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# Synthesis of Some New Thiazolo Pyrimidines Using Cyclocondensation Reactions

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Reaction of pyrimidine derivative **1** with chloroacetyl chloride under reflux condition in dioxane afforded fused pyrimidines **2(a–d)**. In a similar way fused thiazolo pyrimidine compounds **3(a–f)** were synthesized by reaction of **1**, chloroacetic acid, acetic anhydride, acetic acid and corresponding aldehyde. Yields of the products following recrystallization from ethanol were of the order of 66–93%. IR, $^1$H NMR and mass spectrscopies and in some cases elemental analysis were used for identification of these compounds.

**Key Words: Pyrimidine, Thiazolo, Carboxylate, Biginelli Reaction, Methylketone.**

## INTRODUCTION

It is well established that various pyrimidine derivatives show interesting antibacterial and antifungal potential. Some of the pyrimidines have been reported to have remarkable pharmacological effects[1–12]. Therefore pyrimidine has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Various synthetic approaches for the synthesis of pyrimidine derivatives have been reported in the literature[1, 13–19]. Most of them based on the simple Biginelli reaction of β-ketoester, aryl aldehyde and thio (urea) derivatives[1, 14–19] and in some cases based on the multi steps reaction[13].

Due to versatile biological properties of pyrimidine derivatives and as a continuation of our work an attempt has been made to synthesize some of the pyrimidine derivatives in good yield by extending the Biginelli cyclocondensation reaction.

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## EXPERIMENTAL

Pyrimidine thiazole derivatives **1** were prepared using the method of Kappe *et al.*[14]. Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker (500 MHz) spectrometer. The IR spectra were recorded on Glaxy FT-IR 500 spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography. All materials were used as they were received.

**Procedure A:** A mixture of appropriate pyrimidine thiazole derivative **1** (0.01 mol) and chloroacetyl chloride (0.01 mol) in dioxane (10–20 mL) were refluxed for 15–30 min. The reaction mixture was cooled and the precipitate filtered off and then washed with ethanol. The crude product was recrystallized from ethanol. This procedure was used for the synthesis of compounds **2(a–d).**

**Procedure B:** A mixture of appropriate pyrimidine thiazole derivative **1** (0.01 mol), chloroacetic acid (0.012 mol), appropriate aldehyde (0.01 mol), anhydrous sodium acetate (0.02 mol), acetic acid (15 mL) and acetic anhydride (15 mL) were refluxed for 1–9 h. The reaction mixture was added to a beaker containing 75–100 mL water and the precipitate filtered off and then washed with ethanol. The crude product was recrystallized from ethanol. This procedure was used for synthesis of compounds **3(a–f).**

**Ethyl-5-phenyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (2a):** Yield 93%, m.p. 190–192°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3000, 2950, 1770, 1715; $^1$H NMR (DMSO-$d_6$: $\delta$ (ppm) = 1.03 (t, J = 7.2 Hz, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 4.00 (q, J = 7.2 Hz, 2H, —$OCH_2$), 4.17, (s, 2H, —$CH_2$), 5.87 (s, 1H, H-5), 7.30 (m, 5H, $H_{arom}$); Ms: (m/z %) = 315 ($M^+$, 12%), 239 (70%), 211 (30%).

**Ethyl-5-(2-chloro-6-fluoro-phenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (2b):** Yield 65%, m.p. 152–154°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3080, 2940, 1724, 1703; $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm) = 1.00 (t, J = 7.2 Hz, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 4.00, (q, J = 7.2 Hz, 2H, —$OCH_2$), 4.50 (s, 2H, $CH_2$), 6.40 (s, 1H, H-5), 7.45 (m, 3H, $H_{arom}$).

**Ethyl-5-(4-N,N-dimethylaminophenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3] pyrimidine-6-carboxylate (2c):** Yield 68%, m.p. 128–130°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3000, 2829, 1714, 1672; $^1$H NMR (DMSO-$d_6$): $\delta$ (ppm) = 1.46 (t, J = 7.2 Hz, 3H, $CH_3$), 2.70 (s, 3H, $CH_3$), 3.50 (s, 6H, $N(CH_3)_2$, 4.40 (q, J = 7.2 Hz, 2H, —$OCH_2$), 4.55 (s, 2H, $CH_2$), 6.04 (s, 1H, H-5), 7.90 (m, 4H, $H_{arom}$).

**5-Phenyl-7-methyl-3-oxo-2,3-dihydr-5H-thiazolo[a-2,3]pyrimidine-6-methylketone (2d):** Yield 90%, m.p. 195-196°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3000, 2940, 1760, 1660; $^1$H NMR (DMSO-$d_6$): $\delta$ (ppm) = 2.20 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 4.20, (s, 2H, —$CH_2$), 6.00 (s, 1H, H-5), 7.30 (m, 5H, $H_{arom}$); Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.9; H, 4.9; N, 9.8%. Found: C, 62.5; H, 4.7; N, 9.6%.

**Ethyl-5-phenyl-7-methyl-2-phenylmethylene-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (3a):** Yield 88%, m.p. 170–172°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3030, 2975, 1710, 1620; $^1H$ NMR (DMSO-$d_6$): δ (ppm) = 1.07 (t, J = 7.2 Hz, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 4.00, (q, J = 7.2 Hz, 2H, —$OCH_2$), 6.10 (s, 1H, H-5), 7.30 (m, 5H, $H_{arom}$), 7.50 (m, 5H, $H_{arom}$), 7.70 (br s, 1H, ylidene); Anal. Calcd. for $C_{23}H_{20}N_2O_3S$: C, 68.3; H, 5.0; N, 6.9%. Found: C, 68.4; H, 5.0; N, 6.8%.

**Ethyl-5-(2-chloro-6-flurophenyl)-7-methyl-2-phenylmethylene-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (3b):** Yield 66%, m.p. 72–74°C; IR (KBr, $cm^{-1}$): $\nu_{max}$: 3000, 2980, 1709, 1703 1554; $^1H$ NMR (DMSO-$d_6$): δ (ppm) = 1.00 (t, J = 7.2 Hz, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 4.00, (q, J = 7.2 Hz, 2H, —$OCH_2$) 6.50 (s, 1H, H-5), 7.35 (m, 8H, $H_{arom}$), 7.85 (br, 1H, ylidene).

**Ethyl-5-(4-acetamidophenyl)-7-methyl-2-phenylmethylene-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (3c):** Yield 78%, m.p. 146–148°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3000, 1714, 1680, 1543; $^1H$ NMR (DMSO-$d_6$): δ (ppm) = 1.20 (t, J = 7.2 Hz, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 4.00, (q, J = 7.2 Hz, 2H, —$OCH_2$), 6.00 (s, 1H, H-5), 7.35 (m, 9H, $H_{arom}$), 7.80 (brs, 1H, ylidene), 10.00 (s, 1H, NH).

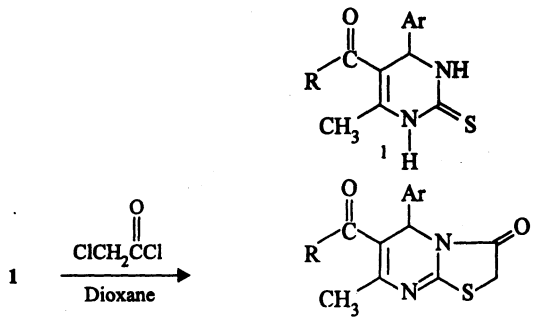
**Ethyl-5-phenyl-7-methyl-2-(4-acetamicophenyl)methylene-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-carboxylate (3d):** Yield 70%, m.p. 110–112°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3327, 3000, 1712, 1678, 1543; $^1H$ NMR (DMSO-$d_6$): δ (ppm) = 1.20 (t, J = 7.2 Hz, 3H, $CH_3$), 2.00 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 4.00, (q, J = 7.2 Hz, 2H, —$OCH_2$), 5.90 (s, 1H, H-5), 7.00 (br, 1H, ylidene), 7.30 (m, 9H, $H_{arom}$), 10.20 (s, 1H, NH).

**5-Phenyl-7-methyl-2-phenylmethylene-3-oxo-2,3-dihydro-5H-thiazolo-[a-2,3]pyrimidine-6-methylketone (3e):** Yield 85%, m.p. 130–131°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3020, 2980, 1710, 1640; $^1H$ NMR (DMSO-$d_6$): δ (ppm) = 2.17 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 6.13 (s, 1H, H-5), 7.27 (m, 5H, $H_{arom}$), 7.47 (m, 5H, $H_{arom}$), 7.80 (br, 1H, ylidene); Ms: (m/z %) = 373 ($M^+$, 30%), 296 (40%), 43 (100%).

**Ethyl-5-(4-N,N-dimethylaminophenyl)-7-methyl-2-phenylmethylene-3-oxo-2,3-dihydro-5H-thiazolo[a-2,3]pyrimidine-6-methylketone (3f):** Yield 80%, m.p. 192–193°C; IR (KBr, $cm^{-1}$) $\nu_{max}$: 3040, 2920, 1697, 1574, 1155; $^1H$ NMR ($CDCl_3$): δ (ppm) = 2.20 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 3.00 (s, 6H, $(NCH_3)_2$, 6.20 (s, 1H, H-5), 6.8–7.3 (m, $9H_{arom}$ and 1H ylidene).

## RESULTS AND DISCUSSION

Compounds **2(a–d)** and **3(a–f)** were synthesized according to procedures A and B respectively. Reaction of the pyrimidine derivative **1** and chloroacetyl chloride in dioxane under reflux condition afforded **2(a–d)** as shown in **Scheme-1.** Then the reaction of **1** with chloroacetic acid and appropriate aldehyde in the presence of anhydrous sodium acetate, acetic acid and acetic anhydride under reflux gave compounds **3(a–f).**

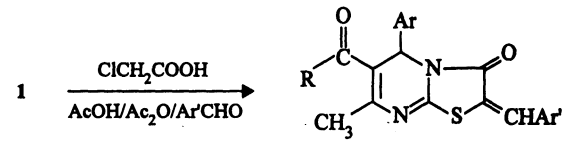



**(2a)** R = OEt, Ar = phenyl

**(2b)** R = OEt, Ar = 2-chloro,6-fluorophenyl

**(2c)** R = OEt, Ar = 4-N,N-dimethylaminophenyl

**(2d)** R = Me, Ar = phenyl




**(3a)** R = OEt, Ar = phenyl, Ar′ = phenyl

**(3b)** R = OEt, Ar = 2-chloro,6-fluorophenyl, Ar′= phenyl

**(3c)** R = OEt, AR = 4-acetamidophenyl, Ar′ = phenyl

**(3d)** R = OEt, Ar = phenyl, Ar′ = 4-acetamidophenyl

**(3e)** R = Me, Ar = phenyl, Ar′ = phenyl

**(3f)** R = Me, Ar = 4-N,N-dimethylaminophenyl, Ar′ = phenyl

**Scheme-1**

Yields of these reactions following recrystallization from ethanol were of the order of 66–93%. Based on $^1$H NMR spectra (500 MHz) these products exhibited high purity. The $^1$H NMR spectra of the compounds are simple and quite similar to each other. The singlet signal at 2.00–2.70 ppm is due to the resonance of the $CH_3$ group of pyrimidine ring. The singlet and multiplet signals at 5.87–6.50 and 7.27–7.90 ppm are assigned to H-5 and aryl protons respectively. The $CH_3$ of the ester group in **2(a–c)** and **3(a–d)** resonate at 1.00–1.46 ppm as a triplet signal and $CH_3$ of the acyl group in **2d** and **3(e–f)** resonate at 2.17–2.20 ppm as a singlet signal.

In the IR spectra of compounds **2(a–d)** and also **3(a–f)**, the absence of absorption at 3500–3300 cm$^{-1}$ and the characteristic absorption of NH group of starting material are a good evidence of the expected reactions.

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