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RESEARCH ARTICLE

A General and Facile One-Pot Synthesis of Napthoquinone-1,3-dithioles in Aqueous Medium

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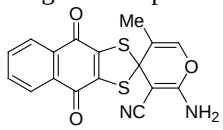
Abstract: A general and facile one pot protocol for the preparation of napthoquinone-1,3-dithioles has been developed from the three-component reaction of primary amine, carbon disulfide and 2,3-dichloro-1,4-napthoquinone under aqueous conditions. Both aliphatic and aromatic primary amines were used to get the corresponding products in moderate to excellent yields. Moreover, this method is advantageous over reported methods.

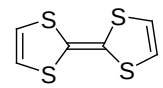
Keywords: One-pot synthesis, Napthoquinone-1,3-dithioles, Three component reaction

Introduction

High yield efficiency and minimum steps are important strategies in synthetic organic chemistry. Combining three or more simple starting materials in a one-pot protocol provides quick and easy access to diverse products. The use of modular reaction sequence (MRS_s) in this context is a useful way of creating diverse scaffolds[1]. In MRS_s technique, a reactive intermediate is generated *in situ*, which can be reacted further with a range of different reaction paths, giving rise to a wide variety of scaffolds. An example of the use of MRS_s is the coupling of *in situ* 1,3-dithiolate from amine and CS_2 in the presence of suitable base with a range of different reaction partners[2], including either 1,2-electrophile or 1,4-electrophiles. The 1,4-napthoquinone structure is common for many natural products. These compounds have been found to posses numerous biological activities such as antifungal[3], antibacterial[4], anticancer[5], antimalerial[6] and antiparasitic activities[7]. Benzoquinones fused with heterocycles such as 1,3-dithioles (**A**) have been widely used as new material for super conducting, optical and electronic switching properties[8]. Tetrathiofulvalenes having 1,3-dithiole moiety (*e.g.*, **B** and **C**) are one of the most important class of organic compound having highly conducting and super conducting properties[9].



A



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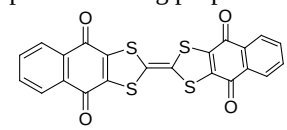


C

In search for agents with better pharmacological properties, wider activity range, better optoelectronic properties, it seemed quite promising to incorporate two "S" hetero atoms into the heterocycle attached to the napthoquinone.

Experimental

Instruments: The chemicals were purchased from Spectrochem and Hi-Media and were used as such. The ^{1}H and ^{13}C NMR spectra were recorded with Bruker instruments. Melting point was determined in a metal bath; uncorrected. IR Spectra: Spectrum 2 (Perkin-Elmer) spectrometer; LC/MS: Micromass (Water) apparatus; HRMS: Micromass-Q-TOF spectrometer. Elemental analyses: Thermo-Finnigton-Flash-EA-1112 analyzer.

*General Procedure for the preparation of **4a -4g***

To a mixture of amine (2.6 mmol) and K_2CO_3 (5.2 mmol) in 20 mL of water, 0.2 mL of CS_2 (3.12 mmol) was added drop wise in a period of 30 mins at room temperature after the addition was complete, the mixture was stirred for several hours. Then the reaction mixture was cooled to 0 ^{o}C and a solution of 0.534 g 2,3-dichloro-1,4-napthaquinone (2.34 mmol) in 20 mL of CH_2Cl_2 was added drop wise. After the addition, stirring was continued until the reaction was complete (TLC). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using ethyl acetate/ petroleum ether as eluent.

*Modified procedure (**4g**)*

To a mixture of amine (2.6 mmol) and K_2CO_3 (5.2 mmol) in 25 mL of water and DMF (~ 4:1), 0.2 mL of CS_2 (3.12 mmol) was added drop wise in a period of 30 mins at room temperature, after the addition was complete, the mixture was stirred for several hours. Then the reaction mixture was cooled to 0 ^{o}C and a solution of 0.534 g 2,3-dichloro-1,4-napthaquinone (2.34 mmol) in 20 mL of CH_2Cl_2 was added drop wise. After the addition, stirring was for continued until the reaction was complete (TLC). The reaction mixture was worked up and the product was separated as earlier.

Spectral and analytical data

*2-Methyliminonaphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4a**)*

^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.196-8.151 (m, 2H), 7.853 – 7.808 (m, 2H), 3.327 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.347, 175.841, 160.340, 143.80, 143.053, 134.910, 134.848, 132.205, 131.852, 128.077, 127.973, 29.933. IR (KBr), γ (cm^{-1}): 1642.05, 1383.80, 708.32. LCMS: *m/z* calcd. for $C_{12}H_7NO_2S_2Na$ (M^+ + Na), 283.98; found 283.99. Anal.: Calcd. for $C_{12}H_7NO_2S_2$ (M. W. 261.32) C, 55.15; H, 2.70; N, 5.36; found: C, 54.98; H, 2.73; N, 5.29.

*2-Butyliminonaphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4b**)*

^{1}H NMR (200MHz, $CDCl_3$), δ: 8.16 - 8.11 (m, 2H), 7.8 -7.75 (m, 2H), 3.28 (t, J = 6.8 Hz, 2H), 1.83 - 1.68 (m, 2H), 1.53 - 1 .35 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR: (50 MHz, $CDCl_3$), δ: 176.232, 175.686, 155.592, 143.965, 143.205, 134.357, 134.308, 134.226, 132.111, 132,041, 127.218, 127.163, 59.426, 31.949, 20.576, 13.847. IR (KBr), γ (cm^{-1}): 1640.11, 1384.89, 705.13. Mass (EI-MS): *m/z*, calcd. for $C_{15}H_{13}NO_2S_2$ 303.0388 (M^+) found 303.0380. Anal.: calcd. for $C_{15}H_{13}NO_2S_2$ (M. W. 303) C, 59.4; H, 4.29; N, 4.62; found: C, 59.23; H, 4.27; N, 4.53.

*2-Cyclohexyliminonaphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4c**)*

^{1}H NMR (200 MHz, $CDCl_3$), δ: 8.16 – 8.10 (m, 2H), 7.80 – 7.74 (m, 2H), 2.93 – 2.88 (m, 1H), 1.51 – 2.25 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$), δ: 176.009, 175.693, 162.800, 143.863, 142.939, 134.247, 134.219, 131.976, 131.930, 127.132, 127.093, 69.033, 31.88, 25.263 and 24.396. IR (KBr), γ (cm^{-1}): 1653.06, 1647.94, 1384.88, 1285.61, 1152.43, 796.92, 698.28. HRMS: *m/z* calcd. for $C_{17}H_{16}NO_2S_2$ 330.0622 (M^++1); found 330.0612.

*2-Phenyliminonaphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4d**)*

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.139 – 8.082 (m, 2H), 7.767 – 7.752 (m, 2H), 7.44 – 7.41 (m, 2H), 7.234 – 7.22 (m, 1H), 7.03 – 7.015 (m, 2H). LCMS: *m/z* calcd. for $C_{17}H_9NO_2S_2Na$ (M^+ + Na), 345.99; found 346.0. Anal.: Calcd. for $C_{17}H_9NO_2S_2$ (M.W. 323.39) C, 63.14; H, 2.81; N, 4.33; found C, 63.25; H, 2.78; N, 4.26.

*2-p-Tolyliminonaphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4e**)*

^{1}H- NMR (200 MHz, $CDCl_3$), δ: 8.05 – 8.17 (m, 2H), 7.79 - 7.74 (m, 2H), 7.22 (d, 2H, J = 8.6 Hz), 6.95 (d, 2H, J = 8.6 Hz), 2.37 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 175.97, 175.59, 159.33, 147.88, 143.36, 143.05, 135.68, 134.67, 134.20, 131.85, 130.33, 129.36, 128.89, 127.05, 119.43 and 20.99. LCMS: Calcd. for $C_{18}H_{11}NO_2S_2Na$ (M^+ + Na), 360.01; found 360.0. Anal.: Calcd. for $C_{18}H_{11}NO_2S_2$ (M.W. 337.41) C, 64.07; H, 3.29; N, 4.15; found C, 64.22; H, 3.24; N, 3.17.

*2-(4-Methoxyphenylimino)naphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4f**)*

^{1}H NMR (200MHz, $CDCl_3$), δ: 8.12 - 8.09 (m, 2H), 7.79 - 7.75 (m, 2H), 7.04-6.92 (m, 4H), 3.84 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ: 175.65, 158.16, 157.52, 143.63, 143.52, 134.17, 131.88, 127.05, 120.96, 114.83 and 55.42. IR (KBr), γ in cm^{-1}: 1647.34, 1611.59, 1586.08, 1502.71, 1384.90, 1283.82, 1247.38, 1152.77, 1023.15, 837.17, 698.93. Mass (EI-MS): *m/z* calcd. for $C_{18}H_{11}NO_3S_2$ 353.0180 (M^+); found 353.0201. Anal.: calcd. for $C_{18}H_{11}NO_3S_2$ (M, W. 353) C, 61.18; H, 3.12; N, 3.97; Found: C, 61.20; H, 3.01; N, 3.90.

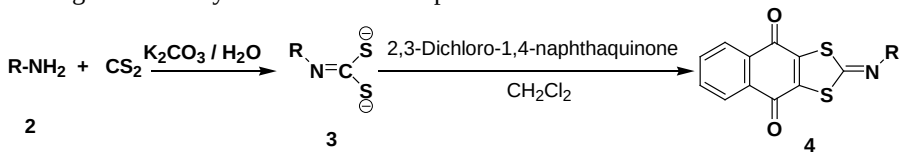
*2-(4-Chlorophenylimino)naphtho[2,3-*d*][1,3]dithiole-4,9-dione (**4g**)*

^{1}H NMR (200MHz, $CDCl_3$) δ: 8.13 (m, 2H), 7.78 - 7.76 (m, 2H), 7.4 (d, 8.8Hz, 2H), 6.98 (d, 8.8Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.298, 175.972, 161.035, 149.232, 143.797, 143.267, 134.588, 132.133, 131.439, 130.867, 130.030, 129.442, 127.439, 126.501 and 121.289. IR (cm^{-1}): 1659.73, 1608.21, 1582.72, 1549.87, 1482.35, 1453.79, 1384.92, 1342.33, 1307.41, 1286.78, 1251.68, 1154.43, 823.31, 698.86. Mass (EI-MS): *m/z* calcd. for $C_{17}H_8ClNO_2S_2$ 358.9655 (M^++2) and 356.9684 (M^+); found 358.9650 and 356.9680 in the intensity ratio of 1:3. Anal.: calcd. for $C_{17}H_8NO_2S_2Cl$ (M.W. 357.5) C, 57.06; H, 2.23; N, 3.92; Cl, 9.93; found: C, 57.15; H, 2.19; N, 3.87; Cl, 9.45.

Results and Discussion

Despite continuous interest in 1,4-napthoquinones fused with heterocycles, only a limited number of napthaquinone-1,3-dithioles with low yield have been reported, no general approach to their synthesis has been proposed. We were interested in developing a general method for the synthesis of napthoquinone-1,3–dithioles using 2,3–dichloro–1,4–napthoquinone, primary amine and CS_2 under aqueous condition. Recently Yujin Li, Jianrong Gao *et al.*,[10] has reported the formation of napthoquinone-1,3–dithioles via 2,3-dichloro-1,4-napthoquinone and amines involving CS_2 in presence of Et_3N as a base. However this method was applicable only to aliphatic amines. Moreover, the yield of the

products was not satisfactory in a few cases. Initially we studied the reaction of aniline to prepare *N*-phenyl dithiocarbamates in the presence of inorganic base, since inorganic bases were more efficient for the conversion of arylamines to *N*-aryl dithiocarbamates in aqueous medium. A rigorous study of the preparation of isothiocyanates via *N*-aryl or *N*-alkyl dithiocarbamates has also been reported by Weimin MO, Xinquar Hu *et al*.,[2] under different basic conditions. They have established that the use of K_2CO_3 as a base in biphasic system (CH_2Cl_2-H_2O) provided a high-yielding method of dithiocarbamates. To evaluate the procedure for the potential scaling up capability, we used aniline as test substrate to scale up the synthesis of *N*-phenyl napthoquinone-1,3-dithiole. Surprisingly this test provided a highly efficient formation of corresponding napthoquinone-1,3-dithiole (Scheme 1). Thereafter, we investigated the substrate scope for this reaction using a series of aromatic as well as aliphatic amine and got excellent yields in all the examples. The results are summarized in Table 1.



Scheme 1

Table 1. Reaction conditions[a] and yields of naphtha-[2,3-*d*]-1,3-dithiole-4,9-diones

Entry	2	R	Time, h	4	M. P. of 4, ^oC	Yield, % CH_2Cl_2-H_2O
1	**2a**	CH_3-	1	**4a**	153.5	86.3
2	**2b**	$CH_3CH_2CH_2CH_2$-	1	**4b**	102.0	78.5
3	**2c**	Cyclohexyl	1	**4c**	158.0	82.1
4	**2d**	Phenyl	2	**4d**	166.0	67.5
5	**2e**	*p*-Tolyl	2	**4e**	171.5	73.4
6	**2f**	4-Methoxyphenyl	2	**4f**	181.0	75.3
7	**2g**	4-Chlorophenyl	3	**4g**	207.0	31.4 65.4[b]

[a]*All the reactions are carried out at room temperature.* [b]*In CH_2Cl_2–H_2O-DMF*

Aliphatic primary amines, linear or branched and most aromatic primary amines gave excellent yield (≈80%), but poor efficiency of the method was noted for the strongly electron-deficient aryl amines. Poor solubility of such amines in water may be one of the reasons. To overcome this problem we used DMF as co-solvent. The DMF/H_2O (1:4)-CH_2Cl_2 solvent system was found to be good.

It may be presumed that the dithiodianion (**3**, Scheme 1) intermediate is generated from CS_2 and primary amine in presence of base initially. Subsequently this dianion undergoes activated nucleophilc substitutions (Michael addition and then elimination of HCl) at C-2 and C-3 of 2,3-dichloro-1,4-napthoquinone successively to furnish the expected napthoquinone-1,3-ditholes.

All the products have been characterised by UV, FTIR, ^1H NMR, ^{13}C NMR and Mass spectroscopic analyses. In conclusion, we report a MCR of a primary amine (aromatic or aliphatic), 2,3-dichloro-1,4-napthoquinone and carbon disulfide to furnish napthoquinone-1,3-dithioles in reasonable to good yields under environmentally friendly conditions. The procedure of the reactions involving aromatic primary amines having electron withdrawing group are a little modified and carried out in DMF-H_2O-CH_2Cl_2 solvent system to obtain better yield.

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