The Reaction of Amines with Isoflavones. 2. [1]. Formation of Phenolic Sulphonamidopyrimidines

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Isoflavones in alkaline dimethylsulphoxide at 100° under a nitrogen atmosphere reacted with sulphaguanidine to give phenolic sulphonamidopyrimidines.

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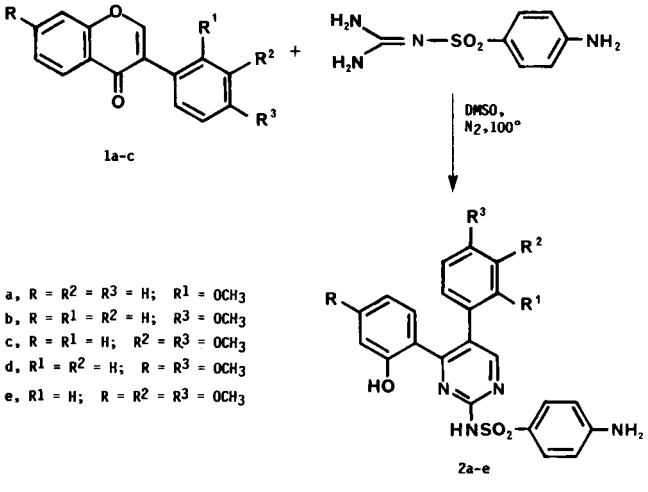
Our previous work [1] showed that isoflavones react with guanidine carbonate in xylene at reflux giving 2-amino phenolic pyrimidines. We have also shown that sulphaguanidine acetate condenses with chalcones [3] in basic dimethyl sulphoxide to give 4,6-diphenylsulphonamidopyrimidine acetates.

In this work, sulphaguanidine was boiled with isoflavones **1a-e** under nitrogen, in alkaline dimethyl sulphoxide, to give phenolic sulphonamidopyrimidines **2a-e** in very good yields.

The structures of the sulphonamides were confirmed by their corresponding physicochemical properties *viz*, ir, ^1H and ^{13}C nmr, ms and elemental analyses. The ir spectra of the sulphonamides showed strong absorption peaks at around 3440 and 3360 cm^{-1} due to the presence of the amino and hydroxyl groups, respectively. The peak at 1630 cm^{-1} is indicative of C=N, 1600 cm^{-1} due to C=C, and 1310 and 1150 cm^{-1} diagnostic for the presence of the sulphonamido group (-SO_2NH-) [4]. The ^1H nmr of these compounds showed deuterium oxide-exchangeable protons at δ 11.45, 9.87 and 6.05, due to the presence of the hydroxyl, secondary amine and primary amine group [6] protons respectively. The H-6 proton of the pyrimidine ring appeared as a singlet at δ 8.50, while the aromatic protons were a mixture of doublets and multiplets between δ 7.70 and 6.50. These doublets have coupling constants of about 9 Hz, indicative of *ortho*-coupling in the system [6]. The methoxy protons appeared as singlets centered around δ 4.25. The mass spectra of the compounds showed the molecular ion (M^+) of moderate intensity (20%). There is generally a loss of 64 mass units (mu) from the molecular ion indicative of M^+-SO_2. The base peak for **2a**, **2d** and **2e** was 108 mu [7] while that of **2b** and **2c** was M^+-SO_2. The results of the elemental analysis confirmed the structures of the sulphonamides as shown in the experimental.

Scheme



a, R = R^2 = R^3 = H; R^1 = OCH_3
b, R = R^1 = R^2 = H; R^3 = OCH_3
c, R = R^1 = H; R^2 = R^3 = OCH_3
d, R^1 = R^2 = H; R = R^3 = OCH_3
e, R^1 = H; R = R^2 = R^3 = OCH_3

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and were uncorrected. The ir spectra were recorded on a Pye Unicam SP3-200 infrared Spectrophotometer as potassium bromide pellets. The ^1H nmr spectra were recorded in deuteriodimethyl sulphoxide at 200 MHz with tetramethylsilane as an internal standard on a Bruker WM 300 nuclear magnetic resonance spectrometer. Mass spectra were obtained on a Varian MAT 445 at 70 eV. Dimethyl sulphoxide (DMSO) was distilled and dried over molecular sieves, anhydrous potassium carbonate was powdered and dried at 120° for 3 days. Silica gel 60 F-254 thin layer chromatography (tlc) plates, (precoated aluminium sheets, 0.2 nm thickness, Merck 5549) were used to monitor the reactions using toluene/ethyl acetate (4:1) as a developing solvent. Isoflavones were prepared by standard methods using 2'-hydroxychalcones and thallium nitrate trihydrate [5] in dry methanol. Deuterium oxide was used to exchange for the exchangeable protons *viz*., hydroxyl, primary and secondary amino groups.

General Procedure for the Preparation of the Phenolic Sulphonamidopyrimidines.

Into a three-necked round bottom flask (100 ml) equipped with a magnetic stirrer and a nitrogen inlet was dissolved isoflavone (0.002 mole) and sulphaguanidine (0.002 mole) in dry dimethyl sulphoxide (25 ml). Powdered potassium carbonate (1 g) was added at once and the mixture boiled with stirring under nitrogen at 100° in an oil bath. The reaction was monitored with tlc until

complete disappearance of the isoflavone, which usually required 2 hours. The hot mixture was poured into cold distilled water and filtered. The filtrate was acidified with 2*N* hydrochloric acid. A heavy precipitate was deposited which was collected by filtration and crystallised from a DMSO-water mixture to give crystalline phenolic sulphonamidopyrimidines.

[4-(2-Hydroxyphenyl)-5-(2-methoxyphenyl)]-2-sulphonamidopyrimidine (**2a**).

2'-Methoxyisoflavone (**1a**, 0.48 g, 0.002 mole) in alkaline DMSO reacted with sulphaguanidine, 0.42 g (0.002 mole) to give [4-(2-hydroxyphenyl)-5-(2-methoxyphenyl)]-2-sulphonamidopyrimidine (**2a**, 0.75 g, 87%), as colourless needles from a DMSO-water mixture, mp 245-246°; ir (potassium bromide): 3440 (NH, NH_2), 3350 (OH), 1610 (O=N), 1580 (C=C), 1300, 1150 (-SO_2NH-) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 11.56 (b, 1H, OH), 10.28 (bs, 1H, NH), 8.42 (s, 1H, H-6 pyrimidine ring), 7.64, 7.21, 6.85 (m, 12H, aromatic protons), 6.06 (bs, 2H, NH_2), 3.80 (s, 3H, OCH_3); ms: 448 (M^+, 16), 384 (M^+-64, 62), 277 (30), 221 (22), 156 (20), 108 (100), 92 (66), 65 (54).

Anal. Calcd. for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49. Found: C, 61.23; H, 4.54; N, 12.76.

[4-(2-Hydroxyphenyl)-5-(4-methoxyphenyl)]-2-sulphonamidopyrimidine (**2b**).

4'-Methoxyisoflavone (**1b**, 0.48 g, 0.002 mole) reacted with sulphaguanidine (0.42 g, 0.002 mole) in alkaline DMSO at 100° according to the general procedure to give [4-(2-hydroxyphenyl)-5-(2-methoxyphenyl)]-2-sulphonamidopyrimidine (**2b**, 0.72 g, 84%), mp 293-294° as rhombohedral colourless crystals from aqueous DMSO; ir (potassium bromide): 3450 (NH, NH_2), 3375 (OH), 1625 (C=N), 1600 (C=C), 1310, 1150 (-SO_2NH-) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide); δ 11.48 (b, 1H, OH), 9.88 (bs, 1H, NH), 8.46 (s, 1H, H-6 pyrimidine ring), 7.68, 7.25, 6.70, 6.60 (m, 12H, aromatic protons), 6.04 (bs, 2H, NH_2), 3.71 (s, 3H, OCH_3); ms: 448 (M^+, 14), 384 (M-64, 100), 277 (34), 108 (72), 92 (20), 65 (18).

Anal. Calcd. for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49. Found: C, 61.36; H, 4.55; N, 12.24.

[4-(2-Hydroxyphenyl)-5-(3,4-dimethoxyphenyl)]-2-sulphonamidopyrimidine (**2c**).

3',4'-Dimethoxyisoflavone (**1c**, 0.56 g, 0.002 mole) was dissolved in dry alkaline DMSO and boiled with sulphaguanidine (0.42 g, 0.002 mole) under nitrogen. Upon working up as above [4-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)]-2-sulphonamidopyrimidine (**2c**, 0.6 g, 63%) was obtained as colourless needles from aqueous DMSO, mp 300-302°; ir (potassium bromide): 3450 (NH, NH_2), 3360 (OH), 1630 (C=N), 1580 (C=C), 1305, 1150 (-SO_2NH-) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 11.43 (b, 1H, OH), 9.86 (bs, 1H, NH), 8.52 (s, 1H, H-6 pyrimidine ring), 7.70, 7.25, 6.82 (m, 11H aromatic protons), 6.04 (bs, 2H, NH_2), 3.71, 3.48 (s each, 6H, 2 x OCH_3); ms: 478 (M^+, 20), 414 (M-64, 100), 307 (32), 108 (98), 92 (24), 65 (18).

Anal. Calcd. for $C_{24}H_{22}N_4O_5S$: C, 60.24; H, 4.63; N, 11.71. Found: C, 60.54; H, 4.68; N, 11.57.

[4-(2-Hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)]-2-sulphonamidopyrimidine (**2d**).

4',7-Dimethoxyisoflavone (**1d**, 0.56 g, 0.002 mole) was boiled with sulphaguanidine (0.43 g, 0.002 mole) at 100° under nitrogen in alkaline DMSO. The residue obtained after acidification gave [4-(2-hydroxy-4-methoxyphenyl)-5-(4-methoxyphenyl)]-2-sulphonamidopyrimidine, (**2d**, 0.86 g, 90%) as colourless needles from aqueous DMSO, mp 319-320°; ir (potassium bromide): 3480, 3400 (NH, NH_2), 3330 (OH), 1610 (C=N), 1590 (C=C), 1350, 1150 (-SO_2NH-) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 11.50 (b, 1H, OH); 9.86 (bs, 1H, NH), 8.42 (s, 1H, H-6, pyrimidine ring), 8.36, 7.30, 7.31, 6.74, 6.36 (m, 11H, aromatic protons), 6.03 (bs, 2H, NH_2), 4.00, 3.93 (s each 6H, 2 x OCH_3); ms: 478 (M^+, 36), 414 (M-64, 36), 307 (34), 108 (100), 92 (16), 65 (14).

Anal. Calcd. for $C_{24}H_{22}N_4O_5S$: C, 60.24; H, 4.63; N, 11.71. Found: C, 60.08; H, 4.64; N, 11.35.

[4-(2-Hydroxy-4-methoxyphenyl)-5-(3,4-dimethoxyphenyl)]-2-sulphonamidopyrimidine (**2e**).

3',4',7-Trimethoxyisoflavone (**1e**, 0.62 g, 0.002 mole) was boiled in alkaline DMSO with sulphaguanidine (0.43 g, 0.002 mole) under nitrogen to give [4-(2-hydroxy-4-methoxyphenyl-5-(3,4-dimethoxyphenyl)]-2-sulphonamidopyrimidine (**2e**, 0.92 g, 91%) after acidification and crystallisation with aqueous DMSO, mp 261-263°; ir (potassium bromide): 3460 (NH, NH_2), 3380 (OH), 1620 (C=N), 1570 (C=C), 1340, 1140 (-SO_2NH-) cm^{-1}; ^1H nmr (deuteriodimethyl sulphoxide): δ 11.80 (b, 1H, OH), 11.01 (bs, 1H, NH), 8.39 (s, 1H, H-6 pyrimidine ring), 7.68, 7.04, 6.78, 6.56, 6.40, 6.20 (m, 10H, aromatic protons), 5.98 (bs, 2H, NH_2), 3.94, 3.89, 3.83 (s each, 9H, 3 x OCH_3); ms: 508 (M^+, 6), 507 (M-1, 20), 489 (68), 444 (M-64, 20), 443 (58), 352 (58), 108 (100), 92 (54), 65 (34).

Anal. Calcd. for $C_{25}H_{24}N_4O_6S$; C, 59.04; H, 4.76; N, 11.02. Found: C, 58.83; H, 4.58; N, 11.07.

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