Research Paper

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Synthesis, Characterisation and Biological Evaluation of Some Novel Substituted Pyrazine and Quinoxaline

Chemistry

KEYWORDS : 1,2-Diones, Pyrazines, Quinaoxalines, anti-bacterial activity

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ABSTRACT

An efficient environmentally benign condensation of 1,2- diketones and 1,2-diamines for a facile synthesis of pyrazines & quinoxalines was carried out in eco-friendly solvent in the presence of an inexpensive, non-toxic and metal ion free catalyst at ambient temperature. Short reaction time, environmentally benign condition, easy workup and high yield are the special features of this method.

INTRODUCTION

Among the various classes of nitrogen containing heterocyclic compounds, quinoxalines and pyrazines are important components of several pharmacologically active compounds. Pyrazine contains two nitrogen atoms in its aromatic ring[1] and it plays an important role as intermediates for perfumes,[2] pharmaceuticals, agricultural chemicals[3] and food spices like cheese, tea coffee, cooked meats nice aroma etc.[4] Quinaoxalines are also

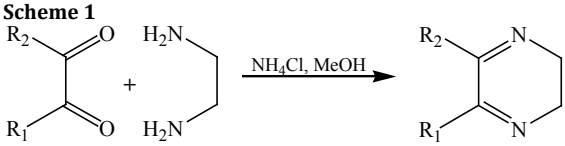
associated with a wide spectrum of biological activities ranging from anticancer to antimicrobial, antifungal, antidepressant, antibacterial and anti-inflammatory activities.[5] Although rarely described in nature, synthetic quinoxaline ring is a part of a number of antibiotics which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors.[6] Moreover, they are well known for their application in dyes, efficient electroluminescent materials,[7] organic semiconductors,[8] building blocks for the synthesis of anion receptors,[9] cavitands,[10] dehydroannulenes[11] and DNA cleaving agents.[12]

In general, these compounds could be achieved via the double condensation of arene-1,2-diamines with 1,2-dicarbonyl compounds in organic solvents for 2-12 h under refluxing conditions with 34-85% yields.[13] From the synthesis standpoint, the traditional processes generally require high reaction temperature, strong acidic media, and mostly long reaction time. Pyrazine is generally prepared by the catalytic reaction of diamines with dioles in a vapour phase, dehydrogenation of piperazine or dealkylation of methyl pyrazine.

RESULTS AND DISCUSSION

1,2-diones were successfully utilized for synthesis of pyrazines by condensation with 1,2-diaminoethane (Scheme 1).

Scheme 1

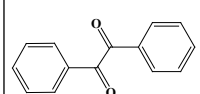
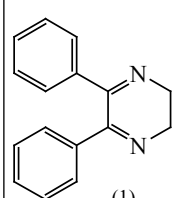
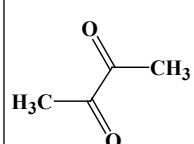
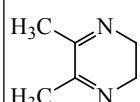


(A) (B) (R_1,R_2 = alkyl, aryl) (C)

Several experiments were carried out to optimize the newly developed general protocol for synthesis of pyrazines. In deciding the best solvent for the above transformation, a series of polar protic and polar aprotic solvents were tried in the above model reaction and methanol was found to be the best The effect of mole % of NH_4Cl on the yield of condensation reaction in MeOH was also studied during the course of table work and it was observed that 50 mole % of NH_4Cl in MeOH is suitable choice for the general reaction.

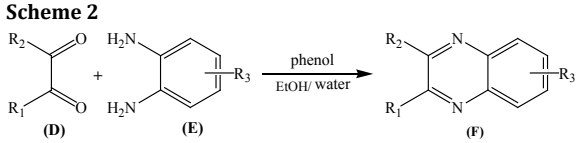
Two different 1,2-diones **(A)** were used to get the corresponding pyrazines **(C)** are listed in table -1.

Table-1

Sr. No.	1,2-DIONES **(A)**	PYRAZINES **(C)**
I		 (1)
II		 (2)

The direct condensation of 1,2 diones **(A)** and 1,2-diaminobenzene **(B)** has been successfully achieved mostly in excellent yields using (Ethano/water-phenol) as a mild, efficient, cost-effective, readily available, acid-free, metal-free and eco-friendly catalyst system at room temperature (Scheme 2).

Scheme 2



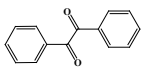
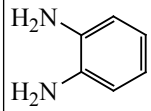
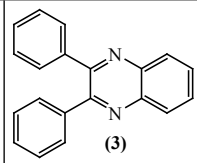
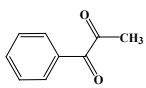
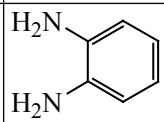
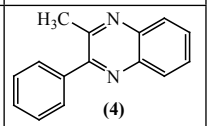
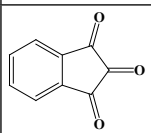
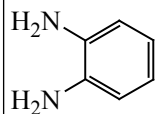
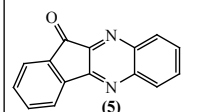
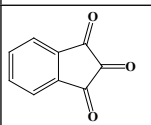
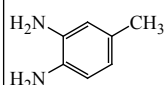
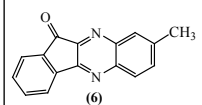
(D) (E) (F)

(R_1,R_2 = alkyl, aryl)
(R_3 = alkyl, alkoxy)

Two different 1,2-diones **(D)** synthesized in above scheme were used to get the corresponding quinoxalines **(F)** are listed in table-2. In deciding the best solvent for the above transformation, a series of polar protic and polar aprotic solvents were tried in the above model reaction and ethanol/water (7:3, v/v) was found to be the best.

It was observed that a 15 mole % of phenol in ethanol/water is the suitable choice for the general reaction.

Table-2

Sr. No.	1,2-DIONE **(D)**	1,2-DIAMIN-OBENZENES **(E)**	QUINOXALINES **(F)**
I			 (3)
II			 (4)
III			 (5)
IV			 (6)

PROCEDURE

I] Synthesis of 5,6-Diphenyl-2,3-dihydropyrazine (1)

2.5 g (0.0119 mole) of Benzil was dissolved in 75 ml of methanol. Ammonium chloride 0.318 g (50 mole %) was added and then 0.785 g (0.0131 mole) of 1,2-diaminoethane was added. Progress of reaction was monitored by TLC (toluene-ethyl acetate 8:2).

After completion of reaction, volume was reduced to 1/4th and chilled to 10-15°C. Precipitated solid was collected by filtration and dried to afford 2.23 g off-white crystalline powder. m.p.: 162°C; IR (KBr, cm^{-1}) :1610 (C=N stretching), 2944 (C-H stretching), 3080 (C-H stretching, aromatic); PMR ($CDCl_3$, δ): 3.9 (4H, 1t, -CH_2), 7.3-7.6 (10H, m, aromatic); Elemental: C (81.97%), H (6.05%), N (11.98%).

II] Synthesis of 5,6-Dimethyl-2,3-dihydro-pyrazine (2)

2.05 g (0.0238 mole) of Butane-2,3-dione was dissolved in 25 ml of methanol. Ammonium chloride 0.636 g (50 mole %) was added and then 1.57 g (0.0262 mole) 1,2-diaminoethane was charged. Progress of reaction was monitored by gas chromatography [Instrument: PE Clarus 500; Column: HP-5 (30 m x 0.32 mm x 0.25 µm); Oven: 50°C (2min.), ramp 20°C/min., final temperature 260°C, injector/detector (FID) temperature 270°C; carrier N_2 , 2 ml/min.].

After completion of reaction, methanol was evaporated under diminished pressure at RT. Residue was extracted in 30 ml of MDC & washed with 2 x 10 ml of chilled water. MDC layer was evaporated under vacuum to afford 1.7 g (Yield: 65%) of compound **(2)** as amber yellowish coloured viscous oil.

PMR (CDCl3, δ): 1.0 (6H, 1s, -CH3) , 1.6 (4H, 1t, –CH2); Elemental: C (65.46%), H (9.13%), N (25.41%).

III] Synthesis of 2,3-Diphenyl-quinoxaline (3)

2.5 g (0.0119 mole) of Benzil was dissolved in 165 ml of ethanol and 70 ml of water. Phenol 0.168 g (15 mole %) was added and then 1.35 g (0.0125 mole) of 1,2-diaminobenzene was added. Progress of reaction was monitored by TLC (toluene-ethyl acetate 8:2).

Water (160 ml) was added to precipitate the product. Crude product was filtered, washed with water and dried. Recrystallization in methanol gave 2.75 g of compound **(3)** as faint yellow crystalline powder.

m.p.: 127-128°C; IR (KBr, cm-1) :1348 (C=N stretching), 3057 (C-H stretching, aromatic); PMR (CDCl3, δ): 7.2-7.5 (10H, m, two phenyl substituents), 7.7 (2H, 1t, quinoxaline ring), 8.1 (2H. 1d, quinoxaline ring); Elemental: C (85.11%), H (4.95%), N (9.94%).

IV] Synthesis of 2-Methyl-3-phenyl-quinoxaline (4)

1.76 g (0.0119 mole) of 1-Phenyl-propane-1,2-dione was dissolved in 165 ml of ethanol and 70 ml of water. Phenol 0.168 g (15 mole %) was added and then 1.35 g (0.0125 mole) of 1,2-diaminobenzene was added. Progress of reaction was monitored by TLC (toluene-ethyl acetate 8:2).

Water (160 ml) was added to precipitate the product. Crude product was filtered, washed with water and dried. Recrystallization in methanol gave 1.95 g of compound **(4)** as faint yellow crystalline powder.

m.p.: 55°C; PMR ($CDCl_3$, δ): 2.8 (3H, 1s, -CH_3), 7.4-7.6 (3H, 2t, phenyl substituent), 7.7 (2H, 1d, phenyl substituent), 8.1 (2H. 1t, quinoxaline ring), 8.2 (2H. 1d, quinoxaline ring); Elemental: C (81.82%), H (5.51%), N (12.67%).

V] Synthesis of Indeno[1,2-b]-quinoxaline-11-one (5)

0.8 g (0.005 mole) of Indane-1,2,3-trione was dissolved in 70 ml of ethanol and 30 ml of water. Phenol 0.071g (15 mole %) was added and then 0.567 g (0.0053 mole) of 1,2-diaminobenzene was added. Progress of reaction was monitored by TLC (petoleum-ether/benzene/1,4-dioxane/ethylacetate 4:3:1:2).

Water (65 ml) was added to precipitate the product. Crude product was filtered, washed with water and dried. Recrystallization in methanol gave 0.93 g of compound **(5)** as yellow crystalline powder.

m.p.: 222-224°C; IR (KBr, cm^{-1}) :1573 (C=N stretching)**,** 1730 (C=O stretching)**,** 3040 (C-H stretching, aromatic)**;** PMR ($CDCl_3$, δ): 7.4-7.6 (2H, 2t, indanone ring)**,** 7.7-7.9 (2H, 2d, indanone ring)**,** 7.7 (2H, 1t, quinoxaline ring)**,** 8.2 (2H, 1d, quinoxaline ring); Elemental: C (77.62%), H (3.46%), N (12.01%).

VI] Synthesis of 8- Methyl- indeno [1,2-b]- quinoxaline- 11-one (6)

0.8 g (0.005 mole) of Indane-1,2,3-trione was dissolved in 70 ml of ethanol and 30 ml of water. Phenol 0.071g (15 mole %) was added and then 0.647 g (0.0053 mole) of 3,4-diaminotoluene was added. Progress of reaction was monitored by TLC (petoleum ether/benzene/1,4-dioxane/ethylacetate 4:3:1:2).

Water (65 ml) was added to precipitate the product. Crude product was filtered, washed with water and dried. Recrystallization in methanol gave 0.95 g of compound **(6)** as yellow crystalline powder.

m.p.: 180-182°C; IR (KBr, cm^{-1}) : 1607 (C=N stretching)**,** 1728 (C=O stretching)**,** 2865 (C-H stretching, methyl)**,** 3063 (C-H stretching, aromatic)**,** PMR ($CDCl_3$, δ): 2.6 (3H, 1s, -CH_3)**,** 7.5-7.6 (2H, 2t, indanone ring)**,** 7.7-7.8 (2H, 2d, indanone ring)**,** 7.5 (1H, 1d, quinoxaline ring)**,** 8.1 (2H, 1d, quinoxaline ring); Elemental: C (77.99%), H (4.06%), N (11.42%).

BIOLOGICAL ACTIVITY

Micro-organisms are very significant for human beings because of their activities. Microbes depending on their types have either detrimental or beneficial effects. Microorganisms are naturally present on human body and in the environment & its effect is causing diseases and other being food spoilage. The substances used against pathogenic microorganisms are classified as bacteriostatic. Disinfectants are strongly bactericidal in action, even destroy bacterial spores. Antiseptics also come under class of disinfectants. The terms germicides and bactericides are also used to describe both disinfectants and antiseptics.[14]

The study is a simple and reliable technique especially applicable in routine bacteriological work. It consists of small discs of a Whattman filter paper soaked with given amounts of a com-

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pound, placing them on plates of culture medium inoculated with the organism to be tested and after incubation, the sensitivity is determined on the basis of areas of inhibition of growth produced by the diffusion of the compound under study from the discs into the surrounding medium.[15]

Some of the newly synthesized pyrazines and quinoxalines were screened for their antimicrobial activity with gram positive bacteria *Bacillus subtilis* and gram negative bacteria *Escherichia coli,* implementing disc diffusion method in nutrient agar medium. Ciproflaxin is used as a standard drug (Table-3).

Table-3

Compound		Test Organisms	
		Gram positive	Gram negative
No.	Molecular Formula	Bacillus subtilis	Escherichia coli
1	C16H14N2	+ + +	_
5	C15H8N2O	+	_
6	C16H10N2O	+	_
Ciprofloxacin		+ + + +	+ + + +

Note-(+ + + +) = Complete Inhibitation, (+ + +) = Moderate Inhibitation
(+ +) = Less Inhibitation, (+) = Least Inhibitation & (–) = No Inhibitation

CONCLUSIONS:
In summary, a new application of ammonium chloride & phenol as an effective, very cheap and non-toxic catalyst for the synthesis of pyrazines and quinoxalines respectively, based on the condensation of 1,2--dicarbonyl compounds with 1,2-diamines under mild reaction conditions is presented. The most important point in this work is that new derivatives of pyrazine and quinoxaline were also synthesized. This method is significant from an environmental point of view and economic considerations because it produces little waste.

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