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AN EFFICIENT SYNTHESIS OF QUINOXALINES IN WATER MEDIATED BY TETRAETHYLAMMONIUM BROMATE

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Abstract- An efficient environmentally benign condensation of 1,2 diketones and 1,2-diamines for a facile synthesis of quinoxalines was carried out in aqueous medium in the presence of tetraethylammonium bromate. Short reaction time , environmentally benign condition , easy workup and high yield are the special features of this method.
Key words -: 1,2-diketones, 1,2- diamines, tetraethylammonium bromate, quinoxaline, aqueous medium, , green synthesis, cationic surfactants, cyclocondensation

INTRODUCTION

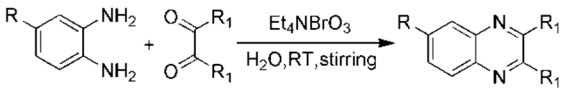
Quinoxaline and its derivatives are integral part of several bioactive molecules which finds applications as anathematic, anticancer [1], antimicrobial [2], antifungal, and antidepressant activities [3,4]. Quinoxaline ring is also part of various antibiotics such as echinomycin, levomycin and actinomycin [5,6] which are known to inhibit the growth of Gram positive bacteria and are active against various transplantable tumors [7]. The classical synthesis of quinoxaline derivatives involves the double condensation of aryl 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid for 2 -12 h in 34-85% yield [8], Synthesis with molecular iodine in ethanol have also been reported [9]. Recently, improved synthetic methods have been reported and to mention a few are the oxidative coupling of epoxides and ene-1,2-diamines catalyzed by Bi(0) [10] , reaction of α-hydroxyketones via a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-TEMPO [11] and MnO_2 [12], cyclization of α-arylimino oximes of α-dicarbonyl compounds under reflux in acetic anhydride [13] and finally condensation of 1,2-diamine with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation at 100^0 C [14] . Further, such condensations have also been affected by palladium acetate catalyzed aerobic oxidation in toluene at ambient temperatures. However , long time required for completion (about 24 h) is a drawback. Other methods using catalytic amount of a variety of metal precursors, acids, zeolites, and molecular iodine have been reported [15, 16a-g, 17a-d]. Recently, quinoxaline derivatives were synthesized using cupric sulfate pentahydrate, IBX, and Zn [*l*-proline] [18a-c], $MnCl_2$[19] , ruthenium catalyzed direct approach [20] , MnO_2 [21], CAN [22] , MnO_2 and octahedral molecular sieves [23], PbO [24] , and solid acids [25]. It my however, be mentioned that these methods suffer from drawbacks such as the requirement of excess reagents (usually 10 equiv) particularly in the case of MnO_2 and high boiling solvents in most cases. This has resulted in their reduced commercial attractiveness and green credentials. In view of the disadvantages, there remains a scope for the development of facile and green method for the synthesis of the quinoxaline derivative .

RESULTS AND DISCUSSION

In this work, we wish to report the efficient use of aqueous tetraethylammonium bromate as an unusual reagent for the double condensation of 1,2-diamines and 1,2 dicarbonyl compounds for the facile synthesis of quinazoline derivatives. In continuation of our investigations with tetraalkylammonium bromates, we observed that an aqueous solution of tetraethylammonium bromate can be conveniently used for the cyclocondensation of 1,2-diamines and the 1,2-diketones to give the quinazoline derivatives in a short time and in excellent yield. Herein, we report the first ever use of a quaternary ammonium salt for carrying out such a cyclocondensation reaction in aqueous medium. The reaction is studied in several organic solvents such as aqueous EtOH, EtOAc, aqueous CH_3CN and dichloromethane at room temperature but these solvents are not found suitable as the yields were poor and the reactions required a long time for completion. Experiments however indicated that at room temperature, best yield of the target products was obtained both in aqueous acetonitrile and water . However, in keeping with our aim of developing a green protocol for the synthesis of the quinazoline derivatives , the synthesis was performed in aqueous medium only and the results are reported herein. The reaction conditions were standardized by taking o-phenylenediamine and benzil as the substrates . The procedure involved the suspension of a homogenized mixture of both reactants in an aqueous solution of tetraethylammonium bromate and

the mixture stirred at room temperature for a varying period of time (20-45 mins). The completion of the reaction was indicated by the appearance of a brown precipitate of the target quinazoline which was identified by comparing melting points from literature and by its spectral characteristics .The yield was found to be as high as 92%. Under this standard condition , other similar reactions were performed with substituted 1,2 diketones and *o*- pheneylenediamines. The reaction carried out is shown in **Scheme 1** and the physical characteristics of the products are given in **Table 1**.

Scheme 1: Synthesis of quinoxaline derivatives in aqueous medium



R = H, Cl, Me
R_1= Ph, 4-MePh, 2-furyl

CONCLUSION

In summary, we have carried out a simple, efficient and environmentally benign synthesis of quinoxaline derivatives mediated by tetraethylammonium bromate in water . One reason for the easy work up being the solubility of spent tetraethylammonium bromate and insolubility of quinoxalines in water which made separation of products from the reaction mixture and their subsequent recovery easy. The mildness of the conversion, experimental simplicity , clean and simple work up together with high yields of the products makes this approach attractive. To the best of our knowledge , the synthesis of quinoxalines using tetraethylammonium bromate in water has not yet been reported.

EXPERIMENTAL

All chemicals were purchased from Merck and Aldrich and used as received. o-phenylenediamine was purified by method reported in literature [26]. Melting points were recorded in open capillaries .^{1}H and ^{13}C NMR spectra were recorded on a Bruker Bio-Spin spectrometer at 300 MHz using TMS as an internal standered (in $CDCl_3$). Mass spectra ESIMS were recorded in waters Q-Tof Premier & Aquity UPLC, LC-MS/MS system and IR spectra were recorded on a Shimadzu FTIR spectrometer in KBr pallets. ET_4NBrO_3 was prepared by a reported procedure [27].

General procedure for the synthesis of substituted Quinoxalines using tetraethyl ammonium bromate:

A homogenized mixture of the aromatic 1,2-diketones (1 mmol) and aromatic 1,2-diamines (1.2 mmol) was added to a round bottomed flask containing 10 ml of water and stirred. To this stirred suspension tetraethylammonium bromate (1mmol, 0.258g) was added and the suspension was further stirred. The progress of the reaction was monitored by TLC in ^{254}F silica gel plates with ethylacetate: *n*-hexane (0.5:9.5) as the eluent. On continuous stirring for a period of time mentioned in Table 1, a brown precipitate was formed which indicated the completion of the reaction and the formation of the desired product. The reaction mixture was filtered and washed several times with distilled water to remove the spent tetraethylammonium bromate and the diamine . Further purification of the brown solid was done by column chromatography using silica gel (Merck) 60-120 mesh and a mixture of ethylacetate and *n*-hexane as the eluent. All the products were found to be solid and are characterized by comparing the melting points of the compound with those found in literature.

2,3-Diphenylquinoxaline (entry1)

^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.193(t, 2H, J_1=2.7 Hz, J_2=3.6 Hz, ArH),7.77-7.803(m, 2H, ArH), 7.519-7.544(m, 4H, ArH), 7.344-7.365(m, 6H, ArH).^{13}C NMR: (75MHz, $CDCl_3$) ∂ 153.43, 141.17, 138.99, 129.95, 129.79,129.15, 128.78, 128.25.IR (cm^{-1}): 3057.17, 3028.24, 1548.84.

2,3-Di(furan-2^l-yl)quinoxaline(entry 2):

^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.127-8.159(m, 2H, ArH), 7.74-7.773(m, 2H, ArH), 7.636(s, 2H, ArH), 6.563-6.662(m, 4H, ArH).^{13}C NMR: (75MHz, $CDCl_3$) ∂ 150.70, 144.22, 142.60, 140.57, 130.41,129.08, 113.01, 111.91.IR(cm^{-1}): 3109.25, 1649.14.

6-Chloro-2,3-diphenylquinoxaline(entry 3):

^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.19-8.15 (m, 1H, ArH), 8.14-8.07 (m, 1H, ArH), 7.74-7.67 (m, 1H, ArH), 7.55-7.40 (m, 4H, ArH), 7.42-7.30 (m, 6H, ArH) ^{13}C NMR ∂154.71, 154.03, 141.92, 140.15, 139.18, 139.11, 136.08, 131.37, 130.87, 130.25, 129.54, 129.46, 128.76, 128.52 IR(cm^{-1}): 3150,2934,1603.

6-Chloro-2,3-di(furan-2^l-yl)quinoxaline(entry 4): ^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.015-8.101(m, 2H, ArH), 7.618-7.670(m,3H, ArH), 6.561-6.682(m, 4H, ArH). ^{13}C NMR: (75MHz, $CDCl_3$) ∂ 150.41, 150.37, 144.48, 144.34, 143.17, 142.50, 140.74, 138.96, 136.05, 131.26, 130.16, 127.84, 113.6, 113.3, 11.99, 111.95. IR(cm^{-1}): 3115.04, 2922.16, 1598.99.

6-Methyl-2,3-diphenylquinoxaline(entry 5)

^{1}HNMR: (300MHz, $CDCl_3$) ∂ 8.079(d, J= 8.4 Hz, 1H, ArH), 7.967(s, 1H,ArH), 7.6(dd, J= 1.2Hz, 1.2 Hz, 1H, ArH), 7.516(t, J= 5.1 Hz, 4.8Hz, 4H, ArH), 7.35(d, J= 5.7, 6H, ArH), 2.624(s, 3H, CH_3). ^{13}C NMR: (75MHz, $CDCl_3$) ∂ 153.25, 152.5, 141.22, 140.43, 139.63, 139.14, 132.25, 129.76, 128.63, 128.57, 128.17, 127.96, 21.88. IR(cm^{-1}): 3101, 3057, 1618.

2,3-Di(furan-2^l-yl)-6-methylquinoxaline(entry 6): ^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.011(d, J= 8.7 Hz, 1H, ArH), 7.902(s, 1H, ArH), 7.583(t, J= 7.5 Hz, 8.7 Hz), 6.552-6.616(m, 4H, ArH), 2.577(s, 3H, CH_3).^{13}C NMR: (75MHz, $CDCl_3$) ∂ 150.8, 144.07, 143.94, 142.5, 141.76,141.07, 140.63, 139.1, 132.73, 128.53, 127.88, 112.77, 112.52, 111.82, 21.87.IR(cm^{-1}): 3111.18, 2916.37, 1618.28, 1568.13.

2,3-Bis(4-methyl-phenyl)quinoxaline (entry 7):
^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.156(t, J= 2.7 Hz, 3.6 Hz, 2H, ArH), 7.747(m, 2H, ArH), 7.442(d, J= 7.8 Hz, 4H, ArH), 7.158(d, J= 7.8 Hz, 4H, ArH), 2.379(s, 6H, CH_3). ^{13}C NMR: (75MHz, $CDCl_3$) ∂ 153.45, 141.18, 138.72, 136.31, 129.68,129.64, 129.07, 128.95, 21.33. Mass: MS (ES^+): 311.1221(experimental), 310.15(calculated).

2,3-Bis(4'-methyl-phenyl)-6-methylquinoxaline (entry 8):^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.0425(d, J= 8.7 Hz, 1H, ArH), 7.932(s, 1H, ArH), 7.578(d, J= 8.4 Hz, 1H, ArH), 7.428(d, J= 7.5 Hz, 4H, ArH), 7.148 (d, J= 7.8 Hz, 4H, ArH), 2.608(s,3H, CH_3), 2.373(s, 6H, $2CH_3$).^{13}C NMR: (75MHz, $CDCl_3$) ∂ 153.28, 152.55, 141.14, 140.08, 139.55,138.56, 138.48, 136.45, 131.93, 129.67, 129.64, 128.90, 128.56, 127.90, 21.85, 21.31. Mass: MS (ES^+):325.1461 (experimental), 324.16 calc).

2,3-Bis(4'-methyl-phenyl)-6-chloroquinoxaline (entry9): ^{1}H NMR: (300MHz, $CDCl_3$) ∂ 8.146(d, J= 2.1 Hz, 1H, ArH), 8.078(d, J= 9 Hz, 1H, ArH), 7.68(dd, J_1= 2.2 Hz, J_2= 2.1 Hz, 1H, ArH), 7.431(d, J= 7.8 Hz, 4H, ArH), 7.1585(d, J= 8.1 Hz, 4H, ArH), 2.438(s, 3H, CH_3), 2.382(s, 3H, CH_3).^{13}C NMR: (75MHz, $CDCl_3$)∂ 154.24, 153.59, 141.34, 139.57, 139.1, 139, 135.96, 135.88, 135.25, 130.59, 130.28, 129.98, 129.68, 129.63, 128.99,127.93, 21.34.IR (cm^{-1}) : 3043, 2958, 1613, 1527.

2,3-Bis(4'-methyl-phenyl)-benzoquinoxaline(entry 10): ^{1}H NMR:(300MHz, $CDCl_3$) ∂ 8.71(s, 2H, ArH), 8.09(m, 2H, ArH), 7.53(m, 6H, ArH), 7.18(d, J= 8 Hz, 4H, ArH), 2.39(s, 6H, CH_3). ^{13}C NMR: (75MHz, $CDCl_3$) ∂ 154.25, 139.04, 138.03, 136.55, 133.97, 129.84, 129.01, 128.54, 127.42, 126.57, 21.45. IR(cm^{-1}) 3037, 2949, 1627, 1531.

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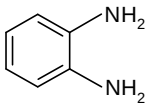
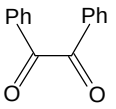
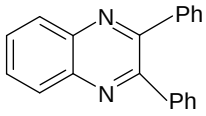
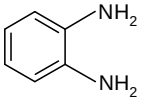
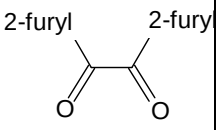
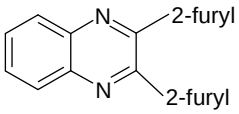
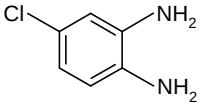
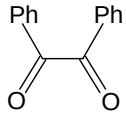
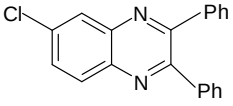
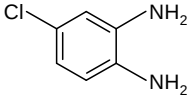
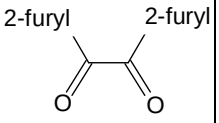
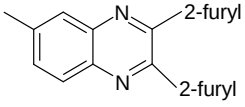
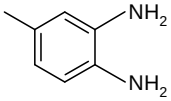
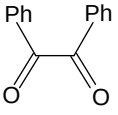
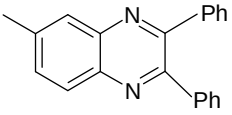
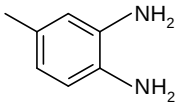
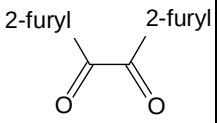
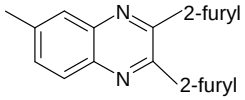
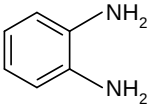
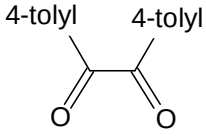
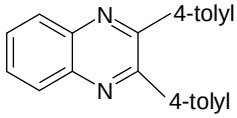
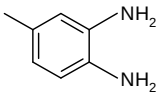
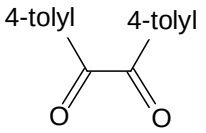
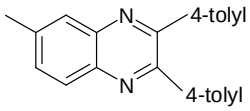
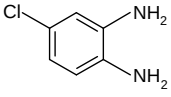
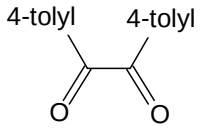
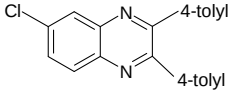
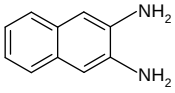
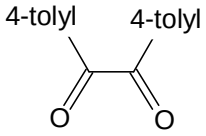
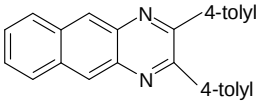
Table 1- Physical characteristics of the product quinoxalines

Entry	diamine	1,2-diketone	Quinoxaline	Time (min)	Yield (%)	Melting Point	
						Obs (^{0}C)	Lit(^{0}C)
1				20	92	124-126	128-129[19]
2				30	88	129-130	131[28]
3				25	82	112-113	115-116[29]
4				30	79	120	122[30]
5				35	77	114-115	117-118[18b]

6				35	75	119-121	119-121[31]
7				25	93	140-142	145-146[9]
8				35	90	138-140	139-140[32]
9				30	91	165-167	169-171[33]
10				45	64	195-197	198[28]