Tetrahedron 65 (2009) 9604–9608

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An expedient approach for the synthesis of pyrrolo[3,2-*d*]pyrimidines (9-deazaxanthines) and furo[3,2-*d*]pyrimidine via radical cyclization

K.C. Majumdar *, Shovan Mondal

Department of Chemistry, University of Kalyani, Kalyani 741235, West Bengal, India

ARTICLE INFO

Article history:
Received 29 August 2009
Received in revised form
14 September 2009
Accepted 15 September 2009
Available online 18 September 2009

Keywords:
Uracil
Aza-Claisen rearrangement
Radical cyclization
9-Deazaxanthines

ABSTRACT

A new efficient route for the synthesis of substituted 9-deazaxanthines in excellent yields via aza-Claisen rearrangement followed by radical cyclization has been achieved. This methodology has also been applied to the synthesis of furo[3,2-*d*]pyrimidine.

1. Introduction

Pyrimidines, being an integral part of DNA and RNA, exhibit diverse pharmacological properties as effective bactericides, fungicides, viricides, insecticides, and medicides.[1–3] Particularly, pyrrolo[3,2-*d*]pyrimidines (9-deazaxanthines) are important due to their proven biological activity and medicinal utility. 9-Deazaxanthines showed structure–activity relationships that are similar to those of xanthines. They were shown to be more or less equipotent to the corresponding xanthines at A2a adenosine receptors. 9-Deazaxanthines are generally at least two- to –threefold more potent than xanthines at A1 receptors and therefore exhibit higher A1 selectivities compared to the xanthines.[4] A number of pyrrolopyrimidine derivatives structurally related to toyocamycin, sangivamycin, and the seco nucleosides of tubercidin have antiviral activity.[5,6] In addition, the furo[3,2-*d*]pyrimidine ring system is of biological interest due to the formal isoelectronic relationship between this ring and purine.[7–10] Therefore, in continuation of our work in radical chemistry and the synthesis of biologically active heterocycles,[11] we became interested to undertake a study on the synthesis of novel pyrrolo[3,2-*d*]pyrimidines (9-deazaxanthines) and furo[3,2-*d*]pyrimidine via radical cyclization.

Several approaches have been reported so far for the preparation of substituted 9-deazaxanthines.[4,12–21] The most widely used ones have been reported by Taylor[18] and Nishigaki.[19] In Taylor's approach the cyclization of the key 5-nitro-1,3-dialkyl-6-styryluracil intermediate is obtained with neat triethyl phosphite[18] at high temperature whereas in Nishigaki's approach formic acid and sodium dithionite[19,20] have been used to accomplish the same reaction. Both the routes are limited by two main drawbacks, the yields of the cyclization reaction are low (11–65%) and both require harsh reaction conditions. Stefanachi et al.[13] modified the same reaction by refluxing the key 5-nitro-1,3-dialkyl-6-styryl-uracil intermediate in DMF in the presence of $SnCl_2$. However, in all these methods the 5-amino uracil intermediate could never be isolated. Herein, we report a new, straightforward, and high yielding method for the synthesis of substituted 9-deazaxanthines that overcome the drawbacks of the previous procedures.

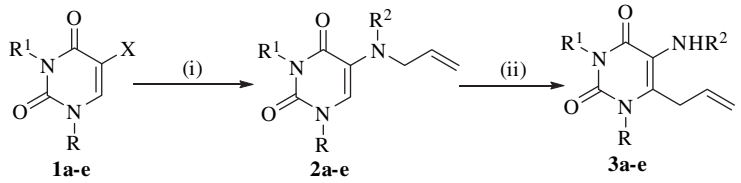
2. Results and discussion

2.1. Preparation of the precursors

The required precursors **3**(**a**–**d**) for the synthesis of substituted 9-deazaxanthines were prepared in 85–90% yield by the Lewis acid catalyzed aza-Claisen rearrangement of **2**(**a**–**d**) using $BF_3 \cdot Et_2O$ in xylene at 120 °C for 4–5 h in a sealed tube. Here it is important to note that Otter et al.[22] achieved the aza-Claisen rearrangement of 5-allylamino-1,3-dimethyluracil to give 6-allyl-5-amino-1,3-dimethyluracil under drastic conditions. For aza-Claisen rearrangement the 5-allylamino-1,3-dimethyluracil (**2a**) was refluxed in tetralin (207 °C) for 12 h to give only 24% yield of 6-allyl-5-amino-

* Corresponding author. Tel.: +91 33 2582 7521; fax: +91 33 2582 8282.
E-mail address: kcm_ku@yahoo.co.in (K.C. Majumdar).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.09.059



a, R = R^1 = Me, X = Br — **a,** R = R^1 = Me, R^2 = H, 84% — **a,** R = R^1 = Me, R^2 = H, 95%
b, R = R^1 = Et, X = Br — **b,** R = R^1 = Et, R^2 = H, 82% — **b,** R = R^1 = Et, R^2 = H, 90%
c, R = Et, R^1 = Me, X = Br — **c,** R = Et, R^1 = Me, R^2 = H, 85% — **c,** R = Et, R^1 = Me, R^2 = H, 93%
d, R = Et, R^1 = H, X = Br — **d,** R = Et, R^1 = R^2 = H, 80% — **d,** R = Et, R^1 = H, R^2 = H, 91%
e, R = R^1 = Me, X = NHMe — **e,** R = R^1 = R^2 = Me, 92% — **e,** R = R^1 = R^2 = Me, 86%

Scheme 1. Synthesis of precursors **3**(**a**–**e**). Reagent and conditions: (i) allyl amine, EtOH, reflux, 5–6 h, for **1**(**a**–**d**) and allylbromide, K_2CO_3, acetone, reflux, 10 h f or **1e**. (ii) $BF_3{\cdot}Et_2O$, xylene, 120 °C, 4–5 h.

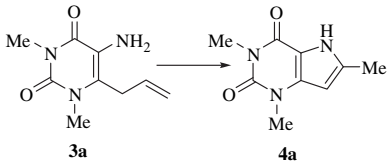
1,3-dimethyluracil (**3a**), whereas our methodology is very simple. We have used 2 equiv of $BF_3{\cdot}Et_2O$ in xylene at 120 °C for 4–5 h to give the products **3**(**a**–**d**) in 90–95% yield. Compounds **2**(**a**–**d**) were prepared in 80–85% yield from 5-bromouracil derivatives **1**(**a**–**d**) using allyl amine in refluxing EtOH for 5–6 h. The alkyl substituted bromouracil derivatives **1**(**a**–**d**) were in turn prepared according to our earlier published procedure.[23] The other precursor **3e** for 9-deazaxanthine has been prepared from 5-methylamino uracil (**1e**) by refluxing with allylbromide in acetone in the presence of anhyd potassium carbonate for 10 h followed by the aza-Claisen rearrangement of **2e**. The synthetic route for the preparation of precursors **3**(**a**–**e**) is depicted in Scheme 1.

2.2. Synthesis of 9-deazaxanthines and furo[3,2-*d*]pyrimidine

We next turned our attention to cyclize the substrates for achieving the synthesis of 9-deazaxanthine derivatives **4**(**a**–**e**). For this purpose, we initially tried the reagent CuI. When compound **3a** was refluxed with CuI in DMF for 10–12 h, the corresponding 9-deazaxanthine (**4a**) was obtained in only 15% yield. This protocol was also applied to other substrates **3b**–**e**, only **3b** afforded the corresponding cyclized product **4b** in only 12% yield. We realized that optimization of the reaction conditions was necessary. The results of optimization with compound **3a** are summarized in Table 1, which shows that use of benzoyl peroxide (0.5 equiv) in refluxing DMF for 3 h is the optimized method for effective cyclization of the aforesaid substrates (entry 5).

The reaction was carried out with other substrates **3b**–**e** under these optimized conditions (0.5 equiv benzoyl peroxide, DMF, reflux, 3 h) to give the corresponding 9-deazaxanthine derivatives **4b**–**e** in excellent yields. These results encouraged us to apply this methodology to the substrate **5**. When 6-allyl-5-hydroxy-1,3-dimethylpyrimidine (**5**) was subjected to the aforesaid conditions, the furo[3,2-*d*]pyrimidine derivative (**6**) was obtained in 95% yield. The results are summarized in Table 2.

Table 1
Optimization f or cyclization of **3a**[a]



3a **4a**

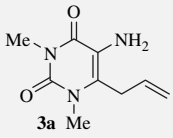
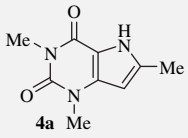
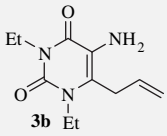
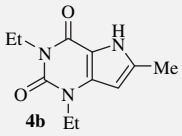
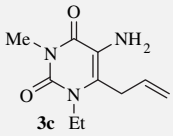
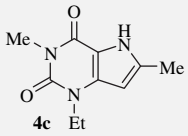
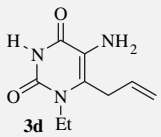
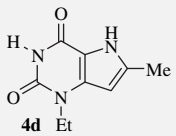
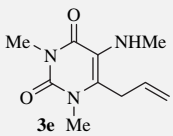
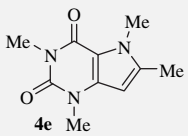
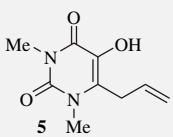
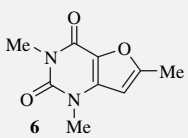
Entry	Reaction conditions	Time (h)	Yield (%)
1	CuI (1.2 equiv), DMF, reflux	10	15
2	CuI (1.2 equiv), benzoyl peroxide (1.2 equiv), DMF, reflux	3	98
3	Benzoyl peroxide (0.05 equiv), DMF, reflux	6	20
4	Benzoyl peroxide (0.25 equiv), DMF, reflux	6	90
5	**Benzoyl peroxide (0.5 equiv), DMF, reflux**	**3**	**99**
6	DMF, reflux	10	NR

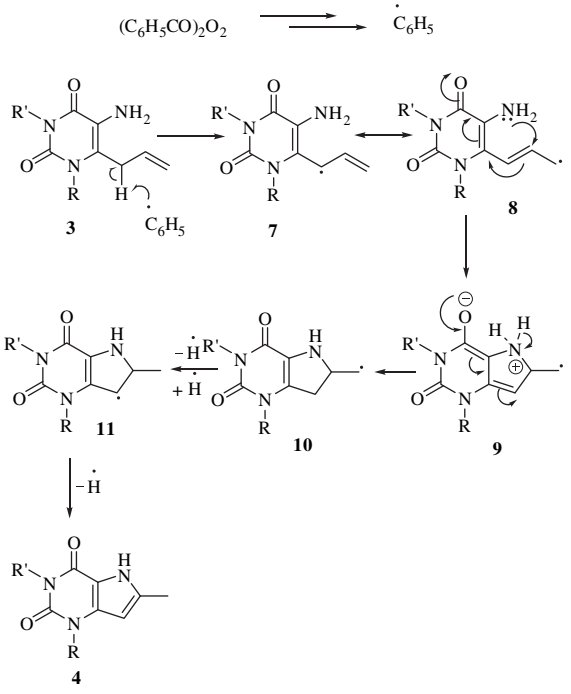
NR—no reaction.
[a] All reactions were done under nitrogen atmosphere.

2.3. Probable mechanism of the radical cyclization

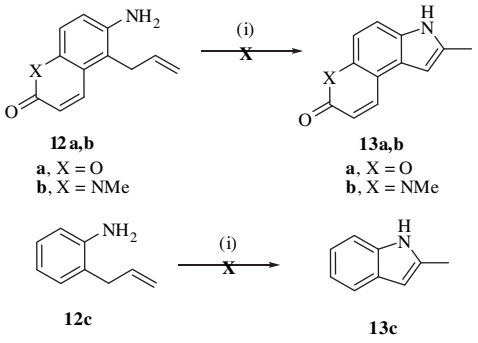
A probable mechanistic rationalization of the benzoyl peroxide mediated radical reaction is shown in Scheme 2.

Table 2
9-Deazaxanthines and furo[3,2-*d*]pyrimidine

Entry	Precursors	Products	Yields (%)
1	 **3a**	 **4a**	99
2	 **3b**	 **4b**	97
3	 **3c**	 **4c**	98
4	 **3d**	 **4d**	95
5	 **3e**	 **4e**	96
6	 **5**	 **6**	95



Scheme 2. Probable pathway f or the benzoyl peroxide mediated radical cyclization.



Scheme 3. Reagent and conditions: (i) benzoyl peroxide (0.5 equiv), DMF, reflux, 12 h.

The possible involvement of radicals in the reaction has been demonstrated by failure of the reaction in the presence of a radical scavenger (hydroquinone). The reaction of **3a** when carried out with azobis(isobutyronitrile) (AIBN) (1.5 equiv) instead of benzoyl peroxide in DMF for 12 h also gave a 30% yield of the product **4a** with the recovery of the starting material (60%). When carried out with other substrates e.g., 5-amino-6-allyl coumarin (**12a**), 5-amino-6-allyl quinolone (**12b**), and 2-allylaniline (**12c**), the reaction failed to give any product with the full recovery of the starting materials. It is worthwhile to note that there is no possibility of any Michael addition in these cases (Scheme 3).

3. Conclusion

In conclusion, we have successfully achieved two important aspects: high yielding methodology for the aza-Claisen rearrangement of *N*-allylated uracil derivatives; and a practical method for the synthesis of 9-deazaxanthine derivatives. We are continuing this work to extend the scope of this methodology to the synthesis of other bio-active heterocycles and our results will be communicated in due course.

4. Experimental section

4.1. General

Melting points were determined in open capillaries and are uncorrected. IR spectra were run for KBr discs on a PerkinElmer 120-000A apparatus (ν_{max} in cm^{-1}) and ^1H NMR spectra were determined for solutions in $CDCl_3$ and DMSO-d_6 with TMS as internal standard on a Bruker DPX-400. ^{13}C NMR spectra were determined for solutions in $CDCl_3$ and DMSO-d_6 on a Bruker DPX-300 and Bruker DPX-400. HRMS were recorded on a Qtof Micro YA263 instrument. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel-G [E-Mark (India)] was used for TLC. Petroleum-ether refers to the fraction between 60 and 80 °C.

4.2. General procedure for the synthesis of 5-allylamino-1,3-disubstituted uracil derivatives: preparation of 5-(allylamino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2a)

In a nitrogen flushed flask was placed 5-bromo-1,3-dimethyluracil (**1a**) (2.19 g, 10 mmol) in ethanol (20 mL) and then allyl amine (3.75 mL, 50 mmol) was added slowly with a syringe. The reaction mixture was refluxed for 5 h and then most of the solvent and allyl amine were evaporated under reduced pressure. The residue was subjected to silica gel chromatography (2% MeOH/$CHCl_3$) to afford 5-allylamino-1,3-dimethyluracil **2a**[22] (1.64 g, 84%) as a white solid.

*4.2.1. 5-(Allylamino)-1,3-diethylpyrimidine-2,4(1H,3H)-dione (**2b**).* Prepared using compound **1b** (2.00 g, 8.09 mmol) and allyl amine (3.00 mL, 40.48 mmol). The product was purified by column chromatography (2% MeOH/$CHCl_3$) to yield compound **2b** (1.48 g, 82%) as a brown liquid; R_f (50% EtOAc/pet. ether) 0.55; IR (KBr, cm^{-1}) ν_{max}: 2981, 1690, 1663; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.17 (3H, t, *J* 7.0 Hz, NCH_2CH_3), 1.22 (3H, t, *J* 7.0 Hz, NCH_2CH_3), 3.54 (2H, d, *J* 4.6 Hz, NCH_2), 3.70 (2H, q, *J* 7.2 Hz, NCH_2CH_3), 3.98 (2H, q, *J* 7.0 Hz, NCH_2CH_3), 5.14 (1H, d, *J* 10.4 Hz, $=CH_aH_b$), 5.22 (1H, d, *J* 17.4 Hz, $=CH_aH_b$), 5.77–5.87 (1H, m, *CH*=), 6.11 (1H, s, *H*-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.8, 13.9, 36.7, 44.4, 46.7, 114.4, 116.5, 124.4, 134.2, 148.7, 160.2; HRMS (ES^+): 224.1406 ($[M+H]^+$ $C_{11}H_{17}N_3O_2$ requires: 224.1394).

*4.2.2. 5-(Allylamino)-1-ethyl-3-methylpyrimidine-2,4(1H,3H)-dione (**2c**).* Prepared using compound **1c** (2.00 g, 8.58 mmol) and allyl amine (3.20 mL, 42.9 mmol). The product was purified by column chromatography (2% MeOH/$CHCl_3$) to yield compound **2c** (1.53 g, 85%) as a brown gummy liquid; R_f (50% EtOAc/pet. ether) 0.52; IR (KBr, cm^{-1}) ν_{max}: 2979, 1694, 1634; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.09 (3H, t, *J* 7.2 Hz, NCH_2CH_3), 3.18 (3H, s, NCH_3), 3.43 (2H, d, *J* 4.5 Hz, NCH_2), 3.60 (2H, q, *J* 7.2 Hz, NCH_2CH_3), 4.03 (1H, bs, N*H*), 4.99 (1H, d, *J* 10.1 Hz, $=CH_aH_b$), 5.08 (1H, d, *J* 17.4 Hz, $=CH_aH_b$), 5.65–5.73 (1H, m, *CH*=), 6.05 (1H, s, *H*-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.6, 27.7, 44.1, 46.2, 114.1, 116.0, 123.9, 133.9, 148.7, 160.2; HRMS (ES^+): 210.1250 ($[M+H]^+$ $C_{10}H_{15}N_3O_2$ requires: 210.1237).

*4.2.3. 5-(Allylamino)-1-ethylpyrimidine-2,4(1H,3H)-dione (**2d**).* Prepared using compound **1d** (2.00 g, 9.13 mmol) and allyl amine (3.42 mL, 45.65 mmol). The product was purified by column chromatography (2% MeOH/$CHCl_3$) to yield compound **2d** (1.43 g, 80%) as a white solid; mp 158–160 °C; R_f (50% EtOAc/pet. ether) 0.50; IR (KBr, cm^{-1}) ν_{max}: 2996, 2823, 1668, 1644; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.27 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 3.59 (2H, d, *J* 4.5 Hz, NCH_2), 3.73 (2H, q, *J* 7.0 Hz, NCH_2CH_3), 4.06 (1H, br s, $NHCH_2$), 5.20 (1H, d, *J* 9.5 Hz, $=CH_aH_b$), 5.27 (1H, d, *J* 17.5 Hz, $=CH_aH_b$), 5.81–5.90 (1H, m, *CH*=), 6.13 (1H, s, *H*-6), 8.52 (1H, br s, N*H*CO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 43.6, 46.7, 115.7, 116.7, 125.2, 134.0, 148.7,

161.0; HRMS (ES^+): 218.0905 ($[M+Na]^+$ $C_9H_{13}N_3O_2$ requires: 218.0905).

*4.2.4. 5-(Allylamino)-1-ethylpyrimidine-2,4(1H,3H)-dione (**2e**).* Prepared using compound **1e** (2.00 g, 11.82 mmol) and allyl amine (4.43 mL, 59.1 mmol). The product was purified by column chromatography (1% MeOH/$CHCl_3$) to yield compound **2e** (2.27 g, 92%) as a brown liquid; R_f (50% EtOAc/pet. ether) 0.59; IR (KBr, cm^{-1}) ν_{max}: 1696, 1651; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.61 (3H, s, CH_2NCH_3), 3.34 (3H, s, NCH_3), 3.36 (3H, s, NCH_3), 3.62 (2H, d, J 6.4 Hz, NCH_2), 5.14 (1H, d, J 9.4 Hz, $=CH_aH_b$), 5.17 (1H, d, J 11.1 Hz, $=CH_aH_b$), 5.74–5.88 (1H, m, $CH=$), 6.55 (1H, s, H-6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.0, 36.8, 39.4, 56.6, 117.8, 126.2, 129.6, 134.0, 150.6, 161.1; HRMS (ES^+): 232.1062 ($[M+Na]^+$ $C_{10}H_{15}N_3O_2$ requires: 232.1062).

4.3. General procedure for aza-Claisen rearrangement products: preparation of 6-allyl-5-amino-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (3a)

Compound **2a** (1.0 g, 5.12 mmol) and $BF_3\cdot Et_2O$ (1.28 mL, 10.24 mmol) were heated in xylene (5 ml) at 120 °C for 4–5 h. The reaction mixture was cooled and neutralized with $NaHCO_3$ solution and extracted with $CHCl_3$ (3×10 mL). The organic extract was washed with water (10 mL), brine (5 mL) and dried (Na_2SO_4). The solvent was distilled off and the crude product was purified by column chromatography over silica gel using MeOH/$CHCl_3$ (1:49) as eluent to afford the aza-Claisen product **3a**[22] (950 mg, 95%).

*4.3.1. 6-Allyl-5-amino-1,3-diethylpyrimidine-2,4(1H,3H)-dione (**3b**).* Prepared using **2b** (1.00 g, 4.48 mmol) and $BF_3\cdot Et_2O$ (1.12 mL, 8.96 mmol). Isolation via column chromatography (2% MeOH/$CHCl_3$) yielded the aza-Claisen product **3b** (900 mg, 90%) as a brown liquid; R_f (50% EtOAc/pet. ether) 0.53; IR (KBr, cm^{-1}) ν_{max}: 2980, 2917, 1687, 1632; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.15–1.26 (6H, m, $2NCH_2CH_3$), 3.25 (2H, br s, NH_2), 3.34 (2H, d, J 4.5 Hz, CH_2), 3.83 (2H, q, J 7.0 Hz, NCH_2CH_3), 4.03 (2H, q, J 7.1 Hz, NCH_2CH_3), 5.09 (1H, d, J 17.2 Hz, $=CH_aH_b$), 5.20 (1H, d, J 10.2 Hz, $=CH_aH_b$), 5.80–5.89 (1H, m, $CH=$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.0, 14.8, 31.3, 37.2, 40.3, 117.5, 119.6, 130.7, 130.8, 150.0, 160.2; HRMS (ES^+): 224.1406 ($[M+H]^+$ $C_{11}H_{17}N_3O_2$ requires: 224.1394).

*4.3.2. 6-Allyl-5-amino-1-ethyl-3-methylpyrimidine-2,4(1H,3H)-dione (**3c**).* Prepared using **2c** (1.00 g, 4.78 mmol) and $BF_3\cdot Et_2O$ (1.20 mL, 9.56 mmol). Isolation via column chromatography (2% MeOH/$CHCl_3$) yielded the aza-Claisen product **3c** (930 mg, 93%) as a white solid; mp 94–96 °C; R_f (50% EtOAc/pet. ether) 0.50; IR (KBr, cm^{-1}) ν_{max}: 2980, 2936, 1686, 1629; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (3H, t, J 7.1 Hz, NCH_2CH_3), 3.26 (2H, bs, NH_2), 3.37 (2H, d, J 4.5 Hz, CH_2), 3.40 (3H, s, NCH_3), 3.85 (2H, q, J 7.0 Hz, NCH_2CH_3), 5.08 (1H, d, J 17.2 Hz, $=CH_aH_b$), 5.21 (1H, d, J 10.1 Hz, $=CH_aH_b$), 5.81–5.90 (1H, m, $CH=$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.8, 28.5, 31.2, 40.4, 117.5, 119.5, 130.6, 130.7, 150.4, 160.6; HRMS (ES^+): 210.1250 ($[M+H]^+$ $C_{10}H_{15}N_3O_2$ requires: 210.1237).

*4.3.3. 6-Allyl-5-amino-1-ethylpyrimidine-2,4(1H,3H)-dione (**3d**).* Prepared using **2d** (1.00 g, 5.12 mmol) and $BF_3\cdot Et_2O$ (1.28 mL, 10.24 mmol). Isolation via column chromatography (2% MeOH/$CHCl_3$) yielded the aza-Claisen product **3d** (910 mg, 91%) as a white solid; mp 176–178 °C; R_f (50% EtOAc/pet. ether) 0.48; IR (KBr, cm^{-1}) ν_{max}: 3408, 3319, 3078, 1674, 1610; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.10 (3H, t, J 6.4 Hz, NCH_2CH_3), 3.31 (2H, br s, NH_2), 3.67 (2H, q, J 6.8 Hz, NCH_2CH_3), 3.89 (2H, d, J 4.5 Hz, CH_2), 5.08–5.12 (2H, m, $=CH_2$), 5.82–5.89 (1H, m, $CH=$), 11.31 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.3, 30.3, 38.3, 116.5, 119.0, 132.6, 134.0, 149.1, 160.2; HRMS (ES^+): 218.0905 ($[M+Na]^+$ $C_9H_{13}N_3O_2$ requires: 218.0905).

*4.3.4. 6-Allyl-1,3-dimethyl-5-(methylamino)pyrimidine-2,4(1H,3H)-dione (**3e**).* Prepared using **2e** (1.00 g, 4.78 mmol) and $BF_3\cdot Et_2O$ (1.20 mL, 9.56 mmol). Isolation via column chromatography (2% MeOH/$CHCl_3$) yielded the aza-Claisen product **3e** (860 mg, 86%) as a brown liquid; R_f (50% EtOAc/pet. ether) 0.57; IR (KBr, cm^{-1}) ν_{max}: 2950, 1651, 1620; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.42 (3H, s, $NHCH_3$), 3.22 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.48 (2H, d, J 6.4 Hz, CH_2), 4.98 (1H, d, J 17.2 Hz, $=CH_aH_b$), 5.11 (1H, d, J 10.2 Hz, $=CH_aH_b$), 5.79–5.86 (1H, m, $CH=$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.3, 31.6, 37.2, 56.4, 117.4, 123.0, 132.4, 142.0, 151.0, 161.7; HRMS (ES^+): 210.1250 ($[M+H]^+$ $C_{10}H_{15}N_3O_2$ requires: 210.1237).

4.4. General procedure for the synthesis of 9-deazaxanthine derivatives and furo[3,2-*d*]pyrimidine: preparation of 1,3,6-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4a)

Nitrogen gas was bubbled through a solution of compound **3a** (100 mg, 0.512 mmol) in dry DMF (2 mL) and benzoyl peroxide (62 mg, 0.256 mmol) was added and the mixture was refluxed for 3 h under a nitrogen atmosphere. The reaction mixture was cooled, poured into ice cooled water (10 mL), and extracted with $CHCl_3$ (3×10 mL). The organic extract was washed with water (2×10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel using EtOAc as eluent to afford the product **4a** (98 mg, 99%) as a white solid; mp 268–270 °C; R_f (50% EtOAc/pet. ether) 0.52; IR (KBr, cm^{-1}) ν_{max}: 2929, 1694, 1637; ^1H NMR (DMSO-d_6, 400 MHz) δ: 2.26 (3H, s, CCH_3), 3.21 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 5.92 (1H, s, H-7), 11.84 (1H, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 12.9, 27.2, 31.5, 93.6, 108.5, 135.6, 137.7, 151.0, 154.0; HRMS (ES^+): 194.0938 ($[M+H]^+$ $C_9H_{11}N_3O_2$ requires: 194.0924).

*4.4.1. 1,3-Diethyl-6-methyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**4b**).* Prepared using compound **3b** (100 mg, 0.447 mmol) and benzoyl peroxide (54 mg, 0.224 mmol). Isolation via column chromatography (EtOAc) yielded the 9-deazaxanthine **4b** (96 mg, 97%) as a white solid; mp 208–210 °C; R_f (50% EtOAc/pet. ether) 0.54; IR (KBr, cm^{-1}) ν_{max}: 2922, 1693, 1643; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (3H, t, J 6.9 Hz, NCH_2CH_3), 1.30 (3H, t, J 7.1 Hz, NCH_2CH_3), 2.40 (3H, s, CCH_3), 3.95 (2H, q, J 7.1 Hz, NCH_2CH_3), 4.11 (2H, q, J 7.0 Hz, NCH_2CH_3), 5.73 (1H, s, H-7), 10.85 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.9, 13.4, 13.5, 36.4, 40.6, 93.6, 109.8, 135.8, 138.8, 150.8; HRMS (ES^+): 222.1250 ($[M+H]^+$ $C_{11}H_{15}N_3O_2$ requires: 222.1237).

*4.4.2. 1-Ethyl-3,6-dimethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**4c**).* Prepared using compound **3c** (100 mg, 0.478 mmol) and benzoyl peroxide (57.9 mg, 0.239 mmol). Isolation via column chromatography (EtOAc) yielded the 9-deazaxanthine **4c** (97 mg, 98%) as a white solid; mp 248–250 °C; R_f (50% EtOAc/pet. ether) 0.51; IR (KBr, cm^{-1}) ν_{max}: 3124, 1697, 1639; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (3H, t, J 6.8 Hz, NCH_2CH_3), 2.42 (3H, s, CCH_3), 3.45 (3H, s, NCH_3), 3.95 (2H, q, J 6.9 Hz, NCH_2CH_3), 5.74 (1H, s, H-7), 11.10 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.3, 13.9, 28.2, 41.1, 94.0, 110.0, 136.2, 139.4, 151.6, 156.1; HRMS (ES^+): 230.0905 ($[M+Na]^+$ $C_{10}H_{13}N_3O_2$ requires: 230.0905).

*4.4.3. 1-Ethyl-6-methyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**4d**).* Prepared using compound **3d** (100 mg, 0.512 mmol) and benzoyl peroxide (62 mg, 0.256 mmol). Isolation via column chromatography (EtOAc) yielded the 9-deazaxanthine **4d** (94 mg, 95%) as a white solid; mp 304–306 °C; R_f (50% EtOAc/pet. ether) 0.49; white solid; mp 304–306 °C, yield 95%. IR (KBr, cm^{-1}) ν_{max}: 2918, 2850, 1691,

1637; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.14 (3H, t, J 6.5 Hz, NCH_2CH_3), 2.24 (3H, s, CCH_3), 3.78 (2H, q, J 6.5 Hz, NCH_2CH_3), 5.90 (1H, s, *H*-7), 10.66 (1H, s, N*H*), 11.78 (1H, s, CON*H*CO); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 12.8, 13.0, 38.6, 93.8, 109.2, 136.3, 137.8, 150.5, 154.5; HRMS (ES^+): 194.0938 ($[M+H]^+$ $C_9H_{11}N_3O_2$ requires: 194.0924).

*4.4.4. 1,3,5,6-Tetramethyl-1H-pyrrolo[3,2-d]pyrimidine-2,4(3H,5H)-dione (**4e**).* Prepared using compound **3e** (100 mg, 0.478 mmol) and benzoyl peroxide (57.9 mg, 0.239 mmol). Isolation via column chromatography (EtOAc) yielded the 9-deazaxanthine **4e** (95 mg, 96%) as a white solid; mp 160–162 °C; R_f (50% EtOAc/pet. ether) 0.58; IR (KBr, cm^{-1}) ν_{max}: 1687, 1643; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.27 (3H, s, CCH_3), 3.37 (3H, s, NCH_3), 3.39 (3H, s, NCH_3), 3.89 (3H, s, NCH_3), 5.68 (1H, s, *H*-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.2, 27.7, 31.6, 93.2, 109.9, 135.5, 139.2, 151.7, 155.6; HRMS (ES^+): 208.1094 ($[M+H]^+$ $C_{10}H_{13}N_3O_2$ requires: 208.1080).

*4.4.5. 1,3,6-Trimethylfuro[3,2-d]pyrimidine-2,4(1H,3H)-dione (**6**).* Prepared using compound **5** (100 mg, 0.510 mmol) and benzoyl peroxide (61.8 mg, 0.255 mmol). Isolation via column chromatography (EtOAc) yielded the 9-deazaxanthine **6** (94 mg, 95%) as a white solid; mp 203–205 °C; R_f (50% EtOAc/pet. ether) 0.60; IR (KBr, cm^{-1}) ν_{max}: 1704, 1659; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (3H, s, CCH_3), 3.40 (3H, s, NCH_3), 3.44 (3H, s, NCH_3), 6.11 (1H, s, *H*-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.4, 28.2, 32.5, 97.7, 129.4, 139.5, 151.8, 153.2, 160.7; HRMS (ES^+): 195.0781 ($[M+H]^+$ $C_9H_{10}N_2O_3$ requires: 195.0764).

Acknowledgements

We thank the DST (New Delhi) and the CSIR (New Delhi) for financial assistance. One of us (S.M.) is thankful to the DST (New Delhi) for a research fellowship.

References and notes

1. Cheng, C. C. *Prog. Med. Chem.* **1969**, *6*, 67–75.
2. Scott McNair, D. B.; Ulbrient, T. L. V.; Rogers, M. L.; Chu, E.; Rose, C. *Cancer Res.* **1959**, *19*, 15–19.
3. Sankyo Ltd; Ube Industries Ltd., Japan Kokai Tokyo Koho JP. 59, 36, 667; *Chem. Abstr.* **1984**, *101*, 110939z.
4. Grahner, B.; Winiwarter, S.; Lanzner, W.; Müller, C. E. *J. Med. Chem.* **1994**, *37*, 1526–1534.
5. Gupta, P. K.; Daunert, S.; Nassiri, M. R.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1989**, *32*, 402–408.
6. Gupta, P. K.; Nassiri, M. R.; Coleman, L. A.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1989**, *32*, 1420–1425.
7. Shimamure, H.; Terajima, K.; Kawase, A.; Ishizuka, Y.; Kimura, I.; Kamya, A.; Kataoka, M.; Sato, M. Japan Kokai Tokyo Koho JP 05, 112, 559; *Chem. Abstr.* **1993**, *119*, 160315k.
8. Yamamoto, Y.; Seko, T.; Nakamura, H.; Nemoto, H.; Hojo, H.; Mukai, N.; Hashimoto, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 157–158.
9. Edie, R. G.; Hackler, R. E.; Krumkains, E. V. Eur. Pat. Appl. Ep. 49; *Chem. Abstr.* **1992**, *116*, 128957y.
10. Gangjee, A.; Devraj, R.; Barrews, L. R. *J. Med. Chem.* **1994**, *37*, 1169–1176.
11. (a) Majumdar, K. C.; Mondal, S.; De, N. *Synlett* **2008**, 2851–2855; (b) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2007**, *48*, 6951–6953; (c) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2008**, *49*, 2418–2420; (d) Majumdar, K. C.; Mondal, S.; Ghosh, D. *Tetrahedron Lett.* **2009**, *50*, 4781–4784; (e) Majumdar, K. C.; Alam, S. *Org. Lett.* **2006**, *8*, 4059–4062; (f) Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633–7636; (g) Majumdar, K. C.; Das, U.; Jana, N. K. *J. Org. Chem.* **1998**, *63*, 3550–3553; (h) Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. *Synthesis* **2005**, 1164–1168; (i) Majumdar, K. C.; Sinha, B.; Maji, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2009**, *65*, 2751–2756; (j) Majumdar, K. C.; Basu, P. K.; Gonzalez, A. *Curr. Org. Chem.* **2009**, *13*, 599–645; (k) Majumdar, K. C.; Basu, P. K.; Chattopadhyay, S. K. *Tetrahedron* **2007**, *63*, 793–826; (l) Majumdar, K. C.; Debnath, P. *Tetrahedron* **2008**, *64*, 9799–9820.
12. Kalla, R.; Elzein, E.; Marquart, T.; Perry, T.; Li, X.; Zablocki, J. Substituted pyrrolo[3,2-*d*]pyrimidine-2,4-diones as A_{2B} adenosine receptor antagonists US7449473B2, 2008.
13. Stefanachi, A.; Leonetti, F.; Cappa, A.; Carotti, A. *Tetrahedron Lett.* **2003**, *44*, 2121–2123.
14. Pfleider, W.; Mosthaf, H. *Chem. Ber.* **1957**, *90*, 738–745.
15. Kawahara, N.; Nakajima, T.; Itoh, T.; Ogura, H. *Chem. Pharm. Bull.* **1985**, *33*, 4740–4748.
16. Modnikova, G. A.; Titkova, R. M.; Glushkov, R. G.; Sokolova, A. S.; Silin, V. A.; Chernov, V. A. *Khim. Farm. Zh.* **1988**, *22*, 185–191; *Chem. Abstr.* **1988**, *109*, 400242.
17. Tsupak, E. B.; Tkachenko, Y. N.; Pozharsky, A. F. *Khim. Geter. Soedin.* **1994**, 1242–1248; *Chem. Abstr.* **1995**, *122*, 334055.
18. Taylor, E. C.; Garcia, E. E. *J. Org. Chem.* **1965**, *30*, 655–657.
19. Nishigaki, S.; Kanamori, Y.; Senga, K. *Chem. Pharm. Bull.* **1980**, *28*, 1636–1641.
20. Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.* **1979**, *44*, 3830–3834.
21. Hirota, K.; Sugiyama, T.; Kitade, Y.; Senda, S.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 583–588.
22. Otter, B. A.; Taube, A.; Fox, J. J. *J. Org. Chem.* **1971**, *36*, 1251–1255.
23. Majumdar, K. C.; Das, T. K.; Jana, M. *Synth. Commun.* **2005**, *35*, 1961–1969.