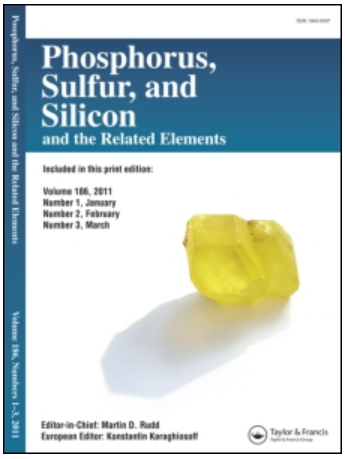

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SYNTHESIS OF SOME BICYCLIC THIAZOLO AND THIAZEPINOPYRIMIDINE DERIVATIVES

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SYNTHESIS OF SOME BICYCLIC THIAZOLO AND THIAZEPINOPYRIMIDINE DERIVATIVES

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*Thiazolo **3**(**a–c**) and oxothialo **5**(**a–b**) pyrimidine compounds were synthesized by a simple one-pot condensation reaction of the pyrimidine derivative **1a** and 1,2-dibromoethane **2** or 2-bromopropanoic acid **4**. In a similar way the thiazepinopyrimidine compounds **7**(**a–b**) were synthesized by reaction of **1b** and 1,4-dichlorobutane **6** in dimethylformamide under reflux condition. The yields of products following recrystallization were of the order of 60–80%.*

Keywords: 1,2-Dibromoethane; 1,4-dichlorobutane; 2-bromopropanoic acid; thiazepinopyrimidine; thiazolo

Pyrimidine is known as a versatile heterocyclic compound, which has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Pyrimidine derivatives have been reported to possess a broad spectrum of pharmacological properties[1–11] including antiviral, antitumor, antibacteria[1] and antihypertensive[3] effects. Several synthetic approaches have been reported for the synthesis of pyrimidine derivatives.[1,12–16] Most of them based on the modification of the classical one-pot Biginelli approach[1,12–15] and in some cases based on the more complex multi steps processes.[16]

As a continuation of our work, and also due to versatile biological properties of pyrimidine derivatives, we have extended the cyclocondensation reactions in order to synthesize some of novel bicyclic thiazolo- and thiazepinopyrimidine compounds.

RESULTS AND DISCUSSION

Compounds **3**(**a–c**) and **5**(**a–b**) were synthesized according to procedures A and B respectively. Reaction of the starting pyrimidine

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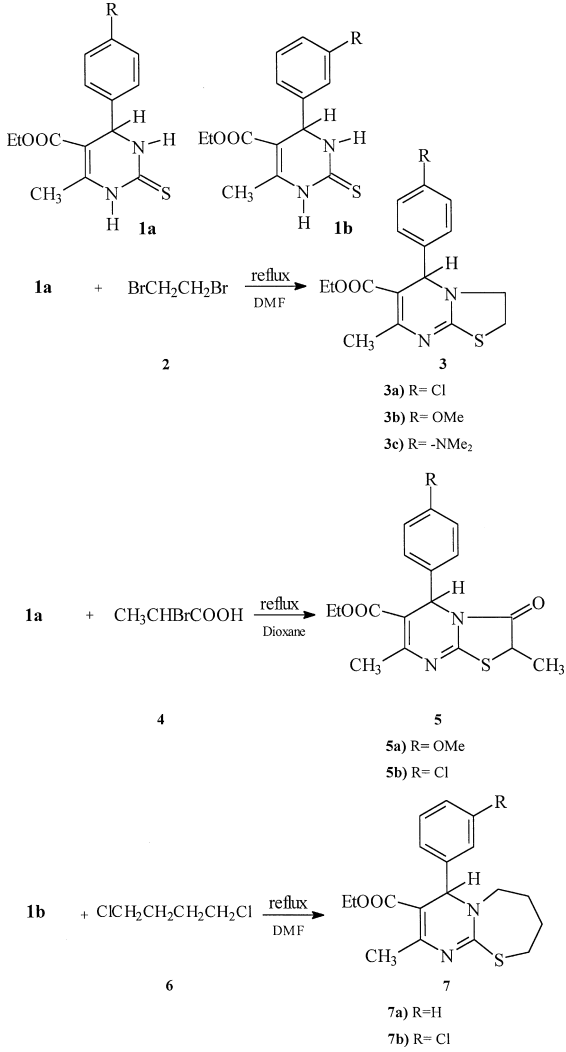
derivative **1a** and 1,2-dibromoethane **2** in dimethylformamide under reflux afforded **3**(**a–c**) as shown in Scheme 1. Also compounds **5**(**a–b**) were prepared from **1a** by the reaction with 2-bromopropanoic acid **4** as a cyclocondensation reagent in dioxane under reflux. The reactions leading to the formation of thiazolo and thiazepinopyrimidine derivatives are outlined in Scheme 1.

In a similar way thiazepinopyrimidine compounds **7**(**a–b**) were easily prepared by reaction of **1b** and 1,4-dichlorobutane **6** in dimethylformamide (Scheme 1).



SCHEME 1

Two isomeric products may be expected from an attack of nucleophile on N-1 and N-2 of **1**. However it is well documented[13,17] that N-3 in compound **1** is more reactive toward electrophiles than the N-1, which is part of a push-pull system with the ester group in 5-position of the pyrimidine ring. Also, the low field shift of the pyrimididine proton in **5** compared to that of **1** is in support of a nucleophilic attack on N-3. The low field shift of the pyrimididine proton in **5** is due to a deshielding effect of the neighboring carbonyl group. These evidences are proof for confirmation of the structure of all products.

Based on ^{1}H NMR spectra (400 and 500 MHz) these products exhibited high purity. The ^{1}H NMR spectra of **3**(**a–d**) show a sharp singlet signal at 2.34–2.38 ppm due to CH_3 resonance of the pyrimidine ring. The multiplet signal at 7.40–7.43 ppm and the singlet signal at 5.70–5.79 ppm are assigned to resonances of aryl and pyrimidine ring protons respectively. Four protons of two CH_2 groups of thiazole ring resonate at 2.56–2.90 ppm.

The ^{1}H NMR spectra of **5**(**a–b**) are very similar to those of **3**(**a–d**). The singlet signal at 2.39–2.48 is due to resonance of the CH_3 group of the pyrimidine ring. The CH_3 group of the thiazole ring resonates as a doublet at 1.70 ppm. The multiplet and singlet signals at 7.2–7.34 and 5.18–5.81 ppm are assigned to aryl protons and H-5 respectively.

In the ^{1}H NMR spectra of **7**(**a–b**) the singlet signal at 2.40–2.54 ppm are attributed to the resonance of the CH_3 group of the pyrimidine ring. The multiplet signal at 1.47–1.73 ppm with the integrating of four protons is assigned to the resonance of two CH_2 groups of the thiazepino ring. The other four protons of the thiazepino ring, which are close to two hetero atoms (N and S), resonate at 3.56–3.62 ppm.

In the IR spectra of compounds **3**, **5** and **7** 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 thiazolo and thiazepino derivatives were prepared using the method of Kappe et al.[13] Melting points were determined with an electrothermal digital melting point apparatus. IR spectra were taken on a Galaxy series FT-IR 5000 spectrophotometer in potassium bromide pellets. ^{1}H NMR spectra were recorded at 25°C 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.

Procedure A

1,2-Dibromoethane (0.011 mmol) was added to a boiling solution of the pyrimidine thiazole derivative (0.001 mmol) in dimethylformamide (2 ml) and then refluxed for 3–4 h. The resulting solution was allowed to stand at room temp over night to produce the product. The precipitate was then filtered off and washed with ethanol. The crude product was recrystallized from ethanol.

Ethyl-2,3-dihydro-5-(4-chlorophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3a)

Yield 70%, m.p. 210–212°C.

IR (KBr): $\nu = 3067, 2984, 1760, 1691, 1533, 1357\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.02$ (t, 3H, J = 7.0 Hz, CH_3), 2.38 (s, 3H, CH_3), 2.56 (m, 4H, CH_2—CH_2), 3.94 (q, 2H, J = 7.0 Hz, OCH_2), 5.79 (s, 1H, H-5), 7.4 (m, 4H, H-arom).

Ms: m/z (%) = 336 (M^+, 50), 307 (90), 224 (100), 196 (100), 150 (20).

Ethyl-2,3-dihydro-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3b)

Yield 75%, m.p. 183–184°C.

IR (KBr): $\nu = 3042, 2982, 2869, 1759, 1693, 1535, 1329\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.03$, (t, 3H, J = 7.0 Hz, CH_3), 2.37 (s, 3H, CH_3), 2.90 (m, 4H, CH_2—CH_2), 3.57 (s, 3H, OCH_3) 4.03 (q, 2H, J = 7.0 Hz, OCH_2), 5.74 (s, 1H, H-5), 7.43 (m, 4H, H-arom).

Ms: m/z (%) = 332 (M^+, 50), 303 (70), 224 (100), 196 (100), 150 (30).

Ethyl-2,3-dihydro-5-(4-N,N-dimethylaminophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3c)

Yield 72%, m.p. 220–222°C.

IR (KBr): $\nu = 3064, 2989, 1762, 1693, 1550, 1323\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.02$ (t, 3H, J = 7.0 Hz, CH_3), 2.34 (s, 3H, CH_3), 2.80 (m, 4H, CH_2—CH_2), 3.80 (s, 6H, NMe_2) 4.01 (q, 2H, J-70 Hz, OCH_2), 5.70 (s, 1H, H-5), 7.40 (m, 4H, H-arom).

Ms: m/z (%) = 345 (M^+, 50), 316 (70), 224 (100), 196 (100), 150 (15).

Procedure B

A mixture of the thiazole pyrimidine derivative (0.001 mmol) and 2-bromopropanoic acid (0.011 mmol) in dioxane (3 ml) was refluxed for 1–2 h. The reaction mixture was cooled and the precipitate filtered off and then washed with ethanol. The crude product was recrystallized from ethanol.

Ethyl-2,3-dihydro-3-oxo-5-(4-chlorophenyl)-2,7-dimethyl-5H-thiazolo[3,2,a]-pyrimidine-6-carboxylate (5a)

Yield 75%, m.p. 220–221°C.

IR (KBr): $\nu = 3015, 2969, 1770, 1717, 1691, 1543, 1323\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.07$ (t, 3H, J = 7.0 Hz, CH_3), 1.7 (d, 3H, J = 7.0 Hz, CH_3), 2.48 (s, 3H, CH_3), 4.04 (q, 2H, J = 7.0 Hz, OCH_2), 4.71 (q, 1H, J = 7.0 Hz, CH), 5.81 (s, 1H, H-5), 7.20 (m, 5H, Harom).

Ms: (m/z %) = 364 (M^+, 40), 336 (30), 253 (90), 225 (90), 197 (50), 80 (90).

Ethyl-2,3-dihydro-3-oxo-5-(4-methoxyphenyl)-2,7-dimethyl-5H-thiazolo[3,2,a]-pyrimidine-6-carboxylate (5b)

Yield 80%, m.p. 200°C.

IR (KBr): $\nu = 3010, 2930, 1770, 1710, 1695, 1535, 1373, 1321\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.04$ (t, 3H, J = 7.0 Hz, CH_3), 1.70 (d, 3H, J = 7.0 Hz, CH_3), 2.29 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.97 (q, 2H, J = 7.0 Hz, CH_2), 4.03 (q, 1H, J = 7.0 Hz, CH), 5.18 (s, 1H, H-5), 7.34 (m, 4H, Harom).

Ms: m/z (%) = 360 (M^+, 70), 329 (50), 253 (90), 225 (90), 197 (30), 80 (70).

Procedure C

A mixture of the thiazole pyrimidine derivative (0.001 mmol) and 1,4-dichlorobutane (0.011 mmol) in dimethylformamide (2 ml) was refluxed for 3–4 h. The solution was allowed to stand at 0°C for 72 h. The precipitate was filtered off and recrystallized from benzene and ethanol (1:10).

Ethyl-2-methyl-4-phenyl-6,7,8,9-tetrahydro-4-H-pyrimido[2,1-b][1,3]thiazepine]-3-carboxylate (7a)

Yield 65%, m.p. 228–230°C.

IR (KBr): $\nu = 3067, 2982, 1761, 1693, 1552, 1367, 1043\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.15$ (t, 3H, J = 7.0 Hz, CH_3), 1.73 (m, 4H, CH_2-CH_2), 2.40 (s, 3H, CH_3), 3.56 (m, 4H, N-CH_2, S-CH_2), 4.06 (q, 2H, J = 7.0 Hz, CH_2), 5.95 (s, 1H, H-6), 7.19 (m, 5H, Harom).

Ethyl-2-methyl-4-(3-chlorophenyl)-6,7,8,9-tetrahydro-4-H-pyrimido[2,1-b][1,3]thiazepine-3-carboxylate (7b)

Yield 60%, m.p. 222–224°C.

IR (KBr): $\nu = 3042, 1692, 1662, 1574, 1462, 1269, 1195\ cm^{-1}$.

^1H NMR (DMSO-d_6): $\delta = 1.21$ (t, 3H, J = 7.0 Hz, CH_3), 1.47 (m, 4H,

CH_2—CH_2), 2.54 (s, 3H, CH_3), 3.62 (m, 4H, N—CH_2, S—CH_2), 4.06 (q, 2H, J = 7.0 Hz, CH_2), 5.95 (s, 1H, H-6), 6.79 (m, 4H, Harom).

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