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SYNTHESIS OF BIOLOGICALLY ACTIVE ISOXAZOLO [5, 4-B] QUINOLINES AT ROOM TEMPERATURE

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ABSTRACT

The K_2CO_3 and DMF has been shown to be an effective and mild catalyst for synthesis of biologically active different derivatives of isoxazolo [5, 4-*b*] quinoline by the cyclization of various substituted oximes of quinoline at ambient temperature.

KEYWORDS

Isoxazolo [5, 4-b] quinoline, K_2CO_3 and Room temperature.

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INTRODUCTION

Heterocyclic compounds are widely distributed in nature. They are essential to life and play a vital role in the metabolism of living cells. These compounds have been an asset to combat various diseases, disorders and provide essential commodities for the survival of mankind. Among various known heterocyclic compounds, the quinoline derivatives signify one of the most successful classes of drugs.

In the earlier reported scheme the 2-chloroquinoline-3-carbaldehyde were prepared by the action of Vilsmeier's reagent from acetanilide in good yields. The reaction is shown to involve successive change of the acetanilide into an imidoyl chloride and then an N-(α-chlorovinyl) aniline. The

latter enamine is diformylated at its α-position and then cyclised to the 2-chloroquinoline-3-carbaldehydes[1].

Quinoline ring system[2] is an essential structural fragment of a large number of natural and synthetic compounds possessing a wide variety of pharmacological activities[3,4]. Quinoline derivatives have attracted considerable attention since they exhibit potent as antiallergic[5], antiproliferative[6], antiparasitic[7], antinflammatory, antiasthmatic, antituberculosis, antibacterial, antihypertensive, antitumor and most notably antimalarial agents[8,9].

Quinolines are employed in numerous commercial products, including pharmaceuticals, fragrances and dyes. In the recent year, the quinoline compounds were extensively considered as a new therapeutic agents that led to the development of some molecules, such as quinoline alkaloids, namely quinine, chloroquine, mepacrine, and pamaquine shown in Figure No.1 are used as efficient drugs for the treatment of malaria[10-17].

In particular the key intermediate 2-chloroquinoline-3-carbaldehyde has been used for the synthesis of variety of medicinally valuable compounds[18].

In literature survey it was revealed that the isoxazolo [5, 4-*b*] quinoline have found much more interest in various field of chemistry because it is associated with diverse pharmaceutical and agrochemical application[19].

A search of the literature revealed that, M. Kidwai *et al.*[20] have synthesized isooxazolo [5, 4-*b*]quinoline by the reaction of hydroxylamine hydrochloride with ethanolic solution of 2-chloro-3-quinoline-carboxaldehyde using acetic acid under reflux condition for 1 h, The resulting Quinoline derivatives were screened for their biological activity and found to be promising analgesic agents.

The methods employed for the synthesis of isooxazolo [5, 4-*b*] quinoline are very few. So, there is still needs to develop an efficient, mild, simple and high yield protocol for the synthesis of isooxazolo [5, 4-*b*] quinoline.

Experimental Part

Melting points were determined in open capillaries in a paraffin bath and are uncorrected. IR spectra were recorded on a Bruker spectrophotometer using KBr discs, and the absorption bands are expressed in cm^{-1}.

All the synthesized compounds were confirmed by their spectral data after comparisons with authentic samples (MS, NMR, and IR spectra) and melting point.

This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. The developed methodology is simple and a good contribution in the field of chemistry.

Spectral Data for representative compounds:

Isoxazolo [5, 4-*b*] quinoline (7): 1622 (C = N str.), 1600, 1576, 1462 (Ar-C = C); ^{1}H NMR (Acetone-d_6): 7.7-8.27 (m, 3H, Ar-H), 8.55 (s, 1H, 3-H);

4-methylisoxazolo[5, 4-*b*]quinoline (8): 1640 (C = N str.), 1585, 1560, 1474 (Ar-C = C str.); ^{1}H NMR (Acetone-d_6): 2.44 (s, 3H, CH_3), 7.42-8.1 (m, 4H, At-H), 8.57 (s, 1H, 3-H).

General procedure

Synthesis of compounds 3(a-h)

In a round bottom flask place a mixture of an ethanolic solution of 2-chloroquinoline-3-carbaldehyde (1mmol), hydroxyl amine hydrochloride (1.5mmol), and sodium acetate (1.5mmol). This mixture was stirred at room temperature for the precised time. The reaction was monitored by TLC. After completion of reaction 20 ml ice cold water was added to the reaction mixture and product was extracted by chloroform (2 × 25 ml). The chloroform was distilled out on rota-evaporator under reduced pressure to afford the pure products. The compound formed was then stirred with DMF and K_2CO_3 which on cyclization gives the corresponding products 3(a-h). All the synthesized compounds were characterized by spectral data and compared (MS, NMR, and IR) with authentic sample.

RESULTS AND DISCUSSION

In continuation of our research work on the development of novel synthetic methodologies[21] herein, we have developed methodology for the synthesis of isooxazolo [5, 4-*b*] quinoline using K_2CO_3 which makes use of mild catalyst in dimethyl formaldehyde.

Firstly, we have carried out the reaction of 2-chloro-3-quinoline-carboxaldehyde with hydroxyl amine hydrochloride in presence of sodium acetate stirred at room temperature for 4-10 min. to give the product 2 (Scheme No.1).

Here we have observed that the oxime group was produced very smoothly with hydroxyl amine hydrochloride and sodium acetate at room temperature, the results are shown in (Table No.1).

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of Cs_2CO_3, KOH, DBU under stirring condition it gave lower yield of product. However, when the same reaction was conducted using potassium carbonate as a catalyst it gave excellent yields of product in short reaction time (Table No.2, entry 4).

After optimizing the conditions, the generality of this method was examined by the reaction of various oximes of quinoline using K_2CO_3 and DMF gave the corresponding product Table No.3 (a-h).

Anti-microbiological Assay of the Compounds

In literature, the antimicrobial activity of pyrazoles, chromones, pyrazolines, chalcones, Schiff bases, β-lactams, thiazolidinone etc. have shown that many of them are useful as bactericides and fungicides against various gram positive and gram negative bacteria and fungi[22-24].

Some of the synthesized compounds were screened for in vitro antibacterial activities against gram +ve and gram –ve bacteria. In gram +ve bacteria, Staphylococcus aureus (S. aureus) and Bacillus subtilis (B. subtilis) were used and in gram –ve Escherichia coli (E. coli) and Salmonella typhi (S. typhi) were used against standard Tetracyclin and Ampicillin.

The antibacterial activities were carried out on nutrient agar with following composition and by standard procedure of paper disc method[25].

1. Peptone: 5 gm
2. Beef extract: 3 gm
3. Sodium chloride: 8 gm
4. Agar-agar powder: 15 gm
5. Distilled water: 1000 mL

Petri dishes and necessary glasswares were sterilized in hot air oven (190^{o}C, 45min). The nutrient agar and saline (0.82% NaCl) were sterilized in autoclave (121 °C, 15psi, 20 min). inoculum was prepared in sterile saline and optical density of all pathogens was adjusted to 0.10 at 625nm on Chemito Spectrscan UV 2600 Spectrophotometer which is equivalent to 0.5 McFarland standards. The nutrient agar plates were prepared by pour plate method[26]. The sensitivity of the compounds was tested by disc diffusion method (paper disc method). All the bacterial cells were cultured in nutrient plates and the compounds to be tested were dissolved in DMSO solvent and were soaked on paper disc. The discs were placed into the plates and incubated at 37 °C for 24 h. The diameter in mm of zone of inhibition around each disc was measured by scale and results were recorded in Table No.4.

Table No.1: Synthesis of various oximes of quinoline from 2-chloro-3-quinoline-carboxaldehyde

Entry	R	Time (min)	Yield[a] (%)	M.P. (°C)
2a	H	10	86	160-162
2b	6-CH_3	8	75	171-173
2c	7-CH_3	4	90	156-158
2d	8-CH_3	8	82	164-167
2e	6-OCH_3	10	80	195-197
2f	7-OCH_3	10	79	196-198
2g	6-F	7	83	218-220
2h	6-OC_2H_5	10	78	206-208

[a]Isolated yield

Table No.2: Screening of catalysts on the model reaction (3a)

Entry	Catalysts	Time (min)	Yield[a] (%)
1	Cs_2CO_3	20	46
2	KOH	20	62
3	DBU	20	76
4	K_2CO_3	20	88

[a]Isolated yield

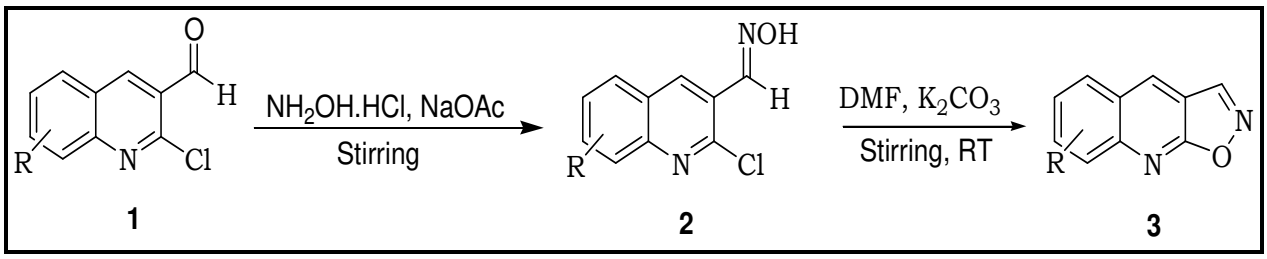
Table No.3: Synthesis of isoxazolo [5, 4-*b*] quinoline

Entry	R	Time (min)	Yield[a] (%)	M.P. (°C)
3a	H	20	88	175-176
3b	6-CH_3	15	80	298-300
3c	7-CH_3	12	92	294-296
3d	8-CH_3	18	79	332-334
3e	6-OCH_3	15	90	280-281
3f	7-OCH_3	14	83	282-285
3g	6-F	25	79	260-261
3h	6-OC_2H_5	20	87	288-290

[a]Isolated yield.

Table No.4: In-*Vitro* Antibacterial activity of Isoxazolo [5, 4-*B*] Quinoline Derivatives

S.No	Entry	Zone of inhibition (mm)			
		Gram positive		Gram negative	
		B. subtilis **(ATCC No. 6633)**	***S. aureus*** **(ATCC No. 25923)**	***S. typhi*** **(ATCC No, 23564)**	***P. aeruginosa*** **(ATCC No. 27853)**
1	3c	18	22	14	15
2	3f	13	11	19	21
3	3g	11	10	13	12
4	3h	----	5	8	9
5	Streptomycin	20	19	22	24
6	Ampicillin	24	23	25	25



Scheme No.1

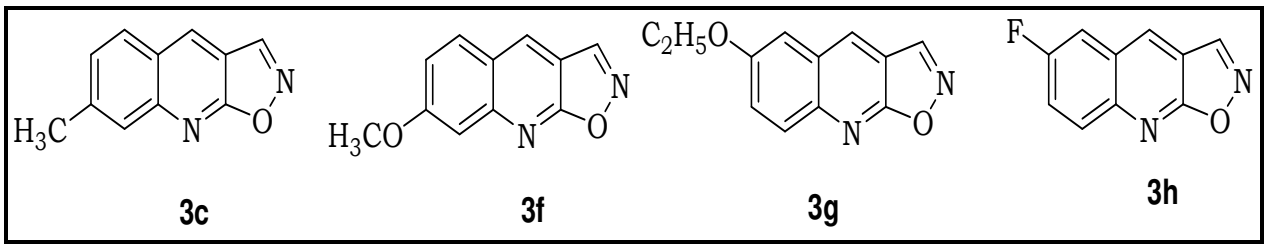


Figure No.1: Quinine, Chloroquine, Mepacrine and Pamaquine

CONCLUSION

In conclusion the K_2CO_3 and DMF was found to be mild and effective catalyst for synthesis of different derivatives of isoxazolo [5, 4-*b*] quinoline by the cyclization of various substituted oximes of quinoline at ambient temperature. We believed that, synthesis of isoxazolo [5, 4-*b*] quinoline using base will be a valuable contribution in the field of medicinal chemistry as compared to the existing processes.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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