ORGANIC LETTERS

2003
Vol. 5, No. 20
3639−3640

Synthesis of a Transition State Analogue Inhibitor of Purine Nucleoside Phosphorylase via the Mannich Reaction

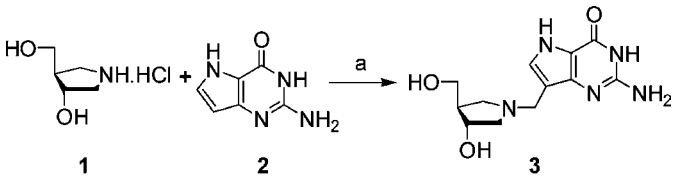
Gary B. Evans,*,† Richard H. Furneaux,† Peter C. Tyler,† and Vern L. Schramm‡

Carbohydrate Chemistry Team, Industrial Research, P.O. Box 31310, Lower Hutt, New Zealand, and Biochemistry Department, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Avenue, Bronx, New York 10461

g.evans@irl.cri.nz

Received July 13, 2003

ABSTRACT

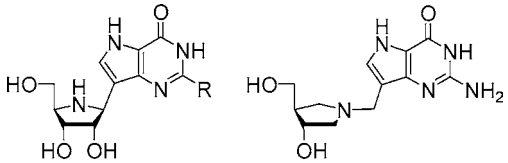


Conditions: (a) 30% Aqueous formaldehyde, NaOAc, H_2O, 95°C.

The expeditious convergent synthesis of the potent human purine nucleoside phosphorylase inhibitor DADMe-Immucillin-G (3) was achieved via the Mannich reaction. The Mannich chemistry of a series of deazapurines and amine hydrochlorides was also investigated.

Immucillin-H and Immucillin-G (Figure 1) are potent transition state analogue inhibitors of human purine nucleoside phosphorylase (PNP),[1−3] a therapeutic target for the control of T-cell proliferative disorders such as T-cell lymphomas, organ transplant rejection, and rheumatoid arthritis.[4,5] Immucillin-H has been readily synthesized via a convergent synthesis and is currently in Phase I/II clinical trials (as BCX-1777) for the treatment of T-cell leukemia.[6] Recently, we reported a new series of transition state analogues[7] which represent a second-generation structural class of Immucillins with greater binding affinities than the current clinical candidate.[8,9] The most potent second-generation inhibitor, DADMe-Immucillin-G, was eight times more active but was prepared by a rather lengthy process.[8] Given the improved potency of DADMe-Immucillin-G against human PNP, there is considerable interest in simplifying its synthesis.

The Mannich reaction provides an extremely versatile method for the concomitant formation of carbon−carbon and carbon−nitrogen bonds.[10] Modnikova et al. reported use of



R = H Immucillin-H
R = NH_2 Immucillin-G

DADMe-Immucillin-G

Figure 1. The immucillins.

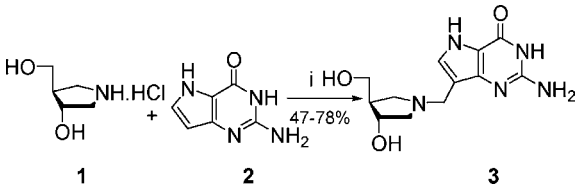
† Carbohydrate Chemistry Team, Industrial Research.
‡ Albert Einstein College of Medicine of Yeshiva University.

(1) Kline, P. C.; Schramm, V. L. *Biochemistry* **1995**, *34*, 1153.
(2) Miles, R. W.; Tyler, P. C.; Furneaux, R. H.; Bagdassarian, C. K.; Schramm, V. L. *Biochemistry* **1998**, *37*, 8615.
(3) Sauve, A. A.; Cahill, S. M.; Basso, L. A.; Zech, S. G.; Lewandowicz, A.; Santos, D. S.; Grubmeyer, C.; Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; McDermott, A.; Girvan, M. E.; Schramm, V. L. *Biochemistry* **2003**, *42*, 5694.
(4) Montgomery, J. A. *Med. Res. Rev.* **1993**, *13*, 209.
(5) Sircar, J. C.; Gilbertsen, R. B. *Drugs Future* **1988**, *13*, 653.
(6) Bantia, S.; Ananth, S. L.; Parker, C. D.; Horn, L. L.; Upshaw, R. *Int. Immunopharmacol.* **2003**, *3*, 879.

10.1021/ol035293q CCC: $25.00
Published on Web 08/29/2003

the Mannich reaction in the synthesis of a series of aminomethyl derivatives of 9-deazahypoxanthine.[11] These 9-aminomethyl-9-deazahypoxanthines share obvious structural features with DADMe-Immucillin-G (**3**) and consequently we decided to test whether such Mannich chemistry could be used to synthesize **3** (Scheme 1). Such an approach

Scheme 1. Synthesis of DADMe-Immucillin-G (**3**)[a]



1 2 3

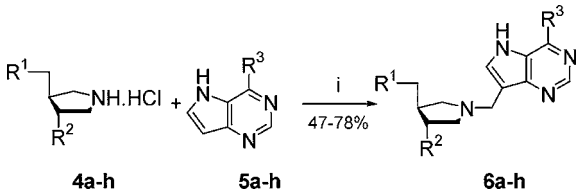
[a] Conditions: (i) 30% aqueous formaldehyde, NaOAc, H_2O, 95 °C, 12 h, 57%.

would provide direct and general access to a variety of substituted DADMe-Immucillins.

The hydrochloride salt of (3*R*,4*R*)-3-hydroxy-4-(hydroxymethyl)pyrrolidine (**1**) was synthesized from D-xylose in 13 steps[8,12] and 9-deazaguanine (**2**) was prepared in three steps from the commercially available 2-amino-6-methylpyrimidin-4-one.[13] The amine hydrochloride **1** in water buffered with sodium acetate was treated with aqueous formaldehyde and compound **2** (Scheme 1) at 95 °C. After 12 h the reaction was adsorbed onto silica gel followed by chromatography affording DADMe-Immucillin-G (**3**) as the acetic acid salt in good yield. After conversion to the HCl salt and ^{1}H and ^{13}C NMR spectra analysis, the compound was found to be identical in all respects with that previously reported.[8]

To investigate the versatility of this reaction, a variety of deazapurines were synthesized and reacted with derivatives of (3*R*,4*R*)-3-hydroxy-4-(hydroxymethyl)pyrrolidine (**1**) (Scheme 2) following a procedure similar to that described above.

Scheme 2. Synthesis of DADMe-Immucillins[a]



4a-h **5a-h** **6a-h**

[a] Conditions: (i) 30% aqueous formaldehyde, NaOAc, H_2O, 95 °C.

Reaction times and yields varied depending on the deazapurine and these results are summarized in Table 1.

Table 1. Synthesis of DADMe-Immucillins

		substituents			
entry	time (h)	R^1	R^2	R^3	yield of **6** (%)
a	16	OH	OH	OH	47
b	1	OH	OH	NH_2	65
c	1	SBn	OH	NH_2	72
d	1	SPhpCl	OH	NH_2	72
e	3	OH	OH	Cl	78
f	3	OH	OH	N_3	65
g	1	OAc	OAc	NH_2	49

In summary, the Mannich reaction has been shown to afford convenient access to DADMe-Immucillin-G, a potent transition state analogue inhibitor of Human PNP. Its general synthetic utility with a variety of deazapurines has been demonstrated.

Acknowledgment. The authors wish to acknowledge the support of the NIH through research grant GM41916 and the New Zealand Foundation for Research, Science & Technology.

Supporting Information Available: Experimental procedures for the synthesis of **3** and **6a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035293Q

(7) Lewandowicz, A.; Shi, W.; Evans, G. B.; Tyler, P. C.; Furneaux, R. H.; Basso, L. A.; Santos, D. S.; Almo, S. C.; Schramm, V. L. *Biochemistry* **2003**, *42*, 6057.
(8) Evans, G. B.; Furneaux, R. H.; Lewandowicz, A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *278*, 31465.
(9) Lewandowicz, A.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Schramm, V. L. *J. Biol. Chem.* **2003**, *278*, 31465.
(10) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1.
(11) Modnikova, G. A.; Sizova, O. S.; Novitskii, K. Y.; Ryabokon, N. A.; Vlasova, T. M.; Chernov, V. A. *Khim.-Farm. Zh.* **1982**, *16*, 548.
(12) Filichev, V. V.; Brandt, M.; Pedersen, E. B. *Carbohydr. Res.* **2001**, *333*, 115.
(13) Furneaux, R. H.; Tyler, P. C. *J. Org. Chem.* **1999**, *64*, 8411.