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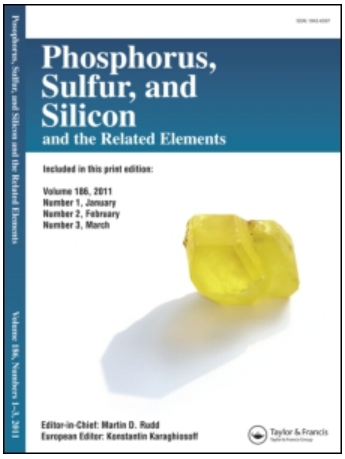

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SYNTHESIS OF SOME BICYCLIC THIAZOLOPYRIMIDINE DERIVATIVES

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*Thiazolopyrimidine compounds **3**(**a–d**) were synthesized by a simple one-pot condensation reaction of starting pyrimidine derivative **1** and 1,2-dibromoethane **2** in dimethylformamide. In a similar way thiazolopyrimidine compounds **5**(**a–e**) were synthesized by reaction of **1** and 2-bromopropionic acid **4** in dioxane under reflux condition. The yields of products following recrystallization from ethanol were of the order of 70–80%.*

Keywords: 1,2-Dibromoethane; 2-bromopropionic acid; carboxylate; pyrimidine; thiazolo

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Pyrimidine derivatives are known as important heterocyclic compounds for their considerable antibacterial and antifungal activities. Some pyrimidines possess remarkable pharmacological efficiency.[1–16] As a result pyrimidine has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological effects. Various synthetic approaches for the synthesis of pyrimidine derivatives have been reported in the literature.[1,17–20] Most of them are based on the simple Biginelli cyclocondensation reaction of β-ketoester, aryl aldehyde, and thio (urea) derivatives,[1,17,18] and in some case they are based on multi-step processes.[19]

Here, due to versatile biological properties of pyrimidine derivatives, we have extended the general method of Kappe[18] in order to synthesize some novel bicyclic pyrimidine derivatives in high yield.

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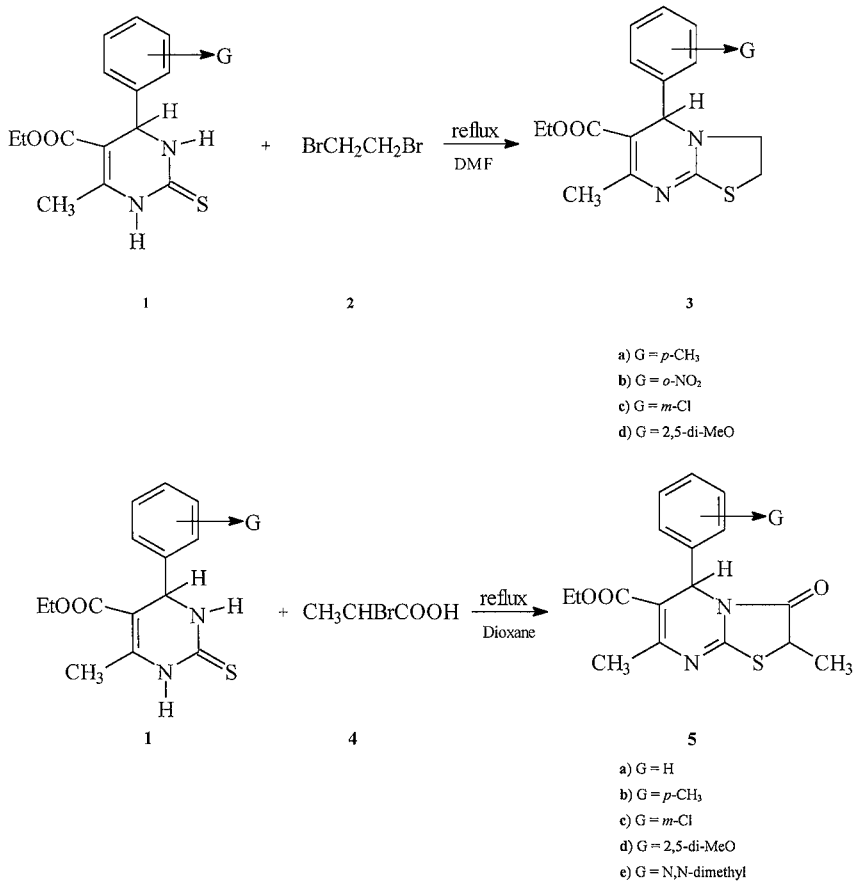
RESULTS AND DISCUSSION

Compounds **3**(**a–d**) and **5**(**a–b**) were synthesized according to procedures A and B respectively.[18] Reaction of the starting pyrimidine derivative **1** and 1,2-dibromoethane **2** in dimethylformamide under reflux afforded **3**(**a–d**) as HBr salts (Scheme 1). Also reaction of **1** and 2-bromopropionic acid **3** as an cyclocondensation reagent in dioxane under reflux gave compounds **5**(**a–e**). These methods are very easy and can be used to prepare various substituted thiazolopyrimidine compounds (Scheme 1).

Reactions were usually carried out for 2 to 4 h. Yields of these one-pot protocol reactions following recrystallization from ethanol were of



SCHEME 1

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the order of 70–80%. In the IR spectra of compounds **3**(**a–d**) and **5**(**a–e**) absence of the absorption at 3200–3400 cm^{-1}, the characteristic absorption of NH group of starting material, is a good evidence of the expected reactions.

EXPERIMENTAL

Pyrimidine thiazole derivatives were prepared using the method of Kappe et al.[18] Melting points were determined with an electrothermal digital melting point apparatus. IR spectra were recorded on a Galaxy series FT-IR 5000 spectrophotometer by using KBr pellets. ^{1}HNMR spectra were recorded on Bruker 400 and 500 MHz spectrometers with using Me_4Si (TMS) as an internal standard. mass spectra were measured with an EI (70 eV)+Q1MSLMR up LP spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography.

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Procedure A

Compound **3** was prepared as a HBr salt. 1,2-Dibromoethane (0.001 mmol) was added to a boiling solution of appropriate pyrimidine thiazole derivatives (0.001 mmol) in dimethylformamide (2 ml) and then refluxed for 2 to 4 h. The reaction mixture was cooled and the precipitate filtered off and washed with ethanol. The crude product was recrystallized from ethanol. This procedure was used for synthesis of compounds **3**(**a–d**) .

Ethyl-5-(4-methylphenyl)-2,3-dihydro-7-methyl-5H-thiazolo [3,2-a]pyrimidine-6-carboxylate (3a) . Yield % 75, m.p. 202–204°C. IR (KBr): $\upsilon = 3100, 2985, 1693, 1535, 1300, 1110$ cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.05$ (t, 3H, $-CH_3$), 2.3 (s, 3H, $-CH_3$), 2.6 (m, 4H, $-CH_2-CH_2$), 3.69 (q, 2H, $-CH_2$), 5.71 (s, 1H, H-5), 7.3 (m, 4H, H-arom). Ms: m/z (%) = 315 (M^+, 24), 287 (43), 224 (100), 196.5 (45).

Ethyl-5-(2-nitrophenyl)-7-methyl-5H-thiazolo pyrimidine-6-carboxylate (3b). Yield % 70, m.p. 233–234°C. IR (KBr): $\upsilon = 3067, 2964, 1692, 1532, 1324, 1264$ cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.0$ (t, 3H, $-CH_3$), 2.3 (s, 3H, $-CH_3$), 2.5 (m, 4H, $-CH_2-CH_2$), 3.6 (q, 2H, $-CH_2$), 6.1 (s, 1H, H-5), 7.6 (m, 4H, H-arom). Ms: m/z (%) = 347 (M^+, 20), 330 (75), 298 (100), 224 (60), 196 (65).

Ethyl-5-(3-chlorophenyl)-2,3-dihydro-7-methyl-5H-thiazolo [3,2-a]pyrimidine-6-carboxylate (3c). Yield % 73, m.p. 204–206°C. IR (KBr): $\upsilon = 3050, 2950, 1676, 1197, 1117$ cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.0$ (t, 3H, $-CH_3$), 2.5 (s, 3H, $-CH_3$), 2.6 (m, 4H, $-CH_2-CH_2$), 3.7

(q, 2H, —CH_2), 6.3 (s, 1H, H-5), 7.2 (m, 4H, H-arom). Ms: m/z (%) = 336 (M^+, 48), 307 (85), 224 (90), 195.5 (100), 150 (30).

Ethyl-5-(2,5-dimethoxyphenyl)-2,3-dihydro-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3d). Yield % 80, m.p. 211–212°C. IR (KBr): $\upsilon = 3060, 2960, 1670, 1530, 1312$ cm^{-1}. ^{1}HNMR (DMSO-d_6): $\delta = 1.07$ (t, 3H, —CH_3), 2.34 (s, 3H, —CH_3), 2.90 (m, 4H, —CH_2—CH_2), 3.96 (q, 2H, —CH_2), 3.72 (s, 6H, —OCH_3), 5.86 (s, 1H, H-5), 6.91 (m, 3H, H-arom). Ms: m/z (%) = 362 (M^+, 48), 333 (80), 289.2 (35), 224.7 (100), 196 (100), 152.90 (40), 150 (25).

Procedure B

A mixture of appropriate pyrimidine thiazole derivatives, (0.001 mmol) and 2-bromo propionic acid (0.001 mmol) in dioxane (3 ml) were refluxed for 1 to 2 h. 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 synthesis of compounds **5**(**a–e**).

Ethyl-2,7-dimethyl-3-oxo-5-phenyl-2,3-dihydro-5H-thiazolo [3,2,a]pyrimidine-6-carboxylate (5a). Yield % 80, m.p. 216°C. IR (KBr): $\nu = 3090, 1760, 1717, 1657, 1359$ cm^{-1}. ^{1}HNMR ($CDCl_3$): $\delta = 1.17$ (t, 3H, CH_3), 2.29 (d, 3H, —CH_3), 2.40 (s, 3H, CH_3), 4.03 (q, 2H, —CH_2), 4.73 (q, 1H, CH), 6.63 (s, 1H, H-5), 7.15 (m, 5H, H-arom). Ms: m/z (%) = 330 (M^+, 70), 302 (25), 285 (22), 273 (30), 253 (90), 225 (90), 197 (30), 67 (40).

Ethyl-2,7-dimethyl-3-oxo-5-(4-methylphenyl)-2,3-dihydro-5H-thiazolo[3,2,a]pyrimidine-6-carboxylate (5b). Yield % 73, m.p. 198°C. IR (KBr): $\upsilon = 3075, 1757, 1685, 1595, 1283$ cm^{-1}. ^{1}HNMR($CDCl_3$): $\delta = 1.07$ (t, 3H, CH_3), 1.45 (d, 3H, CH_3), 2.51 (s, 3H, —CH_3), 4.03 (q, 2H, —CH_2), 4.68 (q, 1H, CH), 5.88 (s, 1H, H-5), 7.1 (m, 4H, Harom). Ms: m/z (%) = 344 (M^+, 60), 316 (25), 287 (20), 271 (60), 253 (90), 225 (90), 197 (25), 169 (20), 80 (80).

Ethyl-2,7-dimethyl-3-oxo-5-(3-chorophenyl)-2,3-dihydro-5H-thiazolo[3,2,a]pyrimidine-6-carboxylate (5c). Yield % 75, m.p. 218–219°C. IR (KBr): $\upsilon = 2997, 1769, 1692, 1552, 1321, 1169, 1102$ $cm^{-}1$. ^{1}HNMR ($CDCl_3$): $\delta = 1.03$ (t, 3H, —CH_3), 1.46 (d, 3H, CH_3), 2.53 (s, 3H, —CH_3), 4.01 (q, 2H, —CH_2), 4.09 (q, 1H, CH), 5.95 (s, 1H, H-5), 7.13 (m, 4H, H-arom). Ms: m/z (%) = 364 (M^+, 30), 336 (20), 307 (15), 253 (90), 225 (90), 197 (30), 80 (60).

Ethyl-2,7-dimethyl-3-oxo-5-(2,5-dimethoxyphenyl)-2,3-dihydro-5H-thiazolo[3,2,a]pyrimidine-6-carboxylate (5d). Yield % 80, m.p. 198–200°C. IR (KBr): $\upsilon = 2953, 2731, 1763, 1712, 1662, 1278$ cm^{-1}. ^{1}HNMR ($CDCl_3$): $\delta = 1.07$ (t, 3H, —CH_3), 1.51 (d, 3H, CH_3),

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2.34 (s, 3H, $-CH_3$), 3.70 (s, 6H, 2-OMe), 4.03 (q, 2H, $-CH_2$), 4.70 (q, 1H, CH), 6.04 (s, 1H, H-5), 6.90 (m, 3H, H-arom). Ms: m/z (%) = 390 (M^+, 75), 359 (50), 334 (25), 253 (90), 225 (90), 197 (25), 181 (35), 153 (20), 80 (45).

Ethyl-2,7-dimethyl-3-oxo-5-[4-(N,N-dimethylamino)phenyl]-2,3-dihydro-5H-thiazolo[3,2,a]pyrimidine-6-carboxylate (5e). Yield % 80, m.p. 213–215°C. IR (KBr): $\upsilon = 2970$, 1762, 1683, 1558, 1278, 1175 cm^{-1}. ^{1}HNMR ($CDCl_3$): $\delta = 1.04$ (t, 3H, $-CH_3$), 1.46 (d, 3H, CH_3), 2.70 (s, 3H, $-CH_3$), 3.51 (s, 6H, $-N(CH_3)_2$), 4.02 (q, 2H, $-CH_2$), 4.07 (q, 1H, CH), 6.40 (s, 1H, H-5), 7.80 (m, 4H, H-arom). Ms: m/z (%) = 373 (M^+, 90), 317 (25), 300 (20), 272 (70), 253 (90), 225 (90), 80 (80).

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