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One-pot Synthesis of Some Novel 2-[(*Z*)-1-(Aryl)]-6,7-dihydro-2*H*-istohiazolo[2,3-a]pyrimidine-3(5*H*)-one Derivatives

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Reaction of 3,4,5,6-tetrahydro-2-pyrimidinethiol, prepared by cyclocondensation reaction of 1,3-diamino propane 1 and carbon disulfide, with ethyl chloroacetate and substituted aromatic aldehydes in the presence of sodium acetate and acetic acid gave 2-[(*Z*)-1-(aryl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one derivatives 3(a-j) in good yields. ^{1}H NMR spectroscopy, and elemental analysis were used for identification of these compounds.

Keywords: Condensation, Pyrimidine, Isothiazole, Synthesis

INTRODUCTION

Multi-component reactions (MCRs) are of special interest in organic and medicinal chemistry [1-3]. They are particularly useful for preparation of various drug like molecules containing biological screening [4,5]. Pyrimidine derivatives have been extensively studied because some of them are well known for their therapeutic and pharmacological activities [5-16]. They exhibit various interesting pharmacological properties such as antitumor [7], anticarcinogenic [9], antiviral [10] and antifolate [11]. Pyrimidine has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological activities. Our literature review reveals that various synthetic approaches for the synthesis of pyrimidine derivatives have been reported [8,17-23]. Furthermore, there has been a considerable interest in the chemistry of thiazolidine-4-one ring system, which is known as a core structure in various synthetic pharmaceutical compounds showing a wide range of biological activities [24-26]. However, synthesis of novel fused heterocyclic systems containing thiazolidine-3-one ring, through multi-component reactions, is still being sought.

Here, due to versatile biological activities of pyrimidines and as a continuation of our research program on the synthesis of pyrimidine derivatives [27-29] we have made an attempt to synthesis some novel 2-[(*Z*)-1-(aryl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one derivatives in good yield via a multi-component reaction.

EXPERIMENTAL

All chemicals used were prepared from Merck or Fluka company. Melting points were determined on an electrothermal digital melting point apparatus and were uncorrected. Microanalyses were performed by an elemental analyzer (Elemental, Varioel III) at Arak University. The results were agreed favorably with the calculated values. NMR spectra were recorded on 300 MHz NMR spectrometer. Chemical shifts (ppm) were referenced to the internal standards tetramethylsilane (TMS). Reactions were monitored by thin layer chromatography.

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Preparation of 3,4,5,6-Tetrahydro-2-pyrimidinethiol (2)

Carbon disulfide (0.2 mol) was added dropwise to a solution of 1,3-diamino propane 1 (0.2 mol) in H_2O/EtOH (20 ml), and the temperature was remained constant at 0-5 ºC. After the completion of addition, the reaction mixture was refluxed for 12 h and then cooled to room temperature. The precipitate was collected by filtration and recrystallized from EtOH to give pure desired compound.

General Procedure for the Preparation of (3)

A mixture of 3,4,5,6-tetrahydro-2-pyrimidinethiol 2 (0.01 mol), ethyl chloroacetate (0.012 mol) and corresponding aromatic aldehyde (0.01 mol) in acetic acid (30 ml) was refluxed in the presence of sodium acetate (2 g) for 5-7 h. The mixture was allowed to cool and poured into cold water (15-20 ml). The solid was collected by filtration to give 3. However, when furfural and benzaldehyde were used as starting materials, the product was obtained after solvent evaporation.

3,4,5,6-Tetrahydro-2-pyrimidinethiol (2). IR (KBr): υ = 3190, 3100, 2990, 2920, 1598, 1480, 1385, 1302, 1200 cm^{-1}, ^1H NMR (DMSO-d_6): δ (ppm):1.66 (m, 2H, CH_2), 3.05 (m, 4H, $2CH_2$), 7.81 (s, 2H, NH). Anal. Calcd for $C_4H_8N_2S$: 41.35; H, 6.94; N, 24.11%. Found: C, 41.51; H, 6.85; N, 24.38%.

2-[(Z)-1-(Phenylmethylidene)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3a). IR (KBr): υ = 3150, 3080, 1710, 1643, 1610, 1492, 1386, 1364 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 2.02 (m, J = 6.0 Hz, 2H, CH_2) , 3.72 (t, J = 6.0 Hz , 2H, CH_2), 3.86 (t, J= 6.0 Hz, 2H, CH_2), 7.45 (m, 5H, H_{arom}), 7.76 (s, 1H, H_{vinyl}), Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47%. Found: C, 64.1; H, 4.76; N, 11.60%.

2-[(Z)-1-(2-Hydroxyphenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3b). IR (KBr): υ = 3173, 2990, 2859, 1711, 1597, 1454, 1385, 1362 cm^{-1}, ^1H NMR (DMSO-d_6): δ (ppm) = 1.84 (m, J = 6.0 Hz, 2H, CH_2), 3.52 (t, J = 6.0 Hz, 2H, CH_2), 3.70 (t, J = 6.0 Hz, 2H, CH_2), 7.23 (m, 4H, H_{arom}), 7.91 (s, 1H, H_{vinyl}), 10.38 (bs, 1H, OH), Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76%. Found: C, 60.22; H, 5.02; N, 10.26%.

2-[(Z)-1-(4-Methylphenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3c). IR (KBr): υ = 3050, 3882, 1707, 1639, 1602, 1509, 1385, 1362 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 1.94 (m, 2H, CH_2), 3.66 (t, 2H, CH_2), 3.76 (t, 2H, CH_2), 7.25 (d, 2H, H_{arom}), 7.38 (d, 2H, H_{arom}), 7.65 (s, 1H, H_{vinyl}). Anal. Calcd for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84%. Found: C, 65.21; H, 5.51; N, 10.71%.

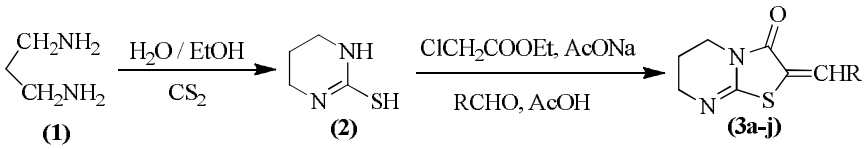
2-[(Z)-1-(3-Methoxyphenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3d). IR (KBr): υ = 3651, 2933, 1708, 1643, 1604, 1385, 1251 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 1.98 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 3.69 (t, 2H, CH_2), 3.82 (s, 3H, OCH_3), 7.09 (m, 4H, H_{arom}), 7.68 (s, 1H, H_{vinyl}), Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21%. Found: C, 60.83; H, 4.77; N, 9.58%.

2-[(Z)-1-(3-Bromophenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3e). IR (KBr): υ = 3692, 3057, 2857, 1702, 1643, 1606, 1386, 1363 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 1.97 (m, J = 6.0 Hz, 2H, CH_2), 3.69 (t, J = 6.0 Hz, 2H, CH_2), 3.82 (t, J = 6.0 Hz, 2H, CH_2), 7.40 (m, 4H, H_{arom}), 7.60 (s, 1H, H_{vinyl}), Anal. Calcd for $C_{13}H_{11}Br\ N_2OS$: C, 48.31; H, 3.43; N, 8.67%. Found: C, 47.88; H, 3.14; N, 8.10%.

2-[(Z)-1-(2-Nitrophenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3f). IR (KBr): υ = 3780, 3503, 1713, 1644, 1524, 1386, 1364 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 2.02 (m, 2H, CH_2), 3.70 (t, 2H, CH_2), 3.87 (t, 2H, CH_2), 7.68 (m, 4H, H_{arom}), 8.07 (s, 1H, H_{vinyl}), Anal. Calcd for $C_{13}H_{11}\ N_3O_3S$: C, 53.97; H, 3.83; N, 14.52%. Found: C, 53.38; H, 3.56; N, 13.67%.

2-[(Z)-1-(3-Nitrophenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3g). IR (KBr): υ = 3450, 2947, 1709, 1649, 1604, 1525, 1386, 1353 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 2.01 (m, J = 6.0 Hz, 2H, CH_2), 3.72 (t, J = 6.0 Hz, 2H, CH_2), 3.86 (t, J = 6.0 Hz, 2H, CH_2), 7.66 (t, 1H, H_{arom}), 7.72 (s, 1H, H_{arom}), 7.80 (d, 1H, H_{arom}), 8.23 (d, 1H, H_{arom}), 8.35(s, 1H, H_{vinyl}), Anal. Calcd. for $C_{13}H_{11}\ N_3O_3S$: C, 53.97; H, 3.83; N, 14.52%. Found: C, 53.38; H, 3.56; N, 13.67%.

2-[(Z)-1-(4-Nitrophenyl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3h). IR (KBr): υ = 3108, 3084, 1712, 1636, 1605, 1505, 1468, 1386, 1345 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 2.01 (m, J = 6.0 Hz, 2H, CH_2), 3.73 (t, J = 6.0 Hz, 2H, CH_2), 3.86 (t, J = 6.0 Hz, 2H, CH_2), 7.63 (d, 2H, H_{arom}), 7.73 (s, 1H, H_{vinyl}), 8.32 (d, 2H,



Scheme 1. The synthetic pathway of pyrimidine-3(5*H*)-one derivatives

Table 1. 2-[(*Z*)-1-(aryl)]-6,7-dihydro-2H-isothiazolo[2,-a]pyrimidine-3(5H)-one Derivatives (3a-j)

Compound	R	Time (h)	M.P. (ºC)	Yield (%)
3a	C_6H_5	7	140-141	82
3b	2-OHC_6H_4	5	262-263	73
3c	4-$CH_3C_6H_4$	4	171-172	68
3d	3-$OCH_3C_6H_4$	6	142-143	76
3e	3-BrC_6H_4	6	178-179	63
3f	2-$NO_2C_6H_4$	6	116-117	55
3g	3-$NO_2C_6H_4$	6	206-207	60
3h	4-$NO_2C_6H_4$	6.5	234-235	54
3i	C_4H_3O(Furyl)	5	150-151	56
3j	C_8H_7	5	190-191	75

H_{arom}) Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52%. Found: C, 54.45; H, 3.94; N, 13.74%.

2-[(Z)-1-(2-Furyl)methylidene]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3(5H)-one (3i). IR (KBr) υ = 3095, 2942, 1709, 1638, 1618, 1473, 1387, 1361, 1285, 1250 cm^{-1}, ^1H NMR (DMSO-d_6): δ (ppm): 1.84 (m, 2H, CH_2), 3.52 (t, 2H, CH_2), 3.67 (t, 2H, CH_2), 7.30 (m, 3H, H_{arom}), 8.00 (s, 1H, H_{vinyl}), Anal. Calcd. for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96%. Found: C, 56.5; H, 4.38; N, 12.11%.

2-[(Z,2Z)-3-Phenyl-2-propenylidene]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidin-3(5H)-one (3j). IR (KBr) υ = 3023, 2956, 1722, 1696, 1637, 1600, 1467, 1385, 1360 cm^{-1}, ^1H NMR ($CDCl_3$): δ (ppm) = 1.96 (m, 2H, CH_2), 3.67 (t, 2H, CH_2), 3.77 (t, 2H, CH_2), 6.74 (t, J = 13,3 Hz, 1H, H_{vinyl}), 6.93 (d, t, J = 15.3 Hz, 1H, H_{vinyl}), 7.38 (m, 5H, H_{arom}), 7.51 (d, 1H, H_{vinyl}), Anal. Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36%. Found: C, 66.70; H, 5.57; N, 9.88%.

RESULTS AND DISCUSSION

Treatment of 1,3-diamino propane with carbon disulfide gave 3,4,5,6-tetrahydro-2-pyrimidinethiol 2. Figure 1 displays the ^1H NMR spectrum of 2 with peak assignments. The resonance signals at 7.81 ppm, 3.05 and 1.66 ppm in the ^1H NMR are ascribed to the protons of N-H, thioamide group (Ha) and aliphatic protons (Hb, Hc), respectively. The

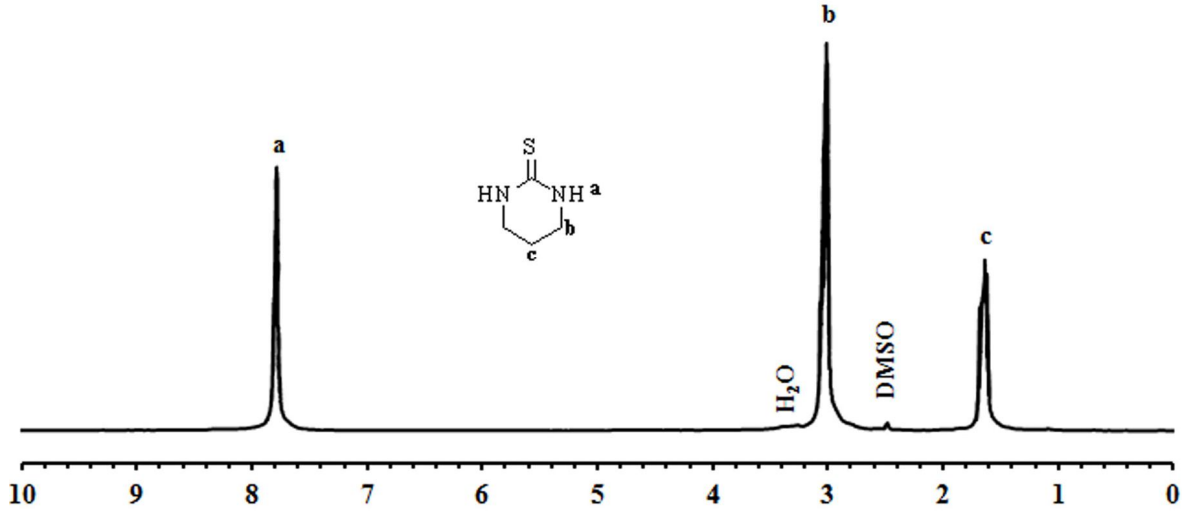


Fig. 1. [1]H NMR spectrum of 3,4,5,6-tetrahydro-2-pyrimidinethiol (2).

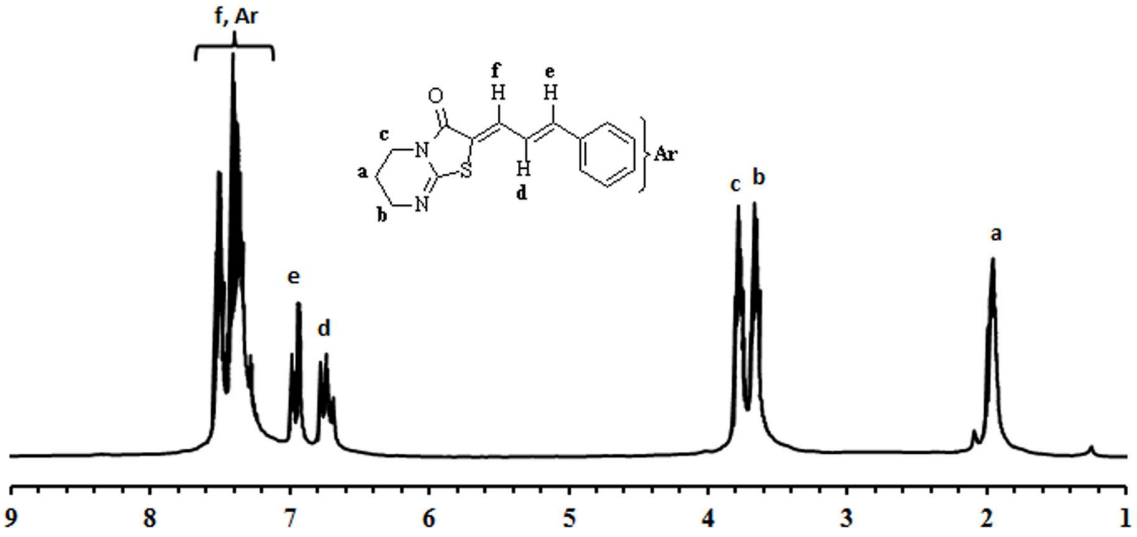


Fig. 2. [1]H NMR spectrum of 2-[(Z,2Z)-3-Phenyl-2-propenylidene]-6,7-dihydro-2H-isothiazolo[2,3-a] pyrimidin-3(5H)-one (3j).

assignments and integral of the peaks are consistent with the proposed structure of 3,4,5, 6-tetrahydro-2-pyrimidinethiol. Further reaction of 2 with ethyl chloroacetate and corresponding aromatic aldehyde in the presence of sodium acetate and acetic acid afforded 3(a-j), as shown in Scheme 1. The reaction was preceded under reflux condition for 5-7 h. The yield of products after recrystallization from EtOH/H_2O was in the range of 54-82%. The results are shown in Table 1.

The IR and [1]H NMR spectral data as well as the elemental analysis data are very informative and provide significant evidences for the formation of the expected structures. In the IR spectra of compounds 3(a-j), the absence of the absorption related to the NH group and the

appearance of the absorption at 1636-1649 cm^{-1}, the characteristic absorption of the carbonyl group, are good evidence of the expected reactions.

^1H NMR spectra of all synthesized compounds are simple and have a singlet and a multiplet signal at low field shift due to the resonance of vinyl and aromatic protons, respectively. The aliphatic protons relative to the pyrimidine ring appear at high field. Two isomeric products may be expected for this reaction. However, we have obtained only the *Z*-isomer, most probably due to the lower satirical interaction between the carbonyl group and the phenyl ring compared to the *Z*-isomer [15]. For example, ^1H NMR spectrum of compound 3j is shown in Fig. 2. Assignments of each proton are also presented in the figure, and the spectrum agrees well with the proposed compound 3j structure. The coupling constant values (J = 13.3 and 15.3 Hz) of the vinyl protons in compound 3j also support the *Z*-isomer structure.

CONCLUSIONS

This work describes the synthesis of some novel 2-[(*Z*)-1-(aryl)]-6,7-dihydro-2H-isothiazolo[2,3-a]pyrimidine-3 (5H)-one derivatives through the reaction of 3,4,5,6-tetrahydro-2-pyrimidinethiol with ethyl chloroacetate and aromatic aldehydes in the presence of sodium acetate and acetic acid.

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