# Synthesis of 7,8,9-Trisubstituted Dihydropurine Derivatives via a '*tert*-Amino Effect' Cyclization

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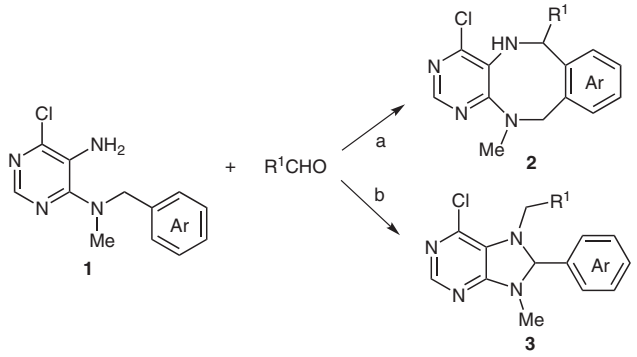
**Abstract:** 7,8,9-Trisubstituted dihydropurine derivatives were prepared from 5-amino-4-(*N*,*N*-disubstituted)aminopyrimidines and aromatic aldehydes via a cascade of reactions. The key transformation for the reaction is a [1,6]-hydrogen shift due to a '*tert*-amino effect'.

**Key words:** *tert*-amino effect, dihydropurine, hydrogen transfer, imines, cyclizations

Natural products are generated via evolutionary selection processes and represent the biologically relevant and prevalidated fractions of chemical spaces. Dihydropurine derivatives are among the natural products that exhibit important pharmacological properties.[1] 7-Methylguanosine is unique since it is involved in certain transfer and messenger RNAs, and is the only naturally occurring nucleoside known to exist as a zwitterion at physiological pH.[2] Methods have been reported for the synthesis of dihydropurine derivatives, for example, the reduction of purine by $NaBH_4$[2,3] and the reaction of urea with an aldehyde or a ketone under basic conditions.[4]

The formation of heterocycles by ring closure of *ortho*-substituted *N*,*N*-dialkylanilines is known as the '*tert*-amino effect' cyclization or α-cyclization of tertiary amines.[5] Viehe investigated the scope and limitations of the '*tert*-amino effect' for the synthesis of heterocycles.[6] The '*tert*-amino effect' has been successfully applied to the synthesis of several heterocyclic scaffolds.[7]

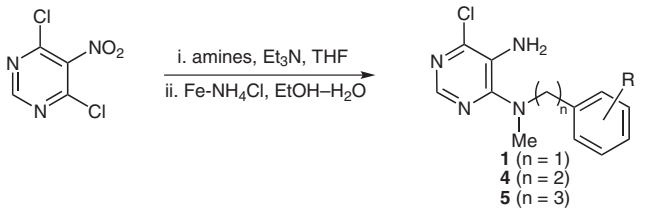



**Scheme 1**

Recently, we discovered that a Pictet–Spengler-type cyclization of pyrimidinediamine **1** with an electron-rich aromatic ring (Ar = 3,5-di-$MeOC_6H_4$ or *N*-Me-indol-2-yl) yielded novel tricyclic pyrimidine-fused eight-membered heterocycle **2** (path a in Scheme 1).[8] However, certain substrates (e.g., when Ar was 3-methoxyphenyl and the aldehyde was aromatic) produced 7,8,9-trisubstituted dihydropurine derivative **3** as the major product (path b in Scheme 1). We reasoned that the formation of **3** was due to the competition of the '*tert*-amino effect' and further investigations of this new mode of reaction may lead to a new method for the synthesis of various dihydropurine analogues. Herein, the preliminary results of this investigation are reported.

Suitably substituted pyrimidines **1**, **4**, and **5** were readily prepared following a two-step process from commercially available 4,6-dichloro-5-nitropyrimidine and corresponding amines (Table 1).[9] Their reactions with aromatic aldehydes proceeded smoothly in the presence of trifluoroacetic acid (TFA) to give 7,8,9-trisubstituted dihydropurine derivatives **3**, and **6**–**8** (Table 2).[10] The structure of compound **8a** was unequivocally determined through an X-ray diffraction analysis (Figure 1).[11]

**Table 1** Synthesis of Pyrimidinediamine Derivatives




| Entry | Product | n | R | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **1a** | 1 | 3-MeO | 52 |
| 2 | **1b** | 1 | H | 65 |
| 3 | **1c** | 1 | 4-Me | 23 |
| 4 | **1d** | 1 | 4-F | 38 |
| 5 | **4a** | 2 | H | 47 |
| 6 | **4b** | 2 | 3,5-di-MeO | 90 |
| 7 | **5** | 3 | H | 20 |

[a] Overall yield in two steps.

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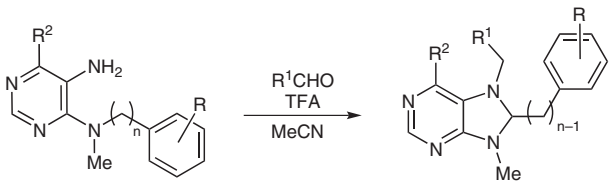
**Table 2** Synthesis of 6-Chloro-7,8,9-trisubstituted Dihydropurines[a]




**1** (n = 1, $R^2$ = Cl)
**4** (n = 2, $R^2$ = Cl)
**5** (n = 3, $R^2$ = Cl)
**6** (n = 2, $R^2$ = 1-pyrrolidinyl)

**3** (n = 1, $R^2$ = Cl)
**7** (n = 2, $R^2$ = Cl)
**8** (n = 3, $R^2$ = Cl)
**9** (n = 2, $R^2$ = 1-pyrrolidinyl)

| Entry | Product | R | $R^1$ | n | $R^2$ | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | 3-MeO | 4-$O_2NC_6H_4$ | 1 | Cl | 12 | 67[c] |
| 2 | **3b** | 3-MeO | Ph | 1 | Cl | 8 | 51 |
| 3 | **3c** | 3-MeO | 4-$MeC_6H_4$ | 1 | Cl | 7 | 68 |
| 4 | **3d** | H | 4-$O_2NC_6H_4$ | 1 | Cl | 12 | 68 |
| 5 | **3e** | 4-Me | 4-$O_2NC_6H_4$ | 1 | Cl | 8 | 74 |
| 6 | **3f** | 4-F | 4-$O_2NC_6H_4$ | 1 | Cl | 12 | 61 |
| 7 | **7a** | H | 4-$O_2NC_6H_4$ | 2 | Cl | 12 | 60 |
| 8 | **7b** | H | Ph | 2 | Cl | 8 | 31 |
| 9 | **7c** | 3,5-$(MeO)_2$ | 4-$O_2NC_6H_4$ | 2 | Cl | 12 | 35 |
| 10 | **8a** | H | 4-$O_2NC_6H_4$ | 3 | Cl | 12 | 65 |
| 11 | **8b** | H | Ph | 3 | Cl | 8 | 59 |
| 12 | **8c** | H | 4-$MeC_6H_4$ | 3 | Cl | 7 | 64 |
| 13 | **9a** | H | 4-$O_2NC_6H_4$ | 2 | X[d] | 12 | 82 |
| 14 | **9b** | H | Ph | 2 | X | 12 | 47 |
| 15 | **9c** | H | 4-$MeC_6H_4$ | 2 | X | 12 | 37 |
| 16 | **9d** | H | *n*-Pr | 2 | X | 3 | 59 |

[a] Reagents and conditions: **1** (1.0 equiv), $R^1$CHO (1.5–2.0 equiv) and TFA (excess) in MeCN, reflux.
[b] Yields are based on pure products isolated by flash chromatography.
[c] 7% Imine intermediate was also isolated.
[d] X = 1-pyrrolidinyl.

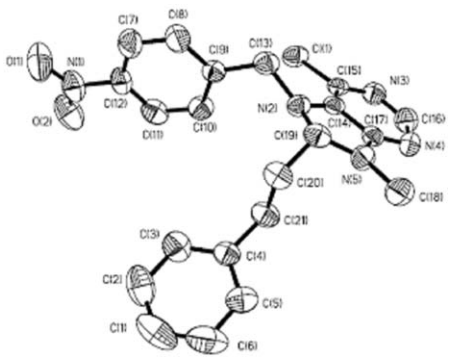
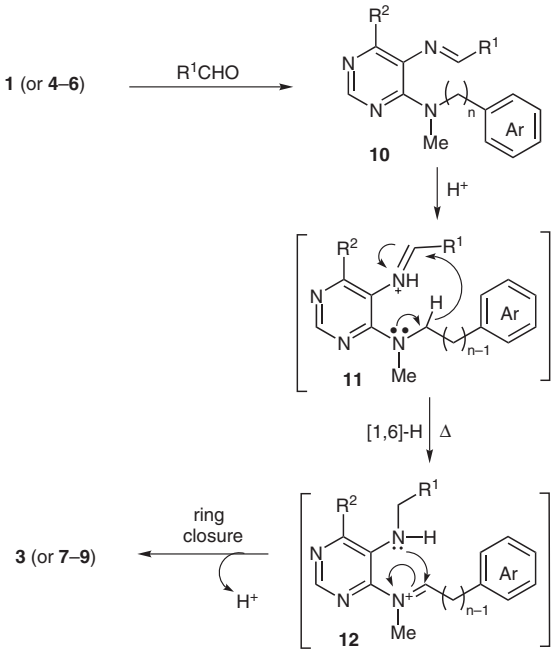


**Figure 1** X-ray crystal structure of **8a**

As shown in Table 2, when an aromatic aldehyde was employed, the desired product was obtained in moderate to good yields. Pyrimidines **1** (n = 1, benzylamino) and **5** (n = 3, phenpropylamino; entries 1–6 and 10–12, Table 2) generally gave higher yields as compared to **4** with a phenethylamino group (n = 2; entries 7–9 and 13–16, Table 2). However, there was no clear correlation between the electronic properties of the substituents on the aromatic rings and product yields.

A plausible mechanism for the formation of dihydropurine derivatives was proposed in Scheme 2. It was envisioned that the cyclization reaction proceeded through an imine intermediate **10** formed between the amino group of pyrimidine **1** (or **4**–**6**) and an aldehyde under acid-catalyzed conditions. Imine **10** was protonated to iminium **11** which underwent a [1,6]-hydrogen shift to give iminium **12**. Ring closure of the iminium **12** and deprotonation generated the expected dihydropurine derivatives.




**Scheme 2** A plausible mechanism for the formation of dihydropurines

In conclusion, a new method was developed for the preparation of 7,8,9-trisubstituted dihydropurine derivatives via a cascade reaction. The key transformation was a possible [1,6]-hydrogen shift or hydride transfer due to a '*tert*-amino effect'. This method complements the existing ones for the preparation of dihydropurine derivatives, and should be applicable to preparation of diverse libraries, which may be useful in field of chemical biology and medicinal chemistry.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) Yang, J.; Che, X.; Dang, Q.; Wei, Z.; Gao, S.; Bai, X. *Org. Lett.* **2005**, *7*, 1541.
(10) **General Procedure for Syntheses of 6-Chloro-7,8,9-trisubstituted Dihydropurines**
Pyrimidinediamine **1** (0.65 mmol), the appropriate aldehyde (0.975 mmol), and TFA (0.6 mL) were dissolved in MeCN (10.0 mL) and stirred under reflux for 1–12 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with sat. $NaHCO_3$ (3 × 15 mL). The water layer was extracted with EtOAc (3 × 10 mL). The combined EtOAc layer was washed with brine, dried over anhyd $Na_2SO_4$, concentrated in vacuo, and purified by flash chromatography on $SiO_2$ to furnish the cyclized product **3**.
**6-Chloro-8-(3-methoxyphenyl)-9-methyl-7-(4-nitrobenzyl)-8,9-dihydro-7*H*-purine (3a)**
Orange solid, yield 67% (elution with EtOAc–PE, 1:2); mp 119.2–120.6 °C. ES-MS: *m/z* = 411.8 $[M + 1]^+$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.4 Hz, 2 H), 7.92 (s, 1 H), 7.30–7.35 (m, 3 H), 6.96 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.88 (d, *J* = 7.5 Hz, 1 H), 6.82 (t, *J* = 1.8 Hz, 1 H), 5.71 (s, 1 H), 5.05 (d, *J* = 16.8 Hz, 1 H), 4.32 (d, *J* = 16.5 Hz, 1 H), 3.80 (s, 3 H), 2.77 (s, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 155.8, 154.2, 144.6, 142.8, 140.0, 132.6, 125.7, 124.1, 122.5, 119.3, 115.7, 111.1, 108.8, 80.4, 50.9, 43.5, 23.9.
**6-Chloro-9-methyl-7-(4-nitrobenzyl)-8-phenethyl-8,9-dihydro-7*H*-purine (8a)**
Yellow solid, yield 65% (elution with EtOAc–PE, 1:2); mp 123–125 °C. ES-MS: *m/z* = 410.1 $[M + 1]^+$. $^1H$ NMR (500 MHz, DMSO): δ = 8.23 (d, *J* = 8.5 Hz, 2 H), 7.70 (s, 1 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 7.17–7.20 (m, 2 H), 7.10–7.13 (m, 1 H), 7.02–7.03 (m, 2 H), 5.32 (s, 1 H), 4.85 (d, *J* = 17.5 Hz, 1 H), 4.69 (d, *J* = 17.0 Hz, 1 H), 2.89 (s, 3 H), 2.46–2.56 (m, 1 H), 2.40–2.44 (m, 1 H), 2.05–2.10 (m, 1 H), 1.85–1.91 (m, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.4, 149.6, 149.5, 147.5, 144.8, 140.4, 128.5, 128.0, 127.6, 126.2, 123.9, 82.5, 50.3, 33.0, 28.4, 27.7.
(11) Crystallographic data for structure **8a** reported in this paper in the form of CIF file has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-689708. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44 (1223)336033; e-mail: deposit @ccdc.cam.ac.uk].