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An expeditious synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidine

A. M. Shah[1]*, A. J. Rojivadiya[2]

[1]Pacific University, Paher, Pratapnagar Exten. Debari, Udiapur-313024 (Rajasthan)

[2]Associate Professor, M. D. Science College, Saurashtra University, Porbandar

*E-mail address: aakash_shah83@yahoo.co.in

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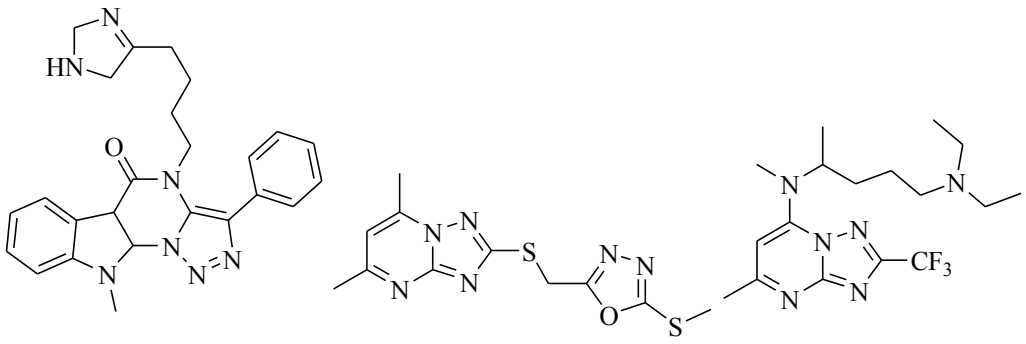
ABSTRACT: A simple, efficient, and diversity oriented synthesis of library of 1,2,4-triazolo[1,5-*a*]pyrimidine was undertaken using 5-amino,1,2,4-triazole as a building block. The synthesized analogues were fully characterized by known spectroscopic techniques like FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

1. INTRODUCTION

One-pot multi-component reactions (MCRs) have been exploited as a powerful tool for the assembly of large libraries of biologically active compounds. Among heterocycles, triazolo-pyrimidines have attracted a great deal of attention due to their therapeutic and pharmacological properties [1,2] such as antitumor potency [3, 4], inhibition of KDR kinase [5], antifungal effect [6] and macrophage activation [7]. They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion [8, 9] as well as cyclin dependent kinases 2 inhibition [10]. Some examples of published derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine with their biological activities are depicted in figure 1.



Antitumor Activity **Antifungal Activity** **Antimalarial Activity**

Thus in view of finding novel analogues of triazole[1,5-*a*]pyrimidine with potential biological activities, we set upon a synthetic program involving 5-amino,1,2,4-triazole as building block. Although different strategies have been employed for the synthesis of these compounds, [11–15] these methods suffer from drawbacks such as long reaction times, cumbersome isolation of the products and harsh reaction conditions. Herein, we report a facile and efficient multi-component synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidine in excellent yields from 3-amino-1,2,4-triazole, aldehydes and ethyl 3-oxo hexanoate respectively by simple fusion followed by adding catalytic amount of dimethylformamide (*Scheme 1*). Synthesis of fifteen novel analogues of 1,2,4-triazolo[1,5-*a*]pyrimidines containing an appropriate 1,3-bifunctional synthon has been undertaken. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, ^{1}H NMR, ^{13}C NMR and elemental analysis.

2. EXPERIMENTAL

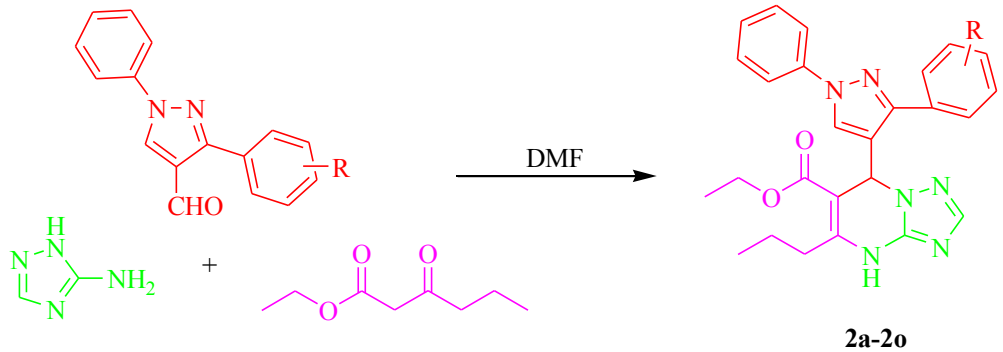
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR and ^{13}C NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

2.1 General procedure for the synthesis of 7-(aryl)-4,7-dihydro-5-propyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides

A mixture of the aminoazole (0.01 mol), ethyl 3-oxohaxenoate (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) was fused in 0.4 mL of DMF for 10-12 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products, which were crystallized from ethanol and subsequently dried in air.

2.1.1 Ethyl 7-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-propyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (2g)

Yield: 77%; mp 205-207 ºC; IR (cm^{-1}): 2958 (C-H asymmetrical stretching of CH_3 group), 2870 (C-H asymmetrical stretching of CH_3 group), 1707 (C=N stretching), 1678 (N-H deformation of pyrimidine ring), 1502, 1452 and 1411 (C=C stretching of aromatic ring), 1465 (C-H asymmetrical deformation of CH_3 group), 1363 (C-H symmetrical deformation of CH_3 group), 1332 (C-N stretching), 833 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d_6) δ ppm: 0.84-0.93 (t, 6H), 1.67-1.69 (d, 2H), 2.10 (s, 1H), 2.53-2.56 (d, 3H), 5.85 (s, 2H), 7.42-7.44 (d, 2H), 7.49 (s, 1H), 7.58-7.64 (d, 2H), 7.87-8.06 (d, 4H), 8.22-8.31 (d, 2H) 9.22-9.31 (d, 2H), 11.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ ppm : 13.19, 21.16, 30.65, 34.15, 97.53, 119.08, 119.17, 127.44, 128.74, 129.64, 130.58, 133.71, 138.71, 147.55, 150.79, 151.84, 152.03, 155.30, 155.82, 156.01, 157.72; MS: *m/z* 533; Anal. Calcd. for $C_{26}H_{25}BrN_6O_2$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.01; H, 5.22; N, 31.48%.



2a-2o

No	Comp.	R	Molecular Formula	Molecular Weight	Yield (%)
1	2a	H	$C_{26}H_{26}N_6O_2$	454.52	68%
2	2b	2-Cl	$C_{26}H_{25}N_6O_2Cl$	488.17	59%
3	2c	2-F	$C_{26}H_{25}N_6O_2F$	472.51	55%
4	2d	2-Br	$C_{26}H_{25}N_6O_2Br$	532.42	58%
5	2e	4-Cl	$C_{26}H_{25}N_6O_2Cl$	488.17	68%
6	2f	4-F	$C_{26}H_{25}N_6O_2F$	472.51	60%

7	2g	4-Br	$C_{26}H_{25}N_6O_2Br$	532.42	70%
8	2h	2-NO_2	$C_{26}H_{25}N_7O_4$	499.52	62%
9	2i	3-NO_2	$C_{26}H_{25}N_7O_4$	499.52	66%
10	2j	4-NO_2	$C_{26}H_{25}N_7O_4$	499.52	68%
11	2k	2-OH	$C_{26}H_{26}N_6O_3$	470.52	74%
12	2l	2-OCH_3	$C_{27}H_{28}N_6O_3$	484.55	81%
13	2m	4-OCH_3	$C_{27}H_{28}N_6O_3$	484.55	86%
14	2n	2-CH_3	$C_{27}H_{28}N_6O_2$	468.55	84%
15	2o	4-CH_3	$C_{27}H_{28}N_6O_2$	468.55	88%

3. RESULTS AND DISCUSSION

The reaction mechanism of this three-component condensation is probably similar to the described [16] mechanism for the "classical" Biginelli reaction (Pathway 1). The first step is a nucleophilic addition of N_2 of the aminoazole to a carbonyl carbon of aldehyde, followed by subsequent cyclization with respective 1,3-carbonyl compound to form the dihydropyrimidine ring. An alternate sequence is also possible and cannot be excluded [17] (Pathway 2), which is the initial formation of an enamine by reaction of aminoazole with respective 1,3-carbonyl followed by cyclocondensation. The third alternative involving the formation of arylidene derivatives as intermediates requires the presence of a strong base [18] and is most likely not possible for the case described herein.

4. CONCLUSION

Recently, 1,2,4-triazolo[1,5-*a*]pyrimidines have aroused increasing from the standpoint of biological activity, due to their diverse pharmacological activities. In this paper, synthesis of Fifteen novel analogues of 1,2,4-triazolo[1,5-*a*]pyrimidines containing an appropriate 1,3-bifunctional synthon has been undertaken. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, ^{1}H NMR, ^{13}C NMR and elemental analysis. In nutshell, we have reported a simple, efficient approach towards synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidines in excellent yield.

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References

[1] Syamala M., *Org. Prep. Proced. Int*. 41 (2009) 1.

[2] Syamala M., *Org. Prep. Proced. Int*. 37 (2005) 103.

[3] Fischer, G., *Adv. Heterocyclic Chem.*57 (1993) 81.

[4] Shaban, M.A.E. Morgan, A.E.A., *Adv. in Hetero. Chem*. 77 (2000) 345.

[5] Shaban, M.A.E. Morgan, A.E.A. *Adv. in Hetero. Chem.*, 73 (2000) 131.

[6] Shaban, M.A.E. Morgan, A.E.A. *Adv. in Hetero. Chem*, 75, (2000) 243.

[7] Zhang, N. Semiramis, A. K. *J. Med. Chem.*, 50 (2007) 319.

[8] Havlicek, L. Fuksova, K. Krystof, V. *Bioorg. And Med. Chem.* 13 (2005) 5399.

[9] Fraley M. E., Hoffman W. F. Rubino R. S. *Bioorg. And Med. Chem. Lett.* 12 (2002) 2767.

[10] Chen, Q. Zhu, X. L. Liu, Z. M. *Europ. J. Med. Chem.* 43 (2008) 595.

[11] Shaabani A., Farhangi E. Rahmati A., *Comb. Chem.* 9 (2006) 771.

[12] Heravi M. M., Derikvand F. Ranjbar L., *Synth. Commun.*, 40 (2010) 677.

[13] Lipson V. V., Desenko S. M., Borodina V. V., Musatov V. I., *Russ. J. Org. Chem.* 41 (2005) 114.

[14] Shankar R. B. Pews R. G., *J. Heterocycl. Chem.* 30 (1993) 169.

[15] Fedorova O. V., Zhidovinova M. S., Rusinov G. L., Ovchinnikova I. G., *Russ. Chem. Bull.,Int. Ed.* 52, (2003) 1768.

[16] Uryu, S., Tokuhiro, S., Murasugi, T., *Brain Research* 946 (2002) 298

[17] Fairfield, B. J.; Andrew, C.; Allan, *J. WO2004108136*, (2004).

[18] Peng, H., Kumaravel, G., Yao, G., Sha, L., Wang, J., Van Vlijmen, H., Bohnert, T., Huang, C., Vu, C. B., Ensinger, C. L., Chang, H., Engber, T. M., Whalley, E. T., Petter, R. C., *J. Med. Chem.* 47 (2004) 6218.