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SYNTHESIS OF FUNCTIONALIZED BENZO[A]PYRANO[2,3-C]PHENAZINE DERIVATIVES BY USING A BASIC IONIC LIQUID AND INVESTIGATION OF THEIR ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY

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Abstract:

In this work, we present a simple, environmentally friendly, and highly efficient route for the synthesis of functionalized benzo[a]pyrano[2,3-c]phenazine derivatives, which was achieved via a four-component condensation reaction of 2-hydroxynaphthalene-1,4-dione, o-phenylenediamine, aldehydes, and malononitrile by using a basic ionic liquid, viz. 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo [2.2.2]octan-1-ium acetate [DMAP-DABCO]AcO, in ethanol as solvent at 80°C. The key benefits of this protocol include higher yields (86-93%) within 20-22 minutes, the ability to reuse the ionic liquid up to five times, easy work-up, and facile catalyst separation. The synthesized compounds have been screened for antimicrobial and antifungal activity using the modified agar well diffusion method. All compound shows potent antimicrobial activity against *B.cereus*, *E.coli*, and antifungal activity against C.*albicans*, except compound 5i.

Keywords: Basic ionic liquid, benzo[a]pyrano[2,3-c]phenazine derivatives, antimicrobial and antifungal activity.

Introduction:

In the past few years, Multicomponent reactions (MCRs) have been the most influential and convenient method for generating libraries of biologically active heterocyclic compounds[i-vi]. MCRs comprise an important class of chemical transformations due to their advantages, such as easy automation, atom economy, short reaction times, high chemoselectivity, and waste reduction resulting from reduced work-up and purification stages[vii-x]. Therefore, the design of novel multicomponent reactions is a significant and attractive task.

Ionic Liquids (ILs) are an excellent alternative to conventional organic solvents for a wide range of synthetic and catalytic applications[xi]. Researchers have concentrated their efforts on ILs due to their unique properties, which include low volatility, non-flammability, environmentally friendly nature, high thermal stability, and recyclability[xii-xiv]. The ionic liquids are efficient catalysts for the synthesis of various bioactive heterocyclic molecules[xv].Phenazines are a large class of nitrogen-containing heterocycles that act as the main core of many natural and synthetic organic materials[xvi-xvii]. They exhibit diverse biological activities, trypanocidal[xviii], antiplatelet[xiv], antimalarial[xx], fungicidal[xxi],antitumor[xxii] , and antimicrobial [xiii] activities.

In the existing literature, various synthetic methods for Benzo[a] pyrano[2,3-c]phenazine and its derivatives have been reported[xxiv-xxxii], but some of these methods have their advantages and disadvantages. Considering the importance of phenazine derivatives, we wish to develop a highly efficient and green synthetic protocol for Benzo[a]pyrano[2,3-c]phenazines via a one-pot, two-step condensation reaction of 2-hydroxynaphthalene-1,4-dione, o-phenylenediamines, aryl aldehydes, and malononitrile as reactants in the presence of a basic ionic liquid, viz. 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo [2.2.2]octan-1-ium acetate [DMAP-DABCO]AcO, in ethanol as solvent at 80 °C.

Experimental Protocols:

Materials and methods

General Information

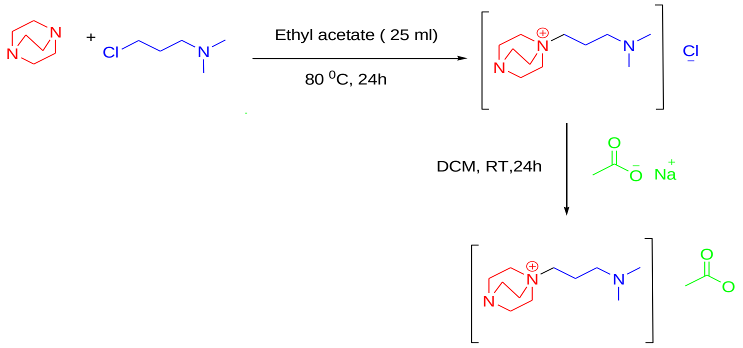
All the chemical reagents, anhydrous solvents andmedia components required for antimicrobial activity used in this work were purchased from commercial suppliers (Sigma-Aldrich, SD Fine Chemical companies andHi-Media India) and used without further purification. Melting points were determined by the open capillary method and were uncorrected. The progress of the reactions was monitored using Thin layer chromatography (TLC method performed on silica gel pre-coated aluminium plates, which were visualized with UV light. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz, respectively, using DMSO-d^6 solvent and tetramethylsilane (TMS) as an internal reference with chemical shifts (δ) being reported in ppm.

2.2. Typical procedure for the synthesis of dual basic ionic liquid [DMAP DABCO]AcO

The preparation of the ionic liquid was carried out as described in our previous research paper. **(Scheme1)** [33]

To a vigorously stirred solution of bicyclo[2.2.2]octane i.e. DABCO (I) (10 mmol), in ethyl acetate (25 ml), 3-chloro-N,N-dimethylpropan-1 amine (II) (11 mmol) was slowly added at room temperature. The quaternization reaction was carried out at 80°Cfor 24 h, and then collected at room temperature. The solvent ethyl acetate was decanted, and the remaining viscous oil was repeatedly washed with diethyl ether to yield pale yellow viscous ionic liquid. This was dried in a vacuum oven to yield 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (III).

The above prepared 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo [2.2.2]octan-1-ium chloride (III) (10 mmol) IL was then dissolved in dichloromethane, followed by the addition of sodium acetate (IV) (11 mmol). It was stirred for 24 h at room temperature. The suspension was filtered to remove the precipitated sodium chloride salt, and the solvent was evaporated under reduced pressure, furnishing 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium acetate (V) (Scheme 1)



Scheme1. Reaction path for preparation of dual basic IL

General procedure for the synthesis of benzo[a]pyrano[2,3-c]phenazine derivatives:

At first, 2-hydroxy-1, 4-naphthoquinone (1 mmol) and benzene-1,2-diamine (1 mmol) were mixed at 75°C under solvent-free conditions until an orange solid of benzo[a]phenazine formed. Afterward, an aromatic aldehyde (1 mmol), malononitrile (1 mmol), and a basic ionic liquid in ethanol (10 ml) were added to the reaction system. This mixture was stirred at 80°C for the appropriate time. Once the reaction was complete, as monitored by TLC using an n-hexane/ethyl acetate (6/4) solvent system, the mixture was cooled to room temperature, and 5 mL of water was added. The resulting crude product was filtered and washed twice with water (2 × 5 mL). The solid crude product was then recrystallized from hot ethanol to yield the pure solid product. The ionic liquid was dissolved in water, and the mixture was evaporated under reduced pressure to recover and reuse the ionic liquid

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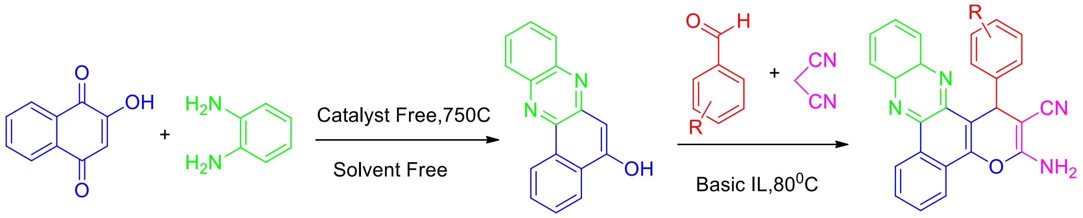


Scheme2. Synthesis of 3-amino-2-cyano-1-aryl-1H-benzo[a]pyrano[2,3-c]phenazines derivatives

Spectral data for selected compounds:

3-Amino-1-(4-nitrophenyl)-1H-benzo[a]pyrano[2,3-c]phenazine-2-carbonitrile (BPP1)[5a]: Yellow solid, mp: 280°C,FT- IR cm^{-1} (KBr): 3479, 3362, 3205, 3067, 2192, 1668, 1628, 1592, 1515, 1387, 1345; ^{1}H NMR (400 MHz, DMSO- d$_6$) (δ, ppm): 5.67 (s, 1H), 7.54 (s, NH$_2$), 7.70–7.72 (m, 2H), 7.92–7.98 (m, 2H), 8.0–8.06 (m, 2H), 8.06–8.12 (m, 2H), 8.14–8.17 (m, 1H), 8.28–8.31 (m, 1H), 8.48- 8.50 (m, 1H), 9.26–9.28 (d, 1H).^{13}C NMR (100 MHz, DMSO): δ C (ppm):37.6, 56.7, 112.4, 119.8, 122.3, 123.6, 125.7, 128.7, 129.1, 129.4, 130.3, 130.4, 130.6, 130.9, 139.9, 140.1, 141.5, 141.8, 146.1, 146.4, 152.8, and 159.7.

3-Amino-1-(3-bromophenyl)-1H-benzo[a]pyrano[2,3-c]phenazine-2-carbonitrile (BPP3)[5c]: Brown solid, mp: 268°C;FT- IR cm^{-1} (KBr): 3371, 3302, 3071, 2923, 2201, 1744, 1627, 1594, 1470, 1387; ^{1}H NMR (400 MHz, DMSO-d6) (δ, ppm): 5.52 (s, 1H), 7.19–7.22 (m, 1H), 7.30–7.32 (m, 1H), 7.41–7.42 (m, 1H), 7.43–7.47 (m,NH$_2$), 7.62–7.63 (m, 1H), 7.92–8.02(m,4H),8.15- 8.17 (m, 1H), 8.28–8.30 (m, 1H), 8.45–8.47 (m, 1H), 9.23–9.25 (m, 1H). ^{13}C

NMR (100 MHz, DMSO): (δppm):37.2, 57.2, 113, 119.9, 121.4, 122.2, 124.9, 125.5, 126.9, 128.6, 129.1, 129.2, 129.5, 130.1, 130.3, 130.5, 130.6,130.9 139.9, 140.1, 140.6, 141.5, 146.2, 147.9, 159.8.

3-Amino-1-(4-benzoloxy phenyl)-1H-benzo[a]pyrano[2,3-c]phenazine-2-carbonitrile (BPP5)[5e]: Brown solid, mp: 245-246°C; FT- IR cm^{-1} (KBr): 3456, 3330, 3194, 2920, 2193, 1738, 1670, 1605, 1468, 1384; ^{1}H NMR (400 MHz, DMSO-d6) (δ, ppm): 4.866(s, 2H) 5.52 (s, 1H), 6.67-6.89(d, 2H), 7.18-7.20 (d, 2H), 7.21–7.25 (s, 5H), 7.35 (s, 2H), 7.77–7.84 (m, 4H), 8.12–8.18 (d, 2H), 8.19–8.41 (s, 1H), 9.23–9.25 (s, 1H), ^{13}C NMR (100 MHz, DMSO): δ C (ppm):37.07, 58.55, 69.57, 94.02, 114.94, 122.6, 126.54, 128.08, 128.22, 128.82, 128.98, 129.18, 129.56, 137.4, 138.04, 141.36, 157.71, 164.62, 176.92.

Result and Discussion:

In the presented work of this research, we first synthesized the basic ionic liquid, i.e., 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo [2.2.2]octan-1-ium acetate [DMAP-DABCO]AcO, as a catalyst in the previous literature procedure(Scheme1). In the next step, the scope of our catalyst was explored for the development of general reactions for the synthesis of benzo[a]pyrano[2,3-c]phenazine derivatives. For this purpose, we find optimization conditions, the one-pot four-component reaction of 2-hydroxynaphthalene-1,4-dione, o-phenylenediamine, 4-nitrobenzaldehyde, and malononitrile in the presence of the basic ionic liquid as a catalyst was selected as a model reaction. So, 2-hydroxynaphthalene 1, 4-dione (1mmol) and o-phenylenediamine (1mmol) were mixed at 75°C until an orange solid of benzo[a]phenazine was formed in the absence of a catalyst under solvent-free conditions. Then, 4-nitrobenzaldehyde (1mmol), malononitrile (1 mmol), and ionic liquid, [DMAP-DABCO]AcO in 10 mL ethanol were added and stirred under thermal conditions. The reaction was carried out with different amounts of catalyst (5, 10, 15, 20, 25 mol%) (**Table 1 entries2-6**). From **Table 1**, it was shown that 20 mol% of [DMAP-DABCO]AcO, as a catalyst, was afforded for the synthesis of 3-amino-2-cyano-1-(4-chlorophenyl)-1H-benzo[a]pyrano[2,3-c]phenazine in 15 min with 95% yield. Further, an increase in the amount of the catalyst did not improve the yield. (**Table 1**, **entry5-6**) Also, the reaction was performed in the absence of a catalyst for a longer time, and no product was formed.

Table1. Optimization of reaction conditions by using different amounts of catalyst[a]

Entry	**Catalyst loading %**	**Time(min)**	**Yield %[b]**
1	0	140	-
2	5	40	30
3	10	30	65
4	15	20	87
5	20	15	95
6	25	15	95

[a]Reaction conditions: 2-hydroxy-1,4-naphthoquinone (1 mmol), benzene-1,2-diamine (1mmol), 4-nitro benzaldehyde (1 mmol), malononitrile (1 mmol), 80^{0}C, [b]Isolated yields.

Afterwards, for optimization of reaction temperature, an increase in temperature of the reaction (25 to 100°C) led to an increased rate of reaction and yields of product. At a temperature of 80°C, the yield of the reaction was 95% and it was similar at 100°C **(Table 2, entries 4 and 5)**.

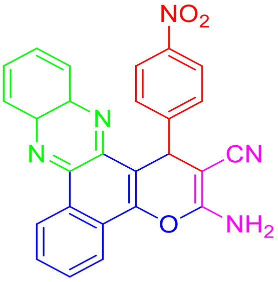
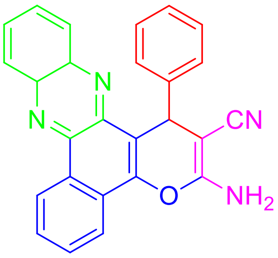
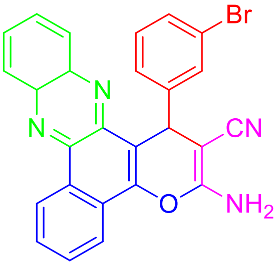
Table2. Optimization of reaction conditions by using different temperature [a]

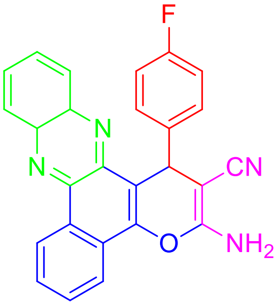
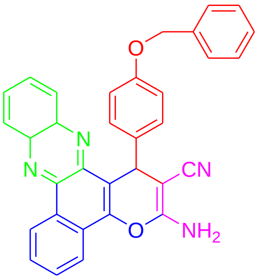
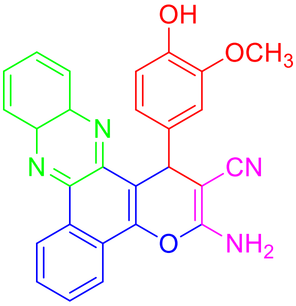
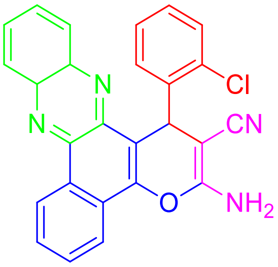
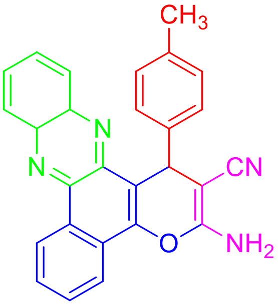
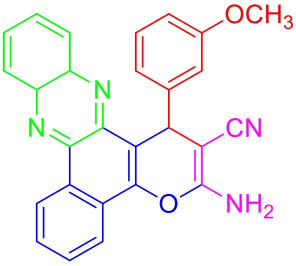
Entry	**T(^{0}C)**	**Time(min)**	**Yield %^{b}**
1	25	60	trace
2	50	60	62
3	60	40	83
4	80	15	95
5	100	15	95

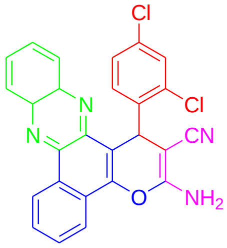
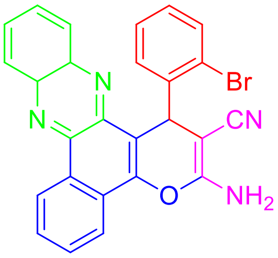
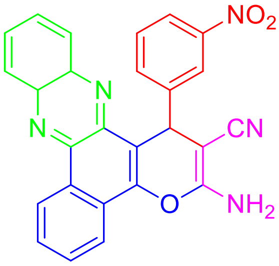
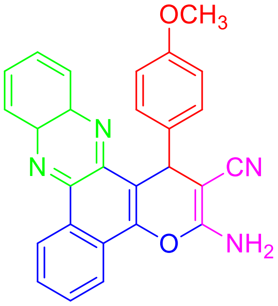
^{a}Reaction conditions: 2-hydroxy-1,4-naphthoquinone (1 mmol), benzene-1,2-diamine (1mmol), 4-nitro benzaldehyde (1 mmol), malononitrile (1 mmol), 80^{0}C, ^{b}Isolated yields.

The excellent result was obtained with 20% of basic IL as a catalyst at 80°C in ethanol as a solvent, which afforded 3-amino-2-cyano-1-(4-nitrophenyl)-1H benzo[a]pyrano[2,3-c] phenazine in 15 min with 95% yield. After establishing the model reaction condition and the proficiency of our protocol, synthesis of benzo[a]pyrano-[2,3-c]phenazine derivatives was performed for a series of different substituted aromatic aldehydes (**Table 3**). As evident from Table 3, the substituted aromatic aldehydes containing electron-withdrawing groups reacted rapidly and gave higher yields than electron-releasing aromatic aldehydes. This result shows that our protocol is versatile and can be used to synthesize a wide range of benzo[a]pyrano-[2,3-c] phenazine derivatives.

Table3. Scope of synthesis of benzo[a]pyrano-[2,3-c]phenazine

Compound	**Product**	**Time(min)**	**Yield %**	**M.P.(Lit.)(^{0}C)**
5a		25	95	280 (277-280) [26]
5b		40	88	301 (300-303) [26]
5c		35	90	268 (268-269) [26]

5d		45	91	278 (275-280) [26]
5e		55	86	245-246(This work)
5f		60	87	248 (247-248) [33]
5g		40	90	300 (300-304) [26]
5h		35	89	294 (293-294) [26]
5i		35	90	242 (238-243) [26]

5j		35	93	308 (307-310) [26]
5k		40	91	285 (284-286)[26]
5l		45	89	278 (278-279) [33]
5m		40	87	272(270-272) [26]

Biological activities

Sample preparation: all samples were prepared in DMSO [Sigma-Aldrich] (1000µg/ml) as a stock from this 100 µl samples were used to study the antimicrobial and antifungal activity of respective synthesized compounds.

Antimicrobial activity:

The antibacterial activity of synthesized compounds [5a, 5b, 5c, 5d, 5e, 5g, 5h, 5i, 5j, 5k, 5m] was performed against Gram-negative (*E. coli* NCIM 2832) and Gram-positive *(B. cereus* 2703) bacterial strains as well as fungal pathogens like *Candida albicans* NCIM 3466, by modified agar well diffusion method[xxxiv]. The suspension of respective test pathogens was prepared in sterile saline and used for further study. For the antimicrobial activity test, pathogens were inoculated on the surface of sterile Muller and Hinton agar and spread on plates using a sterile spreader. After that, an agar well was prepared asepically with the help of a sterilized cork borer having a 0.7 cm diameter[xxxv]. Then, 100 µl volumes of the test sample were added to the different wells of the respective test pathogens. Then plates were placed at 4 °C for 20 min for sample diffusion in a culture medium and transferred to an incubator at 37 °C for 24 hrs. Furthermore, the obtained results were compared with the well containing Streptomycin (1000 µg/ml) as a positive control, and sterile distilled water and DMSO were kept as a negative control. The diameter of the inhibition zone was measured in mm, and the results were recorded (Table 1).

Antifungal activities:

A similar procedure was repeated for antifungal activities; the Malt extract, Glucose, Yeast extract, and Peptone(MGYP agar) agar plates were prepared using submerged inoculation, using the respective fungal strain mentioned above, and MGYP agar plates were incubated at 27 °C temperature for 48 to 72 hrs. After incubation, the plates were examined for a zone of clearance around respective wells. The obtained antifungal results were compared with a standard, ketoconazole drug (1000 µg/ml) as a positive control, while sterile distilled water and DMSO were kept as a negative control for this study. The results of antimicrobial and antifungal screening of all compounds are summarized in **Tables 4 and 5**

All compound shows antimicrobial activity against B.*cereus*, *E.coli,* and antifungal activity against C.*albicans,* except compound 5i [Table 4], which indicates all compounds have potent antimicrobial and antifungal activity against selected pathogens as compared to respective antimicrobial and antifungal standards. From the given compounds, 5g and 5m show higher potency, while the 5d compound shows the lowest potency based on the Zone of inhibition. On the other hand, 5i doesn't show antimicrobial and antifungal activity because no zone of inhibition occurs around the 5i well.

Table 4: Zone of inhibition of nanoparticles in various concentrations against respective test pathogens.

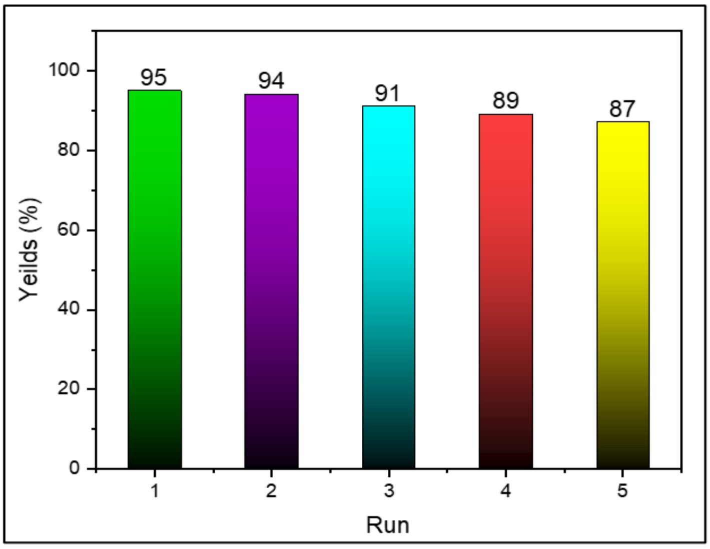
Test organisms	**Zone of inhibition in mm**										
	5a	**5b**	**5c**	**5d**	**5e**	**5g**	**5h**	**5i**	**5j**	**5k**	**5m**
B.cerus	23	24	27	19	26	22	20	00	23	25	24
E.coli	20	21	18	19	24	25	24	00	20	23	20
C.albicans	23	21	25	20	22	24	25	00	26	23	25

Table 5:Zone of inhibition of streptomycin and ketoconazole against respective test pathogens

Test pathogens	Zone of inhibition (mm)		
	Streptomycin	Ketoconazole	DMSO
B.cereus	26	00	00
E.coli	24	00	00
C.albicans	00	25	00

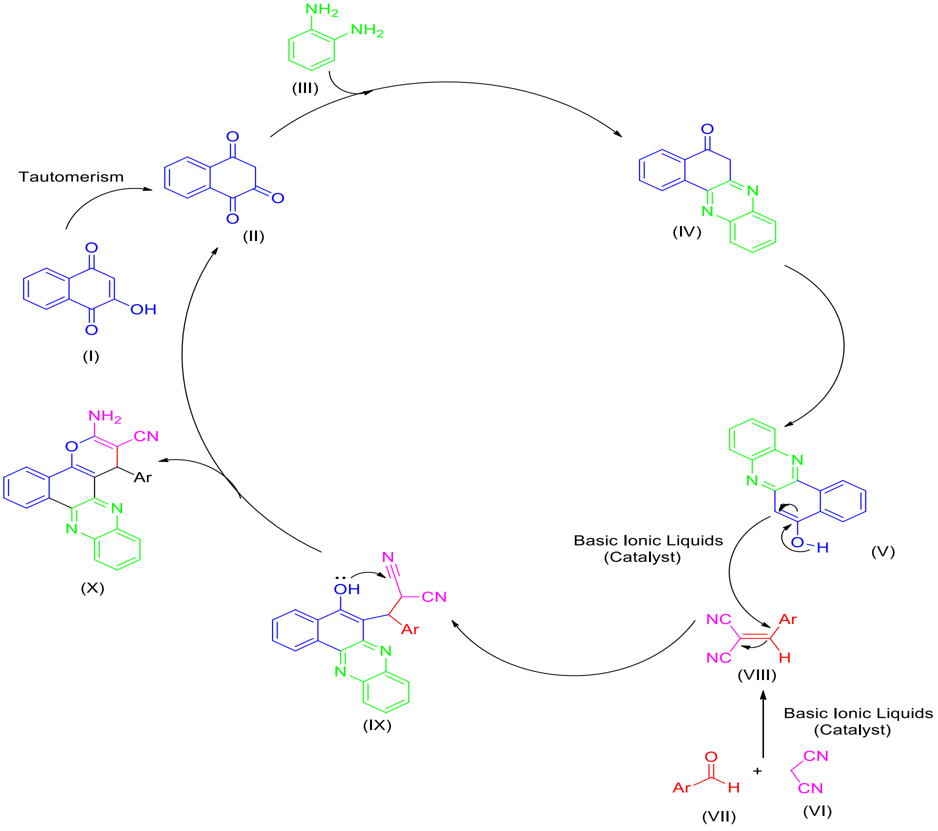
Recovery of catalyst

We also investigated the reusability of the ionic liquid using a model reaction of 2-hydroxynaphthalene 1, 4-dione, o-phenylenediamine, 4-nitrobenzaldehyde, and malononitrile in the presence of basic IL [DMAP-DABCO]AcO. After completion of the reaction (checked by TLC), the precipitated mixture was filtered on Whatman filter paper No.1 for separation of crude products, and the filtrate was collected in a beaker. The filtrate was then evaporated in the oven at 60 °C and purified by washing with diethyl ether. After washing, the ionic liquid has evaporated under reduced pressure, and the ionic liquid was recovered and reused. The recovered catalysts were used very effectively five times with no significant loss.



Mechanism:

The plausible mechanism for the synthesis of 3-Amino-1-aryl-1H-benzo[c]pyrano[3,2-a]phenazine-2 carbonitrile in the presence of basic ionic liquid is represented in Scheme 2. First, 2-hydroxynaphthalene-1, 4-dione(I) tautomericizes to intermediate (II). The initial condensation of intermediate (II) with o-phenylenediamine (III) results in 6H-benzo[a]phenazin-5-one (IV). In addition in the presence of basic ionic liquid malononitrile (VI) and aryl aldehyde(VII) undergoes Knoevenagel condensation to form benzylidenemalononitrile (VIII) The Michael addition of 6H-benzo[a]phenazin-5-ol (V) with benzylidenemalononitrile (VIII) in the presence of IL formed intermediate (IX), which in subsequent cyclization and tautomerism to produce the corresponding products (X).



Conclusion

In this research, we have reported an environmentally friendly and highly efficient synthesis of biological functionalized benzo[a]pyrano[2,3-c]phenazine derivatives by using a basic ionic liquid, viz. 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo [2.2.2]octan-1-ium acetate [DMAP-DABCO]AcO, in ethanol as solvent at 80 °C. The present protocol has some advantages: easy workup, higher yields (86-93%), short reaction time, and recyclable catalysts. The synthesized compounds have been screened for antimicrobial and antifungal activity using the modified agar well diffusion method. All compounds have potent antimicrobial and antifungal activity against selected pathogens as compared to respective antimicrobial and antifungal standards. The compounds 5g and 5m show higher potency, while the 5d compound shows the lowest potency on the basis of the Zone of inhibition.

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