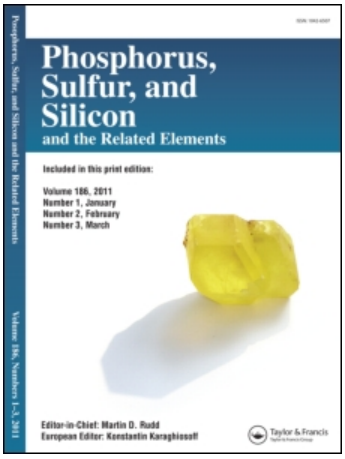

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SYNTHESIS OF SOME BICYCLIC OXAZOLO- AND OXAZEPINOPYRIMIDINE DERIVATIVES

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SYNTHESIS OF SOME BICYCLIC OXAZOLO- AND OXAZEPINOPYRIMIDINE DERIVATIVES

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*Oxazolopyrimidine compounds **2**(**a–c**) and **3**(**a–e**) were synthesized by a simple one-pot condensation reaction of the pyrimidine derivative **1** with 1,2-dibromoethane and 2-bromopropanoic acid, respectively. In a similar way the oxazepinopyrimidine compounds **4**(**a–b**) were synthesized by reaction of **1** and 1,4-dichlorobutane in dioxane under reflux condition. The yields of products following recrystallization were of the order of 55–85%.*

Keywords: 1,2-Dibromoethane; 1,4-dichlorobutane; 2-bromopropanoic acid; oxazepinopyrimidine; oxazolo

INTRODUCTION

The chemistry of pyrimidine derivatives has been studied in depth because these derivatives have a number of diverse biological activities. They possess a broad spectrum of pharmacological properties,[1–12] including antivira,[2] antibacterial,[1,6] antitumor,[7] and antihypertensive[3] effects. Several synthetic approaches have been reported in the literatures for the synthesis of pyrimidines.[1,13–18] Most of them are based on the modification of the classical one-pot Biginelli approach,[1,14–17] and in some cases they are based on the more complex multisteps processes,[18] which may involve use of some expensive, commercially nonavailable materials.

As continuation of our work on the synthesis, and also due to versatile biological properties of pyrimidine derivatives, we wish to report synthesis of some novel bicyclic oxazolo- and oxazepinopyrimidine compounds based on general Biginelli reaction.

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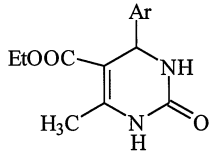
RESULTS AND DISCUSSION

Compounds **2**(**a–c**) and **3**(**a–e**) were synthesized according to procedures A and B, respectively. Reaction of the starting pyrimidine derivative **1** with 1,2-dibromoethane and 2-bromopropanoic acid under reflux afforded **2**(**a–c**) and **3**(**a–e**), respectively, as shown in Scheme 1. Similarly, reaction of **1** and 1,4-dichlorobutane as a cyclocondensation reagent in dioxane led to the formation of **4**(**a–b**). The reactions



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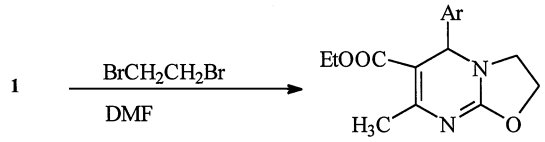
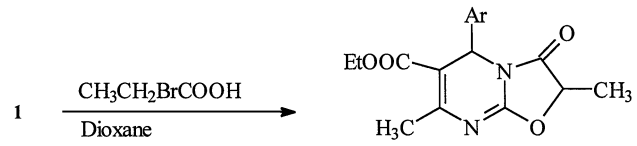
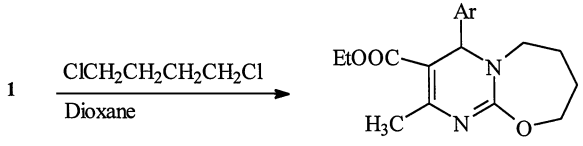


2a) Ar: 4-clorophenyl
2b) Ar: 4-methylphenyl
2c) Ar: 4-methoxyphenyl



3a) Ar: 4-methoxyphenyl
3b) Ar: 4-methylphenyl
3c) Ar: 4-chlorophenyl
3d) Ar: 4-chlorophenyl
3e) Ar: 4-N,N-dimethylaminophenyl



4a) Ar: 4-chlorophenyl
4b) Ar: 4-methoxyphenyl

SCHEME 1

leading to formation of oxazolo- and oxazepinopyrimidine derivatives are outlined in Scheme 1.

Two isomeric products may be expected from an attack of nucleophile on N-1 and N-3 position of starting material **1**. However, it is well established[15,19] that N-3 in compound **1** is more reactive towards electrophiles than N-1, which is part of push-pull system with the ester group in 5-position of pyrimidine ring. Also, the low field shift of pyrimididine proton in product compared to that of starting material is a good support of a nucleophilic attack on N-3 position. The low field shift of the only pyrimididine proton in product is due to a deshielding effect of the neighboring carbonyl group. These evidences are enough for confirmation of the structure of all products.

The ^{1}H NMR spectra of **2** (**a–c**) show a singlet signal at 2.37–2.51 ppm due to CH_3 resonance of the pyrimidine ring. The two multiplet signals at 6.87–7.37 ppm and a sharp singlet signal at 7.12–7.55 ppm are assigned to resonances of the aryl and pyrimidine ring protons, respectively. Four protons of two CH_2 groups of the oxazole ring resonate as two different triplet signals at 3.36–4.75 ppm. The CH_3 of the ester group resonates as a triplet at 1.06–1.10 ppm.

The ^{1}H NMR spectra of **3**(**a–e**) are very similar to those of **2**(**a–c**). The singlet signal at 2.19–2.75 is due to resonance of the CH_3 group of the pyrimidine ring. The CH_3 group of the oxazole ring resonates as a doublet at 1.26–2.75 ppm. The multiplet and the sharp singlet signal at 6.15–7.55 ppm are assigned to the aryl and pyrimidine protons, respectively.

In the ^{1}H NMR spectra of **4**(**a–b**) the singlet signal at 2.49–2.50 ppm is attributed to the resonance of the CH_3 group of the pyrimidine ring. The multiplet signal at 1.45–2.12 ppm with the integrating of four protons is assigned to the resonance of two CH_2 groups of the oxazepino ring. The other four protons of the oxazepino ring, which are close to two hetero atoms (N and O), resonate at 3.56–3.62 ppm.

In the infrared (IR) spectra of compounds **2**, **3**, and **4** 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 oxazole derivatives **1** were prepared using the method of Kappe et al.[15] All melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker (500 MHz) spectrometer. TMS was used as an internal standard. The IR spectra were recorded on Galaxy

Fourier transform infrared (FT IR) 500 spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography.

Procedure A

A mixture of appropriate oxazolopyrimidine derivative **1** (0.0011 mol, 0.32 g) and 1,2-dibromoethane (0.001 mol, 1.2 ml) in dimethylformamide (2 ml) was refluxed for 4.5 h. The reaction mixture was cooled in a refrigerator for 5 days. The precipitate filtered off and then washed with ethanol. The crude product was recrystallized from ethanol. This procedure was used for synthesis of compounds **2**(**a–c**).

Ethyl 5-(4-Chlorophenyl)-7-methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] pyrimidine—6-carboxylate (2a)

Yield, 77%; m.p., 210–211°C. IR (KBr): ν = 3012, 2982, 1707, 1649 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.10 (t, 3H, J = 7.18 Hz, CH_3), 2.51 (s, 3H, CH_3), 4.00 (q, 2H, J = 7.18 Hz, OCH_2), 4.36 (t, 2H, J = 7.0 Hz, N-CH_2), 4.75 (t, 2H, J = 7.0 Hz, S-CH_2), 6.87 (m, 2H, H_{arom}), 7.14 (m, 2H, H_{arom}), 7.55 (s, 1H, H-pyrimidine).

Ethyl 7-Methyl-5-(4-methylphenyl)-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] pyrimidine—6-carboxylate (2b)

Yield, 85%; m.p., 211–212°C. IR (KBr): ν = 3015, 2986, 1712, 1645 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.06 (t, 3H, J = 7.2 Hz, CH_3), 2.37 (s, 3H, CH_3 of $ArCH_3$), 2.51 (s, 3H, CH_3), 3.36 (t, 2H, J = 7.0 Hz, N-CH_2), 3.60 (q, 2H, J = 7.2 Hz, OCH_2), 4.00 (t, 2H, J = 7.0 Hz, S-CH_2), 7.22 (m, 2H, H_{arom}), 7.28 (s, 1H, H-pyrimidine), 7.37 (m, 2H, H_{arom}).

Ethyl 5-(4-Methoxyphenyl)-7-methyl-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] pyrimidine—6-carboxylate (2c)

Yield, 81%; m.p., 203–204°C. IR (KBr): ν = 3024, 2955, 1708, 1649 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.07 (t, 3H, J = 7.2 Hz, CH_3), 2.37 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.61 (q, 2H, J = 7.2 Hz, OCH_2), 3.99 (t, 2H, J = 7.0 Hz N-CH_2), 4.01 (t, 2H, J = 7.0 Hz, S-CH_2), 7.10 (m, 2H, H_{arom}), 7.12 (s, 1H, H-pyrimidine), 7.15 (m, 2H, H_{arom}).

Procedure B

A mixture of appropriate pyrimidineoxazolo derivative **1** (0.0011 mol, 0.32 g) and 2-bromopropanoic acid (0.011 mol) in dioxane (3 ml) was refluxed for 10.5 h. The reaction mixture was cooled in refrigerator over night. The precipitate was filtered off and then washed with ethanol.

The crude product was recrystallized from ethanol. This procedure was used for synthesis of compounds **3**(**a–e**).

Ethyl 5-(4-Methoxyphenyl)-2,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] Pyrimidine—6-carboxylate (3a)

Yield, 69%; m.p., 200–201°C. IR (KBr): ν = 3082, 2912, 1712, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 1.20 (t, 3H, J = 7.2 Hz, CH_3), 1.61 (d, 3H, J = 7.0 Hz, CH_3), 2.75 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.15 (t, 2H, J = 7.2 Hz, OCH_2), 4.52 (q, 1H, J = 7.0 Hz, H-2), 6.15 (m, 2H, H_{arom}), 6.90 (s, 1H, H-pyrimidine), 7.28 (m, 2H, H_{arom}).

Ethyl 2,7-Dimethyl-5-(4-methylphenyl)-3-oxo-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] Pyrimidine—6-carboxylate (3b)

Yield, 67%; m.p., 212–213°C. IR (KBr): ν = 3025, 2980, 1705, 1687 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.11 (t, 3H, J = 7.2 Hz, CH_3), 2.75 (d, 3H, J = 7.0 Hz, CH_3), 2.26 (s, 3H, $ArCH_3$), 2.51 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.2 Hz, OCH_2), 4.56 (q, J = 7.0 Hz, 1H, H-2), 6.15 (s, 1H, H-pyrimidine), 6.98 (m, 2H, H_{arom}), 7.35 (m, 2H, H_{arom}).

Ethyl 5-(4-Chlorophenyl)-2,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3] oxazolo[3,2-a] Pyrimidine—6-carboxylate (3c)

Yield, 61%; m.p., 212–214°C. IR (KBr): ν = 3017, 2947, 1724, 1691 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 1.15 (t, 3H, J = 7.18 Hz, CH_3), 2.24 (d, 3H, J = 7.0 Hz, CH_3), 2.50 (s, 3H,CH_3), 3.98 (q, 2H, J = 7.2 Hz, OCH_2), 4.58 (q, 1H, J = 7.0 Hz, H-2), 6.86 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.67 (s, 1H, H-pyrimidine).

Ethyl 5-(3-Chlorophenyl)-2,7-Dimethyl-3-oxo-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] Pyrimidine—6-carboxylate (3d)

Yield, 59%; m.p., 198–199°C. IR (KBr): ν = 3007, 2939, 1713, 1691 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 0.89 (t, 3H, J = 7.2 Hz, CH_3), 1.26 (d, 3H, J = 7.0 Hz, CH_3), 1.87 (s, 3H, CH_3), 3.1 8 (q, 2H, J = 7.2 Hz, OCH_2), 4.18 (q, 1H, J = 7.0 Hz, H-2), 7.28 (s, 1H, H-pyrimidine), 7.55 (m, 5H, H_{arom}).

Ethyl 5-(4-N,N-dimethylaminophenyl)-2,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]oxazolo[3,2-a] Pyrimidine—6-carboxylate (3e)

Yield, 55%; m.p., 207–208°C. IR (KBr): ν = 3000, 2905, 1710, 1671 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 1.22 (t, 3H, J = 7.2 Hz, CH_3), 1.64 (d, 3H, J = 7.0 Hz, CH_3), 2.19 (s, 3H, CH_3), 2.75 (s, 6H, $N(Me)_2$),

4.19 (t, 2H, $J = 7.2$ Hz, OCH_2), 4.58 (q, 1H, $J = 7.2$ Hz, H-2), 7.22 (m, 2H, H_{arom}), 7.28 (s, 1H, H-pyrimidine), 7.37 (m, 2H, H_{arom}).

Procedure C

A mixture of appropriate pyrimidineoxazolo derivative **1** (0.0011 mol, 0.32 g) and 1,4-dichlorobutane (0.011 mol) in dioxane (3 ml) was refluxed for 5 h. The reaction mixture was cooled in refrigerator for 4 days. The precipitate filtered off and then washed with ethanol. The crude product was recrystallized from ethanol. This procedure was used for synthesis of compounds **4**(**a–b**).

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

Yield, 57%; m.p., 210–211°C. IR (KBr): ν = 3086, 2978, 1705, 1643 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.09 (t, 3H, $J = 7.2$ Hz, CH_3), 1.45 (m, 4H, CH_2-CH_2), 2.50 (s, 3H, CH_3), 3.68 (q, 2H, $J = 7.2$ Hz, OCH_2), 3.98 (m, 2H, NCH_2), 4.46 (m, 2H, OCH_2), 7.12 (m, 5H, H_{arom}), 7.12 (s, 1H, H-pyrimidine).

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

Yield, 62%; m.p., 202–203°C. IR (KBr): ν = 3045, 2957, 1714, 1645 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) = 1.17 (t, 3H, $J = 7.2$ Hz, CH_3), 2.12 (m, 4H, CH_2-CH_2), 2.26 (s, 3H, $ArOCH_3$), 2.49 (s, 3H, CH_3), 3.42 (q, 2H, $J = 7.2$ Hz, OCH_2), 3.90 (m, 2H, NCH_2), 4.78 (m, 2H, OCH_2), 6.68 (s, 1H, H-pyrimidine), 7.34 (m, 5H, H_{arom}).

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