# REACTIONS OF 1-AMINO-5-(4-METHYLBENZOYL)-4-(4-METHYLPHENYL)PYRIMIDINE-2(1*H*)-THIONE WITH VARIOUS ISOTHIOCYANATES

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**Abstract:** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **(1)** react with the various isothiocyanates **(2a-g)** under different conditions to yield the new *N,N'*-disubstituted thioureas **(3a-g)**. The structures of these compounds **(3a-g)** were determined by elemental analysis, IR, $^1$H and $^{13}$C NMR spectroscopic measurements.

**Introduction**

It is obvious that pyrimidine derivatives are an important class of organic compounds. They show various interesting pharmacological properties including antiviral[1], antibacterial[2,3], antitumor[4] and antiflammatory effects[5]. Some of them are frequently encountered in many drugs used for the treatment of hypothyroidy, hypertension, cancer chemotherapy or HIV infection[6-9].

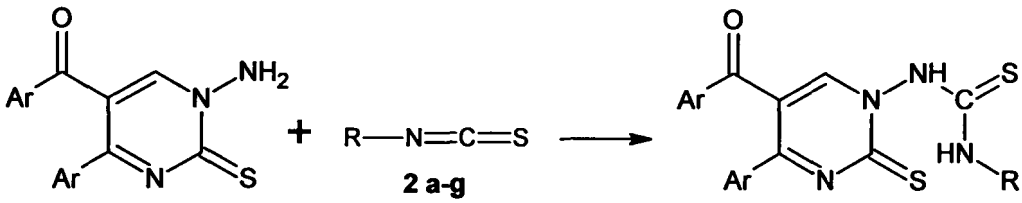
1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione is synthesized in two steps from 4-(4-methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione[10,11]. 1-Aminopyrimidine derivatives exhibiting a free N-$NH_2$– moiety, which should apply to several subsequent reactions. The reactions of aminopyrimidine derivatives with several anhydrides, 1,3-dicarbonyl compounds, isocyanates and isothiocyanates have been reported in different conditions [12-17].

In this paper, the reactions of **1** with the various isothiocyanates **2a-g** under different conditions were presented. We have synthesized the new *N,N'*-disubstituted thioureas **3a-g** from the reactions between 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione and the various alkyl-/arylisothiocyanates **2a-g** (Scheme 1).

**Results and Discussion**

Several N,N'-disubstituted thioureas **3a-g** (Scheme-1) were easily obtained in good yields (55-65%) from nucleophilic addition of **1** to the coresponding alkyl-/arylisothiocyanates **2a-g**. The moderate yield of the reactions can be explained by the chemical behavior of 4,5-substituted pyrimidine-2-thione towards the compounds **2a-g**. The carbon atoms represent the electrophilic site in the molecules of the isothiocyanates so they can be interacted with nucleophilic reactions[15,16]. The reactions were heating without solvent up to (120-135°C) (see Experimental). The structures of the obtained *N,N'*-disubstituted thioureas **3a-g** were confirmed by interpreting their IR, $^1$H NMR and $^{13}$C NMR spectroscopic techniques, besides the elemental analysis (3a as examples).

The compound **3a** was obtained from the reaction of 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** with phenylisothiocyanate **2a** in 64% yield. In the FT IR spectra of compound **3a**, the -NH absorbtion band was found to be at 3400-3300 $cm^{-1}$ and the C=S absorbtion bands were at 1240 $cm^{-1}$. The C=O absorbtion band was observed at 1660 $cm^{-1}$. The $^1$H-nmr signals were found to be at 9.60 (s, 2H, -NH) and 7.61-7.33 ppm (m, 14H, ArH). The $^1$H NMR spectrum **3a**, contains two singlet peaks at 2.35, 2.26 ppm representing the methyl groups. Finally, the elemental analysis data along with spectroscopic data (see Experimental) confirm the structure of **3a**. The results of measurements of **3b-g** were given in the experimental part.




1

Ar: 4-$CH_3$-$C_6H_4$ -

3 a-g

| 2 - 3 | R |
|---|---|
| a | Ph- |
| b | *p*-$CH_3OC_6H_4$- |
| c | *p*-$CH_3C_6H_4$- |
| d | 3,4-Dichlorophenyl- |
| e | 1-Napthly- |
| f | $CH_3CH_2$- |
| g | *p*-$NO_2C_6H_4$- |

**Scheme-1**

**Experimental**

Solvents were dried by refluxing over the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba elemental analyser, model 1108. The ir spectra were recorded on a Shimadzu Model 8400 FT IR spectrophotometer. The $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker-400 MHz Ultra Shield istrument. The chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 $F_{254}$ Merck and Camag TLC lamp (254/366 nm).

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-phenyl-thiourea (3a).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and phenylisothiocyanate **2a** (1.58 mL) (molar ratio 1:20) were heated at 120°C for 1 hour without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the residue was treated with ether and filtered and so formed crude product was recrystallized from n-butanol and allowed to dry on $P_2O_5$; yield: 0.18 g (64%); m.p: 278°C; IR: ν= 3400-3300 (-NH), 3042 (arom. C-H stretch.), 1660 (C=O carbonyl), 1600 (C=C and C=N), 1500-1350 (phenyl groups), 1240 (C=S), 740-660 $cm^{-1}$ (pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO): δ= 9.60 (s, 2H, NH), 7.61-7.33 (m, 14H, ArH), 2.35, 2.26 ppm (6H, 2x$CH_3$). Anal. Cald. For $C_{26}H_{22}N_4OS_2$: C, 66.40; H, 4.68; N, 12.92; S, 13.60. Found C, 66.10; H, 4.74; N, 12.65; S, 13.32.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-*p*-methoxyphenyl-thiourea(3b).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and *p*-methoxyphenylisothiocyanate **2b** (1.78 mL) (molar ratio 1:20) were heated at 120°C for 70 minutes. After cooling to room temperature, the residue was treated with ether and so formed product recrystallized from n-buthanol and allowed to dry on $P_2O_5$; yield: 0.16 g (61%); m.p.: 268°C; IR: ν= 3300-3200 (NH), 3065 (aromatic C-H), 2900 ($CH_3$), 1670 (C=O, carbonyl), 1600-1460 (C=C and C=N), 1340-1280 (aliphatic C-H), 1250 (C=S, thiocarbonyl's), 850-700 $cm^{-1}$(pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO); δ= 9.55 (s, 2H, NH), 7.50 -7.27 (m, 13H, Ar-H), 3.85 (3H, $OCH_3$), 2.36, 2.20 ppm (6H, 2x$CH_3$); $^{13}C$ NMR (DMSO): δ= 193.62 (C=O), 135.42-125.16 (aromatic carbons), 55.93 ($OCH_3$),

21.70 ppm (2x$CH_3$). Anal. Cald. For $C_{27}H_{24}N_4OS_2$: C, 64.81; H, 4.85; N, 12.72; S, 12.82. Found C, 64.59; H, 4.88; N, 12.58; S, 12.96.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-*p*-methylphenyl-thiourea (3c).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and *p*-methylphenylisothiocyanate **2c** (1.63 mL) (molar ratio 1:20) were heated at 135°C for 1 hour. 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: 0.15g (57%); m.p.: 292°C; IR: ν= 3450-3350 (NH), 2920 ($CH_3$), 1662 (C=O), 1600-1450 (C=C and C=N), 1250-1230 (C=S), 680-820 $cm^{-1}$ (pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO): δ= 9.52 (s, 2H, NH), 7.77-7.26 (m, 13H, Ar-H), 2.50, 2.30, 2.26 ppm (s, 9H, 3x$CH_3$); $^{13}C$ NMR (DMSO): δ= 191.83 (PhC=O), 139.33-125.41 (aromatic carbons), 22.70, 21.31 ppm (3x$CH_3$). Anal. Cald. For $C_{27}H_{24}N_4OS_2$: C, 66.90; H, 4.96; N, 11.50; S, 13.20. Found C, 66.65; H, 4.93; N, 11.80; S, 13.35.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-(3,4)-dichlorophenyl-thiourea (3d).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and 3,4-dichlorophenylisothiocyanate **2d** (2.43 g) (molar ratio 1:20) were heated at 135°C for 2 hours without any solvent. 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: 0.20 g (63%); m.p.: 290°C; IR: ν= 3450-3300 (NH), 3034 (aromatic C-H), 2900-2800 (aliphatic C-H), 1655 (C=O, carbonyl), 1605-1450 (C=C and C=N), 1250-1230 (C=S), 680-820 $cm^{-1}$ (pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO): δ= 9.59 (s, 2H, NH), 8.14-7.14 (m, 12H, ArH), 2.25, 2.16 ppm (s, 6H, 2x$CH_3$). Anal. Cald. For $C_{26}H_{20}N_4OS_2Cl_2$: C, 57.88; H, 3.71; N, 10.39; S, 11.87. Found C, 57.59; H, 3.70; N, 10.32; S, 11.56.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-α-napthyl-thiourea (3e).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and α-napthylisothiocyanate **2e** (1.89 mL) (molar ratio 1:20) were heated 135°C for 2 hours 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: 0.16 g (55%); m.p.: 292°C; IR: ν= 3340 (NH), 3080 (aromatic C-H), 2960 (aliphatic C-H), 1663 (C=O, carbonyl), 1600-1520 (C=C and C=N), 1260 (C=S), 820-700 $cm^{-1}$ (pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO): δ= 9.80 (s, 2H, NH), 8.02-7.16 (m, 16H, Ar-H), 2.49, 2.12 ppm (s, 6H, 2X$CH_3$); $^{13}C$ NMR (DMSO): δ= 190.61 (PhC=O), 139.44-112.39 (aromatic carbons), 21.53 ppm (2x$CH_3$). Anal. Cald. For $C_{30}H_{24}N_4OS_2$: C, 69.23; H, 4.61; N, 10.77; S, 12.70. Found C, 69.35; H, 4.35; N, 10.52; S, 12.42.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-ethyl-thiourea (3f).** 0.2 g 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and ethylisothiocyanate **2f** (1.02 mL) (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 135°C for 2 hours without any solvent. 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: 0.15 g (65%); m.p.: 274°C; IR: ν= 3393 (NH), 3011 (arom. C-H ), 2920 (aliphatic C-H), 1650 (C=O carbonyl), 1597-1500 (C=C and C=N), 1232 (C=S), 855-700 $cm^{-1}$ (pyrimidine ring skeleton vib.); $^1H$ NMR (DMSO): δ= 10.60 (s, 2H, NH), 7.65-7.12 (m, 9H, Ar-H), 3.11 (q, 2H, $CH_2$), 2.01, 2.21 (s, 6H, 2x$CH_3$), 1.06 ppm (t, 3H, $CH_3$). Anal. Cald. For $C_{22}H_{22}N_4OS_2$: C, 69.70; H, 5.39; N, 11.62; S, 11.92. Found C, 69.88; H, 5.65; N, 11.92; S, 11.68.

**1-[5-(4-Methylbenzoyl)-4-(4-methylphenyl)-2-thioxo-1,2-dihydro-pyrimidine-1-yl]-3-*p*-nitrophenyl-thiourea (3g).** 1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)pyrimidine-2(1*H*)-thione **1** (0.2 g) and *p*-nitrophenylisothiocyanate **2g** (2.14 g) (molar ratio 1:20) were heated at 130°C forl hour. After cooling to room temperature, the residue was treated with dry ether and so formed product washed with n-butanol and allowed to dry on $P_2O_5$; yield: 0.18 g (60%); m.p.: 193°C; IR: ν= 3400-3330 (NH), 1667 (C=O), 1523-1444 (C=C and C=N), 1385-1328 (N-O), 1247 $cm^{-1}$(C=S); $^1H$ NMR (DMSO): δ= 9.54 (s, 2H, NH), 8.19-7.24 (m, 13H, Ar-H), 2.31, 2.16 ppm (s, 6H, 2x$CH_3$). Anal. Cald. For $C_{26}H_{21}N_5O_3S_2$: C, 60.57; H, 4.10; N, 13.58; S, 12.41. Found C, 60.35; H, 4.01; N, 13.40; S, 12.28.

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