REACTIONS OF 4-(4-METHYLBENZOYL)-5-(4-METHYLPHENYL)-2,3-FURANDIONE WITH SEMI-/THIOSEMI-CARBAZONES

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Abstract: The 4-(4-methylbenzoyl)-5-(4-methylphenyl)-2,3-furandione (**1**) and various semi-/thiosemi-carbazones **2a-h** combine with loss of carbondioxide and water yielding 1-methylenaminopyrimidine-2-one and -thione derivatives **3a-h**, in moderate yields (43-59%). Hydrolysis of 5-(4-methylbenzoyl)-1-(methyl-4-methylphenylmethylenamino)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (**3c**) and 5-(4-methylbenzoyl)-4-(4-methylphenyl)-1-(phenylmethylenamino)-1*H*-pyrimidine-2-thione (**3h**) lead to the 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (4) and the 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (**5**). The newly synthesized compounds were characterized by elemental analyses, IR, ^{1}H and ^{13}C NMR spectral data. All were compared with their previous analogues.

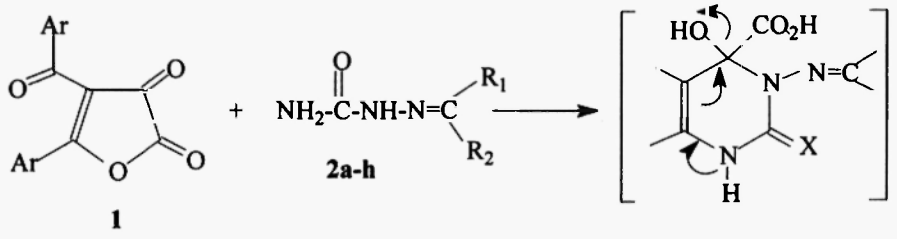
Introduction

The 4-aroyl-5-aryl-2,3-dihydro-2,3-furandiones are obtained starting from 1,3-dicarbonyl compounds with oxalyl halides[1-5]. In general, 2,3-furandiones are considered convenient and versatile synthons in heterocyclic synthesis. These compounds have been demonstrated to be a versatile, multifunctional synthetic building block for the construction of novel heterocyclic systems[6]. The chemistry of the compounds of 2,3-dihydro-2,3-furandione has been the focus of much attention for more than a few decades due to their high reactivity, which belong to the group of γ-lactones, carbon atoms could be used for the construction of many monocyclic or condensed heterocyclic compounds upon reactions with various nucleophiles[7-9]. The reactions of the substituted 2,3-furandiones with several semicarbazones, ureas and their thioanalogues and oximes, amides, anilides and hydrazines in different solvents and at various temperatures have been studied recently[7,10-20]. The reactions are generally initiated by the nucleophilic attack of the nitrogen atom of semicarbazone or urea at the C5 atom of the furane cycle[10,11]. Moreover thermal decomposition of 2,3-furandiones leads to the formation of highly reactive α-oxoketene intermediates[21,22]. Therefore, 4-aroyl-5-aryl-2,3-dihydro-2,3-furandiones have been used as initial materials in the synthesis of the target heterocycles.

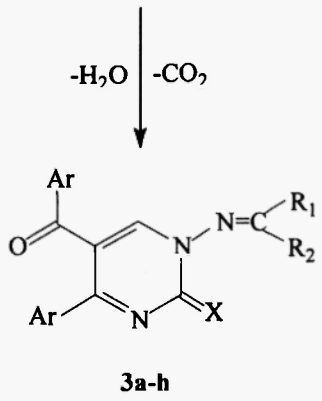
In a previous study, 4-(4-methylbenzoyl)-5-(4-methylphenyl)-2,3-furandione (**1**) was obtained from the cyclocondensation reaction that occurs between 1,3-bis(4-methylphenyl)propane-1,3-dione (di-*p*-methylbenzoyl-methane) and oxalylchloride have been reported [23,24]. In addition, the thermal decomposition and reaction of **1** with some dienophiles such as 1,3-diones (enolic forms) have been reported to give heterocylic compounds at various temperatures and in different solvents[24].

For these reasons, the aim of this study was to synthesize various pyrimidine derivatives to make notable contributions to this class of heterocyclic compounds. Pyrimidines in general have found

much interest for biological and medical reasons, thus their chemistry have been investigated extensively[25]. In particulary, various analogues of pyrimidines possess effective herbicidal, antibacterial, antifungal, antiviral[26,27]. Some of them are frequently encountered in many drugs used for the treatment of hypothyroidy, hypertension, cancer chemotherapy or HIV infection[28-31]. In the present study, we carried out the reactions of **1** with several semi-/thiosemi-carbazones **2a-h**, obtained from semi-/thiosemi-carbazide and the corresponding carbonyl compounds in our laboratories, yielding the new series of 1-methyleneaminopyrimidine-2-one and -thione derivatives **3a-h**. The general outline of the reactions studied is shown in Scheme-1.

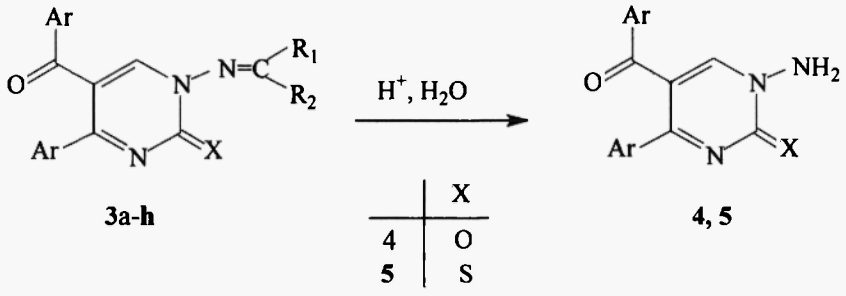


2,3	X	R_1	R_2
a	O	CH_3-	C_6H_5-
b	S	CH_3-	C_6H_5-
c	O	CH_3-	*p*-$CH_3C_6H_4$-
d	S	CH_3-	*p*-$CH_3C_6H_4$-
e	O	CH_3-	*p*-$CH_3OC_6H_4$-
f	S	CH_3-	*p*-$CH_3OC_6H_4$-
g	O	H-	C_6H_5-
h	S	H-	C_6H_5-



Scheme-1

Hydrolysis of **3c** and **3h** afforded the 1-amino-pyrimidine derivatives **4** and **5** exhibiting a free N-NH_2 moiety, which were applied to several subsequent reactions (see Scheme-2). Recently, the reactions of 1-amino-5-benzoyl-4-phenyl-1*H*-pyrimidine-2-one/-thione with several anhydrides, isocyanates and 1,3-dicarbonyl compounds have been reported in different solvents and at various temperatures[32-35]. The reactions are generally initiated by nucleophilic attack of the nitrogen atom of 1-amino-pyrimidine derivatives.



Scheme-2

Results and Discussion

The cyclocondensation reaction of 1,3-bis(4-methylphenyl)propane-1,3-dione with oxalyl dichloride afforded the 2,3-furandione **1** in boiling benzene or toluene[23,24]. Thus, a number of 1,4,5-substituted 1*H*-pyrimidine-2-ones and -thiones **3a-h** were obtained in moderate yields (43-59%) from the reactions of **1** and the corresponding **2a-h** performed either in boiling solvent or heating without solvent up to 140°C (see Exp.). The proposed reaction pathway from **1** to **3a-h** is shown in Scheme-1. The reactions should start with a nucleophilic attack of the -NH_2 group of **3a-h** at the C-5 position of the furandione ring **1** similar to a Micheal-type addition[10]. Syntheses of pyrimidine derivatives *via* Michael-type additions of ureas, thioureas, amidines and similar compounds of this type onto α,β-unsaturated carbonyls are well established[36]. The structural analogy of all compounds **3a-h** was confirmed by elemental analysis, FT IR, ^{1}H NMR and ^{13}C NMR spectroscopic data.

Product **3a** was obtained in 50% yield by treating **1** with acetophenonsemicarbazone (**2a**) and refluxing in boiling benzene for 4 hours. In the FT IR spectrum of compound **3a**, the carbonyl groups characteristic absorption bands were at about 1695, 1650 cm^{-1} respectively. Important structural information about **3a** was obtained from the ^{1}H NMR spectrum. However, the structure of 1*H*-pyrimidine-2-one **3a** was verified unambiguously from NMR data compared with those of a very close analogue (δ in brackets) obtained from a similar reaction employing 4-benzoyl-5-phenyl-2,3-furandione instead of **1**[12]: proton at C6: 8.25 (8.5) ppm, the multiple peaks beetwen 7.97-7.02 (8.1-7.2) ppm were thought to represent the aromatic protons and three singlet peaks 2.35, 2.30, 2.26 (2.3) ppm represent the methyl groups (see Experimental).

As mentioned above, hydrolysis of 1*H*-pyrimidine-2-ones and -thiones **3a-h** leads to the 1-aminopyrimidine-2-one and -thione derivatives in acetic acid and alcohol[11]. In acidic solution, from the hydrolysis of **3c** and **3h** were obtained the 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (**4**) and the 1-amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (**5**), respectively. A reasonable reaction pathway leading to the pyrimidines **4** and **5** are outlined briefly in Formula Scheme-2. Ring opening, decarboxylation reaction of an α-oxocarbonic acid intermediate, eventually initiated by the subsequent ring closure via addition of the -NH to the C=O

moiety, and finally loss of water *via* a fragmentational process[16] should be the additional steps. Their structures were confirmed by elemental analysis and spectroscopic data.

In the FT IR spectrum of compound **5**, the $-NH_2$ absorption bands were found to be at 3262 cm^{-1}. The C=O and C=S absorption bands were observed at 1653 and 1160 cm^{-1}, respectively. In the ^1H NMR spectrum of compound **5** has a singlet signal at 7.26 ppm assignable to the NH band on the pyrimidine molecule. Chemical shift values of **5** are very close to analogues of 1*H*-pyrimidine-2-thiones[11]. Finally, the elemental analysis data along with spectroscopic data (see Experimental) confirm the structure of **5**.

Experimental

Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. The compounds were routinely checked for their homogenity by TLC using DC Alufolien Kieselgel 60 F_{254} Merck and a Camag TLC lamp (254/366 nm). Microanalyses were performed on a Carlo Erba Elemental Analyser Model 1108; the results agreed favorably with the calculated values. The IR spectra were recorded on a Jasco FT IR spectrometer model 460, using potassium bromide discs. ^1H and ^{13}C-NMR spectra were obtained on a Gemini-Varian 200 instrument. The chemical shifts are reported in ppm from tetramethylsilane and are given in δ (ppm). Solvents were dried by refluxing with the appropriate drying agent and distilled before use. All other reagents were purchased from Merck, Fluka and Aldrich Chemical Co. and used without further purification.

5-(4-Methylbenzoyl)-4-(4-methylphenyl)-1-(methylphenylmethylenamino)-1*H*-pyrimidine-2-one (3a).

Compound **1** (0.5 g) and acetophenonsemicarbazone (**2a**) (0.29 g) (molar ratio 1:1) were refluxed in 30 mL benzene for 4 hours. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3a** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.35 g (50%); m.p.: 178°C; IR (*KBr*): υ = 3050-3036 (aromatic C-H), 2911 (aliphatic C-H), 1695 s, 1650 s (C=O), 1602-1573 cm^{-1} (C=C and C=N); ^1H NMR (*DMSO*): δ = 8.25 (s, 1H at C6), 7.97-7.02 (m, 13H, ArH), 2.35, 2.30, 2.26 ppm (s, 9H, $3xCH_3$). Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.93; H, 5.49; N, 9.96. Found: C, 76.70; H, 5.30; N, 9.66.

5-(4-Methylbenzoyl)-4-(4-methylphenyl)-1-(methylphenylmethylenamino)-1*H*-pyrimidine-2-thione (3b).

Compound **1** (0.5 g) and acetophenonthiosemicarbazone (**2b**) (0.30 g) (molar ratio 1:1) were refluxed in 30 mL benzene for 3.5 hours. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3b** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.31 g (43%); m.p.: 228°C; IR (*KBr*): υ = 3050-3044 (aromatic C-H), 2920 (aliphatic C-H), 1650 s (C=O), 1602-1470 cm^{-1} (C=C and C=N); ^1H NMR (*DMSO*): δ = 8.13 (s, 1H, at

C6), 8.00-7.30 (m, 13H, ArH), 2.44, 2.35, 2.31 ppm (s, 9H, 3xCH_3). Anal. Calcd. for $C_{27}H_{23}N_3SO$: C, 74.10; H, 5.26; N, 9.61; S, 7.32. Found: C, 73.90; H, 5.06; N, 9.59; S, 7.05.

5-(4-Methylbenzoyl)-1-(methyl-4-methylphenylmethylenamino)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (3c).

Compound **1** (0.5 g) and *p*-methylacetophenonsemicarbazone (**2c**) (0.34) (molar ratio 1:1) were refluxed in 30 mL toluene for 4 hours. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3c** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.35 g (50%); m.p.: 215°C; IR (*KBr*): υ = 3050-3044 (aromatic C-H), 2920 (aliphatic C-H), 1690 s, 1645 s (C=O), 1602-1473 cm^{-1} (C=C and C=N); ^1H NMR (*DMSO*): δ = 8.47 (s, 1H, at C6) 7.94-7.13 (m, 12H, ArH), 2.39, 2.33, 2.31, 2.27, ppm (s, 12H, 4xCH_3). Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.21; H, 5.78; N, 9.64. Found: C, 77.40; H, 5.57; N, 9.50.

5-(4-Methylbenzoyl)-1-(methyl-4-methylphenylmethylenamino)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (3d).

Compound **1** (0.5 g) and *p*-methylacetophenonthiosemicarbazone (**2d**) (0.31 g) (molar ratio 1:1) were refluxed in 30 mL benzene for 5 hours. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3d** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.38 g (53%); m.p.: 216°C; IR (*KBr*): υ = 3028 (aromatic C-H), 2911 (aliphatic C-H), 1650 s (C=O), 1582-1450 m (C=C and C=N), 1181 cm^{-1} (C=S); ^1H NMR (*DMSO*): δ = 8.09-7.02 (m, 13H, ArH), 2.40, 2.35, 2.33, 2.29 ppm (s, 12H, 4xCH_3). Anal. Calcd. for $C_{28}H_{25}N_3OS$: C, 74.47; H, 5.58; N, 9.31; S, 7.10. Found: C, 74.50; H, 5.47; N, 9.52, S, 7.20.

5-(4-Methylbenzoyl)-1-(methyl-4-methoxyphenylmethylenamino)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (3e).

Compound **1** (0.5 g) and *p*-methoxyacetophenonsemicarbazone (**2e**) (0.34 g) (molar ratio 1:1) were refluxed in 30 mL benzene for 4 hours. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3e** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.43 g (58%); m.p.: 240°C; IR (*KBr*): υ = 3050-3036 (aromatic C-H), 2990-2910 (aliphatic C-H), 1640 s (C=O), 1602-1570 cm^{-1} (C=C and C=N); ^1H NMR (*DMSO*): δ = 8.70 (s, 1H, at C6), 7.99-7.07 (m, 12H, ArH), 3.92 (s, 3H, -OCH_3), 2.35, 2.29, 2.21 ppm (s, 9H, 3xCH_3). Anal. Calcd. for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.30. Found: C, 74.20; H, 5.35; N, 9.14.

5-(4-Methylbenzoyl)-1-(methyl-4-methoxyphenylmethylenamino)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (3f).

Compound **1** (0.5 g) and *p*-methoxyacetophenonthiosemicarbazone (**2f**) (0.35 g) (molar ratio 1:1) were homogeniously mixed. The mixture was heated at 140°C and kept at this temperature for 20 min. without any solvent in a calcium cloride guard tube fitted round bottom flask of 50 mL. Then, the

residue was treated with dry diethyl ether and filtered and so formed crude product **3f** was recrystallized from ethanol and allowed to dry on P_2O_5; yield 0.45 g (59%); m.p.: 213°C; IR (*KBr*): υ = 3036 (aromatic C-H), 2911 (aliphatic C-H), 1640 s (C=O), 1582-1463 m (C=C and C=N), 1172 cm^{-1} (C=S); ^1H NMR (*DMSO*): δ = 8.65 (s, 1H, at C6), 8.03-7.07 (m, 12H, ArH), 3.85 (s, 3H, $-OCH_3$), 2.35, 2.29, 2.26 ppm (s, 9H, $3xCH_3$). Anal. Calcd. for $C_{28}H_{25}N_3OS$: C, 71.90; H, 5.35; N, 8.99; S, 6.85. Found: C, 71.64; H, 5.25; N, 8.67, 6.70.

5-(4-Methylbenzoyl)-4-(4-methylphenyl)-1-(phenylmethylenamino)-1*H*-pyrimidine-2-one (3g).

Compound **1** (0.5 g) and benzaldehydesemicarbazone (**2g**) (0.33 g) (molar ratio 1:1) were refluxed in 30 mL acetonitrile for 3 hours in a calcium cloride guard tube fitted round bottom flask of 50 mL. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3g** was recrystallized from methanol and allowed to dry on P_2O_5; yield 0.38 g (53%); m.p.: 182°C; IR (*KBr*): υ = 3061 (aromatic C-H), 2930 (aliphatic C-H), 1655 s, 1645 s cm^{-1} (C=O); ^1H NMR (*DMSO*): δ = 8.27 (s, 1H, at C6), 7.95-7.17 (m, 14H, ArH), 2.30, 2.28 ppm (s, 6H, $2xCH_3$). Anal. Calcd. for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.38; H, 5.05; N, 10.10.

5-(4-Methylbenzoyl)-4-(4-methylphenyl)-1-(phenylmethylenamino)-1*H*-pyrimidine-2-thione (3h).

Compound **1** (0.5 g) and benzaldehydethiosemicarbazone (**2h**) (0.33 g) molar ratio 1:1) were refluxed in 30 mL benzene for 2 hours in a calcium cloride guard tube fitted round bottom flask of 50 mL. The solvent was evaporated. Then, the residue was treated with dry diethyl ether and filtered and so formed crude product **3h** was recrystallized from methanol and allowed to dry on P_2O_5; yield 0.38 g (53%); m.p.: 178°C; IR (*KBr*): υ = 3050-3036 (aromatic C-H), 2920 (aliphatic C-H), 1645 s (C=O), 1561-1464 m (C=C and C=N), 1185 cm^{-1} (C=S); ^1H NMR (*DMSO*): δ = 8.75 (s, 1H, at C6), 7.95-7.17 (m, 14H, ArH), 2.35, 2.29 ppm (s, 6H, $2xCH_3$). Anal. Calcd. for $C_{26}H_{21}N_3OS$: C, 73.70; H, 4.96; N, 9.92; S, 7.56. Found: C, 73.86; H, 5.13; N, 9.69; S, 6.75.

1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-one (4).

20 mL of water and 5 mL of acetic acid were added to a solution of 1 g **3c** in 20 mL of ethanol and the mixture was the heated under reflux for 45-50 minutes. With cooling 0.43 g (57%) of **4** precipitated and was recrystallized from ethanol; m.p.: 198°C; IR (*KBr*): υ= 3250 ($-NH_2$), 3036 (aromatic C-H), 2911 (aliphatic C-H), 1680 s (C=O), 1650 s (C=O), 1507-1461 cm^{-1} (C=C and C=N); ^1H NMR (*DMSO*): δ= 7.71-6.99 (m, 9H, ArH), 7.26 (s, 2H, $N-NH_2$), 2.38 ppm (s, 6H, $2xCH_3$). Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.36; N, 13.15. Found: C, 71.19; H, 5.20; N, 12.95.

1-Amino-5-(4-methylbenzoyl)-4-(4-methylphenyl)-1*H*-pyrimidine-2-thione (5).

20 mL of water and 5 mL of acetic acid were added to a solution of 1 g **3h** in 20 mL of butanol and the mixture was the heated under reflux for 45-50 minutes. With cooling 0.46g (58%) of **5** precipitated and was recrystallized from ethanol; m.p.: 202°C; IR (*KBr*): υ= 3262 (-NH_2), 3069 (aromatic C-H), 2930 (aliphatic C-H), 1653 s (C=O), 1598-1462 m (C=C and C=N), 1160 cm^{-1} (C=S); ^1H NMR (*DMSO*): δ= 7.71-6.99 (m, 9H, ArH), 7.26 (s, 2H, N-NH_2), 2.24, 2.19 ppm (s, 6H, 2xCH_3). Anal. Calcd. for $C_{19}H_{17}N_3OS$: C, 68.06; H, 5.11; N, 12.53; S, 9.56. Found: C, 67.93; H, 4.82; N, 12.24; S, 9.62.

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