Synthesis of New Heterocycles *via* the Reaction of β-Lapachone with 1,2-Diamines Using Triton X-100 Surfactant as Catalyst in Aqueous Medium

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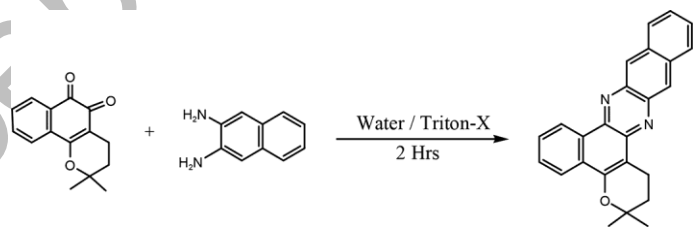
Abstract

An efficient and an environmentally benign protocol has been developed for the synthesis of new naphtha-azaquinoxaline and naphtha-benzoquinoxaline derivatives from the reaction of β-lapachone, a naturally occurring 1,2-naphthoquinone with various 1,2-diamines using surfactant as catalyst in aqueous medium. This method has advantage of easy handling and good yield of products in shorter time. The structures were assigned with the help of analytical and ^{1}H, ^{13}C NMR, IR and mass spectral studies.

Graphical Abstract



KEYWORDS: β-Lapachone, Lapachol, 1,2-Diamines, Surfactants, Triton X -100.

INTRODUCTION

Quinones form an important class of natural products exhibiting a wide range of biological properties (cytotoxic[1], antimalarial[2], anti-inflammatory[3] antifungal and antiviral[4,5]) together with a great structural diversity and complexity, which makes them interesting challenges to organic synthesis.

Lapachol and its congener β-Lapachone occur naturally in heartwood of various trees of Bignoniaceous family. β-Lapachone, an 1,2-naphthoquinone exhibited a wide variety of pharmacological effects including anticancer, antibacterial, antifungal, and trypanocidal activities[6-9]. Literature[10-13] has revealed that the introduction of heterocyclic moieties modified the pharmacological properties of the parent skeleton. Thus the transformation in the quinonoid skeleton has recently been a subject of great interest from the pharmacological point of view. Further the synthesis of novel and specific heterocyclic compounds by the using recent synthetic methodologies is an intense area of research. In this regard, efforts have been constantly made to introduce new methodologies that are efficient and more compatible with an environment.

The high catalytic activity and benign character of surfactants have fascinated considerable interest in organic synthesis.[14,15] The formation of vesicular cavities or micelles with hydrophobic core and hydrophilic corona at ambient conditions of

surfactants in aqueous medium has been proved to increase the reactivity of aqueous mediated reactions.

RESULTS AND DISCUSSION

Earlier the reactions of lapachol and β-lapachone with ethylene diamine, 1,2-diaminopropane, *o*-phenylene diamine and 2,3-diaminopyridine by conventional heating and with solid support under microwaves irradiation have been studied by our group.[16,17] Considering the significance of surfactants, herein we report new efficient protocol for the reaction of β-lapachone with 2,3-diaminopyridine employing green tools. Using this protocol, we have synthesized naphthazaquinoxaline and naphthabenzoquinoxaline derivatives as new polycyclic heterocycles by the reaction of β-lapachone with other 1,2-diamines i.e. 5-bromo-2,3-diaminopyridine, 3,4-diaminotoluene, 3,4-diaminopyridine and 2,3-diaminonaphthalene. This report represents a new entry into the synthesis of heterocyclic compounds from β-lapachone in aqueous media using surfactant as catalyst. The similar reactions on lapachol did not succeed.

Initially, the reaction of β-lapachone **2** with 2,3-diaminopyridine **3**, as a model reaction was investigated to optimize the reaction conditions and established the feasibility of the strategy. When the reaction was performed in water only at room temperature as well as on heating, no product was formed. When the β-lapachone with 2,3-diaminopyridine were stirred at room temperature in water using surfactant, products were obtained in 21 hrs. On heating along with stirring gave product in shorter time. In order to study the effect of surfactant, various ionic (cationic and anionic) and non ionic surfactants were

tested and the results are summarized in Table-1. In the presence of SDS (Sodium dodecyl sulphate- an anionic surfactant) and CTAB (Cetyl trimethylammonium bromide-cationic surfactant), the desired products were obtained in 4-5 hours. In the presence of TBAB (Tetrabutyl ammonium bromide - cationic surfactant) the desired products were obtained in 12 hours. The best result (good yields in shorter reaction time) was obtained in aqueous medium with non ionic surfactant Triton X-100 (TX-100).

Further, above reaction was carried out at different temperatures with varying concentration of the surfactant and the data are presented in Table 2. It is clear from the data that the rate of reaction increased continuously with increasing catalyst concentration upto 15 mol% without any considerable difference on increasing catalyst concentration further. Thus it was concluded that the concentration of catalyst plays a significant role in controlling the rate of the reaction and in aqueous medium 15 mol % of Triton X-100 gave best results at 80^0C.

It was noticed that on introduction of surfactants followed by stirring, the initially floating reactants in the mixture converted to an orange-brown turbid emulsion, which implies that there is formation of micelle like colloidal aggregates. It can assume that most of the organic substrates are concentrated in the spherical particles, which act as a hydrophobic reaction site and results in the rapid reaction in water. In the micellar solution, the organic substrates which are hydrophobic, escape away from water molecule towards the hydrophobic core of micelle droplets where the reaction occurs more easily. The hydrophobic interior of the micelles rapidly excludes the water molecules generated during the reaction, thus shifting the equilibrium towards the product side.[18]

Mechanism of condensation of β-lapachone **2** with 2,3-diaminopyridine **3** has been explained in our previous report[17] and it was concluded that **4a** should be major product, if reaction was conducted by thermal method. But when the reaction is carried out in aqueous medium using surfactant as catalyst, the percentage yield of **4b** increases. The structure of **4b** was unambiguously established by single crystal X-ray studies[17] and it was characterized as 6,7-dihydro-8,8-dimethyl-8H-pyrano [3´,2´:4]naphtha[2,1-e] pyrido[2,3-b] pyrazine; **4b**.

Encouraged by these results, the reaction of β-lapachone **2** was extended to other diamines i.e. 5-bromo-2,3-diaminopyridine, 3,4-diaminotoluene, 3,4-diaminopyridine and 2,3-diamino- naphthalene using triton X-100 (15 mol%) in distilled water at 80°C. Results are shown in Table 3 and probable products are given in Fig 1.

Reaction of β-lapachone with 5-bromo- 2,3-diaminopyridine gave two regioisomeric products **5a** and **5b** in the ratio of 3:5. Here **5b** is major product rather than **5a**. It can be explained by attack of more nucleophilic 2-amino group on the more electrophilic 1-carbonyl function of β-lapachone. 2-Amino group is more nucleophilic rather than 3-amino group due to the presence of Br. There are several reports in the literature[12-13] mentioning that the carbonyl nearest to the aromatic ring is more reactive than 2-carbonyl group in β-lapachone. The ESI mass spectra of **5a** and **5b** showed two base peak with equal intensity at 394 and 396, which indicates the presence of bromine. Further both regioisomers were identified on the basis of ^{1}H NMR spectrum.

Exclusive formation of product **6** in the reaction of β-lapachone with 3, 4-diaminotoluene can be understood by the presence of methyl group in the ring, which makes 4-amino group more reactive than the 3-amino group. The formation of product **7** in the case of reaction of β-lapachone with 3,4-diaminopyridine is thought to arised from the attack by more nucleophilic 3-amino group[19] on the more electrophilic 1-carbonyl function of β-lapachone (Scheme-II). The isolated products were characterized on the basis of their IR, ^{1}H and ^{13} CNMR spectroscopy and mass spectrometry. All the products showed absence of carbonyl group in IR Spectra.

The similar methodology was applied for the reaction of lapachol **1** with above diamines, but the reactions were not successful in the all optimized conditions. The reaction of lapachol **1** with diamines in the presence of some drops of H_2SO_4 using above methodology were successful and gave the same products which are obtained by the reaction of β-lapachone with diamines. These results indicate that lapachol first converted in β-lapachone in the presence of H_2SO_4 and then reaction proceeds.

CONCLUSION

In conclusion, we have developed an exceedingly simple, mild and clean synthetic protocol for the synthesis of new naphthazaquinoxaline and naphtha-benzoquinoxaline derivatives in water. Non ionic surfactant (Triton X-100) was found to be an efficient catalyst to accelerate the reaction in water.

EXPERIMENTAL

Melting points were determined in soft glass capillaries in an electrothermal melting point apparatus and are uncorrected. Qualitative and quantitative thin layer chromatography was conducted on TLC aluminium sheets Kieselgel $60F_{254}$ (E. Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 and JEOL 400 FT NMR spectrophotometer using $CDCl_3$ as solvent. FAB Mass spectra were generated on a JEOL SX-102 mass spectrometer. All compounds were homogenous on TLC in various solvent systems.

Typical Procedure For Synthesis Of 4a And 4b

A mixture of β-lapachone **2** (1.0 mmol), 2,3-diaminopyridine (1.0 mmol), Triton X-100 (15 mol%) and distilled water (5.0 ml) were taken in a round bottom flask. The reaction mixture was allowed to stir magnetically at 80°C for 2 hours. Progress of the reaction was monitored by TLC. After completion of the reaction, the crude mass was obtained. The residue was purified over a column of silica gel (100-200 mesh) eluting with a mixture of hexane and ethyl acetate in different ratio, to yield regioisomers (**4a** and **4b**).

Characterization Data For Compounds

6,7-Dihydro-8,8-Dimethyl-8H-Pyrano[3',2':4]Naphtha[1,2-E]Pyrido[2,3-B]Pyrazine (4a)

Bright yellow needles; mp 210-12^{0}C[17]; IR (KBr cm^{-1}): 3150-2960, 1625, 1600, 1540 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.54 (6H, S, 2 Me), 2.06 (2H, t, J=6.57 Hz,-CH_2-), 3.31 (2H, t, J=6.57 Hz, -CH_2-), 7.73 (1H, dd, J=8.43, 4.02 Hz, 1×Ar-H), 7.80

(2H, m, 2×Ar-H), 8.31-8.34 (1H, m, 1×Ar-H), 8.57 (1H, dd, J=8.43, 1.83 Hz, 1×Ar-H), 9.21 (1H, dd, J=1.83, 4.02 Hz, 1xAr-H) and 9.48-9.51 (1H, m, 1xAr-H). ^{13}C NMR (75.45 MHz; $CDCl_3$; DEPT, Me_4Si): 26.7 (C-CH_3), 26.7 (C-CH_3), 18.2 (CH_2), 32.30 (CH_2), 76.6 (C_8), 109.23 (C_{5b}), 124.59-128.09 (aromatic C), 129.71 (C_{9b}), 130.47 (aromatic C), 137.72 (aromatic C), 147.5 (C_{9a}), 142.25 (C_{14a}), 145.59 (C_{5a}), 152.65 (aromatic C); FAB MS (m/z): 316 (100) $[M+H]^+$, 300 $[M-Me]^+$, 260, 120, 107; Anal $C_{20}H_{17}N_3O$. Cald For: C, 76.19; H, 5.39; N, 13.33. Found: C, 76.09; H, 5.31; N, 13.25.

6,7-Dihydro-8,8-Dimethyl-8H-Pyrano[3',2':4]Naphtha[2,1-E]Pyrido[2,3-B]Pyrazine (4b)

Bright orange needles; mp 202-05^{0}C [17]; IR (KBr cm^{-1}): 3140-2975, 1600, 1625, 1550 (C=N), 1400; ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): δ 1.54 (6H, s, 2 Me), 2.09 (2H, t, J=6.60 Hz,-CH_2-), 3.41 (2H, t, J=6.60 Hz, -CH_2-), 7.69 (1H, dd, J=8.40, 4.20 Hz, 1×Ar-H), 7.79 (2H, m, 2×Ar-H), 8.32-8.35 (1H, m, 1×Ar-H), 8.64 (1H, dd, J=8.43, 1.83 Hz, 1×Ar-H), 9.22 (1H, dd, J=4.20, 2.01 Hz, 1×Ar-H) and 9.27-9.30 (1H, m, 1×Ar-H). ^{13}C NMR (75.45 MHz; $CDCl_3$; DEPT, Me_4Si): 26.8 (C-CH_3), 26.7 (C-CH_3), 18.2 (CH_2), 32.32 (CH_2), 76.6 (C_8), 109.23 (C_{5b}), 122.47- 148 (aromatic C), 153 (C_2), 153.98 (C_{14a}); FAB MS (m/z): $[M+H]^+$ 316 (100) , 300 $[M-Me]^+$, 260, 120, 107; Anal $C_{20}H_{17}N_3O$. Cald For: C, 76.19; H, 5.39; N, 13.33. Found: C, 76.01; H, 5.35; N, 13.03.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION

Experimental detail, ^{1}H and ^{13}C NMR spectra of novel compounds are given in supporting information.

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Table 1. Study of 4a and 4b under different reaction conditions[a]

Entry	Solvent/ Surfactant	Temp.(◦C)	Reaction time	Yield[b](%)	
				4a	4b
1.	Ethanol	Reflux	72 hr	30	10
2.	Ethanol + GAA	Reflux	24 hr	36	13
3.	Ethanol + Piperidine	Reflux	24 hr	29	8
4.	Water	RT	24 hr	N R[c]	
5.	Water	Reflux	24 hr	N R[c]	
6.	Water/TX-100[e]	RT	21 hr	35	25
7.	Water/TX-100[e]	80	2 hr	45	39
8.	Water/SDS[e]	80	5 hr	30	20
9.	Water/CTAB[e]	80	4 hr	40	32
10.	Water/TBAB[e]	80	12 hr	39	30
11.	Water/PEG-1000	80	6 hr	27	21

[a] Reaction conditions: 1.0 mmol of both β-lapachone **2** and 2,3-diaminopyridine **3**; GAA (glacial acetic acid); Triton X-100 (TX-100);

[b] Isolated yield;

[e] Surfactant (15 mol%);

[c] No reaction

Table 2. Effect of the different surfactant concentration and temperature on the yield of 4a and 4b.

Entry	Solvent/Surfactant	Temp.(◦C)	Reaction Time	Yield[b](%)	
				4a	4b
1.	Water/TX-100[e]	60	4.5 hr	35	28
2.	Water/TX-100[e]	80	2.0 hr	45	39
3.	Water/TX-100[e]	100	2.5 hr	40	35
4.	Water/TX100[c]	80	4.0 hr	30	25
5.	Water/TX-100[d]	80	3.5 hr	36	29
6.	Water/TX-100[f]	80	2.0 hr	39	32

[a] Reaction conditions: 2.0 mmol of both β-lapachone **2** and 2,3-diaminopyridine **3**;

[b] Isolated yield;

[c]Triton X-100 (5 mol%);

[d] Triton X-100 (10 mol%);

[e]Triton X-100 (15 mol%);

[f]Triton X -100 (20 mol%)

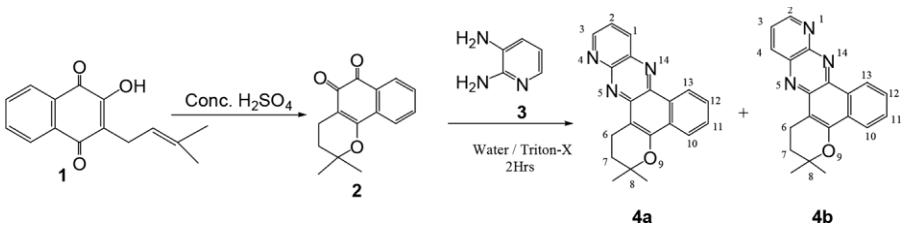
Table 3: Study of reaction of β-lapachone with various diamines

Entry	Diamine	Reaction time	Product	Yield[b](%)
1.	5-bromo-2,3-diaminopyridine	2 hrs	5a & 5b	30 & 50
2.	3,4-diamino toluene	2 hrs	6	90
3.	3,4-diaminopyridine	4 hrs	7	70
4.	2,3-diamino naphthalene	2 hrs	8	85

[a] Reaction conditions: 1.0 mmol of β-lapachone **(2)** and 1.0 mmol of diamine in Water/Triton X- 100[e] **(**15 mol%) at 80° C;

[b] Isolated yield.

Scheme 1.



Scheme 2.

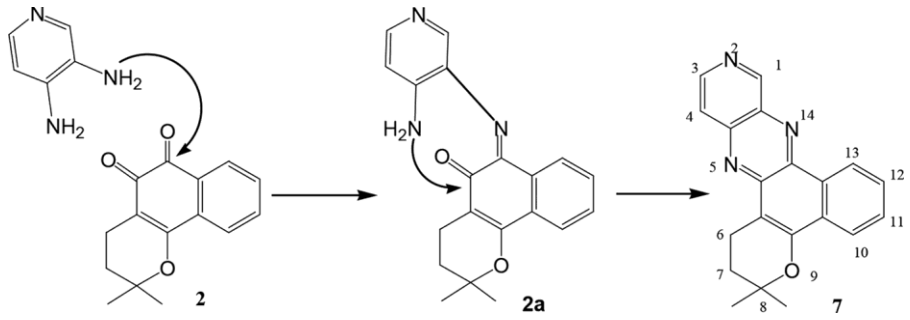
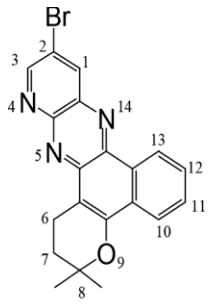
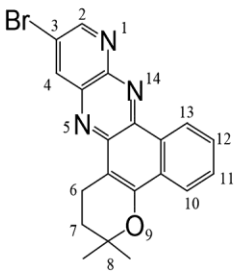


Figure 1.



5a



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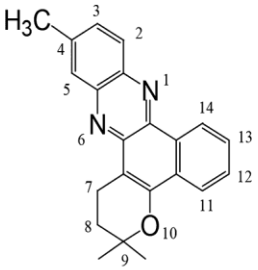

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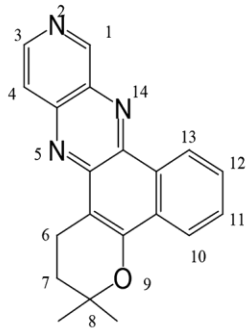

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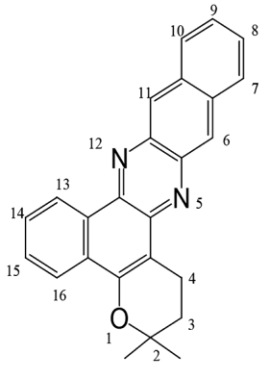

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