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Reactions of 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione with Carbonyl Reactives

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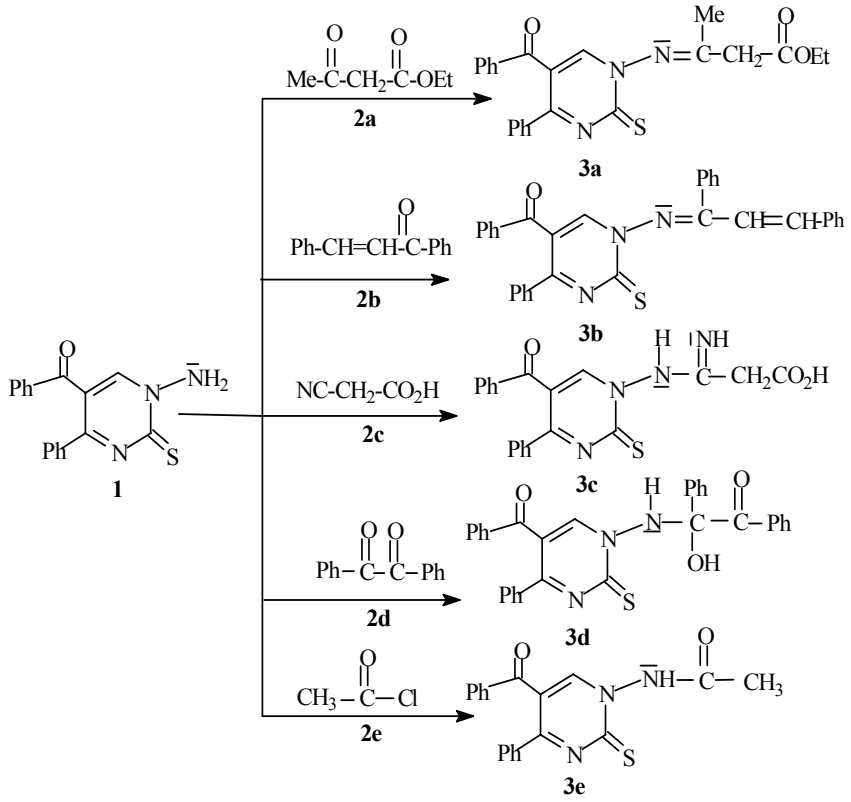
The 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**) was obtained by starting from 4-benzoyl-5-phenyl-2,3-furandione and acetophenonthiosemicarbazone. In this study, the investigations were extended to reactions of the compound **1** with ethylacetoacetate, benzalacetophenone, cyanoacetic acid, benzyl and acetylchloride (**2a-e**). Thus, some new pyrimidine derivatives (**3a-e**) were synthesized. The structures of these compounds were determined by elemental analysis, IR, ^{1}H NMR spectroscopic measurements.

Key Words: Pyrimidine-2-thione, Ketimine, Amide, Addition-condensation.

INTRODUCTION

It is obvious that pyrimidine derivatives are an important class of organic compounds. 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**) are synthesized in two steps from 4-benzoyl-5-phenylfuran-2,3-dione and acetophenonthiosemicarbazone[1,2]. In general, pyrimidines have found much interest for biological and medicinal reasons, thus their chemistry has been investigated extensively[3,4]. Some of these compounds have been shown to exhibit antimicrobial, antifungal, antiviral, anticancer, antiparasitic and herbicide properties[5-8].

For these reasons, the aim of this study was to synthesized various pyrimidine derivatives to make notable contributions to this class of heterocyclic compounds that are generally well known for their potential biologicial activities. 1-Aminopyrimidine derivatives exhibiting a free N-NH_2 moiety, which should apply to several subsequent reactions. The reactions of **1** with several anhydrides, 1,3-dicarbonyl compounds, isothiocyanates and isocyanates have been reported in different conditions[9-11]. In this paper, the reactions of **1** with ethylacetoacetate, benzalaceto-phenon, cyanoacetic acid, benzyl and acetyl chloride **2a-e** under different conditions were presented (**Scheme-I**).



Scheme-I

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined by use of Büchi melting point apparatus and not corrected. The compounds were routinely checked for their homogenity by TLC using, kieselgel GF_{254} 60 as absorbant. Microanalyses were performed on a Carlo Erba elemental analyzer, Model 1108; the results agreed favorably with the calculated values. The IR spectra were recorded on a Shimadzu Model 435 V-04 spectrometer, using potassium bromide discs. ^{1}H NMR spectrum was recorded on a Gemini-Varian 200 MHz instrument. The chemical shifts are reported in ppm from tetramethylsilane and are given in δ (ppm). Chemicals were from Merck and Aldrich chemicals.

3-(5-Benzoyl-4-phenyl-2-thioxo-1,2-dihydro-pyrimidinyl-amino)-1-ethoxy-1-oxo-ethylmethylketimine (3a): 0.2 g of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**) and 1 mL of ethylacetoacetate (**2a**), (molar ratio 1:14), 0.05 g of *p*-toluensulfonic acid were homogeneously mixed. The mixture in a 50 mL round bottomed flask by fitting calcium

chloride gard-tube was heated at 135 ºC for 2 h. without any solvent. After cooling to room temperature, the residue was treated with dry diethyl ether. The crystals which precipitated were filtered off and washed thoroughly with hot *n*-butanol and and allowed to dry on P_2O_5; yield: (60 %); m.p. 248 ºC; IR (cm^{-1}) (KBr): 3100 ν(aromatic C-H), 3000-2900 ν(aliphatic C-H), 1730-1650 ν(C=O), 1620 ν(C=C and C=N), 1230 (C=S), 800-640 ν(pyrimidine ring); ^{1}H NMR ($CDCl_3$, δ): 7.02-7.38 (m, 11H, ArH), 4.30 (q, 2H, -OCH_2-CH_3), 3.36 (s, 2H, C-CH_2-C), 2.07 (s, 3H, N=C-CH_3), 1.29 ppm (t, 3H, -OCH_2-CH_3). Anal. calcd. for $C_{23}H_{21}N_3O_3S$: C, 65.87; H, 5.01; N, 10.00; S, 7.63. Found: C, 65.72; H, 4.91; N, 9.73; S,7.91.

N-(5-Benzoyl-4-phenyl-2-thioxo-1,2-pyrimidinyl)-1,3-diphenyl-2-ethenylketimine (3b): 0.2 g of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**), 0.4 g of benzalacetophenon (**2b**) (molar ratio 1:3) and 0.05 g of *p*-toluensulfonic acid were homogeneously mixed. The mixture in a 50 mL round bottomed flask by fitting calcium chloride gard-tube was heated at 130 ºC for 3 h without any solvent. After cooling to room temperature, the residue was treated with dry diethyl ether. The crystals which precipitated were filtered off and washed thoroughly with hot *n*-butanol and allowed to dry on P_2O_5; yield: % 40, m.p. 195 ºC; IR (KBr, cm^{-1}): 3020 ν(aromatic C-H), 1740 ν(C=O), 1630-1600 ν(C=C and C=N), 1240 ν(C=S), 780-680 ν(pyrimidine ring); ^{1}H NMR ($CDCl_3$, δ): 3.40-3.84 (d, 2H, -CH=CH-), 6.48-7.90 ppm (m, 21H, ArH). Anal. calcd. for $C_{32}H_{23}N_3OS$: C,77.25; H, 4.65; N, 8.44; S, 6.44. Found: C, 77.01; H, 4.50; N, 8.40; S,6.25.

3-(5-Benzoyl-4-phenyl-2-thioxo-1,2-dihydro-pyrimidinyl-amino)-3-imino-propanoic acid (3c): 0.2 g of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**) and 0.2 g of cyanoacetic acid (**2c**) (molar ratio1:4) were refluxed in 30 mL benzene for 11 h. The solvent was evaporated. Then, the residue was treated with ether and filtered. The crude product was washed thoroughly with hot petroleum ether and allowed to dry on P_2O_5; yield (50 %); m.p. 255 ºC; IR (KBr, cm^{-1}): 3400-3200 ν(-COOH), 1730 ν(C=O), 1620 ν(C=N), 690-790 ν(pyrimidine ring); ^{1}H NMR ($CDCl_3$, δ): 9.57 (s, 1H, N-H), 7.14-8.01 (m, 11H, ArH), 3.90 ppm (s, 2H,-CH_2-). Anal. calcd. for $C_{20}H_{16}N_3O_3S$: C, 63.48; H, 4.25; N, 11.10; S, 8.47. Found: C, 63.30; H, 4.05; N,10.95; S, 8.28.

1-(5-Benzoyl-4-phenyl-2-thioxo-1,2-dihydro-pyrimidinyl-amino)-1,2-diphenyl-1-hydroxy-2-oxoethane (3d): 0.2 g of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**), 1.32 g of benzyl **2d** (molar ratio 1:4) and 0.05 g of *p*-toluensulfonic acid were homogeneously mixed. The mixture in a 50 mL round bottomed flask by fitting calcium chloride gard-tube was heated at 135 ºC for 5 h. without any solvent. After cooling to room temperature, the residue was treated with dry diethyl ether and allowed to

dry on P_2O_5; yield: 50 %; m.p. 368 ºC; IR (KBr, cm^{-1}): 3400 ν(N-H), 1650 ν(C=O), 1600-1580 ν(C=C and C=N), 800-700 ν(pyrimidine ring); ^1H NMR (DMSO, δ): 10.44 (s, 1H, -NH), 8.34 (s, 1H, H-C_6), 7.01-7.84 (m, 20H, ArH), 3.40 ppm (s, 1H, -OH). Anal. calcd. for $C_{31}H_{23}N_3O_3S$: C, 71.94; H, 4.47; N, 8.11; S, 6.19. Found: C, 71.75; H, 4.35; N, 8.01; S, 6.09.

N-(5-Benzoyl-4-phenyl-2-thioxo-1,2-dihydro-pyrimidine-1-yl)acetamide (3e): 0.2 g of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**) and 0.3 mL of acetyl chloride (**2e)** (1:4 mol) were dissolved in 3 mL water and to this solution was added 1 g of CH_3COONa. The mixture was stirred by a magnetic stirrer at room temperature for 48 h. The solvent was evaporated. The residue was treated with dry diethyl ether and filtered. The crude product was washed thoroughly with water and recrystallized from ethanol and allowed to dry on P_2O_5; yield 45 %; m.p. 330 ºC; IR (KBr, cm^{-1}): 3200 ν(-N-H), 3030 ν(-CH_3), 1720-1660 ν(C=O), 1610-1590 ν(C=C and C=N), 1200 ν(C=S), 800-670 ν(pyrimidine ring). Anal. calcd. for $C_{19}H_{15}N_3O_2S$: C, 61.33; H, 4.81; N, 13.41; S, 10.23. Found: C, 61.15; H, 4.67; N,13.32; S, 10.07.

RESULTS AND DISCUSSION

As mentioned above, 1-methylenaminopyrimidine was synthesized from the reaction of 4-benzoyl-5-phenyl-furan-2,3-dione with acetophenone thiosemicarbazones. Its hydrolysis afforded the 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1**)[1,2]. In the present study, we carried out the nucleophilic additions reaction of **1** to the corresponding some carbonyl reactives **2a-e** (**Scheme-I**). The reactions were performed by heating them without any solvent. The structures of synthesized compounds **3a-e** were assigned on the basis of analytical results as well as spectroscopic data.

Product **3a** was obtained in 60 % yield by treating **1** with ethyl acetoacetate **2a** and heating them without any solvent up to 135 ºC. In the IR spectra of compound **3a**, the C=O absorption bands were found to be at about 1730 and 1650 cm^{-1}. Important structural information about **3a** was obtained from the ^1H NMR spectrum. The multiple peaks beetwen 7.38-7.02 ppm are thought to represent the aromatic protons and 4.30 (q, 2H, -OCH_2-), 1.29 (t, 3H, -OCH_2-CH_3), 2.07 (s, 3H, N=C-CH_3), 3.36 ppm (s, 2H, -C-CH_2-C-)[12]. The ^1H NMR spectra of **3a** contain two weak peaks between 10.94 and 5.29 ppm for enolic O-H and the enolic =CH- taotomeric proton. This indicates the existence of a keto-enol equilibirium and the proportion of the keto form of **3a** was found to be dominant in $CDCl_3$ solution. As previously known, 1,3-diones show keto-enol taotomerism and the proportion of the tautomers depends on the temperature and solvent used[13,14]. The reaction of **1** with benzalacetophenone (**2b**) has the same mechanism as compound **3a**.

Product **3c** was obtained in 50 %, yield by treating **1** with cyanoacetic acid (**2c**) and refluxing the mixture in benzene for 11 h. In the IR spectra of compound **3c**, the O-H absorption band was observed at 3400-3200 cm^{-1}. The ^1H NMR signals were observed at δ 9.57 (s, 1H, NH) and 7.14-8.01 (m, 13H, Ar-H) and 3.90 ppm (s, $-CH_2-$, 2H).

Product **3d** with 50 % yield was obtained by treating **1** with benzyl **2d** at 135 ºC for 5 h. The formation of **3d** was supported by the results of spectroscopic measuremants. The -NH and -OH absorption bands were observed at *ca.* 3400-3150 cm^{-1}. The elemental analytical and spectroscopic data for **3d** agree well with the proposed structure.

The reaction of **1** with acetylchloride **2e** at room temperature for 24 h given new amide derivative with 45 % yields. The structure of compound **3e** was determined from IR. In the IR spectra of compound **3e**, the N-H absorption band was found to be at about 3200 cm^{-1}. The carbonyl and thiocarbonyl 1720, 1660 and 1200 cm^{-1}, respectively.

All the newly synthesized compounds **3a-e** were purified by recrystallization and their structures were confirmed by elemental analysis and IR, ^1H NMR spectroscopic techniques that supported the assigment.

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