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Micelles catalyzed one pot regio- and chemoselective synthesis of benzo[a]phenazines and naphtho[2,3-d]imidazoles "in H_2O"

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ABSTRACT

An efficient, novel and concise one pot regio- and chemoselective synthesis of benzo[*a*]phenazines (**4**) and naphtho[2,3-d]imidazoles (**8**) has been accomplished in excellent yields by nucleophilic substitution reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with o-phenylenediamine (**2**) and benzamidines (**7**) respectively "in H_2O" using base and micelles (SDS) as catalyst. Analogues reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with 2-aminobenzenethiol (**9**) under identical conditions led to formation of a mixture of benzo[*b*]phenothiazine (**10**), benzo[*a*]phenothiazine (**11**) and benzo[*a*]-1,4-benzothiazino-3,2-phenothiazine (**12**) in 17, 23 and 57 % yields respectively.

The extensive data available on the isolation of natural products containing phenazine nucleus and their synthetic derivatives is due to their biological properties which include antibiotic, antimalarial, antiparasitic and antitumor activities.[1] The pronounced antitumor activity of benzo[*a*]phenazine derivatives NC-190 and XR-11576[2,3] (Fig. 1) led to exploration of new synthetic routes of various benzo[*a*]phenazine derivatives.[3,4]

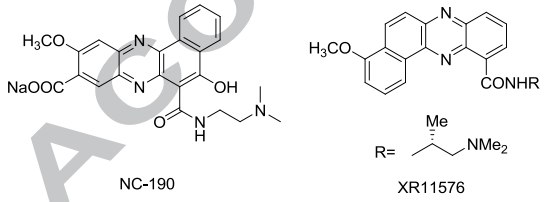

Figure 1. Pronounced antitumor benzo[*a*]phenazine derivatives

The recent synthetic routes to benzo[*a*]phenazines involve (i) regioselective condensation reaction of 1,2-naphthoquinones derived from α-tetralone with 4,5,6-trisubstituted-2,3-diami nobenzoic acids in two steps,[4] (ii) acid catalyzed regioselective condensation reaction of hydroxyimino-oxo acids derived from 2-hydroxy-3-naphthoic-3-acids with 2,3-diaminotoluene in two steps,[3] (iii) reaction of benzofuroxan with 2-hydroxynaphthoic-3-acids leading to the formation of benzophenazine di-*N*-oxides and their subsequent reaction in two steps,[3] (iv) Stoichiometric cascade reaction involving condensation between 2-hydroxy-1,4-naphthoquinone and o-phenylenediamine.[5]

The use of water as a green solvent and as a medium of organic synthesis has mushroomed since the use of concept and language by Sharpless *et al.* who has described the successful reactions "on-H_2O" for cases where reactants are insoluble in water.[6] Further more successful reactions "in H_2O" have been carried out using buffers or catalysts.[7,8] The role of catalytic influence of surfactant to act as micelles "in H_2O" has been elegantly demonstrated by Engberts *et al.*[9] Porphyrin synthesis in anionic sodium dodecyl sulphate (SDS) micelles has been elegantly demonstrated by Bonar-Law.[10] Recently aqueous SDS micelles promoted acid catalyzed domino imino Diels-Alder reaction has been employed to synthesize tetrahydroquinoline scaffolds.[11]

This motivated us earlier to develop a green methodology approach to carry out nucleophilic substitution reactions in aqueous medium[12-15] leading to excellent yields of the desired products.

In connection with our studies on the reactivity of quinones with nitrogen, sulfur and oxygen nucleophiles in aqueous medium[12-15] and the utility of surfactants in aqueous medium,[16] we first explored the nucleophilic substitution reaction of 2,3-dichloro-1,4-

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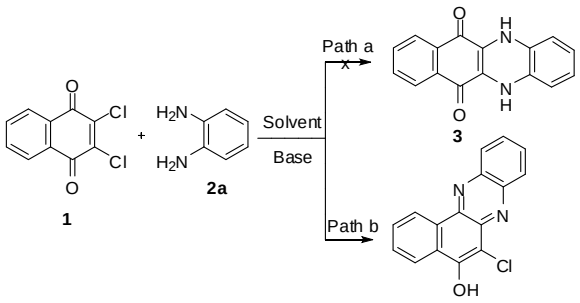
naphthoquinone (**1**) with o-phenylenediamine (**2a**) in aqueous medium. Our results in aqueous medium using micelles as catalyst have shown that the reaction proceeded regioselectively following path b resulting in the formation of 6-chlorobenzo[*a*]phenazine-5-ol (**4a**). In order to optimize the yield of **4a**, the reaction was investigated with other bases with or without surfactant (micelles) as catalyst (Table 1).

Table 1
Reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with o-phenylenediamine (**2a**)



Solvent	Base	Surfactant	T (°C)	t (h)	Yield **4a** (%)
EtOH	-	-	reflux	12	65[17]
H_2O	K_2CO_3	-	90	12	32
H_2O	NaOH	SDS	90	5	89
H_2O	CH_3COONa	SDS	90	5	92
H_2O	K_2CO_3	SDS	90	5	96

The use of surfactant SDS (Sodium dodecyl sulfate; 0.5 mole%) as a catalyst in addition to K_2CO_3 as a base "in-H_2O" resulted in 96% yield of **4a**. It is pertinent to note that Katritzky *et al.*[17] have reported 65% yield of **4a** by reaction of **1** with **2a** in refluxing absolute ethanol.[17] The plausible mechanism of formation of benzo[*a*]phenazines in aqueous micelles involves nucleophilic substitution followed by condensation and cyclization (Fig. 2).

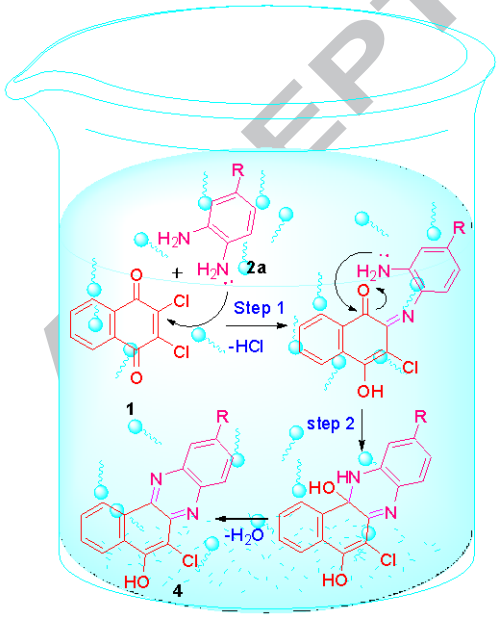
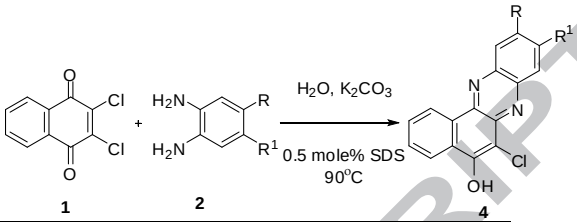


Figure 2. Plausible mechanism for the formation of benzo[*a*]phenazines (**4**)

Based on excellent yield of benzo[*a*]phenazines obtained in aqueous medium using SDS as a catalyst, various synthetic analogs of benzo[*a*]phenazine were synthesized and are shown in Table 2.

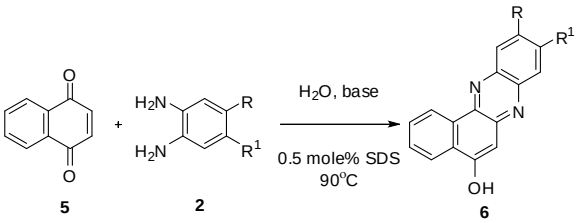
Table 2
Synthesis of benzo[*a*]phenazine in aqueous K_2CO_3 using SDS as a catalyst[34]



Com.	R	R^1	t (h)	Mp (°C)	Yield of **4** (%)
4a	H	H	5	274-276[17]	96
4b	F	H	5	>310	92
4c	Cl	H	5	258-260[18]	92
4d	Br	H	5	288-289	96
4e	Me	H	5	280-282	95
4f	$(CH_3)_2CH$	H	5	290-291	96
4g	$(CH_3)_3C$	H	5	>310	92
4h	CH_3	CH_3	6	290-292[19]	95
4i	F	F	6	>310	92
4j	Cl	Cl	6	>310	94

The nucleophilic addition reaction of 1,4-naphthoquinone (**5**) with o-phenylenediamine (**2**) in aqueous K_2CO_3 using SDS as a catalyst leads to desired benzo[*a*]phenazine (**6**) *albeit* in lower yields when compared to nucleophilic substitution reaction with 2,3-dichloro-1,4-naphthoquinone (**1**) as shown in Table 3.

Table 3
Synthesis of benzo[*a*]phenazines (**6**) in aqueous base from 1,4-naphthoquinone (**5**).



Compound[a]	R	R^1	Base	t (h)	Mp (°C)	Yield of **5** in (%)
6a	H	H	K_2CO_3	6	70-71[5]	65
6b	F	H	K_2CO_3	6	105-106	55
6c	Cl	H	K_2CO_3	6	88-89	58
6d	Me	H	K_2CO_3	6	79-80	61

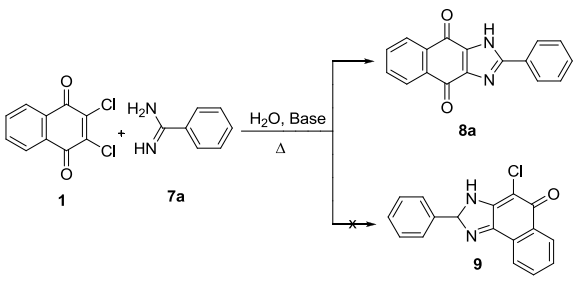
[a] Compounds were purified by column chromatography using silica gel in hexane and ethyl acetate

In recent years a large number of naphtho[2,3-*d*]imidazoles have been isolated from natural products.[20] Naphtho[2,3-*d*]imidazole derivative kealiquinone, an alkaloid isolated from a marine sponge, *Leucetta chagosensis* and a metaboloite of pyranoamidine is a cytotoxic agent[21] and was synthesized by Kawasaki *et al.* from *N*-methylimidazole in six steps.[22] Various routes to synthesis of naphtha[2,3-*d*]imidazoles and their analogs have been explored owing to their cytotoxic activities.[23,24] The routes to synthesis of antitumor marine imidazole alkaloids by ohta *et al.* involve five and seven steps respectively using 1-methyl-2-phenylimidazole as a precursor.[23,24] Cytotoxic imidazoquinoxaline diones and imidazophthalazinediones were synthesized earlier in four steps from appropriate 1,4-quinone derivatives in moderate yields.[25-27] Cytotoxic 1*H*-naphtho[2,3-*d*]imidazole-4,9-diones have been synthesized in three steps from

2-amino-3-chloro-1,4-naphthoquinones in good yields.[28] Recently Ally et al. have reported the synthesis of 1*H*-naphtho[2,3-*d*]-imidazole-4,9-diones by heterocyclization of 2,3-diamino-1,4-naphthoquinone with appropriate aldehydes in non-aqueous medium.[29]

In order to explore the synthesis of naphtho[2,3-*d*]imidazoles "in H_2O", we carried out reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with benzamidine (**7a**) in aqueous medium with or without base using SDS as a catalyst. The reaction involves nucleophilic substitution and condensation resulting in one pot regio-selective synthesis of 2-phenyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**8a**). The optimization of reaction conditions led to 91% yield of **8a** using K_2CO_3 as a base and SDS as a catalyst, Table 4.

Table 4
Reaction of 2,3-dichloronaphthoquinone (**1**) with benzamidine (**7a**)

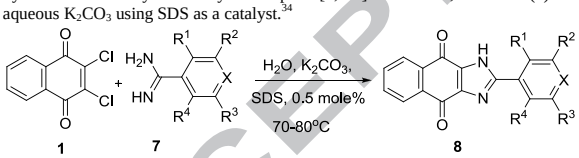


Solvent	Base	Surfactant	T (^{0}C)	t (h)	Yield **8a** (%)
H_2O	K_2CO_3	-	90	12	26
H_2O	Et_3N	SDS	70	8	69
H_2O	K_2CO_3	SDS	70	6	91
H_2O	KOH	SDS	70	3	81[a]

[a]No increase in yield was observed even after 12 h

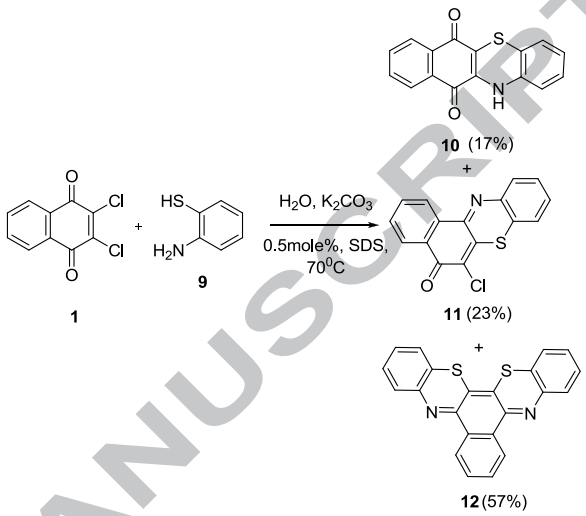
On the basis of excellent yields of 2-phenyl-1*H*-naphtho[2,3-*d*] imidazole-4,9-diones (**8a**) obtained in aqueous medium using SDS as a catalyst, various synthetic analogs of nahtho[2,3-*d*]imidazole-4,9-dione (**8**) were synthesised and are shown in Table 5.

Table 5
Synthesis of 2-aryl/heteroaryl-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones (**8**) in aqueous K_2CO_3 using SDS as a catalyst.[34]



Com.	X	R^1	R^2	R^3	R^4	T (h)	Mp(^{o}C)	Yield 8 %
8a	CH	H	H	H	H	6	341[30]	91
8b	CH	H	CH_3	H	H	8	>350	93
8c	CH	H	Cl	Cl	H	8	>350	95
8d	N	H	H	H	H	7	>350	90
8e	C-OMe	H	H	H	H	8	322[30]	95
8f	C-Cl	H	H	H	H	8	301[30]	94
8g	N	H	Cl	Cl	H	7	>350	92
8h	C-F	H	H	H	H	7	>350	90
8i	C-Br	H	H	H	H	8	>350	96

In order to study the regio-selectivity of nucleophilic substitution and condensation reaction of 2,3-dichloro-1,4-naphthoquinone with 2-aminobenzenethiol, analogous reaction of **1** with 2-aminobenzene thiol **9** "in H_2O" using K_2CO_3 as base and SDS as a catalyst however resulted in isolation of a mixture of 6*H*-benzo[*b*]phenothiazine-6,11(12*H*)-dione (**10**),[31,32] 6-chloro-5*H*-benzo[*a*]phenazine-5-one (**11**)[32] and benzo[*a*][1,4]benzothiazino (**12**)[32,33] in 17%, 23% and 57% yields respectively as shown in Scheme 1.



Scheme 1. Nucleophilic substitution followed by condensation reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with 2-aminobenzenethiol **9** (2eq.) in basic aqueous media using SDS as a surfactant.

The competitive nucleophilic substitution reaction between SH and NH_2 leads to preferential initial attack of SH group as a nucleophile leading to formation of a mixture of products **10** and **11**. The formation of **12** can be explained by nucleophilic substitution of both chlorine atoms of **1** with preferentially SH group of **9** and cyclocondensation.

In conclusion, we have developed a regio- and chemo-selective expeditious one pot synthesis of benzo[*a*]phenazines and naphtha[2,3-*d*]imidazoles from 2,3-dicholoro-1,4-naphthoquinone "in H_2O" using micelles as catalyst in excellent yields not reported so for. Further work is in progress to explore micelles catalyzed nucleophilic substitution and condensation reactions in water for the synthesis of benzo[*a*]phenazine derivative NC-190 and its analogs as well as others polycyclic heterocycles of pharmaceutical significance.

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34. *Representative procedure for synthesis:* 1 mmol nucleophile (**2, 7** or **9**) was added to 5 mL aqueous suspension of surfactant (0.5 mole % SDS). After stirring for five minutes, quinone **1** or **5** (1 mmol) was added and stirred at temperatures represented in Tables or Schemes. The products were filtered and purified after neutralization with 5% HCl, followed by column chromatography (if required) of the reaction mixture (hexane/EtOAc) leading to desired products. *6-chlorobenzo[a]phenazin-5-ol* (**4a**): red powder; IR (KBr): 1597 and 1675 (>C=O), 3443 (OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.72 (m, 1H), 7.87 (m, 3H), 8.12 (m, 2H), 8.26 (s, 1H), 8.33 (m, 1H), 9.06 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 104.8, 124.6, 125.0, 125.5, 127.3, 128.1, 129.5, 129.8, 130.0, 131.0, 136.3, 137.0, 140.0, 143.9, 146.1, 167.1; m/z: 283.2 $[M+H]^+$; Anal. Calcd. for $C_{16}H_9ClN_2O$: C, 68.46; H, 3.23; N, 9.98%. Found: C, 68.57; H, 3.30; N, 10.10%. Beilstein test: Cl positive; *2-phenyl-1H-naphtho[2,3-d]imidazole-4,9-dione* (**8a**): dark red needles; IR (KBr): 1671 (>C=O of quinone), 3342 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40-7.54 (m, 5H), 7.71 (m, 1H), 7.83-7.97 (m, 3H), 8.19 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 127.5, 128.3 (2C), 129.0 (2C), 129.8 (2C), 129.9 (2C), 130.0, 130.1, 131.4, 133.6, 136.0, 166.8, 187.1 (2C); m/z: 274.8 $[M]^+$; Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21%. Found: C, 74.28; H, 3.74; N, 10.34%.

Graphical Abstract

Micelles catalyzed one pot regio- and chemoselective synthesis of benzo[*a*]phenazines and naphtho[2,3-d]imidazoles "in H_2O"

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