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Water-promoted unprecedented chemoselective nucleophilic substitution reactions of 1,4-quinones with oxygen nucleophiles in aqueous micelles

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ABSTRACT

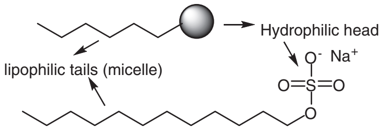
Unique nucleophilic substitution and addition reactions of nitrogen and sulfur nucleophiles with 1,4-quinones in aqueous suspension with amines and thiols have recently been demonstrated by us.[2] However, the reactivity of oxygen nucleophiles toward nucleophilic substitution compared to nitrogen and sulfur nucleophiles 'on water' is not facile. An unprecedented economical, green methodology approach using ordinary laundry detergent (LD; washing powder, 0.5 mol %, reusable)/SDS as surfactant 'in water' for nucleophilic substitution by oxygen nucleophiles in 1,4-quinones in excellent yields has been demonstrated.

Aqueous environment has been currently receiving considerable attention in organic chemistry. Water has profound economic, environmental, safety, and societal advantages over conventional reactions in organic solvents leading further to the development of ideology of Green Chemistry.[1]

The reactions in organic solvents occur in homogenous solution phase, however, the reactions of solid reactants in aqueous medium occur on the surface of water and hence the collision of molecules of two reactants is retarded, therefore, an agent that lowers the surface tension of water and allows the easier spreading and lowering of the interfacial tension between two reactants was required. Surfactants[3] which are usually organic compounds that are amphiphilic and contain both hydrophobic (their lipophilic tails called micelle) and hydrophilic groups (their heads) (Fig. 1) have been recently employed to facilitate the reactions 'in water'. A micelle in a surfactant sticks with the reactant and due to heavy head settles down into the water from surface and thus increases the collision of two reactants and makes a favorable condition for reaction 'in water' as compared with reaction 'on water' surface.[2]

In recent years, the surfactant-promoted deprotection of oximes and imines to carbonyls[4] and cross-coupling reactions of arylboronic acids with carboxylic anhydrides or acyl chlorides[5] using surfactant sodium dodecyl sulfate (SDS), dehydrative nucleophilic substitution of benzyl alcohols with a variety of carbon- and heteroatom-centered nucleophiles,[6] and Mannich reaction[7] using surfactant dodecylbenzenesulfonic acid (DBSA), Cetyltrimethylammonium bromide (CTAB), a cationic surfactant mediated Heck and Suzuki coupling,[8] and many such reactions have been studied in water using different surfactants.[9]

The nucleophilic substitution and addition reactions of 1,4-quinones have been extensively[9–20] studied in nonaqueous media. In connection with our studies on nucleophilic addition and substitution reactions of 1,4-naphthoquinones in nonaqueous media,[10–20] we were encountered with drastic reaction conditions, isolation, and purification with low yields of products by reaction with oxygen nucleophiles due to less nucleophilicity of oxygen nucleophiles (Phenols and alcohols) as compared with sulfur and nitrogen nucleophiles. Due to less reactivity and drastic conditions of preparation, only a few reports on the reactivity of quinones with oxygen nucleophiles are available such as RONa in EtOH,[21,22] MF



Example: Sodium dodecyl sulfate
(a common surfactant used in laundary detergents)

Figure 1.

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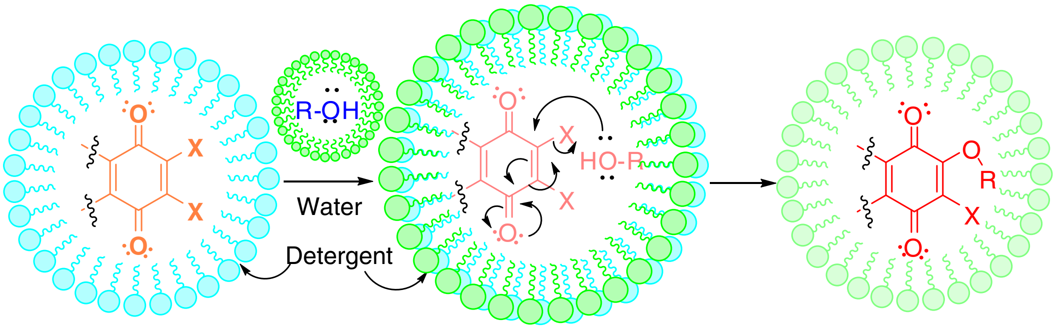
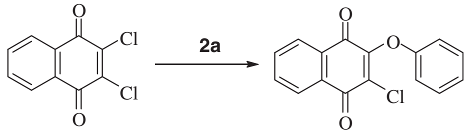


Figure 2. Reaction mechanism of quinone in water using detergent as surfactant.

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



1a **3a**

Solvents	Reactant/base	T[c] (°C)	Time[c]	Yields (%)
Anhydrous THF	PhONa	rt	5 min	78[a,24]
H_2O with 0.5% SDS	PhOH/Et_3N	60	2 h	94[b]
H_2O with 0.5% LD	PhOH//Et_3N	60	2 h	94[b]

[a] Reaction in THF required extraction with chloroform and chromatographic purification.

[b] While in water, product is directly filtered as pure form and does not need extraction or purification.

[c] Optimized time and temperature.

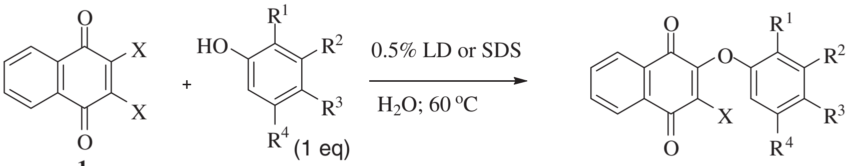
and Al_2O_3,[23] RONa and ArONa in THF,[24] phenols in pyridine,[25,26] alcohols in potassium carbonate,[27] and phenols and alcohols without solvent.[28,29]

In connection with our studies on the reactivity of quinones with nitrogen and sulfur nucleophiles 'on water'[2] and the utility of surfactants in aqueous medium,[4–9] we explored the reaction of 1,4-quinones with phenols 'in water' using laundry detergent (LD, washing powder) as surfactant (Fig. 2). Laundry detergent (LD; washing powder) has low cost and as economically viable[30] as compared to traditional expensive surfactants employed for various synthetic reactions.[9]

Profound biological effects of 1,4-naphthoquinones bearing a phenyl ether moiety at 2-position,[31,33] prompted us to explore the preparation of 2-chloro-3-phenoxynaphthalene-1,4-dione (**3a**) from 2,3-dichloro-1,4-naphthoquinone (**1a**) by the nucleophilic substitution reaction with phenol (**2a**) in water which was first synthesized by Lien et al.[24] as depicted in Table 1. The typical reaction conditions involve stirring **1a** with sodium phenoxide in anhydrous THF for 5 min and extraction in water with chloroform and purification by column chromatography to afford product **3a** in 78% yield. In contrast, when a mixture of **1a** and **2a** is stirred 'in water' with laundry detergent (LD), the reaction leads to the formation of chemoselective product **3a** exclusively in 94% yield which is directly filtered from water and does not need further extraction or purification as shown in Table 1.

Thus a variety of nucleophilic substitution reactions of **1a–b** with a variety of aromatic phenols **2a–i** have been efficiently carried out in aqueous suspension using laundry detergent or SDS as surfactant in good to excellent yields (Scheme 1, Table 2). Thus water alone is the medium of choice compared to THF and the reactions are chemoselective yielding only mono substituted product. On comparison with the corresponding thioethers,[2,18] both mono and di substituted derivatives in protic and nonprotic solvents are formed. The pure product is isolated by simple filtration. It is noteworthy that only 0.5 mol % of surfactant is used which is reusable for further reaction.

On the basis of these results, we studied the preparation of 2-alkoxy-3-halo-1,4-naphthoquinones and explored the reaction of



1 **2** **3**

1a: X=Cl
1b: X=Br

2a: R^1=R^2=R^3=R^4=H
2b: R^1=R^2=R^4=H; R^3=Me
2c: R^1=R^2=R^4=H; R^3=OMe
2d: R^1=R^3=H; R^2=R^4=Me
2e: R^1=R^2= R^4=H; R^3=Cl
2f: R^1=OH; R^2=R^3=R^4=H
2g: R^3=R^4=H;R^1=R^2=
2h: R^1=R^4=H; R^2=R^3=
2i: R^1=R^2=R^4=H; R^3=NO_2

3a: X=Cl; R^1=R^2=R^3=R^4=H
3b: X=Cl; R^1=R^2=R^4=H; R^3=Me
3c: X=Cl; R^1=R^2=R^4=H; R^3=OMe
3d: X=Cl; R^1=R^3=H; R^3=R^4=Me
3e: X=Cl; R^1=R^2=R^4=H; R^3=Cl
3f: X=Cl; R^1=OH; R^2=R^3=R^4=H
3g: X=Cl; R^3=R^4=H; R^1=R^2=
3h: X=Cl; R^1=R^4=H; R^2=R^3=
3i: X=Cl; R^1=R^2=R^4=H; R^3=NO_2
3j: X=Br; R^1=R^2=R^4=H; R^3=Me

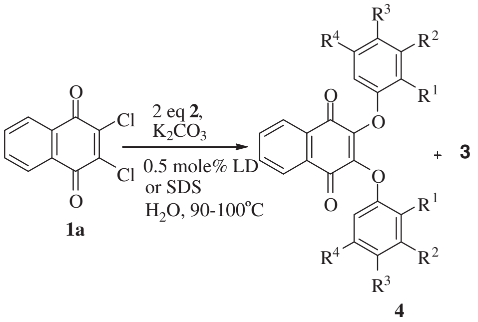
Scheme 1. Chemoselective synthesis of 2-phenyl-3-halo-1,4-naphthoquinones (**3a–j**): Reaction of 2,3-dihalo-1,4-naphthoquinones (**1**) with phenols (**2**) in aqueous medium using laundry detergent (LD)[30]/SDS as surfactant.

Table 2
Reaction of 2,3-dihalo-1,4-naphthoquinones (**1**) with phenols (**2a–i**)[32]

3	Base[a]	Time[b]	Yields (%)	
			In LD	In SDS
3a	Et_3N	2 h	94	93
3b	N	30 min	99	97
3c	N	1.5 h	84	83
3d	N	2 h	90	91
3e	N	1.5 h	90	90
3f	N	1 h	83	83
3g	N	5 h	92	90
3h	N	5 h	89	87
3i	Et_3N	12 h	25	26
3j	Et_3N	2 h	72	70

[a] Et_3N used 1 equiv, N = no base used.
[b] Optimized time.

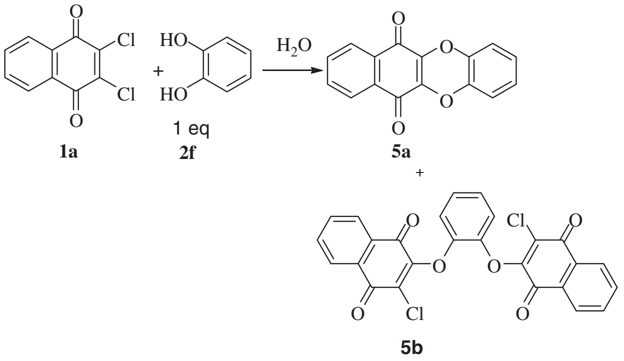
Table 3
Reaction of 2,3-dichloro-1,4-naphthoquinone (**1a**) with phenols (**2a–f**) in K_2CO_3



3, 4	R[1]	R[2]	R[3]	R[4]	Time[a] (h)	Yields (%) in				
						LD		SDS		C_5H_5N
						4	**3**	**4**	**3**	**4**
a	H	H	H	H	30	15	81	16	80	—
b	H	H	Me	H	24	50	46	48	47	43[26]
c	H	H	OMe	H	40	35	61	35	60	34[26]
d	H	Me	H	Me	40	15	71	15	70	—
e	H	H	Cl	H	40	26	61	27	62	—

[a] Optimized time. Products filtered as compounds **3** and filtrate as compounds **4** which are neutralized by 5% HCl and extracted with EtOAc.

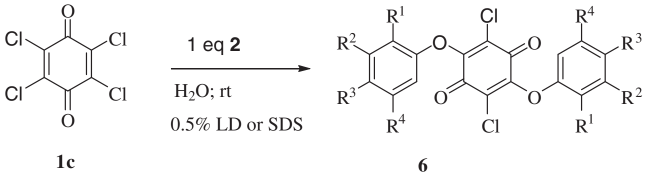
Table 4
Reaction of 2,3-dichloro-1,4-naphthoquinone (**1a**) with catechol (**2f**)



Solvents	Promoter/surfactant	Base	*T* (°C)	Time (h)	Yields (%)	
					5a	**5b**
Pyridine	N_2 atmosphere	—	100	5–6	69[25]	—
H_2O	0.5% SDS	K_2CO_3	70[a]	1[a]	35	40
H_2O	0.5% LD	K_2CO_3	70[a]	1[a]	36	42

[a] Optimized time and temperature.

Table 5
Reaction of chloranil (**1c**) with phenols (**2a–d**)[a,b]



6[a,b]	R[1]	R[2]	R[3]	R[4]	*T*[c] (°C)	Time[c] (min)	Yields (%) in	
							LD	SDS
6a	H	H	H	H	30	60	30	31
6b	H	H	Me	H	rt	15	40	39
6c	H	H	OMe	H	rt	45	42	41
6d	H	H	Cl	H	rt	30	45	44

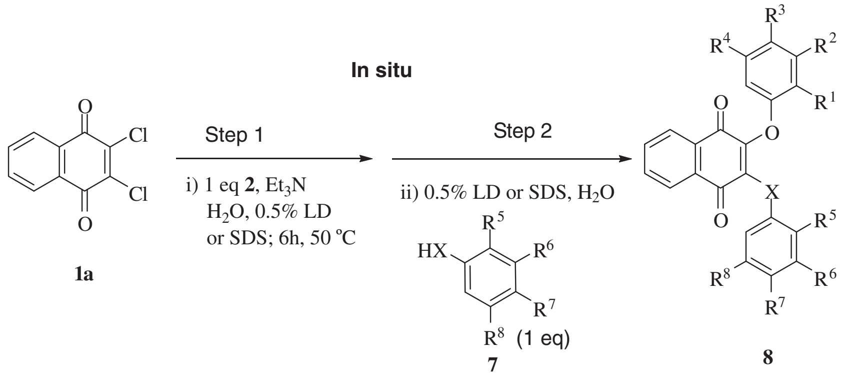
[a] All the products **6a–d** are directly filtered and recrystallized by hexane/DCM.
[b] Other compounds are not isolated.
[c] Optimized time and temperature.

2a with tertiary butyl alcohol, allyl alcohol, lactic acid, and cyclohexanol. Attempts to prepare mono substituted products were unsuccessful and only 5–10% mono alkoxy derivatives were obtained chemoselectively at 70 °C for 24 h stirring in the presence of Et_3N or K_2CO_3 and laundry detergent (LD, washing powder) or SDS in aqueous medium.

In analogy with high chemoselectivity achieved with products **3a–j**, we further explored the reaction of **1a** with 2 equiv phenols and its derivatives (**2a–f**) and found that both mono (**3a–e**) and di substituted derivatives (**4a–e**) are formed in K_2CO_3 at 90–100 °C by stirring for more than 24 h in the presence of 0.5–1.0 mol % laundry detergent or SDS in aqueous medium (Table 3). Thus the formation of both mono and di substituted derivatives evinces that the chemoselectivities of compound **3a–j** are critically dependent on the reagents and reaction conditions.

In order to study the chemoselectivity of product **3f** (Scheme 1, Table 2), we studied the reaction between **1a** and catechol (**2f**) in the presence of Et_3N (4 equiv) at 90 °C for 10 h in water with 1.0 mol % laundry detergent (LD) and observed that products **5a** and **5b** are also formed along with mono substituted derivative. On the basis of the above-mentioned results, we explored the reaction of **1a** with catechol (**2f**) (1 equiv) in the presence of K_2CO_3 (1 equiv) at 70 °C for 1 h stirring in water with 0.5 mol % laundry detergent (LD) and SDS in separate experiments as mixture of products benzo[*b*]dibenzo[*b*,*e*][1,4]dioxine-6,11-dione (**5a**) and 3,3′-(1,2-phenylenebis(oxy))bis(2-chloronaphthalene-1,4-dione) (**5b**). The potent charge-transfer complex (**5a**) was synthesized by Czekanski et al. under N_2 atmosphere at 100 °C and 5 h in pyridine as shown in Table 4. It is evident that the reaction of **1a** with **2f** in the absence of a base such as K_2CO_3 or Et_3N is chemoselective leading exclusively to the formation of **3f** as shown in Scheme 1 (Table 2) while the condensation of *O*-nucleophiles with dichloro-1,4-naphthoquinones and its analogs using cesium carbonate leading to the formation of monosubstituted derivatives has been reported by Lee et al.[34]

Based on the reactivity of 2,3-dichloro-1,4-naphthoquinone (**1a**), we studied the reaction between chloranil (**1c**) and substituted phenol (**2**) leading to the formation of disubstituted products as reported in Table 5. The reaction is highly chemoselective with substituted phenol (**2**) leading to the formation of disubstituted products (**6a–d**).



Scheme 2. In situ one-pot synthesis of **8a–f**: Reaction of 2,3-dichloro-1,4-naphthoquinone (**1a**) with **2** and **7**, respectively (in situ), as shown in Table 6.

Table 6
Reagent and reaction conditions of reaction between 2,3-dichloro-1,4-naphthoquinone (**1a**) with phenols (**2**) and **7** as shown in Scheme 2

7, **8**[a]	Step 1[b] (**2**)	Step 2 (**7**)							Yields (%) of **8** in	
		X	R^5	R^6	R^7	R^8	*T*[b] (°C)	*t*[b]	LD	SDS
a	**2b**	S	H	H	H	H	rt	30 min	90	91
b	**2b**	S	H	H	Me	H	rt	30 min	95	94
c	**2b**	NH	H	H	H	H	90	8 h	75	73
d	**2d**	NH	H	H	Cl	H	90	8 h	78	78
e	**2e**	NH	H	H	Cl	H	50	1 h	81	80
f	**2b**	O	OH	H	H	Me	60	2 h	51	50

[a] All compounds directly filtered as single product as monitored by TLC except **8f**.
[b] Optimized time and temperature.

Chemoselectivity in the formation of monosubstituted quinone phenyl ethers (**3a–j**) as shown in Table 2 prompted us to further study the reactivity of adjacent chlorine atom in compound **3** in water and we, therefore, studied in situ one-pot reaction of 2,3-dichloro-1,4-naphthoquinone (**1a**) first with phenols (**2**) (step 1) and after completion, in situ reaction with thiophenols, substituted anilines, and phenol derivatives (step 2) as shown in Scheme 2. Thus 2,3-hetero disubstituted products of 1,4-naphthoquinoe can be synthesized in good to excellent yields in water (Table 6) using laundry detergent (LD, washing powder) in comparison with the disubstituted products synthesized in the presence of excess methanol/ethanol[18] or DMSO[31] in the absence of water in two steps.

It is noteworthy that the in situ reaction with substituted anilines and thiophenols (in step 2) is chemoselective. However, the reverse process to synthesize in situ products **8** by reaction of aniline with quinone **1** (step 1) followed by reaction with phenol (**2a**) (step 2) does not lead to the desired product by in situ one-pot synthesis of **8**.

In conclusion, we are the first to report the synthesis of the quinone phenyl ethers in water using low cost and economically viable laundry detergent (LD, washing powder) as well as SDS as surfactant. Results in laundry detergent (LD, washing powder) are further being explored for various base-catalyzed reactions which will be cost effective compared to other surfactants for various synthetic applications.[9]

Further work is in progress to explore 'in water' nucleophilic substitution reactions for industrial applications and substituted quinones with other nucleophiles.

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