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Green protocol for conjugate addition of amines to *p*-quinones accelerated by water

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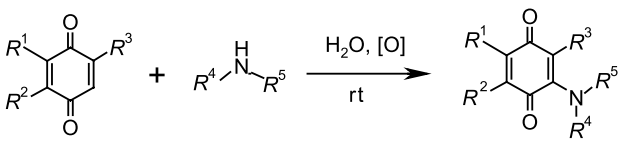
Abstract Amines undergo smooth conjugate addition to *p*-quinones in H_2O at ambient temperature in the absence of a catalyst to produce 2-aminoquinones in excellent yields. Significant rate acceleration of this reaction is observed in H_2O compared to organic solvents. H_2O played a dual role in simultaneously activating the *p*-quinone and amine. This new methodology constitutes an easy, highly efficient, and green synthesis of substituted *p*-quinones.

Keywords Amines; Conjugate addition; *p*-Quinones; 2-Aminoquinones.

Introduction

The serious environmental impact associated with the use of volatile organic solvents in chemical transformations has led to the quest for safer green solvents. Thus, over the last decade investigations on the use of several alternative solvents such as ionic liquids [1] and supercritical fluids [2] as viable reaction media have been the focus of increasing attention. Recently, organic synthesis using H_2O has received considerable attention because of its unique properties such as environmental acceptability, abundance, and low cost [3]. Furthermore, H_2O exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents [4, 5]. Substituted *p*-quinones exist widely in nature and exhibit various important biological activities [6]. The catalyst-free preparation of aza-hydroquinone in H_2O is desirable as the tight legislation on the maintenance of greenness in synthetic pathways and processes demand us to prevent waste, avoid the use of hazardous (halogenated and high-boiling solvents) auxiliary substances (additional reagents), and minimize energy requirements [7]. Thus, the use of H_2O instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry [3, 8]. Thus, continuous efforts have been made to develop newer methodologies for the *Michael* addition that led to the development of various catalysts [9, 10]. A number of procedures either based on activation of amine by a base or an activation of the acceptor olefin with *Lewis* acids have been developed [11, 12]. However, there are several limitations with the reported methodologies such as long reaction times, use of halogenated solvents, difficulty in recovery of high boiling solvents, high temperatures, requirement of special efforts for the preparation of catalysts, use



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Scheme 1

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of costly catalysts, moderate yields, use of toxic chemicals, *etc*. In view of environmental consciousness, there have been some reports on the use of water as a reaction medium for the C–N coupling reactions of amines and quinones [13]. Furthermore, there have also been some reports on the use of enzymes for the preparation of N-substituted quinones [14]. However, some of these procedures require acid catalysts and high temperature and the reported yields are far from satisfactory. Therefore, the development of simple, greener, and cost-effective procedures would extend the scope of this reaction.

Results and discussion

In this report, we wish to highlight our results on the conjugate addition of amines to *p*-quinones in H_2O without a catalyst. Initially, we attempted the *Michael* addition of 1,4-naphthoquinone (**1a**, 1 mmol) with *n*-propyl amine (**2a**, 1 mmol) in H_2O at room temperature. The reaction went to completion within 5 min and the product, 2-aminonaphthoquinone (**3a**) was obtained in 95% yield (Scheme 1, entry **a**, Table 1). We assume that the primarily formed hydrochinon is oxidized by atmospheric oxygen to the final product.

Similarly, various amines such as diethylamine, morpholine, *N*-phenylpiperazine, and substituted aromatic amines underwent smooth addition to 1,4-naphthoquinone and *p*-benzoquinone to give the corresponding products in excellent yields (entries **b**–**l**, Table 1). In addition, sterically hindered *p*-quinones such as 2-methyl- and 2,6-dimethyl-*p*-benzoquinones also reacted efficiently with different amines to provide the corresponding aminoquinones in high yields (entries **m**–**r**, Table 1). In all cases, the reactions proceeded rapidly at room temperature without the need of a catalyst. The reactions were clean and the products were obtained in excellent yields. The products were characterized by ^{1}H NMR, IR, and HRMS. Mechanistically, it is possible that H_2O promotes the reaction through H-bond formation with the carbonyl O-atom of the *p*-quinone, thereby increasing the electrophilic character at the C-atom, which is attacked by the nucleophilic amine. On the other hand, H-bond formation involving the O-atom of H_2O and the H-atom of the amine increases the nucleophilic character of the N-atom of the amine. Thus, H_2O activates the amine as well as the *p*-quinone and thereby facilitates the conjugate addition.

This method involves very simple experimental and product isolation procedures. Several primary

Table 1 Conjugated addition of amines to *p*-quinones in water

Entry	R^1	R^2	R^3	R^4	R^5	Time / min	Yield / %[a]	mp/°C	
								Found[b]	Reported
a	Benzo		H	*n*–C_3H_7	H	5	95	114–116	115–117 [15]
b	Benzo		H	*Et*	*Et*	5	92	125–127	–
c	Benzo		H	–$(CH_2)_2O(CH_2)_2$–		5	96	152–154	151–153 [16]
d	Benzo		H	–$(CH_2)_2N(Ph)(CH_2)_2$–		7	90	141–143	–
e	Benzo		H	*Ph*	H	10	92	187–189	188–190 [17]
f	Benzo		H	4-*MePh*	H	10	90	135–138	–
g	Benzo		H	4-*MeOPh*	H	12	91	155–156	155–157 [18]
h	H	H	H	*n*-C_3H_7	H	10	85	110–112	–
i	H	H	H	–$(CH_2)_2O(CH_2)_2$–		8	88	133–135	135 [19]
j	H	H	H	*Ph*	H	12	86	131–133	–
k	H	H	H	4-*MePh*	H	15	85	137–139	–
l	H	H	H	4-*MeOPh*	H	15	85	132–134	–
m	*Me*	H	H	*Ph*	H	10	90	154–156	155–156 [20]
n	*Me*	H	*Me*	*n*–C_3H_7	H	8	90	80–82	–
o	*Me*	H	*Me*	–$(CH_2)_2O(CH_2)_2$–		8	93	91–93	–
p	*Me*	H	*Me*	*Ph*	H	10	91	75–77	–
q	*Me*	H	*Me*	4-*MePh*	H	10	88	115–117	–
r	*Me*	H	*Me*	4-*MeOPh*	H	15	85	123–125	–

[a] All products were characterized by ^{1}H NMR, IR, and mass spectroscopy; yield refers to pure products after chromatography
[b] M.p. was determined after recrystallization from appropriate solvents

and secondary amines underwent smooth additions with *p*-quinones in H_2O in absence of a catalyst. The scope and generality of this process is illustrated in Table 1. In conclusion, we have developed an efficient and greener protocol for the synthesis of 2-amino-*p*-quinones in H_2O. This method offers several advantages including mild reaction conditions, enhanced rates, cleaner reactions with improved yields, no production of by-products, and ready availability of starting materials, high regioselectivity, operational and experimental simplicity which makes this method a useful and attractive strategy for the synthesis of 2-amino-*p*-quinones.

Experimental

Melting points were recorded on a Büchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometers in $CDCl_3$ using *TMS* as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Typical procedure

A mixture containing 1 mmol *p*-quinone **1**, 1 mmol amine **2** in 1 cm^3 water was stirred at 50–70°C for the specified time (see Table 1). After completion of the reaction, the crude product was filtered off, washed with water, and dried under reduced pressure to afford pure 2-aminoquinone which was purified by chromatography.

2-(Diethylamino)naphthalene-1,4-dione (**3b**, $C_{14}H_{15}NO_2$)
Solid, mp 125–127°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 1.29–1.32 (m, 6H), 3.51–3.60 (m, 4H), 5.85 (s, 1H), 7.56–7.74 (m, 2H), 7.95–8.06 (m, 2H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3452, 3302, 2933, 2871, 1605, 1591, 1482, 1208, 1123, 765 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{16}NO_2$ 230.1181, found 230.1172.

2-(4-Phenylpiperazin-1-yl)naphthalene-1,4-dione
(**3d**, $C_{20}H_{18}N_2O_2$)
Solid, mp 141–143°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.38$ (t, $J = 10.5$ Hz, 4H), 3.70 (t, $J = 10.5$ Hz, 4H), 6.03 (s, 1H), 6.84–6.91 (m, 2H), 7.21–7.27 (m, 3H), 7.61–7.72 (m, 2H), 7.99–8.05 (m, 2H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3452, 3312, 2945, 2864, 1613, 1583, 1482, 1221, 1218, 1123, 773 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{18}N_2O_2Na$ 341.1265, found 341.1255.

2-(p-Tolylamino)naphthalene-1,4-dione (**3f**, $C_{17}H_{13}N_2O_2$)
Solid, mp 135–138°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.02$ (s, 3H), 6.35 (s, 1H), 7.15–7.25 (m, 2H), 7.32–7.41 (m, 2H), 7.60–7.72 (m, 2H), 8.12 (d, $J = 8.0$ Hz, 2H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3445, 3323, 2924, 2832, 1651, 1612, 1518, 1462, 1236, 1164, 1023, 825, 732 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{14}N_2O_2$ 264.1024, found 264.1015.

2-(Propylamino)cyclohexa-2,5-diene-1,4-dione
(**3h**, $C_9H_{11}NO_2$)
Solid, mp 110–112°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 0.992–1.03 (m, 3H), 1.62–1.69 (m, 2H), 3.10–3.15 (m, 2H), 5.19 (s, 1H), 6.51–6.61 (s, 2H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3454, 3314, 2932, 2852, 1609, 1573, 1482, 1213, 1201, 1149, 753 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{12}NO_2$ 166.0868, found 166.0860.

2-(Phenlamino)cyclohexa-2,5-diene-1,4-dione (**3j**, $C_{12}H_9NO_2$)
Solid, mp 131–133°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 6.55–6.61 (m, 4H), 6.91–7.05 (m, 3H), 8.1 (s, 1H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3465, 3312, 2932, 2855, 1609, 1571, 1471, 1222 1201, 1152, 755 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{10}NO_2$ 200.0711, found 200.0702.

2-(p-Tolylamino)cyclohexa-2,5-diene-1,4-dione
(**3k**, $C_{13}H_{11}NO_2$)
Solid, mp 137–139°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3H), 6.53 (s, 1H), 6.83 (d, $J = 8.7$ Hz, 1H), 7.08–7.22 (m, 4H), 7.26 (d, $J = 8.7$ Hz, 1H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3445, 3310, 2932, 2886, 1662, 1642, 1553, 1297, 1108, 968, 866, 774 cm^{-1}; HRMS (ESI): m/z calcd for $C_{13}H_{11}NO_2Na$ 236.0653, found 236.0647.

2-(4-Methoxyphenylamino)cyclohexa-2,5-diene-1,4-dione
(**3l**, $C_{13}H_{11}NO_3$)
Solid, mp 132–134°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H), 6.75 (s, 1H), 6.81 (d, $J = 8.7$ Hz, 1H), 6.92–7.02 (m, 4H), 7.23 (d, $J = 8.7$ Hz, 1H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3454, 3324, 2931, 2872, 1609, 1571, 1481, 1223, 1154, 753 cm^{-1}; HRMS (ESI): m/z calcd for $C_{13}H_{12}NO_3$ 230.0817, found 230.0810.

3,5-Dimethyl-2-(Propylamino)cyclohexa-2,5-diene-1,4-dione
(**3n**, $C_{11}H_{15}NO_2$)
Solid, mp 80–82°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.99$–1.02 (m, 3H), 1.65–1.73 (m, 2H), 2.14 (s, 3H), 2.35 (s, 3H), 3.02–3.15 (m, 2H), 6.02 (s, 1H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3451, 3312, 2923, 2853, 1662, 1642, 1521, 1282, 1232, 1172, 1034, 956 cm^{-1}; HRMS (ESI): m/z calcd for $C_{11}H_{16}NO_2$ 194.1181, found 200.0702.

3,5-Dimethyl-2-morpholinocyclohexa-2,5-diene-1,4-dione
(**3o**, $C_{12}H_{15}NO_3$)
Solid, mp 91–93°C, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.21$ (s, 3H), 2.30 (s, 3H), 3.52 (t, $J = 8.5$ Hz, 4H), 3.82 (t, $J = 8.5$ Hz, 4H), 6.23 (s, 1H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3435, 3312, 2985, 1614, 1583, 1456, 1435, 1208, 1155 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{16}NO_3$ 222.1130, found 222.1120.

3,5-Dimethyl-2-(phenylamino)cyclohexa-2,5-diene-1,4-dione
(**3p**, $C_{14}H_{13}NO_2$)
Solid, mp 75–77°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.45$ (s, 3H), 2.15 (s, 3H), 6.59–6.62 (m, 2H), 6.83 (d, $J = 8.0$ Hz, 2H), 6.94 (d, $J = 8.0$ Hz, 2H) ppm; IR (KBr): $\bar{\nu}_{max} =$ 3452, 3315, 2927, 2855, 1660, 1632, 1521, 1262, 1170, 1033, 962, 764 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{14}NO_2$ 228.1024, found 228.1014.

2-(p-Tolylamino)-3,5-dimethylcyclohexa-2,5-diene-1,4-dione (**3q**, $C_{15}H_{15}NO_2$)
Solid, mp 115–117°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.51$ (s, 3H), 2.16 (s, 3H), 2.35 (s, 3H), 6.53 (s, 1H), 6.64 (d, $J = 8.2$ Hz, 2H), 6.82 (d, $J = 8.5$ Hz, 2H) ppm; IR (KBr): $\bar{\nu}_{max} = 3442$, 3315, 2920, 2851, 1660, 1645, 1510, 1272, 1216, 1149, 1050, 960, 760 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1175.

2-(4-Methoxyphenylamino)-3,5-dimethylcyclohexa-2,5-diene-1,4-dione (**3r**, $C_{15}H_{15}NO_3$)
Solid, mp 123–125°C, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.51$ (s, 3H), 2.18 (s, 3H), 3.75 (s, 3H), 6.49 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 2H), 6.92 (d, $J = 8.0$ Hz, 2H) ppm; IR (KBr): $\bar{\nu}_{max} = 3447$, 3317, 2923, 2853, 1664, 1642, 1511, 1288, 1236, 1177, 1036, 960, 832, 764 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{15}NO_3Na$ 280.0949, found 280.0937.

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