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One Pot Synthesis of Substituted [1,2,4]-Triazolo [1',2':1,2]pyrimido [6,5-*b*]-quinoline and Its Antibacterial Activity

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A convenient synthesis of substituted **[**1,2,4]-triazolo [1',2':1,2]pyrimido[6,5-*b*]-quinoline **4(a-i)** from substituted 2-chloroquinoline-3-carbaldehyde **1(a-i)** and *4H*-1,2,4-triazol-3-amine **2** by using SiO_2/K_2CO_3 under microwave irradiation. This method affords the [1,2,4]-Triazolo [1',2':1,2]pyrimido[6,5-*b*]-quinoline **4(a-i)** under the influence of microwave irradiation in solvent-free conditions within short span (12 - 20 min), & gaves excellent yields (89 - 95%). All the synthesized compounds were further screened for their antibacterial activities. Some of our compounds showed excellent antibacterial activities against control drugs.

Key Words: **[**1,2,4]-Triazolo [1',2':1,2]pyrimido[6,5-*b*]-quinoline, SiO_2/K_2CO_3, Microwave irradiation, Antibacterial activity

Introduction

Quinolines and their hetero-fused analogues have attracted great attention of medicinal and synthetic chemists due to their presence in natural products and physiological activities.[1,2] The hetero fused quinolines are known to bind DNA with high affinity, inhibit DNA topoisomerase II, display cytotoxic and antitumor activities.[3] Many synthetic routes have been developed for hetero-fused quinolines[4] and still continuing efforts are being made to explore new synthetic routes for this class of compounds. Quinoline-based fused heterocyclic systems are found as potential anticancer agents[5] and have antimalarial activities.[6] Quinoline derivatives form a component in a number of useful drugs and are associated with many biological pharmaceutical and therapeutical activities.[7]

On the other hand, 1,2,4-triazoles are associated with diverse pharmacological activities such as analgesic, anti-asthmatic, diuretic, antihypersensitive, anticholinergic, antibacterial, antifungal and anti-inflammatory activities.[8-11] Some fused triazole moiety with quinoline ring possess anti-inflammatory and analgesic properties.[12-14]

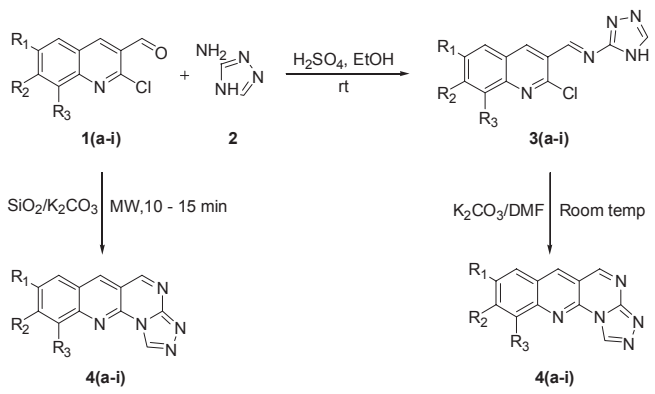
There has been a growing interest over the past few years to carry out organic reactions over heterogeneous catalysts, because of simple set ups and work-ups, lesser chemical degradation, higher product purity and chemical yields.[15] Microwave activation as a nonconventional energy source especially when coupled to dry-media conditions has become a very popular and useful technology in organic chemistry in terms of reduced reaction times, enhanced product purity and chemical yields in an environmentally friendly approach called green chemistry.[16] Dry media conditions are particularly suitable for doing away with the safety hazards usually associated with low-boiling solvents under microwave irradiation.

In the organic synthesis and reactions, increasing attention is being focused on green chemistry using environmentally benign reagents and conditions, particularly solvent-free procedures[17-19] which often lead to clean, eco-friendly and highly efficient procedures involving simplified work-ups.

In recent years, the use of solid acids as heterogeneous catalysts has received tremendous interest in different areas of organic synthesis.[20] Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used after activation or without activation, thereby making the process economically more viable. During the last few years, SiO_2/K_2CO_3 has emerged as a substitute for conventional catalysts.[21]

Results and Discussion

In continuation, of our research programme[22-23] for exploring Vilsmeier-Haack reagent aided synthesis of quinolines based fused heterocyclic system herein, we report the one pot synthesis of the [1,2,4]-triazolo [1',2':1,2]pyrimido[6,5-*b*]-quinoline and evaluating their antibacterial activity against standard drug. We became interested in the possibility of developing a



Scheme 1. Synthesis of substituted [1,2,4]-triazolo [1',2':1,2]pyrimido [6,5-*b*]-quinoline

Table 1. Optimization of solvent effect on the model reaction[a]

Entry	Catalyst	With MW[a] Yield[c] (%)	Without MW[b] Yield[c] (%)
1	No catalyst	-	-
2	H_2SO_4	22[c]	20[d]
3	$AlCl_3$	26[c]	22[d]
4	SiO_2 (acidic)	46[c]	32[d]
5	DBU	25[c]	20
6	CAN	43[c]	25[d]
7	K_2CO_3	40[c]	36[d]
8	SiO_2/CAN	65	52[d]
9	SiO_2/DBU	73	78[d]
10	SiO_2/K_2CO_3	95	63[e]

Reaction Condition – [a]Reaction of **1a** (10 mmol) with **2** (10 mmol) in presence of catalyst. [b]Reaction of **1a** (10 mmol) with **2** (10 mmol) in presence of catalyst at 70 °C. [c]imine as intermediate of **1a** (10 mmol) with **2** (10 mmol) in the presence of catalyst. [d]imine as intermediate of **1a** (10 mmol) with **2** (10 mmol) in presence of in ethanol. [e]Reaction of **1a** (10 mmol) with **2** (10 mmol) in presence of catalyst in *N*,*N*-dimethylformamide.

Table 2. Effect of microwave irradiation powers for synthesis of compounds **4a**[a]

Entry	Power	Time (min)	Yield[b] (%)
1	180	17	90
2	270	14	92
3	360	12	95
4	450	10	81
5	540	10	80

[a]Reaction of **1a** (10 mmol) with **2** (10 mmol) in solvent-free condition using SiO_2/K_2CO_3. [b]Isolated yields based upon starting aldehyde.

Table 3. Charactersation data of compounds **4(a-i)**

Sr. No.	R			Time (Min)	Yield[a] (%)	mp (°C)
	R_1	R_2	R_3			
4a	H	H	H	12	95	156-158
4b	$-CH_3$	H	H	17	92	153-154
4c	H	$-CH_3$	H	15	91	164-165
4d	H	H	$-CH_3$	16	89	127-128
4e	$-OCH_3$	H	H	14	92	145-146
4f	H	$-OCH_3$	H	12	94	172-173
4g	Et	H	H	11	90	139-140
4h	H	H	-Et	17	91	153-154
4i	H	H	-OEt	19	93	120-121

[a]Reaction of 2-chloro-3-formyl quinoline (10 mmol) with 4*H*-1,2,4-triazol-3-amine (10 mmol) in presence of catalyst under microwave irradiation. [b]Isolated yield. [c]synthesised compound characterised by spectral data.[25]

one pot analogue of the fused quinoline, in which intermediate imine was not isolated, but rather immediadetaly converted in situ to a [1,2,4]-triazolo [1',2':1,2]pyrimido[6,5-*b*]-quinoline, we anticipated that the fused quinolines molecule were firstly synthesized by the conventional method and further used non conventional method such as microwave irradiation.

The starting compound 2-chloro-3-formyl quinoline **1(a-i)**, were synthesized according to the literature method,[24] fused quinolines were obtained by the cyclisation of 2-chloro-3-formyl quinolines with 4*H*-1,2,4-triazol-3-amine **2** in presence of SiO_2/K_2CO_3 catalyst under microwave irradiation in single step in excellent yield. In conventional method the goal has been achieved by two steps, in first step substituted 2-chloro-3-formyl quinoline reacts with 4*H*-1,2,4-triazol-3-amine in presence of H_2SO_4 in ethanol at room temperature to furnished imines further cyclisation were carried out by using K_2CO_3/DMF at room temperature, this products were used as reference compounds. Consequently, we have determined that reaction carried out in the distinct steps using the conventional method but it not gave satisfactory result.

In search of an efficient reaction condition, the reaction of 2-chloroquinoline-3-carbaldehyde **1a** and 4*H*-1,2,4-triazol-3-amine **2** under the influence of microwave irradiation has been considered as model reaction. When the reaction was carried out in the absence of catalyst the desired product was not formed, even after prolonged reaction time (Table 1, entry 1). Further we have observed that when acid catalyst was used the reaction gave the imines intermediately, where as in the presence of basic catalyst the reaction did not go efficiently. Therefore, we have focused our attention on the solid support acidic alumina on the various basic catalysts such as DBU, CAN, K_2CO_3. Finally, we can conclude that (SiO_2/K_2CO_3) proves to be the best catalyst for the synthesis of anticipated product. The result without microwave irradiation low yield and time require for the competition for the reaction was high**.** In microwave, product was formed in very short time with excellent yield (95%) (Table 1, entry 10).

Further, we have also optimized the effect of different microwave irradiation powers such as 180, 270, 360, 450 and 540 W. It was observed that the irradiation at low power requires longer reaction time and elevated power gives lower yield (Table 2). So, we can conclude that irradiation at 360 W gave best results (Table 2, entry 3).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted quinoline aldehydes with 4*H*-1,2,4-triazol-3-amine. The results are shown in Table 3. The newly synthesized compounds were compared with reference compound. The compounds were found to be exactly similar in all aspects to the reference compounds.

***In vitro* antibacterial screening.** For the bioassay, the compounds were dissolved in DMSO. No antibacterial activity was noted in the solvent employed. Streptomycin and Ampicilline (Hi-media) controls were included for comparison with compounds **4(a-i)**. All samples were tested in triplicate, and average results are reported. The compounds were assayed for antibacterial activity against four registered bacterial isolates, which were obtained from the NCIM (National Collection of Industrial Microorganisms, National Chemical Laboratories, Pune-411 003, India): Two Gram positive bacterial isolates, *Bacillus subtilis* (NCIM No. 2063, ATCC No. 6633), *Staphylococcus aureus* (NCIM No. 5021, ATCC No. 25923), and two Gram negative bacteria, *Salmonella typhimurium* (NCIM No. 2501, ATCC No, 23564), *Pseudomonas aeruginosa* (NCIM No. 5029, ATCC No. 27853). The bacterial liquid cultures were prepared

Table 4. Minimal inhibitory concentrations (MIC μg/mL of tested compounds **4(a-j)**

Tested Compounds	*B. subtilis* ZI[a] (MIC)[b]	*S. aureus* ZI[a] (MIC)[b]	*S. typhi* ZI[a] (MIC)[b]	*P. aeroginosa* ZI[a] (MIC)[b]
4a	9.5 (15)	9.4 (15)	10.5 (10)	10.9 (10)
4b	11.3 (10)	11.1 (10)	9.8 (15)	9.7 (15)
4c	**14.1 (10)**	**14.2 (10)**	**14.4 (15)**	**14.3 (15)**
4d	**14.8 (10)**	**14.6 (10)**	**15.9 (15)**	**15.8 (15)**
4e	8.5 (15)	8.4 (15)	9.5 (10)	9.9 (10)
4f	10.1 (15)	10.3 (15)	9.4 (10)	9.7 (10)
4g	11.1 (15)	10.5 (15)	9.8 (10)	9.5 (10)
4h	11.9 (15)	12.5 (15)	9.2 (10)	9.1 (10)
4i	**13.6 (10)**	**14.3 (10)**	**11.7 (15)**	**11.2 (15)**
Streptomycin	15.1 (10)	14.9 (10)	16.4 (5)	16.1 (5)
Ampicilline	14.3 (10)	14.7 (10)	16.3 (5)	15.9 (5)

[a]Zone of inhibition. [b]Minimum inhibitory concentration.

in fusion broth for their activity tests. The compounds were dissolved in DMSO at concentration of 1 mgmL^{-1}. Antibacterial activity of DMSO against the test organisms was investigated, and was found to be nil. Molten nutrient agar (15 cm^3), kept at 45 ^{o}C, was then poured into the Petri dishes and allowed to solidify. Ten millimeter diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37 ^{o}C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial activity was determined by measuring the diameter of inhibition zone and examining the minimal inhibitory concentration (MIC).

The antibacterial screening results revealed that most of the newly synthesized compounds exhibited good antibacterial activities. Generally, the test compounds showed better activity against the Gram negative bacteria Table 4. Out of the compounds tested, compounds **4c**, **4d** and **4i** exhibited good antibacterial activity against the Gram negative bacteria i.e. *Salmonella typhi* and *Pseudomonus aeroginosa* and moderate activity against gram positive bacteria i.e. *Bacillus subtilis* and *Staphylococcus aureus* as compared with the broad spectrum antibiotic Streptomycin and Ampicilline.

Conclusions

Hence, we have developed the efficient and environmentally friendly one pot synthesis of the fused quinoline using SiO_2/K_2CO_3 as catalyst under microwave irradiation and solvent free condition. These methods have several advantages such as very short span, easy workup, availability of catalyst and environmentally friendly. All the synthesized compounds were further screened for their antibacterial activities. Some of our compounds showed good antibacterial activities against control drugs.

Experimental Section

Microwave oven (LG Smart Chef MS-255R operating at 2450 MHz having maximum out put power of 960 W was used for microwave irradiation. ^{1}H NMR spectra were recorded on Mercury plus Varian at 400 MHz in $CDCl_3$ as a solvent and TMS as an internal standard. IR spectra were recorded on a Perkin Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique.

Conventional method.

General method for the synthesis of *N*-((2-chloroquinoline-3-yl) methylene-4*H*-1,2,4,-triazol-3-amine (3a): An equimolar mixture of 2-chloroquinoline-3-carbaldehyde **1a** (10 mmol) and 4*H*-1,2,4-triazol-3-amine **2** (10 mmol) in 10 mL ethanol containing few drops of sulphuric acid was stirred at room temperature for 3 - 5 hr. After completion of reaction (checked by TLC), the excess of solvent was removed on rotary evaporator to yield solid which was washed with petroleum ether followed by crystallization in ethanol.

Cyclisation of *N*-((2-chloroquinoline-3-yl) methylene-4*H*-1,2,4,-triazol-3-amine (3a): To a solution of potassium bicarbonate (20 mmol) in *N*,*N*-dimethyl formamide, *N*-((2-chloroquinoline-3-yl)methylene-4*H*-1,2,4,-triazol-3-amine (10 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. After completion of reaction, the reaction mass was quenched in ice cold water, the solid product precipitates out which was collected by filtration, and dried by suction. The obtained solid thus was triturated with diethyl ether and filtered to yield a pure crystalline solid (Yield = 63%). The physical and spectral data of the compounds are presented below.

Non conventional method.

General procedure synthesis of compounds 4(a-i): A mixture of 2-chloroquinoline-3-carbaldehyde (10 mmol) and 4*H*-1,2,4-triazol-3-amine **2** (10 mmol) was adsorbed on silica gel (2 g) in a 50 mL beaker. The content was then irradiated under microwave at 360 W for 5 min. To this mixture 5 mol % of K_2CO_3 was added, stirred the content with help of glass rod and further irradiated for 12 - 20 min (Table 3). After completion of reaction, as monitored by TLC, the product was extracted by ethyl acetate (2 × 25 mL). The organic layer was washed with brine (2 × 20 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure. The obtained crude product was recrystallized from ethyl acetate.

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25. (**3a**) IR (KBr, cm^{-1}) 2980 (N-H); 1676 (C=N); 962 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 7.56 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.81 (s, 1H, Ar-H), 8.12 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.53 (td, 1H, *J* = 8.2 & 2.4 Hz, Ar-CH), 8.98 (s, 1H, Ar-H), 10.33 (s, 1H, N-H), MS *m*/*z* 258 (m+1) 260 (m+3); (**4a**) Yellow solid, IR (KBr, cm^{-1}) 1689 (C=N), 1223 (C-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 7.51 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.75 (s, 2H, Ar-H), 7.89 (d, 1H *J* = 8.8 Hz, Ar-H), 8.13 (d, 1H, Ar-CH), 8.21 (s, 1H, Ar-CH), 8.43 (s, 1H, Ar-H), MS *m*/*z* 222 (m+1); (**4b**) Yellow solid, IR (KBr, cm^{-1}) 1685 (C=N), 1221 (C-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 2.43(s, 3H, Ar-CH_3), 7.45 (d, 1H, *J* = 9.4 Hz, Ar-H), 7.65 (d, H, *J* = 8.8 Hz, Ar-H), 7.93 (d, 1H, Ar-H), 8.20 (s, 1H, Ar-CH), 8.25 (s, 1H, Ar-CH), 8.53 (s, 1H, Ar-H), MS *m*/*z* 236 (m+1); (**4e**) Yellow solid, IR (KBr, cm^{-1}) 1690 (C=N), 1229 (C-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 3.80 (s, 3H, Ar-OCH_3), 7.35 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.49 (d, H, *J* = 8.2 Hz, Ar-H), 7.98 (d, 1H, Ar-H), 8.26 (s, 1H, Ar-CH), 8.42 (s, 1H, Ar-CH), 8.65 (s, 1H, Ar-H), MS *m*/*z* 251 (m+1); (**4g**) Yellow solid IR (KBr, cm^{-1}) 1675 (C=N), 1234 (C-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 1.53 (t, 3H, -CH_3), 2.98 (q, 2H, -CH_2), 7.45 (d, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 8.35 (s, 1H, Ar-H), MS *m*/*z* 251 (m+1); (**4i**) Yellow solid, IR (KBr, cm^{-1}) 1678 (C=N), 1232 (C-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 1.41 (t, 3H, -CH_3), 3.76 (q, 2H, -CH_2), 7.43 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 8.09 (s, 1H, Ar-H), 8.34 (s, 1H, Ar-H), 8.53 (s, 1H, Ar-H), MS *m*/*z* 266 (m+1).