Bulletin of Faculty of Science ,Zagazig University (BFSZU) **2022**

Bulletin of Faculty of Science, Zagazig University (BFSZU)
e-ISSN: 1110-1555
Volume-2022, Issue-2, pp-101-104
https://bfszu.journals.ekb.eg/journal
Research Paper DOI: 10.21608/bfszu.2022.134859.1129

==========

Novel Synthesis of Some Novel Pyrimidine heterocycles

Atef M. Abdel Hamid[1], Mohamed G. Assy[1], Wael Farid[1*], Mohamed H. M. Abd El-Azim[1]

[1]Department of Chemistry, Faculty of Science, Zagazig University, Zagazig 44519, Egypt
Corresponding e-mail: drwaelfarid@gmail.com

ABSTRACT **:** The utilization of thioxouracil **1** as a precursor for the synthesis of some novel functionalized and annulated azines was reported here, thus amination of compound **1** afforded diaminopyrimidine scaffold **3** which upon treatment with benzoyl isothiocyanate furnished functionalized pyrimidine **5**. Also, diazotization of **3** yielded tetrazolopyrimidine **7**. The structures of the newly synthesized compounds were confirmed by different spectral tools.

KEYWORDS: Diaminopyrimidine, Heterocyclization, Azolopyrimidine, Cycloaddition, Thioxouracil..

Date of Submission: 27-04-2022 Date of acceptance: 12-05-2022

I. INTRODUCTION

Importance of pyrimidine in the medical field as therapeutic agents is well known [1-4]; also, it is used for the synthesis of a wide variety of bioactive azines [5-8]. Fused pyrimidines are among those azines which are found to exhibit many pharmacological activities such as antimicrobial [9, 10] anti-inflammatory [11], anticancer [12], analgesic, anticonvulsant [13], antidiabetic [14], antioxidant [15], and antiviral [16] activity. In continuation of our efforts aimed to synthesize of fused azines derivatives [17, 18]; we report herein about the utilization of thiopyrimidine derivative 1 for the construction of some novel annulated pyrimidines with expected biological activity**.**

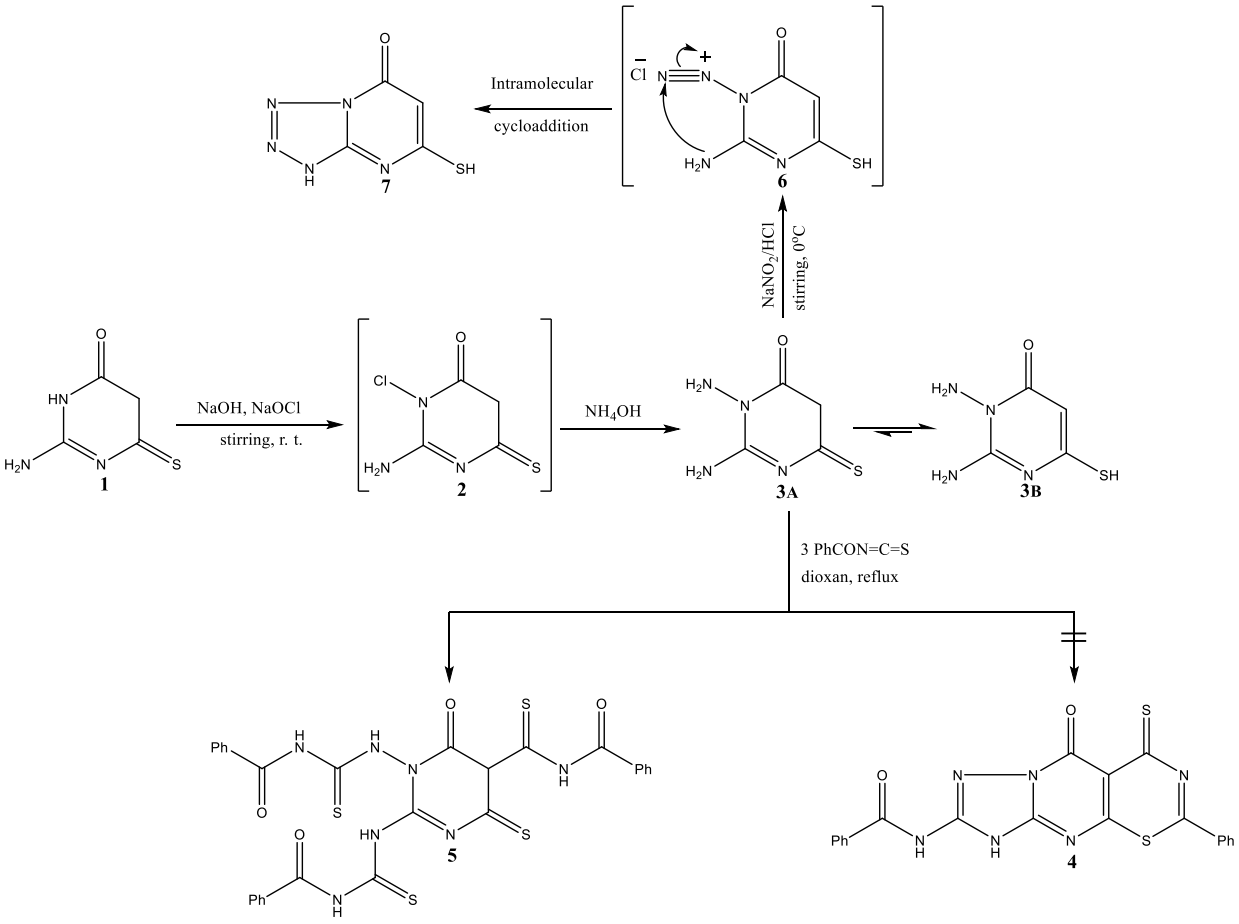
II. RESULTS AND DISCUSSION

Diaminopyrimidine **3** was obtained as a result of treatment of the target **1**[19] with oxidative mixture of NaOH/NH_4OH and NaOCl, the reaction may be proceed via the formation of non-isolable *N*-chloropyrimidine derivative **2** followed by amination. ^{1}H NMR of the target **3** clarified two NH_2 signals at 3.16 and 4.70 ppm; in addition to two singlet signals at 6.37 and 11.57 ppm for, pyrimdine-CH, and SH, respectively; also, IR spectrum of **3** showed an amide C=O absorption band at 1671 cm^{-1}.

Diaminopyrimidine **3** seemed to be suitable for further functionalization and heterocyclization; thus, reaction of compound **3** with three moles of benzoyl isothiocyanate led to formation of functionalized pyrimidine **5** via addition of active centers ($2NH_2$ and CH_2) to activated electrophilic allene carbon; and none of the expected tricyclic **4** was obtained. The target **5** produced down field D_2O exchangeable signals at 11.62, 11.45, 11.24, 9.86, and 9.57 ppm for 5 NH protons; in addition to aromatic and pyrimine-CH signals. The IR spectrum of **5** provided NH, CO, and C=S bands at 3315, 1671, and 1267 cm^{-1}.

Acid-mediated reaction of amino derivative **3** with equivalent amount of $NaNO_2$ resulted in tetrazole cyclization producing fused compound **7** through the non-isolable salt **6** followed by losing HCl via intramolecular cycloaddition.

The NH, C=O, C=N and C=S frequencies were located at 3448, 1684, 1643, and 1233 cm^{-1}, respectively. The deshielded signals for NH and pyrimidine-CH were detected at 11.22, 7.71 ppm (**Scheme 1**).



Scheme: Functionlization and annulation of the target 1

EXPERIMENTAL

Melting points were measured using an Electro thermal IA 9100 apparatus with open capillary tube and are uncorrected. The IR spectrum (KBr disc) were recorded on a PyeUnicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL-JNM-LA 300 MHz spectrometer using DMSO as a solvent. All chemical shifts were expressed on the δ (ppm) scale using TMS as an internal standard reference. Analytical data were obtained from the Microanalysis Center at Cairo University, Giza, Egypt.

2,3-Diamino-6-thioxo-5,6-dihydropyrimidin-4(3*H*)-one (3)

A mixture of compound **1** (0.01 mol), NaOCl (0.01 mol), NaOH (0.01 mol), NH_4OH (0.01 mol), in ethanol (20 ml) was stirred at room temperature for 3hrs; and the precipitate formed after acidification with HCl was collected by filtration and recrystallized from ethanol to give yellow crystals of compound **3**.

Yield 71%, mp > 300 °C. IR spectrum, υ, cm^{-1}: 3315 (NH), 1671 (C=O), 1641 (C=N). ^{1}H NMR spectrum δ, ppm: 3.16 (s, 2H, NH_2), 4.70 (s, 2H, NH_2), 6.37 s (1H, pyrimidine-CH), 11.57 s (1H, SH). Mass spectrum, *m/z*: 158.03 (M^+, 100.0%), 159.03 (M^++1, 4.3%), 160.02 (M^++2,4.5%). Found, %: C 30.35; H 3.80; N 35.41. $C_4H_6N_4OS$. Calculated, %: C 30.37; H 3.82; N 35.42.

_N,N'_-({[5-(benzoylcarbamothioyl)-6-oxo-4-thioxo-5,6-dihydropyrimidine-1,2(4*H*)-diyl]bis(azanediyl)} bis(carbonothioyl))dibenzamide (5)

A solution of compound **3** (0.01 mol) and benzoyl isothiocyanate (0.035 mol) in dioxane (20 ml) was heated under reflux for 6 hrs and the precipitate obtained after cooling was collected by filtration and recrystallized from methanol to give yellow crystals of compound **5**.

Yield 69%, mp 245 ºC. IR spectrum, υ, cm^{-1}: 3315 (NH), 1671 (C=O), 1641 (C=N), 1267 (C=S). ^{1}H NMR spectrum δ, ppm: 6.38 s (1H, Pyrimidine-CH), 7.45-7.94 m (15H, Ar-H), 9.57 s (1H, exchangeable with D_2O, NH) , 9.86 s (1H, exchangeable with D_2O,NH), 11.24 s (1H, exchangeable with D_2O, NH), 11.52 s (1H, exchangeable with D_2O, NH) 11.62 s (1H, exchangeable with D_2O, NH). Mass spectrum, *m/z*: 616.10 (M^+, 100.0%), 617.11 (M^++1, 31.4%), 618.10 (M^++2, 13.6%). Found, %:C 56.46; H 3.90; N 13.61. $C_{29}H_{24}N6O_4S_3$. Calculated, %:C 56.48; H 3.92; N 13.63.

5-Thioxo-5,6-dihydrotetrazolo[1,5-a]pyrimidin-7(1*H*)-one (7)

A mixture of compound **3** (0.01 mol), $NaNO_2$ (0.01 mol) and HCl (3 ml) in H_2O (20 ml) was stirred for 5 hrs, and the obtained solid was filtered and recrystallized from ethanol to give yellow crystals of compound **7**.

Yield 71%, mp 312ºC. IR spectrum, υ, cm^{-1}: 3448 (NH), 1684 (C=O), 1643 (C=N), 1233 (C=S). ^{1}H NMR spectrum δ, ppm: 7.71 s (1H, Pyrimidine-CH), 11.22 s (1H, exchangeable with D_2O, NH), 12.51 s (1H, exchangeable with D_2O, SH). Found, %: C 56.46; H 3.90; N 13.47. $C_4H_3N_5OS$. Calculated, %: C 56.48; H 3.92; N 13.63.

REFERENCES

1. Shehta, W., Abdel Hamid A. M., *Russ. J. Org. Chem*., 2020, vol. 56, p. 869. doi 10.1134/S1070428020050218

2. Taher, A.T. and Abou-Seri, S.M., *Molecules*,2012, vol. 17, p. 9868. Doi 10.3390/molecules17089868.

3. Awadallah, F.M., Piazza, G.A., Gary, B.D., Keeton, A.B. and Canzoneri, J.C., *Eur. J. Med. Chem.*, 2013, vol. 70, p. 273. Doi 10.1016/j.ejmech.2013.10.003.

4. Awad, S.M., Fathalla, O.A., Wietrzyk, J., Milczarek, M., Soliman, A.M. and Mohamed, M.S., *Res. Chem. Intermed*.,2015, vol. 41, p. 1789. Doi 10.1007/s11164-013-1312.

5. Shehta, W., Abdel Hamid A. M., *Russ. J. Gen. Chem.*, 2019, vol. 89, p. 806. doi 10.1134/S1070363219040273

6. Mohamed, M.S., Youns, M.M. and Ahmed, N.M., *Med. Chem. Res.*, 2014, vol. 23, p. 3374. doi 10.1007/s00044-014-0916-1

7. Mohamed, M.S., Youns, M.M. and Ahmed, N.M., *Eur. J. Med. Chem.*, 2013, vol. 69, p. 591. doi 10.1016/j.ejmech.2013.08.032

8. Abdel Hamid A. M., Hamed E. O., *J. Heterocyclic Chem*., 2020, 57, 2194. doi 10.1002/jhet.3939

9. Atta, K.F.M., Farahat, O.O.M., Ghobashy, S.M. and Marei, M.G., *Molecules*, 2011, vol. 16, p. 10387. doi 10.3390/molecules161210387

10. Saikia, L., Das, B., Bharali, P. and Thakur, A.J., *Tetrahedron Lett.*, 2014, vol. 55, p. 1796. doi 10.1016/j.tetlet.2014.01.128

11. Tolba, M. S., Kamal El-Dean, A. M, Ahmed, M., Hassanien, R., *J. Chin. Chem. Soc*., 2019, 66, 548. doi 10.1002/jccs.201800292

12. Abdelhamid, A.O., Gomha, S.M., Abdelriheem, N.A. and Kandeel, S.M., *Molecules*, 2016, vol. 21, p. 929. doi 10.3390/molecules21070929

13. Said, S.A., Amr, A.E., Sabry, N.M. and Abdalla, M.M., *Eur. J. Med. Chem.*, 2009, vol. 44, p. 4787. doi 10.1016/j.ejmech.2009.07.013

14. Lee, H.W., Kim, B.Y., Ahn, J.B., Kang, S.K., Lee, J.H., Shin, J.S., Ahn, S.K., Lee, S.J. and Yoon, S.S., *Eur. J. Med. Chem.*, 2005, vol. 40, p. 862. doi 10.1016/j.ejmech.2005.03.019

15. Abu-Hashem, A.A., Youssef, M.M. and Hussein, H.A.R., *J. Chin. Chem. Soc.*, 2011, vol. 58, p. 41. doi 10.1002/jccs.201190056

16. Wang, Y., Xu, F., Zhu, Y., Song, B., Luo, D., Yu, G., Chen, S., Xue, W. and Wu, J., *Bioorg. Med. Chem. Lett.*, 2018, vol. 28, p. 2979. Doi 10.1016/j.bmcl.2018.06.049

17. Abdelghani, E., Said, A.S., Assy, M.G. and Abdel Hamid, A.M., *J. Iran. Chem. Soc.*, 2015, vol. 12, p. 1809. doi 10.1007/s13738-015-0656-2

18. Abdel Hamid, A.M., Shehta, W., *Russ. J. Gen. Chem.*, 2019, vol. 89, p. 806. doi 10.1134/S1070363219040273

19. Srreenivas, B.,Akhila, M., Mohammed, B.,*Int. J.Pharm. Pharm. Sci*., 2012, vol4, p. 307.