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A new and highly expedient synthesis of pyrido[2,3-*d*]pyrimidines

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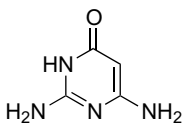
Abstract—2,6-Diaminopyrimidin-4-one was reacted with a number of butynones in a range of different solvents at room temperature or 60°C. The Michael addition and subsequent cyclodehydration provided a new method for the synthesis of pyrido[2,3-*d*]pyrimidines in excellent yield without need for further purification. This new facile procedure lends itself well to combinatorial methods, providing the target heterocycle in one or two steps with total regiocontrol.

For small organic molecules, simple nitrogen-containing heterocycles receive a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Of these heterocycles, the synthesis, reactions and biological activities of pyridine containing molecules stands as an ever-expanding area of research in heteroaromatic chemistry and this structural motif appears in a large number of pharmaceutical agents and natural products.[1] In contrast, pyrido[2,3-*d*]pyrimidine heterocycles (also known as 5-deazapteridines) have received much less attention in the literature in spite of their structural relationship to both pyridines and pterins, the latter isolated from the wing pigments of European butterflies as long ago as the nineteenth century.[2] Interest in pyrido[2,3-*d*]pyrimidine derivatives has increased dramatically in recent years, based upon a diverse range of biological properties and the potential for folate antagonists[3] to elicit highly species-specific responses as antitumour,[4] antibacterial,[5] anti-inflammatory[6] and insecticidal agents.[7]

To continue our interest in the synthesis of simple nitrogen-containing heterocycles,[8,9] we set out to develop a new method for the synthesis of highly-functionalised pyrido[2,3-*d*]pyrimidine heterocycles that would be appropriate for the rapid assembly of a targeted library of folate inhibitors. Central to our approach was the need to develop a novel method, using readily available starting materials and simple experimental procedures, for the rapid synthesis of structurally diverse heterocycles with complete control of regiochemistry. This paper describes a new and highly efficient method for the preparation of pyrido[2,3-*d*]pyrimidines that exhibits all of these features.

A number of methods have been reported previously for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives based upon condensation reactions and pyridine annelation reactions, both in solution[10] and on solid phase.[11] Following the success of our modified Bohlmann–Rahtz[12] conditions for the synthesis of pyridines,[9] it was proposed that a similar Michael addition–cyclodehydration strategy should be successful for the synthesis of highly functionalised 5-deazapteridine heterocycles. Approaches that employ 6-aminouracil derivatives as the enamine component, in a Michael-[13] or Hantzsch-type condensation,[14] have been reported for the synthesis of the reduced form of the target heterocycle in a highly regioselective manner. Our strategy would offer a number of advantages over existing methodology, employing readily-available alkynones[15]



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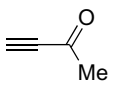

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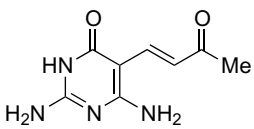

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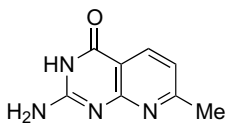

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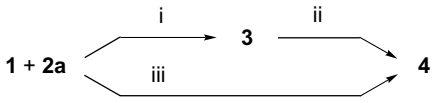
as Michael acceptors and thus obviating the need for subsequent oxidation, to provide pyrido[2,3-*d*]pyrimidine derivatives directly without need for purification and with total regiochemical control.

In order to assess the validity of this approach, 2,6-diaminopyrimidin-4-one **1** was treated with one equivalent of but-3-yn-2-one **2a** in a range of solvents at 50°C according to standard conditions for Bohlmann–Rahtz pyridine synthesis.[12] After 72 h, the solvent was evaporated in vacuo, or water was added to precipitate the product, and the resultant solid analysed by ^{1}H NMR spectroscopy (Table 1). It was noteworthy that the choice of solvent had a large influence upon the course of the reaction. In acetone, acetonitrile or 1,2-dimethoxyethane (DME) only a trace of the Michael addition product **3** was formed. The predominance of unreacted starting materials was attributed to the insolubility of pyrimidinone **1** in the reaction solvent. The use of ethanol, methanol or dimethyl sulfoxide (DMSO) as solvent overcame these difficulties and facilitated the *C*-alkylation of pyrimidinone **1** to give (3-oxobut-1-enyl)pyrimidine **3** as a single regioisomer in good to excellent yield. However, when reactions were conducted in acetic acid or *N*,*N*-dimethylformamide, the solubility behaviour of the solid that was isolated was very different, being totally insoluble in nearly all conventional organic solvents. ^{1}H NMR spectroscopic analysis in deuterated trifluoroacetic acid revealed that the identity of the product, in both instances, was pyrido[2,3-*d*]pyrimidine **4**, the poor solubility being characteristic of pteridine and deazapteridine derivatives.[3a,16]

In order to confirm the structural identity of pyrido[2,3-*d*]pyrimidine **4**, and verify the regiochemistry of the reactions conducted in acetic acid and DMF, (3-oxobut-1-enyl)pyrimidine **3** was heated to 180°C to facilitate Bohlmann–Rahtz cyclodehydration according to standard conditions.[12] The resultant solid, generated in quantitative yield, was identical to pyrido[2,3-*d*]pyrimidine **4** in every respect, displaying the same solubility profile and spectroscopic properties as the material isolated by the previous method. This analysis indicated that both the one and two-step method for pyrido[2,3-*d*]pyrimidine synthesis proceeded with total regiocontrol (Scheme 1) and in 72–95% yield, depending upon choice of solvent, by *C*-alkylation and subsequent cyclodehydration of Michael addition product **3**.

Table 1. Reaction of pyrimidinone **1** and butynone **2a** at 50°C

Solvent	Compound (yield%)
Acetone	**1** (98), **3** (trace)
Acetonitrile	**1** (97), **3** (trace)
1,2-Dimethoxyethane	**1** (99), **3** (trace)
Ethanol	**3** (95)
Dimethyl sulfoxide	**3** (72)
Methanol	**3** (91)
Acetic acid	**4** (90)
N,*N*-Dimethylformamide	**4** (92)



Scheme 1. *Reagents and conditions*: (i) EtOH, MeOH or DMSO, 50°C, 72 h, 72–95%; (ii) 180°C, 100%; (iii) AcOH or DMF, 50°C, 72 h, 90–92%.

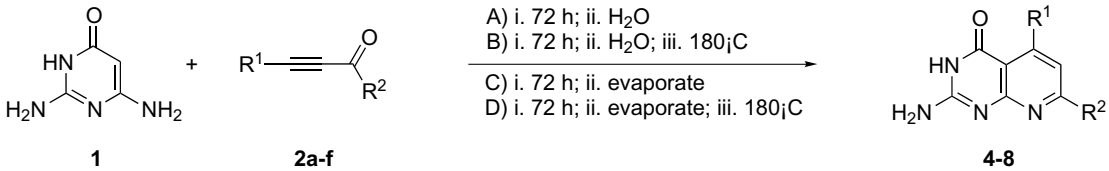
Although the course of the reaction conducted in acetic acid was easy to rationalise, based upon previous findings within the group,[9] the isolation of pyridopyrimidine **4** from the reaction conducted in DMF was somewhat surprising. In most cases the crude yield of this reaction was good, although the presence of a small quantity of impurities was noted (except in the case of DMSO when pyrimidine **3** precipitated as a pure solid following the addition of water). Increasing the number of equivalents of but-3-yn-2-one **2a** did not improve the purity of the product or the efficiency of the reaction and so alternative conditions for conjugate addition were sought. Stirring one equivalent of 2,6-diaminopyrimidin-4-one **1** with one equivalent of but-3-yn-2-one **2a** in a number of different solvents at room temperature improved the course of this reaction dramatically (Table 2). Under these milder conditions, reactions conducted in acetone, acetonitrile or DME provided only unreacted pyrimidine starting material **1**. In ethanol, methanol or DMSO, (3-oxobut-1-enyl)pyrimidine **3** was generated as a single regioisomer in excellent yield and very high purity (>95%) as determined by ^{1}H NMR spectroscopic analysis. Pyridine annelation could then be facilitated by heating the solid to 180°C to affect complete conversion to pyrido[2,3-*d*]pyrimidine **4**. As before, reactions conducted in acetic acid or DMF resulted in spontaneous cyclodehydration to provide pyridopyrimidine **4** directly in excellent yield and as the only reaction product. Thus, our new approach, based upon a Bohlmann–Rahtz pyridine annelation,[12] had been successful for the synthesis of pyrido[2,3-*d*]pyrimidine **4** by either a one or two-step procedure.

In order to ascertain whether this methodology could be extended to provide a new general route to pyrido[2,3-*d*]pyrimidine derivatives, 2,6-diaminopyrimidin-4-one **1** was treated with a range of 4-substituted alkynones **2a**–**f**[17] at room temperature in acetic acid, ethanol, DMF or DMSO according to the new procedure. It was found that the course of reaction varied

Table 2. Reaction of pyrimidinone **1** and butynone **2a** at room temperature

Solvent	Compound (yield%)
Acetone	**1** (98)
Acetonitrile	**1** (99)
1,2-Dimethoxyethane	**1** (98)
Ethanol	**3** (99)
Dimethyl sulfoxide	**3** (86)
Methanol	**3** (97)
Acetic acid	**4** (98)
N,*N*-Dimethylformamide	**4** (94)

Table 3. Reaction of pyrimidinone **1** and alkynone **2a–f** in different solvents by method A, B, C or D



1 **2a-f** **4-8**

Entry	**2**	R^1	R^2	Solvent	Method	Temperature	Product	R^1	R^2	Yield (%)
1	**2a**	H	Me	DMSO	B	rt	**4**	H	Me	86[a]
2	**2b**	TMS	Me	DMSO	B	rt	**4**	H	Me	96[a,b]
3	**2b**	TMS	Me	DMF	C	60°C	**4**	H	Me	71[a,b]
4	**2b**	TMS	Me	EtOH	D	60°C	**4**	H	Me	96[a,b]
5	**2c**	Et	Me	DMSO	A	rt	**5**	Et	Me	43
6	**2c**	Et	Me	DMSO	A	60°C	**5**	Et	Me	84
7	**2d**	Ph	Me	DMSO	A	rt	**6**	Ph	Me	[c]
8	**2d**	Ph	Me	DMF	C	rt	**6**	Ph	Me	[c]
9	**2d**	Ph	Me	DMSO	A	60°C	**6**	Ph	Me	62
10	**2e**	TMS	CO_2Et	DMSO	A	rt	**7**	H	CO_2Et	[c]
11	**2e**	TMS	CO_2Et	DMSO	B	60°C	**7**	H	CO_2Et	95[a,b]
12	**2e**	TMS	CO_2Et	DMF	C	rt	**7**	H	CO_2Et	[c]
13	**2e**	TMS	CO_2Et	EtOH	C	rt	**7**	H	CO_2Et	[c]
14	**2f**	Ph	CO_2Et	DMSO	A	rt	**8**	Ph	CO_2Et	79

[a] Cyclodehydration was facilitated by heating to 180°C in a two-step process.
[b] Spontaneous desilylation accompanied Michael addition.
[c] Only unreacted pyrimidinone **1** was isolated.

with choice of alkynone and solvent. When reactions were run in acetic acid, in almost all cases, an intractable black tar was produced. Alkynone substitution appeared to slow down the reaction, as evidenced by the presence of starting material after stirring at room temperature for 72 h in DMSO or DMF (Table 3, entries 7, 8, 10 or 12). The only reliable method, that tolerated a wide range of substituents, was to stir pyrimidinone **1** with one equivalent of butynone **2a–f** in DMSO for 72 h at either room temperature or 60°C, followed by addition of water and filtration of the precipitated solid.[18] Using 4-(trimethylsilyl)but-3-yn-2-one **2b** at 60°C, desilylation accompanied Michael addition to generate (3-oxobut-1-enyl)pyrimidine **3** in 96% yield. As before, in cases where cyclodehydration did not occur spontaneously under the reaction conditions, pyridine annelation could then be affected by heating the resultant solid to 180°C to give pyridopyrimidine **4** or **7** in excellent yield (entries 1–4 and 11). In the other experiments that were investigated in DMSO at either room temperature or 60°C (the higher temperature often necessary to facilitate the reaction of substituted butynones), spontaneous cyclodehydration accompanied Michael addition to give pyrido[2,3-*d*]pyrimidine **5–8** in 79–87% isolated yield. The purity of pyridopyrimidines **4–8** prepared by method A or B in DMSO (>95% by ^{1}H NMR) was much higher than similar reactions conducted in either ethanol or DMF and thus the use of this solvent has become our method of choice for the synthesis of these heterocycles.

The Michael addition and subsequent cyclodehydration of 2,6-diaminopyrimidin-4-one and a range of alkynones can generate pyrido[2,3-*d*]pyrimidines in excellent yield (optimum yield for preparation of **4–8** varies between 62 and 98%). This new method is effective in a number of different solvents but is most reliable and versatile in DMSO. The experimental procedure is facile and lends itself well to combinatorial methods, requiring no further purification and providing the target heterocycles in one or two steps with total regiocontrol. Work is now underway to apply this new reaction to the synthesis of a library of pyridopyrimidine derivatives so that their biological properties may be examined and this work will be reported in due course.

Acknowledgements

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References

1. Roth, H. J.; Kleemann, A. In *Pharmaceutical Chemistry. Volume 1: Drug Synthesis*; John Wiley & Sons: New York, 1988.
2. Hopkins, F. G. *Nature* **1889**, *40*, 335; *Nature* **1891**, *45*, 197; *Nature* **1892**, *45*, 581.
3. (a) Taylor, E. C.; Palmer, D. C.; George, T. J.; Fletcher, S. R.; Tseng, C. P.; Harrington, P. J.; Beardsley, G. P. *J. Org. Chem.* **1983**, *48*, 4852; (b) Degraw, J. I.; Christie, P. H.; Colwell, W. T.; Sirotnak, F. M. *J. Med. Chem.* **1992**, *35*, 320.
4. Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327.

5. (a) Matsumoto, J.; Minami, S. *J. Med. Chem.* **1975**, *18*, 74; (b) Suzuki, N. *Chem. Pharm. Bull.* **1980**, *28*, 761; (c) Oakes, V.; Rydon, H. N. *J. Chem. Soc.* **1956**, 4433; (d) DeGraw, J. I.; Kisliuk, R. L.; Gaumont, Y.; Baugh, C. M. *J. Med. Chem.* **1974**, *17*, 470; (e) Zakharov, A. V.; Gavrilov, M. Yu.; Novoselova, G. N.; Vakhrin, M. I.; Konshin, M. E. *Khim-Farm. Zh.* **1996**, *30*, 39.
6. Deyanov, A. B.; Niyazov, R. K.; Nazmetdinov, F. Y.; Syropyatov, B. Y.; Kolla, V. E.; Konshin, M. E. *Khim-Farm. Zh.* **1991**, *25*, 26.
7. Heckler, R. E.; Jourdan, G. P. Eur. Patent 414 386, 1991; *Chem. Abstr.* **1991**, *115*, 71630.
8. Bagley, M. C.; Tovey, J. *Tetrahedron Lett.* **2001**, *41*, 351.
9. Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.
10. Srivastava, P.; Saxena, A. S.; Ram, V. J. *Synthesis* **2000**, 541 and references cited therein.
11. Gordeev, M. F.; Patel, D. V.; Wu, J.; Gordon, E. M. *Tetrahedron Lett.* **1996**, *37*, 4643.
12. Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
13. (a) Youssif, S.; El-Bahaie, S.; Nabih, E. *J. Chem. Res. (S)* **1999**, 112 and references cited therein; (b) Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 568.
14. Kajino, M.; Meguro, K. *Heterocycles* **1990**, *31*, 2153.
15. For related heterocyclisations using alkynyl ketones, see: Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311 and references cited therein.
16. (a) Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1981**, *46*, 1394; (b) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1987**, *52*, 3997 and reference 18 cited therein.
17. But-3-yn-2-one **2a**, 4-phenylbut-3-yn-2-one **2d**, 4-(trimethylsilyl)but-3-yn-2-one **2b** and hex-3-yn-2-one **2c** were commercially available. Ethyl 2-oxo-4-phenylbut-3-ynoate ($R^1=Ph$, $R^2=CO_2Et$) **2f** and ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate ($R^1=TMS$, $R^2=CO_2Et$) **2e** were prepared by the addition of the corresponding lithium acetylide to the Weinreb amide, see: Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763.
18. In a typical procedure, 4-(trimethylsilyl)but-3-yn-2-one **2b** (0.31 ml, 0.26 g) was added to a stirred solution of 2,4-diamino-6-hydroxypyrimidine **1** (0.24 g) in DMSO (5 ml). The mixture was stirred for 72 h, water (30 ml) was added and the precipitated solid was filtered, washed with water and dried to give *E*-2,4-diamino-5-(3-oxobut-1-enyl)pyrimidin-6-one **3** (0.35 g) as an off-white solid. The solid was heated at 180°C for 4 h and allowed to cool to give 2-amino-7-methyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one **4** (0.32 g, 95%) as a pale yellow solid, mp >330°C (decomp.) (found MH^+, 177.0776. $C_8H_9N_4O$ requires 177.0776); ν_{max} (Nujol)/cm^{-1} 3248, 3198, 1666, 1581, 1294, 1173, 1137, 879, 786, 722; ^1H NMR (CF_3CO_2D, 400 MHz) δ (ppm) 9.52 (1 H, d, *J* 8.1, 5-H), 8.09 (1 H, d, *J* 8.1, 6-H), 3.45 (3 H, s, Me); ^{13}C NMR (CF_3CO_2D, 100 MHz) δ (ppm) 161.6 (C), 156.4 (C), 154.6 (C), 147.3 (C), 127.0 (C), 121.8 (CH), 113.4 (CH), 20.6 (Me); *m*/*z* 177 (MH^+, 91%).