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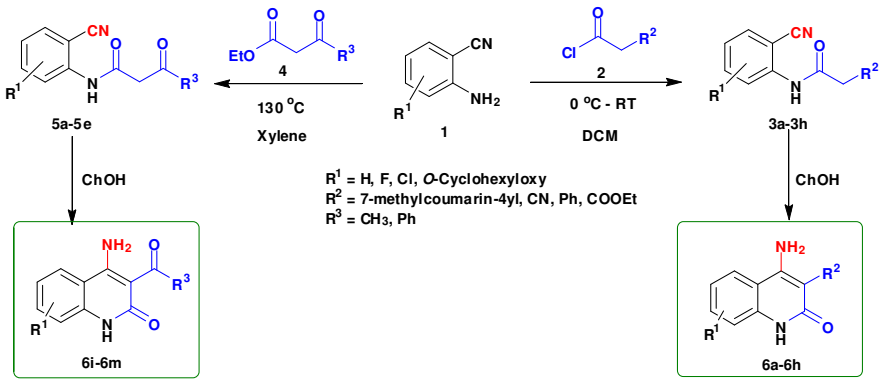

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PAPER

Environmentally benign synthesis of 4-aminoquinoline-2-ones using recyclable choline hydroxide

Anita Kailas Sanap, and Ganapati Subray Shankarling*

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Greener synthesis of 4-aminoquinoline-2-ones was achieved by intramolecular cyclization of 2-cyanophenylamide derivatives using biodegradable and recyclable choline hydroxide (ChOH). Reaction proceeds rapidly and affords the corresponding 4-aminoquinoline-2-ones with good to excellent yield. The protocol has the advantage of easy workup, high yield, and an environmentally benign methodology compared to other reported methods. The simplicity of this method makes it an interesting alternative to other approaches.

Introduction

4-Amino-2(1*H*)-quinolone scaffold can be found in a large variety of biologically active compounds. 4-Amino-2(1*H*)-quinolone derivatives have attracted attention of researchers not only because of their strong pain-relief activity but also due to their extremely weak acidic properties. Many non-narcotic analgesics are strong acids; even their salts can cause ulcers. There is no basis for such a side effect in case of 4-amino-2(1*H*)-quinolone derivatives, at least, in such pronounced form. 4-Amino-3-phenylquinolin-2(1*H*)-one shows antagonist activity at the glycine site on the NMDA (*N*-methyl-D-aspartate) receptor and anticonvulsant activity.[1] Additionally, 4-amino-3-benzimidazol-2-ylhydroquinolin-2-one was reported as tyrosine kinase receptor and their analogues are reversible ATP competitive inhibitors of VEGFR-2, FGFR-1, and PDGFR with IC50 values <0.1μM.[2,3] Considering the significant applications of quinolones in the field of medicinal and agrochemical, there has been tremendous interest in developing new efficient synthetic strategies which involves rapid functionalization and diversification of quinolones.

Therefore, various synthetic methodologies have been reported to access these molecules as backbone in their active moieties. Literature survey on the synthesis of 4-amino-3-substituted-2(1*H*)-quinolones did not show uniform reaction conditions. 4-Amino-1,2-dihydro-2-oxo-3-quinolinecarbonitrile was synthesized in five steps starting from isatoic anhydride and dimethyl malonate to give 4-hydroxyquinolone derivative which on further reactions gave a title compound.[4] Direct reaction of 2-aminobenzonitriles with dialkyl malonates gave very low yield of the product.[5] In alternative approach, the intramolecular cyclization of malonyl ester amide of 2-aminobenzonitrile and 2-cyanophenyl-*N*-acetoacetamide were reported using tin (IV) chloride, sodium methoxide and sodium ethoxide to give low yield of quinolone derivatives.[5,6] Low yields were obtained in the cyclisation of the malonyl ester amide of 2-aminobenzonitrile and 2-cyanophenyl-*N*-acetoacetamide due to difficulty in coordinating both the β-dicarbonyl moiety and the cyano group of the same molecule, possibly due to geometric reasons.[5] In some cases intramolecular cyclisation of corresponding amides of 2-aminobenzonitriles were reported using sodium hydride,[7,8] potassium *tert*-butoxide,[9] and LiHMDS.[10] 4-Amino-2(1*H*)-quinolones were synthesized from the reaction of 4-hydroxy-2-quinolones with benzylamine and cleavage of the benzyl group by catalytic hydrogenation.[11] Synthesis of 4-amino-2-quinolones were also reported using conventional amination of 4-hydroxy or 4-chloro derivatives with NH_3 in a sealed tube[12] or from the reaction of 4-hydroxyquinolones with benzyl ammonium chloride at high temperature.[13] Recently, Toche R. B. *et al* reported the synthesis of ethyl-4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate by the reaction of 2-aminobenzonitrile with diethylmalonate using sodium ethoxide in long reaction times.[14]

These methods, however, suffer from one or another drawback, such as the use of metal mediated catalysis, more number of steps, strong basic conditions, longer reaction times, moisture-sensitive catalysts, or expensive reagents, and low conversions, which limit its practical utility in organic synthesis. Our protocol describes a simple method for the synthesis of 4-amino-2(1*H*)-quinolones from its corresponding amides that were prepared from 2-aminobenzonitriles.

In recent years, the use of environmentally benign catalysts is receiving tremendous interest in different areas of organic synthesis.[15] Choline hydroxide (ChOH) is an environmentally benign, easy to prepare base, which display strong basicity. It has received considerable interest as an economical, easily available, and recyclable catalyst for various organic transformations. It was thought worthwhile to explore the catalytic potential of ChOH for this particular conversion. In view of the above and as a part of our ongoing program to develop viable protocols,[16–22] we report herein a ChOH catalyzed, mild, simple, and efficient procedure for the construction of 4-amino-2-quinolones.

*Dyestuff Technology Department, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai - 400019, India
Tel.: 91-22-33612708, Fax: +91-22-33611020
E-mail address: gsshankarling@gmail.com

Experimental

Materials and equipments

All the solvents and chemicals were procured from S D fine chemicals (India) and were used without further purification. The reactions were monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated plates, which were visualized with UV light. ^{1}H NMR spectrums were recorded on Bruker 400 MHz spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with micromass-Q-Tof (YA105) spectrometer. Infrared spectra were recorded on Jasco-FT/IR 4100 LE ATR PRO450-S spectrometer.

Preparation of choline hydroxide

To a solution of choline chloride in methanol, potassium hydroxide was added at room temperature. Then it was heated to 61 ^{o}C for 12 h with constant stirring. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl and solution was obtained. This was concentrated to remove methanol and used without further purification.

General procedure for preparation of 3a-3h

To a solution of 2-aminobenzonitrile (**1**) (10 mmol) in dichloromethane (15 mL), **2** (10 mmol) was added at 0 °C. The mixture was stirred at room temperature for 1 h. After completion of the reaction, volatile components of the reaction mixture were removed under reduced pressure to give oil. It was quenched with ice cold water (10 mL) and the solution was extracted with ethyl acetate (25 mL x 3). The combined extracts were washed with saturated $NaHCO_3$ (2x10 mL) and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization in ethyl acetate to afford **3** as a pale yellow solid.

General procedure for preparation of 5a-5e

To a solution of 2-aminobenzonitrile (**1**) (10 mmol) in dry xylene (15 mL), **4** (12 mmol) was added. The reaction mixture was refluxed for 4 h in a round-bottomed flask fitted with a Dean-Stark apparatus, kept in an oil bath. After completion of the reaction, it was cooled to 0 °C to let the products solidify and filtered. The crude product was washed with diethyl ether to afford **5** as a pale yellow solid.

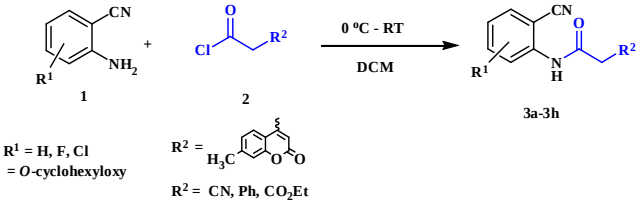
General procedure for preparation of choline hydroxide catalyzed synthesis of 4-aminoquinoline-2-ones (6a-6m)

Compound **3/5** (1 mmol) was dissolved in 3 mL of choline hydroxide at room temperature and then heated for appropriate time. After completion of reaction, cold water was added to the reaction mixture. The precipitated solid product (**6**) was filtered off, and purified by column chromatography using hexane: ethyl acetate.

Results and discussion

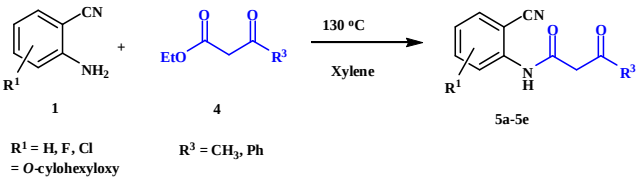
Preparation of 2-cyanophenylamides (3a-3h and 5a-5e)

In the first part, we carried out the reactions of 2-aminobenzonitriles with various acid chlorides like cyanoacetylchloride, phenyl acetyl chloride, monoethylmalonyl chloride, and 7-methylcoumarin-4-acetyl chloride to give corresponding amide derivatives (**3a-3h**) using the literature procedure[23] (Scheme 1).



Scheme 1 : Synthesis of **3a-3h** using 2-aminobenzoniriles and acid chlorides

N-(2-Cyanophenyl)-3-oxobutanamides (**5a-5d**) and *N*-(2-cyanophenyl)-3-oxo-3-phenylpropanamide (**5e**) were prepared by the reaction of 2-aminobenzonitriles (**1**) with ethylacetoacetate and ethyl benzoylacetate in boiling xylene as per reported procedures[24] (Scheme 2).



Scheme 2: Synthesis of *N*-(2-cyanophenyl)-3-oxobutanamides (**5a-5d**) and *N*-(2-cyanophenyl)-3-oxo-3-phenylpropanamide (**5e**) using 2-aminobenzoniriles and β-ketoester

Optimization of reaction conditions

In order to optimize the reaction conditions for cyclization, the effect of different organic bases and solvents were investigated in detail for the reactions of 2-cyano-*N*-(2-cyanophenyl)acetamide (**3a**) and *N*-(2-cyanophenyl)-3-oxobutanamide (**5a**). The outcome is presented in Table 1. It is evident that no conversion into the product was obtained in the absence of base even after a prolonged reaction time of 24 h (Table 1, entry 1). Deep eutectic mixtures (DES) such as choline chloride (ChCl): urea, ChCl: malonic acid, ChCl: oxalic acid, have intrinsic advantages as green catalysts.[16,17] Hence, attempts were made to study the model reactions using these catalysts, which resulted in no net reaction for ChCl: malonic acid/ oxalic acid DES (Table 1, entries 2, 3). Low yield of products were obtained in ChCl: urea DES (Table 1, entry 4). However, many other organic bases such as Et_3N, piperidine, and pyridine, promoted the reaction quite well for **3a** in a short time as compared to **5a**. (Table 1, entries 5-7). Whereas inorganic bases such as sodium hydride, potassium hydroxide, sodium hydroxide, and potassium *tert*-butoxide provided a good yield of the product as compared to organic bases (Table 1, entries 8-11). Out of all the bases monitored, ChOH was concluded to be the best at 80 °C and gave products **6a** and **6i** in 83 % and 80% yield respectively (Table 1, entry 12). In order to screen the effect of solvent, the model reactions was carried out using 1 equiv of ChOH in different solvents at reflux condition (Table 1, entries 13-18). It was observed that in polar solvents like ethanol and acetonitrile (Table 1, entries 14 & 15) good yields of product were obtained in short reaction times as compared to non polar solvent (Table 1, entries 16-18). In water, it gave very low yield of the product under the same reaction

Table 1. Optimization study for cyclisation reaction of **3a** and **5a**

3a, R^2 = CN
5a, R^2 = COOEt

6a, R^2 = CN
6i, R^2 = COOEt

Entry	Base/Solvent	[a]For reactant **3a**		[a]For reactant **5a**	
		Time (h)	Yield[f] of **6a**	Time (h)	Yield[f] of **6i**
1	Without catalyst/reagent	24	NR	24	NR
2[b]	ChCl: Urea	10	21	11	17
3[b]	ChCl:Malonic acid	10	NR	10	NR
4[b]	ChCl:Oxalic acid	10	NR	10	NR
5[c]	Et_3N/Ethanol	4.5	48	24	36
6[c]	Piperidine/Ethanol	1.5	61	10	57
7[c]	Pyridine/THF	2.5	47	11	42
8[c]	Sodium hydride/THF	4	58	10	51
9[c]	Potassium *tert*-butoxide /THF	6	62	9	54
10[c]	Sodium hydroxide/Ethanol	1.5	70	4.5	69
11[c]	Potassium hydroxide/Ethanol	1.5	72	4.5	63
12[d]	ChOH	20 min	83	50 min	80
13[e]	Water	12	30	12	21
14[e]	Ethanol	1	63	4	64
15[e]	Acetonitrile	1.5	61	6	67
16[e]	Tetrahydrofuran	2	55	10	50
17[e]	Dichloromethane	6	43	12	30
18[e]	Toluene	2	49	2	51

[a]Reaction conditions: **3a/5a** (1 mmol), [b]DES used (3 mL/ 80°C), [c]Base used (2.5 equiv/ reflux) [d]ChOH (3 mL/ 80 °C), [e]ChOH used (1 equiv/ reflux), [f]Isolated yields, NR: No reaction

conditions (Table 1, entry 13). As solvent-free synthesis has gained much current interest, it was considered important to investigate the reaction under these conditions as well. The best conversion was finally achieved under solvent-free conditions using ChOH at 80 °C (Table 1, entry 12).

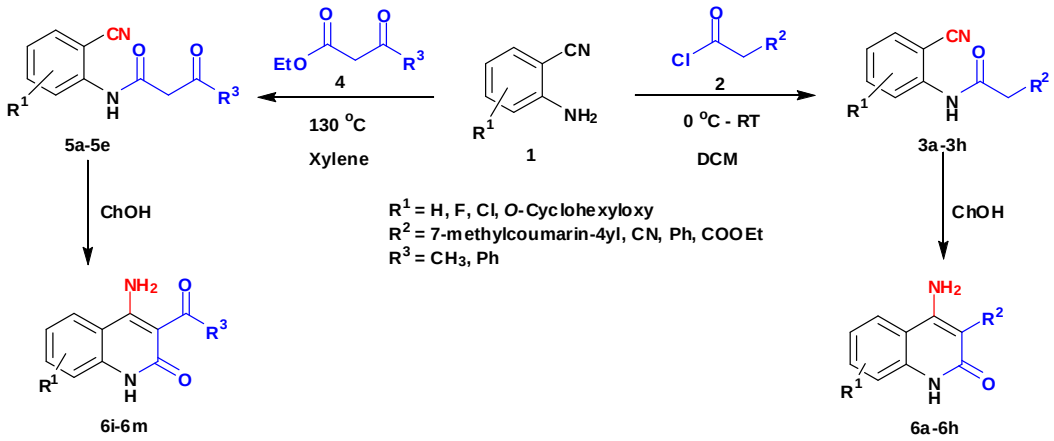
Synthesis of 4-aminoquinoline-2-ones in choline hydroxide

With the optimal conditions in hand, we extended our studies to the variety of substrates to evaluate the scope of this methodology and the results were presented in Table 2. The amides (**3a-3h & 5a-5e**) have Ar*N*HCOCH$_2$R type of structure; where Ar group consist of cyano substituent at 2-position with respect to NH$_2$ group. R^1 may be H/ F/ Cl/ *O*-Cyclohexyloxy; R^2 group may be CN/ Ph/ CO$_2$Et/ 7-methylcoumarin-4-yl; and R^3 group may be CH$_3$ or Ph. The substituent effect on the yield and rate of cyclisation was observed.

When R^1 = H, then rate of cyclisation was fast and higher yield of the desired product (Table 2, entries 1, 4, 7-9 and 13) was observed as compared to other substituents (R^1 = F, Cl and *O*-cyclohexyloxy). When R^1 = F, Cl, decreased reactivity in the cyclization due to their electron withdrawing effects. The longer reaction time required for *O*-cyclohexyloxy group was due to its steric hindrance. Hence, more time was required for cyclisation of **3** giving lesser yield of the 4-aminoquinoline-2-ones (Table 2, entries 2, 3, 5, 6, and 10-12). All the reactions were successful and gave better yield of the products.

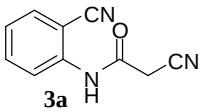
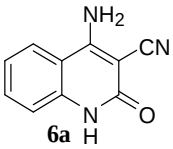
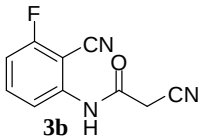
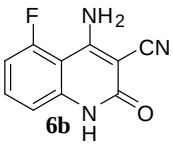
The time required for cyclisation reaction also depends upon nature of R^2/R^3 group, as the electron withdrawing power of R^2/R^3 group increases the cyclisation reaction becomes faster. When R^2 = CN, CO$_2$Et (**3a-3e**), reaction completed in very short time and gave best yield of the **6a-6e** (Table 2, entries 1-5). For the substrate **3f**, deliberately we carried out the reaction for longer time to see the effect of ChOH on ester functionality (R^2= CO$_2$Et) (Table 2, entry 6). It was observed that hydrolysis and decarboxylation results in the formation of **6f** rather than desired product. Initially, the reaction was very rapid giving corresponding cyclized product. After that ester was hydrolyzed to acid and then acid was decarboxylated to give 62% of **6f** in 2h.

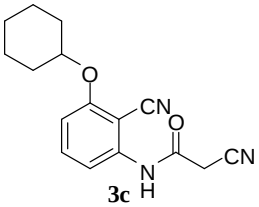
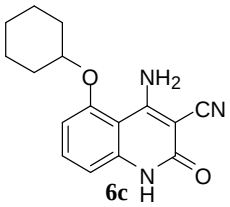
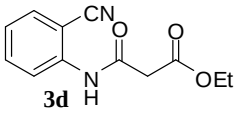
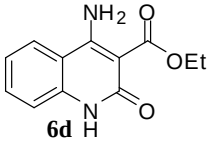
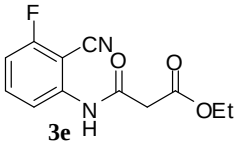
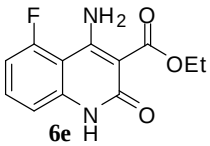
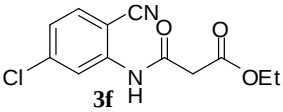
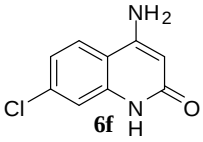
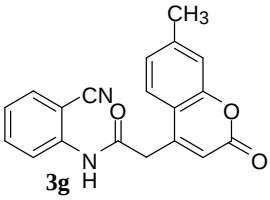
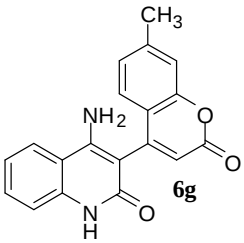
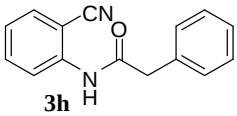
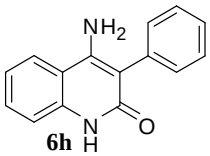
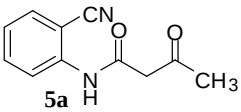
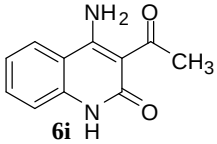
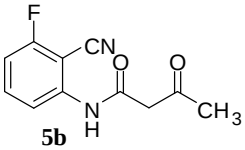
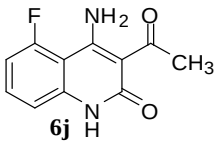
In case of **3g** and **3h** (R^2 = Ar) carbanion is better stabilized by aromatic ring thereby decreasing its nucleophilicity which results in longer reaction time (Table 2, entries 7 and 8). When R^3 = CH$_3$ or Ar (**5a-5e**), reaction requires less time and gave good yield of the **6i-6m** (Table 2, entries 9-13).

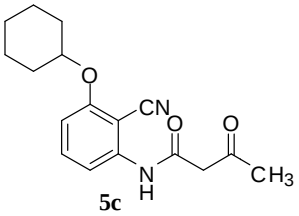
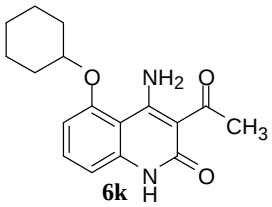
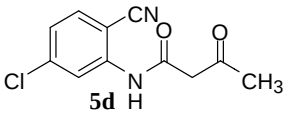
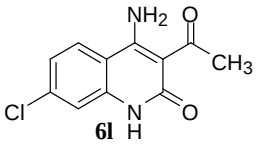
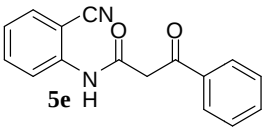
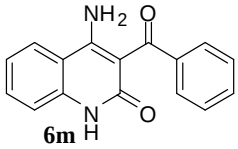


Scheme 3: Synthesis of 4-aminoquinoline-2-ones in choline hydroxide

Table 2: Synthesis of 4-aminoquinoline-2-ones

Entry	Starting Material	Products[a]	Time (min)	Yield (%)[b]
1	 **3a**	 **6a**	20	83
2	 **3b**	 **6b**	30	74

3	 **3c**	 **6c**	30	69
4	 **3d**	 **6d**	25	75
5	 **3e**	 **6e**	30	72
6	 **3f**	 **6f**	120	62
7	 **3g**	 **6g**	120	74
8	 **3h**	 **6h**	8 h	82
9	 **5a**	 **6i**	50	80
10	 **5b**	 **6j**	50	72

11	 **5c**	 **6k**	90	67
12	 **5d**	 **6l**	60	74
13	 **5e**	 **6m**	90	73

[a]Reaction conditions: amide (1 mmol), choline hydroxide (3 mL), Temperature 80 °C, [b]Isolated yields

Recovery of the ChOH

The recovery was very simple involving evaporation of water after isolation of product by filtration. The recycled ChOH was used for the next batch with minimal loss of activity till four consecutive runs (Fig. 1).

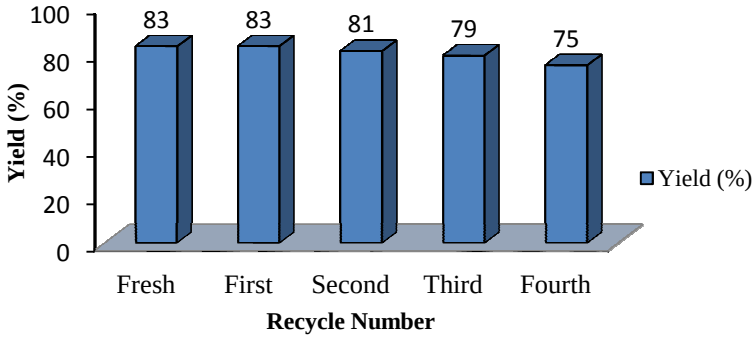


Fig. 1: Recyclability studies for product **6a**

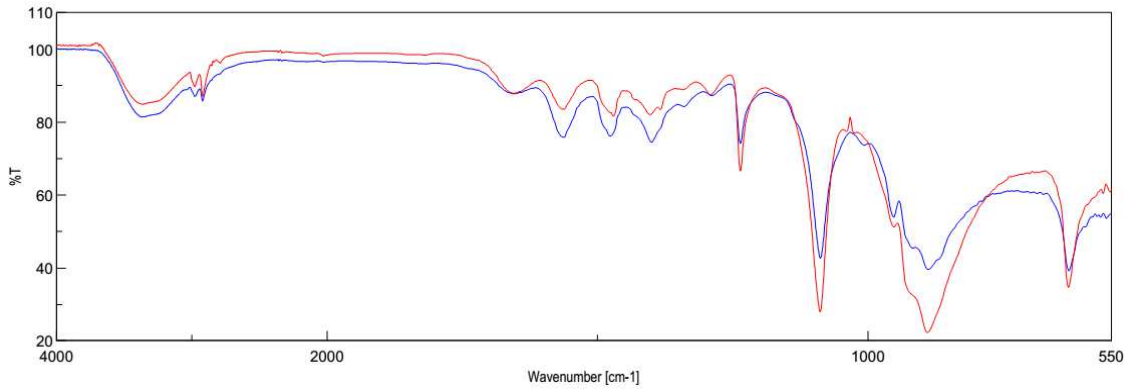


Fig. 2: FT-IR spectra of a) ChOH before reaction (blue curve) b) ChOH after four runs (red curve)

FT-IR analysis

The compound having covalent bond absorbs various frequencies of electromagnetic radiation in the infrared region of the electromagnetic spectrum. Infrared spectrum is used to determine structural information about a molecule. ChOH before reaction and after reaction were characterized using ATR-FTIR spectroscopy. The absorption peak at around 3365 cm^{-1} is the characteristic of O-H stretching vibration. The band at 1236 and 1087 cm^{-1} result from C-N and C-O stretching. Also band at 888 and 628 cm^{-1} is due to C-H bending vibration. There is no change observed in the IR spectra of ChOH before the reaction and after four runs (fig. 2).

Proposed mechanism

Although the mechanism illustrating the role of such ChOH in 4-aminoquinoline-2-ones synthesis is yet to be confirmed, we suggest a mechanism that highlights the probable role of ChOH in synthesis. Hydroxide ion of ChOH forms hydrogen bonding with acidic protons of amide (Fig. 3). ChOH assist in improving reactivity and finally promoting cyclization to form the 4-aminoquinoline-2-ones core.

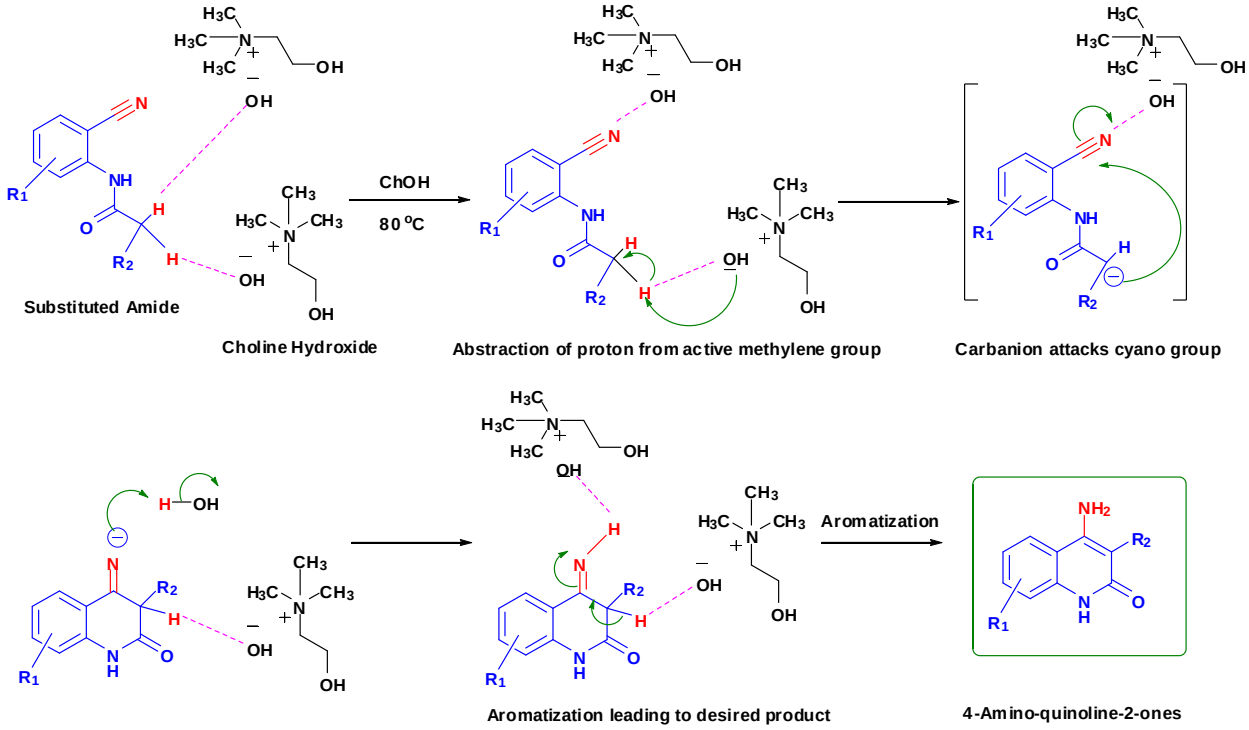


Fig. 3: Mechanism proposing the role of ChOH in synthesis of 4-aminoquinoline-2-ones derivatives

Conclusion

In this study, we have described an efficient and practical methodology for the synthesis of 4-aminoquinoline-2-ones in ChOH. Moreover, the influence of substituent type (-CN, -$COCH_3$, -COPh, -CO_2Et, -Ph, 7-methylcoumarin-4-yl substituents) and position on the rate of cyclisation of amide to 4-aminoquinoline-2-ones was investigated. When R^1 = H, then rate of cyclisation was fast as compared to other substituents (R^1 = F, Cl and *O*-Cyclohexyloxy). The time required for cyclisation reaction depends upon nature of R^2/R^3 group. The electron withdrawing cyano group increases the cyclisation reaction rate and gave high yield of the product (**6a-6c**) and when R^2/R^3 = Ar (**3g** and **3h**), reaction required longer time. This may be due to stabilization of carbanion by benzene ring. FTIR spectra of fresh ChOH and recycled ChOH remain unchanged. Hence, ChOH can be recycled and reused. These features will facilitate this procedure to find extensive applications in the field of organic synthesis.

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Notes and references

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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