Synthesis of potential inhibitors of GTP-cyclohydrolase I: an efficient synthesis of 8-substituted 7-deazaguanines

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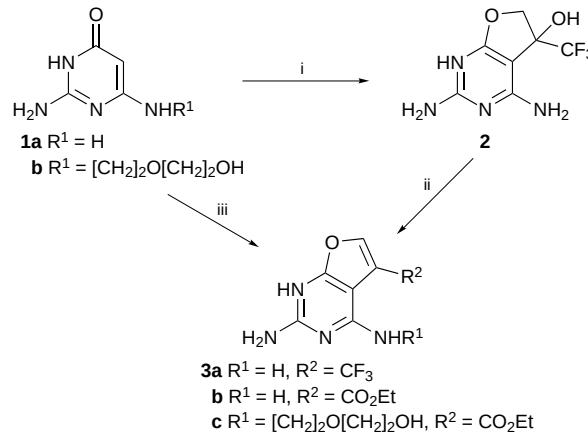
A novel two step synthesis of 8-substituted 7-deazaguanines is developed and involves the regioselective alkylation of pyrimidinones 1a and 1b with nitrosoalkenes derived from α-halo oximes followed by transoximation to give the 7-deazaguanines 6a–d in 41–65% overall yield

GTP-cyclohydrolase I catalyses the conversion of GTP into dihydroneopterin triphosphate and involves the opening of the imidazole and ribose rings with the loss of C-8 as formate, and Amadori rearrangement of the ribose portion.[1] Very little is known about the elementary steps of the process but the mechanism has been the subject of some discussion.[2–4] While there is consensus that the first step of the sequence involves attack of a nucleophile at C-8, the nature of the nucleophile (H_2O, cys_{110}-S-S-cys_{181} or his) is still the subject of speculation. In order to address the issue of the nature of the nucleophile we wished to prepare potential inhibitors of GTP cyclohydrolase that had been designed to give stable tetrahedral nucleophilic C-8 addition intermediates. In this context, we proposed that 7-deazaguanines {pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-ones} would not undergo subsequent imidazole ring opening and that by locating a strongly electron-withdrawing substituent at C-8, would afford stable tetrahedral intermediates.

Linear syntheses of 8-alkyl-7-deazaguanines have been reported involving the condensation of substituted ethyl cyanoacetate derivatives with guanidine hydrochloride.[5] This approach has been exploited by Seela and Chen for the synthesis of 8-methyl-7-deazaguanosine which was used in the synthesis of modified DNA oligionucleotides.[6] More direct convergent syntheses of 8-alkyl-7-deazaguanines have been carried out by the condensation of 2,6-diaminopyrimidin-4(3*H*)-ones with α-halo carbonyl compounds.[7] This latter approach suffers from problems of regiochemistry in that either 7-deazaguanines or furo[2,3-*d*]pyrimidines or mixtures of both are produced. In view of the fact that linear syntheses were unattractively long we carried out an initial study of the viability of the condensation routes involving α-halo ketones carrying α-electron-withdrawing groups. Thus, reaction of 2,6-diaminopyrimidin-4(3*H*)-one **1a** with 3-bromo-1,1,1-trifluoropropanone afforded, exclusively, the dihydrofuro[2,3-*d*]pyrimidine **2** in 67% yield (Scheme 1). The dihydrofuro[2,3-*d*]pyrimidine **2** could be dehydrated to the corresponding furo[2,3-*d*]pyrimidine **3a** (71% from **1a**) by treatment with concentrated sulfuric acid. Similarly, condensation of ethyl bromopyruvate with pyrimidinones **1a** or **1b** yielded the furo[2,3-*d*]pyrimidines **3b** and **3c**, directly, in 92 and 33% yields, respectively.

The failure of pyrimidinones **1a** and **1b** to yield 7-deazaguanines on reaction with α-halo ketones led to an evaluation of alternative novel routes to such species. In this context, nitrosoalkenes, generated *in situ* from α-halo oximes, are powerful electrophiles that have been shown to react with carbon nucleophiles at the β-carbon.[8] Given this reactivity pattern of nitrosoalkenes we anticipated that reaction with 2,6-diaminopyrimidin-4(3*H*)-one would provide short convergent syntheses of 8-substituted 7-deazaguanines. Accordingly, 3-bromo-1,1,1-trifluoropropanone oxime **4a** reacted with excess pyrimidinone **1a** in DMF to afford the C-5 alkylated pyrimidinone **5a** in 80% yield (entry 1, Table 1 and Scheme 2). Similarly, the oximes **4b**–**d** were treated with pyrimidinone **1a** in DMF in the presence of a base (excess **1a**, Na_2CO_3 or Et_3N) to give the C-5 alkylated pyrimidinones **5c** (57–79%, entries 5–7), **5e**‡ (38%, entry 10) and **5f** (47%, entry 11), respectively. The pyrimidinone **1b** carrying the 2-(2-aminoethoxy)ethanol side chain was also reacted with the oximes **4a** and **4b** in the presence of triethylamine or potassium carbonate to afford the C-5 alkylated pyrimidinones **5b** (43–58%, entries 3 and 4) and **5d** (47–61%, entries 8 and 9), respectively. In the syntheses of the pyrimidinones **5a**–**f** the only products were those derived from nucleophilic substitution of the C-5 position of pyrimidinones **1a** and **1b** at the α-carbon of the halo oximes **4a**–**d**, thus substantiating the potential of this method.

With an efficient method for the syntheses of pyrimidinones **5** with a C-5 alkyl oxime group we turned our attention to the cyclisation of these compounds to give 8-substituted 7-deaza-



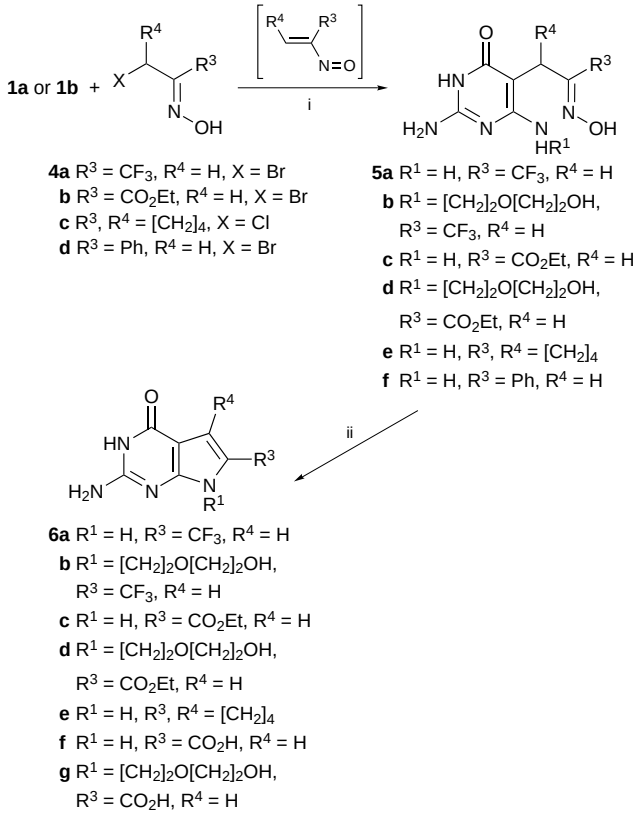
Scheme 1 *Reagents and conditions*: i, 3-bromo-1,1,1-trifluoropropanone, DMF, 60 °C; ii, C H_2SO_4; iii, ethyl bromopyruvate, DMF, 60 °C

Table 1 Synthesis of alkylated pyrimidinones **5** and cyclisation to 7-deazaguanines **6**

Entry	Base	Product **5**	Yield of **5** (%)	Aldehyde	Product **6**	Yield of **6** (%)
1	**1a**	**a**	80	PhCHO	**a**	81
2	NaOAc[a]	**a**	42	[b]	**a**	43
3	Et_3N	**b**	58	PhCHO	**b**	71
4	Na_2CO_3	**b**	43	EtCHO	**b**	52
5	**1a**	**c**	79	PhCHO	**c**	60
6	Na_2CO_3	**c**	63	MeCHO[c]	**c**	30
7	Et_3N	**c**	57	—	—	—
8	Et_3N	**d**	61	MeCHO[c]	**d**	71
9	Na_2CO_3	**d**	47	PhCHO	**d**	49
10	Na_2CO_3[d]	**e**	38[e]	—	—	—
11	Et_3N	**f**	47	PhCHO or MeCHO[c]	decomp.	0

[a] Reaction carried out in MeOH at 50–60 °C, 5 min. [b] Reaction carried out in DMF at 100–120 °C without aldehyde. [c] At room temperature. [d] At 60 °C for 96 h. [e] 64 : 36 Mixture of **5e** and **6e**.

guanines **6**. Thermal cyclisation of the trifluoro compound **5a** by heating in DMF at 100–120 °C gave the 8-trifluoromethyl-7-deazaguanine **6a** in 43% yield (Table 1, entry 2).[1] Unfortunately, this thermal procedure was not successful for the remaining oximes as slow decomposition was observed. An alternative method of transoximation involving heating the C-5 alkyl oximes **6a**–**d** with benzaldehyde in aqueous ethanol with a catalytic quantity of hydrochloric acid proved highly successful to afford the 8-substituted 7-deazaguanines **6a** (81%, entry 1), **6b** (71%, entry 3), **6c** (60%, entry 5) and **6d** (49%). The more reactive C-5 alkyl oximes **5b,c** and **d** could also be cyclised to the deazaguanines **6b** (52%, entry 4), **6c** (30%, entry 6) and **6d** (71%, entry 8) using the transoximation procedure with propanal or acetaldeyde. The phenyl substituted oxime **5f** failed to cyclise but underwent decomposition under a variety of conditions.



Scheme 2 *Reagents and conditions*: i, DMF, base (see Table 1), room temp. 4–72 h; ii, EtOH–H_2O, benzaldehyde or acetaldehyde, cat. HCl, heat, 24–72 h

The 8-carboxy-7-deazaguanines **6f** (85%) and **6g** (83%) were also available by lithium hydroxide saponification of the respective esters **6c** and **6d**. Investigation of the 8-substituted 7-deazaguanines **6a**–**d** and **6f,g** and their triphosphorylated derivatives as inhibitors of GTP cyclohydrolase I is currently underway and these results will be reported in due course.

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Footnotes

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‡ 64 : 36 mixture of oxime **5e** and 7-deazaguanine **6e**.

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