SHORT PAPER

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A concise synthesis of pyrimidinophanes from 6-aryl-5-cyano-2-thiouracil†

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A convenient synthesis of 2,3- and 2,4-pyrimidinophanes (**3,5,6**) has been described from 6-aryl-5-cyano-2-thiouracils (**1a–c**). A reaction of 2-thiouracil with dibromomethane produced **2a–c,** which on further interaction with dihaloalkane under basic condition produced 2,3-pyrimidinophanes (**3a,b**). Halogenation of **2a,c** with $POCl_3$ led to yield respective chloropyrimidines (**4a,b**), which on further reaction with diaminoalkane and 1,4-phenylenediamine separately yielded 2,4-pyrimidinophanes (**5a–d** and **6a,b**).

Keywords: pyrimidinophane, thiouracil, chloropyrimidine

The chemistry of pyrimidinophanes have aroused considerable interest in connection with synthetic receptors in molecular recognition.[1] The importance of these compounds has been greatly realised due to presence of pyrimidine, a nucleic acid base in their molecular make-up and property of photodimerisation in DNA by ultraviolet light.[2] The chemistry of 1,3- and 1,5-pyrimidinophanes[3] has been developed more compared to 2,3- and 2,4-pyrimidinophanes.

Pyrimidinophanes are generally prepared[4] from the reaction of thymine, a pyrimidine derivative with dihaloalkanes. Later on, Reznik *et al*. have reported[5] the synthesis of this class of compounds from the interaction of 1-(4-bromobutyl)uracil with *p*-toluenesulfonamide. The reaction of sodium salts of uracil derivatives with dihaloalkanes also led to the formation[6] of title compound. Pyrimdinophanes containing sulfur atom have also been synthesised and reported by Reznik *et al.*[7] and Kinoshita *et al*.[8] However, little attention has been paid towards the direct synthesis of pyrimidinophanes. This manuscript delineates the synthesis of 2,3-and 2,4-pyrimidinophanes **3**, **5** and **6** from 6-aryl-5-cyano-2-thiouracil (**1a–c**) Scheme 1. The latter was synthesised from the reaction of aromatic aldehyde, thiourea and ethyl cyanoacetate as reported earlier[9] and has been used as a precursor for the synthesis of 2,3- and 2,4-pyrimidinophanes (**3, 5, 6**). A reaction of **1** with dibromomethane under basic condition below 25°C led to yield S-alkylated product, 4-aryl-2-[({[4-aryl-5-cyano-6-oxo-1,6-dihydro-2-pyrimidinyl] sulfanyl}methyl)sulfanyl]-6-oxo-1,6-dihydro-5-pyrimidine carbonitriles (**2a–c**) which after N-alkylation with dihaloalkanes in presence of K_2CO_3 in DMF at 100°C produced 2,3-pyrimidinophanes (**3a, b**). Halogenation of **2** with $POCl_3$ afforded 6-aryl-4-chloro-2-[({[6-aryl-4-chloro-5-cyano-2-pyrimidinyl]sulfanyl}methyl) sulfanyl]-5-pyrimidine-carbonitriles (**4**) which was further used as an intermediate for the synthesis of 2,4-pyrimidinophanes (**5, 6**). A condensation of **4** with diaminoalkanes in acetone using K_2CO_3 as a base at reflux temperature produced tricyclic pyrimidinophanes (**5a–d**) while reaction with 1,4-phenylenediamine yielded tetracyclic pyrimidinophanes (**6a,b**).

The structure of all the synthesised compounds was corroborated with the help of NMR, Mass and IR spectroscopy. The ^{1}H NMR of **3a** showed a multiplet at δ 7.55–7.88 due to eight aromatic protons. Two singlets at δ 5.06 and δ 3.18 were assigned for protons of S-CH_2-S and two methylene groups. IR spectrum of **3a** showed two sharp peaks at 1666 and 2233 cm^{-1} due to presence of CO and CN groups. The M^++1 peak at 565 in FAB mass spectrum and its fragmentation pattern matched with proposed structure. Similarly the ^{1}H NMR of **5a** showed a broad peak for 2 NH protons at δ 8.54 while a multiplet at δ 7.34–8.04 due to eight aromatic protons. Two singlets at δ 5.72 and δ 3.59 were assigned for protons of S–CH_2–S and N–$(CH_2)_2$–N respectively. The IR spectrum of this compound showed two intense peaks at 2212 and 3178 cm^{-1} due to CN and NH stretching frequency. The presence of M^++1 peak at 531 in FAB MS and its fragmentation pattern matched with proposed structure. The conformation of pyrimidinophanes could not be ascertained by X-ray diffraction due to its amorphous nature.

Experimental

Melting points were measured in open capillary on an electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Perkin-Elmer AC-1 spectrometer (ν_{max} in cm^{-1}), ^{1}H NMR spectra were recorded on a Brucker WM-200 MHz. Chemical shifts (δ) are expressed in ppm downfield from the internal standard tetramethylsilane (TMS). Mass spectra were recorded on a FAB Mass spectrometer SX-102, JEOL (Japan) data system-6000. TLC plates were prepared with silica gel and spots visualized with iodine vapours. Elemental analyses were also carried out to determine the % of C, H and N.

Synthesis of 6-aryl-5-cyano-2-thiouracils (**1a–c**)**:** These were prepared from the reaction of aryl aldehyde, ethyl cyanoacetate, thiourea under basic condition and isolated as reported earlier.[9]

General procedure for the synthesis of (**2a–c**): To a mixture of **1** (8.08 mmol) and K_2CO_3 (8.08 mmol) in 20ml DMF, dibromomethane (8.08 mmol) was added drop-wise and stirred for 5 hours at room temperature. Reaction mixture was poured into ice-cold water with vigorous stirring. The aqueous solution after filtration was neutralised with glacial acetic acid. The precipitate obtained was filtered, washed with water and dried. The compound was crystallised from DMF.

4-(3-Fluorophenyl)-2-[({[4-(3-fluorophenyl)-5-cyano-6-oxo-1, 6-dihydro-2-pyrimidinyl]sulfanyl}-methyl)sulfanyl]-6-oxo-1, 6-dihydro-5-pyrimidinecarbonitrile (**2a**)**:** Yield: 39%; m.p. >250°C; δ_H (DMSO-d_6) 11.35 (brs, 2H, NH), 8.23–7.54 (m, 8H, ArH), 5.06 (s, 2H, SCH_2); ν_{max}/cm^{-1} 1674, 2208, 3084; MS (FAB), *m/z* 507 (M^++1); (Found: C 54.34, H 3.11, N 16.45. $C_{23}H_{12}F_2N_6O_2S_2$ requires C 54.54, H 2.37, N 16.60 %).

4-(3-Chlorophenyl)-2-[({[4-(3-chlorophenyl)-5-cyano-6-oxo-1, 6-dihydro-2-pyrimidinyl]sulfanyl}- methyl)sulfanyl]-6-oxo-1, 6-dihydro-5-pyrimidinecarbonitrile (**2b**)**:** Yield: 44%; m.p. >250°C; δ_H (DMSO-d_6) 11.20 (brs, 2H, NH), 7.97–7.57 (m, 8H, ArH), 5.11 (s, 2H, SCH_2); ν_{max}/cm^{-1} 1654, 2225, 3200; MS (FAB), *m/z* 539 (M^++1); (Found: C 51.17, H 2.69, N 16.00. $C_{23}H_{12}Cl_2N_6O_2S_2$ requires C 51.00, H 2.58, N 15.52 %).

4-(4-Methoxyphenyl)-2-[({[5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-2-pyrimidinyl]-sulfanyl}methyl)sulfanyl]-6-oxo-1, 6-dihydro-5-pyrimidinecarbonitrile (**2c**): Yield: 50%; m.p. >250°C; δ_H (DMSO-d_6) 11.20 (brs, 2H, NH), 7.84 (d, 4H, ArH), 6.90 (d, 4H, ArH), 4.90 (s, 2H, SCH_2), 3.65 (s, 6H, 2OMe); ν_{max}/cm^{-1} 1654, 2366, 3408; MS (FAB), *m/z* 531 (M^++1); (Found: C 56.69, H 3.45, N 15.94. $C_{25}H_{18}N_6O_4S_2$ requires C 56.60, H 3.39, N 15.84 %).

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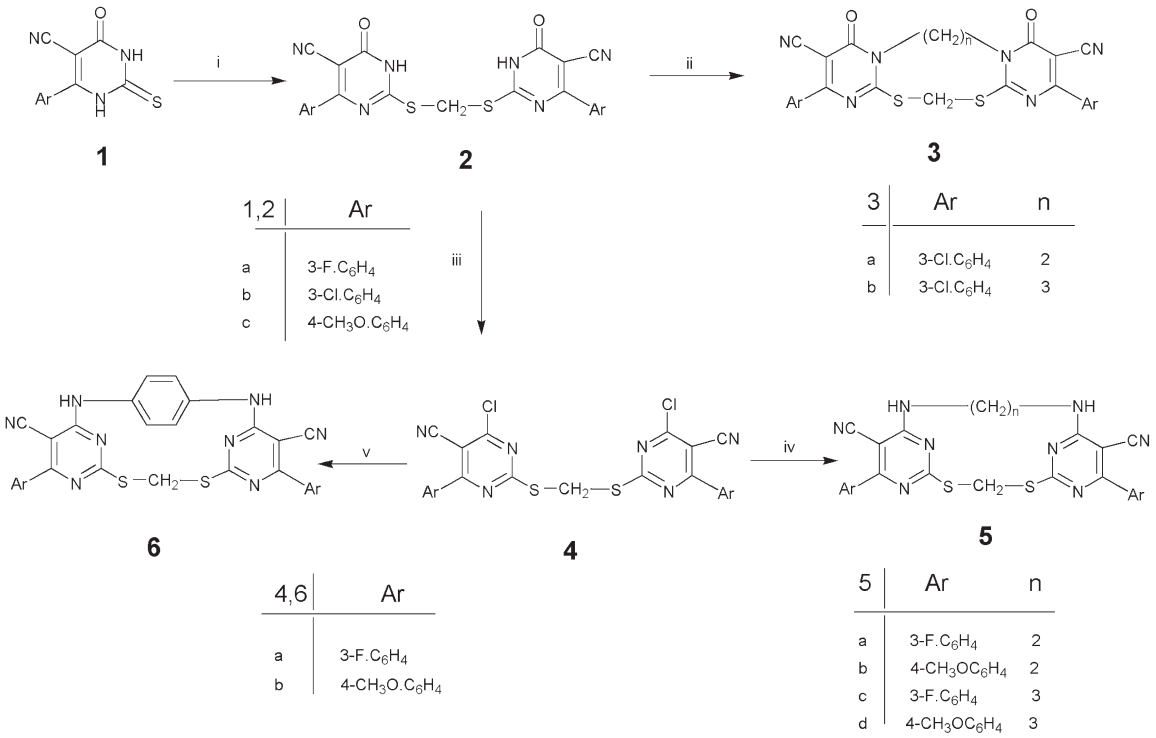

Scheme 1 Reagents and conditions: (I) CH_2Br_2/K_2CO_3/DMF; (ii) $(CH_2)_nBr_2/K_2CO_3$/DMF; (iii) $POCl_3$; (iv) $(CH_2)_n(NH_2)_2/K_2CO_3$/acetone; (v) $C_6H_4(NH_2)_2/K_2CO_3$/acetone.

General procedure for the synthesis of (**3a,b**): To a solution of **2** (1 mmol) in dry DMF (15 ml) in presence of K_2CO_3 (1 mmol), 1, 3-dibromoethane (1 mmol) was added drop-wise. Reaction mixture was stirred and heated on waterbath for 6 hours. Reaction mixture was cooled and poured into cold water with stirring. Precipitate was allowed to settle down and filtered, washed with plenty of water and methanol. Compound was dried and purified using column chromatography.

2,11-Bis-(3-chlorophenyl)-4,9-dioxo-6,7-dihydro-4H,9H-dipyrimido[2,1-d:1,2-h][1,3,5,8]dithia-diazonine-3,10-dicarbonitrile (**3a**): Yield: 11%; m.p. >250°C; δ_H (DMSO-d_6) 7.88–7.55 (m, 8H, ArH), 5.06 (s, 2H, SCH_2), 3.18 (s, 4H, $2CH_2$); ν_{max}/cm^{-1} 1666, 2233; MS (FAB), *m/z* 565 (M^++1); (Found: C 53.29, H 2.57, N 15.01. $C_{25}H_{14}Cl_2N_6O_2S_2$ requires C 53.09, H 2.47, N 14.86 %).

2,12-Bis-(3-chlorophenyl)-4,10-dioxo-7,8-dihydro-4H,6H,10H-dipyrimido[2,1-d:1,2-i][1,3,5,9] dithiadiazecine-3,11-dicarbonitrile (**3b**): Yield: 9.5%; m.p. 242°C; δ_H (DMSO-d_6) 7.86–7.44 (m, 8H, ArH), 5.03 (s, 2H, SCH_2), 4.58 (t, 2H, CH_2), 3.50 (t, 2H, CH_2), 2.34–2.18 (m, 2H, CH_2); ν_{max}/cm^{-1} 1652, 2160; MS (FAB), *m/z* 579 (M^++1); (Found: C 53.67, H 2.86, N 14.60. $C_{26}H_{16}Cl_2N_6O_2S_2$ requires C 53.89, H 2.78, N 14.50 %).

General procedure for the synthesis of (**4a,b**): A solution of **2** (1 mmol) in 5 ml $POCl_3$ was refluxed for 5 hrs, cooled and poured slowly on crushed ice, with stirring. The precipitate obtained was filtered, dried and crystallised from acetone.

4-Chloro-2-[({[4-chloro-5-cyano-6-(3-fluorophenyl)-2-pyrimidinyl]sulfanyl}methyl)sulfanyl]-6-(3-fluorophenyl)-5-pyrimidinecarbonitrile (**4a**)**:** Yield: 58.9%; m.p. 184°C; δ_H (DMSO-d_6) 8.02–7.49 (m, 8H, ArH), 5.25 (s, 2H, SCH_2); ν_{max}/cm^{-1} 2200; MS (FAB), *m/z* 543 (M^++1); (Found: C 50.84, H 1.86, N 15.45. $C_{23}H_{10}Cl_2F_2N_6S_2$ requires C 50.82, H 1.84, N 15.47 %).

4-Chloro-2-[({[4-chloro-5-cyano-6-(4-methoxyphenyl)-2-pyrimidinyl]sulfanyl}methyl)sulfanyl]-6-(4-methoxyphenyl)-5-pyrimidinecarbonitrile (**4b**): Yield: 93.6%; m.p. 164°C; δ_H (DMSO-d_6) 8.11 (d, 4H, ArH), 6.95 (d, 4H, ArH), 5.07 (s, 2H, SCH_2), 3.90 (s, 6H, $2OCH_3$); ν_{max}/cm^{-1} 2219; MS (FAB), *m/z* 567 (M^++1); (Found: C 49.43, H 3.13, N 13.36. $C_{25}H_{16}Cl_2N_6O_2S_2$ requires C 52.91, H 2.82, N 14.81%).

General procedure for the synthesis of (**5a–d**): A mixture of **4** (1.05 mmol), K_2CO_3 (2.10 mmol) and ethylenediamine (1.05 mmol) in 50 ml acetone was refluxed for 6 hours. The reaction mixture was cooled and excess of acetone was removed under vacuum. The crude product was purified on silica gel column.

7,16-Bis-(3-fluorophenyl)-2,4-dithia-6,10,13,17,18,19-hexa-azatricyclo[12.3.1.1^{5,9}]nonadeca-1(18),5(19),6,8,14,16-hexaene-8,15-dicarbonitrile (**5a**): Yield: 24.92%; m.p. 241°C; δ_H (DMSO-d_6) 8.54 (brs, 2H, NH), 8.04–7.34 (m, 8H, ArH), 5.72 (s, 2H, SCH_2), 3.59 (s, 4H, CH_2); ν_{max}/cm^{-1} 2212, 3178; MS (FAB), *m/z* 531 (M^++1); (Found: C 56.64, H 3.27, N 20.82. $C_{25}H_{16}F_2N_8S_2$ requires C 56.60, H 3.01, N 21.13 %).

7,16-Bis-(4-methoxyphenyl)-2,4-dithia-6,10,13,17,18,19-hexaazatricyclo[12.3.1.1^{5,9}]nonadeca-1(18), 5(19),6,8,14,16-hexaene-8,15-dicarbonitrile (**5b**): Yield: 22.09%; m.p. >250°C; δ_H (DMSO-d_6) 8.41 (brs, 2H, NH), 8.06 (d, 4H, ArH), 7.26 (d, 4H, ArH), 5.13 (s, 2H, SCH_2), 3.88 (s, 6H, $2.OCH_3$), 3.55 (s, 4H, CH_2); ν_{max}/cm^{-1} 2204, 3327; MS (FAB), *m/z* 555 (M^++1); (Found: C 58.17, H 4.26, N 20.01. $C_{27}H_{22}N_8O_2S_2$ requires C 58.47, H 4.00, N 20.20 %).

7,17-Bis-(3-fluorophenyl)-2,4-dithia-6,10,14,18,19,20-hexaazatricyclo[13.3.1.1^{5,9}]icosa-1(19),5(20),6,8,15,17-hexaene-8,16-dicarbonitrile (**5c**): Yield: 30%; m.p. >250°C; δ_H (DMSO-d_6) 8.57 (brs, 2H, NH), 7.86–7.39 (m, 8H, ArH), 5.45 (s, 2H, SCH_2), 3.59 (s, 4H, CH_2), 2.15 (brs, 2H, CH_2); ν_{max}/cm^{-1} 2230, 3128; MS (FAB), *m/z* 545 (M^++1); (Found: C 56.40, H 3.51, N 20.10. $C_{26}H_{18}F_2N_8S_2$ requires C 57.35, H 3.30, N 20.58 %).

7,17-Bis-(4-methoxyphenyl)-2,4-dithia-6,10,14,18,19,20-hexaazatricyclo[13.3.1.1^{5,9}]icosa-1(19),5(20),6,8,15,17-hexaene-8,16-dicarbonitrile (**5d**): Yield: 10.09%; m.p. >250°C; δ_H (DMSO-d_6) 8.41 (brs, 2H, NH), 7.93 (d, 4H, ArH), 7.08 (d, 4H, ArH), 5.41 (s, 2H, SCH_2), 3.81 (s, 6H, $2OCH_3$), 3.57 (s, 4H, CH_2), 1.97 (brs, 2H, CH_2); ν_{max}/cm^{-1} 2204, 3346; MS (FAB), *m/z* 569 (M^++1); (Found: C 58.82, H 4.62, N 19.42. $C_{28}H_{24}N_8O_2S_2$ requires C 59.14, H 4.25, N 19.70 %).

General procedure for the synthesis of (**6a,b**): A mixture of **4** (1.05 mmol), K_2CO_3 (2.10 mmol) and 4-phenylenediamine (1.05 mmol) in 50 ml acetone was refluxed for 6 hours. The reaction mixture was cooled and excess of acetone was removed under vacuum. The crude product was purified on silica gel column.

5,13-Bis-(3-fluorophenyl)-8,10-dithia-2,6,12,16,22,23-hexaazatetracyclo[15.2.2.1^{3,7}.1^{11,15}]tricosa-1(19),3(23),4,6,11(22), 12,14,17,20-nonaene-4,14-dicarbonitrile (**6a**): Yield: 25%; m.p. >250°C; δ_H (DMSO-d_6) 9.97 (brs, 2H, NH), 7.88–7.34 (m, 12H, ArH), 4.83 (s, 2H, SCH_2); ν_{max}/cm^{-1} 2212, 3074; MS (FAB), *m/z* 579 (M^++1); (Found: C 60.27, H 2.81, N 19.45. $C_{29}H_{16}F_2N_8S_2$ requires C 60.20, H 2.76, N 19.37 %).

5,13-Bis-(4-methoxyphenyl)-8,10-dithia-2,6,12, 16,22,23-hexaazatetracyclo[15.2.2.1^{3,7}.1^{11,15}]tricosa-1(19), 3(23),4, 6,11(22),12,14,17,20-nonaene-4,14-dicarbonitrile (**6b**): Yield: 21.30%; m.p. 242°C; δ_H (DMSO-d_6) 9.90 (brs, 2H, NH), 8.01–7.03 (m, 12H, ArH), 4.75 (s, 2H, SCH_2), 3.81 (s, 6H, $2OCH_3$); ν_{max}/cm^{-1} 2208, 3298; MS (FAB), *m/z* 603 (M^++1); (Found: C 61.50, H 3.92, N 18.51. $C_{31}H_{22}N_8O_2S_2$ requires C 61.58, H 3.97, N 18.54.

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