EFFICIENT SYNTHESIS OF NOVEL 6-PHENYLTHIO-2,4-DISUBSTITUTED PYRIMIDINES

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Abstract: 6-Phenylthio-2,4-disubstituted pyrimidines were prepared in five steps starting from barbituric acid. Reaction of barbituric acid with $POCl_3$ in presence of *N, N*-dimethylaniline furnishes the 2,4,6-trichloropyrimidine, which on reaction with aq. NaOH under reflux yielded the 6-chlorouracil. Reaction of 6-chlorouracil with thiophenol under basic condition furnishes the 6-phenylthiouracil, which on chlorination using excess $POCl_3$ under reflux yielded the key synthon, 6-phenylthio-2,4-dichloropyrimidine. Aromatic nucleophilic substitution reaction of 6-phenylthio-2,4-dichloropyrimidine with a oxygen nucleophile like sodium benzylate and nitrogen nucleophiles like heterocyclic primary amines, aliphatic primary amines and substituted aromatic primary amines furnished the target compounds, 6-phenylthio-2,4-disubstituted pyrimidines respectively in 40-80% yield.

Introduction

In the last few years, uracil and pyrimidinone analogs substituted at the C_6-position have emerged as potential antiviral agents in the field of chemotherapy[1]. Among the important 6-substituted uracil derivatives, 1-[(2-hydroxyethyl)methyl]-6-phenylthiouracil (HEPT) and its analog, 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (Emivirine, EMV) have been chosen as a candidate for clinical trials in the treatment of acquired immunodeficiency virus (AIDS)[2]. 3,4-Dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs) shown potent and selective activity against human immunodeficiency type-1 (HIV-1)[3]. The C_6-substituted pyrimidine analogs also exhibited selective antitumor[4], antiviral[5] and antibacterial activity[6-9] suggesting the importance of this class of compounds as broad-spectrum drugs. Thus, the excellent biological activities exhibited by these 6-substituted uracil analogs prompted us to develop a novel methodology in order to generate a large number of various 2,4,6-substituted pyrimidine analogs for biological evaluation.

Our initial interest is to synthesize various 6-phenylthio-2,4-alkoxy and/or aryloxy and/or amine pyrimidines. In this context, 6-phenylthio-2,4-bis(benzyloxy)pyrimidine was prepared starting from barbituric acid[10]. This method requires expensive reagents like organolithiums, diphenyldisulphide, etc. The key reaction in this method is the metal halogen exchange reaction under inert atmosphere followed by addition of electrophile at very low temperature (-80°C). Hence, this method is not suitable to synthesize a series of 6-phenylthio-2,4-aryloxy pyrimidines in normal laboratory conditions. Herein, we report a facile methodology for the synthesis of various 6-phenylthio-2,4-aryloxy and/or amine pyrimidines starting from barbituric acid.

Experimental

Barbituric acid, thiophenol, $POCl_3$, benzyl alcohol and anilines were purchased from SISCO Research Laboratories Pvt. Ltd., Mumbai (India). All the solvents used were analytical grade or were purified according to standard procedures. Melting points were determined by using a Thomas-Hoover melting point apparatus and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FT IR spectrophotometer (v_{max} in cm^{-1}) and ^1H NMR and ^{13}C NMR spectra in DMSO-d_6 and/or $CDCl_3$ on amx 400, 400 MHz spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on a JEOL SX 102 Mass spectrometer using Argon/Xenon (6kv, 10 mA) as the FAB gas. Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator. 2,4,6-Trichloropyrimidine **2** and 6-chlorouracil **3** were prepared by adopting the literature procedures[11].

1. Preparation of 6-phenylthiouracil (4)

A mixture of 6-chlorouracil **3** (2.92 g, 0.02 mol) and thiophenol (2.2 g, 0.02 mol) in dry pyridine (40 ml) was heated under reflux with stirring for 3 hrs and allowed to cool to room temperature. The mixture was then poured onto ice water (500 ml) and the separated solid product was filtered, washed with water, dried and crystallized from EtOH. Yield: 3.35 g. ^1H NMR (400 MHz, DMSO): δ 11.4 (s, 1H, NH), 7.9 (s, 1H, NH), 7.0-7.4 (m, 5H, SC_6H_5), 5.6 (s, 1H, C_5H). Anal. Calcd for $C_{10}H_8N_2SO_2$: C, 54.54; H, 3.63; N, 12.72; S, 14.54. Found: C, 54.52; H, 3.62; N, 12.70; S, 14.53.

2. Preparation of 6-phenylthio-2,4-dichloropyrimidine (5)

A mixture of 6-phenylthiouracil 4 (3 g, 0.0125 mol) and $POCl_3$ (12.2 ml, 0.125 mol) was refluxed for 4-5 hrs. Excess $POCl_3$ was removed under reduced pressure and the mixture was treated with ice/water. The separated solid was extracted with ether (3 x 50 ml) and washed with 5% aq sodium bicarbonate solution (1 x 25 ml). Ether layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished the title compound **5**. Yield: 2.9 g. ^1H NMR ($CDCl_3$): δ 7.2-7.6 (m, 5H, SC_6H_5), 5.9 (s, 1H, C_5H). ^{13}C NMR ($CDCl_3$): δ 177 (C_6), 161 (C_4), 159 (C_2), 126-135 (ArC), 114 (C_5). MS m/z = 257 (M^+, 100%), 259 (M^{+2}, 80%), 261 (M^{+4}, 30%), 221, 149, 113. Anal. Calcd for $C_{10}H_6N_2SCl_2$: C, 46.91; H, 2.43; N, 10.94; S, 12.88. Found: C, 46.45; H, 2.36; N, 10.60; S, 12.39.

3. Preparation of 6-phenylthio-2,4-bis(benzyloxy)pyrimidine (6a)

A stirred solution of benzyl alcohol (2.16 g, 0.02 mol) in toluene (30 ml) was treated with 60% w/w sodium hydride in oil (0.41 g, 0.02 mol) under an inert atmosphere. The mixture was warmed to 55-60°C for 30 minutes to facilitate the formation of sodium salt. After all the sodium hydride had reacted, the suspension was cooled and a solution of 6-phenylthio-2,4-dichloropyrimidine **5** (1.28 g, 0.005 mol) in toluene (30 ml) was added slowly at room temperature. After stirring the reaction mixture at 75-80°C overnight, the precipitate of sodium chloride was filtered and the solid washed with toluene. The filtrate was then evaporated under reduced pressure and crude compound was recrystallized from EtOH furnished the title compound **6a**. Yield: 1.24 g. IR: 1566 N=C, 1135, 1167 C-O-C. ^1H NMR ($CDCl_3$): δ 7.6-7.2 (m, 15H, C_6H_5), 5.8 (s, 1H, C_5H), 5.372 (s, 2H, CH_2), 5.314 (s, 2H, CH_2). MS: 401 (M^+, 50%). Anal. Calcd for $C_{24}H_{20}N_2O_2S$: C, 72.00; H, 5.00; N, 7.00. Found: C, 71.98; H, 4.99; N, 6.97.

4. General procedure for the preparation of 6-phenylthio-2, 4-bis(anilino)pyrimidines (6b-h)

To a solution of 6-phenylthio-2,4-dichloropyrimidine **5** (1.28 g, 0.005 mol) in methanol (20 ml) and pyridine (5 ml), appropriate amine (0.01 mol) was added. The reaction mixture was refluxed for 4-5 hrs on a water-bath. Methanol was removed under reduced pressure and the residue triturated with a little crushed ice. Collected the separated solid and recrystallized from EtOH yielded the desired compounds. If the compound is semisolid then extracted with ether (3 x 50 ml), ether layer was collected and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished the pure desired compounds **6b-h**.

6-Phenylthio-2,4-bis(pyridine-2-yl-amino)pyrimidine (6b). Yield: 0.87 g. IR: 3393, 3274 NH/NH. ^{1}H NMR ($CDCl_3$): 7.8 (s, 1H, NH), 7.75 (s, 1H, NH), 7.6-7.4 (m, 13H, ArH), 6.4 (s, 1H, C_5H). Anal. Cacld for $C_{20}H_{16}N_6S$: C, 64.51; H, 4.30; N, 22.58. Found: C, 64.50; H, 4.29; N, 22.57.

6-Phenylthio-2,4-bis(acetamido)pyrimidine (6c). Yield: 0.81 g. IR: 3159, 3152 NH/NH, 1574 N=C, 1650 C=O. ^{1}H NMR ($CDCl_3$): 7.6-7.4 (m, 5H, Ar), 6.6 (s, 1H, C_5H), 5.7 (s, 1H, NH), 5.5 (s, 1H, NH), 1.6 (s, 6H, CH_3). Anal. Cacld for $C_{14}H_{14}N_4O_2S$: C, 55.62; H, 4.63; N, 18.54. Found: C, 55.60; H, 4.61; N, 18.53.

6-Phenylthio-2,4-bis(benzamido)pyrimidine (6d). Yield: 1.1 g. IR: 3180, 3165 NH/NH, 1660 C=O, 1574 N=C. ^{1}H NMR ($CDCl_3$): 7.5-7.0 (m, 15H, ArH), 6.0 (s, 1H, NH), 5.7 (s, 1H, NH), 5.1 (s, 1H, C_5H).Anal. Cacld for $C_{24}H_{18}N_4O_2S$: C, 67.60; H, 4.22; N, 13.14. Found: C, 67.58; H, 4.20; N, 13.13.

6-Phenylthio-2,4-bis(4-methoxyanilino)pyrimidine (6e). Yield: 1.45 g. IR: 3314, 3150 NH/NH, 1508 N=C. ^{1}H NMR ($CDCl_3$): 10.2 (s, 1H, NH), 9.3 (s, 1H, NH), 7.5-6.5 (m, 13H, ArH), 6.0 (s, 1H, C_5H), 3.8 (s, 6H, OCH_3). MS: 430 (M^+, 100%), 398, 323, 307, 215, 120, 107. Anal. Cacld for $C_{24}H_{22}N_4O_2S$: C, 66.97; H, 5.11; N, 13.02. Found: C, 66.96; H, 5.10; N, 13.01.

6-Phenylthio-2,4-bis(4-methylanilino)pyrimidine (6f). Yield: 1.4 g. IR: 3393, 3274 NH/NH, 1591 N=C. ^{1}H NMR ($CDCl_3$): 10.3 (s, 1H, NH), 9.3 (s, 1H, NH), 7.8-6.8 (m, 13H, ArH), 5.8 (s, 1H, C_5H), 2.3 (s, 6H, CH_3). Anal. Calcd for $C_{24}H_{22}N_4S$: C, 72.36; H, 5.52; N, 14.07. Found: C, 72.33; H, 5.50; N, 14.04.

6-Phenylthio-2,4-bis(4-nitroanilino)pyrimidine (6g). Yield: 1.1 g. IR: 3215, 3110 NH/NH, 1578 N=C, 1548 N=O. ^{1}H NMR ($CDCl_3$): 8.5 (s, 1H, NH), 8.2 (s, 1H, NH), 7.9-6.5 (m, 13H, ArH) 5.2 (s, 1H, C_5H). Anal. Cacld for $C_{22}H_{16}N_6O_4S$: C, 57.39; H, 3.47; N, 18.26. Found: C, 57.36; H, 3.45; N, 18.24.

6-Phenylthio-2,4-bis(4-carboxyanilino)pyrimidine (6h). Yield: 0.9 g. IR: 3180, 3167 NH/NH, 1574 N=C, 1710 C=O. ^{1}H NMR ($CDCl_3$): 10.1 (s, 1H, COOH), 10.0 (s, 1H, COOH), 8.6 (s, 1H, NH), 8.7 (s, 1H, NH), 7.5-7.0 (m, 13H, ArH) 5.5 (s, 1H, C_5H). Anal. Cacld for $C_{24}H_{18}N_4O_4S$: C, 62.88; H, 3.93; N, 12.22. Found: C, 62.85; H, 3.91; N, 12.20.

Results and Discussion

Synthesis of 6-phenylthio-2,4-disubstituted pyrimidines **6a-h** (Table-1) were obtained in five steps starting from 6-chlorouracil **3** (Scheme-1). The key synthon of the present synthetic route, 6-phenylthio-2,4-dichloropyrimidine **5** was prepared from barbituric acid **1**. Reaction of compound **1** with $POCl_3$ in presence of a catalytic amount of *N, N*-dimethylaniline at refluxing temperature for 3 hrs gave 2,4,6-trichloropyrimidine **2** in 75-85% yield[11], which was subsequently hydrolyzed with aqueous NaOH at refluxing temperature for 1 hr furnished 6-chlorouracil **3** in 82% yield, m.p. 292-296°C (decomp). Reaction of **3** with thiophenol in pyridine under reflux for 24 hrs furnished the desired 6-phenylthiouracil 4 in 65% yield, as a brown crystalline solid. Chlorination of **4** with $POCl_3$ yielded the 6-phenylthio-2,4 dichloropyrimidine **5** in 72% yield, having m.p. 65-67°C. Formation of this compound **5** was confirmed by the presence of C-Cl stretching absorptions at 749 and 705 cm^{-1} in its IR spectrum. Further confirmation of compound **5** is by the presence of aromatic proton signals around δ 7.7-7.4 (m, 5H, Ar), characteristic absorption of C_5 proton of pyrimidine ring at δ 6.6 (s, 1H, C_5H) and absence of NH proton signals in its ^1H NMR spectrum. Additional evidence for compound **5** is by the ^{13}C NMR chemical shift assignment of C_5 carbon of pyrimidine ring at 114 ppm, aromatic carbon signals at 126 ppm-135 ppm and C_2, C_4 and C_6 carbons of pyrimidine ring at 159 ppm, 161 ppm and 177 ppm respectively. Final confirmation of compound **5** is by the appearance of molecular ion peak at m/z = 257 (M^+, 100%), isotopic peaks at 259 (M^{+2}, 80%), 261 (M^{+4}, 30%) and fragmented ion peaks at 149 (50%), 113 (10%), 221 (10%) in its mass spectrum.

Reaction of compound **5** with oxygen nucleophile via aromatic nucleophilic substitution such as sodium benzylate in dry toluene under inert N_2 atmosphere for 48 hrs at room temperature furnished the desired compounds **6a** in 62% yield as a white crystalline solid having m.p. 102-103°C. The IR (cm^{-1}) spectrum shows characteristic absorption of –C-O-C- at 1167, 1135 and ^1H NMR signals are at δ 7.6-7.2 (m, 15H, Ar), 5.8 (s, 1H, C_5H), 5.37 and 5.31 (2s, 4H, CH_2). The mass spectrum shows molecular ion peak at m/z = 401 (M^+, 100%).

Similarly, 6-phenylthio-2,4-bis(amino)pyrimidines **6b-h** were obtained in 40-70% yield by the reaction of **5** with various heterocyclic primary amines, aliphatic primary amines and substituted aromatic primary amines. Compound **6e** was obtained in 68% yield as a white crystalline solid having m.p. 190-193°C. The IR (cm^{-1}) spectrum shows characteristic absorption of NH at 3314, 3150, N=C 1508 and ^1H NMR signals are at δ 10.2 (s, 1H, NH), 9.3 (s, 1H, NH), 7.5-6.5 (m, 13H, Ar), 6.0 (s, 1H, C_5H), 3.8 (s, 6H, OCH_3). The mass spectrum shows molecular ion peak at m/z = 430 (M^+, 100%) and fragmented ion peaks 398, 323, 307, 215, 120 and 107. All the intermediates and final compounds **6b-h** were characterized by IR, ^1H-NMR and elemental analysis.

Conclusion

The versatility of barbituric acid to synthesize various 6-phenylthio-2,4-disubstituted pyrimidines was demonstrated. This approach constitutes a facile and efficient way to synthesize several pyrimidine analogues which are not easily accessible in good yield and in few steps utilizing inexpensive reagents. Some of these compounds could be useful for biochemical studies and are presently under investigation.

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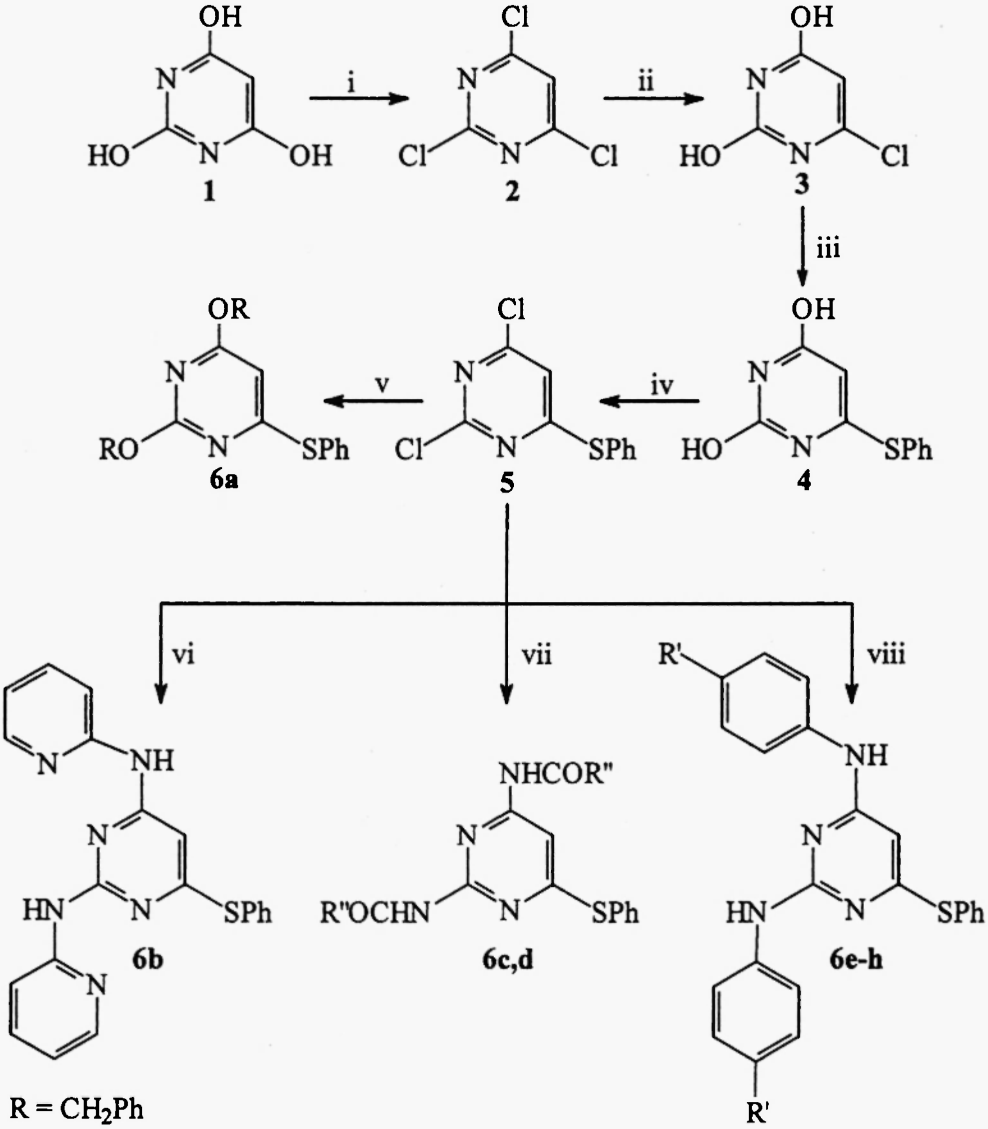
Table I. Synthesis of 6-phenylthio-2,4-disubstituted pyrimidines (4-6a-h)

Compound	R	R'	R''	mp[a] (°C)	Yield[b] (%)
4	-	-	-	238-240	76
5	-	-	-	49-51	80
6a	CH_2Ph	-	-	102-103	62
6b	-	-	-	semi-solid	47
6c	-	-	CH_3	semi-solid	54
6d	-	-	Ph	semi-solid	50
6e	-	OMe (*p*)	-	190-193	68
6f	-	Me (*p*)	-	164-165	70
6g	-	NO_2 (*p*)	-	semi-solid	46
6h	-	COOH (*p*)	-	semi-solid	43

[a] Melting points are uncorrected, [b] Yield refers to purified product.



R = CH_2Ph
R' = CH_3, OCH_3, NO_2, COOH
R" = CH_3, Ph

Scheme-1: Reagents and Conditions: (i) $POCl_3$, *N, N*-dimethylaniline; (ii) aq NaOH; (iii) PhSH, pyridine; (iv) $POCl_3$; (v) $NaOCH_2Ph$, toluene; (vi) 2-Aminopyridine, MeOH; (vii) R''$CONH_2$, MeOH; (viii) Substituted aromatic primary amines, MeOH.

Received on June 6, 2008