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Reactions of 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine Derivatives with Various Isothiocyanates

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1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine derivatives **1** react with the various isothiocyanates **2a-l** under different conditions to yield the new N,N´-disubstituted thioureas **3a-l**. The structures of these compounds **3a-l** were determined by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopic measurements.

Key Words: 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one/thione, Isothiocyanate, Addition, Thiourea.

INTRODUCTION

It is obvious that pyrimidine derivatives are an important class of organic compounds. 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one and its pyrimidine-2-thione anologue are synthesized in two steps from 4-benzoyl-5-phenylfuran-2,3-dione[1,2]. 1-Aminopyrimidine derivatives **1** 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 and isocyanates have been reported in different conditions[3-5]. In general, pyrimidines have found much interest for biological and medicinal reasons, thus their chemistry has been investigated extensively[6,7]. Some of these compounds have been shown to exhibit antimicrobial, antifungal, antiviral, anticancer, antiparasitic and herbicide properties[8-11].

In this paper, the reactions of **1** with the various isothiocyanates **2a-l** under different conditions were presented. The new N,N´-disubstituted thioureas **3a-l** were synthesized from the reactions between 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one/thione and the various alkyl-/arylisothiocyanates **2a-l** (**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 were not corrected. The compounds were routinely checked for their homogenity by TLC using, kiesel gel $GF_{254}60$

as absorbant. Microanalyses were performed on a Carlo Erba Elemental Analyser, Model 1108. The infrared spectra were recorded on a Shimadzu Model 435 V-04 spectrometer, using potassium bromide discs. ^{1}H and ^{13}C NMR spectra were 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 comp.

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-thiourea (3a): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one **1a** (0.2 g, 0.069 mmol and phenylisothiocyanate **2a** (2 mL, 16.7 mmol) (1:25 molar ratio) were heated at 100ºC for at 4 h without any solvent in a calcium chloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with ether and filtered and the crude product was recrystallized from *n*-butanol and allowed to dry on P_2O_5; yield: 0.124 g (62 %); m.p. 230ºC; IR (KBr, cm^{-1}): 3400-3300 ν(-NH), 3050 ν(arom. C-H stretch.), 1690-1650 ν(C=O carbonyl), 1600 ν(C=C and C=N), 1500-1350 ν(phenyl groups), 1240 ν(C=S), 740-660 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 9.65 (s, 2H, NH), 8.59 (s, 1H pyrimidine ring), 8.50-7.04 ppm (m, 15H, ArH). Elemental analysis: Found (Calcd.) %: C = 67.74 (67.60), H = 4.09, (4.25), N = 12.88 (13.13), S = 7.40 (7.51).

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-phenyl-thiourea (3b): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.2 g, 0.065 mmol) and phenylisothiocyanate (**2b**) (1.95 mL, 16.32 mmol) (1:25 molar ratio) were refluxed in 30 mL acetonitrile for 5 h. The solvent was evaporated. The remaining oily residue was then treated with ether and stirred for 24 h to give a yellow product which was recrystallized from *n*-butanol and allowed to dry on P_2O_5; yield: 0.12 g (60 %); m.p.; 260ºC; IR (KBr, cm^{-1}): 3500-3300 ν(NH), 3050 ν(aromatic C-H), 1660 ν(C=O), 1250-1230 ν(C=S), 1600 ν(C=C and C=N), 760-740 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 9.64 (s, 2H, NH), 7.87-7.32 ppm (m, 16H, ArH); ^{13}C NMR (DMSO, δ): 193.61(s, PhCO), 137.83-126.91 ppm (m, aromatic carbons). Elemental analysis: Found (Calcd.) % : C = 65.46 (65.16), H = 4.44 (4.10), N = 12.59 (12.66), S = 14.72 (14.47).

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-methylphenyl-thiourea (3c): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.2 g, 0.069 mmol) and *p*-methylphenylisothiocyanate (**2c**) (1.71 mL, 13.67 mmol) (molar ratio 1:20) were heated at 135ºC for 2 h. After cooling to room temperature, the residue was treated with ether and the product recrystallized from *n*-buthanol and allowed to dry on P_2O_5; yield: 0.15 g (75 %); m.p. 348ºC; IR (KBr, cm^{-1}): 3300-3200 ν(NH), 3050 ν(aromatic C-H), 2800 ν(CH_3), 1680-1660 ν(C=O, carbonyl), 1590 ν(C=C and C=N), 1580-1440 ν(phenyl groups), 1340-1280 ν(aliphatic C-H),

850-700 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ); 10.78 (s, 2H, NH), 7.60 -7.11 (m, 15H, Ar-H), 2.30 ppm (CH_3); ^{13}C NMR (DMSO, δ): 193.62 (Ph-C=O), 155.04 (C4), 152.12 (pyrimidine ring, C=O), 139.62 (C6), 120.13 (C5), 138.56-110.19 (aromatic carbons), 21.10 ppm (CH_3). Elemental analysis: Found (Calcd.) % : C = 67.90 (68.18), H = 4.23 (4.50), N = 12.40 (12.72), S = 7.11 (7.27).

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-methylphenyl-thiourea (3d): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.2 g, 0.65 mmol) and *p*-methylphenylisothiocyanate (**2d**) (1.63 mL, 13.01 mmol) (molar ratio 1:20) were heated at 135ºC for 2 h. After cooling to room temperature, the residue was treated with ether and so formed product recrystallized from *n*-butanol and allowed to dry on P_2O_5; yield: 0.14 g (70 %); m.p. 268ºC; IR (KBr, cm^{-1}): 3450-3350 ν(NH), 2900 ν(CH_3), 1660 ν(C=O), 1600 ν(C=C and C=N), 1250-1230 ν(C=S), 680-820 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 9.61 (s, 2H, NH), 7.32-7.89 (m, 15H, Ar-H), 2.44 ppm (s, 3H, CH_3); ^{13}C NMR (DMSO, δ): 193.52 (PhC=O), 157.17 (C4), 158.77 (pyrimidine ring, C=O), 140.73 (C6), 137.72-129.12 (aromatic carbons), 22.67 ppm (CH_3). Elemental analysis: Found (Calcd.) % : C = 65.50 (65.78), H = 4.05 (4.38), N = 12.10 (12.28), S = 14.15 (14.00).

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-methoxyphenyl-thiourea (3e): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.2 g, 0.069 mmol) and *p*-methoxyphenylisothiocyanate (**2e**) (1.92 mL, 13.7 mmol) (molar ratio 1:20) were heated 125ºC for 70 min without any solvent. After cooling to room temperature, the residue was treated with dry ether. The yellow crystals were filtered off and washed thoroughly with hot *n*-butanol and allowed to dry on P_2O_5; yield: 0.148 g (74 %); m.p. 335ºC; IR (KBr, cm^{-1}): 3450-3300 ν(NH), 2920 ν(OCH_3), 1660-1620 ν(C=O, carbonyl), 1600-1520 ν(C=C and C=N), 820-700 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 10.71 (s, 2H, NH), 7.63-7.00 (m, 15H, Ar-H), 3.77 ppm (s, 3H, OCH_3); ^{13}C NMR (DMSO, δ): 193.60 (PhC=O), 153.90 (pyrimidine ring, C=O), 154.09 (C4), 142.04 (C6), 140.20-110.19 (aromatic carbons), 57.12 ppm (OCH_3). Elemental analysis: Found (Calcd.) % : C = 65.75 (65.79), H = 4.68 (4.41), N = 11.96 (12.28), S = 7.24 (7.01).

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-methoxyphenylthiourea (3f): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.2 g, 0.65 mmol) and *p*-methoxyphenylisothiocyanate (**2f**) (1.81 mL, 12.95 mmol) (molar ratio 1:20) were heated 135ºC for 5 h without any solvent. After cooling to room temperature, the residue was treated with dry ether. The precipitated crystals were filtered off and recrystallized from *n*-butanol; yield: 0.146 g (73 %); m.p. 247.6ºC; IR (KBr,

cm^{-1}): 3500-3300 ν(N-H), 1690 ν(C=O), 1600 ν(C=C and C=N), 1240-1230 ν(C=S), 760-700 ν(pyrimidine ring skeleton); ^{1}H NMR (DMSO, δ): 9.63 (s, 2H, NH), 7.89-7.16 (m, 15H, Ar-H), 3.86 ppm (s, 3H, OCH^3); ^{13}C NMR (DMSO, δ): 192.62 (C=O), 149.25 (pyrimidine ring, C=O), (138.46-115.92 (arom. carbons), 57.29 ppm (OCH_3). Elemental analysis: Found (Calcd.) % : C = 63.91 (63.56), H = 4.28 (4.26), N = 11.84 (11.89), S = 13.17 (13.55).

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-nitrophenyl-thiourea (3g): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.2 g, 0.069 mmol) and *p*-nitrophenylisothiocyanate (**2g**) (2.47 g, 13.70 mmol) (molar ratio 1: 20) were homogeneously mixtured. The mixture in a 50 mL round bottomed flask by fitting calcium chloride gard-tube was heated at 130ºC for 1 h without any solvent. After cooling to room temperature, the residue was treated with ether. The precipitated crystals were filtered off and washed thoroughly with hot *n*-butanol and and allowed to dry on P_2O_5; yield: 0.156 g (78 %); m.p. 227ºC; IR (KBr, cm^{-1}): 3400-3300 ν(NH), 3082 ν(arom. C=CH), 1685 ν(C=O carbonyl), 1592-1447 ν(C=C and C=N), 1350 ν(NO_2), 1240 ν(C=S), 855-700 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 10.66 (s, 2H, NH), 8.30-6.84 ppm (m, 15H, Ar-H). Elemental analysis: Found (Calcd.) % : C = 61.13 (61.15), H = 3.98 (3.63), N = 14.51 (14.86), S = 7.13 (6.79).

1-(5-Benzoyl-2-thioxo-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-*p*-nitrophenyl-thiourea (3h): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.2 g, 0.65 mmol) and *p*-nitrophenylisothiocyanate (**2h**) (2.34 g, 13.01 mmol) (molar ratio 1:20) were heated at 135ºC for 2 h. After cooling to room temperature, the residue was treated with dry ether and the product washed with *iso*-propanol and allowed to dry on P_2O_5; yield: 0.15 g (76 %); m.p. 193ºC; IR (KBr, cm^{-1}): 3400-3330 ν(NH), 1667 ν(C=O), 1523-1444 ν(C=C and C=N), 1385-1328 ν(N-O), 1247 ν(C=S); ^{1}H NMR (DMSO, δ); 9.54 (s, 2H, NH), 8.19-7.24 ppm (m, 15H, Ar-H). Elemental analysis: Found (Calcd.) % : C = 59.49 (59.14), H = 3.51 (3.55), N = 14.02 (14.37), S = 13.01 (13.13).

1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-(3,4)-dichlorophenyl thiourea (3i): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.2 g, 0.069 mmol) and 3,4-dichlorophenylisothiocyanate (**2i**) (0.28 g, 1.36 mmol) (molar ratio 1:2) were refluxed in 30 mL acetonitrile for 3 h. The solvent was evaporated. The remaining oily residue was then treated with ether and stirred for 24 h to give a yellow product which was washed with hot ethanol and allowed to dry on P_2O_5; yield: 0.144 g (71 %); m.p. 225ºC; IR (KBr, cm^{-1}): 3450-3300 ν(NH), 1690-1590 ν(C=O, carbonyl), 1500 ν(C=C and C=N), 680-820 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 10.30 (s, 2H, NH), 7.98-6.95 ppm (m, 14H, ArH).

Elemental analysis: Found (Calcd.) % : C = 57.88 (58.19), H = 3.44 (3.25), N = 10.97 (11.31), S = 6.05 (6.46).

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-(3,4)-dichlorodiphenyl thiourea (3j): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1a**) (0.2 g, 0.65 mmol) and 3,4-dichloridephenylisothiocyanate (**2j**) (0.26 g, 1.29 mmol) (molar ratio 1:2) were refluxed in 30 mL acetonitrile for 3 h. The solvent was evaporated. The remaining oily residue was then treated with ether and stirred for 24 h to give a yellow product which was recrystallized from ethanol and allowed to dry on P_2O_5; yield: 0.14 g (70 %); m.p. 28ºC; IR (KBr, cm^{-1}): 3500-3300 ν(N-H), 1670 ν(C=O, carbonyl), 1500 ν(C=C and C=N), 1260-1250 ν(C=S), 790-720 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 9.69 (s, 2H, NH), 8.08-7.30 ppm (m, 14H, ArH). Elemental analysis: Found (Calcd.) % : C = 56.48 (56.37), H = 3.40 (3.15), N = 10.86 (10.56), S = 12.40 (12.51).

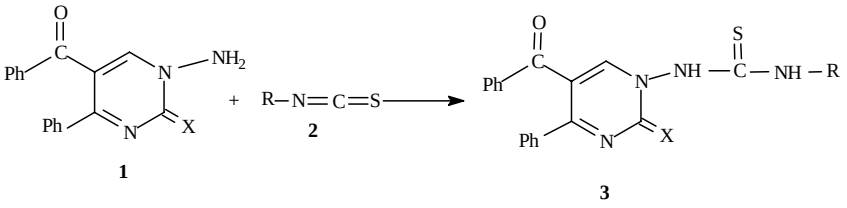
1-(5-Benzoyl-2-oxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-cyclohexyl thiourea (3k): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) (0.2 g, 0.069 mmol) and cyclohexylisothiocyanate (**2k)** (1.94 g, 13.73 mmol) (molar ratio 1: 20) were heated 130ºC for 2 h without any solvent. After cooling to room temperature, the residue was treated with ether. The precipitated yellow product was filtered and washed with hot petroleum ether and allowed to dry on P_2O_5; yield: 0.12 g (60 %); m.p. 185ºC; IR (KBr, cm^{-1}): 3500-3300 ν(N-H), 2950-2800 ν(aliphatic C-H, at cyclohexane), 1681, 1657 ν(C=O), 1520-1447 ν(C=C and C=N), 1476 ν(phenyl groups), 778-622 ν(pyrimidine ring skeleton vib.); ^{1}H NMR (DMSO, δ): 9.69 (s, 2H, NH), 8.01-7.33 (m, 11H, Ar-H), 3.73-1.53 ppm (m, 11H, aliphatic). Elemental analysis: Found (Calcd.) % : C = 67.01 (66.66), H = 5.89 (5.59), N = 12.58 (12.96), S = 7.05 (7.40).

1-(5-Benzoyl-2-thioxo-4-phenyl-1,2-dihydro-pyrimidine-1-yl)-3-cyclohexyl-thiourea (3l): 1-Amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) (0.2 g, 0.65 mmol) and cyclohexylisothiocyanate (**2l**) (1.84 g, 13.01 mmol) (molar ratio 1: 20) were heated 130ºC for 3 h without any solvent. After cooling to room temperature, the residue was treated with ether. The precipitated yellow product was filtered and washed with hot petroleum ether and allowed to dry on P_2O_5; yield: 0.13 g (65 %); m.p. 190ºC; IR (KBr, cm^{-1}): 3600-3300 ν(N-H), 2950-2800 ν(aliphatic C-H at cyclohexane), 1681 ν(C=O), 1530-1447 ν(C=C and C=N arom.), 1476 ν(phenyl groups), 1240 ν(C=S), 778-622 ν(pyrimidine ring. skeleton. vib.); ^{1}H NMR (DMSO, δ): 9.60 (s, 2H, NH), 8.50-7.40 (m, 11H, Ar-H), 3.50-1.45 ppm (m, 11H, aliphatic). Elemental analysis: Found (Calcd.) % : C = 64.35 (64.28), H = 5.33 (5.39), N = 12.35 (12.35), S = 14.52 (14.27).

RESULTS AND DISCUSSION

Several N,N´-disubstituted thioureas **3a-l** (**Scheme-I**) were easily obtained in good yields (60-78 %) from nucleophilic addition[4] of **1** to the coresponding alkyl-/arylisothiocyanates **2a-l**. The moderate yield of the reactions can be explained by the chemical behaviour of 4,5-substituted pyrimidine-2-one/thione towards the compounds **2a-l**. The carbon atoms represent the electrophilic site in the molecules of the isothiocyanates so that they can be interacted with nucleophilic reactions. The reactions were performed either in boiling acetonitrile or heating without solvent up to (80-135ºC) (Experimental). The structures of the synthesized compounds assigned on the basis of analytical results as well as spectroscopic data (**3a-b** as examples).

3a was obtained from the reaction of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one (**1a**) with phenylisothiocyanate (**2a**) in 62 % yield. In the IR spectra of compound **3a**, the -NH absorbtion band was found to be at 3400-3300 cm^{-1} and the (C=S) absorbtion was at 1240 cm^{-1}. The (C=O) absorbtion bands were observed at 1690, 1650 cm^{-1}. The ^1H NMR signals were found to be at 9.65 (b, 2H, -NH) and 8.50-7.04 ppm (m, 16H, ArH). Finally, the elemental analysis data along with spectroscopic data (Experimental) confirm the structure of **3a**.



1-3	X	R
a	O	Ph-
b	S	Ph-
c	O	*p*-$CH_3C_6H_4$-
d	S	*p*-$CH_3C_6H_4$-
e	O	*p*-$CH_3OC_6H_4$-
f	S	*p*-$CH_3OC_6H_4$-

1-3	X	R
g	O	*p*-$NO_2C_6H_4$-
h	S	*p*-$NO_2C_6H_4$-
i	O	3,4-Dichlorophenyl-
j	S	3,4-Dichlorophenyl-
k	O	Cyclohexyl-
l	S	Cyclohexyl-

Scheme-I

In a similar way, the reaction of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-thione (**1b**) with phenylisothiocyanate (**2b**) leads to form **3b**, (**Scheme-I**). The structure of compound **3b** is determined from its IR and

^{1}H NMR spectra. The -NH and (C=S) absorbtion bands were found to be at 3500-3300 cm^{-1} and 1250-1230 cm^{-1}, respectively. The (C=O) absorbtion, was at 1660 cm^{-1}. ^{1}H NMR signals were found to be at 9.64 (s, 2H, -NH) and 7.87-7.32 ppm (m, 16H, ArH). The ^{13}C NMR signals were observed at d 193.61 (s, PhCO), 137.83-126.91 ppm (m, aromatic carbons).

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