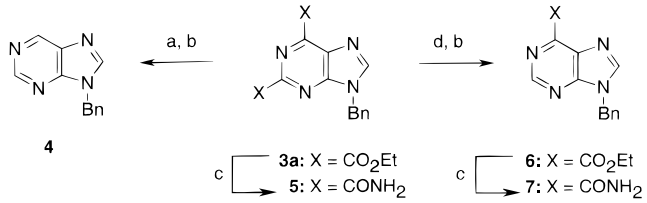
Scheme 1[a]



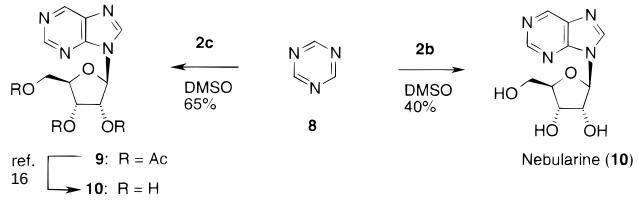
[a] R groups: (a) Bn; (b) β-D-ribofuranosyl; (c) 2,3,5-tri-O-acetyl-β-D-ribofuranosyl.

Scheme 2[a]



[a] Reagents and conditions: (a) NaOH (2 equiv), THF, EtOH, H_2O; (b) Ac_2O, AcOH, 130 °C; (c) NH_3, MeOH; (d) NaOH (1 equiv), THF, EtOH, H_2O.

Scheme 3



9-benzylpurine (**4**),[11] was prepared by hydrolysis of both esters with sodium hydroxide (THF/EtOH/H_2O, 25 °C, 1 h) followed by decarboxylation (AcOH/Ac_2O, 130 °C, 24 h, 55%). Alternatively, **3a** was converted to 9-benzyl-2,6-bis(carbamoyl)purine (**5**) via aminolysis (NH_3/MeOH, 25 °C, 24 h, 99%). Selective functionalization of the 2- or 6-ethoxycarbonyl group can be readily achieved because of the large difference in reactivity between the ester groups. For example, treatment of **3a** with one equivalent of sodium hydroxide followed by decarboxylation gave 9-benzyl-6-ethoxycarbonylpurine (**6**, 65%) with no detectable 9-benzyl-2-ethoxycarbonylpurine or 9-benzylpurine. Aminolysis of **6** under the above-mentioned conditions gave 9-benzyl-6-carbamoylpurine (**7**) in 72% yield. The regioselective modification of the 2-ester group is attributed to the presence of the imidazole ring annulated to the 4- and 5-positions of the pyrimidine nucleus which sterically hinders nucleophilic attack to the 6-ester group. This result is analogous to Boger's early observations[12] that substituents at the 5-position of 2,6-bis(ethoxycarbonyl)pyrimidines provide a steric bias that enables selective reduction of the 2-ester group.

The successful synthesis of purine analogues via **2a** prompted us to investigate the use of 5-amino-1-(β-D-ribofuranosyl)-4-imidazolecarboxylic acid (**2b**)[13] for the synthesis of purine nucleoside analogues. Using similar reaction conditions, the 2,6-diethyl carboxylate ester of purine riboside (**3b**) was prepared in good yield and without significant cleavage of the glycosidic bond (Table 1, entries 7−11). Reaction times, however, were longer compared with those of **2a** possibly because of the insolubility of the potassium salt of **2b** in DMF. The utility of this reaction was further demonstrated by the one-step synthesis of nebularine[14] from reaction of 1,3,5-triazine (**8**)[15] with the unprotected **2c** and the triacetyl-protected nebularine (**9**)[16] from reaction of **8** with **2b** (Scheme 3). Efficient synthesis of nebularine and its congeners is of interest[17] because of the unique biological activity predicted[2] and observed for these compounds.[18] However, few nebularine analogues with carbon substituents at either the 2- or 6-positions are described.[5b] Earlier efforts synthesized 6-substituted purine analogues using either Eschenmoser's sulfide contraction reaction[19] or a carbanion substitution reaction with 6-methylsulfonyl purine nucleosides.[5a] More recently, analogues with carbon substituents were prepared from 6-halopurines via palladium-catalyzed coupling reactions.[20] Our results suggest that a variety of purine and purine nucleoside analogues can be prepared using an efficient and versatile strategy entailing 5-amino-4-imidazolecarboxylic acids and 1,3,5-triazines in a tandem decarboxylation/Diels−Alder reaction.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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