The Pharmaceutical and Chemical Journal, 2022, 9(1):5-10

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Synthesis of New Thiazolopyrimidines and 2-Alkylthiopyrimidines Derivatives

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Received 05/01/2022, Accepted 24/01/2022, Published 31/01/2022

Abstract In this work, we reported the synthesis of derivative's 2-thiopyrimidine substituted on the positions -1 and -2 by the alkyl groups. The bicyclic scaffold (**6a** and **6b**) were obtained via condensation of 2-thiopyrimidines (**4a** and **4b**) with dihalogenated ethane **5** in the presence of potassium carbonate**.** We got the 2-thioalkylpyrimidine derivatives (**8a-f**) with the same workup, condensing halogenated alkyls **7** with 2-thiopyrimidines (**4a** and **4b**). All the structures of the synthesized compounds were confirmed by Nuclear Magnetic Resonance (NMR ^{1}H and ^{13}C) and High-Resolution Mass Spectrometry (HRMS).

Keywords 2-thiopyrimidine, 2-thioalkylpyrimidine, halogenated alkyls, potassium carbonate

Introduction

Thiazolopyrimidine is a heterocyclic scaffold originated from contiguous pyrimidine and thiazole cores. Several pyrimidine derivatives fused to heterocycles exhibited a wide range of biological activities [1-3]. According to the literature, among many others activities, the pyrimidine derivatives showed antibacterial [4], anti-inflammatory [5], anti-tuberculosis [6], anticancer [7-8], antihypertensive [9], antiviral [10-11], antimicrobial [12], anthelmintic [13], calcium channel antagonists [14-16], anticonvulsants [17], antimalarials [18], anti-HIV [19-20], antitumor [21-22] and antiepileptics [24] activities. About thiazolopyrimidine ring, they have been shown to possess very good biological activities [25-31]. The most common examples of commercialized drugs with thiazolopyrimidine as active substance are ritanserine and setoperone [32]. Recent work has shown that when 2-thiopyrimidine derivatives are coupled with halogenated derivatives such as benzyl chloride, this improves antibacterial activity [33]. Inspiring by this founding, we report in this framework a new method of synthesis of thiazolopyrimidines and 2-thioalkylpyrimidines.

Materials and Methods

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75MHz or 400 and 101 MHz or 600 and 151MHz, respectively, in $CDCl_3$, DMSO and Acetone solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singulet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of

doublet), t (triplet), q (quartet), m (multiplet) and further qualified as app (apparent), br (broad) coupling constants, *J* are reported in Hz. HRMS were mesured in the electrospray (ESI) mode on a LC-MSD TOF mass analyser

Method of synthesis of compounds 4a and 4b

In a round bottom flask, thiourea (12.5 mmol), benzaldehyde (13 mmol) and ethyl acetoacetate (19 mmol) were dissolved in 10 mL on anhydrous ethanol. Then 10 drops of concentrated HCl (37%) were added and the mixture was stirred under reflux. At the end of the reaction, ice water was added until a white precipitate was obtained. The precipitate was then filtered and washed with cold ethanol. The crystals obtained were purified by recrystallization in ethanol.

General procedure for the synthesis of compounds (6a-b) and (8a-8f)

2-thiopyrimidine derivatives **4a** and **4b** (1mmol) were dissolved in 10 mL of dimethylformamide (DMF), then 1.5 eq. of potassium carbonate (K_2CO_3, 1.5 mmol) were also added to the solution. The reaction was allowed to stay under magnetic agitation at room temperature and then 1.5 eq of alkyl chloride or bromide (1.3 mmol) were dropwise added. At the end of the reaction, the mixture was neutralized by a dilute solution of HCl (2M). The precipitate formed was filtered, dried and then purified by silica gel chromatography. Compounds (**6a-b**) were obtained with yields 50 % and 66 % respectively and (**8a–f**) with yields range between 50 % to 79 %.

Ethyl 5-methyl-7-phenyl-2,3-dihydro-7H-thiazolo]pyrimidine-6-carboxylate 6a

Yield= 50%, ^{1} H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34-7.25 (m, 5H, H_{Ar}), 5.38 (s, 1H, CH), 4.06-3.95 (m, 2H, CH_2-O), 3.60-3.55 (m, 1H, CH_2), 3,45-3.35 (m, 1H, CH_2), 3.26-3.14 (m, 1H, CH_2), 3.10-3.02 (m, 1H, CH_2), 2.35 (s, 3H, CH_3), 1.11 (td, *J* = 7.1, 1.5 Hz, 3H, CH_3). **^{13} C NMR (75 MHz, $CDCl_3$)** δ (ppm):166.66, 156.16, 144.95, 141.46, 128.64, 128.31, 127.59, 127.03, 127.00, 103.18, 59.83, 59.67, 51.41, 25.82, 23.10, 14,14. **HRMS(ESI):** Calc for $C_{16}H_{19}N_2O_2S$ $(M+H)^+$: 303.1321, Found 303.1324.

Ethyl 5-methyl-7-(p-tolyl)-2,3-dihydro-7H-thiazolopyrimidine-6-carboxylate 6b

Yield= 66%, ^{1} H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.25-7.20 (m, 2H, H_{Ar}), 7.13 (d, *J = 7,9* Hz, 2H, H_{Ar}), 5.39 (s, 1H, CH), 4.11-3.98 (m, 2H, CH_2), 3.64-3.59 (m, 1H, CH_2), 3.48-3.37 (m, 1H, CH_2), 3.30-3.19 (m, 1H, CH_2), 3.10-3.03 (m, 1H, CH_{2a}), 2.40 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.17 (t, *J = 7.1 Hz*, 3H, CH_3). **^{13} C NMR (101 MHz, $CDCl_3$)** δ (ppm): 166.75, 154.89, 138.45, 138.23, 129.38, 129.05, 127.56, 126.94, 103.43, 59.81, 59.59, 51.42, 25.92, 22.99, 21.17, 14.18. **HRMS(ESI):** Calc for $C_{17}H_{21}N_2O_2S$ $(M+H)^+$: 317.1536 , Found 317.1539.

Ethyl 2-(ethylthio)-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate 8a

Yield= 50%, m.p.= 223°C, ^{1} H NMR (300 MHz, $CDCl_3$) δ (ppm):7.39-7.21 (m, 5H, H_{Ar}), 5.66 (s, 1H, CH), 4.12 (q, *J = 7.1 Hz*, 2H, CH_2-O), 3.14 (dq, *J= 14.5, 7.3 Hz*, 1H, -S-CH_2), 3.03-2.89 (m, 1H, -S-CH_2), 2.36 (s, 3H, CH_3), 1.28 (t, *J = 7,4 Hz*, 3H, CH_3), 1.22 (dd, *J = 9.4, 4.8 Hz*, 3H, CH_3). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm): 166.84, 144.68, 128.35, 126.91, 59.81, 25.50, 14.78, 14.25. **HRMS(ESI):** Calc for $C_{16}H_{21}N_2O_2S$ $(M+H)^+$: 305.1635 , Found : 305.1636

Ethyl 2-(ethylthio)-6-methyl-4-(p-tolyl)-1,4-dihydropyrimidine-5-carboxylate 8b

Yield= 65%, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J = 8.1 Hz*, 2H, HAr), 7.08 (d, *J = 7.9 Hz*, 2H, HAr), 5.60 (s, 1H, CH), 4.14-4.05 (m, 2H, CH_2-O), 3.15-3.03 (m, 1H, -S-CH_2), 2.94-2.88 (m, 1H, -S-CH_2), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.24 (t, *J = 6.4 Hz*, 3H, CH_3), 1.20 (dd, *J = 7.8, 4.4 Hz*, 3H, CH_3). **^{13} C NMR (101 MHz, $CDCl_3$)** δ (ppm): 166.97, 141.90, 136.74, 129.18, 128.97, 128.30, 126.82, 59.76, 25.36, 14.71, 14.25. **HRMS(ESI):** Calc for $C_{17}H_{23}N_2O_2S$ $(M+H)^+$: 319.2241 , Found: 319.2244.

Ethyl 6-methyl-2-(methylthio) -4-phenyl-1,4-dihydropyrimidine-5-carboxylate 8c

Yield= 57%, ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.30-7.03 (m, 5H, H_{Ar}), 5.60 (s, 1H, CH-), 4.13 (q, *J = 7,1 Hz*, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 1.23 (t, *J = 7,1 Hz*, 3H, CH_3).**^{13} C NMR (151 MHz, $CDCl_3$)** δ (ppm): 166.90, 141.80, 137.00, 134.33, 129.23, 129.07, 128.93, 126.91, 59.83, 35.15, 21.16, 14.28. **HRMS(ESI):** Calc for: $C_{15}H_{19}N_2O_2S$ $(M+H)^+$: 291.0921, Found: 291.0924.

Ethyl 6-methyl-2-(methylthio)-4-(p-tolyl)-1,4-dihydropyrimidine-5-carboxylate 8d

Yield= 70%, ^{1} H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.23 (d, *J = 8.1 Hz*, 2H, H_{Ar}), 7.12 (d, *J = 7.9 Hz*, 2H, H_{Ar}), 5.21 (s, 1H, CH), 4.10 (q, *J = 7.1 Hz*, 2H, CH_2), 3.01 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 1.23 (t, *J = 7.1 Hz*, 3H, CH_3). **^{13} C NMR (151 MHz, $CDCl_3$)** δ (ppm): 167.07, 162.72, 154.26, 139.12, 137.84, 129.14, 127.12, 104.06, 63.36, 59.60, 36.48, 21.15, 14.23. **HRMS(ESI):** Calc for: $C_{16}H_{21}N_2O_2S$ $(M+H)^+$: 305.1783, Found: 305.1788

Ethyl 6-methyl-2-(butylthio) -4-phenyl-1,4-dihydropyrimidine-5-carboxylate 8e

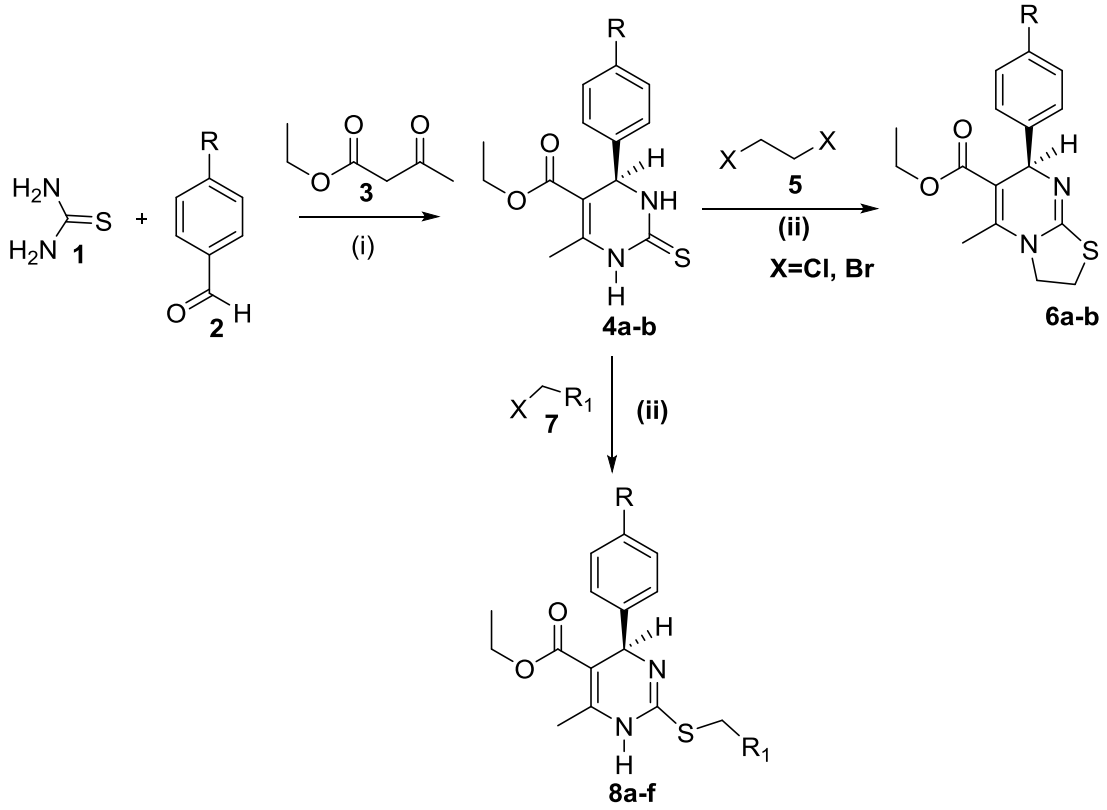
Yield= 79%, ^{1} H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44-7.16 (m, 5H, H_{Ar}), 5.58 (s, 1H, CH), 4.10 (q, *J* = 7.1 Hz, 2H, CH_2-O), 3.09 (d, *J* = 5.9 Hz, 1H, CH_2), 2.98-2.83 (m, 1H, CH_2), 2.28(s, 3H, CH_3), 1.63-1.47 (m, 2H, CH_2), 1.42-1.27 (m, 2H, CH_2), 1.20 (t, *J* = 7,1 Hz, 3H, CH_3), 0.87 (t, *J* = 7.3 Hz, 3H, CH_3). **^{13} C NMR (75 MHz, $CDCl_3$)** δ (ppm): 167.03, 144.98, 128.27, 126.94, 60.06, 31.52, 30.72, 21.83, 14.26, 13.62. **HRMS(ESI):** Calc for: $C_{18}H_{24}NaN_2O_2S$ $(M+Na)^+$: 335. 1983, Found: 335.1988.

Ethyl 2-(butylthio)-6-methyl-4-(p-tolyl)-1,4-dihydropyrimidine-5-carboxylate 8f

Yield= 72%, ^{1}H NMR (300 MHz, $CDCl_3$). δ(ppm): 7.68-7.61 (m, 2H, H_{Ar}), 7.50-7.41 (m, 2H, H_{Ar}), 5.31 (s, 1H, CH), 4.22-4.11 (m, 2H, CH_2-O), 3.23 (dd, *J = 9.7, 4.9 Hz*, 2H, CH_2), 2.57 (s, 6H, 2 CH_3), 1.83-1.66 (m, 2H, CH_2), 1.57-1.42 (m, 2H, CH_2), 1.08-1.01 (m, 3H, CH_3), 0.96 (t, *J* = 7.3 Hz, 3H, CH_3) **^{13} C NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.43, 168.16, 165.50, 163.57, 137.83, 128.42, 128.32, 103.61, 61.67, 31.38, 30.66, 22.64, 21.99, 13.70, 13.61.**HRMS(ESI) :** Calc for : $C_{19}H_{27}N_2O_2S$ $(M+H)^+$: 347.2139 , Found : 347.2145.

Results and Discussion

The aromatic aldehydes derivatives, thiourea and ethyl acetoacetate were condensed under reflux in ethanol with addition of few drops of hydrochloric acid according to the classical Biginelli method [34] resulting to the derivatives of ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a** and **4b**) (Scheme 1).



Scheme 1: Synthesis of compounds **6a**, **6b** and **8a-f**. Reagents and operating conditions: (i): $ZnCl_2$, HCl/ ethanol (reflux), (ii): K_2CO_3/DMF.

Using the method of Hanna I. Severina et *al*. [35], we were able to condense compounds (**4a** and **4b**) with 1,2-dichloroethane in the presence of sodium carbonate during 24 hours to lead to thiazolopyrimidines (**6a** and **6b**). When 1,2-dibromoethane was used under the same conditions, the reaction led to the bicyclic compounds (**6a** and **6b**) after eight hours of reaction. The gap time between both reactions could be explained by the fact that bromine is a better leaving group than chlorine. The structures of compounds **6a** and **6b** were confirmed by NMR ^1H, ^{13}C and HRMS. The NMR ^1H spectra show between 3 and 4 ppm, four multiplets, correspondig to one proton each one and attributed to the two methyl groups in coupmpounds **6a** and **6b**. 2-thioalkylpyrimidine derivatives (**8a-f**) were also synthesized by reaction between deuce derivatives of 2-thiopyrimidine (**4a** and **4b**) and alkyl halides using the the same Severina et *al.* [35] method's. Again NMR ^1H spectra confirmed the obtained compound **8a** by the appearance of two signals that appear as multiplets. One of them between 3.10-3.16 ppm corresponding to a hydrogen of the SCH_2 group and the other one between 2.89-3.04 ppm attributed to the second hydrogen of this methylene group. For compound **8b**, the two S-CH_2 hydrogens appear in two multiplets. One between 3.12-3.19 ppm corresponding to one hydrogen and the second one between 2.79-3.10 ppm. The appearance of these protons in two multiplets is due to the fact that they are magnetically different because of the tetrahedral geometry of the carbon sp3 bound to the sulfur atom. Analysis of the carbon spectra of both compounds **8a** and **8b** confirm the presence of methylenic carbons (SCH_2) which appear at around 26 ppm. The formation of **8c** and **8d** were also confirmed via NMR ^1H spectra by the presence of the three thiomethyl protons (S-CH_3) signal which appear as singlet around 3.01 ppm for both compounds. While the ^{13}C NMR spectra indicate the presence of a 14.23 ppm signal due to S-CH_3 carbon. Compound **8e** was confirmed by the presence of two multiplets between 2.90-3.09 ppm in NMR ^1H spectrum, corresponding to both protons of the methylene bound to sulfur atom (S-CH_2). Finally, the formation of compound **8f** was confirmed by the presence of doublet split around 3.23 ppm due to the two protons of group S-CH_2. For compounds **8e** and **8f**, the ^{13}C spectra indicate the presence of a signal around 31 ppm corresponding to methylenic carbon (-CH_2-S).

Conclusion

This work resulted in the synthesis of two (02) novel ethyl 5-methyl-7-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives (**6a** and **6b**) with yields 72 and 79 % respectively. Also, six (06) novel 2-alkylthiopyrimidine derivatives (**8a-f**). All structures of the synthesized compounds were confirmed by NMR spectroscopic analyses and high-resolution mass spectrometry. The study opens an avenue for biological activities and quantitative structure activities of these compounds to obtain lead structure for drugs development.

Acknowledgement

We wish to thank the laboratory (Laboratoire de Méthodologie et Synthèse de Produits Naturels) of the University of Quebec in Montreal (Canada) and the Laboratory LG2A of Jules Verne Picardic University (France) for providing us the chemical reagents and material for the spectroscopic analyzes.

Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this paper.

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