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Preparation and characterization of triamterene complex with Diethyl 1-chlorohydrazine-1, 2-dicarboxylate

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Abstract

A triamterene complex was synthesized by using 2-chloroquinoline-3-carbonitrile as a starting material. The reaction processed in mild conditions with alkyl amine and appropriate substituted aryl nitrile to give the desired derivative in good yields. The respective structure of synthesized compound confirmed by IR, ^1H NMR, ^{13}C NMR and mass spectrometry. The proposed research work offers a simple, cost effective and general entry into the synthesis of quinoline fused triamterene derivatives, which are biologically potent and significant. The study also provides future applications of the useful intermediates of the quinoline based nitrogen heterocycles for broad pharmacological application.

Keywords: Nitrogenheterocycles; 2-aminoquinoline-3-carbonitrile; Alkyl nitrile; Triamterene; quinoline derivatives; cytotoxicity

1. Introduction

Hetero-cycles compound, have one odd ring atom other than carbon, like nitrogen, oxygen or sulfur. In various natural product the nitrogen containing hetero-cycles are an core part, such as vitamins, drugs, alkaloids, dyes etc. The nitrogen containing hetero cyclic compound exhibit various biological activities such as antibacterial, anticancer, and antimicrobial properties. Thus they are extensively consider in chemical and pharmaceutical fields for molecular design [1-5, 7, 9, 20, 27, 40, 56]. In this paper the synthesis of triamterene derivative which is a heterocyclic nitrogen compounds from 2-aminoquinoline as an precursor has been discussed. Quinoline derivatives have been shown various kind of biological activities such as antimalarial, antitumor, antibacterial, anthelmintic, antiplatelet and antiasthmatic [10, 23, 27]. Amongst various aminoquinoline derivatives Ortho-aminoquinoline derivatives are very significant because as they possess strong biological activity and are significant intermediates for the synthesis of new heterocyclic compounds [6, 8, 23, 31, 48]. As reported Cheng [8] 2-aminoquinoline derivatives as a potential inhibitors of protein cleaving enzyme 1 (BACE1), which involved in Alzheimer's disease. Reporting result confirms the utility of ortho-aminoquinoline as a valuable precursor for developing new drugs [8, 40]. Related studies show that nitrogen-containing compound can be modified and improve synthetic value and biological activity [2, 5, 7, 11, 13, 15, 37, 39, 49, 51, 55]. Beside structural diversity, substitution pattern and basicity of nitrogen heterocycles as well as C2 amination and metal-complex studies show the synthetic and material relevance of aminopyridine-type systems [18, 24, 41, 45, 52, 54, 56] which further support their importance in medicinal and synthetic chemistry, justifies the present design a new quinoline-fused triamterene derivative using a simple and cost-effective synthetic route [3, 4, 20, 29].

2. Review of Literature

Several methods for synthesizing aminoquinoline derivatives have been reported using 2-chloroquinoline-3-carbonitrile, as shown in Fig. 1 [31].

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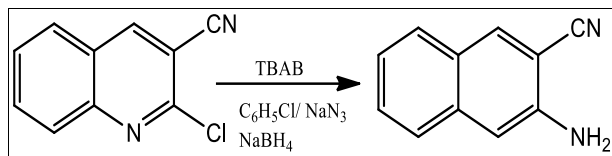


Fig 1: Formation of ortho-aminoquinoline-3-carbonitrile.

Ali Khalafi-Nezhad ^[36] reported a multi-component reaction for the formation of aminoquinoline derivatives (Fig. 2).

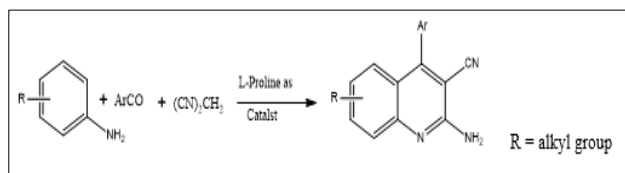


Fig 2: Formation of alkyl derivatives of aminoquinoline

As reported in the patent by Helmut Hagen. ^[31, 47] amination of chloro-cyanoquinoline (Fig. 3),

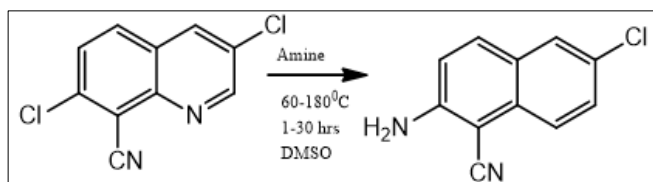


Fig 3: Amination process.

Jiang *et al.* ^[28] described amination followed by intramolecular nitrogen insertion under high-temperature (Fig. 4) R – alkyl group.

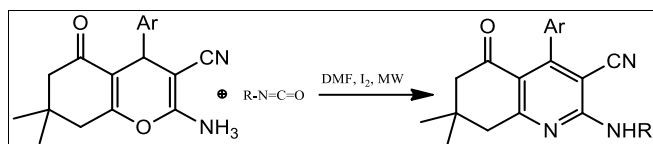


Fig. 4: Amination and intramolecular insertion.

Shujiang Tu ^[46] reported a synthesis with aminonaphthyridine (Fig. 5).

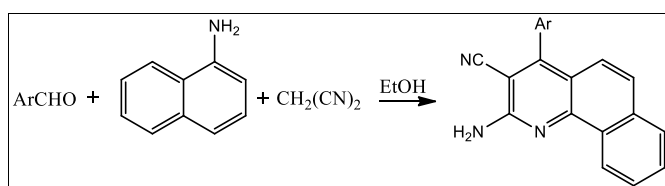


Fig. 5: Formation of ortho-aminoquinoline-3-carbonitrile.

Formation of ortho-aminoquinoline-3-carbonitrile.

Several nitrogen-based heterocycles have synthesized from 2-aminoquinoline as precursors. For example, benzo[b][1,8]naphthyridine derivatives synthesis (Fig. 6) ^[6].

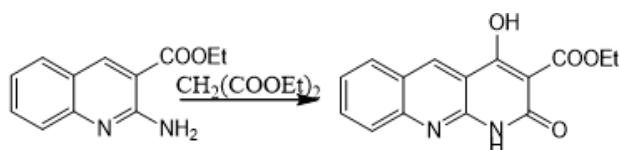


Fig 6: Synthesis of diazaanthracene benzo [b][1,8]naphthyridine.

Further, the synthesis of pyrimidoquinoline derivatives from intermolecular cyclization using DMF-DMA reported (Fig. 7) ^[22].

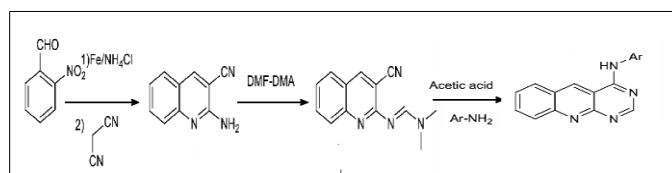


Fig 7: Intermolecular cyclization of 2-aminoquinoline.

Pyrimido ^[4, 5] quinolines can also be formed under Vilsmeier-Haack reaction conditions (Fig. 8) ^[48].

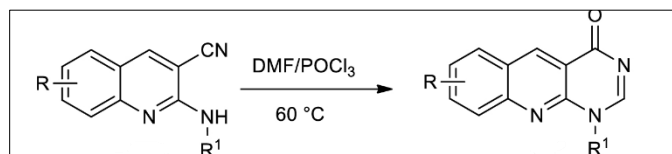


Fig 8: Vilsmeier-Haack process.

The synthesis of pyrimido ^[4, 5] quinolin-4(1H)-ones in the presence of an acid catalyst has also been reported (Fig. 9) (Dow, 1995).^[48]

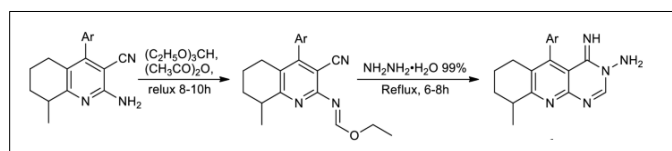


Fig 9: Reaction of ortho-aminoquinoline in an acid catalyst.

Another research report disclose synthesis of pyrimido ^[4, 5] quinoline-2(1H)-one/thione derivatives using thiourea or urea (Fig. 10) ^[14].

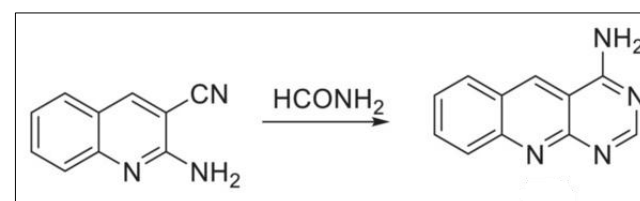


Fig 10: Reaction of ortho-aminoquinoline in a polar solvent and base.

Recently, the synthesis reported from 2-amino-dimethyl-5-oxo-hexahydroquinoline-3-carbonitrile and acetic acid (Fig. 11) ^[22].

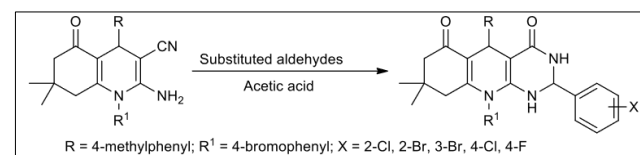


Fig. 11: Synthesis of pyrimido ^[4, 5] quinolone

Further using DMF, sulfonamide isothiocyanates, and 2-aminoquinoline-3-carbonitrile as the starting precursor through intermolecular cyclization synthesis has also been reported (Fig. 12) ^[22, 12, 16, 17, 19, 21, 25, 26, 30, 34, 38, 42-44, 50, 57, 58, 17, 19, 25, 26, 42-44].

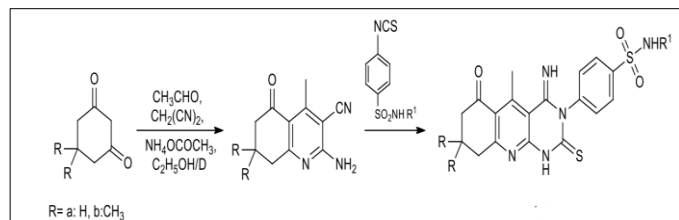
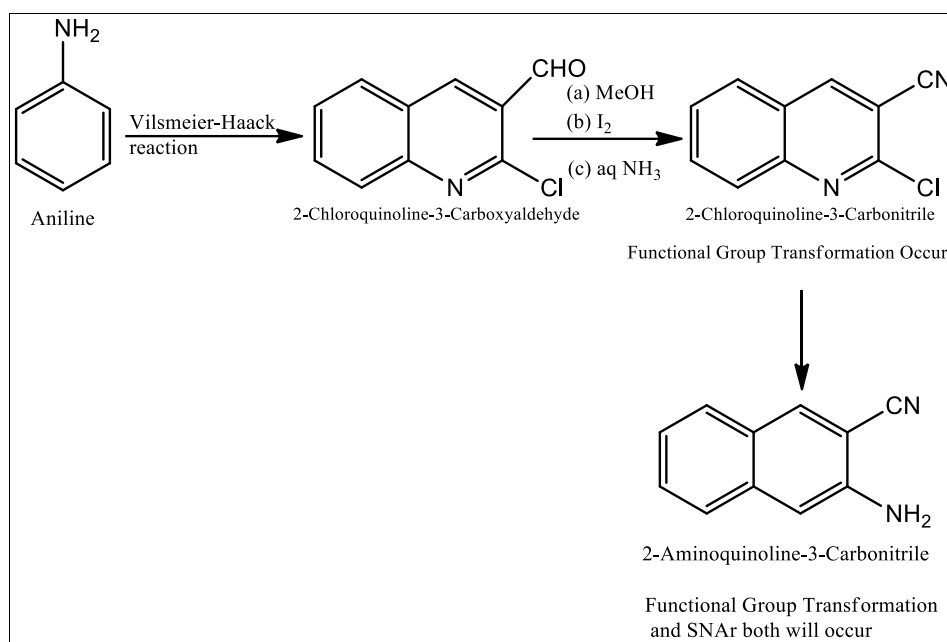


Fig. 12. Synthesis of 2-Amino-3-Cyanoquinoline through intermolecular cyclization.

The Aminoquinolines are very important compounds that have biological activities and are members of the Quinoline class of Heterocyclic which has been well studied in recent decades. They exist in several isomeric forms such as 2-aminoquinoline, 2, 4-aminoquinoline and 4-aminoquinoline. They have multiple pharmacological properties that have

generated interest in their use as synthetic precursors and medicine scaffolds [8, 10, 23, 27, 40]. The present work is directed towards the synthesis of pyrimidine derivatives with the aim of devising an efficient synthetic procedure and studying their spectral properties using cost effective and readily available reagents [6, 22, 31, 36, 47, 48]. It is also evaluated the role of basicity and steric hindrance with respect to the formation of isomeric product [18, 41].

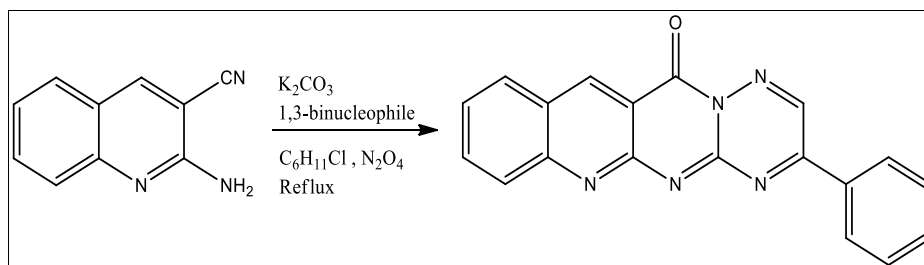
Aniline was used as a starting material to prepare the ortho-aminoquinoline precursor under standard conditions for Vilsmeier-Haack reactions. The following reactions are represented in a schematic way: intramolecular cyclization and functional group transformation of the precursor [31, 36, 48]. The major steps involved in this transformation are outlined in Scheme 1.



Scheme 1: Formation of the precursor.

Triamterene is a nitrogen containing heterocyclic medication with diuretic properties which spares potassium. It is diuretic, euresis and antipotassium diuretic due to its effect on the distal renal tubule [53]. Triamterene is clinically

effective as a treatment for hypertension and edema caused by heart failure, renal failure, and other diseases. It has the property of retaining potassium, which is good for patients who are losing potassium through diuretics [53].



Scheme 2: Formation of the final derivative.

Scheme 2. Synthesis of a triamterene derivative from an 2-aminoquinoline-3-carbonitrile precursor.

Molecular formula: C₁₉H₁₀N₅O.

2.1 General Procedure for the Synthesis of the Triamterene Derivative

The precursor molecule ortho-aminoquinoline were used to synthesize the triamterene 3-phenyl-1, 2, 4-triazino [5, 6]

quinolin-4(3H)-3 derivative. Alkylamine, in EtOH and were used for treatment of the precursor. This reaction led to formation of the triamterene derivative by an intramolecular cyclization of the intermediate formed. The reaction was

followed using thin-layer chromatography (TLC) with silica gel as a stationary phase and an ethyl acetate/petroleum ether mixture as the mobile phase. Melting points were measured by a digital melting point apparatus. Silica gel thin layer (0.25 mm, 60G F254) plates were used for the TLC. Synthetic compound was characterized by spectroscopic techniques.

Step 1: Formation of the intermediate: A solution of 2-aminoquinoline-3-carbonitrile (1 mmol) was prepared in ethanol (2 mL) containing ethanol (15%). A catalytic amount of K_2CO_3 were then added. The reaction mixture was refluxed for 2-3 h and the completion of the reaction was followed by TLC. Once the mixture was completed it was taken out and allowed to Pour in ice-cold water at room

temperature. Reaction mixture was casted into ice cold water and yellow green precipitation was obtained. The precipitate was filtered, washed with ethanol and dried for overnight.

Step 2: Cyclization with $C_6H_{11}CIN_2O_4$: The imine intermediate (1 mmol) was dissolved in ethanol (5 mL). Substituted Diethyl 1-chlorohydrazine-1, 2-dicarboxylate in EtOH (1 mmol) and a small amount of 1, 3 binucleophile (1 mmol) were added to the alcoholic solution. The triamterene derivative was prepared by refluxing the mixture at 80-90 °C for 2 h. The reaction product was then worked up with ice-cold water. The solid material was filtered, washed, dried overnight and recrystallized from ethanol to give the pure compound.

Table 1: Optimization with different solvents and molar ratios.

Sr. No. Exp.	Solvent (0.3 M unless noted)	Base (equiv)	$C_6H_{11}CIN_2O_4$ (equiv)	Temp. (°C)	Time	Method
1	EtOH	K_2CO_3 (0.5)	1.0	80	2h	Oil Bath
2	MeOH	K_2CO_3 (0.5)	1.0	80	2.5h	Oil Bath
3	DMF	K_2CO_3 (0.5)	1.0	90	3h	Oil Bath
4	DMSO	K_2CO_3 (0.5)	1.0	90	5h	Oil Bath
5	EtOH/Water (5:1)	K_2CO_3 (0.5)	1.0	90	-	Oil Bath
6	CH ₃ CN	K_2CO_3 (0.5)	1.0	109	6h	Oil bath
7	PhCH ₃	K_2CO_3 (0.5)	1.0	150+	-	Oil Bath

Table 2: Optimization with different bases.

Sr. No. Exp.	Solvent (0.3 M unless noted)	Base (equiv)	$C_6H_{11}CIN_2O_4$ (equiv)	Temp. (°C)	Time	Method
1	EtOH	K_2CO_3 (0.5)	1.0	80	2h	Oil Bath
2	EtOH	Na_2CO_3 (0.5)	1.0	90	2h	Oil Bath
3	EtOH	NaOH (0.5)	1.0	100	6h	Oil Bath
4	EtOH	KOH (0.5)	1.0	100	6h	Oil Bath
5	EtOH	NaI (0.5)	1.0	90	5 h	Oil Bath
6	EtOH	KI (0.5)	1.0	130	5 h	Oil bath

Table 3: Optimization with different molar ratios of $C_6H_{11}CIN_2O_4$.

Sr. No. Exp.	Solvent (0.2 M unless noted)	Base (equiv)	$C_6H_{11}CIN_2O_4$ (equiv)	Temp. (°C)	Method
1	EtOH	K_2CO_3 (0.5)	0.5	80	Oil Bath
2	EtOH	K_2CO_3 (0.5)	1.0	80	Oil Bath
3	EtOH	K_2CO_3 (0.5)	2.5	80	Oil Bath
4	EtOH	K_2CO_3 (0.5)	3	80	Oil Bath

Table 4: Optimization with different 1, 3 binucleophile.

Sr. No. Exp.	Solvent (0.3 M unless noted)	1, 3 binucleophile (equiv)	$C_6H_{11}CIN_2O_4$ (equiv)	Temp. (°C)	Time	Method
1	EtOH	Guanidine.HCl (1)	1.0	80	2h	Oil Bath
2	EtOH	Urea (1)	1.0	80	-	Oil Bath
3	EtOH	Thiourea (1)	1.0	90	-	Oil Bath
4	EtOH	Azide (1)	1.0	90	-	Oil Bath
5	EtOH	Diazoalkane (1)	1.0	90	-	Oil Bath

2.2 Characterization Data

The synthesized compound was obtained in good yield (72.1%). The IR spectrum showed characteristic stretching bands for NH_2 at 3357 cm^{-1} , $C=N$ at 1622 cm^{-1} , $NHCO$ at 3302 cm^{-1} , $COCl$ at 1799 cm^{-1} , and aromatic $C=C$ at 1600 cm^{-1} . Signals were observed in the ^1H NMR spectrum at δ 7.1-8.5 ppm for the aromatic protons, δ 5.4 ppm for the NH_2 and δ 10.8 ppm for NH . Signals at δ 110-155 ppm were observed in the ^{13}C NMR spectrum, which were consistent with the presence of triazoloquinoline carbons. The mass spectrum showed a molecular ion peak which agreed with the proposed molecular formula, though it is best to confirm

the HRMS value prior to submission.

Yield: 72.1%; m.p. 105 °C; IR (KBr): 3032 (CH Ar), 1677 ($C=O$), 1595 ($C=N$ triazine), 1022 (N-N), 1260 ($C=N$) cm^{-1} ; ^1H NMR (400 MHz, $DMSO-d_6$): δ 7.4-8.9 (m, Ar-H), 7.2-7.8 (Quartet, Ph-H), 8.2-9.3 (H adjacent to N), ^{13}C NMR (400 MHz, $DMSO-d_6$): δ 165, 149, 135, 130, 110. HRMS (ESI): molecular formula and exact calculated/found m/z values should be repeated to check for consistency. This method is performed with inexpensive reagents and has a good functional group tolerance. This makes it possible that it can find application in scale-up and subsequent heterocycle variation [32-35].

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Conclusion

In the current study, a fused triamterene derivative was synthesized in a simple and efficient manner, with an economical and scalable route, was reported. Synthetic compound has good yield and characterized with standard spectroscopic method. An alternative to classical synthetic approaches of related N-containing heterocyclic systems is provided by the work. Nitrogen heterocycles continue to play a significant role in organic and medicinal chemistry as many biologically active compounds feature nitrogen as an important heteroatom. Their structures provide wide opportunities for chemical modification, and their structure can aid in optimizing physicochemical and pharmacokinetic properties. The study suggests that the efficient design and synthesis of N-based compounds is possible with future applications in medicines and synthesis [3, 4, 20].

Conflict of Interest

The authors declare no conflict of interest.

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