Synthesis of *N*-Heterocycles *via* Chalcone Epoxides. 1. Amino and Hydrazinopyrimidines

Rasaki Abayomi Osisanya and James Olabisi Oluwadiya* [1]

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ife, Ile-Ife, Nigeria

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Chalcone epoxides have been used as precursors in the synthesis of 2-amino- and 2-hydrazinopyrimidines.

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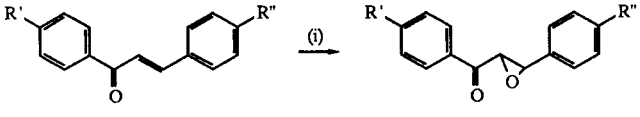
In continuation of our search for heterocyclic based antiinfective agents [2,3] chalcone epoxides have been used as precursors in the synthesis of pyrimidines. 4'-Methoxychalcone (**1a**) and its derivatives **1b** and **1c** were treated with hydrogen peroxide [4] in an alkaline medium to give chalcone epoxides **2a-c** in good yields.



1a-c **2a-c**

a: R' = OCH_3, R" = H

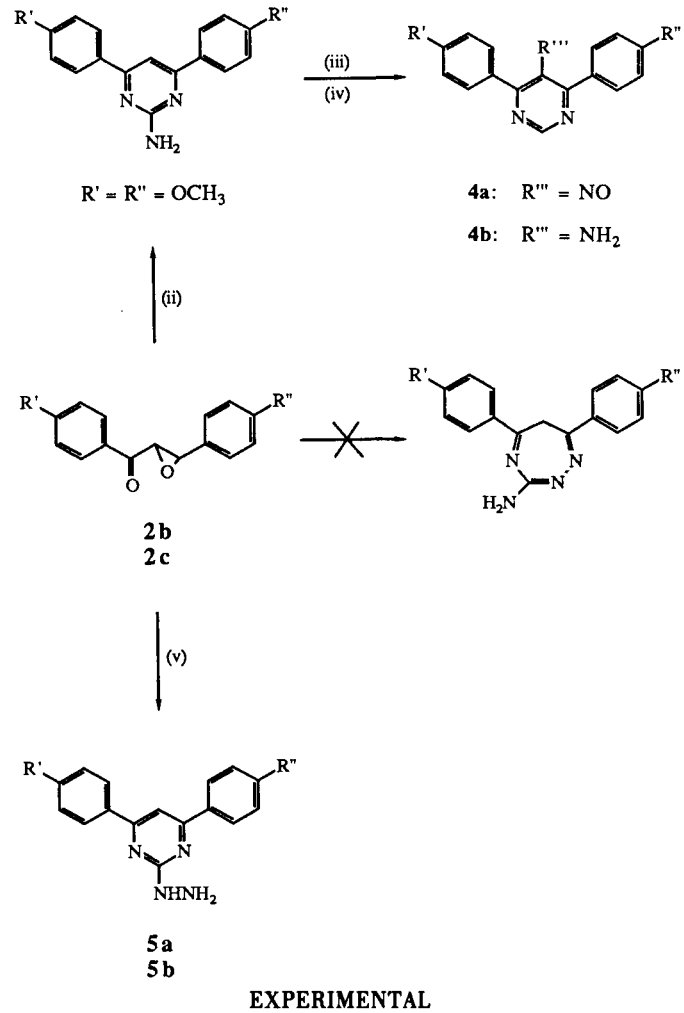
b: R' = R" = OCH_3

c: R' = OCH_3, R" = Cl

(i) H_2O_2/OH^-

In this work, chalcone epoxide **2b** was reacted with guanidine carbonate in boiling xylene to give 2-aminopyrimidine **3** which on nitrosation gave 5-nitrosopyrimidine **4a** since nitrosation usually occurs at C-5 and this is accompanied by diazotisation at C-2 with concomitant loss of nitrogen [5]. Reduction of the nitroso compound **4a** gave 5-aminopyrimidine **4b**. The epoxides **2b** and **2c** when treated with aminoguanidine obtained through Schwen-Papa reduction [6] of nitroguanidine in dilute sodium hydroxide gave 2-hydrazinopyrimidine **5a** and **5b** respectively and not the triazepine **6**.

The structures of the pyrimidines were unambiguously confirmed by use of physico-chemical methods, *viz.* ir, pmr, elemental analyses and ms. The ir spectra [7] of the compounds showed absorptions at 3500-3440 cm^{-1}, characteristic of primary aromatic amino moiety, 1690-1630 cm^{-1} which is due to the presence of C=N and also 1610-1580 cm^{-1} due to C=C. The pmr signals of the compounds showed characteristic aromatic *ortho* coupling as doublets, J = 9 Hz while the pyrimidine ring C-5 or C-2 protons appeared as singlets in all cases. The -NH_2 was deuterium oxide exchangeable. The mass spectra of the 2- and 5-aminopyrimidines showed the parent ion as the molecular ion (relative abundance 100% which showed that they are more stable than the hydrazinopyrimidines whose ions are of low intensity.



R' = R" = OCH_3 **4a**: R'" = NO **4b**: R'" = NH_2

2b **2c**

5a **5b**

EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra were run on Pye Unicam SP3-300 instrument. Proton magnetic resonance (pmr) were run on either Varian FT-80A or Nicolet 360 MHz instrument while the mass spectra (ms) were determined using LKB mass spectrometer both at 12 eV or 70 eV.

General Procedure for the Formation of 4'-Methoxychalcone Epoxides.

Hydrogen peroxide (30%, 1 ml) was added to a solution of sodium carbonate (1 g, anhydrous) in water (1 ml). This was added to a warm solution of chalcone (1.0 g) in ethanol (10 ml). The mixture was then left at room temperature overnight. A solid precipitate which was deposited was filtered and washed throughly with

water (filterate neutral to litmus). This solid was then recrystallised from ethanol. 4'-Methoxychalcone **2a** (2.15 g) was obtained from 4'-methoxychalcone **1a** (3.0 g) as colourless needles, mp 97-99° (Lit [8], 101°), 4,4'-dimethoxychalcone epoxide **2b** (2.50 g) was obtained from 4,4'-dimethoxychalcone **1b**, (3.0 g) as colourless needles mp 104-105° (Lit [8], 106°) and 4'-methoxy-4-chlorochalcone epoxide **2c**, (3 g) was obtained from 4'-methoxy-4-chlorochalcone **1c**, (3 g) as colourless flat needles mp 117-118° (Lit [9], 110°).

2-Amino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**3**).

4,4'-Dimethoxychalcone epoxide **2b** (5.64 g, 0.02 mole) and guanidine carbonate (3.60 g, 0.03 mole) in xylene (100 ml) were boiled under reflux for 7 hours. The mixture was concentrated to a small volume (5 ml) and then allowed to cool. Ethanol (20 ml) was added to the mixture and the solvent removed *in vacuo* to leave a brown oily residue (5 g). The residue was dissolved in chloroform and placed on top of a silica gel column and subsequently eluted with mixtures of petroleum spirit (60-80°) and chloroform (9:1 → 1:9). Two products were obtained from the column eluates. The first product was identical in all respects (comparable tlc properties, mixed mp, ir and pmr) with starting chalcone epoxide. The second product **3** (1.2 g, 20%) was a yellowish crystalline material, mp 168-170°; ir (potassium bromide): 3500-3405 (broad doublet, NH_2), 1640 (C=N) cm^{-1}; pmr (DMSO-d_6 + TMS): δ 3.86 (s, 6H, 2 x OCH_3); 6.59 (bs, 2H, deuterium oxide exchangeable, NH_2); 6.98-7.01 (d, 4H, J = 9 Hz, C-3', C-5', C-3'', C-5''); 7.35 (s, 1H, pyrimidine ring C-5) and 8.00-8.03 (d, 4H, J = 9 Hz, C-2', C-6', C-2'', C-6''); ms: (EI) m/z 307 (M^+, 100), 308 (M+1), 306, 292, 250, 154, 132, 117, 89.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.67. Found: C, 70.31; H, 5.59; N, 13.63.

5-Amino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**4b**).

2-Amino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**3**) (0.5 g, 0.0014 mole) and sodium nitrite (1.50 g) were suspended in water (20 ml). Acetic acid (glacial, 10 ml) and ice were added to the mixture with stirring. The mixture was left at room temperature for 2 hours. A yellow precipitate was collected and this was recrystallised from ethanol to give yellow needles of 5-nitroso-4,6-bis(*p*-methoxyphenyl)pyrimidine (**4a**) (0.40 g, 14%), mp 230° dec, ir (potassium bromide): 1630 (C=N), 1605 (C=C), 1530 (N=O) cm^{-1}; pmr (DMSO-d_6 + TMS): δ 3.86 (s, 6H, 2 x OCH_3), 7.08-7.11 (d, 4H, J = 9 Hz, C-3', C-5', C-3'', C-5''), 7.35 (s, 1H, pyrimidine ring C-5) and 8.00-8.03 (d, 4H, J = 9 Hz, C-2', C-6', C-2'', C-6''). 5-Nitroso-4,6-bis(*p*-methoxyphenyl)pyrimidine (**4a**) (0.5 g, 0.0015 mole) was suspended in sodium hydroxide (20 ml, 10%) and Raney nickel alloy (5 g) was added in portions with stirring. Stirring was continued for another 2 hours after which the mixture was extracted with ethyl acetate. The volume of the solvent was reduced *in vacuo* and a solid precipitate was collected. Recrystallization of the solid from hot ethanol furnished 5-amino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**4b**) (0.4 g, 87%) as colourless needles, mp 224-226°; ir (potassium bromide): 3400 (NH_2), 1690 (C=N), 1620 (C=C) cm^{-1}; pmr (DMSO-d_6 + TMS): δ 3.86 (6H, 2 x OCH_3), 6.30 (bs, 2H, deuterium oxide exchangeable, NH_2), 7.05-7.09 (d, 4H, J = 9 Hz, C-3', C-5', C-3'', C-5''), 8.10-8.13 (d, 4H, J = 9 Hz, C-2', C-6', C-2'', C-6''), 7.40 (s, 1H, pyrimidine ring C-2); ms: (EI) m/z 307, (M^+, 100), 308 (M+1), 292, 264, 154.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.69. Found: C, 70.30; H, 5.54; N, 13.65.

2-Hydrazino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**5a**).

To a solution of aminoguanidine (10 ml) prepared *in situ* by the reduction of nitroguanidine (40 g) with Raney nickel alloy in sodium hydroxide (10 g in 100 ml water) was added 4,4'-dimethoxychalcone epoxide (**2b**) (2.89, 0.01 mole) and the mixture was boiled for 10 hours. This mixture was left to cool and a solid precipitate was collected. The solid precipitate was dissolved in hot methanol and on cooling afforded 2-hydrazino-4,6-bis(*p*-methoxyphenyl)pyrimidine (**5a**) (0.65, g, 20%) as yellow needles, mp 80°; ir (Nujol): 3445 (NH_2), 3420 (NH), 1645 (C=N), 1600 (C=C) cm^{-1}; pmr (DMSO-d_6 + TMS): δ 3.84 (s, 6H, 2 x OCH_3), 7.40 (s, 1H, deuterium oxide exchangeable, NH), 7.25 (s, 2H, deuterium oxide exchangeable, NH_2), 7.02 (s, 1H, pyrimidine ring C-5), 7.54-7.60 (d, 4H, J = 9 Hz, C-3', C-5', C-3'', C-5''), 8.00-8.04 (d, 4H, J = 9 Hz, C-2', C-6', C-2'', C-6''); ms: (EI) m/z 322 (M^+), 307, 268 (100), 253, 225, 160, 153, 135.

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 66.98; H, 5.65; N, 17.34.

2-Hydrazino-4-(*p*-methoxyphenyl)-6-(*p*-chlorophenyl)pyrimidine (**5b**).

To an alkaline solution of aminoguanidine (10 ml) prepared as in **5a** was added 4'-methoxy-4-chlorochalcone epoxide **2c**, (2.89 g, 0.01 mole) and the mixture was boiled under reflux for 10 hours. A solid precipitate was collected after cooling. This was recrystallised from hot methanol to give 2-hydrazino-4-(*p*-methoxyphenyl)-6-(*p*-chlorophenyl)pyrimidine (**5b**) (0.8 g, 35%) as yellow needles, mp 286-287° dec; ir (Nujol): 3400 (NH_2), 1630 (C=N), 1605 (C=C) cm^{-1}; pmr (DMSO-d_6 + TMS): δ 3.75 (s, 3H, OCH_3), 6.91-9.94 (d, 2H, J = 9 Hz, C-2', C-6'), 7.16-7.19 (d, 2H, J = 9 Hz, C-2'', C-6''), 7.25-7.29 (d, 2H, J = 9 Hz, C-3', C-5'), 7.43-7.46 (d, 2H, J = 9 Hz, C-3'', C-5''), 8.33 (s, 1H, pyrimidine ring C-5), 8.25 (bs, deuterium oxide exchangeable); ms: (EI) m/z 327 (M+1), 326 (M^+), 204 (100), 134, 119, 91.

Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.14; Cl, 10.85. Found: C, 62.51; H, 4.59; N, 16.98; Cl, 10.96.

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[1] To whom enquiries should be sent. Present address: Division of Organic Chemistry 1, Chemical Centre, P. O. Box 124, S-22100 Lund, Sweden.

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