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# AN EFFICIENT PROTOCOL FOR THE SYNTHESIS OF 1,2,4-TRIAZOLO[1,5-*A*]PYRIMIDINES

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## ABSTRACT

An efficient protocol for the synthesis of diversified 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives was undertaken by using 5-amino,1,2,4-triazole as a building block via one-pot Biginelli synthesis. The synthesized analogues were fully characterized by known spectroscopic techniques like FT-IR, $^{1}$H NMR, $^{13}$C NMR, and mass spectroscopy.

**KEYWORDS:** An Efficient protocol, 1,2,4-triazolo[1,5-*a*]pyrimidine, 5-amino,1,2,4-triazole, Spectroscopic techniques.

## INTRODUCTION

In 1893 Pietro Biginelli reported one-pot cyclocondensation reaction of b-ketone ester with aldehydes and urea in the presence of acid and it provides the most covenant and straightforward route for the synthesis Dihydropyrimidines. However this protocol often provides poor to moderate yields (20–50%). Recently, due to the various therapeutic and pharmacological properties such as antitumor potency[1,2], inhibition of KDR kinase[3], antifungal effect[4] and macrophage activation[5], the Biginelli reaction has received renewed interest. In order to enhance the efficiency of the Biginelli reaction, various catalysts and reaction conditions have been studied and many improved procedures catalyzed by different Lewis and protic acids such as $CeCl_3$[6], $Cu(OTf)_2$[7]a, $Cu(BF_4)2$[7]b, $Mg(ClO_4)_2$[8]a, heteropoly acids[8]b, $Y(NO_3)_3$[8]c, Ziegler–Natta[8]d, $PhB(OH)_2$[9]a, propane phosphonic acid anhydride[9]b.

As part of our continued interest in the Biginelli reaction[10], Herein, we report a facile and efficient multi-component synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidine in excellent yields. The use of 3-amino-1,2,4-triazole, aldehydes and ethyl 3-oxo hexanoate in the presence of catalytic amount of dimethylformamide **(*Scheme-I*)** preserving the simplicity of Biginelli's one-pot reaction. 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.

**[Insert table I here]**

## MATERIALS AND METHODS

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.

***General procedure for the synthesis of ethyl 7-(2,6-dimethoxyphenyl)-5-propyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate***

A mixture of the 3-aminotriazole (0.01 mol), ethyl-3-oxohexanoate (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) with the addition of catalytic amount of dimethylformamide was fused on an oil bath for 20-25 min at 140ºC. 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.

**Ethyl 7-(2,6-dimethoxyphenyl)-5-propyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (1a)**

Yield: 84%; mp 119-122ºC; IR (cm$^{-1}$): 2935, 1699, 1581, 1552, 1496, 1462, 1219, 1022, 871; $^{1}$H NMR (DMSO-d$_6$) δ ppm: 0.973 (t, 3H, H$_a$), 1.031-1.066 (t, 3H), 1.615-1.633 (m, 2H), 2.88 (m, 2H), 3.624 (s, 3H), 3.656 (s, 3H), 3.917-3.930 (m, 2H) 6.459 (s, 1H), 6.708-6.716 (d, 1H), 6.782-6.811 (dd, 1H), 6.863-6.884 (d, 1H), 7.570 (s, 1H), 10.68 (s, 1H),13.143 (s, 1H); MS: m/z 373; Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.33; H, 6.59; N, 15.10%.

**Ethyl 7-phenyl-5-propyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate** (**1b**)

Yield: 72%; mp 106-108ºC; IR ($cm^{-1}$): 3030, 2922, 2874, 1695, 1604, 1551, 1511, 1485,1442, 1411, 1332, 1245, 1027, 690; $^1H$ NMR (DMSO-$d_6$) δ ppm: 0.90-0.95 (m, 6H), 1.54-1.57 (d, 2H), 2.51-2.58 (m, 2H), 3.58-3.87 (m, 2H), 5.22 (s, 1H), 6.77-6.79 (d, 1H), 7.24-7.26 (d, 2H), 7.40-7.42 (d, 2H), 10.69 (s, 1H), 13.15 (s, 1H); MS: m/z 312; Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.48; H, 6.54; N, 17.96%.

**Ethyl 7-(4-bromophenyl)-5-propyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (1g)**

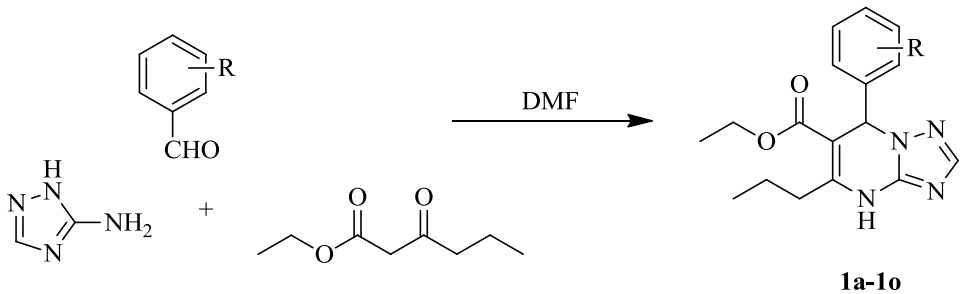
Yield: 70%; mp 117-119ºC; IR ($cm^{-1}$): 3024, 2922, 2868, 1690, 1618, 1550, 1510, 1479, 1442, 1413, 1329, 1280, 1247, 1033, 696; $^1H$ NMR (DMSO-$d_6$) δ ppm: 0.92-0.95 (m, 6H), 1.54-1.57 (d, 2H), 2.51-2.57 (m, 2H), 3.39-3.90 (m, 2H), 5.17 (s, 1H), 7.27-7.28 (d, 2H), 7.46-7.48 (d, 2H), 10.60 (s, 1H), 13.16 (s, 1H); MS: m/z 392; Anal. Calcd. for $C_{17}H_{19}BrN_4O_2$: C, 52.19; H, 4.89; N, 14.32. Found: C, 52.22; H, 4.93; N, 14.46%.

## RESULTS AND DISCUSSION

In order to develop efficient synthesis, we first examined the reaction in different solvents including acetonitrile, ethanol, dioxane, toluene and solvent-free at 100 C. The best results were obtained under solvent-free conditions. The reaction with aromatic aldehydes carrying electron-donating substituents gave the corresponding triazolopyrimidines in good yields with the use of catalytic amount of dimethylformamide.

**[Insert Scheme-I here]**

**Scheme-1**




**1a-1o**

**Table 1**

| No | Comp. | R | Molecular Formula | Molecular Weight | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1a | 2,5-$(OCH_3)_2$ | $C_{19}H_{24}N_4O_4$ | 372 | 84% |
| 2 | 1b | H | $C_{17}H_{20}N_4O_4$ | 312 | 72% |
| 3 | 1c | 2-F | $C_{26}H_{25}N_6O_2F$ | 330 | 60% |
| 4 | 1d | 2-Br | $C_{26}H_{25}N_6O_2Br$ | 390 | 66% |
| 5 | 1e | 4-Cl | $C_{26}H_{25}N_6O_2Cl$ | 346 | 68% |
| 6 | 1f | 4-F | $C_{26}H_{25}N_6O_2F$ | 330 | 65% |
| 7 | 1g | 4-Br | $C_{26}H_{25}N_6O_2Br$ | 390 | 70% |
| 8 | 1h | 2-$NO_2$ | $C_{26}H_{25}N_7O_4$ | 357 | 62% |
| 9 | 1i | 3-$NO_2$ | $C_{26}H_{25}N_7O_4$ | 357 | 66% |
| 10 | 1j | 4-$NO_2$ | $C_{26}H_{25}N_7O_4$ | 357 | 68% |
| 11 | 1k | 2-OH | $C_{26}H_{26}N_6O_3$ | 328 | 74% |
| 12 | 1l | 2-$OCH_3$ | $C_{27}H_{28}N_6O_3$ | 342 | 81% |
| 13 | 1m | 4-$OCH_3$ | $C_{27}H_{28}N_6O_3$ | 342 | 86% |
| 14 | 1n | 2-$CH_3$ | $C_{27}H_{28}N_6O_2$ | 326 | 84% |
| 15 | 1o | 4-$CH_3$ | $C_{27}H_{28}N_6O_2$ | 326 | 88% |

## CONCLUSION

In nutshell, an efficient method for the preparation of substituted triazolopyrimidine catalyzed by dimethylformamide under neutral and solvent-free conditions. Moderate to good yields of the corresponding to triazolopyrimidine were obtained from readily available starting materials.

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## CONFLICT OF INTEREST

The authors have reported no conflict of interest.

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