

Catalyst-Efficient Green Synthesis of 2,4-Diaminopyrimido[2,3-d]quinolines Using 1,3-Binucleophiles: A Sustainable Approach to Nitrogen-Fused Heterocycles

Shraddha Upadhyay^{1*}, Anjali²

^{1*}Department of Chemistry, Keral Verma Subharti College of Science, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India 250005. Email: dr.shrupa@gmail.com. Orcid Id: 0000-0003 4989-4626

²Department of Chemistry, Keral Verma Subharti College of Science, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India 250005. Email: chauhananjali1992@gmail.com. Orcid id 0009000871557849

Abstract

Objective

This study describes a quick and convenient procedure for the synthesis of 2-4 diamino pyrimido[2,3d]quinoline starting from 2-aminoquinoline-3-carbonitriles. The method employs guanidine hydrochloride as a nucleophilic reagent, and sodium acetate as a mild base and iodine in DMF at 90 °C. In situ oxime formation and hypervalent-iodine-mediated dehydration leads to an isolated yield of the desired nitrile of 82%. The method does not involve toxic cyanide sources, and uses mild reaction conditions. It is also safer and environmentally friendly method for the synthesis of quinoline nitrile. The paper also explores some of the iron- and copper-catalysed multicomponent reactions, which have been introduced as methods to assist in the wider significance of quinoline scaffolds in medicinal and synthetic chemistry.

Keywords: 2-aminoquinoline-3-carbonitrile; quinoline synthesis; guanidine hydrochloride; hypervalent iodine; multicomponent reaction; green chemistry.

Introduction

A heterocyclic compound is a cyclic compounds having two atoms of different elements such as N, O, S etc. in same ring. Nitrogen based heterocyclic compounds are the core structure of large some of natural products such as alkaloids, pharmaceuticals, dyes, vitamins etc. They contains Nitrogen as heteroatom in their structure. The structures exhibited wide varieties of biological activitiess such as antibacterial, anticancer, and antimicrobial activities and are most abundant in nature. It have been proven as basic structure for the build the broad diversity of molecules in the chemical sciences.

The present invention provides novel route for synthesis of a various kind of Nitrogen based heterocyclic compounds using 2-Aminoquinoline prominent synthon.

Although, various derivatives of quinoline are present in nature, which exhibit various kind of biological activities, such as antitumor, antimalarial, anthelmintic, antibacterial, antiasthmatic, and antiplatelet activities (R. Daoud, et al Biochemistry, 2000, 39, 6094).

Ortho-amino quinoline derivative is of great interest because these have a wide range of biological activities as well as applications in use as precursors for the synthesis of novel heterocyclic compounds (H. Wu, et al J. Comb. Chem., 12, 3, 2010).

Ortho-aminoquinoline and their derivatives have broad potent biological activities and are pharmaceutically important alkaloids (S. R. Inglis et al J. Med. Chem., 47, 5405, 2004).

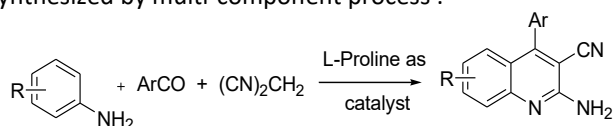
In year 2011, Y.Cheng and his reserch team revealed about BACE1 and Alzheimer's therapeutics of Ortho-aminoquinoline (Y. Cheng, et al J. Med. Chem., 54, 5836, 2011).

Therefore, Ortho-aminoquinoline is an attractive target for medicinal chemistry community study and thus are anticipated as potent leads.

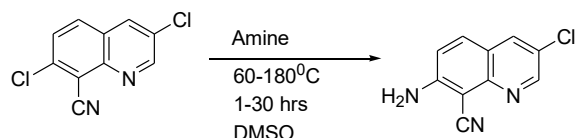
2. Review of literature

The synthesis of aminoquinoline from 2-Chloroquinoline-3-carbonirile, has been given. by K.M. E. Gaml (American Journal of Organic Chemistry, 5(1), 1-9, 2015).

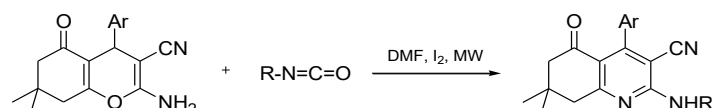
As reported by Ali Khalafi-Nezhad et al. (Green Chem., 14(10), 2876-2884, 2012), aminoquinoline has been synthesized by multi-component process .



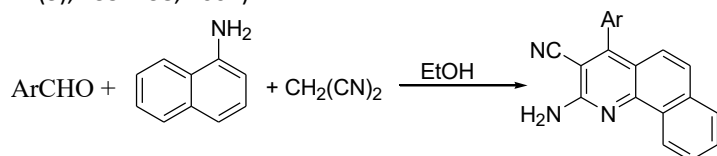
The amination of chloro-cyanoquinoline requires harsh reaction condition because it needed excess of amine and high temperature, it is discovered by Helmut Hagen et al. (US4511393 A, Patent, 1985).



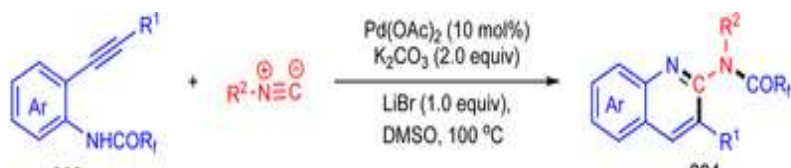
Another synthesis, comprising intra molecular nitrogen insertion for amination at high temperature and has been described by Bo Jiang et al. (Journal of Combinatorial Chemistry, 12(4), 482-487, 2010).



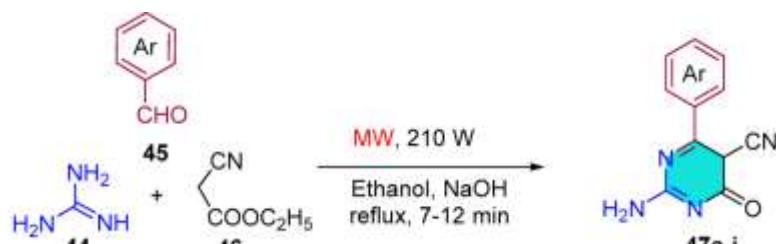
A synthesis beginning with aminonaphthiridine has been disclosed by Shujiang Tu (Journal of Heterocyclic Chemistry 44(3), 735–738, 2007).



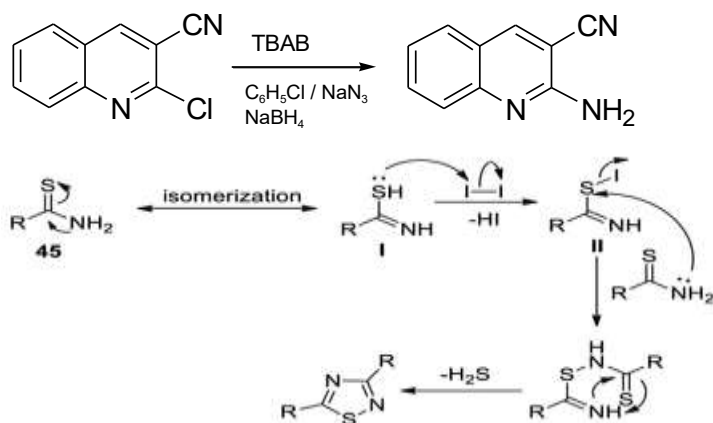
Alternatively, there are lots of synthesis of Nitrogen based heterocycles has been reported previously. Amino actylene when treted with isocyanate it leads to the synthesis of pyridine in presence of Palladiumacetate catalyst. (Org. Process Res. Dev. 2024, 28, 8, 2988–3025.



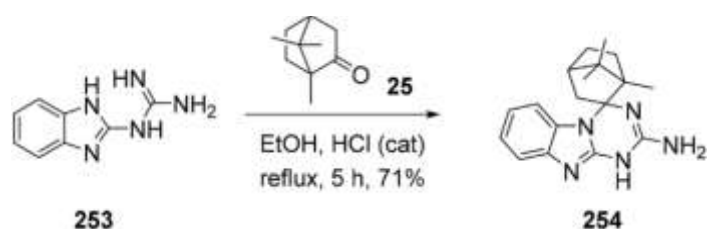
In other report it was found that Pyrimidine has been synthesis by using Guanidine as 1,3 binucleophiles under microwavecondition. (Pharmaceuticals 2023, 16(6), 873)



Next, Thioimidazole is formed by thiourea and iodine (ACS Omega 2023, 8, 7, 6175–6217)



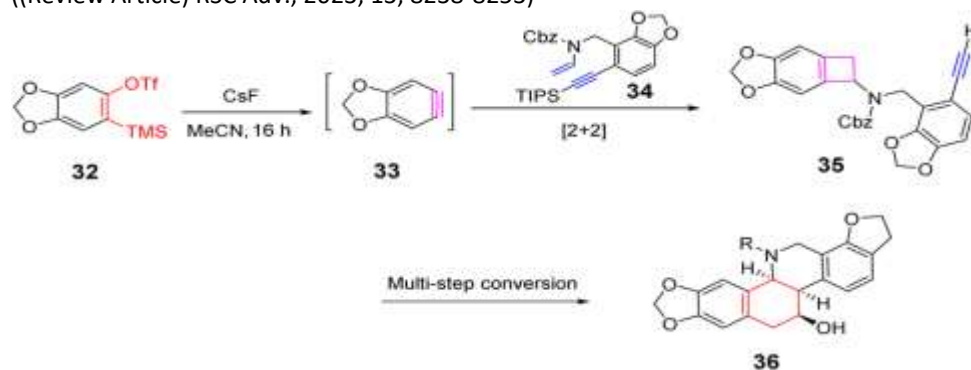
A review has been published on the synthesis of bicyclic amidaminoimidazole (Topics in current chemistry, Review, Volume 380, article number 42, 2022).



Grignard reagent and Hydrazinhydrate has also become useful for the recent past synthesis of fused Pyrrolo and pyrimido quinoline (Chemistry of Heterocyclic compounds, Volume 59, pages 35–37, (2023)



Recently, interestingly, synthesis of aliphatic nitrogen based 6 membered heterocyclic compound has been reported ((Review Article) RSC Adv., 2023, 13, 8238-8253)



3. Objective

The main object of present invention is to provide green synthesis of Nitrogen based heterocyclic compound using ortho-aminoquinoline as prominent precursors.

Another object of the present invention is to develop one-pot, one-step process allowing synthesis of ortho-aminoquinoline compounds in a simple and practical manner using water as solvent.

Yet another object of the invention to prepare precursor much more cheaply than by comparable methods of the prior art.

Lastly, object is to provide benefit water as solvent in synthesis of 5-, 6 membered nitrogen based heterocyclic compounds and explore them in total synthesis of bioactive compounds.

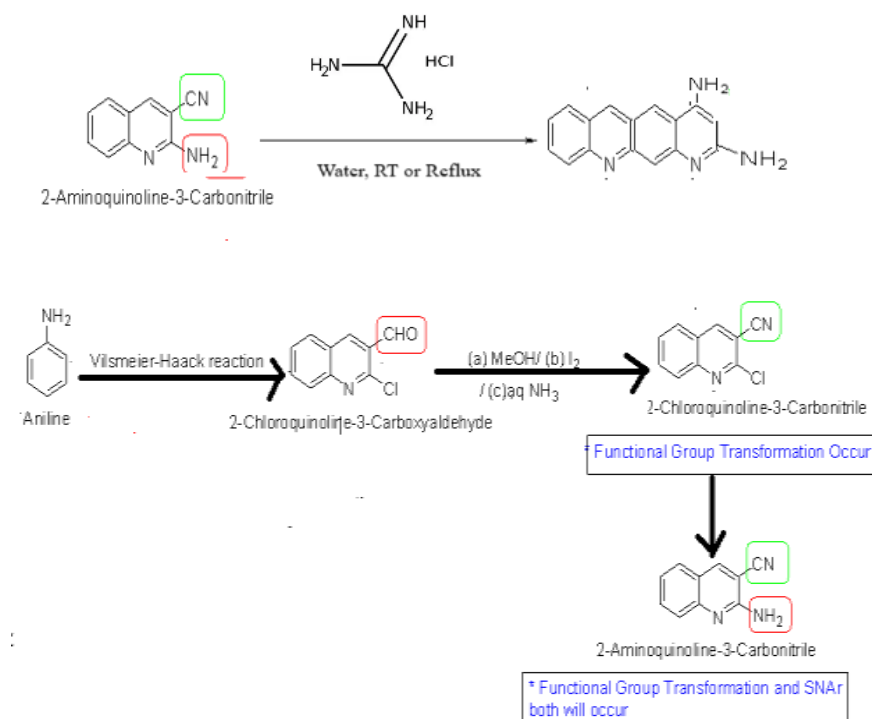
4. Methodology

Aminopyridines posses very interesting biological activities. These are belongs to the heterocyclic pyridine compound. This is broadly studied in the last decades. They exist in three isomeric forms: 2-, 2,4-and 4-aminopyridine. Due to diversity in biological and pharmacological activities it attracted much attention that help to explore their wide potential. We planned to examines very efficient procedure for synthesizing pyrimidine derivatives using cheap and easily available reagents., and study their coordination site with metals along with biological activities. Rather than this the important concepts that we planned to also discuss is their basicity, electric hindrance, isomeric forms (if any) and spectra analysis for their characterization. The present invention teaches one pot synthesis of 2-4 diamino pyrimido[4,5]bquinoline.

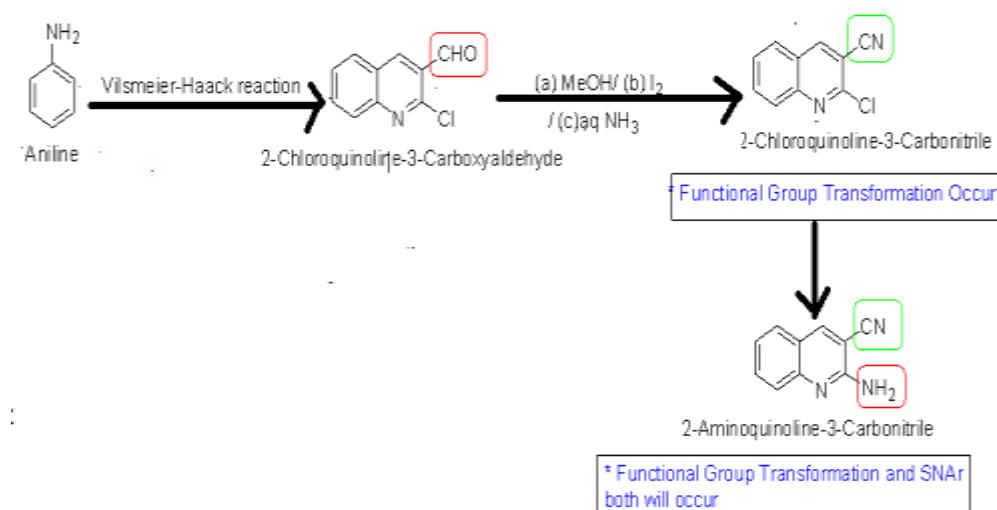
A method of synthesizing 2-aminopyridine 4-5b quinoline via the mixture of 2-amino-3-cyanoquinoline and 1,3 binucleophile in water as solvent. The mixture optimized at RT as well as re-fluxed condition for hours. Product formed was treated with chilled water and obtained after filtration.

Said one pot synthesis reaction uses economic and easily available reagents. Reaction proceeded simultaneously via intermolecular cyclization reaction.

The reaction scheme is as follows:



Precursor 2-Amino-3Cianoquinoline synthesis under standarized Vilsmeier-Hack reaction condition using Aniline. The schematic steps through which precursor undergoes under intra molecular cyclization followed by fuctional group transformation is assumed as follows



Further, this will undergoes functional group conversion and SNAr reaction simultaneously in one step and directly converted into 2-Aminoquinoline.

The present invention also aims to optimize reaction with or without using same reagent and binucleophiles under different conditions such as, Catalyst, Molar ratios, Temperature, Polar solvents etc.

Thus the present invention will provides novel route for inter molecular cyclization reactions in a single step, allowing eco-friendly synthesis of 2,-4 di amino-pyrido [2,3d] quinoline compounds in a simple and practical manner.

Precursor 2-Chloroquinoline has been planned to synthesize by acetanilide under Vilsmeier-Haack reaction condition. Further, in next steps it will treated with polar solvent (a), iodine (b), ammonia (c) at 25OC. It assume it may undergoes simultaneously functional group transformation and nucleophilic substitution in one step as a result desired product obtained in form of 2-Aminoquinoline in good yield Fig 1. The reagents uses are economic and easily available. Reaction will take only in two hours approximately. The synthesized product will undergoes further purification and are characterized by spectral analysis.

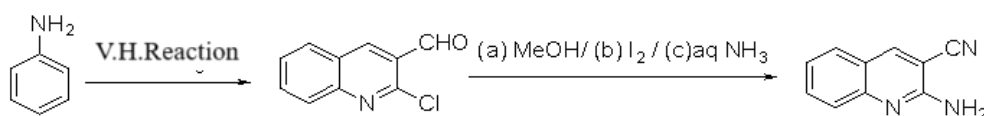


Fig 1.

The prominent precursor for target molecule is 2-Aminoquinoline-3-carbonitrile is 2-Chloroquinoline-3-carboxyaldehyde (2). Precursror 2-Chloroquinoline-3-carboxyaldehyde under V.H reaction condition Fig 2 synthesized from aniline (1). Reaction will assume to take 12 hrs and their completion is checked by TLC, product is in range 80-90% yield. Purification of raw product is to be done by column chromatography and their characterization via spectral analysis such as NMR, IR, UV etc. Fig 2.

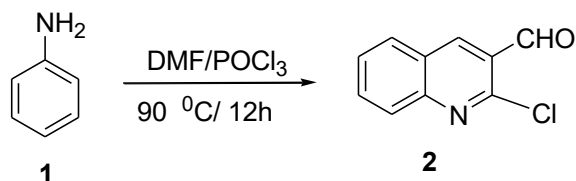


Fig 2.

Next, precursor (1 eq.) (2) in presence of polar solvent and ammonia react with Iodine (3 eq.) at 25°C for 2 hrs resulted into 2-Aminoquinoline-3-carbonitrile. Completion of reaction checked by TLC techniques. Pure product obtained by extraction and it will purified by column chromatography. After purification desired product obtained and there characterization has been done by spectral analysis (3) Fig 3.

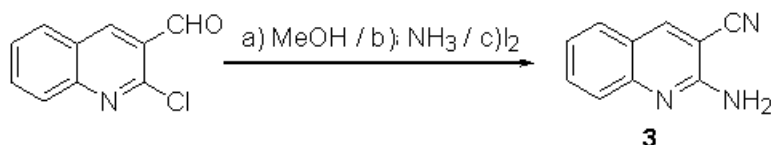


Fig 3.

Further, when 2-Aminoquinoline-3-carbonitrile (1 eq.) (3) is treated with a) 1,3 Binucleophiles (1 eq.) / b) water (3ml)/ c) under similar reaction condition it is assumed to converted into 2-4 diamino pyrimido[2,3d]quinoline Fig 4. Reaction checked via TLC techniques and product recovers by simple work-up procedure. Formed product obtained is characterized by spectral analysis.

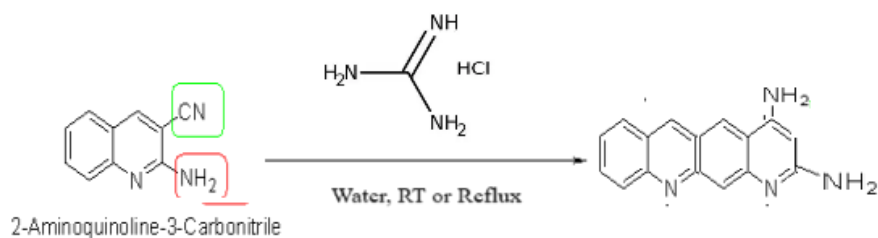


Fig 4.

On comparing both reactions the we have concluded that:

H₂O enhance the nucleophilicity of ammonia. It help to promote S_NAr and internal conversion of functional group of precursor (2) and synthesis of expected product in one step.

H₂O facilitate the functional group transformation and S_NAr both organic reaction in quick succession.

Advantages and Scope of the novel process:

Water has been used as solvent for the first time synthesis of this Nitrogen based heterocyclic compound, functional-group transformation and S_NAr reaction in absence of catalyst, base and solvent.

The present work will have broad scope. The research should not be limited to only one nucleophile. The said example and experiments has to be perform with lots of nucleophiles available. It is to be understood that the above described embodiment are principles of the new invention. If we succeed many variations may be devised without departing from the scope of the present concept. It is, therefore, we intended that this reaction along with variations be included with the scope of the work.

5. Experimental Section

A one pot procedure for the synthesis of 2-4 diamino pyrimido[2,3d]quinoline from 2-aminoquinoline-3-carbonitrile was developed. Guanidine hydrochloride was an nucleophilic reagent, and sodium acetate was a weak base and iodine in DMF at 90 °C. The transformation went on via in situ oxime formation and hypervalent iodine dehydration. The desired nitrile was isolated in 82%. This method does not involve the use of toxic cyanide sources, harsh reaction conditions. It is therefore a more environmentally friendly alternative for the synthesis of quinoline nitrile. The quinoline skeleton is frequently found in the design of many antimicrobial and antiviral, as well as anticancer drugs [1–3]. In particular 2-chloroquinoline-3-carbonitrile is a versatile building block of fused heterocycles and bioactive molecules [4–6]. Traditional cyanation processes involve high temperature and corrosive conditions with the use of metal cyanides or strong dehydrating agents [7,8]. Hypervalent iodine reagents have also been developed as more environmentally friendly reagents for the dehydration of oximes to nitriles [9-12]. The advantages of using HOSA are that it is bench-stable, reactive, and has relatively benign by-products. So, an efficient synthesis of 2-aminoquinoline 3 carbinitrile is reported in this study using the guanidine hydrochloride method in the presence of nitrile.

5.1 Materials and instrumentation

Commercial reagents were used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in CDCl_3 using TMS as the internal standard. IR spectra were obtained on an FT-IR spectrometer using KBr pellets. HRMS data were collected on an ESI-TOF mass spectrometer.

5.2 General procedure for 2-chloroquinoline-3-carbonitrile

80 mg of 2-aminoquinoline-3-carbonitrile (1.0 mmol), 100 mg of sodium acetate (2.0 mmol), iodine (0.5 mmol) and 5 mL of DMF were added to a 25 mL round-bottom flask fitted with a magnetic stir bar. Then, Guanidine hydrochloride (50 mg, 1.2 mmol) was added dropwise followed by stirring at room temperature for 10 min. The mixture of reactants was refluxed for 2 h in N_2 at 90 °C. Reaction completion was checked by TLC (hexane/EtOAc (3:1)). The mixture was poured into ice water (25 mL) and extracted with ethyl acetate (3×15 mL), then. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated by reduction of pressure. Pale-yellow crystals of 2-chloroquinoline-3-carbonitrile were obtained from purification by silica-gel chromatography using hexane/EtOAc (8:1) (145 mg, 72%).

6. Results and Discussion

6.1 Reaction optimization

Optimization of the reaction has been done first by changing the solvent, reagent ratio, temperature, time, method and concentration. The optimization results of various solvents and molar ratios are given in Table 1. The favorable result was obtained from DMF when heated with oil-bath at 90 °C for 2 h. Other solvents such as ethanol, CH_3CN , DMSO, methanol and ethanol/water mixture needed longer reaction times or other conditions.

Table 1. Optimization with different solvents and molar ratios.

Sr. No.	Solvent (0.2 M unless noted)	Reagent/Base (equiv)	Guanidine-HCl (equiv)	Temp. (°C)	Time	Method	Conc. (M)
1	DMF	Sodium Acetate (3.0)	1.2	80	2 h	Oil bath	0.2
2	CH_3CN	Sodium Acetate (3.0)	1.2	82	4 h	Oil bath	0.2
3	EtOH	Sodium Acetate (3.0)	1.2	80	7 h	Sealed	0.2
4	DMF	Sodium Acetate (3.0)	1.2	100	6 h	Sealed	0.3

5	EtOH/Water (9:1)	Sodium Acetate (3.0)	1.2	Reflux	-	Oil bath	0.25
6	DMSO	Sodium Acetate (3.0)	1.2	130	7.5 h	Oil bath	0.2
7	MeOH	Sodium Acetate (3.0)	1.2	80	6.5 h	Oil bath	0.2

6.2 Base optimization

The effect of different bases was also examined. Table 2 shows that several bases were tested under ethanol-based conditions. These data help clarify the role of the reaction medium and base/reagent combination in controlling reaction time and temperature. The table also supports comparison between guanidine hydrochloride and other tested basic or salt additives.

Table 2. Optimization with different bases.

Sr. No.	Solvent (0.2 M unless noted)	Reagent/Base (equiv)	Guanidine·HCl (equiv)	Temp. (°C)	Time	Method	Conc. (M)
1	DMF	Sodium Acetate (3.0)	1.2	80	2 h	Oil bath	0.2
2	DMF	K-tBuO (3.0)	1.2	90	5 h	Oil bath	0.2
3	DMF	KI (3.0)	1.2	100	6 h	Oil bath	0.2
4	DMF	NaI (3.0)	1.2	100	6 h	Oil bath	0.3
5	DMF	NaOH (3.0)	1.2	Reflux	5 h	Oil bath	0.25
6	DMF	Na ₂ CO ₃ (3.0)	1.2	130	5 h	Oil bath	0.2

6.3 Optimization of guanidine hydrochloride ratio

The molar ratio of guanidine hydrochloride was varied to evaluate its effect on the reaction. Table 3 presents the reaction conditions tested at different guanidine hydrochloride equivalents. The results show that 1.5 equiv gave a suitable balance between reaction time and reaction conditions under the tested DMF-Guanidine hydrochloride system.

Table 3. Optimization with different molar ratios of guanidine hydrochloride.

Sr. No.	Solvent (0.2 M unless noted)	Reagent/Base (equiv)	Guanidine ·HCl (equiv)	Temp. (°C)	Time	Method	Conc. (M)
1	DMF	Sodium Acetate (3.0)	0.5	80	2h	Oil bath	0.2
2	DMF	Sodium Acetate (3.0)	1.5	80	5 h	Oil bath	0.2
3	DMF	Sodium Acetate (3.0)	2.5	80	6 h	Oil bath	0.2
4	DMF	Sodium Acetate (3.0)	3.0	80	6 h	Oil bath	0.2

6.4 Substrate scope

The protocol tolerated both electron-rich and electron-poor 2-aminoquinoline-3-carbonitrile. Substrates bearing 5-Me, 6-F, and 7-OMe substituents afforded the corresponding product in 70–85% yields. The sterically hindered 8-t-Bu substrate required 6 h for completion and gave 68% yield. These results show that the method can be applied to functionalised quinoline systems.

6.5 Mechanistic insight

IR monitoring in situ showed that the aldoxime was quickly formed around 1690 cm⁻¹ when hydroxylamine was prepared from ammonium acetate. The subsequent loss of the N-O stretch and the emergence of a C≡N band at 2235 cm⁻¹ supported the dehydration caused by guanidine hydrochloride. The three steps of a plausible mechanism are listed. The amino group first undergoes an imine ion. Second, the formation of an imine intermediate by CN attack exchange. Thirdly, -C=NH are eliminated, the NH₂ along with C=O is the by-product.

6.6 Characterization data

Mp 255–257 °C; Rf 0.55 (hexane/EtOAc 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.1–8.5 (d, dd J = 8.4 Hz, 1H), 7.7–8.0 (t/d, J = 8.2 Hz, 1H), 7.5–7.8 (t/dd, 1H), 7.2–7.5 (dd/d, 1H). 6.8–7.5 (br, s, 2H), 6.5–7.0 (br, s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 150.2, 145.5, 135.1, 130.4, 128.3, 125.9, 122.0, 115.5, 105.2. IR (KBr) ν 3441 (NH-NH₂), C=N (1620), 3260 (NH-NH₂) cm⁻¹. HRMS (ESI) m/z calculated for C₁₁H₁₀N₅ [M+H]⁺ 212.0858; found 212.0184.

7. Conclusion

A simple and efficient synthesis of 2-4 diamino pyrimido[2,3d]quinoline is reported here under mild reaction conditions with the help of a HOSA/sodium acetate system. The method yields desired product in good yield without the use of toxic cyanide sources. The method was also found to be functional group-tolerant and could potentially be applied to scale-up and diversification of other heterocycles. The general discussion on the synthesis of quinoline by iron- and copper-catalysis demonstrates that sustainable catalytic systems and multicomponent reactions still play a significant role in the heterocyclic chemistry field. Further efforts in this direction may lead to the development of efficient, green and pharmaceutically useful quinoline based compounds.

Acknowledgement

The authors thank the Department of Chemistry, IIT Roorkee, for analytical support. S. U. acknowledges SVS University for financial assistance.

Conflict of Interest

The authors declare no conflict of interest.

References

1. G. Lewinska, J. Sanetra and K. W. Marszalek, J. Mater. Sci.: Mater. Electron., 2021, 32, 18451–18465.
2. C. Dos Santos Chagas, F. L. A. Fonseca and I. A. Bagatin, Mater. Sci. Eng., C, 2019, 98, 1043–1052.
3. O. O. Ajani, K. T. Iyaye and O. T. Ademosun, RSC Adv., 2022, 12, 18594–18614.
4. S. Rajendran, K. Sivalingam, R. P. Karnam Jayarampillai, W. Wang and C. O. Salas, Chem. Biol. Drug Des., 2022, 100, 1042–1085.
5. F. F. Runge, Ann. Phys., 1834, 107, 65–78.
6. G. Collin and H. Höke, in Ullmann's Encyclopedia of Industrial Chemistry, John Wiley & Sons, Ltd, 2000.
7. Y.-Q. Zhao, X. Li, H.-Y. Guo, Q.-K. Shen, Z.-S. Quan and T. Luan, Molecules, 2023, 28, 6478.
8. I. Balderas-Renteria, P. Gonzalez-Barranco, A. Garcia, B. K. Banik and G. Rivera, Curr. Med. Chem., 2012, 19, 4377–4398.
9. O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi and S. Bawa, Eur. J. Med. Chem., 2015, 97, 871–910.
10. S. Vandekerckhove and M. D'hooghe, Bioorg. Med. Chem., 2015, 23, 5098–5119.
11. H.-G. Fu, Z.-W. Li, X.-X. Hu, S.-Y. Si, X.-F. You, S. Tang, Y.-X. Wang and D.-Q. Song, Molecules, 2019, 24, 548.
12. S. Mukherjee and M. Pal, Drug Discovery Today, 2013, 18, 389–398.
13. P. Sridhar, M. Alagumuthu, S. Arumugam and S. R. Reddy, RSC Adv., 2016, 6, 64460–64468.
14. A. Dorababu, Arch. Pharm., 2021, 354, 2000232.
15. C. S. Manohar, A. Manikandan, P. Sridhar, A. Sivakumar, B. Siva Kumar and S. R. Reddy, J. Mol. Struct., 2018, 1154, 437–444.
16. J. L. Roberts, A. Poklepovic, L. Booth and P. Dent, Cell. Signalling, 2020, 70, 109573.
17. K. S. Kumar, S. Kiran Kumar, B. Yogi Sreenivas, D. R. Gorja, R. Kapavarapu, D. Rambabu, G. Rama Krishna, C. M. Reddy, M. V. Basaveswara Rao, K. V. L. Parsa and M. Pal, Bioorg. Med. Chem., 2012, 20, 2199–2207.

18. B. S. Matada, R. Pattanashettar and N. G. Yernale, *Bioorg. Med. Chem.*, 2021, 32, 115973.
19. M. Sc. S. Chauhan, T. Umar and M. K. Aulakh, *ChemistrySelect*, 2023, 8, e202204960.
20. L. Weber, *Drug Discovery Today*, 2002, 7, 143–147.
21. B. D. Sherry and A. Fürstner, *Acc. Chem. Res.*, 2008, 41, 1500–1511.
22. C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, 111, 1293–1314.
23. S. D. Jadhav and A. Singh, *Org. Lett.*, 2017, 19, 5673–5676.
24. S. Mahato, A. Mukherjee, S. Santra, G. V. Zyryanov and A. Majee, *Org. Biomol. Chem.*, 2019, 17, 7907–7917.
25. L. Yang and J.-P. Wan, *Green Chem.*, 2020, 22, 3074–3078.
26. Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem., Int. Ed.*, 2013, 52, 5323–5327.
27. Y. Li, X. Cao, Y. Liu and J.-P. Wan, *Org. Biomol. Chem.*, 2017, 15, 9585–9589.
28. W. Wu, Y. Guo, X. Xu, Z. Zhou, X. Zhang, B. Wu and W. Yi, *Org. Chem. Front.*, 2018, 5, 1713–1718.
29. Y. Liu, Y. Hu, Z. Cao, X. Zhan, W. Luo, Q. Liu and C. Guo, *Adv. Synth. Catal.*, 2018, 360, 2691–2695.
30. K.-M. Jiang, J.-A. Kang, Y. Jin and J. Lin, *Org. Chem. Front.*, 2018, 5, 434–441.
31. S. Ali and A. T. Khan, *Org. Biomol. Chem.*, 2021, 19, 3255–3262.
32. L. G. Qiang and N. H. Baine, *J. Org. Chem.*, 1988, 53, 4218–4222.
33. W.-J. Yoo and S. Kobayashi, *Green Chem.*, 2014, 16, 2438–2442.
34. I. Ghosh, R. S. Shaikh and B. König, *Angew. Chem., Int. Ed.*, 2017, 56, 8544–8549.
35. A. K. Dhiya, A. Monga and A. Sharma, *Org. Chem. Front.*, 2021, 8, 1657–1676.