Synthesis of Fused Aromatic [1,3]Dioxoles from 2-Hydroxymethylphenols

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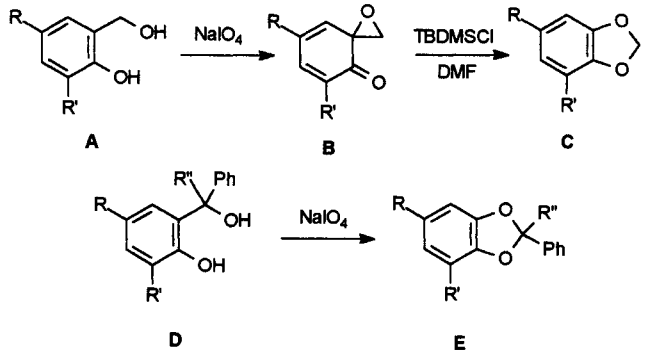
Received 27 June 1997

Abstract: The rearrangement of spiroepoxycyclohexadienones to benzo[1,3]dioxoles is best carred out in a non polar solvent (toluene, CCl_4) in presence of TBDMSCl. Application to the synthesis of naphthalene and tetrahydronaphthalene derivatives is described.

The benzo[1,3]dioxole unit is present in many natural and/or bioactive compounds, ranking from simple ones such as piperonal or safrole to complex ones such as podophyllotoxine and liriodenine.[1] This type of cyclic acetal is usually made from 1,2-dihydroxy aromatic compounds (i.e. catechols) using base-catalyzed condensation with a dihalomethane.[2] Common preparations of the required diphenol have been reported from a monophenol either by direct chemical[3] or enzymatic[4] hydroxylation or more conveniently by *ortho* acylation followed by Bayer-Villiger oxidation and hydrolysis.[5]

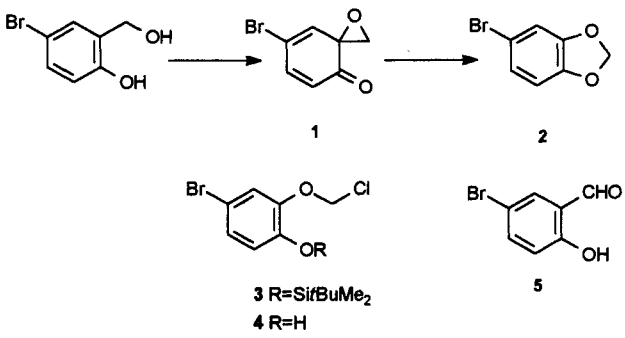
An alternative strategy may be the rearrangement of spiroepoxy cyclohexadienones **B**, easily prepared by Adler-Becker oxidation ($NaIO_4$) of salicyl alcohols **A**, to give dioxoles **C** (Scheme 1). Indeed, a limitation is the easy Diels-Alder dimerization of these dienones which occurs at room temperature except in some cases.[6] Such a rearrangement has been reported by Becker[7] to spontaneously occur (41-67%) in the oxidation of sterically hindered *ortho*-hydroxy diarylcarbinols **D** (R= *t*Bu or Br, R'= *t*Bu or Me, R"=H or Ph) to **E**. Furthermore a study of the reaction of hindered salicyl alcohols with various nucleophiles has been reported by Cacioli and Reiss.[8] These authors have shown that on treatment with $tBuMe_2SiCl$ (TBDMSCl) and Et_3N in DMF, spirodienones **B** (R= *t*Bu, R'= Me or *t*Bu, R"=H and R=R'=R"=Me) give the corresponding benzo[1,3]dioxoles **C** in yields ranging from 23 to 58% (Scheme 1).



Scheme 1

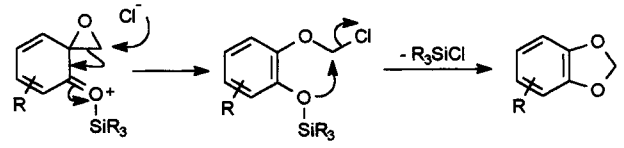
A study of the reaction conditions (chlorosilane and solvent) using dienone **1** (Scheme 2) and its application to the synthesis of naphtho[1,2-*d*][1,3]dioxole (and the corresponding 6,7,8,9-tetrahydro derivative) is described below.

Oxidation of 4-bromo-2-(hydroxymethyl)phenol affords dienone **1** in 60 % isolated yield.[9] Dimerization being very slow at 60°C, **1** was treated with R_3SiCl in different solvents.[10] Results reported in Table 1 show that isomerization to **2** proceeds in better yield (65-70%) with TBDMSCl in non polar solvents such as tetrachloromethane and toluene than in DMF (30%). When the reaction is carried out at room temperature in toluene (1.5 equiv of TBDMSCl) the silylated chloromethyl ether **3** is rapidly obtained and rearrange to **2** on heating.



Scheme 2

Lowering the amount of TBDMSCl from 1.5 to 0.3 equiv resulted in lower yields although this reagent may, in principle, be used as a catalyst. TMSCl gave a lower yield of **2** together with the chloromethyl ether **4**. On the other hand increasing the bulkiness of the chlorosilane resulted in isomerization to aldehyde **5**. Overall, these results are consistent with an initial complexation of the ketone by the silane followed by opening of the epoxide with chloride to give a silylated chloromethylether which then undergoes cyclization (Scheme 3). As shown above, the first step should therefore be favored in non polar solvents and the use of a bulkier chlorosilane may hinder nucleophilic attack by the chloride anion.



Scheme 3

Table. Rearrangement of dienone **1** to **2** with TBDMSCl

TBDMSCl [equiv]	Solvent	Conditions [°C, h]	Yield [%]
1.5	toluene	70, 4.5	65
0.5	*id*	*id*	55
0.3	*id*	*id*	38
1.5	CCl_4	id	70
1.5	DMF	70, 3	30
1.5	CH_3CN	70, 4.5	20
1.5	CH_2Cl_2	40, 4.5	17

These conditions were then applied to the synthesis of naphthodioxoles. Thus the synthesis of **6** was studied starting from the known dienone **8**[11] which was prepared from 1-hydroxy-2-naphthoic acid **7** (Scheme 4). Treatment of **8** with TBDMSCl and Et_3N in toluene (typical procedure, 8 h) gives naphthodioxole **6** (52%)[12] together with aldehyde **9** (7%). The same naphthodioxole was also prepared from the isomeric spirodienone **10**[13] available in two steps from aldehyde **11** (50% overall). Upon treatment with TBDMSCl (20 h), **10** affords **6** (58%) together with the chloromethylether **12** (11%).[14]

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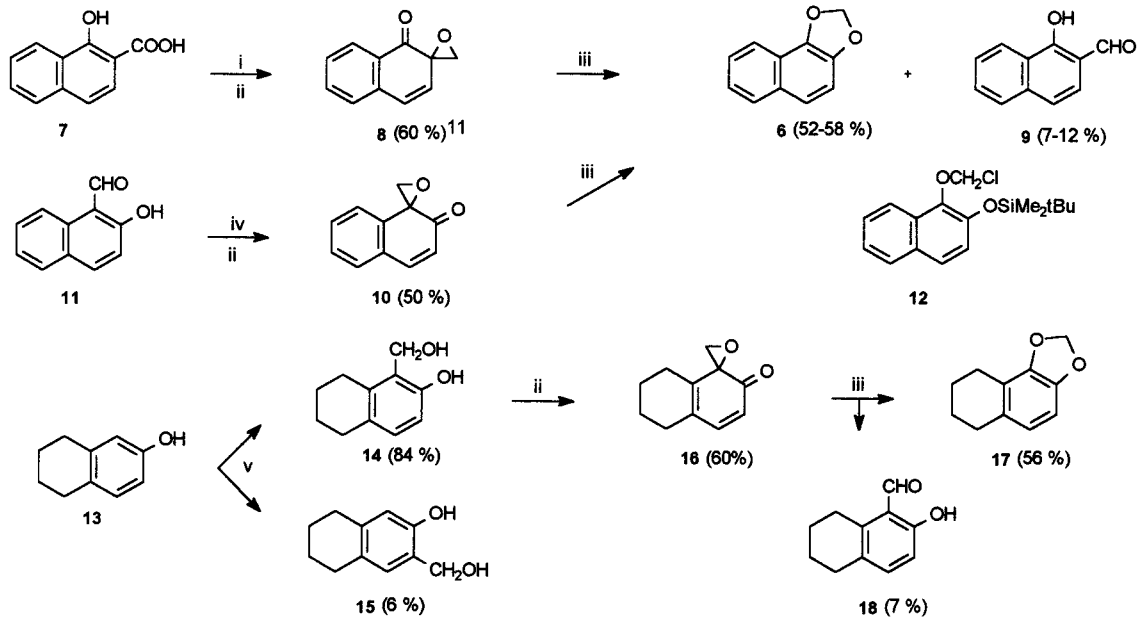

Reagents: i: $LiAlH_4$, THF; ii: $NaIO_4$, MeOH; iii: TBDMSCl, Et_3N, toluene; iv: $NaBH_4$, MeOH; v: CH_2O, $PhB(OH)_2$, AcOH, then H_2O_2

Scheme 4

This method was then extended to a tetrahydronaphthodioxole. Condensation of 5,6,7,8-tetrahydronaphthol **13** with methanal in presence of benzeneboronic acid, followed by treatment of the intermediate dioxaborin with H_2O_2,[15] affords a mixture of alcohols **14**[16,17] (84%) and **15** (6%). $NaIO_4$ oxidation of **14** gives dienone **16** which upon isomerization (1 h) leads to dioxole **17** (56%)[18] and aldehyde **18** (7%).

In conclusion, the TBDMSCl catalyzed rearrangement of spiroepoxydienones may be used to prepare 1,3-dioxoles from readily available alcohols under mild conditions. This method appears well suited to bi- or polycyclic phenols whose corresponding dienones are stable at room temperature.

References and Notes

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(9) **1**: mp 73-74 °C; IR (CCl_4, cm^{-1}) 1687, 1624, 1610; ^1H NMR (200 MHz, $CDCl_3$) δ 3.23 and 3.32 (2H, ABq, J = 8 Hz), 6.20 (1H, d, J = 10.2 Hz), 6.37 (1H, d, J = 2 Hz), 7.20 (1H, dd, J = 10.2 and 2 Hz); **2**: ^1H NMR ($CDCl_3$) 5.96 (s, 2H), 6.67 (d, 1H, J=7 HZ), 6.94 (dd, 1H, J=7 and 2 Hz), 6.96 (broad s, 1H).

(10) **Typical procedure**. Spiroepoxide (1 mmol) and TBDSMCl (1.5 equiv) were dissolved in the appropriate solvent (4 mL) containing Et_3N (1.5 equiv) and were heated at 70-80° C. After an appropriate reaction time (see text and Table), the solution was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. Products were purified or separated by flash chromatography.

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(12) **6**: oil, ^1H NMR ($CDCl_3$); 6.13 (s, 2H), 7.17(d, 1H, J=8.8 Hz), 7.30 (t, 1H, J=7.3 Hz), 7.38 (d, 1H, J=8.8 Hz), 7.42 (t, 1H, J=7.3 Hz), 7.78 (t, 2H, J=7.3 Hz).

(13) **10**: oil, ^1H NMR ($CDCl_3$); 3.12 (d, 1H, J=8 Hz), 3.38 (d, 1H, J=8 Hz), 6.33 (d, 1H, J=10 Hz), 7.25 (m, 1H), 7.39 (m,3H), 7.59 (d, 1H, J=10 Hz).

(14) **12**: mp 57°C, ^1H NMR ($CDCl_3$); 0.22 (s, 6H), 1.04 (s, 9H), 6.09 (s, 2H), 7.12 (d, 1H, J=8.8 Hz), 7.38 (t, 1H, J=8 Hz), 7.50 (t, 1H, J=8 Hz). 7.60 (d, 1H, J=8.8 Hz), 7.76 (d, 1H, J=8 Hz), 8.18 (d, 1H, J=8 Hz).

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(16) **14**: mp 64-66° C (Litt. 64-66)[17]; ^1H NMR ($CDCl_3$); 1.72 (m, 4H), 2.63 (m,4H), 4.84 (s, 2H), 6.63 (d,1H, J=8 Hz), 6.87 (d, 1H, J=8 Hz)

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(18) **17**: mp 64° C; ^1H NMR ($CDCl_3$); 1.60-1.89 (m,6H), 2.31 (s, 2H), 3.12 (d, 1H, J=8 Hz), 3.22 (d, 1H, J=8 Hz), 6.12 (d, 1H, J=9.5 Hz), 6.95 (d, 1H, J=9.5 Hz). **15**: ^1H NMR ($CDCl_3$);1.76 (m, 4H), 2.68 (m, 4H), 5.90 (s, 2H), 6.54 and 6.61 (ABq, 2H, J=8 Hz).

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