SHORT PAPER

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Synthesis of new 4-amino-2,6-diarylpyrimidine-5-carbonitriles†

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A facile synthesis of the title compounds **5a–e**, from appropriate amidines and benzylidenemalononitriles, is described.

Keywords: aminopyrimidines, amidines

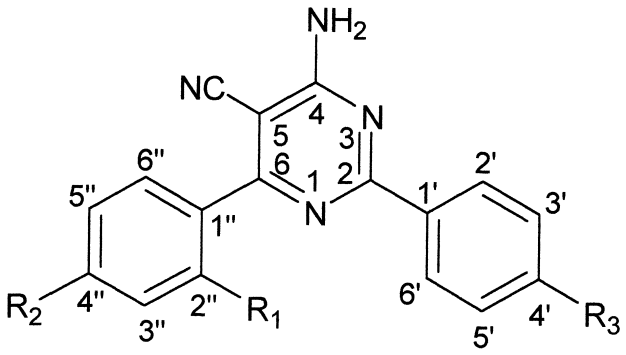
Pyrimidines in general have enormous synthetic and biological significance. A review by Brown deals with the details of these compounds.[1] When the amino group is present in the system, certain interesting biological activities are observed. For example, lipophilic antifolate drugs such as trimethoprim (TMP)[2], pyrimethamine[3], trimetrexate (TMQ)[4,5], and piritrexim (PTX)[6] are currently used for the treatment of opportunistic infections which are caused by *Pneumocystis carinii* and *Toxoplasma gondii*. These infections lead to the death of patients suffering from Aquired Immunodeficiency Syndrome (AIDS). All these compounds possess amino groups at the 2 and 4 positions.

Modifications of the above-mentioned drugs have been made by Gangjee *et al*.[7] and one of the compounds, a 5-deaza n10-Me 3,4,5-trimethoxy analogue, showed high potency and selectivity against both *Toxoplasma gondii* and *Pneumocystis carinii* dihydrofolate reductase (tgDHFR and pcDHFR). This compound was slightly less selective when compared with trimethroprim, but was 300-fold more potent against tgDHFR.

Considering the importance of a large member of pyrimidine derivatives, we decided to synthesise 4-amino-2,6-diarylpyrimidine-5-carbonitriles by modification of previous procedures.[8,9] The reason for undertaking this work was that 4-aminopyrimidines possess excellent pharmacological properties. Just to show the importance of such pyrimidines, thiamin (vitamin B_1)[10] is considered as an example; it is an antineuritic vitamin and is essential for growth and the prevention of beriberi. Thiamin functions in the body in the form of coenzyme thiamine pyrophosphate (TPP). The present communication deals with the synthesis and characterisation of five new substituted pyrimidines **5a–e** (Fig.1).

The synthesis of unsaturated bisnitriles **3a,b,c** was achieved when aldehydes **1a,b,c** were allowed to react with malonitrile **2** by a modification of the literature procedure.[11,12] Compounds **3a**,**b**,**c** were condensed individually with arylamidines **4** in the presence of piperidine to form **5a–e** (Scheme 1).[8,9]

All these compounds gave a single spot on thin-layer chromatograms. The mass spectra of all compounds showed the molecular ions. The infrared as well as the ^{1}H NMR spectra agreed with the proposed structures of **5a–e**. However, the ^{1}H NMR spectra of **5c** and **5d** showed identical chemical shifts for H-5″ and H-6″. This equivalence may be explained considering that the electron-withdrawing power of the pyrimidine ring is approximately equal to the two chlorine atoms attached at the R_1 and R_2 positions of the phenyl ring.



5a: R_1=H; R_2=Cl; R_3=OCH_3
5b: R_1=R_3=H; R_2=F
5c: R_1=R_2=Cl; R_3=OCH_3
5d: R_1=R_2=Cl; R_3=H
5e: R_1=H; R_2=F; R_3=OCH_3

Fig. 1 4-Amino-2,6-diarylpyrimidine-5-carbonitriles.

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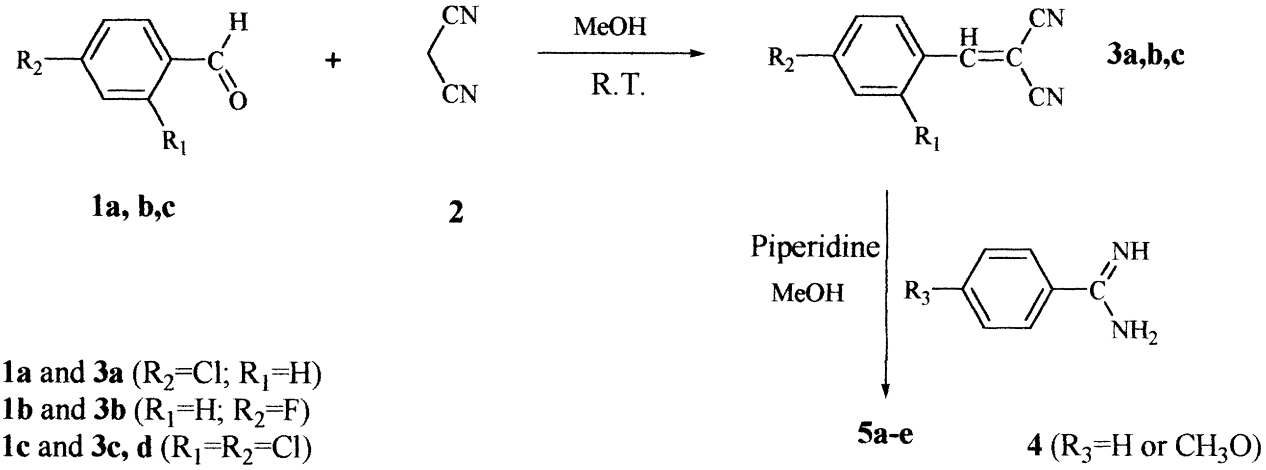

Scheme 1

Experimental

The infrared spectra (IR) were recorded with a Bruker spectrophotometer, model IFS 66 (Fourier transform) utilising KBr pellets. The EI mass spectra were obtained with a Delsi-Nermag mass spectrometer, coupled to GC (HP 5890) at an ionisation potential of 70eV. The ^{1}H NMR spectra were recorded with a 300MHz Varian spectrophotometer model UNITY.

Preparation of bisnitriles (**3**): The appropriate aldehyde **1** (24 mmol) and malonitrile **2** (24mmol) were dissolved in methanol under stirring, and the contents were stirred for 4h at room temperature. The reaction was monitored by thin layer chromatography. Solvent evaporation left a solid mass, which was chromatographed over a silica gel column. Elution with *n*-hexane–ethyl acetate (8 : 2) afforded the desired compound. The nitriles described in this work are known and their m.ps agreed with the literature.[11, 12]

Preparation of 4-amino-2,6-diarylpyrimidine-5-carbonitriles (**5a–e**): Bisnitrile **3** (5.36 mmol) and arylamidine **4** (5.36 mmol) were dissolved in methanol (20 ml) and refluxed for 7h . The contents were cooled to room temperature and solvent evaporated to give a solid mass, which was chromatographed over silica gel. The desired compound was eluted using a mixture of *n*-hexane–ethyl acetate (8 : 2). The fractions containing **5** were combined, the solvent evaporated, and the product crystallised from methanol in every case.

4-Amino-2-(p-anisyl)-6-(p-chlorophenyl)-pyrimidine-5-carbonitrile (**5a**): Colourless crystals (1.02g), yield 56%; m.p. 234–235°C; R_f = 0.32 (*n*-hexane–ethyl acetate 8 : 2); $\nu_{max.}$/ cm^{-1} (KBr) 3444, 3382, 2205, 1606; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 8.35 (2H, d, *J* = 8.8Hz, H$_2'$, H$_6'$); 8.0 (2H, d, *J* = 8.40 Hz, H$_3''$,H$_5''$); 7.9 (2H, b, NH$_2$); 7.67 (2H, d, *J* = 8.70 Hz, H$_2''$, H$_6''$); 7.08 (2H, d, *J* = 8.80 Hz, H$_3'$, H$_5'$); 3.82 (3H, s, OCH$_3$); *m/z* (rel. int.) 336 (M$^+$, 100), 338 (29), 203 (53); [Found: C 62.60; H 3.98; N 16.63; Calc. for C$_{18}$H$_{13}$ClN$_4$O.½H$_2$O: C 62.52; H 4.08; N 16.20%].

4-Amino-2-(pheny)-6-(p-fluorophenyl)-pyrimidine-5-carbonitrile (**5b**): Colourless crystals (1.20g), yield: 77%; m.p. 225–227°C; R_f = 0.52 (*n*-hexane–ethyl acetate 8 : 2); $\nu_{max.}$/ cm^{-1} (KBr): 3474, 3350, 2217, 1640; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 8.40 (2H, dd, *J* = 7.00 Hz, H$_2'$, H$_6'$); 8.07 (2H, dd, *J* = 8.08 Hz, *J* = 5.60 Hz, H$_3''$, H$_5''$); 8.00 (2H, b, NH$_2$); 7.43–7.58 (3H, m, H$_2''$, H$_4'$ and H$_6''$); 7.43 (2H, t, *J* = 8.80Hz, H$_3'$ and H$_5'$). *m/z* (rel. int) 290 (M$^+$,100), 187 (78): [Found: C 68.29; H 3.82; N 18.50; Calc. for C$_{17}$H$_{11}$FN$_4$.½H$_2$O: C 68.25; H 4.04; N 18.71%].

4-Amino-2-(p-anisyl)-6-(2,4-dichlorophenyl)-pyrimidine-5-carbonitrile **5c**: Colourless crystals (0.62g), yield: 31%; m.p. 193–196°C; R_f = 0.51 (*n*-hexane–ethyl acetate 8:2); $\nu_{max.}$/ cm^{-1} (KBr) 3429, 3319, 2278, 1634; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 8.26 (2H, d, *J* = 9.0 Hz, H$_2'$, H$_6'$); 7.93 (2H, b, NH$_2$); 7.81 (1H, bs, H$_3''$); 7.6 (2H, bs, H$_5''$, H$_6''$); 7.03 (2H, d, *J* = 9.0Hz, H$_3'$,H$_5'$); 3.65 (3H, s, OCH$_3$); *m/z* (rel. int) 371 (21), 370 (71); 237 (M$^+$, 100): [Found: C 58.39; H 3.50; N 15.18; Calc. for C$_{18}$H$_{12}$Cl$_2$N$_4$O.¼H$_2$O: C 58.24; H 3.26; N 15.09%].

4-Amino-2-phenyl-6-(2,4-dichlorophenyl)-pyrimidine-5-carbonitrile (**5d**): Colourless crystals (0.30g), yield: 16%; m.p. 170–174°C; R_f = 0.31 (*n*-hexane–ethyl acetate 8 : 2); $\nu_{max.}$/ cm^{-1} (KBr) 3468, 3330, 2228, 1631; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 8.30 (2H, dd, *J* = 8.1Hz, *J* = 1.2Hz, H$_2'$, H$_6'$); 8.04 (2H, b, NH$_2$); 7.82 (1H, bs, H$_3''$); 7.62 (2H, bs; H$_5''$ and H$_6''$); 7.46–7.58 (3H, m, H$_3'$, H$_4'$, H$_5'$); *m/z* (rel. int) 340 (M$^+$,100), 342 (67), 237 (61): [Found: C 59.77; H 3.31; N 16.64; Calc. for C$_{17}$H$_{10}$Cl$_2$N$_4$: C 59.84; H 2.95; N 16.42%].

4-Amino-2-(p-anisyl)-6-(p-fluorophenyl)-pyrimidine-5-carbonitrile (**5e**): Colourless crystals (0.84g), yield: 49%; m.p. 215–217°C; R_f = 0.38 (*n*-hexane–ethyl acetate 8 : 2); ν_{max}/ cm^{-1} (KBr) 3446, 3356, 2209, 1648; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 8.34 (2H, d, *J* = 9.15 Hz, H$_2'$, H$_6'$); 8.01 (2H, dd, *J* = 8.72 Hz, *J* = 5.52Hz, H$_3''$, H$_5''$); 7.75 (2H, b, NH$_2$); 7.39 (2H, t, *J* = 9.00 Hz, H$_2''$, H$_6''$); 7.05 (2H, d, *J* = 9.15Hz, H$_3'$, H$_5'$); 3.65 (3H, s, CH$_3$O); *m/z* (rel. int) 320 (M$^+$,100), 187 (99,5): [Found: C 66.61; H 4.39; N 17.35; Calc. for C$_{18}$H$_{13}$FN$_4$O.¼H$_2$O: C 66.57; H 4.19; N 17.25%].

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