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A novel one-pot synthesis of derivatives of aryldioxins and aryldithiins

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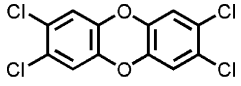
Abstract—One-pot reactions between *ortho*-dihydroxyarenes with 1,2-diols or dithiols in the presence of *p*-toluenesulfonic acid yielded the corresponding dioxins or dithiins in good to excellent yields.

Aryldioxins are of high versatility and have fascinating chemistry. While some halogenated dibenzodioxin derivatives, for example, 2,3,7,8-tetrachloro-dibenzo[1,4]dioxin (TCDD), are regarded notoriously as highly ecotoxic chemicals, some analogues are recognized as compounds with promising biological activities, being antitumor,[1] antihyperglycemic,[2] and α-adrenoreceptor antagonists for antidepression and antihypertension therapy.[3] In addition, reports have revealed possible use of dioxins as donors for cation radicals[4] and thus their application as potential candidates in the design and synthesis of new organic materials.



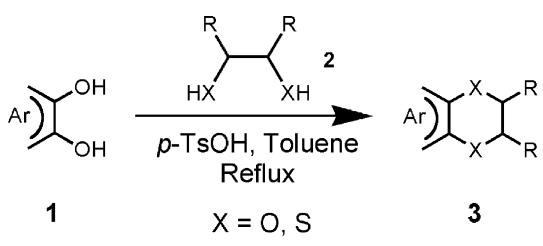
TCDD

The complexity of syntheses of aryldioxins depends upon the nature of the functional groups attached. Simple dioxins can be prepared by direct nucleophilic displacement by *ortho*-dihydroxyarenes with electrophiles having leaving groups at the 1,2-positions.[3d,5] Palladium catalyzed processes[6] may also be applied and, in certain cases, provide chiral products.[7] In cases where straightforward S_N2 reactions cannot be conducted, the preparation may be effected by direct coupling of *ortho*-halo-phenols[8] or by condensation between *ortho*-dihydroxyarenes with dihaloarenes activated by either electron withdrawing groups[9,4a] or by transition metal complexes.[10]

Less is known for sulfur analogues aryldithiins[11] due to the limited accessibility of the sulfur containing materials. The synthesis of these compounds has, in general, been complicated, either employing several steps[12] or involving molecular skeleton rearrangements.[13]

We have recently reported a straightforward acid catalyzed transformation of dihydroxyarenes to their corresponding bisalkylthio derivatives.[14] Interestingly it can be envisioned that this procedure, when applied to *ortho*-bisphenols, could lead effectively to the preparation of oxygen and sulfur heterocycles. Thus we wish to report here novel one-pot syntheses of 2,3-naphtho- and 9,10-phenanthro-derivatives of dioxins and dithiins whose yields vary from good to excellent. The mechanisms of the reactions will also be discussed.

Reactions between 2,3-dihydroxynaphthalene **1a** or 9,10-diacetoxyphenanthrene **1b**[15] and a variety of 1,2-diols **2a–c** or 1,2-dithiols **2d–e** were conducted in the presence of *p*-toluenesulfonic acid in refluxing toluene for 4–6 h. The yields are presented in Table 1.



1 3

Keywords: Arylsulfide; Dioxin; Dithiin; Heterocyclic compounds; Tautomerization.
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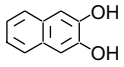
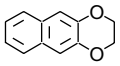
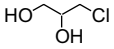
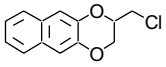
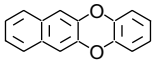
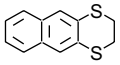
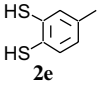
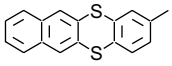
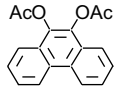
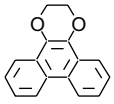
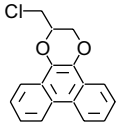
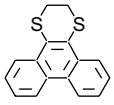
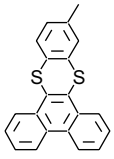
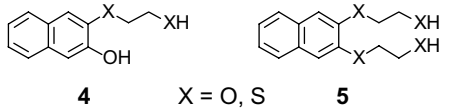
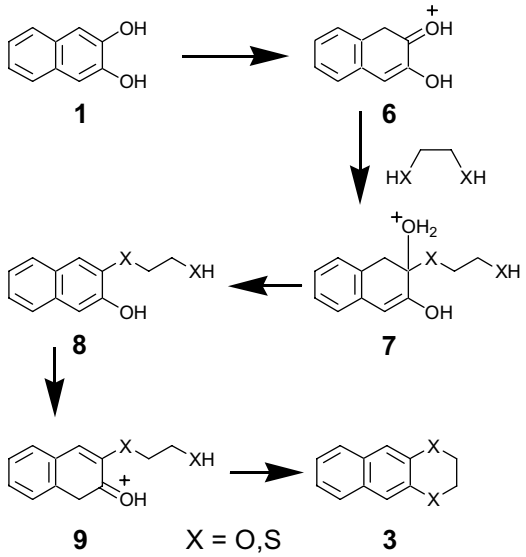
Table 1. Yields of reactions between dihydroxyarenes **1** and diols or dithiols **2**

Entry	$Ar(OH)_2$	**2**	Time (h)	Product[17]	% Yield
1	 **1a**	 **2a**	6		68
2	**1a**	 **2b**	4		95
3	**1a**	 **2c**	6		63
4	**1a**	 **2d**	4		91
5	**1a**	 **2e**	4		87
6	 **1b**	**2a**	6		62
7	**1b**	**2b**	6		71
8	**1b**	**2d**	6		64
9	**1b**	**2e**	6		65

This reaction was very effective with both alkyl- and aryl-diols or dithiols. Remarkably, reactions with dithiols gave better yields than those with diols (e.g., entry 4 vs entry 1), possibly due to the greater nucleophilicity of sulfur than that of oxygen. In addition, it is worth noting that neither the non-cyclization products **4** nor the bis-adduct **5** was observed, thus implying a strong preference for six-membered ring formation.[16]



Similar to the analogous replacements of phenolic hydroxyl groups previously reported,[14,18] the mechanism proposed for this reaction, depicted in Scheme 1, involves the addition of the diol or dithiol to the keto tautomer of the phenol. Then the cyclization follows by



Scheme 1. Mechanism of dioxin/dithiin formation.

addition of the terminal alcohol or thiol moiety to the keto tautomer of the remaining phenolic group. Consequently rearomatization by removal of H_2O readily furnishes the corresponding dioxin or dithiin **3**.

We have thus introduced a novel and highly efficient methodology for the synthesis of aryldioxins and aryldithiins. The reaction is straightforward and requires simple and inexpensive starting materials. It may be widely applicable for the preparation of a variety of dioxins or dithiins.

General procedure. 2,3-Dihydroxynaphthalene (200 mg, 1.25 mmol) and 1,2-ethanedithiol (0.53 mL, 6.24 mmol) were allowed to reflux in toluene (4 mL) in the presence of *p*-toluenesulfonic acid (119 mg, 0.62 mmol) for 4 h. After aqueous workup, the crude product was chromatographed with ethyl acetate/hexane as the eluent.

Acknowledgements

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15. 9,10-Dihydroxynaphthalene is readily oxidized thus, for convenience, its hydroxyl groups need to be protected. The preparation of 9,10-diacetoxyphenanthrene used a standard reductive acetylation with Zn and Ac_2O/K_2CO_3.
16. When 1,3-propanedithiol was reacted with 2,3-dihydroxynaphthalene under the same reaction conditions, only 2,3-bis(1-propylthio)naphthalene was formed exclusively. Wittayakran, S.; Thongpanchang, T. Unpublished results.
17. ***Compound characterization. Entry 1.*** *2,3-Dihydronaphtho[2,3-b][1,4]dioxin*: IR νC–H (Ar) 3058, C=C (Ar) 1603, C–O 1288, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.71 (m, 2H), 7.36 (m, 4H), 4.36 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.9, 129.5, 126.3, 124.1, 112.5, 64.4 ppm; MS (EI [70 eV], m/z (%)): 186 (100) [M^+], 171 (17) [M^+−CH3]; UV (λ_{max}, nm, logε) in CH_3CN: 277 (4.7), 287 (4.4), 298 (4.7), 314 (4.6), 321 (4.5), 329 (4.7); elemental analysis (%): calcd: C 77.42, H 5.38; found: C 77.69, H 5.64; mp 68–73 °C. ***Entry 2.*** *2-Chloromethyl-2,3-dihydronaphtho[2,3-b][1,4]dioxin*: IR νC–H (Ar) 3060, C=C (Ar) 1605, C–O 1274, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (m, 2H), 7.38 (m, 4H), 4.50 (m, 1H), 4.43 (dd, 2.41, 11.53 Hz, 1H), 4.27 (m, 1H), 3.77 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.1, 142.6, 129.6, 129.4, 126.4, 124.4, 112.7, 112.6, 72.4, 65.0, 41.5 ppm; MS (EI [70 eV], m/z (%)): 234 (100) [M^+], 198 (7) [M^+−Cl], 185 (31) [M^+-CH_2Cl], 171 (24) [$M^+-C_2H_5Cl$]; UV (λ_{max}, nm, logε) in CH_3CN: 276 (4.8), 286 (4.9), 298 (4.8), 313 (4.6), 320 (4.5), 328 (4.8); elemental analysis (%): calcd: C 66.52, H 4.69; found: C 66.05, H 5.13; mp 60–63 °C. ***Entry 3.*** *Benzo[b]-naphtho[2,3-e][1,4]dioxin*: IR νC–H (Ar) 3058, C=C (Ar) 1609, C–O 1304, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56 (m, 2H), 7.26 (m, 2H), 7.17 (m, 2H), 6.86 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.8, 141.7, 130.8, 126.8, 125.2, 123.7, 116.5, 112.1 ppm; MS (EI [70 eV], m/z (%)): 234 (100) [M^+]; UV (λ_{max}, nm, logε) in CH_3CN: 228 (4.8), 243 (4.7), 253 (4.6), 281 (4.2), 339 (3.8); elemental analysis (%): calcd: C 82.05, H 4.27; found: C 82.16, H 4.64; mp 194–198 °C. ***Entry 4.***

2,3-Dihydronaphtho[2,3-b][1,4]dithiin: IR *v*C–H (Ar) 3040, C=C (Ar) 1618, C–S 743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 2H), 7.56 (m, 2H), 7.30 (m, 2H), 3.24 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.6, 130.3, 126.9, 126.6, 125.8, 29.7 ppm; MS (EI [70 eV], *m/z* (%)): 218 (100) [M^+], 203 (92) [M^+-CH_3], 190 (16) [$M^+-C_2H_4$]; UV (λ_{max}, nm, logε) in $CHCl_3$: 238 (5.4), 275 (5.1); elemental analysis (%): calcd: C 66.06, H 4.59; found: C 65.96, H 4.86; mp 79–83 °C. ***Entry 5.*** *2-Methyl-5,12-dithianaphthacene*: IR *v*C–H (Ar) 3033, C=C (Ar) 1568, C–S 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88 (s, 2H), 7.66 (m, 2H), 7.35 (m, 3H), 7.28 (d, 2.1 Hz, 1H), 6.98 (dd, 1.04, 7.94 Hz, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.9, 135.4, 133.6, 133.4, 132.6, 132.0, 129.4, 128.6, 127.2, 127.0, 126.9, 126.5, 126.5, 20.9 ppm; MS (EI [70 eV], *m/z* (%)): 280 (100) [M^+], 248 (50) [M^+-S]; UV (λ_{max}, nm, logε) in CH_3CN: 216 (4.9), 232 (4.9), 259 (4.7), 276 (4.6); elemental analysis (%): calcd: C 72.86, H 4.29; found: C 72.29, H 4.88; mp 157–160 °C. ***Entry 6.*** *2,3-Dihydro-phenanthro[9,10-b]-[1,4]dioxin*: IR *v*C–H (Ar) 3070, C=C (Ar) 1626, C–O 1251, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.63 (m, 2H), 8.18 (m, 2H), 7.60 (m, 4H), 4.56 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.4, 126.6, 126.5, 126.4, 124.8, 122.4, 120.5, 64.6 ppm; MS (EI [70 eV], *m/z* (%)): 236 (100) [M^+]; UV (λ_{max}, nm, logε) in $CHCl_3$: 260 (5.1), 275 (4.6), 299 (4.4), 314 (4.5); elemental analysis (%): calcd: C 81.35, H 5.12; found: C 81.84, H 5.68 ; mp 134–138 °C. ***Entry 7.*** *2-Chloromethyl-2,3-dihydrophenanthro-[9,10-b][1,4]dioxin*: IR *v*C–H (Ar) 3061, C=C (Ar) 1628, C–O 1247, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.63 (m, 2H), 8.20 (m, 2H), 7.62 (m, 4H), 4.69 (m, 1H), 4.62 (dd, 2.27, 2.28 Hz, 1H), 4.47 (m, 1H), 3.90 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.0, 132.3, 126.8, 126.7, 126.7, 126.0, 126.0, 125.2, 125.1, 122.5, 120.8, 120.6, 72.7, 65.3, 41.6 ppm; MS (EI [70 eV], *m/z* (%)): 284 (100) [M^+]; UV (λ_{max}, nm, logε) in $CHCl_3$: 251 (5.0), 259 (5.1), 276 (4.6), 300 (4.4), 312 (4.6); elemental analysis (%): calcd: C 71.70, H 4.57; found: C 72.06, H 4.94; mp 65–68 °C. ***Entry 8.*** *2,3-Dihydro-1,4-dithiatriphenylene*: IR *v*C=C (Ar) 1603, C–S 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.57 (m, 2H), 8.30 (m, 2H), 7.54 (m, 4H), 3.38 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 130.7, 128.4, 128.3, 126.9, 126.3, 123.3, 122.8, 30.1 ppm; MS (EI [70 eV], *m/z* (%)): 268 (100) [M^+], 240 (32) [$M^+-C_2H_4$]; UV (λ_{max}, nm, logε) in CH_3CN: 206 (4.4), 246 (4.5), 265 (4.4), 282 (4.1), 292 (4.0), 328 (4.0); mp 93–97 °C. ***Entry 9.*** *12-Methyl-9,14-dithia-benzo[b]triphenylene*: IR *v* C–H (Ar) 3062, C=C (Ar) 1607, C–S 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.67 (m, 4H), 7.69 (m, 4H), 7.54 (m, 2H), 7.13 (d, 7.56 Hz, 1H), 2.37 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.1, 136.7, 133.3, 130.6, 129.9, 129.5, 128.8, 128.6, 127.3, 127.0, 127.0, 125.3, 125.3, 123.00, 20.9 ppm; MS (EI [70 eV], *m/z* (%)): 330 (100) [M^+], 314 (22) [M^+-CH4], 298 (42) [M^+-S] ; UV (λ_{max}, nm, logε) in CH_3CN: 208 (4.3), 253 (4.5), 267 (4.3), 332 (3.3); mp 131–135 °C.

18. (a) Dreher, S. D.; Paruch, K.; Katz, T. J. *J. Org. Chem.* **2000**, *65*, 806–814; (b) footnotes 5–10 therein; (c) Dreher, S. D.; Katz, T. J.; Lam, K. C.; Rheingold, A. L. *J. Org. Chem.* **2000**, *65*, 815–822; (d) Drake, N. L. *Org. React.* **1942**, *1*, 105–128; (e) Seeboth, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 307–317.