Environmentally Benign Reaction of Naturally Ocurring Napthoquinones with 1,2-diaminesvia Ionic Liquids

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Abstract: **An environmentally benign protocol has been developed for the reaction of napthoquinones with 1,2-diamines thus forming napthaquinoxaline derivatives. Three different ionic liquids [BBIM]Br, [BMIM]Br and [BMIM]BF_4were employed for this strategy. It offers several advantages such as easy product isolation, high yield, eco-compatibility and no hazardous by-products.**

Key Words: **Ionic Liquid, Napthoquinones, Lapachol, *β*-lapachone.**

1. INTRODUCTION

Quinones are widely distributed in nature with great structural variety. They represent an important class of heterocyclic compounds found naturally in several plants, fungi and bacteria [1].They have been extensively studied for their cytotoxic as well as cellular protective properties and are particularly useful in rational drug design[2]. Napthoquinones are also ubiquitous natural pigments having promising potential for the treatment of various diseases. They also posses valuablebiological activities such as anti-bacterial, anti-fungal, anti-parasitic, anti-viral etc [3]. In folk medicine, plants containing naphthoquinones have been employed for the treatment of a number of diseases, including cancer [4]. These observations have led to an extensive search towards the development of novel quinones for use in malaria treatment and chemotherapy. Among the significant biologically active naphthoquinones are lapachol (**1**), *β*-lapachone **(2)**, lawsone **(3)**, juglone **(4)** and atovaquone **(5)**[5].

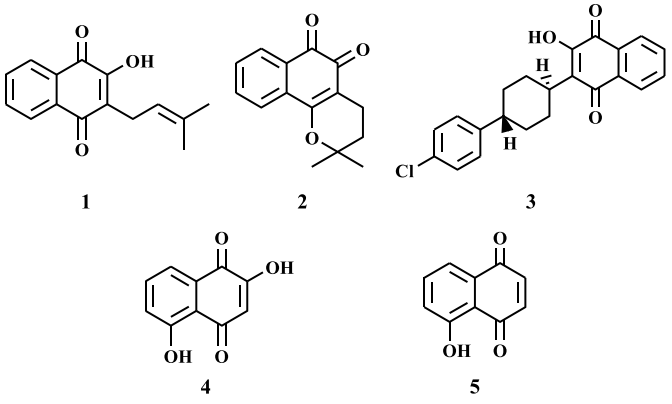


Fig.1. Some biologically important napthoquinones

Lapachol (2-hydroxy-3-(3-methylbut-2-enyl)naphthalene-1,4-dione) an important class of naphthoquinones, precisely 1,4-naphthoquinone is isolated from the heartwood of *Tectona grandis*. It displays analgesic, anti-inflammatory, antineoplasic, anticancer, antifungal, antinociceptive and antidermatogenic activities.The striking feature of chemistry of lapachol is the ease with which the prenyl side chain cyclizes into an oxygen functional group to give an array of pyrano and furano naphthoquinone derivatives [6].

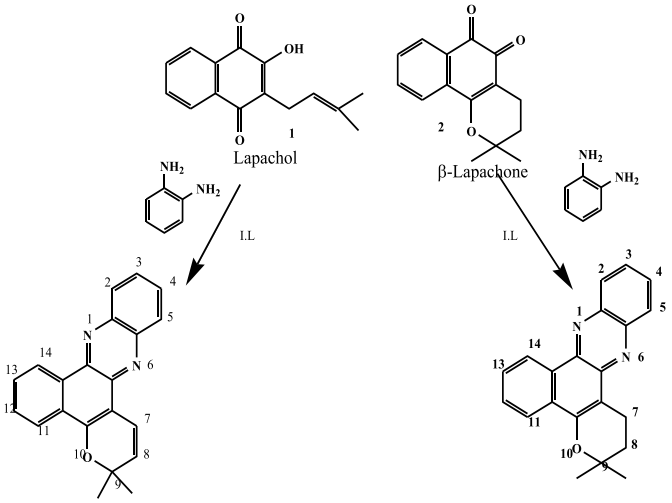
β-Lapachone(3,4-dihydro-2,2-dimethyl-2H-naphtho(1,2-b)pyran-5,6-dione) has been found to be cytotoxic to a variety of human cancers [7-11]. This naphthoquinone is now under investigation for the treatment of specific cancers associated with elevated NQO1 levels, such as breast, pancreatic, colon, and prostate cancers [12-15], and is currently in phase II clinical trials for the treatment of pancreatic cancer [16].Particularly promising is the synergistic lethality of *β*-lapachone with taxol [17]and genistein on several tumour cell lines implanted into mice. DNA topoisomerase-I was the first biochemical target of *β*-lapachone to be reported. *β*-lapachone acts on this enzyme in a manner distinct from other known inhibitors, such as campthotecin [18,19].

Great attention directed now a days to lapachol is motivated by its anti cancer activity, antiviral action, inhibiting the replication of virus RNA [20]. It has been noticed that the structural modification by way of introducing new heterocyclic moieties, modify the pharmacological properties of the parent skeleton.

The Literature survey reveals that the chemical transformations of naturally occurring quinones leads to the designing and development of new synthetic procedures for the preparation of various heterocyclic compounds. In our endeavour to develop a green methodology for the transformation of Lapachol and *β*-Lapachone into quinoxaline derivatives herein, we have carried out the above reaction in ionic liquids.

Ionic liquids are emerging as a green reaction medium. The use of ionic liquids as reaction medium offers a solution to both solvent emission and catalytic recycling problem. The use of ionic liquids (ILs) as non-conventional media in chemical synthesis is gaining momentum because of their physical and

chemical properties [21]. Their growing application in organic chemistry stems from their favourable physicochemical properties, such as the lack of vapour pressure, good thermal and chemical stability and very good dissolution properties of both organic and inorganic compounds [22-25]. Thus herein we have used ionic liquids as the solvent for the synthesis of various quinoxalines from naturally occurring lapachols and *β*-Lapachone**(Scheme I).**



9, 9-dimethyl-9H-pyrano[3',2': 4] -naphtha [1,2-b] quinoxaline **(3)**

7,8-Dihydro-9,9-dimethyl-9H-pyrano[3',2':4] -naphtha [1, 2-b]quinoxaline **(4)**

Scheme I. Reaction of Lapachol/ *β*-Lapachone with o-phenylenediamine

2. RESULTS AND DISCUSSION

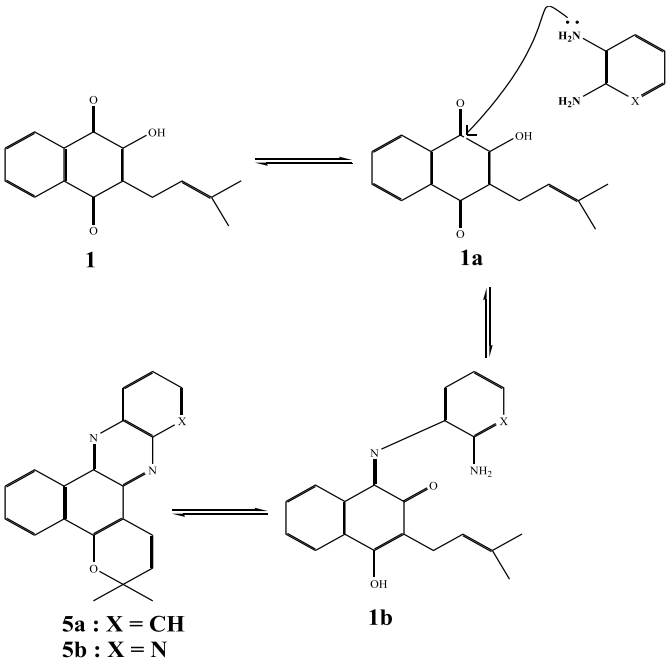
In pursuit of optimizing the reaction conditions,the reaction of lapachol with o-phenylene diamine was carried out in ethanol at room temperature. The reaction was very slow initially but on refluxing for 24 hrs , a yellow coloured product was formed which was 9,9-Dimethyl-9*H*-pyrano[3′,2′:4]naphtha [1,2-b]quinoxaline. The same reaction was then performed in various solvents like DCM, methanol, acetonitrile and also in ionic liquids *viz;* [BBIM]Br, [BBIM]BF_4 and [BMIM]Br at 26-30^{0}C . It was observed that better yield was obtainedin ionic liquids as compared to conventional solvents. Among the ionic liquids also best results were obtained in [BBIM]BF_4 as shown in Table-1. Thus [BBIM]BF_4 was choosen as the solvent of choice for further reactions.

Reaction of *β*-lapachone with 1,2-phenylenediamine was also performed in above mentioned solvents and ILs to afford 7,8-Dihydro-9,9-dimethyl-9*H*-pyrano[3′,2′:4]naphtha[1, 2-b]quinoxaline [29,30]. Similar results were observed as shown in Table 1.

TABLE-I Yield of products of transformation reactionin various solvents and ionic liquids

Entry	Solvent	Yield %/Time (h)	
		Product 3	Product 4
1	**Ethanol**	55/24	52/32
2	**DCM**	63/24	60/30
3	**CCl_4**	61/24	58/32
4	**Acetonitrile**	73/23	73/30
5	**Methanol**	59/24	57/32
6	**[BBIM]Br**	80/7.5	72/11
7	**[BMIM]Br**	84/7	79/8
8	**[BMIM]BF_4**	88/5	82/6

The formation of quinoxaline derivatives from lapachol can be rationalized by the reaction of tautomeric form **1a** of lapachol with one amino group of o-phenylene diamine leading to the formation of Schiff base **1b**. The later undergoes cyclocondensation by the reaction of remaining keto group with second amino group of 1,2-diamino followed by cyclization of isoprenyl side chain into pyran ring **5a** & **5b (Scheme –III)**



Scheme III Plausible mechanism for formation of quinoxaline derivatives

Recyclability of Ionic Liquid

The recyclability of ionic liquid was also examined by carrying out five subsequent runs of the model reaction in the recovered IL. Very slight decrease in the product yield was observed as shown in Fig.2.

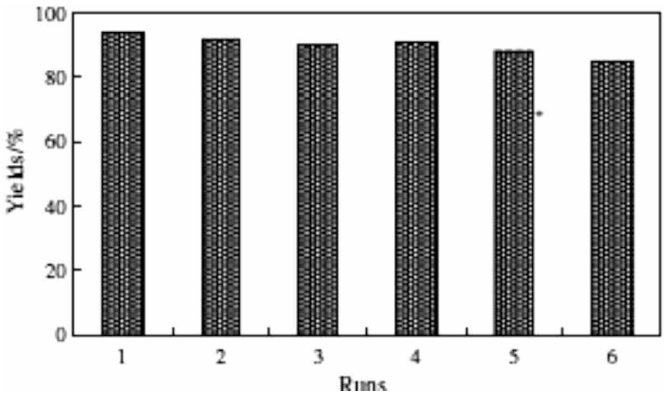


Fig.2 Recyclability of ionic liquid

3. EXPERIMENTAL

Melting points of all the synthesized compounds were determined in open capillary and are uncorrected. IR spectra were recorded on SHIMADZU FT-IR spectrometer using KBr pellets. ^{1}HNMR and ^{13}C NMR spectra were recorded on a JEOL-AL-300 MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard (chemical shift in δ ppm). The purity of each compound was checked by TLC using silica gel 60F254 aluminium sheets as adsorbant and visualization was accomplished by an iodine/U.V. light.

GENERAL PROCEDURE

REACTION OF LAPACHOL/ β-LAPACHONE WITH O-PHENYLENEDIAMINE

Lapachol/*β*-Lapachone (0.01 mol) and *o*-phenylenediamine (0.01mol) in [BBIM]BF_4 (5 mL) were taken in round bottom flask. The contents of the flask were stirred magnetically at 28 $\pm$2°C for the time specified in **Table 1**. The progress of the reaction was monitored on TLC plate (Silica gel 60 F254 aluminium sheet) in benzene: ethyl acetate (8:2). After completion of the reaction as indicated by TLC, the reaction mixture was poured in ice cold water. The separated solid was filtered, washed with water and extracted with pet ether-benzene (3:1). The organic layer was dried over anhydrous sodium sulphate and distilled under reduced pressure to afford the desired products.

4. SPECTRAL DATA OF THE PRODUCTS

9,9-Dimethyl-9H-pyrano[3′,2′:4]naphtha[1,2-b] quinoxaline, 3:

Yellow needles, m.p. 122-24°C, IR ν_{max} [KBr] 2960-2900 (C-H Stretch), 1565-1500, (-C=N stretch), 1256 (C-O Stretch). ^{1}H NMR (δ ppm, $CDCl_3$) 1.51 (s, 2 x Me), 5.63(d, J= 10.08 Hz, =CH), 7.34 (m, 3 x Ar-H), 8.13 (m, 2 x Ar-H), 8.22(m, 2 x Ar-H) and 9.26 (m, Ar-H). ^{13}C NMR (δ ppm, $CDCl_3$) 26.8, 27.4, 70.6, 114.5, 121.3, 122.9, 125.3, 127.7, 128.8, 129.3, 130.7, 141.5, 144.2, 156.8. Mass (*m/z*)313 $[M+H]^+$ (100) ($C_{21}H_{16}N_2O$), 297 $[M-Me]^+$ (40).

7,8-Dihydro-9,9-dimethyl-9H-pyrano[3′,2′:4]naphtha[1,2-b]quinoxaline, 4

Bright yellow needles, m.p. 112-14°C. ^{1}H NMR (δ ppm, $CDCl_3$) 1.49 (s, 2 x CH_3), 2.02 (t, J= 7.0 Hz,-CH_2-), 3.32 (t, J= 7.0 Hz, -CH_2-), 7.72 (m, 3 x Ar-H), 8.35 (m, 1 x Ar-H), 9.30 (m, 1 x Ar-H). ^{13}C NMR(δ ppm, $CDCl_3$) 16.9, 28.3, 49.3, 75.0, 114.2, 123.2, 126.4, 128.7, 129.6, 130.1, 143.2, 145.4, 162.0. Mass (*m/z*) 314 $[M]^+$ ($C_{12}H_{18}N_2O$) (75), 299 $[M-Me]^+$ (15), 285 [299-CH_2]$^+$ (10), 271 [285-CH_2]$^+$, 229 (20) etc.

5. CONCLUSION

Naturally occurring napthoquinones like lapachol and *β*-Lapachone show higher reactivity towards transformation reaction in imidazolium based ionic liquids thus giving higher yields of quinoxalines. This protocol is highly efficient and environmentally benign due to the recyclability of ionic liquid.

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