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An Expeditious Room Temperature Stirring Method for the Synthesis of Isoxazolo[5,4-b]quinolines

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ABSTRACT. The synthesis of different derivatives of isoxazolo[5,4-b]quinoline by the cyclization reaction of various substituted oximes of quinoline using mild base at ambient temperature. The formation of isoxazolo[5,4-b]quinoline, as a consequence of cheaper and more readily available K_2CO_3 and DMF participating in the reaction, is documented.

Key words: Isoxazolo[5,4-b]quinoline, K_2CO_3, Room temperature

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 systems, quinolines represent one of the most successful yet poorly understood classes of drugs.

As the earlier reported method the 2-chloroquinoline-3-carbaldehyde were prepared from acetanilide in good yields by the action of Vilsmeier's reagent in phosphoryl chloride solution. The reaction is shown to involve successive conversion of the acetanilide into an imidoyl chloride and then an N-(α-chlorovinyl)aniline. The latter enamine is diformylated at its α-position and subsequently 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 have occupied a unique position in the design and synthesis of novel biologically active compounds since they are often used as antiallergic,[5] antiproliferative,[6] antiparasitic,[7] antinflammatory, antiasthmatic, antituberculosis, antibacterial, antihypertensive, antitumor and most notably antimalarial agents.[8,9]

Quinolines are found in numerous commercial products, including pharmaceuticals, fragrances and dyes. In the recent past, quinoline compounds were extensively studied for the development of new therapeutic agents that led to the development of some molecules, such as quinoline alkaloids, namely quinine, chloroquine, mepacrine, and pamaquine which are used as efficient drugs for the treatment of malaria.[10-17]

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

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

In a report 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 in the presence of acetic acid under reflux condition for 1 h, The resulting compounds 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. Consequently, there is still needs to develop a more efficient, simple, milder and high yield protocol for the synthesis of isooxazolo[5,4-*b*]quinoline.

EXPERIMENTAL

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}. ^{1}H-NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, Mass spectra were taken on a Macro mass spec-

trometer (Waters) by electro-spray method (ES).

All the synthesized compounds were characterized by spectral data and compared (MS, NMR, and IR) with authentic sample. 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

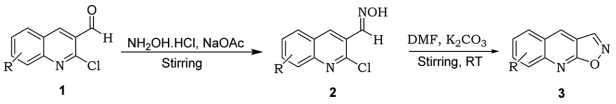
Synthesis of compounds 3(a-h): A mixture of an ethanolic solution of 2-chloroquinoline-3-carbaldehyde (1 mmol), hydroxyl amine hydrochloride (1.5 mmol), and sodium acetate (1.5 mmol) were placed in a round bottom flask. This mixture was stirred at room temperature for the precised time. After the completion of reaction as monitored by TLC; 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* 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* 1).



***Scheme* 1.**

***Table* 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* 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* 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

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* 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 **3(a-h)** in *Table* 3.

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 chemistry as compared to the existing processes.

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