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Original Research Article

Green and Efficient Synthesis of Thiazolo[3,2-a]pyrimidin-3(5H)-one Derivatives under Catalyst-Free Conditions

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ABSTRACT

Heterocycles containing sulphur and nitrogen atoms in the core structure, possess a number of pharmacologically and biologically active compounds. So, in the past decade, various fused pyrimidines including purines, pteridines, quinazolines, pyridopyrimidines, triazolopyrimidines, pyrazolopyrimidines, pyrimidoazepines, furopyrimidines and pyrrolopyrimidines were studied and were found to possess remarkable pharmacological properties. Thus, our work was focused on the development of novel, green and efficient method for the synthesis of a series of 6-acetyl-7-methyl-5-aryl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one derivatives using 5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1H)-thione derivatives as starting materials. The precursor pyrimidine derivatives were prepared by Biginelli reaction of pentan-2,4-dione, thiourea and an appropriate aromatic aldehyde in the presence of an ionic liquid, and then reacted with ethyl bromoacetate in a concise sequence involving condensation/cyclization reaction to give the corresponding thiazolopyrimidines in good yields under catalyst-free conditions in the presence of acetone as solvent. The structure of the whole synthesized compounds was determined by NMR and IR spectroscopy, and a plausible mechanism of their formation was proposed.

Keywords: Dihydropyrimidinthiones, thiazole, ionic liquid, condensation, fused, thiazolopyrimidines

1. Introduction

A number of fused heterocyclic compounds formed from the condensation of two biologically active rings are found to possess potent biological actions. Thus, recently, the synthesis of such compounds has attracted the attention of researchers. Amongst, ring fused pyrimidine and their innumerable derivatives continue to hold the attention of chemists in different countries because of their broad range of biological and pharmacological activities encompassing anticancer, anxiolytic, antioxidant, antiviral, antifungal, anticonvulsant, antidepressant, and antibacterial activities [1]. While dihydropyridinthiones have emerged as potential backbones of several calcium channel blockers, antihypertensive agents and neuropeptide Y antagonists [2], thiazole derivatives have been reported to possess anti-microbial, analgesic, anti-inflammatory, anti-convulsant, cardiogenic, anti-cancer, anti-tubercular and anthelmintic activities [3]. Recently, thiazolopyrimidine derivatives have received much attention, due to their wide range of biological activities [4] including antimicrobial, anti-inflammatory [5, 6], analgesic [7], antioxidant [8], anticancer [9] and calcium channel blockers [7]. Other possible applications include their use as pesticides [10], phosphate and acetylcholinesterase inhibitor agents [11, 12] and against virulent Lewis lung tumor in mice [13]. Prompted by the aforementioned biological and medicinal activities, we report, herein, a novel and green method for the synthesis of some differently substituted thiazolopyrimidines **3a-h**, using pyrimidine derivatives (DHPMs) **1a-h** as precursors in acetone under catalyst-free conditions with the aim of acquiring agents displaying tougher potent biological activities (Scheme 1).

Experimental Section

Chemicals and General Procedures.

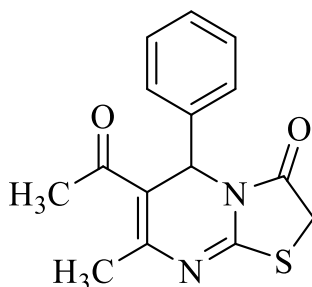
All reagents were purchased from commercial sources and used without further purification. Melting temperatures were measured with Banc Kofler apparatus and are uncorrected. ^1H NMR spectra were recorded on Fourier transformer DP 400 or 250 spectrometer, operating at 400 or 250.13 MHz. ^{13}C NMR spectra were recorded on the same instruments operating at 100 or 62.5 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (J) are reported in Hz. Low-resolution mass spectra (LC-MS) are performed using an *Agilent Technologies MSD 1200 SL* single quadrupole multimode source ESI/APCI spectrometer equipped with a *Thermo Hypersil Gold* 1.9 μm , 1x30 m column.

Preparation of dihydropyrimidinthiones) (1a-h)

Compounds (**1a-h**) were synthesized as previously described [10]. Briefly, a mixture of an aromatic aldehyde (1 mmol), pentan-2,4-dione (1 mmol), thiourea (1 mmol) in [H-Val][HSO₄] (100 mol%) was heated at 120 °C for an appropriate time. After completion of the reaction, as monitored by thin layer chromatography (TLC), the reaction mixture, cooled to room temperature, was poured onto ice (30 g) and stirred for 5-10 minutes. The solid formed was filtered and recrystallized from ethanol to afford the pure products.

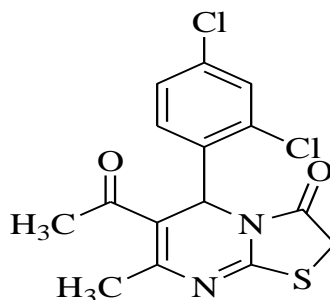
Preparation of thiazolo [3,2-a] pyrimidin-3(5H)-ones (3a-h)

A mixture of DHPM (1.0 mmol) and ethyl bromoacetate (0.5 mmol) in anhydrous acetone (10 ml) was refluxed with magnetic stirring for a time defined by TLC. After evaporation of the solvent, the product obtained was recrystallized from ethanol.



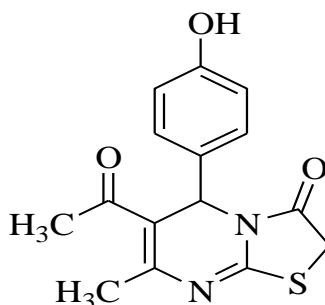
6-Acetyl-7-methyl-5-phenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one **3a**

Yellow crystals; yield: 80 %; m.p. 244-246 °C; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3039 (CH aromatic), 2939 and 2900 (CH aliphatic), 1762 (C=O of thiazolidinone ring) and 1591, 1556 (C=N and C=C); ¹H NMR (250 MHz, DMSO-d₆) δ 7.14 -7.06 (m, 5H, Ar-H), 5.56 (s, 1H, CH); 3.76 (s, 2H, CH₂), 2.31 (s, 3H, CH₃), 1.70 (s, 3H, CH₃); ¹³C NMR (DMSO-d₆) δ 196.81 (COCH₃), 172.63 (C9), 163.70 (C2), 151.71 (C6), [143.3, 128.8, 127.6, 126.8] C_{arom}, 131.90 (C5), 53.81 (C4), 30.70 (C8), 27.00 (COCH₃), 21.00 (Me); LCMS-ESI (m/z): calcd for C₁₅H₁₄N₂O₂S (M+H)⁺ 287.08, found 287.09.



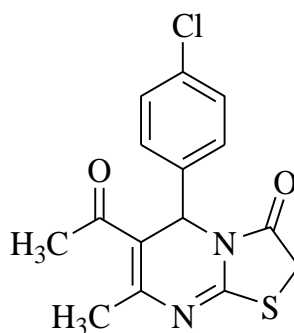
6-Acetyl-5-(2,4-dichlorophenyl)-7-methyl-2H-thiazolo [3,2-a]pyrimidin-3(5H)-one 3b

Orange solid; yield: 72 %; m.p. 231-233 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3026 (CH aromatic), 1761 (C=O of thiazolidinone ring) and 1590 (C=N); ^1H NMR (250 MHz, DMSO- d_6) δ 7.12-6.92 (m, 3H, Ar-H); 5.71 (s, 1H, CH); 3.76 (s, 2H, CH₂); 2.31 (s, 3H, CH₃); 1.7 (s, 3H, CH₃); ^{13}C NMR (DMSO- d_6) δ 196.52 (COCH₃), 172.61 (C9), 163.71 (C2); 151.73 (C6), [140.30; 133.70; 133.70; 130.20; 129.80; 126.80] C_{arom}, 131.90 (C5), 49.82 (C4), 27.00 (COCH₃), 21.00 (Me); LCMS-ESI (m/z) calcd for : C₁₄H₉Cl₂N₂O₂S [M+H]⁺: 355.00, found 355.02.



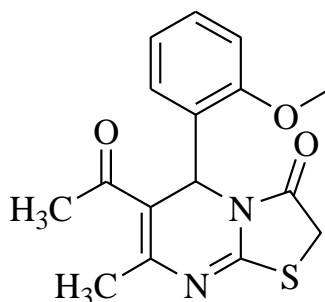
6-Acetyl-5-(4-hydroxyphenyl)-7-methyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 3c

Light green solid; yield: 78 %; m.p. 236-237 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3419 (OH), 3039 (CH aromatic), 2939 and 2900 (CH aliphatic), 1762 (C=O of thiazolidinone ring) and 1600 (C=N); ^1H NMR (250 MHz, DMSO- d_6) δ 9.18 (s, 1H, OH), 7.19-6.89 (m, 4H, C₆H₄), 5.37 (s, 1H, CH), 3.76 (s, 2H, CH₂), 2.31 (s, 3H, CH₃), 1.70 (s, 3H, CH₃); ^{13}C NMR (DMSO- d_6) δ 196.52 (COCH₃); 172.61 (C9), 163.71 (C2), 151.71 (C6), [156.30, 135.70, 128.40, 128.40, 115.80, 115.80] C_{arom}, 131.90 (C5), 49.80 (C4), 27.00 (COCH₃), 21.00 (Me) ; LCMS-ESI (m/z): calcd for C₁₅H₁₄N₂O₃S [M+H]⁺: 303.08, found 303.07.



6-Acetyl-5-(4-chlorophenyl)-7-methyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 3d

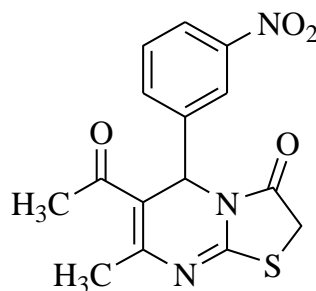
Yellow crystals; yield: 82 %; m.p. 228-229 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3040 (CH aromatic), 2940 (CH aliphatic), 1762 (C=O of thiazolidinone ring) and 1591 (C=N); ^1H NMR (250 MHz, DMSO- d_6 , δ ppm, J Hz) : 7.40 (d, $J=8.4\text{Hz}$, 2H, CH_{arom}), 7.25 (d, $J=8.4\text{Hz}$, 2H, CH_{arom}), 5.12 (s, 1H, CH), 3.76 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , δ ppm): 196.51 (COCH_3); 172.62 (C9); 163.71 (C2); 151.73 (C6), [141.30, 132.30, 128.70, 128.70; 128.40; 128.40] C_{arom} , 131.91 (C5), 49.82 (C4), 27.10 (COCH_3), 21.09 (Me); LCMS-ESI (m/z): calcd for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 321.05, found 321.04.



6-Acetyl-5-(2-methoxyphenyl)-7-methyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 3e

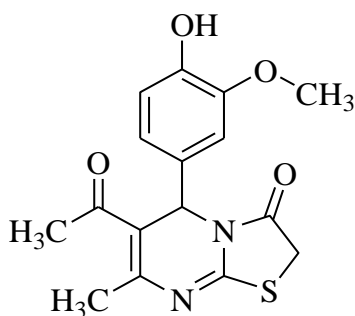
Brownish solid; yield: 77 %; m.p. 238-239 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3040 (CH aromatic), 2939 and 2900 (CH aliphatic), 1762 (C=O of thiazolidinone ring) and 1592 (C=N); ^1H NMR (250 MHz, DMSO- d_6 , δ ppm, J Hz): 7.35-7.22 (m, 1H, CH_{arom}), 7.10-7.01 (m, 2H, CH_{arom}), 6.93-6.74 (m, 1H, CH_{arom}), 5.12 (s, 1H, CH); 3.95 (s, 3H, CH_3); 3.76 (s, 2H, CH_2); 2.31 (s, 3H, CH_3); 1.71 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , δ ppm): 196.51 (COCH_3); 172.62 (C9); 163.72 (C2); 151.72 (C6); [156.60; 128.00; 127.70; 121.30; 120.9; 114.1] C_{arom} ; 131.93 (C5); 56.2 (COMe); 49.84 (C4); 27.03 (COCH_3); 21.00 (subst Me); LCMS-ESI (m/z): calcd

for $C_{16}H_{16}N_2O_3S$ $[M+H]^+$: 317.09, found 317.06.



6-acetyl-7-methyl-5-(3-nitrophenyl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 3f

Brownish solid; yield: 78 %; m.p. 195-196 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3039 (CH aromatic), 2940 and 2900 (CH aliphatic), 1761 (C=O of thiazolidinone ring) and 1590 (C=N), 1526.5 (N-O nitro); ^1H NMR (250 MHz, DMSO- d_6 , δ ppm, J Hz): 7.75-7.62 (m, 4H, CH_{arom}); 5.12 (s, 1H, CH); 3.76 (s, 2H, CH_2); 2.31 (s, 3H, CH_3); 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , δ ppm): 196.51 (COCH₃); 172.62 (C9); 163.70 (C2); 151.70 (C6); [156.60; 128.00; 127.70; 121.30; 120.90; 114.10] C_{arom} ; 131.93 (C5); 56.2 (COMe); 49.81 (C4); 27.00 (COCH₃); 21.08 (Me); LCMS-ESI (m/z): calcd for : $C_{15}H_{13}N_3O_4S$ $[M+H]^+$: 332.07, found 332.06.



6-Acetyl-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 5g

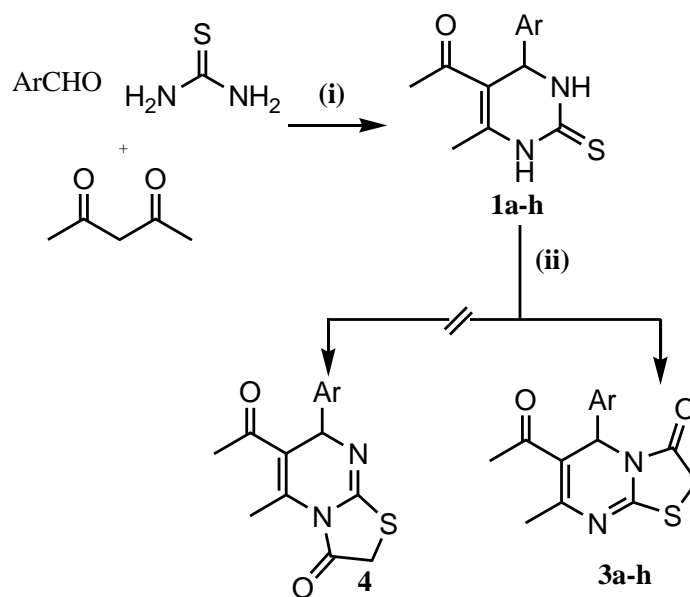
Light green solid; yield: 71 %; m.p. 220-203 °C; IR ($\nu_{\max}/\text{cm}^{-1}$): 3040 (CH aromatic), 2940 (CH aliphatic), 1762 (C=O of thiazolidinone ring) and 1591, 1556 (C=N and C=C); ^1H NMR (250 MHz, DMSO- d_6 , δ ppm, J Hz): 9.12 (s, 1H, OH); 6.77 (d, 1H, $J=8.3\text{Hz}$, CH_{arom}); 6.69 (d, 1H, $J=2.1\text{Hz}$, CH_{arom}); 6.65 (dd, 1H, $J=8.3\text{Hz}$, $J=2.15\text{Hz}$, Hz, CH_{arom}); 5.12 (s, 1H, CH); 3.95 (s, 3H, CH_3); 3.76 (s, 2H, CH_2); 2.31 (s, 3H, CH_3); 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , δ ppm): 196.50 (COCH₃); 172.62 (C9); 163.71 (C2); 151.72 (C6); [156.60; 128.00; 127.70; 121.30; 120.90; 114.10] C_{arom} ; 131.91 (C5); 56.2 (COMe); 49.82

(C4); 27.00 (COCH₃); 21.01 (Me); LCMS-ESI (**m/z**): **calcd for** : C₁₆H₁₆N₂O₄S [M+H]⁺: 333.09, found 333..10.

3. Results and Discussion

3.1. Chemistry

The synthesis of **5**-(5-acetyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidines (3a–h) was achieved through an efficient and versatile synthetic route outlined in Scheme 1. Initially **5**-(Acetyl)-6-methyl-4-(aryl)-3,4-dihydropyrimidin 2(1*H*)-thione derivatives (1a–h) were prepared *via* Biginelli condensation of an aromatic aldehyde with pentan-2,4-dione and thiourea in an ionic-liquid [15]. Treating each of 1a–h with ethyl bromoacetate under catalyst free conditions in an acetone solution yielded in each case a single product which could in principle be formulated to be either the 5*H*-thiazolo[3,2-*a*]pyrimidine structure 3 or the isomeric 7*H*-thiazolo[3,2-*a*]pyrimidine structure 4 (Scheme 1).



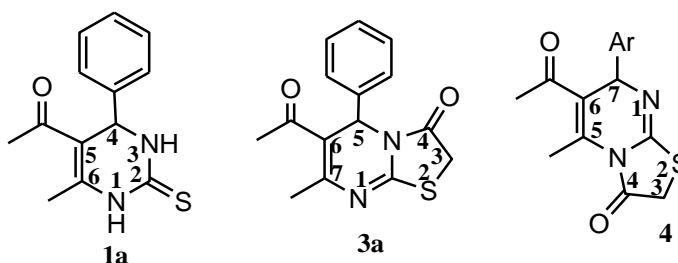
Scheme 1: Synthetic pathway for thiazolopyrimidines from DHPMs

Reagents and conditions: (i) *H*-Val][HSO₄], 120°C; (ii) BrCH₂COOEt, acetone, reflux

All the synthesized compounds were obtained from moderate to high yields. Products were purified and characterized by various spectroscopic techniques.

3.2. General spectral analysis

The IR spectra of compounds (**3a-h**) showing the complete absence of NH absorption band which is characteristic for the precursors (**1a-h**) and the appearance of another band at about ν 1762 cm^{-1} which is due to the C=O of the thiazolopyrimidine ring. The $^1\text{H-NMR}$ spectral data for compound **1a** (Ar = PhCHO) and the corresponding thiazolopyrimidine showed, in addition to the acetyl and aromatic proton signals, the appearance of the CH_3 proton signal of the obtained product in the same position as that for the CH_3 proton signal in **1a** (δ = 2.30 and 2.31 ppm respectively) and also the downfield shift for the pyrimidine H-5 in the obtained product (δ = 5.56 ppm) compared with the pyrimidine H-4 in **1a** (δ = 5.27 ppm), these indicate that the moiety around H-5 in the thiazolopyrimidine product differs from that around H-4 in **1a**. Also, the moiety around CH_3 at C-7 in the obtained product is almost similar to that around CH_3 at C-6 in **1a**. Consequently, structure **3a** could be tentatively assigned for the reaction product and this is in agreement with literature indicating that the acylation of Biginelli compounds takes place at N-3 when treated with appropriate reagents [14]. Structure **4** would be expected to show different δ values for the CH_3 groups in **4a** and **1a**, and similar δ values for H-7 in **4** and H-4 in **1a**.



Furthermore, the structure of the obtained compound was strictly proved by X-ray diffraction analysis, whose data unambiguously agree with the structure (3a) (Figure 1).

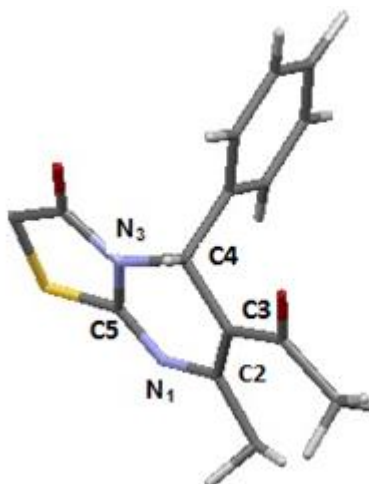
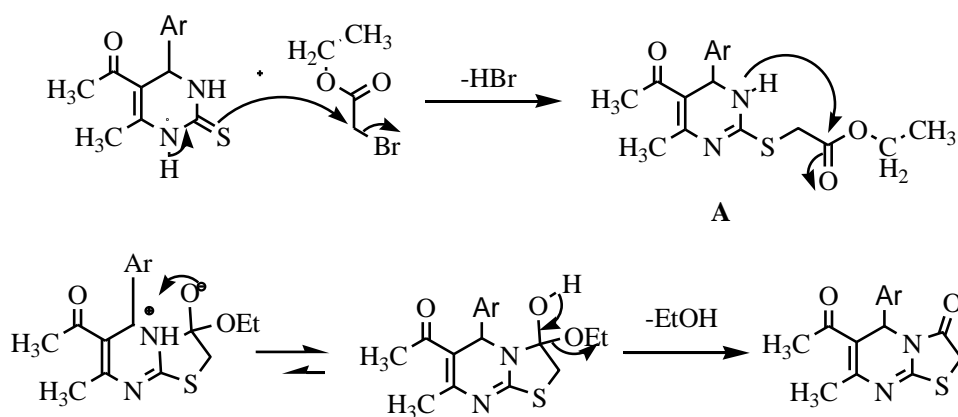


Figure 1: The structure of 6-Acetyl-7-methyl-5-phenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one 3a

3.3. Proposed reaction mechanism

The first step is a condensation between dihydropyrimidinethione and ethyl bromoacetate which led to the formation of intermediate **A**. The nucleophilic attack of the NH group on the carbon of the ester group gives the desired product after departure of ethanol (Scheme 2).



Scheme 2: Proposed mechanism of thiazolopyrimidine synthesis

Conclusion

In conclusion, we have developed a new, soft, eco-compatible, efficient and easy-to-use synthesis route of thiazolpyrimidine derivatives. In addition to the previously mentioned biological and medicinal activities, from the chemical point of view, in recent years, the interest for these compounds is growing because they have an active methylene that makes them good nucleophiles in organic synthesis. Thus, these compounds will serve us as starting synthons for the synthesis of heterocyclic products of significant physiology.

Conflict Of Interest

The authors have no conflict of interest.

Acknowledgements

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