One or Two-Step Bohlmann–Rahtz Heteroannulation of 6-Aminouracil Derivatives for the Synthesis of Pyrido[2,3-*d*]pyrimidines

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Abstract: The Michael addition-cyclodehydration of a 6-aminouracil and alkynone proceeds to give 5-deazapterin derivatives with total control of regiochemistry. This simple and facile cyclocondensation process is catalyzed by zinc(II) bromide or ytterbium(III) trifluoromethanesulfonate at 110 °C, providing the heteroannulated products in up to 94% yield.

Key words: pyridopyrimidines, uracil derivatives, Bohlmann–Rahtz heteroannulation, heterocycles, Lewis acids

The versatility of uracil derivatives for the synthesis of nitrogen-containing heteroaromatic species of biological importance has been well documented in the literature.[1] Pyrazolopyridines,[2] pyrimidopyrimidines,[3] pyridopurines,[4] pyrazolopyrimidines[5] and xanthine derivatives[6] have all been prepared by the functionalization of these important heterocyclic building blocks, whose structures are interesting in their own right as biologically-active pyrimidine nucleosides.[7] In recent years, interest in pyrido[2,3-*d*]pyrimidine derivatives has increased dramatically as the structural relationship between 5-deazapterins and the vitamin folic acid,[8] with its essential role in the prevention of disease,[9] has been recognised. The diverse range of biological properties and highly species-specific tissue responses elicited by compounds containing the 5-deazapterin motif have been well documented.[10] However, although pyrido[2,3-*d*]pyrimidines have been prepared from uracil derivatives in the past, many of these reactions suffer from low yields, use expensive or not readily available starting materials and exhibit limited substrate tolerance.[11] This paper describes the facile synthesis of a number of 5-deazapterins from commercially available 6-aminouracil derivatives using a simple one-pot Bohlmann–Rahtz heteroannulation procedure.

The two-step Bohlmann–Rahtz reaction,[12] which proceeds by Michael addition-cyclodehydration of an enamine and alkynone, was first reported in 1957 for the synthesis of simple pyridines but has seen very little use since that date.[13] Following our discovery of a facile one-pot heteroannulation procedure, catalysed by acetic acid, amberlyst 15 ion exchange resin[14] or a Lewis acid,[15] we developed new conditions for the synthesis of 5-deazapterin **2** from 2,4-diaminopyrimidinone **1** (Scheme 1).[16]

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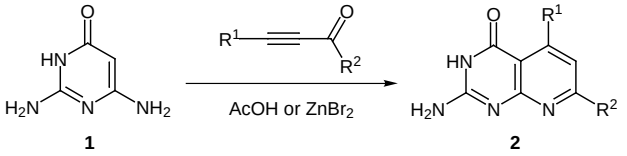
Replacing pyrimidinone **1** with a range of different uracil derivatives will not only increase the scope of this hitherto poorly understood reaction, but it will expand the synthetic versatility of uracil derivatives and provide diversity in the nature of the heterocyclic motif in a targeted library of potential folate antagonists that could be elaborated from these compounds in subsequent studies.

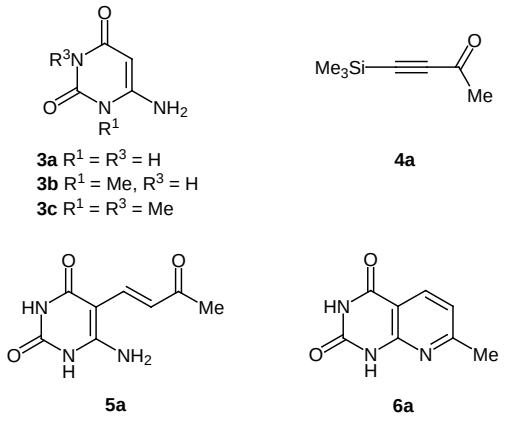


1 **2**

Scheme 1

Judging by the poor reactivity exhibited by 6-aminouracil derivatives in related cyclocondensation reactions,[11] it remained to be established whether the Bohlmann–Rahtz heteroannulation of these substrates would proceed at all. To this end, a solution of 6-aminouracil **3a** and 4-(trimethylsilyl)but-3-yn-2-one (**4a**) in DMSO was stirred at room temperature. However, after 72 hours, ^{1}H NMR spectroscopic analysis established that no reaction had occurred. When the procedure was repeated at 110 °C using 3 equivalents of alkynone **4a**, Michael addition product **5a** (Figure) was generated in 97% isolated yield after addition of water and precipitation of the product. The cyclodehydration of **5a** failed according to standard conditions (returning unreacted starting material **5a**), even at temperatures of 180 °C, but when a solution of this intermediate in DMSO was stirred at 110 °C overnight in the presence of zinc(II) bromide or ytterbium(III) triflate, the heteroannulated product pyridine **6a** (Figure) was generated in quantitative yield. This new modified two-step procedure demonstrated both the advantage of our new Lewis acid catalysed cyclodehydration conditions and the poor/unpredictable reactivity of 6-aminouracil derivatives (lacking 1,3-substitution) in heteroannulation reactions.

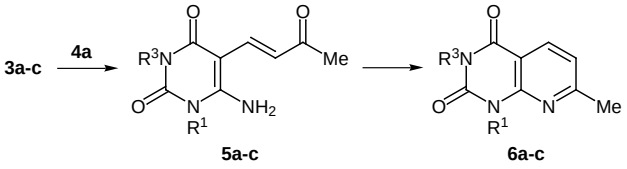
Following the success of our two-step modified Bohlmann–Rahtz reaction, it remained to be seen if a one-pot heteroannulation procedure could be facilitated in the presence of a Lewis acid catalyst. A solution of 6-aminouracil **3a** and one equivalent of 4-(trimethylsilyl)but-3-yn-2-one (**4a**) in DMSO was stirred at 110 °C for 72 hours in the presence of either zinc(II) bromide[17] or ytterbium(III) triflate (20 mol%) to give 5-deazapterin **6a** as the sole product in 60% or 52% yield, respectively. Spontaneous



Figure

desilylation occurred throughout the course of the reaction. Although the yield in this case was lower than for the two-step process, the simplicity of the facile one-pot Michael addition-cyclodehydration reaction made it an attractive alternative that warranted further study.

With successful conditions established for the one- and two-step heteroannulation of 6-aminouracil, it remained to explore whether these conditions were appropriate for a range of different uracil derivatives. 6-Amino-1-methyl- and 6-amino-1,3-dimethyluracil, **3b** and **3c** respectively, were stirred for 72 h with one equivalent of 4-(trimethylsilyl)but-3-yn-2-one (**4a**) in DMSO either in the presence or absence of a Lewis acid. Although uracil **3b** gave heteroannulation product **6b** in excellent yield (Scheme 2) under Lewis acid catalysed conditions at elevated temperatures, 1,3-dimethyluracil **3c** yielded the Michael addition product **5c** at room temperature and cyclodehydration could not be completed under any of the conditions investigated (Table 1).



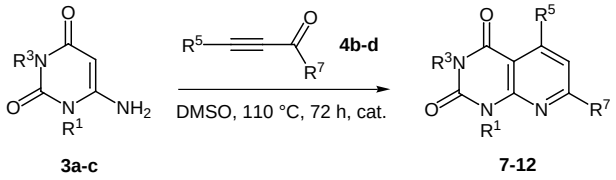
Scheme 2

To examine further the scope of the heteroannulation reaction, uracils **3a**–**c** were treated with different 4-substituted alkynones **4b**–**d** in DMSO at 110 °C for 72 hours in the presence of a Lewis acid catalyst (Scheme 3). When ethyl propynoate **4b** was reacted with uracil **3a,b** (entries 1–4, Table 2) spontaneous desilylation accompanied Michael addition-cyclodehydration to generate pyridopyrimidine **7**,**8** (R^5 = H). When these reactions were conducted either in the absence of a Lewis acid (entry 2) or at room temperature (entry 3) the efficiency of reaction was reduced. The optimum experimental conditions reacted uracil **3a**–**c** with alkynone **4b**–**d** at 110 °C in the presence of zinc(II) bromide for 72 h to give product **7**–**12** in good yield (60–75%). Replacing zinc(II) bromide with ytterbium(III) triflate (entries 6 and 10) always caused a small reduction in the efficiency of the cyclocondensation process, but offered some improvement over the uncatalysed reaction (entry 8, 42% yield) which always proceeded in a low yield. It was apparent that the new Lewis acid catal-

Table 1 Heteroannulation Reactions of Uracil Derivatives **3a–c**

Entry	**3**	R^1	R^3	Temp. °C	Lewis acid	Compound	Yield[a] %
1	**3a**	H	H	110	None	**5a**	97
2	**3a**	H	H	110	$ZnBr_2$	**6a**	60
3	**3b**	Me	H	110	None	**6b**	74
4	**3b**	Me	H	110	$ZnBr_2$	**6b**	94
5	**3b**	Me	H	110	$Yb(OTf)_3$	**6b**	90
6[b]	**3c**	Me	Me	r.t.	$ZnBr_2$	**5c**	53
7[b]	**3c**	Me	Me	r.t.	$Yb(OTf)_3$	**5c**	54

[a] Isolated yield.
[b] Reactions were run over 96 hours.



Scheme 3

Table 2 Reaction of Uracil **3a–c** with 4-Substituted Alkynone **4b–d**

Entry	**3**	**4**	R^5	R^7	Lewis acid	Compound	Yield[a] %
1	**3a**	**4b**	$SiMe_3$	CO_2Et	$ZnBr_2$	**7**	60[b]
2	**3b**	**4b**	$SiMe_3$	CO_2Et	None	**8**	43[b]
3	**3b**	**4b**	$SiMe_3$	CO_2Et	$ZnBr_2$	**8**	39[b,c]
4	**3b**	**4b**	$SiMe_3$	CO_2Et	$ZnBr_2$	**8**	65[b]
5	**3b**	**4c**	Et	Me	$ZnBr_2$	**9**	71
6	**3b**	**4c**	Et	Me	$Yb(OTf)_3$	**9**	68
7	**3b**	**4d**	Ph	Me	$ZnBr_2$	**10**	62
8	**3c**	**4c**	Et	Me	None	**11**	42
9	**3c**	**4c**	Et	Me	$ZnBr_2$	**11**	75
10	**3c**	**4c**	Et	Me	$Yb(OTf)_3$	**11**	72
11	**3c**	**4d**	Ph	Me	$ZnBr_2$	**12**	72

[a] Isolated yield;
[b] Spontaneous disilylation accompanied the reaction (R^5 = H).
[c] Reaction was carried out at room temperature.

ysed cyclocondensation reaction was appropriate for a number of different alkynones and a range of uracil derivatives **3a–c**.

In conclusion the zinc(II) bromide catalysed heteroannulation, for the synthesis of pyrido[2,3-*d*]pyrimidines **6–12** in up to 94% yield, proceeds by cyclocondensation of a 6-aminouracil **3a–c** and alkynone **4a–d** in a single preparative step using a simple and facile experimental procedure. Work is now underway to apply this new general method to the synthesis of a number of biologically active heterocycles based upon modified uracil derivatives for the preparation of diverse 5-deazapterin libraries as inhibitors of folate-dependent enzymes.

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(17) *In a typical experimental procedure*, 4-(trimethylsilyl)but-3-yn-2-one **4a** (0.34 g, 2.4 mmol) was added to a stirred solution of 6-aminouracil **3a** (0.31 g, 2.4 mmol) and zinc(II) bromide (55 mg, 0.24 mmol) in DMSO (5 mL). The mixture was stirred at 110 °C for 72 hours, allowed to cool and water (30 mL) was added. The precipitated solid was washed with water and dried to give **6a** (0.26 g, 60%) as a pale yellow solid, mp >260 °C (decomp.) (Found: C, 54.66; H, 4.27; N, 23.56. Calc. for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72%) (Found MH^+, 178.0619. $C_8H_7N_3O_2$ requires 178.0616); IR(nujol)/cm^{-1}: 3310, 3120, 1705, 1695; ^{1}H NMR (d_6-DMSO, 400 MHz) δ(ppm) 11.41 (1 H, s, NH), 11.12 (1 H, s, NH), 7.96 (1 H, d, *J* = 7.9 Hz, 5-H), 6.92 (1 H, d, *J* = 7.9 Hz, 6-H), 2.33 (3 H, s, Me); ^{13}C NMR (d_6-DMSO, 100 MHz) δ (ppm) 163.9 (C), 161.8 (C), 151.5 (C), 149.9 (C), 135.9 (CH), 118.1 (CH), 106.8 (C), 23.8 (Me); *m/z* (CI) 178 (MH^+, 24%).