SHORT PAPER

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Syntheses of 1-allyl-6-(arylamino)methyl-7-methyl-3-phenylpteridine-2,4-dione, a methanopterin analogue†

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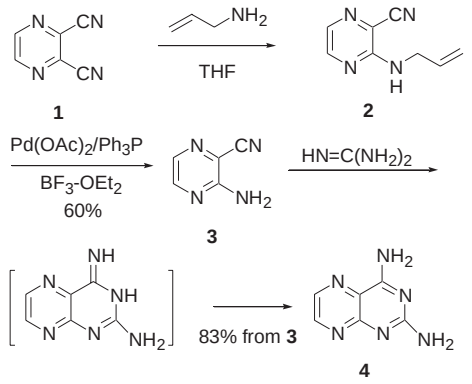
The nucleophilic substitution of 2,3-dicyanopyrazine (**1**) with allylamine is useful for the construction of pteridine ring. A methanopterin analogue, 1-allyl-6-(mesitylamino)methyl-7-methy-3-phenylpteridine (**12**), was synthesised by this method from 2,3-dicyano-5-hydroxymethyl-6-methylpyrazine (**5**) deriving from 2,3-dicyanopyrazine (**1**).

Keywords: radical substitution of pyrazine, nucleophilic substitution of pyrazine**,** pteridine synthesis, methanopterin analogue

Folic acid[1,2] and methanopterin[3] contain a pteridine moiety. Most pteridine syntheses start from the pyrimidine moiety of the pteridine structure, but a few syntheses start from the pyrazine moiety of pteridine ring.[4] We have reported the substitution of 2,3-dicyanopyrazine with amines[5] and its application to syntheses of pteridine-2,4-diones.[6]

Results and discussion

Pyrazines are π-electron deficient heteroaromatics which permit substitution reactions with nucleophiles.[5] Thus 2,3-dicyanopyrazine (**1**) affords the substitution product, 2-allylamino-3-cyanopyrazine (**2**), upon reaction with allylamine. Removal of the allyl group was achieved by the palladium catalysed reductive cleavage[7] to give 2-amino-3-cyanopyrazine (**3**)[8] which was converted to 1,3-diaminopteridine (**4**)[9] *via* an imino derivative (Scheme 1).

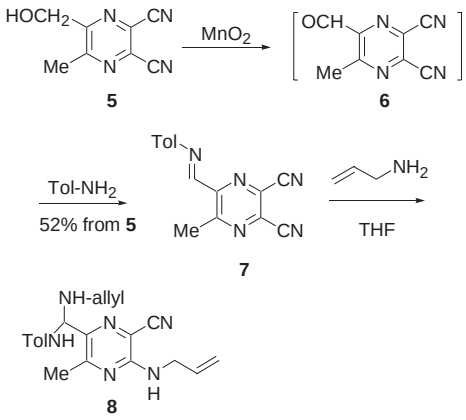


Scheme 1

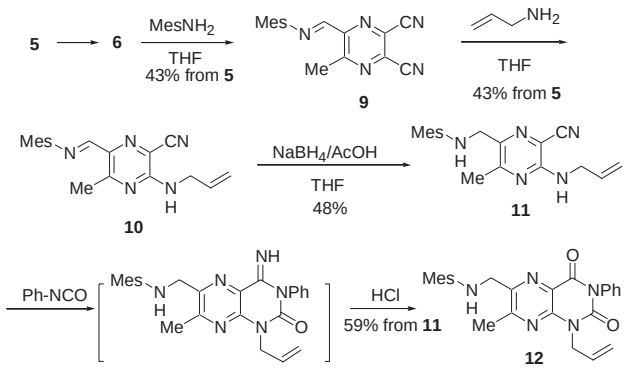
This findings prompted us to utilise dicyanopyrazine for the synthesis of a more complex pteridine ring as shown in Scheme 2.

Compound **5**[6c] was subjected to MnO_2-oxidation to **6** followed by condensation with toluidine to give 2,3-dicyano-5-methyl-6-(tolylimino)methylpyrazine (**7**). Next, one of the cyano groups on **7** was substituted with allylamine. This reaction gave a mixture containing diaza-acetal **8** formed by the addition of the allylamine to the imino-moiety of **7** in addition to the substitution on the pyrazine ring (Scheme 2).

The reaction of **6** with mesitylamine gave 2,3-dicyano-6-(mesitylimino)methyl-5-methylpyrazine (**9**). Reaction of **9** with allylamine gave the cyano-substitution product **10** without diaza-acetal formation as a consequence of steric



Scheme 2



Scheme 3

inhibition at the imino-moiety. Only the *para* cyano group to the imino-group was substituted due to the electron withdrawing effect of the imino-group. Compound **10** was readily reduced to 3-allylamino-2-cyano-6-(mesitylamino) methyl-5-methylpyrazine (**11**). The stepwise treatment of **11** with phenylisocyanate and hydrochloric acid gave 1-allyl-6-(mesitylamino)methyl-7-methyl-3-phenylpteridine-2,4-dione (**12**). Removal of the allyl group from **12** by the same procedure for 2-allylamino-3-cyanopyrazine (**2**) failed and resulted in complete recovery of **12**. This property must originate from the steric hindrance to the formation of allyl-palladium intermediate (Scheme 3).

In conclusion, we synthesised a methanopterin analogue, 1-allyl-6-(mesitylamino)methyl-7-methyl-3-phenylpteridine-2,4-dione (**12**), starting from 2,3-dicyanopyrazine (**1**) by utilising nucleophilic substitution of the cyano group with allylamine on the pyrazine ring.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

*Synthesis of 2,4-diaminopteridine (**4**) from 2,3-dicyanopyrazine (**1**):* In a dried and nitrogen flushed flask were placed 10 ml of THF, 650 mg of 2,3-dicyanopyrazine (5.0 mmol) and 3.8 ml of allylamine (50 mmol). The mixture was stirred for 2h under nitrogen at room temperature. Concentration of the reaction mixture and chromatography on alumina (hexane–EtOAc, 5:1) gave 314 mg of the allylamino-substitution product **2** (39%).

2, m.p. 76.5–77.8°C(EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12–4.18(2H, m), 5.20–5.25(1H, m), 5.25–5.33(1H, m), 5.37(1H, br. s, NH), 5.88–6.02(1H, m), 7.91(1H, d, *J* 2.6 Hz), 8.22(1H, d, *J* 2.6 Hz); ^{13}C NMR(125 MHz) δ 43.4, 114.5, 115.2, 117.3, 133.4, 133.7, 146.1, 155.5; IR 3430, 2224, 1677, 1534, 1507 cm^{-1}; MS(FAB) *m/z* 161 (M + H). Anal C, 59.95; H, 4.79; N, 34.88. Cacd for $C_8H_8N_4$ C, 59.99; H, 5.03; N, 34.98.

In a nitrogen flushed flask were placed 22.5 mg of palladium acetate (0.1 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 3 ml of EtOH, and the mixture was stirred for 1h at room temperature. To the above mixture were added compound **2** (160 mg, 1.0 mmol) and 3 ml of BF_3-etherate dissolved in 7 ml of EtOH, and the mixture was refluxed for 21h. Concentration of the reaction mixture, chromatography on silica gel (hexane-EtOAc, 7:3) and recrystallisation from EtOH gave the aminopyrazine (**3**) in 60% yield.

3,[8] m.p. 187.5–188.5°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (2H, br. s, NH), 8.03(1H, d, *J* 2.6 Hz), 8.22(1H, d, *J* 2.6 Hz).

A mixture of 90 mg of guanidinium carbonate (0.5 mmol), 54 mg of NaOMe (1.0 mmol) and 60 mg of compound **3** (0.5 mmol) in 1.5 ml of MeOH was refluxed for 4h. Filtration, concentration and washing with MeOH gave diaminopteridine **4** in 83% yield.

4,[9] ^{1}H NMR(400 MHz, $CDCl_3$) δ 6.66(2H, br. s, NH_2), 7.70(2H, br. s, NH_2), 8.27(1H, d, *J* 2.2 Hz), 8.68(1H, d, *J* 2.2 Hz).

*Imidation of 2,3-dicyano-6-hydroxymethyl-5-methylpyrazine (**5**):* Compound **5**[6c] (520 mg, 3.0 mmol) in 30 ml of CH_2Cl_2 was treated with freshly prepared MnO_2 (2.7 g, 30 mmol) and the mixture was stirred for 21h at the room temperature. Filtration and concentration of the mixture gave the crude aldehyde **6**. The aldehyde **6** thus obtained was directly subjected to imination by toluidine (223 mg, 2.1 mmol) using one drop of AcOH, 750 mg of molecular sieves (4A) and 10 ml of EtOH (stirring for 2h). Concentration of the mixture and chromatography on silica gel (CH_2Cl_2) gave crude crystals. Recrystallisation of the crude crystals from $CHCl_3$ yielded the imine **7** in 52% yield.

7, m.p. 176.5–178.5°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.42(3H, s), 3.17(3H, s), 7.29(4H, diff. s), 8.77(1H, s); ^{13}C NMR (125 MHz) δ 21.3, 25.1, 112.8, 113.0, 121.5, 130.3(2C),130.9, 139.6, 146.8, 149.9, 155.9, 159.0; IR 2243, 1592, 1524, 1503 cm^{-1}; MS(EI) *m/z* 261(36%, M$^+$). Anal C, 68.91, H, 4.05; N, 27.04. Calcd for $C_{16}H_{11}N_5$ C, 68.95; H, 4.24; N, 26.80.

*Synthesis of pteridinedione (**12**) from hydroxymethylpyrazine (**5**). The* imine **9** was synthesised from 2,3-dicyano-6-hydroxymethyl-5-methylpyrazine **5**[6c] by the same procedure for the synthesis of the imine **7** and was obtained in 43% yield. The substitution of the imine **9** with allylamine was carried out in the same manner as the reaction of the imine **7** and produced allylaminopyrazine **11**, which was thermally unstable and could not be recrystallised. Compound **11** was dissolved in 4 ml of THF and treated with 189 mg of $NaBH_4$ (5.0 mmol) in 5 ml of THF containing 0.91 ml of AcOH (16 mmol) and the mixture was stirred for 2h at room temperature. After adding aq-$NaHCO_3$, the product **11** was obtained in 48% yield from **10** after silica gel chromatography (hexane-EtOAc, 7:3) and recrystallisation from EtOH. The product **11** was converted to the dione **12** by treatment with phenylisocyanate (18 ml, 0.16mol) and NaH (81 mmol) in 1.l ml of THF. After stirring for 1h at room temperature, the mixture was treated with 2 mol/l HCl and extracted with CH_2Cl_2. Further treatment of the extract with 2 mol/l HCl under reflux for 1h gave the dione **12** in 59% yield.

9: m.p. 177.5–170.3°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.18(6H, s), 2.31(3H, s), 3.18(3H, s), 6.95(2H, s), 8.48(1H, s, N=CH); ^{13}C NMR (125 MHz) δ 18.6, 20.8, 25.1, 112.7, 112.9, 126.8, 129.4, 130.3, 131.3, 135.5, 147.1, 149.4, 158.9, 161.1; IR 2244, 1635, 1526 cm^{-1}; MS(EI) *m/z* 289(29%, M$^+$). Anal C, 70.38; H, 5.11; N, 24.29. Calcd for $C_{17}H_{15}N_5$ C, 70.57; H, 5.23; N, 24.21.

10 was thermally unstable, and recrystallisation caused a slight decomposition. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.12(6H, s), 2.28(3H, s), 2.93(3H, s), 4.23–4.26(2H, diff. s), 5.23–5.26(1H, m), 5.29–5.34(1H, m), 5.54(1H, br. s, NH), 5.91–6.01(1H, m), 6.90 (2H, s), 8.24(1H, s, N=CH); ^{13}C NMR δ 18.4, 20.7, 24.9, 43.5, 110.5, 115.1, 117.6, 126.4, 128.9, 133.3, 133.4, 137.7, 148.5, 153.5, 158.6, 162.0; HRMS(FAB) *m/z* 320.1884. Calcd for ($C_{19}H_{21}N_5$ + H) *m/z* 320.1875.

11: m.p. 91.5–93.0°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.24(3H, s), 2.31(6H, s), 2.42(3H, s), 4.09(2H, s), 4.14–4.17(2H, m), 5.19–5.22(1H, m), 5.25–5.30(1H, m), 5.89–5.99(1H, m), 6.84(2H, s); ^{13}C NMR (125 MHz) δ 18.4, 20.6, 21.6, 43.4, 50.0, 109.3, 115.9, 117.0, 129.5, 130.0, 131.8, 133.9, 141.6, 143.3, 154.1, 155.0; IR 3429, 3375, 2218, 1575, 1487 cm^{-1}; MS(FAB) *m/z* 321(M$^+$). Anal C, 70.72; H, 7.16; N, 21.98. Calcd for $C_{19}H_{23}N_5$ C, 71.00; H, 7.21; N, 21.79.

12: ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.23(3H, s), 2.37(6H, s), 2.64(3H, s), 4.38(2H, s), 4.97(2H, d, *J* 5.9 Hz), 5.25(1H, dd, *J* 10.3 and 1.2 Hz), 5.34(1H, dd, *J* 17.1 and 1.2 Hz), 5.99(1H, ddt, *J* 5.9, 17.1, and 10.3 Hz), 6.83(2H, s), 7.30–7.32(2H, m), 7.45–7.49 (1H, m), 7.52–7.56(2H, m); ^{13}C NMR δ 18.7, 20.5, 21.7, 44.6, 50.5, 119.0, 124.6, 128.3, 129.0, 129.5(2C), 131.4, 131.5, 134.9, 143.5, 146.4, 149.0, 150.3, 157.1, 159.8; IR 3375, 1729, 1684 1558 1486 cm^{-1}; HRMS(FAB) *m/z* 442.2262. Calcd fior ($C_{26}H_{27}N_5O_2$ + H) *m/z* 442.2243.

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