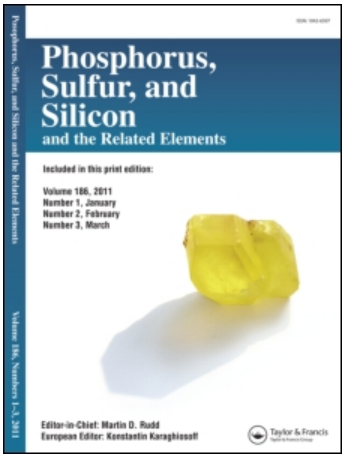

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Synthesis of Some Bicyclic Thiazolo- and Oxothiazolo-Pyrimidines

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*Oxothiazolopyrimidine compounds **2(a–e)** were synthesized under reflux condition by a simple one-pot condensation reaction of the pyrimidine derivative **1** and chloroacetylchloride in the presence of silver acetate as a catalyst. In a similar way the thiazolopyrimidine **3** and oxothiazolopyrimidine **4** were synthesized by reaction of pyrimidine derivative **1** with 1,2-dibromoethane and 2-bromopropanoic acid respectively. The yields of products following recrystallization from ethanol were of the order of 55–89%.*

Keywords 1,2-Dibromoethane; 2-bromopropanoic acid; chloroacetylchloride; oxothiazolo; pyrimidine; thiazolo

INTRODUCTION

Pyrimidine derivatives constitute an important chemical class of heterocyclic compounds having a number of diverse biological activities.[1–12] They show various interesting pharmacological properties including antiviral,[2] antibacterial,[1,5] antitumor[6] and antihypertensive[4] effects. Various synthetic approaches have been reported in the literature for the synthesis of pyrimidines.[1,13–19] Most of them based on the modification of the classical one-pot Biginelli approach[1,14–18] and in some cases based on more complex multi steps processes,[19] which may involve use of some expensive or commercially nonavailable materials.

In continuation of our work on the synthesis and also pursuing our continuous interest in synthesis of fused pyrimidine derivatives, we wish to report synthesis of some novel bicyclic thiazolo- and oxothiazolopyrimidines based on the general Biginelli reaction.

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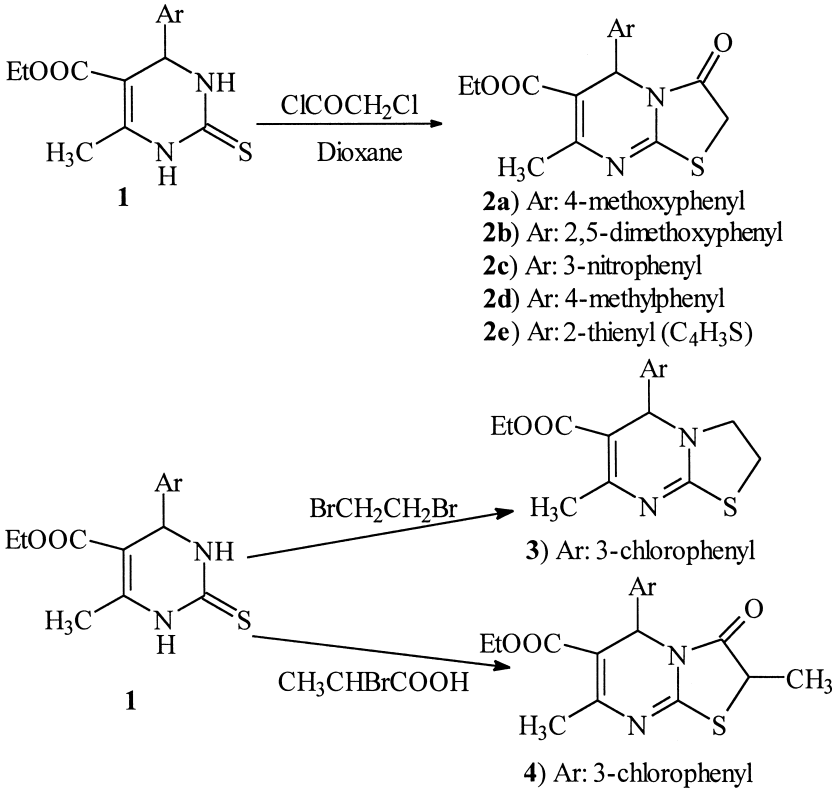
RESULTS AND DISCUSSION

Reaction of appropriate pyrimidine derivative **1** and chloroacetylchloride in dioxane as a solvent under reflux afforded **2**(**a–e**). Also reaction of starting pyrimidine derivative **1** with 1,2-dibromoethane and 2-bromopropanoic acid afforded **3** and **4** respectively as shown in Scheme 1. In all reactions silver acetate was used as a catalyst to remove the NH proton of the pyrimidine ring.



SCHEME 1

Two isomeric products may be expected from an attack of nucleophile on N-1 and N-3 position of **1**. However it is well documented[15,18,20,21] that N-3 in pyrimidine compound **1** is more reactive towards electrophiles than the N-1 position, which is conjugated with the ester group in 5-position of pyrimidine ring. Also the low field shift of the pyrimidine proton in oxothiazolopyrimidine compounds compared to that of the starting material is a good support of a nucleophilic attack on N-3 position. The low field shift of the only pyrimidine proton in

these products is due to a deshielding effect of the neighboring carbonyl group.

The ^{1}H NMR spectra of **2**(**a–e**) show a singlet signal at 2.74–2.60 ppm due to CH_3 resonance of the pyrimidine ring. The multiplet signal at 7.63–6.93 ppm and the sharp singlet signal at 6.59–6.11 ppm are assigned to resonances of the aryl and pyrimidine ring protons, respectively. Two protons of one CH_2 group of the oxothiazolo ring resonate as a singlet signal at 3.72–3.59 ppm. The CH_3 of the ester group resonates as a triplet at 1.10–1.25 ppm.

The ^{1}H NMR spectra of **3** and **4** are very similar to those of **2**(**a–e**). In compound **3** the two CH_2 groups of the thiazolo ring resonate as a triplet at 3.98 ppm and 4.84 ppm respectively. In compound **4** the quartet signal at 5.10 ppm and the doublet signal at 2.25 ppm are attributed to the resonance of the CH_3 group and the only CH group of the oxothiazolo ring, respectively.

In the IR spectra of compounds **2**(**a–e**), **3** and **4** absence of the absorption at 3200–3400 cm^{-1}, the characteristic absorption of NH group of starting material is in support of the expected reactions.

EXPERIMENTAL

Pyrimidine derivative **1** was prepared following a procedure in our earlier reports.[17,22,23] The 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 Glaxy FT-1R 500 Spectrometer. Reaction courses and product mixtures were monitored by thin layer chromatography.

PREPARATION OF ETHYL-6-METHYL-4-(THIOPHEN-2-YL)-2-THIO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE (1e)

A mixture of 2-thiophencarbaldehyde (0.02 mol), thiourea (0.022 mol) and ethyl acetoacetate (0.02 mol) and 2–3 drops of HCl (37%) in ethanol (4 ml) was refluxed for 3 h. The result was cooled at 0°C for 3 days. The precipitate was filtered off and then washed with ethanol. The crude product was recrystallized from ethanol.

Yield: 75%, mp: 216–217°C
IR (KBr): $\nu = 3310, 3190, 2990, 1670, 1640$ cm^{-1}
^{1}H NMR (DMSO-d_6): δ (ppm) = 1.22 (t, 3H, J = 7.2 Hz, $CH_{3-ester}$), 2.43 (s, CH_3), 4.21 (q, 2H, J = 7.2, $CH_{2-ester}$), 5.71 (s, 1H, $H_{-pyrimidine}$), 7.00 (m, 3H, $H_{-thiophenyl}$), 7.80 (bs, 1H, NH), 9.09 (bs, 1H, NH)

GENERAL PREPARATION FOR 2(a–e)

A mixture of appropriate thiazolopyrimidine derivative **1** (0.002 mol), chloroacetylchloride (0.002 mol) and 10 mg silver acetate in dioxan (7 ml) was refluxed for 30 min. The mixture was filtered and the filtrate cooled at room temperature for 2 h. The precipitate was filtered off and washed with ethanol. The crude product was recrystallized from ethanol.

5-(4-METHOXYPHENYL)-7-METHYL-3-OXO-2,3-DIHYDRO-5H-THIAZOLO[3,2-a]PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (2a)

Yield: 81%, mp: 205–206°C
IR (KBr): $\nu = 3100, 3000, 1725, 1660, 1610\ cm^{-1}$
^1H NMR ($CDCl_3$): δ (ppm) = 1.21(t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.74 (s, 3H, CH_3), 3.72 (s, 2H, $CH_{2\text{-thiazole}}$), 3.81 (s, 3H, OCH_3), 4.13 (q, 2H, J = 7.2, $CH_{2\text{-ester}}$), 6.11 (s, 1H, $H_{\text{–pyrimidine}}$), 6.93 (m, 4H, $H_{\text{–arom}}$)

5-(2,5-DIMETHOXYPHENYL)-7-METHYL-3-OXO-2,3-DIHYDRO-5H-THIAZOLO[3,2-a] PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (2b)

Yield: 89%, mp: 206–207°C
IR (KBr): $\nu = 3200, 2990, 1710, 1675, 1615\ cm^{-1}$
^1H NMR ($CDCl_3$): δ (ppm) = 1.25 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.60 (s, 3H, CH_3), 3.59 (s, 2H, $CH_{2\text{-thiazole}}$), 3.85, 3.88 (s, 6H, 2 $OCH_{3\text{–arom}}$), 4.25 (q, 2H, J = 7.2, $CH_{2\text{-ester}}$), 6.12 (s, 1H, $H_{\text{–pyrimidine}}$), 7.01 (m, 3H, $H_{\text{–arom}}$)

5-(3-NITROPHENYL)-7-METHYL-3-OXO-2,3-DIHYDRO-5H-THIAZOLO[3,2-a] PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (2c)

Yield: 55%, mp: 185–186°C
IR (KBr): $\nu = 3200, 2950, 1720, 1675, 1640\ cm^{-1}$
^1H NMR ($CDCl_3$): δ (ppm = 1.22 (t, 3H, j = 7.2 Hz, $CH_{3\text{-ester}}$), 2.64 (s, 3H, CH_3), 3.65 (s, 2H, $CH_{2\text{-thiazole}}$), 4.17 (q, 2H, J = 7.2 Hz, $CH_{2\text{-ester}}$), 6.24 (s, 1H, $H_{\text{–pyrimidine}}$), 7.63 (m, 4H, $H_{\text{–arom}}$)

5-(4-METHYLPHENYL)-7-METHYL-3-OXO-2,3-DIHYDRO-5H-THIAZOLO[3,2-a] PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (2d)

Yield: 85%, mp: 224–225°C
IR (KBr): $\nu = 3130, 2950, 1750, 1720, 1670\ cm^{-1}$
^1H NMR ($CDCl_3$): δ (ppm) = 1.10 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.41 (s, 3H, $CH_{3\text{-phenyl}}$), 2.72 (s, 3H, CH_3), 3.70 (s, 2H, $CH_{2\text{-thiazole}}$), 4.21 (q, 2H, J = 7.2 Hz, $CH_{2\text{-ester}}$), 6.19 (s, 1H, $H_{\text{–pyrimidine}}$), 7.17 (m, 4H, $H_{\text{–arom}}$)

7-METHYL-3-OXO-5-THIOPHEN-2-YL-2,3-DIHYDRO-5H-THIAZOLO[3,2-a]PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (2e)

Yield: 62%, mp: 207–208°C
IR (KBr): $\nu = 3150, 3075, 1770, 1720, 1680\ cm^{-1}$
^1H NMR ($CDCl_3$): δ (ppm) = 1.23 (t, 3H, J = 7.2 Hz, $CH_{3\text{-ester}}$), 2.72 (s, 3H, CH_3), 3.71 (s, 2H, $CH_{2\text{-thiazole}}$), 4.31 (q, 2H, J = 7.2 Hz, $CH_{2\text{-ester}}$), 6.59 (s, 1H, $H_{\text{–pyrimidine}}$), 7.09 (m, 3H, $H_{\text{–thiophenyl}}$)

5-(3-CHLOROPHENYL)-7-METHYL-2,3-DIHYDRO-5H-THIAZOLO[3,2-a] PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (3)

A mixture of ethyl-6-methyl-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.0011 mol), 1,2-dibromoethane (0.003 mol), and a catalytic amount of silver acetate (10 mg) in dimethylformamide (2 ml) was refluxed for 8 h. The mixture was filtered and the filtrate was allowed to stand at −4°C for overnight to produce the oily product. The oily product was taken to water (5 ml) and separated by separatory funnel. The aqueous layer was kept at room temperature for one week. The resulting precipitate was then filtered and washed with ethanol. The crude product was recrystallized from ethanol.

Yield: 88%, mp: 205–207°C
IR (KBr): $\nu = 3150, 2988, 1722, 1681\ cm^{-1}$
^1H NMR(DMSO-d_6): δ (ppm) = 1.01 (t, 3H, J = 7.18Hz, $CH_{3\text{–ester}}$), 2.26 (s, 3H, CH_3), 3.55 (q, 2H, J = 7.18 Hz, $CH_{2\text{-ester}}$), 3.98 (t, 2H, J = 7.0Hz, N-CH_2), 4.84 (t, 2H, J = 7.0Hz, S-CH_2), 6.15 (s, 1H, $H_{\text{–pyrimidine}}$), 7.13 (m, 4-H, $H_{\text{–arom}}$)

5-(3-CHLOROPHENYL)-2,-7-DIMETHYL-3-OXO-2,3-DIHYDRO-5H-THIAZOLO[3,2-a] PYRIMIDINE-6-CARBOXYLIC ACID ETHYL ESTER (4)

A mixture of ethyl-6-methyl-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.0011 mol), 2-bromopropanoic acid (0.003 mol), and 10 mg silver acetate in dimethylformamide (2 ml) was refluxed for 2 h. The mixture was filtered and the filtrate cooled at 0°C to precipitate the desired compound. The precipitate was filtered off and washed with ethanol. The crude product was recrystallized from ethanol.

Yield: 80%, mp: 215–217°C

IR (KBr): $\nu = 3150, 2988, 1725, 1719, 1699\ cm^{-1}$

^1H NMR (DMSO-d_6): δ (ppm) = 1.10 (t, 3H, J = 7.20 Hz, $CH_{3\text{-ester}}$), 2.25 (d, 3H, $CH_{3-\text{oxazole}}$), 2.50 (s, 3H, CH_3), 3.98 (q, 2H, J = 7.20 Hz, $CH_{2\text{-ester}}$), 5.10 (q, 1H, J = 7.20 Hz, H-2), 7.12 (s, 1H, $H_{-\text{pyrimidine}}$), 7.79–8.04 (m, 4-H, $H_{-\text{arom}}$)

REFERENCES

[1] C. O. Kappe, *Tetrahedron*, **49,** 6937 (1993).
[2] R. S. Varma, *Green Chem.*, **1,** 43 (1999).
[3] K. Funahashi, F. Satah, M. Morita, and T. Noguchi, *J. Med. Chem.*, **32,** 2399 (1989).
[4] K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, *J. Med. Chem.*, **34,** 806 (1991).
[5] W. Xie, Y. Jin, and P. G. Wang, *Chemtech.*, **2,** 23 (1999).
[6] C. O. Kappe, W. M. F. Fabian, and M. A. Semones, *Tetrahedron*, **53,** 2803 (1997).
[7] C. G. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, and M. F. Malley, *J. Med. Chem.*, **35,** 3254 (1992).
[8] C. O. Kappe, and F. S. Falsone, *Synlett*, 718 (1998).
[9] G. J. Grover, S. Dzwonczyk, D. M. McMullen, C. S. Normadinam, P. G. Sleph, and S. J. Moreland, *Cardiovasc. Pharmacol.*, **26,** 289 (1995).
[10] N. Foroughifar, A. Mobinikhaledi, S. M. Shariatzadeh, and M. Masoudnia, *Asian Journal of Chemistry*, **14,** 782 (2002).
[11] M. M. Ghorba, Y. A. Mohamed, S. A. Mohamed, and Y. A. Ammar, *Phosphorus, Sulfur, and Silicon*, **108,** 249 (1996).
[12] K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Lett.*, **4,** 1601 (1994).
[13] M. Kidwai and A. D. Mishra, *Bull. Korean Chem. Soc.*, **24,** 1038 (2003).
[14] P. Biginelli, *Gazz Chim. Ital.*, **23,** 360 (1893).
[15] C. O. Kappe and P. Rochge, *J. Heterocyclic Chem.*, **26,** 55 (1989).
[16] H. Lin, J. Ding, X. Chen, and Z. Zhang, *Molecules*, **5,** 1240 (2000).
[17] N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi, *Phosphorus, Sulfur, and Silicon*, **178,** 495 (2003).
[18] M. A. F. Sharaf, F. A. Abdel Aal, A. M. Abdel Fattah, and A. M. R. Abdel Khalil, *J. Chem. Research (S)*, 354 (1996).
[19] A. D. Shutalev, E. A. Kishko, N. Sivova, and A. Y. Kuznetsov, *Molecules*, **3,** 100 (1989).

[20] N. Foroughifar, S. M. Shariatzadeh, A. Mobinikhaledi, E. Khasnavi, and M. Masoudnia, *UltraScience*, **12,** 277 (2000).
[21] N. Foroughifar, A. Mobinikhaledi, and F. Goodarzi, *Phosphorus, Sulfur, and Silicon*, **178,** 2539 (2003).
[22] N. Foroughifar, A. Mobinikhaledi, and H. Fathinejad Jirandehi, *Phosphorus, Sulfur, and Silicon*, **178,** 1241 (2003).
[23] N. Foroughifar, A. Mobinikhaledi, H. Fathinejad Jirandehi, and S. Memar, *Phosphorus, Sulfur, and Silicon*, **178,** 1269 (2003).