

Organic synthesis in water: Green protocol for the conjugate addition of thiols to *p*-quinones

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Abstract

The Michael addition of thiols to *p*-quinones proceeds efficiently in water at room temperature without a catalyst. Significant rate acceleration of this reaction is observed in water compared to organic solvents. Water played a dual role in simultaneously activating the quinones and thiols. This new methodology constitutes an easy, highly efficient and green synthesis of diaryl sulfides and aryl alkyl sulfides.

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Keywords: Thia-Michael addition; Quinones; Diaryl sulfides; Aryl alkyl sulfides

1. Introduction

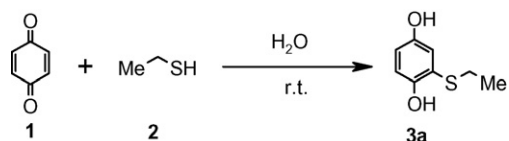
Organic reactions in water have received considerable attention primarily because of its environmental acceptability, abundance and low cost [1,2]. However, water exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents [3–5]. The catalyst-free preparation of sulfido hydroquinones in water 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 (e.g. halogenated and high-boiling solvents) auxiliary substances (e.g. additional reagents) and minimize energy requirements [6]. Thus, the use of water instead of organic solvents has gained importance as an essential component of the development of sustainable chemistry [2,7–13]. The Michael addition is an important transformation and apart from its versatile applications in synthetic organic chemistry, it plays a crucial role in biosynthesis [14] and synthesis of bioactive compounds [15,16]. Thus, continuous efforts have been made to develop newer methodologies for the Michael addition that lead to the development of various catalysts [17–21]. A number of procedures either based on activation of thiol by a base or activation of the acceptor olefins with Lewis acids have been developed [22–27]. More recently, tetrabutylammonium halides have been

used as phase transfer catalysts [28]. However, there are various 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 of costly catalysts, moderate yields and use of toxic chemicals, etc. However, the development of simple and cost-effective procedures would extend the scope of this reaction. Furthermore, there are no reports on the Michael addition of thiols onto *p*-quinones in water without the use of any catalyst.

2. Results and discussion

In this report, we wish to highlight our results on the Michael addition of thiols to quinones in the water media without any catalyst. Thus, treatment of *p*-benzoquinone with ethanethiol gave 2-(ethylthio)benzene-1,4-diol **3a** in 94% yield (Scheme 1).

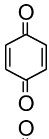
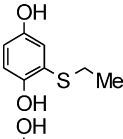
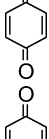
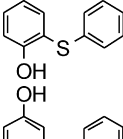
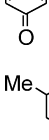
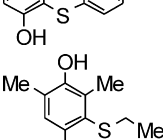
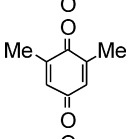
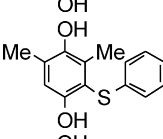
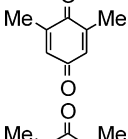
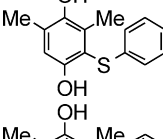
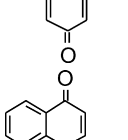
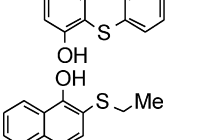
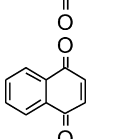
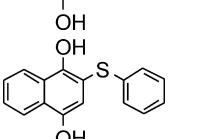
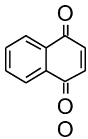
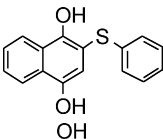
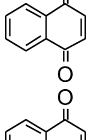
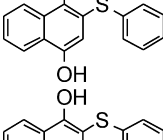
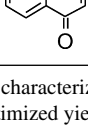
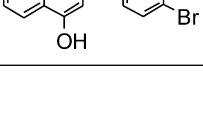
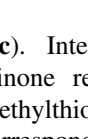
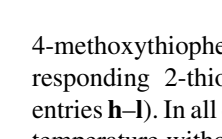
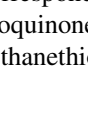
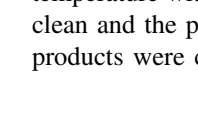
Similarly, thiophenol and 4-methylthiophenol reacted smoothly with *p*-benzoquinone to give the corresponding 2-thio-benzene-1,4-diol derivatives in excellent yields (Table 1,



Scheme 1.

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

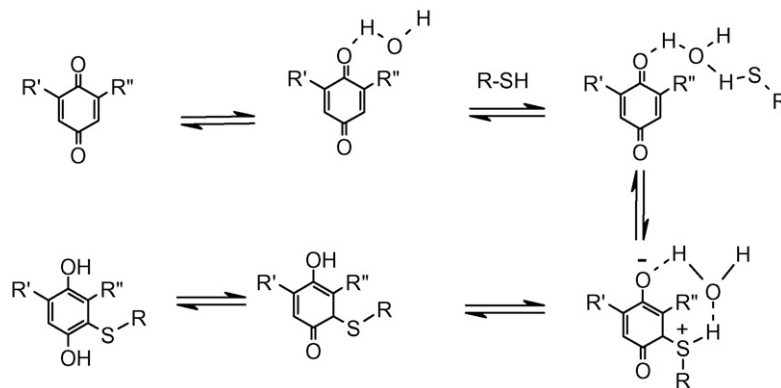
Entry	Quinone 1	Thiol 2	Product 3 ^a	Time (min)	Yield (%) ^b
a		Me-SH		8	94
b		SH		10	92
c		SH Me		10	92
d		Me-SH		5	90
e		SH		10	88
f		SH Me		10	85
g		SH OMe		15	84
h		Me-SH		8	88
i		SH		10	86
j		SH Me		12	85
k		SH OMe		15	86
l		SH Br		15	82

^a All products were characterized by ¹H NMR, IR and mass spectroscopy.

^b Isolated and unoptimized yield.

entries **b** and **c**). Interestingly, sterically hindered 2,6-dimethylbenzoquinone reacted efficiently with ethanethiol, thiophenol, 4-methylthiophenol and 4-methoxythiophenol to give the corresponding thioethers (Table 1, entries **d–g**). Like benzoquinone, 1,4-naphthoquinone also reacted smoothly with ethanethiol, thiophenol, 4-methylthiophenol,

4-methoxythiophenol and 4-bromothiophenol to give the corresponding 2-thio-naphthalene-1,4-diol derivatives (Table 1, entries **h–l**). 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 ¹H NMR, IR and mass spec-



Scheme 2.

troscopic data. It is possible that water promotes the reaction through hydrogen bond formation with the carbonyl oxygen atom of the *p*-quinone thereby increasing the electrophilic character at the carbon center, which is attacked by the nucleophilic thiol. On the other hand, hydrogen bond formation involving the oxygen atom of water and the H-atom of the thiol increases the nucleophilic character of the sulfur atom of thiol. Thus, water activates the thiol as well as the *p*-quinone and thereby facilitates the Michael addition (Scheme 2).

The scope and generality of this process is illustrated with respect to various thiols and quinones and the results are presented in Table 1.

3. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ¹H-NMR spectra were recorded on Gemini-200 and Varian Bruker-300 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

3.1. Typical procedure

A mixture of *p*-quinone (2 mmol) and thiol (2 mmol) in water (5 mL) was stirred at room temperature for the specified time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane) afforded pure thioether.

3.1.1. 2-Phenyl sulfanyl-1,4-benzenediol (Table 1, entry 3b)

Liquid, ¹H NMR (200 MHz, CDCl₃): δ 1.50 (brs, 1H, OH), 4.80 (brs, 1H, OH), 6.05 (s, 1H), 6.81–6.95 (m, 3H), 7.15–7.36 (m, 3H), 7.40–7.56 (m, 2H). IR (KBr): ν_{max} 3399, 3058, 1580, 1488, 1444, 1329, 1204, 777, 740, 690 cm⁻¹. ESIMS: 217 (*M*⁺ – 1) (100).

3.1.2. 3,5-Dimethyl-2-[(4-methylphenyl)sulfanyl]-1,4-benzenediol (Table 1, entry 3f)

Solid, mp: 95–97 °C. ¹H NMR (200 MHz, CDCl₃): δ 2.26 (s, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 4.24 (s, 1H, OH), 6.31 (s, 1H), 6.71 (s, 1H, OH), 6.86 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.3, 2H). IR (KBr): ν_{max} 3416, 3021, 2920, 1651, 1491, 1306, 1201, 1015, 806 cm⁻¹. ESIMS: 259 (*M*⁺ – 1) (100), 244(50), 227(15), 212(10), 197(15).

3.1.3. 2-(Ethylsulfanyl)-1,4-naphthalenediol (Table 1, entry 3h)

Solid, mp: 93–94 °C. ¹H NMR (200 MHz, CDCl₃): δ 1.46 (t, *J* = 7.5 Hz, 3H), 2.86 (q, *J* = 7.5 Hz, 2H), 6.56 (s, 1H), 7.66–7.75 (m, 2H), 8.04–8.11 (m, 2H). IR (KBr): ν_{max} 3447, 2923, 2853, 2361, 1668, 1642, 1550, 1297, 1118, 968, 866, 774 cm⁻¹. LCMS: 221 (*M*⁺ + 1).

4. Conclusion

In summary, this paper describes an efficient protocol for the synthesis of diaryl sulfides and aryl alkyl sulfides in water. This method offers several advantages including mild reaction conditions, enhanced rates, cleaner reactions with improved yields, no production of by-products such as disulfides 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 diaryl sulfides and aryl alkyl sulfides.

Acknowledgements

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References

- [1] C.J. Li, T.H. Chang, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
- [2] P.A. Grieco (Ed.), *Organic Synthesis in Water*, Blackie Academic and Professional, London, 1998.
- [3] N. Azizi, M.S. Saidi, *Org. Lett.* 7 (2005) 3649.
- [4] N. Azizi, F. Aryanasab, L. Torkiyani, A. Ziyaei, M.S. Saidi, *J. Org. Chem.* 71 (2006) 3634.
- [5] G.L. Khatik, R. Kumar, A.K. Chakraborti, *Org. Lett.* 8 (2006) 2433.

- [6] P. Tundo, P. Anastas, D.S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff, W. Tumas, *Pure Appl. Chem.* 72 (2000) 1207.
- [7] N. Azizi, M.R. Saidi, *Org. Lett.* 7 (2005) 3649.
- [8] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* 10 (1971) 496.
- [9] C. Larpent, H. Patin, *Tetrahedron* 44 (1988) 6107.
- [10] C. Larpent, G. Meignan, H. Patin, *Tetrahedron* 46 (1990) 6381.
- [11] G. Jenner, *Tetrahedron* 52 (1996) 13557.
- [12] E. Keller, B.L. Feringa, *Tetrahedron Lett.* 37 (1996) 1879.
- [13] Y. Mori, K. Kakumoto, K. Manabe, S. Kobayashi, *Tetrahedron Lett.* 41 (2000) 3107.
- [14] E. Fujita, Y. Nagao, *Bioorg. Chem.* 6 (1977) 287.
- [15] A.L. Fluharty, S. Patai, *The Chemistry of the Thiol Group, Part 2*, Wiley Interscience, New York, 1974, p. 589.
- [16] A. Kumar, R.V. Salunkhe, R.A. Rane, S.Y. Dike, *J. Chem. Soc., Chem. Commun.* (1991) 485.
- [17] M. Bandini, P.G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A. Umani-Ronchi, *J. Org. Chem.* 67 (2002) 3700.
- [18] N. Srivastava, B.K. Banik, *J. Org. Chem.* 68 (2003) 2109.
- [19] J.S. Yadav, B.V.S. Reddy, G. Baishya, *J. Org. Chem.* 68 (2003) 7098.
- [20] S.K. Garg, R. Kumar, A.K. Chakraborti, *Tetrahedron Lett.* 46 (2005) 1721.
- [21] C.M. Chu, S. Gao, M.N.V. Sastry, C.F. Yao, *Tetrahedron Lett.* 46 (2005) 4971.
- [22] S. Cheng, D.D. Comer, *Tetrahedron Lett.* 43 (2002) 1179.
- [23] M. Jahouily, Y. Abrouki, A. Rayadh, S. Sebti, H. Dhimane, M. David, *Tetrahedron Lett.* 44 (2003) 2463.
- [24] M. Bandini, P.G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A.U. Ronchi, *J. Org. Chem.* 67 (2002) 3700.
- [25] Y. Abrouki, M. Zahouily, A. Rayadh, B. Bahlaouan, S. Sebti, *Tetrahedron Lett.* 43 (2002) 8951.
- [26] S. Kangasabapathi, A. Sudalai, B.C. Benicewicz, *Tetrahedron Lett.* 42 (2001) 3791.
- [27] E. Emori, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* 120 (1998) 4043.
- [28] B.C. Ranu, S.S. Dey, A. Hajra, *Tetrahedron* 59 (2003) 2417.