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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF [1,2,4] TRIAZOLOQUINAZOLINONE DERIVATIVES.

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ABSTRACT: We have developed a simple, eco-friendly friendly and efficient procedure for the synthesis of quinazolines via multi-component reaction of 3-amino, 1,2,4-triazole, dimedone and different aromatic aldehydes in the presence of Phthalimide-N-Sulfonic Acid as a catalyst through a one-pot reaction. The significant advantages of this protocol are mild reaction conditions, low toxicity compound, green approach, short reaction times, good yields, simple work-up.

KEYWORDS: Quinazolinones, 3-Amino1,2,4-triazole, Aromatic aldehyde, Dimedone, Phthalimide-N-Sulfonic Acid.

INTRODUCTION:

Triazolo*quinazolinone* and its derivatives are an important class of nitrogen containing heterocyclic compounds present in natural product with biological and pharmacological activities of [1,2,4] triazoloquinazolinone are antimicrobial, [i-ii] antihistaminic, [iii] anticonvulsant, [iv] antihypertensive, [v] etc. Among various reported procedures for the synthesis of 1,2,4-triazoloquinazolinone derivatives, the one pot three-component reaction of 1,3-dicarbonyls, 3-amino-1,2,4-triazole, and aromatic aldehydes has been known. Some recent examples include DABCO based ionic liquid [vi] TiO2 nanoparticles supported ionic liquids [vii] sulfonic acid functionalized SBA-15[viii] p-toluenesulfonic acid monohydrate[ix],nano-SiO2 [x] $H_4[W_{12}SiO_{40}]$ grafted on magnetic chitosan[11], Melamine@TMG [xii] anthranilic acid [xiii], sulfamic acid [xiv] molecular iodine [xv], L-Proline [xvi] 1-n-butyl- 3-methylimidazolium tetrafluoroborate ([Bmim]BF4) [xvii] 1-butyl-3-methylimidazolium bromide ([bmim]Br)[xviii] acetic acid [xix] Many of these protocols suffer from some weaknesses such as the use of expensive, non-environment reagents, dangerous catalysts, low yields, non-recyclable catalyst and long reaction times.

In this present work, we hereby report a green approach for the synthesis of 1,2,4-triazoloquinazolinones catalyzed Phthalimide-N-Sulfonic Acid as a catalyst through a one-pot

reaction. The significant advantages of this protocol are mild reaction conditions, low toxicity bismuth compound, inexpensive material, short reaction times, good yields, simple work-up.

EXPERIMENITAL:

All reactions were performed at room temperature. High speed stirring was carried out with magnetic force. All the starting materials were got from commercially accessible sources and used without further purification. Melting points were measured by open capillary technique and are uncorrected. FTIR spectra were noted on alpha T BRUKER model. ^{1}HNMR and ^{13}CNMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-500 MHz spectrophotometer using $CDCl_3$ as the solvent and TMS as an internal standard. The purity of newly synthesized compounds and the changes of reaction were observed by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminium sheets, visualized by UV light.

GENERAL PROCEDURE: A mixture of dimedone (1 mmol), aromatic aldehyde (1 mmol) and 3-Amino-1, 2, 4-triazole (1 mmol) in the presence 10 mol% PISA was heated at 90 ^{O}C under solvent free condition for appropriate time. Progress of the reaction monitored by TLC (n- hexane: ethyl acetate, 75:25) After completion of reaction, it was cooled at room temperature and added 5 ml of cold water in mixture and filtered for separation of the crude product the separated product was recrystalized with ethanol and filtrate contains PISA Catalyst are recovered.

6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro[1,2,4]-triazolo[5,1b]quinazolin-8(4H)-One 4a:M.p.=248–250 ◦C; IR (KBr): 3090, 2962, 1650, 1594, 1373, 1252, 721cm−1; 1 H NMR (DMSO-D 6 , 500 MHz): δ = 0.95(s, 3H, -CH 3), 1.03 (s, 3H, -CH 3), 2.05(d, J =16Hz, 1H,-CH 2), 2.19 (d, J = 16Hz, 1H,-CH 2), 2.52-2.59 (m, 2H,-CH 2), 6.19 (s, 1H, -CH), 7.17-7.29 (m, 5H, Ar–H) 7.68 (s, 1H, NH) 11.14 (s, 1H, NH); ^{13} C NMR (DMSO-D 6 , 125 MHz) δ 26.77, 28.45, 32.16, 49.74, 57.89, 105.55, 126.92, 127.69, 128.23, 141.55, 146.82, 150.24, 150.39, 192.96.

6,6-dimethyl-9-(4-Chlorophenyl)-5,6,7,9-tetrahydro[1,2,4]-triazolo[5,1b]quinazolin-8(4H)-one4b: M.P =303 305 ◦C; IR (KBr): 3124, 3088, 2962, 1649, 1579, 1367, 1253, 795 cm -1; 1 H NMR (DMSO-D 6 , 500 MHz): δ = 0.96 (s, 3H, -CH 3), 1.08 (s, 3H, -CH 3), 2.07(d, J = 16Hz, 1H,-CH 2), 2.27 (d, J = 16Hz, 1H,-CH 2), 2.50-2.58 (d, J =16Hz, 2H,-CH 2), 6.22 (s, 1H, -CH), 7.19–7.37 (m, 4H, Ar–H) 7.71 (s, 1H, NH) 11.19 (s, 1H, NH); 13 C NMR (DMSO-D 6 , 125MHz) δ 193.48, 151.06, 150.68, 147.29, 141.01, 132.77, 129.38, 128.76, 105.69, 57.86, 50.24, 32.69, 31.73, 28.86, 27.40.

6,6-Dimethyl-9-(4-nitro-phenyl)-5,6,7,9-tetrahydro-4H 1,2,4-triazolo [5,1- b] quinazolin-8-one 4g: M.P =307 309 ◦C; IR (KBr): 3105, 3080, 2961,1643, 1593, 1346 cm−1;1H-NMR(DMSO-d6,500MHz): δ 0.96(s, 3H). 1.05 (s, 3H), 2.07(d, J= 16Hz, 1H), 2.21 (d, J = 16Hz, 1H), 2.57 (d, J=16Hz, 1H), 2.50 (d, J = 16Hz, 1H), 6.37 (s, 1H), 7.50 (d, J = 8Hz, 2H), 7.74 (s, 1H), 8.17(d, J = 8Hz, 2H), 11.31 (s, 1H), 13 C NMR (DMSO-D 6 ,125 MHz): δ 27.45, 28.78, 32.72, 50.17, 58.01, 105.24, 124.06, 128.97, 147.33,147.43, 148.90, 150.92, 151.48, 193.52; ESI- MS: m/z 340 [M+H] +

6,6-dimethyl-9-(4-methoxyphenyl)-5,6,7,9-tetrahydro [1,2,4] triazolo[5,1b] quinazolin-8 (4H)-one 4e; M.P =242–244 ^{O}C: IR (KBr): 765, 829, 1252, 1364, 1580, 1635, 2950, 3095 cm $^{-1}$.1 H NMR (DMSO-D 6, 500) δ 0.75 (s, 3H). 0.82 (s, 3H), 2.07(d, J = 16Hz, 1H), 1.83 (d, J = 16Hz, 1H), 1.98 (d, J =16Hz, 1H), 2.28-2.37 (m, 2H), 3.47 (s, 3H), 5.93 (s, 1H), 6.60 (d, J = 8Hz, 2H), 6.87 (d, J = 8Hz, 2H), 7.45 (s, 1H), 10.87 (s, 1H), 13 C NMR (DMSO-D 6 , 125 MHz): δ 26.79, 28.49, 32.15, 49.78, 54.99, 57.30, 105.71, 113.54, 128.09, 133.82, 146.72, 150.14, 158.66, 192.94; ESI-MS: m/z 325 [M+H] +

RESULTS AND DISCUSSION:

Initially, we selected the reaction of benzaldehyde, 3-amino-1,2,4-triazole and dimedone as model reactions (Scheme 1). There was no product conversion during the experimental reaction since no reagent was used. When the reaction was carried out without the use of solvents and with a phthalimide-N-sulfonic acid (PISA) (5 Mol%) catalyst present, 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-4H- [1,2,4] triazolo[5,1-b] quinazolin-8-one derivatives were produced with a 47% yield. As we raised the temperature from room temperature to 90°C and the mole percentage of phthalimide-N-sulfonic acid (PISA) from 5 to 15 mol%, we saw the formation of 4A with a yield of 47% to 96% (Table 1, Entry 2–8).

The effects of various solvents, including EtOH, DMF, and $CHCl_3$, were examined under these ideal reaction conditions (Table 2). Without a solvent, the reaction was easier to perform and had the maximum yield at 90^OC (Table 2, entry 4).

Table1 Effect of the amounts of the PISA and temperature on the synthesis of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-4H-[1,2,4] triazolo[5,1-b] quinazolin-8-one .

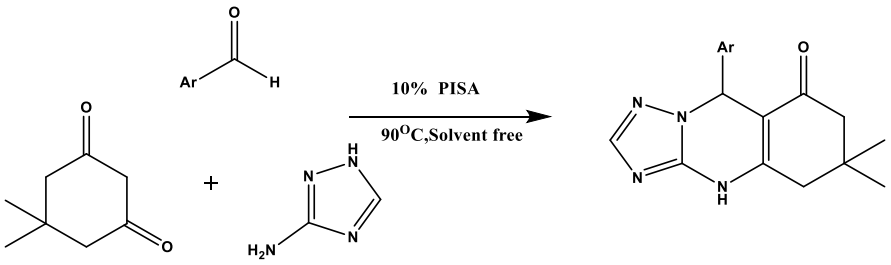
Entry	Catalyst (mol%)	Temperature (^OC)	Time(min)[b]	Yield (%) [c]
1	**-**	**90**	**90**	**Trace**
2	**5**	**90**	**90**	**47**
3	**10**	**90**	**10**	**96**
4	**15**	**90**	**10**	**95**
5	**10**	**RT**	**90**	**0**
6	**10**	**50**	**90**	**48**
7	**10**	**60**	**90**	**60**
8	**10**	**80**	**10**	**85**

[a] **Reaction conditions**: 3-Amino 1,2,4-triazole (1.0 mmol); benzaldehyde (1.0mmol) Dimedone (1.0 mmol) Solvent free at 90^OC temperature. [b] Isolated yields.

Table 2 Synthesis of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-4H- [1,2,4] triazolo[5,1-b] quinazolin-8-one in the presence of 10% PISA in different solvents

Entry	**Solvent**	**Temperature (^OC)**	**ReactionTime (Min)**	**Yield (%)[b]**
1	EtOH	80	60	70
2	DMF	90	40	55
3	$CHCl_3$	85	30	45
4	Solvent free	90	10	96

[a]Reaction conditions: 3-Amino 1,2,4-triazole (1.0 mmol); benzaldehyde (1.0mmol) Dimedone (1.0 mmol) Solvent free at 90OC temperature. b Isolated yields.



Scheme-1 synthesis of 6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-4H- [1,2,4] triazolo[5,1-b] quinazolin-8-one

Table 3 synthesis of [1,2,4] triazolo[5,1-b] quinazolin-8-one in the presence of 10% PISA

Sr.no.	Aldehyde	Product 4	Time (min)	Yield %	M.P ^{O}C
1	PhCHO	**4a**	**10**	**96**	250–252
2	4-ClC_6H_4CHO	**4b**	**8**	**96**	303–305
3	4-MeC_6H_4CHO	**4c**	**15**	**89**	262–264
4	4-HOC_6H_4CHO	**4d**	**15**	**90**	305–308
5	4-MeOC_6H_4CHO	**4e**	**18**	**92**	242–244
6	3-O_2NC_6H_4CHO	**4f**	**7**	**93**	267–269
7	4-O_2NC_6H_4CHO	**4g**	**6**	**94**	290–294
8	4-FC_6H_4CHO	**4h**	**6**	**96**	258–260

[a] **Reaction conditions**: Reaction conditions: 3-Amino 1,2,4-triazole (1.0 mmol); benzaldehyde (1.0mmol) Dimedone (1.0 mmol) and PISA (10% mol) Solvent free at 90^{O}C temperature. [b] Isolated yields.

Antibacterial Activity Screening of Compound 4b

In table 4 presents the results of the inhibition zone observed for the synthesized product against several bacteria. The strains tested included *Proteus mirabilis*, *Escherichia coli*, Bacillus subtilis, and Staphylococcus aureus. The inhibition zone ranged from 14 mm to 15 mm for *E. coli* and *S. aureus*, and from 9 mm to 19 mm for *B. subtilis* and *P. mirabilis*. Among the tested strains, the highest inhibition zone of 9 mm was obtained for compound 4b against *B. subtilis*. The compound 4b demonstrated the ability to inhibit the growth of the majority of the bacteria tested, as presented in Table 4. It exhibited the strongest inhibitory effects against *Proteus mirabilis*, with a minimum inhibitory concentration of 1.875 mg/mL, and against *Escherichia coli*, with a MIC of 3.75 mg/mL. This should be ascribed to the compound's hydrophobic nature, as hydrophobic compounds with high partition coefficients can easily diffusion. Additionally, many proteins contain hydrophobic amino acids that can interact with lipophilic molecules.

Table 4. Antibacterial activity of 6,6-dimethyl-9-(4-Chlorophenyl)-5,6,7,9-tetrahydro[1,2,4]-triazolo[5,1b] quinazolin-8(4H)-one (4**b**)

	Staphylococcus aureus		Escherichia coli		Bacillus subtilis		Proteus mirabilis	
	Antibacterial Activity (mm)	MIC (mg/Ml)	Antibacterial Activity (mm)	MIC (mg/Ml)	Antibacterial Activity (mm)	MIC (mg/Ml)	Antibacterial Activity (mm)	MIC (mg/Ml)
4b	**14**	**7.4**	**15**	**3.70**	**9**	**7.4**	**17**	**3.70**
	14	**7.4**	**14**	**3.70**	**9**	**7.4**	**17**	**1.875**
	14	**7.4**	**15**	**3.70**	**9**	**7.4**	**19**	**1.875**
Streptomycin	**24**	**1.875**	**27**	**0.92**	**24**	**1.875**	**25**	**0.92**
	24	**1.875**	**27**	**0.92**	**24**	**1.875**	**25**	**0.92**
	24	**1.875**	**27**	**0.92**	**24**	**1.875**	**25**	**0.92**
DMSO	**RS**	-	**RS**	-	**RS**	-	**RS**	-

CONCLUSION:

In summary, we have developed a novel and efficient method for the synthesis of functionalized [1,2,4] triazoloquinazolinone derivatives through the one-pot multi-components reaction in presence of Phthalimide-*N*-Sulfonic Acid (PISA) as a catalyst. This protocol offers several advantages including good to excellent yield, simple work-up

procedure, and inexpensive, environmentally friendly catalyst. These results will offer considerable applications to complex targets in organic and medicinal chemistry.

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