A Swift, Expedient and Solvent Less Synthesis of Highly Diversified 1,2,4-Triazolo [1,5-A] Pyrimidines Bearing Pyridine Scaffold

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ABSTRACT

The biological importance of 1,2,4-triazolo[1,5-a]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. A, synthesis of 1,2,4-triazolo[1,5-a]pyrimidines bearing pyridine scaffold is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetamide with aminoazoles containing a guanidine fragment. The structures of all the newly synthesized compounds (4a-t) were elucidated by various analytical techniques like FT-IR spectroscopy, mass spectrometry and ^{1}H NMR spectroscopy.

Keywords: 1,2,4-Triazolo [1,5-A] Pyrimidines, Pyridine, Biginelli, Aminoazoles, Analytical Techniques.

I. INTRODUCTION

By far the most triazolo[1,5-a]pyrimidine synthesis are condensations of dinucleophilic 5-amino-1,2,4-triazoles with 1,3-bifunctional synthons as shown in the formation of triazolo[1,5-a]pyrimidine [1-4]. New synthetic conditions recently described involve melting under microwave irradiation, a reaction that is environmental friendly and gives higher yields than conventional heating in solvent [5]. Furthermore, certain lithium 1,3-diketonates have proven to be better synthons than the corresponding diketones [6]. Previous mechanistic conclusions have been confirmed by isolating stable intermediate 5-amino-1,2,4-triazole derivatives such as enamine on reacting 5-amino-1,2,4-triazoles with 3-ketovinyl ethers [7], 3-ketoenamines [8], 3-ketoaldehydes [9], enamine-2-carboxylic esters [10] or ethoxymethylene malonates [11]. That means, the overall reaction starts with the interaction of the amino-1,2,4-triazole amino group and the enolic (or analogous) functionality of the three-carbon synthon. In the two-step examples, just mentioned, the first step proceeds under milder conditions (sometimes just in ethanol at room temperature), but the final cyclization (or the one-step reaction, if the intermediate is not trapped) requires stronger means (e.g., polyphosphoric acid or boiling acetic acid). Under extreme conditions, triazolylamide was subject to flash vacuum pyrolysis between 300 and 450 ℃ to give about 50% triazolo[1,5-a]pyrimidine [12]. Libraries of fused 3-aminopyrimidin-4-ones and other compounds were just recently prepared by the solid-phase and by the solution-phase parallel synthesis [13]. The latter method turned out to be advantageous with respect to yield and purity.

A report shows two parallel paths of pyrimidine ring annulation: the conventional method, route A and a route B using a reactive amino-1,2,4-triazole derivative [14]. Amidine, formed from 5-amino-1,2,4-triazole and DMF dimethylacetal, can be regarded as the result of incorporating one carbon of the three-carbon synthon into the 5-amino-1,2,4-triazole molecule; condensation with a reactive two-carbon component leads to target triazolo[1,5-a]pyrimidine. Path B also serves in confirming the structure of product. Similar syntheses of 7-aryl and 7-heterocyclyl triazolo[1,5-a]pyrimidines have been described [15-17], for example, that of an antipyrine derivative [18].

In recent years, 3-ketoenamines have growing interest as building blocks for 7-aryl triazolo[1,5-a]pyrimidines [19, 20]. They also serve to synthesize 7-heterocyclyl triazolo[1,5-a]pyrimidines [21, 22]. In addition to usual N, N-dimethyl compounds also analogues having a free amino group can be used as in the synthesis of 7-trifluoromethyl derivatives [23]. Enaminones can be formed in situ, for instance, from dimedone and DMF dimethylacetal [24]. In the course of the cyclization of the stable tetrafluorobenzoyl derivative fluorine at the o-position is involved in the reaction and is replaced to

give trifluorobenzo triazolo[1,5-a]pyrimidine [25]. Acetonyl is introduced as substituent into the 7-position by the use of triketone heptan-2,4,6-trione [26].

II. EXPERIMENTAL

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 was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer.
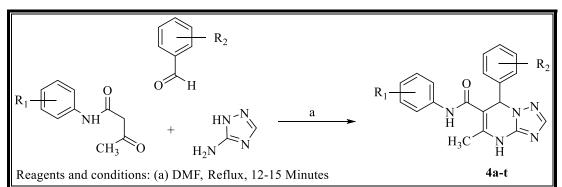
Reaction scheme

Reagents and conditions: (a) DMF, Reflux, 12-15 Minutes   **4a-t**

Table 1

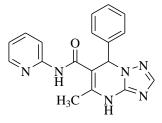| Code	R_1	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	pyridin-2-yl	H	$C_{18}H_{16}N_6O$	332	189-191	76	0.54	0.72
4b	pyridin-2-yl	4-CH$_3$	$C_{19}H_{18}N_6O$	346	179-181	74	0.53	0.69
4c	pyridin-2-yl	4-OCH3	$C_{19}H_{18}N_6O_2$	362	222-224	85	0.50	0.64
4d	pyridin-2-yl	4-Cl	$C_{18}H_{15}ClN_6O$	366	215-217	78	0.53	0.68
4e	pyridin-2-yl	4-F	$C_{18}H_{15}FN_6O$	350	261-263	66	0.50	0.66
4f	pyridin-2-yl	4-NO$_2$	$C_{18}H_{15}N_7O_3$	377	226-228	75	0.42	0.74
4g	pyridin-2-yl	3-NO$_2$	$C_{18}H_{15}N_7O_3$	377	231-233	68	0.51	0.79
4h	pyridin-2-yl	2-NO$_2$	$C_{18}H_{15}N_7O_3$	377	225-227	73	0.50	0.63
4i	pyridin-2-yl	3-Cl	$C_{18}H_{15}ClN_6O$	366	212-214	81	0.43	0.62
4j	pyridin-2-yl	2-Cl	$C_{18}H_{15}ClN_6O$	366	199-201	71	0.59	0.75
4k	pyridin-3-yl	H	$C_{18}H_{16}N_6O$	332	256-258	75	0.52	0.68
4l	pyridin-3-yl	4-CH$_3$	$C_{19}H_{18}N_6O$	346	202-204	80	0.56	0.65
4m	pyridin-3-yl	4-OCH3	$C_{19}H_{18}N_6O_2$	362	257-259	77	0.49	0.66
4n	pyridin-3-yl	4-Cl	$C_{18}H_{15}ClN_6O$	366	213-215	74	0.61	0.73
4o	pyridin-3-yl	4-F	$C_{18}H_{15}FN_6O$	350	227-229	70	0.53	0.66
4p	pyridin-3-yl	4-NO$_2$	$C_{18}H_{15}N_7O_3$	377	242-244	67	0.55	0.61
4q	pyridin-3-yl	3- NO$_2$	$C_{18}H_{15}N_7O_3$	377	203-205	77	0.53	0.75
4r	pyridin-3-yl	2-NO$_2$	$C_{18}H_{15}N_7O_3$	377	199-201	72	0.64	0.78
4s	pyridin-3-yl	3-Cl	$C_{18}H_{15}ClN_6O$	366	207-209	68	0.45	0.63
4t	pyridin-3-yl	2-Cl	$C_{18}H_{15}ClN_6O$	366	217-219	77	0.60	0.74

Synthesis of N-(aryl)-3-oxobutanamides

Synthesis of N-(aryl)-3-oxobutanamides was achieved using previously published methods [97].

General procedure for the synthesis of 4,7-dihydro-5-methyl-7-aryl-N-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides (4a-j)
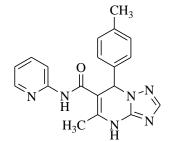
A mixture of the aminoazole (0.01 mol), 3-oxo-N-(pyridin-2-yl)butanamide (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) was refluxed in 0.4 mL of dimethyl formamide (DMF) for 12 to 15 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products 4a-j, which were crystallized from ethanol and subsequently dried in air.

4,7-dihydro-5-methyl-7-phenyl-N-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4a)

Yield: 76%; mp 189-191 ℃; MS: m/z 332.

4,7-dihydro-5-methyl-N-(pyridin-2-yl)-7-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4b)
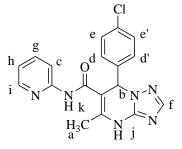

Yield: 74%; mp 179-181 ℃; MS: m/z 346.

4,7-dihydro-7-(4-methoxyphenyl)-5-methyl-N-(pyridin-2-yl)[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4c)

Yield: 85%; mp 222-224 ℃; IR (cm^{-1}): 3379 (N-H stretching of secondary amine), 3059 (C-H stretching of aromatic ring), 3012 (C-H symmetrical stretching of CH$_3$ group), 2895 (C-H asymmetrical stretching of CH$_3$ group), 1676 (C=O stretching of amide), 1645 (C=N stretching of triazole ring), 1552 (N-H deformation of pyrimidine ring), 1514 and 1458 (C=C stretching of aromatic ring), 1429 (C-H asymmetrical deformation of CH$_3$ group), 1329 (C-H symmetrical deformation of CH$_3$ group), 1301 (C-N stretching), 1145 (C-O-C asymmetrical stretching of ether linkage), 1064 (C-O-C symmetrical stretching of ether linkage), 1031 (C-H in plane deformation of aromatic ring), 840 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.30 (s, 3H, H$_a$), 3.72 (s, 3H, H$_b$), 6.55 (s, 1H, H$_c$), 6.79-6.81 (d, 2H, H$_{dd'}$, J = 8.0 Hz), 6.96-6.99 (m, 1H, H$_e$), 7.28-7.30 (d, 2H, H$_{ff'}$, J = 8.0 Hz), 7.49 (s, 1H, H$_g$), 7.58-7.63 (m, 1H, H$_h$), 7.96-7.98 (d, 1H, H$_i$, J = 8.0 Hz), 8.22-8.24 (m, 1H, H$_j$), 9.78 (s, 1H, H$_k$), 10.11 (s, 1H, H$_l$); MS: m/z 362.
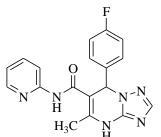
7-(4-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-2-yl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4d)

Yield: 78%; mp 215-217 ℃; IR (cm^{-1}): 3456 (N-H stretching of secondary amine), 3093 (C-H stretching of aromatic ring), 3012 (C-H symmetrical stretching of CH$_3$ group), 2922 (C-H asymmetrical stretching of CH$_3$ group), 1670 (C=O stretching of amide), 1591 (C=N stretching of triazole ring), 1573 (N-H deformation of pyrimidine ring), 1516 and 1492 (C=C stretching of
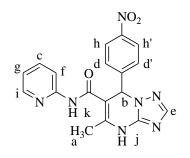
aromatic ring), 1431 (C-H asymmetrical deformation of CH$_3$ group), 1334 (C-H symmetrical deformation of CH$_3$ group), 1300 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 831 (C-H out of plane deformation of 1,4-disubstitution), 771 (C-Cl stretching); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.31 (s, 3H, H$_a$), 6.61 (s, 1H, H$_b$), 6.97-7.00 (m, 1H, H$_c$), 7.24-7.26 (d, 2H, H$_{dd'}$, J = 8.0 Hz), 7.31-7.33 (d, 2H, H$_{ee'}$, J = 8.0 Hz), 7.52 (s, 1H, H$_f$), 7.59-7.64 (m, 1H, H$_g$), 7.96-7.98 (d, 1H, H$_h$, J = 8.0 Hz), 8.24-8.25 (d, 1H, H$_i$, J = 4.0 Hz), 9.85 (s, 1H, H$_j$), 10.20 (s, 1H, H$_k$); MS: m/z 366.

7-(4-fluorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-2-yl)[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4e)
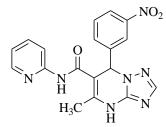

Yield: 66%; mp 261-263 ℃; MS: m/z 350..

4,7-dihydro-5-methyl-7-(4-nitrophenyl)-N-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4f)

Yield: 75%; mp 226-228 ℃; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3095 (C-H stretching of aromatic ring), 3020 (C-H symmetrical stretching of CH$_3$ group), 2916 (C-H asymmetrical stretching of CH$_3$ group), 1670 (C=O stretching of amide), 1622 (N-H deformation of pyrimidine ring), 1593 (C=N stretching of triazole ring), 1521 (C-NO$_2$ stretching), 1473 (C=C stretching of aromatic ring), 1431 (C-H asymmetrical deformation of CH$_3$ group), 1346 (C-H symmetrical deformation of CH$_3$ group), 1315 (C-N stretching), 1240 (C-H in plane deformation of aromatic ring), 823 (C-H
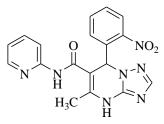
out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.31 (s, 3H, H$_a$), 6.75 (s, 1H, H$_b$), 6.97-7.00 (m, 1H, H$_c$), 7.53-7.63 (m, 4H, H$_{d-f}$), 7.90-7.97 (m, 1H, H$_g$), 8.12-8.14 (d, 2H, H$_{hh'}$, J = 8.0 Hz), 8.24-8.25 (d, 1H, H$_i$, J = 4.0 Hz), 10.10 (s, 1H, H$_j$), 10.33 (s, 1H, H$_k$); MS: m/z 377.

4,7-dihydro-5-methyl-7-(3-nitrophenyl)-N-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4g)
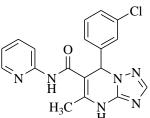

Yield: 68%; mp 231-233 ℃; MS: m/z 377.

4,7-dihydro-5-methyl-7-(2-nitrophenyl)-N-(pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4h)
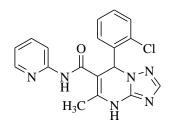

Yield: 73%; mp 225-227 ℃; MS: m/z 377.

7-(3-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-2-yl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4i)

Yield: 81%; mp 212-214 ℃; MS: m/z 366.

7-(2-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-2-yl)-[1,2,4]triazo lo[1,5-a]pyrimidine-6-carboxamide (4j)
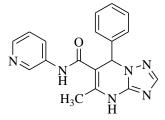
Yield: 71%; mp 199-201 ºC; MS: m/z 366.

General procedure for the synthesis of 4,7-dihydro-5-methyl-7-aryl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamides (4k-t)
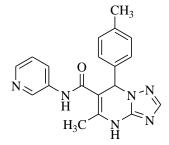
A mixture of the 5-amino-1,2,4-triazole (0.01 mol), 3-oxo-N-(pyridin-3-yl)butanamide (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) was refluxed in 0.4 mL of dimethyl formamide (DMF) for 12 to 15 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products 4k-t, which were crystallized from ethanol and subsequently dried in air.

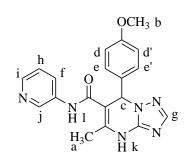## 4,7-dihydro-5-methyl-7-phenyl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4k)

Yield: 75%; mp 256-258 ºC; MS: m/z 332.

4,7-dihydro-5-methyl-N-(pyridin-3-yl)-7-p-tolyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4l)
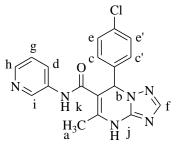

Yield: 80%; mp 202-204 ºC; MS: m/z 346.

4,7-dihydro-7-(4-methoxyphenyl)-5-methyl-N-(pyridin-3-yl)[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4m)

Yield: 77%; mp 257-259 ºC; IR (cm^{-1}): 3159 (N-H stretching of secondary amine), 3099 (C-H stretching of aromatic ring), 3041 (C-H symmetrical stretching of CH$_3$ group), 2897 (C-H asymmetrical stretching of CH$_3$ group), 1664 (C=O stretching of amide), 1593 (C=N stretching of triazole ring), 1533 (N-H deformation of pyrimidine ring), 1512 and 1481 (C=C stretching of aromatic ring), 1417 (C-H asymmetrical deformation of CH$_3$ group), 1329 (C-H symmetrical deformation of CH$_3$ group), 1284 (C-N stretching), 1149 (C-O-C asymmetrical stretching of ether linkage), 1093 (C-O-C symmetrical stretching of ether linkage), 1035 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.24 (s, 3H, H$_a$), 3.71 (s, 3H, H$_b$), 6.56 (s, 1H, H$_c$), 6.80-6.82 (d, 2H, H$_{dd'}$, J = 8.0 Hz), 7.19-7.22 (m, 3H, H$_{e-f}$), 7.52 (s, 1H, H$_g$), 7.95-7.97 (d, 1H, H$_h$, J = 8.0 Hz), 8.19-8.20 (d, 1H, H$_i$, J = 4.0 Hz), 8.68 (s, 1H, H$_j$), 9.80 (s, 1H, H$_k$), 10.17 (s, 1H, H$_l$); MS: m/z 362.

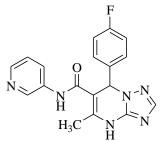## 7-(4-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4n)

Yield: 74%; mp 213-215 ºC; IR (cm^{-1}): 3103 (N-H stretching of secondary amine), 3032 (C-H stretching of aromatic ring), 3005 (C-H symmetrical stretching of CH$_3$ group), 2974 (C-H asymmetrical stretching of CH$_3$ group), 1662 (C=O stretching of amide), 1595 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1535 and 1489 (C=C stretching of
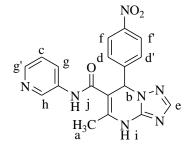
aromatic ring), 1419 (C-H asymmetrical deformation of CH$_3$ group), 1390 (C-H symmetrical deformation of CH$_3$ group), 1329 (C-N stretching), 1089 (C-H in plane deformation of aromatic ring), 837 (C-H out of plane deformation of 1,4-disubstitution), 771 (C-Cl stretching); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.23 (s, 3H, H$_a$), 6.60 (s, 1H, H$_b$), 7.21-7.27 (m, 3H, H$_{c-d}$), 7.31-7.33 (d, 2H, H$_{ee'}$, J = 8.0 Hz), 7.58 (s, 1H, H$_f$), 7.93-7.95 (d, 1H, H$_g$, J = 8.0 Hz), 8.18-8.21 (m, 1H, H$_h$), 8.66-8.67 (d, 1H, H$_i$, J = 4.0 Hz), 9.88 (s, 1H, H$_j$), 10.32 (s, 1H, H$_k$); MS: m/z 366.

7-(4-fluorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4o)
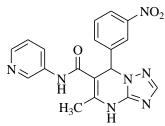

Yield: 70%; mp 227-229 ºC; MS: m/z 350.

4,7-dihydro-5-methyl-7-(4-nitrophenyl)-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4p)

Yield: 67%; mp 242-244 ºC; IR (cm^{-1}): 3205 (N-H stretching of secondary amine), 3101 (C-H stretching of aromatic ring), 3028 (C-H symmetrical stretching of CH$_3$ group), 2902 (C-H asymmetrical stretching of CH$_3$ group), 1662 (C=O stretching of amide), 1587 (C=N stretching of triazole ring), 1533 (N-H deformation of pyrimidine ring), 1518 and 1479 (C=C stretching of aromatic ring), 1423 (C-H asymmetrical deformation of CH$_3$ group), 1384 (C-H symmetrical deformation of CH$_3$ group), 1350 (C-NO$_2$ stretching), 1292 (C-N stretching), 1105 (C-H in plane deformation of aromatic ring), 831 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d$_6$) δ ppm: 2.29 (s, 3H, H$_a$), 6.77 (s, 1H,

H$_b$), 7.18-7.22 (m, 1H, H$_c$), 7.50-7.52 (d, 2H, H$_{dd'}$, J = 8.0 Hz), 7.56 (s, 1H, H$_e$), 7.95-7.97 (d, 2H, H$_{ff'}$, J = 8.0 Hz), 8.14-8.16 (d, 2H, H$_{gg'}$, J = 8.0 Hz), 8.21-8.24 (m, 1H, H$_h$), 8.67 (s, 1H, H$_i$), 9.85 (s, 1H, H$_j$); MS: m/z 377.

4,7-dihydro-5-methyl-7-(3-nitrophenyl)-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4q)
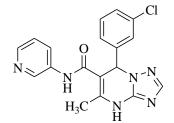

Yield: 77%; mp 203-205 ºC; MS: m/z 377.

4,7-dihydro-5-methyl-7-(2-nitrophenyl)-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4r)
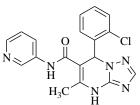

Yield: 72%; mp 199-201 ºC; MS: m/z 377.

7-(3-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4s)

Yield: 68%; mp 207-209 ºC; MS: m/z 366.

7-(2-chlorophenyl)-4,7-dihydro-5-methyl-N-(pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4t)

Yield: 77%; mp 217-219 ºC; MS: m/z 366.

III. RESULTS AND DISCUSSION

The biological importance of 1,2,4-triazolo[1,5-a]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. For example, they have demonstrated activity against malaria and bronchospasm and shown activity as coronary vasodilators, antihypertensive agents, leishmanicides, antibiotics, adenosine A_{2a} antagonists, immunosuppressants, antitumor agents, fungicides, xanthine oxidase inhibitors and phosphodiesterase inhibitors. Keeping in mind these facts, synthesis of 1,2,4-triazolo[1,5-a]pyrimidines is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with aminoazoles containing a guanidine fragment. There are literary data about the synthesis of triazolopyrimidines by treatment of 5-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and ethyl acetoacetate or cyclic β-diketones. The cyclocondensations were realized by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions or using DMF as solvent. The use of acetoacetamides in these or similar reactions has not been described.

IV. CONCLUSION

In conclusion, we have explored the diversity associated with the use of Biginelli reaction. The present paper is worthy modification of Biginelli reaction to achieve fused heterocycles bearing pyridine scaffold. There are optimum chances of biological active compound using such reaction and substitution. The acetoacetamide fragment used herein is pyridine derivative prepared from pyridine amine using known method. The execution of synthetic program offers vast opportunities to prepare diverse derivatives of 1,2,4-triazolo[1,5-a]pyrimidine derivatives.

V. REFERENCES

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