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A FACILE PREPARATION OF N^2-ARYLISOCYTOSINES

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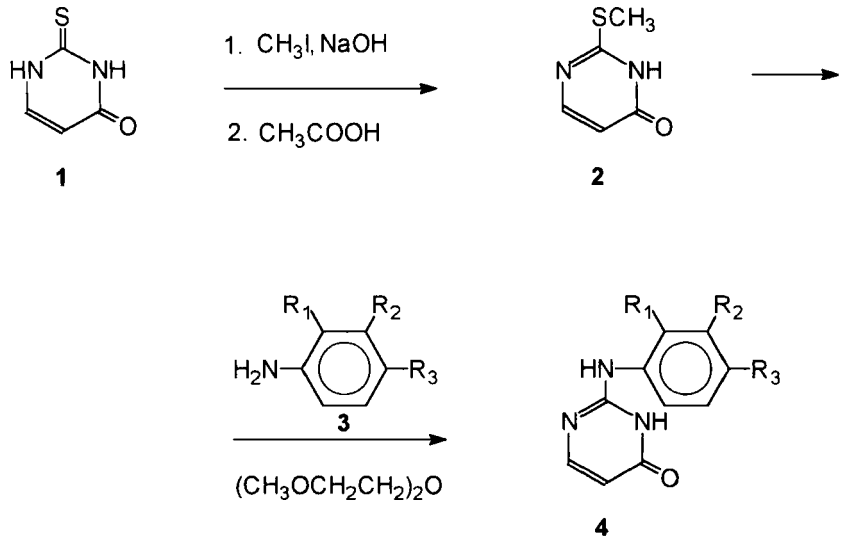
Abstract: N^2-Arylisocytosines were obtained in good yields varying from 59 to 96% by a simple two-step process starting from 2-thiouracil *via* readily accessible 2-(methylthio)pyrimidin-4(3*H*)-one.

Although N^4 - substituted cytosines have for a long time attracted much attention due to their various biological effects, the parent isocytosines are comparatively little known.[1-5] Already sometime ago, we published the syntheses and properties of certain cytosines.[6-10] Our MS, NMR and FTIR studies have shown that N^4-substituted cytosines differ significantly from the corresponding isocytosines.[11-19]

In this communication , I report a general and facile procedure for the synthesis of N^2-arylisocytosines. Treatment of 2-(methylthio)pyrimidin-4(3*H*)-one (**2**) with a small excess of an arylamine **3** in refluxing bis(2-methoxyethyl) ether[8] results in precipitation of N^2-arylisocytosines **4**. N^2-Phenylisocytosine (**4a**) has been prepared previously, but with no mention of the yield obtained.[20] The S-alkylated

intermediate **2** was obtained by methylation of 2-thiouracil (**1**) with methyl iodide. This is a slight modification of a literature method developed for 6-methyl--4-(methylthio)pyrimidin-2(1*H*)-one.[21] Previous synthesis of **2** involved a direct ring formation.[22] All the synthesized compounds gave analytical and spectral data in agreement with their structures. We have already described their mass spectrometric behavior (compounds **4a-g**).[17] Moreover, some isocytosine derivatives **4e-g** have been studied by ^{35}Cl-NQR spectroscopy.[23]



Scheme. **a)** R_1= R_2= R_3= H, **b)** R_1= CH_3, R_2= R_3= H, **c)** R_1= R_3= H, R_2= CH_3, **d)** R_1= R_2= H, R_3= CH_3, **e)** R_1= Cl, R_2= R_3= H, **f)** R_1= R_3= H, R_2=Cl, **g)** R_1= R_2= H, R_3= Cl, **h)** R_1= R_2= H, R_3= CN, **i)** R_1= R_2= H, R_3= CH_2CN.

Experimental

Melting points were recorded in a Boetius melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were determined on Varian Gemini (300 MHz) or Jeol JNM-GX (270 MHz) spectrometers in DMSO-d_6 using TMS as internal reference. UV spectra were recorded in methanol in a Shimadzu UV-160 spectrophotometer. Mass spectra were made in a Jeol JMS D-100 double-focusing mass spectrometer. TLC analyses were performed with silica gel 60 F_{254} plates (Merck), and developed with $CHCl_3$: CH_3OH=18:1 or 9:1 (v/v). 2-Thiouracil (**1**) was purchased from Fluka and Aldrich Chemical Companies, and used without purification. Starting anilines **3** were commercially available and distilled before use if necessary.

Synthesis of 2-(methylthio)pyrimidin-4(3*H*)-one (**2**)

2-Thiouracil (128.15 g, 1mol) was dissolved in a sodium hydroxide solution (80 g of solid NaOH in 700 ml of water), then methyl iodide (70 ml, 1.12 mol) was added, and the resulting mixture was stirred overnight at room temperature. Then, the solution was acidified with glacial acetic acid (55 ml) and refrigerated. The separated white precipitate was collected, washed several times with cold water, and dried to afford chromatographically pure product (117.30g, 88 %), which can be recrystallized from boiling ethanol (1g from 20 ml), or water, m.p. 203-4 °C (lit.[22] 188-189 °C).

^{1}H-NMR (CD_3OD, TMS), δ, 2.55 (s, 3H), 6.13 (d, 1H, J= 6.84 Hz), 7.84 (d, 1H, J= 6.84 Hz). MS,[24] m/z (rel. int.), 142 (100), 114 (4), 95 (18), 70 (9), 69 (8).

Syntheses of N^2-arylisocytosines (**4**)

A mixture of 2-(methylthio)pyrimidin-4(3*H*)-one (**2**, 5g, 0.0352 mol), and an appropriate arylamine **3** (0.0422 mol) in bis(2-methoxyethyl) ether (10 ml) was refluxed overnight (18 h). The heating results in precipitation of crystals, which were collected by filtration with the aid of ethyl ether, and then washed with ethyl ether and water. The resulting solid was recrystallized from methanol or extracted in a Soxhlet apparatus if necessary to give chromatographically pure **4** in the yield of 59-96 %. Product **4i** was recrystallized from boiling aqueous DMF.

2-(Phenylamino)pyrimidin-4(3*H*)-one (**4a**)

M. p. 236-7 °C (lit.[20] 230-1°C), yield 96 %.

^{1}H-NMR, δ, 5.86 (d, 1H, J= 6.51 Hz), 7.07 (t, 1H, J= 7.33 Hz), 7.34 (t, 2H, J= 7.83 Hz), 7.60 (d, 2H, J= 7.77 Hz), 7.76 (d, 1H, J= 6.59 Hz).

UV, λ_{max} 300 nm, ε_{max} 11130.

2-[(2-Methylphenyl)amino]pyrimidin-4(3*H*)-one (**4b**)

M. p. 221-2 °C, yield 59 %.

^{1}H-NMR, δ, 2.23 (s, 3H), 5.74 (d, 1H, J= 6.60 Hz), 7.06 (t, 1H, J= 7.39 Hz), 7.17 (d, 1H, J= 7.69 Hz), 7.22 (d, 1H, J= 7.42 Hz), 7.63 (d, 1H, J= 6.53 Hz), 7.75 (d, 1H, J= 7.97 Hz).

UV, λ_{max} 295 nm, ε_{max} 9327.

2-[(3-Methylphenyl)amino]pyrimidin-4(3*H*)-one (**4c**)

M. p. 258-9 °C, yield 90 %.

^{1}H-NMR, δ, 2.30 (s, 3H), 5.82 (d, 1H, J= 6.32 Hz), 6.87 (d, 1H, J= 7.27 Hz), 7.21 (t, 1H, J= 7.97 Hz), 7.36-7.49 (m, 2H), 7.76 (d,1H, J= 6.59 Hz).

UV, λ_{max} 302 nm, ε_{max} 11354.

2-[(4-Methylphenyl)amino]pyrimidin-4(3*H*)-one (**4d**)

M. p. 275-6 °C, yield 94 %.

^{1}H-NMR, δ, 2.26 (s, 3H), 5.78 (d, 1H, J= 6.32 Hz), 7.12 (d, 2H, J= 8.24 Hz), 7.47 (d, 2H, J= 8.30 Hz), 7.72 (d, 1H, J= 6.59 Hz).

UV, λ_{max} 302 nm, ε_{max} 11169.

2-[(2-Chlorophenyl)amino]pyrimidin-4(3*H*)-one (**4e**)

M. p. 226-7 °C, yield 63 %.

^{1}H-NMR, δ, 5.82 (d, 1H, J= 6.35 Hz), 7.13 (t, 1H, J= 7.66 Hz), 7.34 (t, 1H, J= 7.80 Hz), 7.50 (d, 1H, J= 8.03 Hz), 7.69 (d, 1H, J= 6.35 Hz), 8.15 (br. d, 1H, J= 7.96 Hz), 11.25 (br. s, 1H).

UV, λ_{max} 285 nm, ε_{max} 10359.

2-[(3-Chlorophenyl)amino]pyrimidin-4(3*H*)-one (**4f**)

M. p. 247-9 °C, yield 77 %.

^{1}H-NMR, δ, 5.93 (d, 1H, J= 6.32 Hz), 7.06 (d, 1H, J= 7.97 Hz), 7.33 (t, 1H, J= 7.97 Hz), 7.46 (d, 1H, J= 8.25 Hz), 7.86 (d, 1H, J= 6.31 Hz), 7.95 (s, 1H).

UV, λ_{max} 298 nm, ε_{max} 13134.

2-[(4-Chlorophenyl)amino]pyrimidin-4(3*H*)-one (**4g**)

M. p. 244-5 °C, yield 79 %.

^{1}H-NMR, δ, 5.90 (d, 1H, J= 6.53 Hz), 7.38 (d, 2H, J= 8.52 Hz), 7.37 (d, 2H, J= 8.58 Hz), 7.82 (d, 1H, J= 6.32 Hz).

UV, λ_{max} 291 nm, ε_{max} 12351.

2-[(4-Cyanophenyl)amino]pyrimidin-4(3*H*)-one (**4h**)

M. p. 307-9 °C, yield 68 %.

^{1}H-NMR, δ, 6.03 (d, 1H, J= 6.35 Hz), 7.74 (d, 2H, J= 8.79 Hz), 7.88 (d, 2H, J= 8.79 Hz), 7.95 (d, 1H, J= 6.35 Hz).

UV, λ_{max} 306 nm, ε_{max} 29836.

MS, m/z (rel. int.), 212 (54), 211 (100), 143 (13), 105 (11), 95 (13).

2-{[4-(Cyanomethyl)phenyl]amino}pyrimidin-4(3*H*)-one (**4i**)

M. p. 227-9 °C (dec.), yield 64 %.

^{1}H-NMR, δ, 3.98 (s, 2H), 5.84 (d, 1H, J= 6.31 Hz), 7.29 (d, 2H, J= 8.76 Hz), 7.63 (d, 2H, J= 8.46 Hz), 7.78 (d, 1H, J= 5.34 Hz), 8.95 (br. s, 1H), 10.85 (br. s, 1H).

UV, λ_{max} 299 nm, ε_{max} 12910.

MS, m/z (rel. int.), 226 (68), 225 (100), 198 (5), 185 (6), 116 (11).

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