SYNTHESIS AND CHARACTERIZATION OF QUINOXALINES & THEIR ANTIMICROBIAL STUDY

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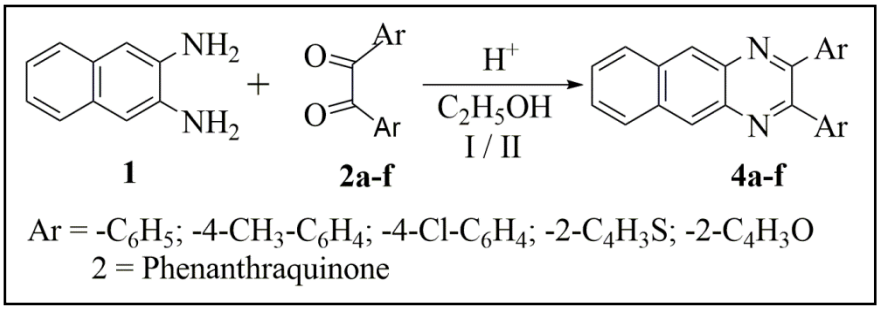
Abstract

Mineral acid catalyzed cyclocondensation reaction between naphthalene-2,3-diamine and various 1,2-diarylketones in the presence of ethanol as a solvent under two different energy source such as Microwave and thermal energy sources to afford various quinoxalines. All the synthesized compounds are well characterized by different spectroscopic techniques and tested for antimicrobial activity.



KEYWORDS: Quinoxaline, Antimicrobial Activity, Microwave, Spectroscopy.

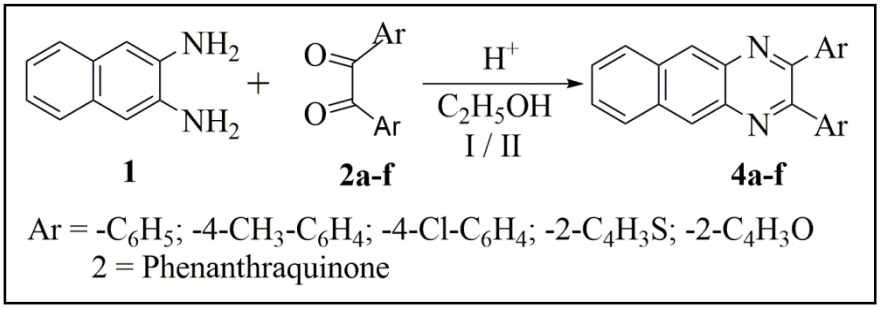
1.1 Introduction

Heterocyclic quinines containing nitrogen atom are known to possess antibacterial [**1, 2**], antifungal [**3-5**] and cytotoxic activities [**6-9**]. The clinical significance of this class of compounds has stimulated the synthesis of new lead compounds retaining the 'core' quinone chromophore [**10-12**]. Quinoxaline derivatives are nitrogen containing heterocyclic compounds and their importance has been reported in the literature [**13-15**]. They possess well known biological activities including anti-viral, anti-bacterial, anti-inflammatory, antiprotozoal, anthelmintic, anticancer and as kinase inhibitors. Quinoxaline derivatives constitute the basis of many insecticides, fungicides, herbicides, as well as being important in human health and as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of several antibiotics like as levomycin, echinomycin and actinomycin which are familiar transplantable lumb. In addition, quinoxaline derivatives are reported for their application in dyes, efficient electroluminescent materials, organic semiconductors and DNA cleaving agents. These are useful as intermediates for many target molecules in organic synthesis and also as synthon**s.**

This work deals with the new synthetic rout of quinoxaline synthesis from 1,2-diamine & 1,2-diketone using mineral acid as the catalyst.

1.2 Reaction Scheme

The cyclocondensation reaction between naphthalene-2,3-diamine (0.0105 mole) and 1,2-diarylketone (0.01 mole) **2a-f** in ethanol (10 mL) under Microwave and thermal energy sources to afford quinoxalines **4a-f** using 5mmol % HCl (Scheme 1).



Scheme 1

1.3 Result and Discussion

1.3.1 Optimization of reaction condition

The cyclocondensation reaction between naphthalene-2,3-diamine (0.0105 mole) and benzil (0.01 mole) in ethanol (10 mL) under Microwave to afford quinoxaline **4a** (**Scheme 1**) was chosen as the model reaction for optimization. The amount of HCl was used in the ratio of mmole % with respect to naphthalene-2,3-diamine. The reaction was studied under Microwave at power level 240 Watt. Reaction was also optimized by varying HCl (Table 1, entries 1-6). It was observed that 5 mmole % amount of catalyst on the basis of naphthalene-2,3-diamine is suitable to complete the reaction in moderate time with high yield.

Table 1 Effect of different catalyst on the condensation of benzil and naphthalene-2,3-diamine in ethanol as the solvent under microwave.

Entry	Catalyst	Under Microwave	
		Time[a] (min)	Yields[b] (%)
1	1mmol % HCl	2	80
2	2mmol % HCl	2	80
3	3mmol % HCl	2	80
4	4mmol % HCl	3	85
5	5mmol % HCl	3	90
6	6mmol % HCl	3	85

[a] Reaction was monitored by TLC, [b] Isolated yields.

Thus, it was found that the condensation reaction carried out in the presence 5mmol mmole % HCl under Microwave showed the highest conversion rate and this was chosen as the optimized condition to perform a series of reactions to check substrate dependency of the protocol.

Our next target of the present work was to synthesize all the quinoxaline derivatives by taking the assistance of microwave irradiation (MWI) technique using ethanol as the solvent. These series of experiments were also optimized with respect to power levels. The reactions as presented in Scheme 1 were carried out under microwave irradiation. The MWI reactions were carried out in the Scientific Microwave system CATA-R CATALYST SYSTEM. The optimization of the power levels was checked with reference to duration of reaction, yield improvement. The characteristic data are given in Table 2.

Table 2 Data representing the optimization for synthesis of quinoxalines by the assistance of MWI technique.[a, b]

Power Levels in Watt	Reaction Time (min)[a]	% Isolated Yield[b]
140	4	75
210	3.5	85
240	3	90
280	3	80
350	3	80

[a]Reaction was monitored by TLC.; [b]Isolated yields.

From the above experimental data, it becomes clear that more efficient results were obtained at 240 W power level of the MW instrument. At this power level quinoxaline derivative were obtained in 90% yield with very good purity in 3 min.

1.4 Experimental

1.4.1 Chemicals and Reagents

All chemicals utilized are of LR grade. HCl, 2,3-naphthalenediamines, Various 1, 2- and diketone, were obtained from Samir Tech Chem. Pvt. Ltd., Vadodara, India. All the solvents were supplied by Sisco Chem. Pvt. Ltd., Mumbai, India.

1.4.2 Analytical Methods

M. P. was measured by capillary process and data are uncorrected. ^{1}H NMR & ^{13}C NMR data were detected in DMSO-d_6 solution using Bruker Avance 400 spectrometer (100 MHz for ^{13}C NMR & 400 MHz for ^{1}H NMR operating frequency). δ ppm (Parts per million) unit is used for Chemical shifts (δ) expression. IR data found using spectrophotometer name ABB Bomem Inc. FT-IR 3000 7 & wave numbers (cm^{-1}) unit for data expression. Molecular mass were determined using spectrometer name Shimadzu LCMS-2010. Hydrogen, Carbon and Nitrogen were found using Elemental Analyzer PerkinElmer 2400 Series II CHNS/O. All the product formation were regulated by TLC using aluminum sheet precoated with silica gel 60 f254 (Merck).

1.4.3 General Experimental procedure

To a mixture of an 2,3-naphthalenediamine (1 mmol) and benzil (1 mmol) in ethanol (5mL), 5 mmole % HCl with respect to 2,3-naphthalenediamine was added and the mixture was reflux under microwave at optimum power level. Reaction completion was regulated by TLC having Al sheet precoated with silica gel 60 f_{254} (Merck). After compilation of reaction, solvent was evaporated with care and the pure product was obtained. The product obtained had been characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and GC-MS.

Table 3 Synthesis of quinoxalines 4a-4f by using HCl as a catalyst in ethanol under microwave and convectional energy source.

Code	Ar	Thermal Conditions		Microwave Irradiation	
		Reaction Time[a] (h)	Yield[b] (%)	Reaction Time[a] (min)	Yield[b] (%)
4a	C_6H_5-	3	80	3	88
4b	4-CH_3-C_6H_4-	4	70	6	86
4c	4-Cl-C_6H_4-	3	80	5	86
4d	2-Cl-C_6H_4-	3.5	78	7	85
4e	4-NO_2-C_6H_4-	3	90	6	85
4f	2-NO_2-C_6H_4-	3	84	4	84

[a]Reaction was monitored by TLC.; [b]Isolated yields.

1.5 Antimicrobial activity of Compounds 4a-4f

(I) **Against *Staphylococcus aureus*:**

Maximum activity were found in compound (4f) zone of inhibition-10.0 m.m. and minimum activity were found in compounds (4a, 4d) zone of inhibition -7.0 m.m

(II) **Against *Bacillus megaterium*:**

Maximum activity were found in compounds (4f) zone of inhibition -14.0 m.m where as minimum activity were found in compound (4b) zone of inhibition -6.0 m.m.

(III) **Against *Escherichia coli*:**

Maximum activity were found in compound (4f) zone of inhibition -11.0 m.m and minimum activity were found in compound (4c) zone of inhibition -5.0 m.m

(IV) **Against *Proteus vulgaris*:**

Maximum activity were found in compound (4f) zone of inhibition -15.0 m.m (near to standard drug) and minimum activity were found in compounds (4a, 4d) zone of inhibition -5.0 m.m

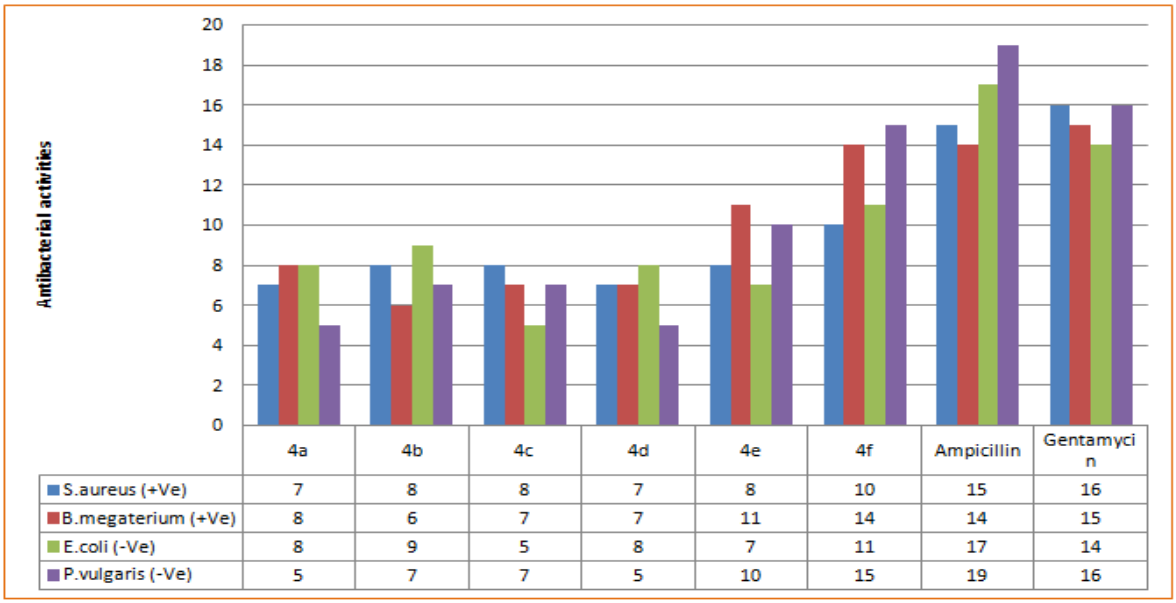


Figure 1 Antimicrobial activity of Compounds 4a-4f.

1.6 Characterization

1.6.1 2,3-diphenylbenzo[g]quinoxaline (4a)

Molecular Formula: $C_{24}H_{16}N_2$

IR (KBr): 1608, 1467, 1335, 1242, 1185, 1065, 980, 818, 726, 612 cm^{-1}.

^{1}H NMR (400 MHz, DMSO, δ ppm): 7.6- 7.4 (m, 10H, Ar-H), 7.8-7.6 (m, 6H, Ar-H).

^{13}C NMR (DMSO-*d6*, δ ppm): 127.9, 128.9, 129.1, 129.2, 129.4, 129.6, 130.1, 131.1, 131.2, 134.8, 136.1, 139.0, 139.1, 139.5, 141.1, 153.8, 154.4, 155.3, 155.5.

ESI-MS: m/z $(M+H)^+$: 332.12.

% C, H, N Analysis: Cal. : C, 86.72; H, 4.85; N, 8.43; **Found:** C, 86.78, H, 4.86; N, 8.45

1.7 Conclusion:

We have reported green protocol for one-pot synthesis of quinoxaline derivatives from readily available 2,3-naphthalenediamines and 1, 2- diaryl ketones, by a simple and convenient protocol. The conditions are mild and a wide range of functional groups can be tolerated in the building blocks for synthesized quinoxalines.

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