An Efficient Synthesis of Some Novel Bicyclic Thiazolopyrimidine Derivatives

Akbar Mobinikhaledi*, Mojgan Zendehdel, Mahdia Hamidi Nasab and Mohammad Ali Bodaghi Fard

Department of Chemistry, Faculty of Sciences, Arak University, Arak, Iran
Email: akbar_mobini@yahoo.com
Fax number: +98 861 2774031

Abstract

An efficient and rapid synthesis of some thiazolopyrimidine derivatives from pyrimidinthiones and chloroacetyl chloride in refluxing tetrahydrofurane (THF) is described. The method is simple and practical, and generating thiazole derivatives in good isolated yields.

Keywords Thiazolopyrimidine, dihydropyrimidinthions, silica sulfuric acid, cyclization.

1. Introduction

Thiazole derivatives are very useful in various fields of chemistry including medicine and agriculture (1). On the other hand, over the years, research interest in multi-functionalized dihydro pyrimidinones and their sulfur analogs [DHPMs] has surged rapidly, owing to the diverse pharmacological properties associated with many derivatives of this heterocyclic core (2,3). DHPMs have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties (4,5).

Recently, the preparation of silica sulfuric acid (SSA) as a versatile heterogeneous stable acidic reagent and its catalytic activities in synthetic methodology have been reported (6,7). As a continuation of our works (8-11), and also due to the versatile biological effects of pyrimidine derivatives, herein we have extended the cyclocondensation reactions in order to synthesize some novel bicyclic thiazolopyrimidines.

2. Experimental

All of products characterized by their physical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis data. Melting points were obtained in open capillaries on an electrothermal 5000 digital apparatus and are not corrected. IR spectra were recorded on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on a Brucker 300 MHz spectrometer in DMSO-d6 with TMS as an internal standard. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III) at the Arak University. Silica sulfuric acid was prepared according to reported procedure (8). Progresses of the reactions were followed by monitoring by TLC using n-Hexane/EtOAc (3:1 v/v) as an eluent.

2.1 General procedure for synthesis of ethyl-1-(2-chloroacetyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-6-aryl pyrimidine-5-carboxylate

A mixture of prepared dihydropyrimidinones (1 mmol) and chloroacetyl chloride (3 mmol) was refluxed in THF for 4 h. The progress of reaction was followed by TLC using n-Hexane/Ethylacetate (3:1) as an eluent. After cooling of the reaction mixture, the precipitated product was filtered and recrystalized from ethanol.

2.2 General procedure for synthesis of 5-aryl -7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate

A mixture of prepared dihydropyrimidinthiones (1 mmol) and chloroacetyl chloride (5 mmol) was refluxed in THF for appropriate time. The progress of reaction followed by TLC using n-Hexane/Ethylacetate(3:1) as an eluent. After cooling of the reaction the precipitated product filtered and recrystalized from ethanol.

3. Physical and spectroscopic data for DHPMs

3.1. Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4- tetra hydro pyrimidine-5-carboxylate (4d), (80%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.05-1.29 (3H, t, *J* 7.03 Hz, CH_3), 1.73 (3H, s, CH_3), 3.79 (3H, s, CH_3), 3.85 (3H, s, CH_3), 3.98-4.9 (2H, q, *J* 7.4 Hz, CH_2), 5.4 (1H, s, 4-H), 6.67-6.73 (4H, aromatic, CH), 9.70 (1H, s, NH) and 10.13 ppm (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 14.2 (CH_3), 15.5 (CH_3), 61.7 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 100.2, 105.7, 115, 160,(CH aromatic), 181.5 (C-2),55.1 (C-4), 104 (C-5), 162 (C-6) and 167.35 ppm (C-O ester); ν_{max} (KBr): 3171-3308 (NH), 2884-3109 (CH aromatic, olefinic, aliphatic), 1662 (CO), 1456-1575 (C=C olefin, aromatic), 1265-1334 cm^{-1} (C-O ester); Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.17; H, 6.03; N, 8.41; S, 9.63.

3.2. Ethyl-4-(2-chlorophenyl-6-fluoro)-6-methyl-2-thioxo-1,2,3,4- tetra hydro pyrimidine-5-carboxylate (4k), (80%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.04-1.2 (3H, t, *J* 7.03 Hz, CH_3), 1.71 (3H, s, CH_3), 3.90-4.20 (2H, q, *J* 7.4 Hz, CH_2), 4.60 (1H, s, 4-H), 6.73-7.12 (4H, aromatic, CH), 9.73 (1H, s, NH) and 10.15 ppm (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 11.2 (CH_3), 15.01 (CH_3), 62.03 (CH_2), 110.1, 125.1, 129.3, 129.9, 133.2, 160.5 (CH aromatic), 182 (C-2), 42.9 (C-4), 104.2 (C-5), 160.5 (C-6) and 167.2 ppm (C-O ester); ν_{max} (KBr): 3192-3257 (NH), 2903-3128 (CH aromatic, olefinic, aliphatic), 1712 (CO), 1456-1577 (C=C olefin, aromatic), 1290-1321 cm^{-1} (C-O ester); Anal. Calcd for $C_{14}H_{14}ClFN_2O_2S$: C, 51.14; H, 4.29; N, 8.52; S, 9.75. Found: C, 51.07; H, 4.35; N, 8.65; S, 9.79.

3.3. Ethyl-4-(2,6-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4- tetra hydro pyrimidine-5-carboxylate (4l), (86 %) as a solid; δ_H (300 MHz, DMSO-d_6): 1.02-1.3 (3H, t, *J* 7.03 Hz, CH_3), 1.75 (3H, s, CH_3), 3.89-4.19 (2H, q, *J* 7.4 Hz, CH_2), 4.59 (1H, s, 4-H), 6.73-7.12 (4H, aromatic, CH), 9.68 (1H, s, NH) and 10.13 ppm (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 14.5 (CH_3), 15.1 (CH_3), 63.2 (CH_2), 55.8 (CH_3), 56.1 (CH_3), 126.1, 126.2, 129.3, 129.5, 133.6, 144.2 (CH aromatic), 180.2 (C-2), 44.8 (C-4), 159.1 (C-5), 166.3 (C-6) and 167.4 ppm (C-O ester); ν_{max} (KBr): 3190-3260 (NH), 2910-3120 (CH aromatic, olefinic, aliphatic), 1713 (CO), 1456-1476 (C=C olefin, aromatic), 1288-1325 cm^{-1} (C-O ester); Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_2S$: C, 48.70; H, 4.09; N, 8.11; S, 9.29. Found: C, 48.61; H, 4.05; N, 8.22; S, 9.37.

3.4. Ethyl-4-(2,4-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4- tetra hydro pyrimidine-5-carboxylate (4m), (87 %) as a solid; δ_H (300 MHz, DMSO-d_6): 0.99-1.02 (3H, t, *J* 7.03 Hz, CH_3), 1.71 (3H, s, CH_3), 3.96-4.13 (2H, q, *J* 7.4 Hz, CH_2), 4.49 (1H, s, 4-H), 6.95-7.20 (4H, aromatic, CH), 9.68 (1H, s, NH) and 10.13 ppm (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 14.2 (CH_3), 15.1 (CH_3), 62.7(CH_2), 55.8 (CH_3), 56.1 (CH_3), 126.6, 128.7, 131.1, 134.3, 134.6, 140.9 (CH, aromatic), 181.2 (C-2), 49.1 (C-4), 105.2 (C-5), 163.3 (C-6) and 167.2 ppm (C-O ester); ν_{max} (KBr): 3184-3418 (NH), 2982-3109 (CH, aromatic, olefinic, aliphatic), 1712 (CO), 1457-1465 (C=C olefin, aromatic), 1285-1323 cm^{-1} (C-O ester); Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_2S$: C, 48.70; H, 4.09; N, 8.11; S, 9.29. Found: C, 48.74; H, 4.14; N, 8.25; S, 9.31.

4. Physical and spectroscopic Data of products

4.1. Ethyl-1(2-chloroacetyl)-4-methyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidin-5-carboxylate (5g), (63%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.18 (3H, t, *J* 7.05 Hz, CH_3), 2.31 (3H, s, CH_3), 4.12 (2H, q, *J* 7.05 Hz, CH_2), 4.82-4.98 (2H, dd, *J* 15.9 Hz, CH_2), 6.45 (1H, s, 4-H), 7.20-7.34 (4H, aromtic, CH) and 10.34 ppm (1H, s, NH); δ_C (75 MHz, DMSO-d_6): 14.59 (CH_3), 17.06 (CH_3), 46.79 (CH_2), 53.63 (CH_3), 60.49 (CH_3), 66.81, 103.96, 126.66, 128.41, 129.13, 140.18 (CH, aromatic), 147.77 (C), 151.02, 165.15 and 168.35 ppm (C-O ester); ν_{max} (KBr): 3120-3245 (NH), 2950-3005 (CH, aromatic, olefinic, aliphatic), 1701, 1724 (CO), 1440-1465 (C=C olefin, aromatic), 1238-1303 cm^{-1} (C-O ester); Anal. Calcd for $C_{16}H_{17}ClN_2O_4$: C, 57.06; H, 5.09; N, 8.32. Found: C, 57.01; H, 5.13; N, 8.40.

4.2. Ethyl-1(2-chloroacetyl)-4-methyl-2-oxo-6-p-tolyl-1,2,3,6-tetrahydropyrimidin-5-carboxylate (5h), (65%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.17 (3H, t, *J* 7.08 Hz, CH_3), 2.25 (3H, s, CH_3), 2.31 (3H, s, CH_3), 4.11 (2H, q, *J* 7.01 Hz, CH_2), 4.81-4.96 (2H, dd, *J* 15.84 Hz, CH_2), 6.41 (1H, s, 4-H), 7.08-7.15 (4H, aromatic, CH) and 10.29 ppm (1H, s, NH); ν_{max} (KBr): 3122-3217 (NH), 2943-3055 (CH aromatic, olefinic, aliphatic), 1705, 1725 (CO), 1448-1512 (C=C olefin, aromatic), 1236-1303 cm^{-1}(C-O ester); Anal. Calcd for $C_{17}H_{19}ClN_2O_4$: C, 58.21; H, 5.46; N, 7.99. Found: C, 58.14; H, 5.51; N, 8.07.

4.3. Ethyl 5-(4-cholorophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6a), (60%) as a solid; δ_H (300 MHz, DMSO-d_6) 1.06-1.11 (3H, , *J* 7.06 Hz, CH_3), 2.37 (3H, s, CH_3), 4.00-4.05 (2H, q, *J* 3.47 Hz, CH_2), 4.16 (2H, s, CH_2), 5.89 (1H, s, 4-H) and 7.14-7.34 ppm (4H, aromatic, CH); ν_{max} (KBr): 2931-3013 (CH, aromatic, olefinic, aliphatic), 1716, 1766 (CO), 1554 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{15}ClN_2O_3$ S: C, 54.78; H, 4.31; N, 7.99; S, 9.14. Found: C, 54.83; H, 4.37; N, 7.97; S, 9.08.

4.4. Ethyl 5-(3-cholorophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6b), (55%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.07-1.12 (3H, t, J 7.07 Hz, CH_3), 2.35 (3H, s, CH_3), 4.00-4.05 (2H, q, *J* 6.99 Hz, CH_2), 4.14 (2H, s, CH_2), 5.86 (1H, s, 4-H) and 7.25-7.40 ppm (4H, aromatic, CH); ν_{max} (KBr): 2953-3014 (CH, aromatic, olefinic, aliphatic), 1716, 1776 (CO), 1560 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{15}ClN_2O_3S$: C, 54.78; H, 4.31; N, 7.99; S, 9.14. Found: C, 54.62; H, 4.29; N, 7.95; S, 9.09.

4.5. Ethyl 5-(4-boromophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6c), (53%) as a solid; δ_H (300 MHz, DMSO-d_6) 1.08-1.12 (3H, t, *J* 7.09 Hz, CH_3), 2.36 (3H, s, CH_3), 3.98-4.05 (2H, q, *J* 2.76 Hz, CH_2), 4.16 (2H, s, CH_2), 5.86 (1H, s, 4-H) and 7.20-7.57 ppm (4H, aromatic, CH); ν_{max} (KBr): 2868-2989 (CH, aromatic, olefinic, aliphatic), 1709, 1751 (CO), 1552 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{15}BrN_2O_3S$: C, 48.62; H, 3.82; N, 7.59; S, 8.11. Found: C, 48.67; H, 3.79; N, 7.52; S, 8.17.

4.6. Ethyl 5-(4-nitrophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6d), (54%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.08-1.12 (3H, t, *J* 7.07 Hz, CH_3), 2.37 (3H, s, CH_3), 3.97-4.05 (2H, q, *J* 7.06 Hz, CH_2), 4.16 (2H, s, CH_2), 5.98 (1H, s, 4-H), 7.55-8.23 (4H, aromatic, CH) ν_{max} (KBr): 2866-2984 (CH, aromatic, olefinic, aliphatic), 1705, 1753 (CO), 1527 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{15}N_3O_5$ S: C, 53.18; H, 4.18; N, 11.63; S, 8.87. Found: C, 53.25; H, 4.12; N, 11.60; S, 8.81.

4.7. Ethyl 5-(2-nitrophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6e), (86%) as a solid; δ_H (300 MHz, DMSO-d_6): 0.94-0.99 (3H, t, *J* 7.08 Hz, CH_3), 2.37 (3H, s, CH_3), 3.92-3.99 (2H, q, *J* 3.6 Hz, CH_2), 4.07 (2H, s, CH_2), 6.79 (1H, s, 4-H) and 7.97-7.48 ppm (4H, aromatic, CH); ν_{max} (KBr): 2887-3003 (CH, aromatic, olefinic, aliphatic), 1710, 1759 (CO), 1554 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{15}N_3O_5$ S: C, 53.18; H, 4.18; N, 11.63; S, 8.87. Found: C, 53.12; H, 4.12; N, 11.58; S, 8.83.

4.8. Ethyl 5-(3,4-dimethoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6f), (76%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.10-1.15 (3H, t, *J* 7.08 Hz, CH_3), 3.71 (3H, s, CH_3), 3.72 (3H, s, CH_3), 4.00-4.07 (2H, q, *J* 7.02 Hz, CH_2), 4.21 (2H, s, CH_2), 5.82 (1H, s,4-H) and 6.74-6.93 ppm (4H, aromatic, CH); δ_C (75 MHz, DMSO-d_6): 14.31 (CH_3), 19.80 (CH_3), 34.58 (CH_2),55.41 (CH_3), 55.95 (CH_3), 56.03 (CH), 60.94 (CH_2), 108.21, 112.15, 112.21, 132.19, 145.86, 148.85 (aromatic, CH), 120.50, 145.86, 164.56(C), 166.59 (C-O ester) and 171.24 ppm (CO); ν_{max} (KBr): 2947-2997 (CH, aromatic, olefinic, aliphatic), 1716, 1759 (CO), 1556 cm^{-1} (CN); Anal. Calcd for $C_{18}H_{20}N_2O_5S$: C, 57.43; H, 5.36; N, 7.44; S, 8.52. Found: C, 57.33; H, 5.31; N, 7.36; S, 8.49.

4.9. Ethyl 5-(2-methoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6g), (75%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.16-1.09 (3H, t, *J* 7.08 Hz, CH_3), 2.34 (3H, s, CH_3), 3.76 (3H, s, CH_3), 3.99-4.06 (2H, q, *J* 7.04 Hz, CH_2), 4.13-4.29 (2H, dd, *J* 18.16 Hz, CH_2), 6.00 (1H, s, 4-H) and 6.89-7.32 ppm (4H, aromatic, CH); ν_{max} (KBr): 2941-2995 (CH aromatic, olefinic, aliphatic), 1710, 1766 (CO), 1562 cm^{-1} (CN); Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; S, 9.26. Found: C, 58.99; H, 5.28; N, 8.14; S, 9.21.

4.10. Ethyl 5-(2-choloro-6-folorophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6h), (54%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.01-1.06 (3H, t, *J* 7.08 Hz, CH_3), 2.27 (3H, s, CH_3), 3.94-3.99 (2H,q, *J* 3.67 Hz, CH_2), 4.01-4.16 (2H, dd, J 17.84 Hz, CH2), 6.41 (1H, s, 4-H) and 6.18-7.38 ppm (4H, aromatic, CH); ν_{max} (KBr): 2953-2978 (CH, aromatic, olefinic, aliphatic), 1689, 1776 (CO), 1529 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{14}ClFN_2O_3$ S: C, 52.11; H, 3.83; N, 7.61; S, 8.69. Found: C, 52.19; H, 3.78; N, 7.56; S, 8.76.

4.11. Ethyl 5-(2,6-dicholorophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6i), (53%) as a solid; δ_H (300 MHz, DMSO-d_6): 0.94-1.01 (3H, t, *J* 6.38 Hz, CH_3), 2.25 (3H, s, CH_3), 3.91-3.99 (2H, q, *J* 4.63 Hz, CH_2), 4.01-4.19 (2H, dd, *J* 18 Hz, CH_2), 6.64 (1H, s, 4-H) and 7.30-7.48 ppm (4H, aromatic, CH); ν_{max} (KBr): 2951-3036 (CH, aromatic, olefinic, aliphatic), 1689, 1776 (CO), 1556 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_3$ S: C, 49.88; H, 3.66; N, 7.27; S, 8.32. Found: C, 49.79; H, 3.69; N, 7.33; S, 8.37.

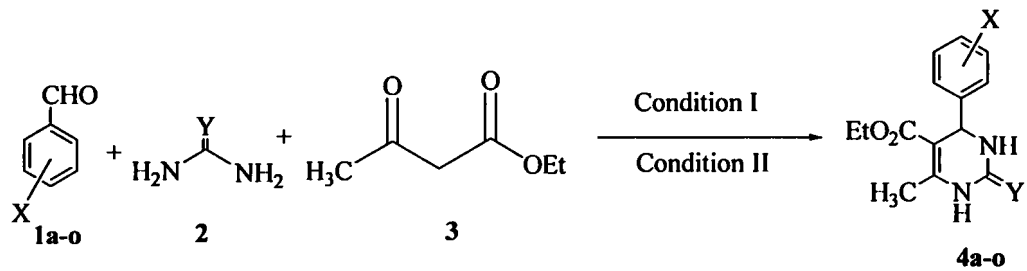
4.12. Ethyl 5-(2,4-dicholorophenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6j), (86%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.05-1.09 (3H, t, *J* 7.09 Hz, CH_3), 2.34 (3H, s, CH_3), 3.96-4.03(2H, q, *J* 7.08 Hz, CH_2), 4.1 2 (2H, s, CH_2), 6.19 (1H, s, 4-H) and 7.38-7.58 ppm (4H, aromatic, CH); ν_{max} (KBr): 2953-3014 (CH, aromatic, olefinic, aliphatic), 1691, 1776 (CO), 1560 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_3S$: C, 49.88; H, 3.66; N, 7.27; S, 8.32. Found: C, 49.96; H, 3.73; N, 7.21; S, 8.39.

4.13. Ethyl 5-(4-hydroxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylat (6k), (67%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.05-1.13 (3H, t, *J* 7.19 Hz, CH_3), 2.35 (3H, s, CH_3), 3.99-4.07(2H, q, *J* 3.38 Hz, CH_2), 4. 2 (2H, s, CH_2), 5.81 (1H, s, 4-H) and 6.71-7.18 ppm (4H, aromatic, CH); ν_{max} (KBr): 2951-2995 (CH, aromatic, olefinic, aliphatic), 1689, 1776 (CO), 1556 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.88; H, 4.89; N, 8.40; S, 9.69.

4.14. Ethyl 7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-]pyrimidine-6-carboxylate (6l), (81%) as a solid; δ_H (300 MHz, DMSO-d_6): 1.07-1.12 (3H, t, *J* 6.73 Hz, CH_3), 2.37 (3H, s, CH_3), 3.99-4.06 (2H, q, *J* 4.1 Hz, CH_2), 4.18 (2H, s, CH_2), 5.89 (1H, s, 4-H) and 7.26-7.37 ppm (4H, aromatic, CH); ν_{max} (KBr): 2930-2989 (CH aromatic, olefinic, aliphatic), 1712, 1763 (CO), 1556 cm^{-1} (CN); Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85; S, 10.14. Found: C, 60.83; H, 5.19; N, 8.81; S, 10.19.

5. Results and Discussion

At first stage, we used previously reported methods for preparation of dihydropyrimidinones and their sulfur analogous (8). The reactions proceeded smoothly in refluxing ethanol (condition I) or in solvent-free condition (condition II, Scheme 1).



Condition I: SSA, Ethanol
Condition II: SSA, Solvent free

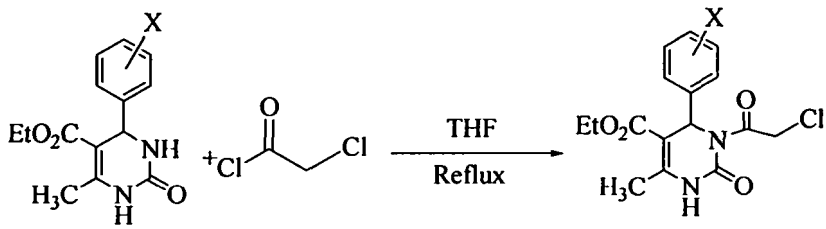
(Scheme 1)

Some of these dihydropyrimidinthiones are new compounds and to the best knowledge of us prepared for first time (Table 1).

Table 1. Synthesis of DHPMs using SSA as a heterogeneous catalyst

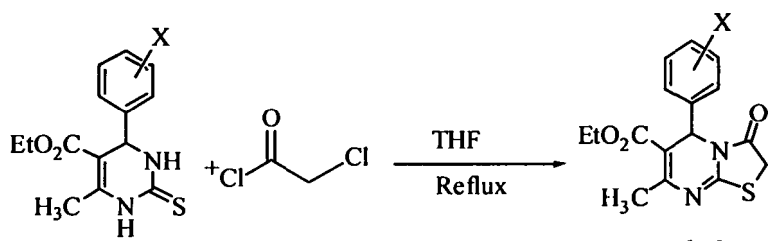
DHPMs	X	Y	condition	Time/h	Yield/%	Mp Found/°C	Mp Reported [lit]/°C
4a	4-Cl	S	I	6	86	190-191	192-194 (12)
4b	3-Cl	S	I	6	83	204-205	183-184 (16)
4c	2-NO_2	S	I	7	85	195-197	159-161 (16)
4d	3,4-$(OMe)_2$	S	I	4	80	177-179	-
4e	2-(OMe)	S	I	5	75	230-231	235-236 (16)
4f	H	S	I	2.5	85	208-210	209-211(8)
4g	H	O	II	1	90	200-201	200-202 (13)
4h	4-Me	O	II	1	93	218-219	213-216 (17)
4i	4-Br	S	II	1.5	88	191-192	181-183 (15)
4j	4-NO_2	S	II	2	85	193-194	109-111 (14)
4k	2-Cl-6-F	S	II	1.5	80	206-207	-
4l	2,6-$(Cl)_2$	S	II	1.5	86	228-229	-
4m	2,4-$(Cl)_2$	S	II	1.5	87	117-118	-
4n	4-OH	S	II	2	87	197-198	193-194 (13)
4o	H	S	II	2	89	208-210	209-211 (8)

At the second step, we extended the cyclocondensation reaction using prepared DHPMs and chloroacetyl chloride as a dielectrophile precoursour. Cyclization of pyrimidinones under the reflux conditions was not successful and afforded ethyl-1-(2-chloroacetyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-6-aryl pyrimidine-5-carboxylate **5g** and **5h** (Scheme 2). However the reaction of pyrimidinthione derivatives and chloroacetyl chloride under the same conditions afforded novel bicyclic thiazolopyrimidine derivatives **6a-l** in good yields (Scheme 3). The results are summarized in Table 2.



4g-h **5g-h**

(Scheme 2)



4a-o **6a-l**

(Scheme 3)

Table 2. Synthesis of *N*-chloroacetyl pyrimidinones **5g-h** and bicyclic thiazolopyrimidines **6a-l**

Product	X	Time/min	Yield/%	Mp/°C
5g	H	240	63	220-221
5h	4-Me	240	65	207-208
6a	4-Cl	60	60	215-216
6b	3-Cl	45	55	210-211
6c	4-Br	60	53	216-217
6d	4-NO_2	45	54	204-205
6e	2-NO_2	15	86	208-209
6f	3,4-$(OMe)_2$	45	76	209-210
6g	2-(OMe)	45	75	220-222
6h	2-Cl-6-F	60	54	226-227
6i	2,6-$(Cl)_2$	60	53	206-207
6j	2,4-$(Cl)_2$	15	86	218-220
6k	4-OH	20	67	260-261
6l	H	20	81	215-217

In the IR spectra of bicyclic thiazolopyrimidine derivatives the absence of the absorbtion at 3150-3350 cm^{-1}, the characteristic absorption of NH group of starting material, is a good evidence of the expected products. Also the CHN analysis and NMR spectra have given to establish the structure of products.

Conclusion

In conclusion, we extend an efficient cyclocondensation reaction for the synthesis of some novel thiazolopyrimidine in good yields. Simplicity of procedure, ease of work-up, avoiding toxic catalyst, and stability of reagent are features of this reaction.

Acknowledgment

We gratefully acknowledge the financial support from the Research Council of Arak University

References

1. (a) T. M. Potewar, S. A. Ingale and K.V. Srinivasan, *Tetrahedron*, **63**,11066 (2007). (b) L C. Santos, F. T. Uchoa, A R. P. A. Canas, I. A Sousa, R. O. Moura, , M. C. A. Lima, S. L Galdino, I. R. Pitta, J Barbe, *Heterocycl. Commun*, **11**, 121 (2005)
2. C O. Kappe, *Eur J. Med. Chem* , **35**, 1043 (2000)
3 B. B. Snider and Zh. Shi, *J Org Chem* , **58**, 3828 (1993)
4. C. O. Kappe, *Tetrahedron*, **49**, 6937 (1993)
5 C. O Kappe, *Acc Chem Res*, **33**, 879 (2000).

6. M. A. Zolfigol, *Tetrahedron*, **57**, 9509 (2001).
7. (a) P. Salehi, M. A. Zolfigol, F. Shirini and M. Baghbanzade, *Curr. Org. Chem*, **10**, 2171 (2006). (b) D. Habibi, M. A. Zolfigol, M. Safaiee, *S. Afr. J. Chem.*, **61**, 93 (2008). (c) D. Habibi, M. A. Zolfigol, F. Shirini, M. Safaiee, M. Abedini, P. Rahmani, *S. Afr. J. Chem.*, **60**, 17 (2007).
8. (a) P. Salehi, M. Dabiri, M. A. Zolfigol and M. A. Bodaghi Fard, *Tetrahedron Lett.*, **44**, 2889 (2003). (b) P. Salehi, M. Dabiri, M. A. Zolfigol and M. A. Bodaghi Fard, *Heterocycles*, **6**, 2435 (2003).
9. A. Mobinikhaledi, N. Foroughifar and F.Goodarzi, *Phophorus, Sulfur, and Silicon*, 2004, **179**, 507 (2003).
10. A. Mobinikhaledi, N. Foroughifar and F. Goodarzi, *Phophorus, Sulfur, and Silicon*, **178**, 2539 (2003).
11. N. Foroughifar, A. Mobinikhaledi and H. Fathinejad Jirandehi, *Phophorus, Sulfur, and Silicon*, **178**, 495 (2003).
12. J. S. Yadav, B. V. Subba Reddy, E. Jagan Reddy and T. Ramalingan, *J. Chem. Res.(s)*, 354 (2000).
13. Ch. V. Reddy, M. Mahesh, P. V. K. Raju, T. R. Babu and V. V. N. Reddy, *Tetrahedron Lett*, **43**, 2657 (2002).
14. N. Fu, Y. Yuan, Z. Cao, S. Wang, J. Wang and C. Peppe, *Tetrahedron*, **58**, 4801 (2002).
15. M. Yarim, B. Tozkoparan, S. Saraç, M. Ertan, B. özçelik and U. Abbasoğlu, *FABAD, J. Pharm. Sci.*, **27**, 65 (2002).
16. İ. S. Zorkun, S. Saraç, S. Çelebi and K. Erol, *Bioorg. Med. Chem*, **14**, 8582 (2006).
17. Y. Yu, D. Liu, C. Liu and G. Luo, *Bioorg. Med. Chem. Lett.*, **17**, 3508 (2007).

Received on March 8, 2009.