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Condensation of naphthalenediols with benzene in the presence of aluminum bromide: an efficient synthesis of 5-, 6-, and 7-hydroxy-4-phenyl-1- and 2-tetralones

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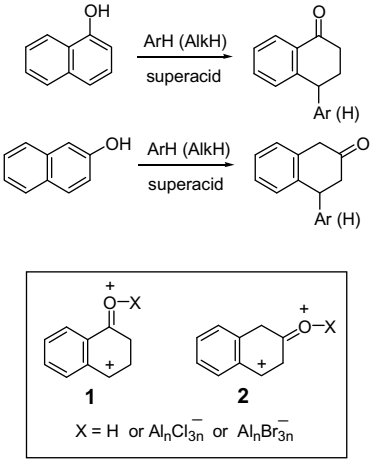
Abstract

Isomeric 1,5-, 1,6-, 1,7-, 2,6-, and 2,7-naphthalenediols react smoothly with benzene at room temperature in the presence of an excess of aluminum bromide to give 5-, 6-, and 7-hydroxy-4-phenyl-1-tetralones and 5- and 6-hydroxy-4-phenyl-2-tetralones, respectively. The mechanism of these reactions is interpreted in terms of key di- or tri-cationic (superelectrophilic) intermediates.

1. Introduction

Tetralones are useful starting materials for the synthesis of biologically active compounds.[1] In particular, hydroxy- and methoxy-tetralones, despite their considerable cost, are of significant current interest in pharmaceutical chemistry for construction of steroid frameworks[2] and production of antidepressants.[1,3]

An efficient route to tetralones is based on the one-step condensation of 1- and 2-naphthols with benzene and other aromatic compounds under the influence of aluminum halides or in the $HF–SbF_5$ superacid medium (Scheme 1).[4] Furthermore, the selective ionic reduction of naphthols by alkanes leads to tetralones under similar conditions (Scheme 1).[5] The mechanism of these reactions was recognized to involve superelectrophilic[6] dications formed by *C*,*C*-diprotonation (structures **1** and **2**, Scheme 1) as the key intermediates and a number of analogous dications have indeed been generated as long-lived species by dissolving naphthols and/or their derivatives in liquid superacids.[7] Moreover, a set of isomeric naphthalenediols was reacted successfully with cyclohexane in $AlBr_3–CH_2Br_2$ medium to afford the corresponding hydroxytetralones (Scheme 2).[8]



Scheme 1. Reactions of naphthols with arenes (ArH) and alkanes (AlkH).

Further, it has been found recently that, in contrast to 1-naphthol, 5-amino-1-naphthol is activated by *N*,*C*-diprotonation in superacids and reacts with benzene and cyclohexane under the influence of aluminum halides through

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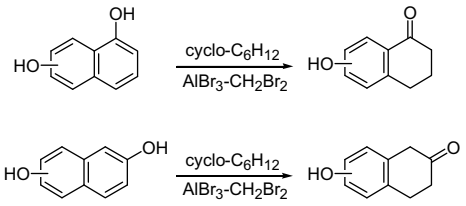
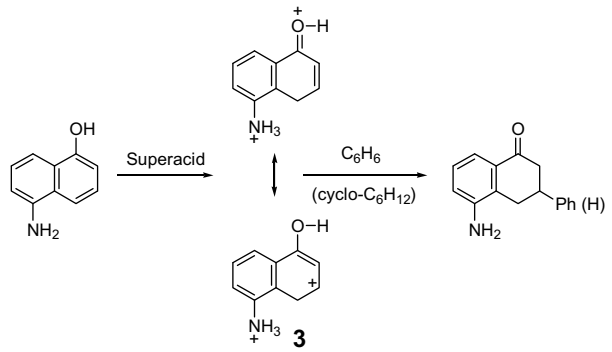


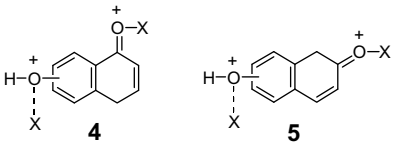
Scheme 2. Ionic reduction of naphthalenediols with cyclohexane.



Scheme 3.

dications **3** to give 5-amino-3-phenyl-1-tetralone and 5-amino-1-tetralone, respectively, (Scheme 3).[9]

Therefore, the question about the nature of key electrophilic intermediates in the case of reactions of naphthalenediols with cyclohexane is still open because of the two possible methods of activation: *C*,*C*-diprotonation resulting in dications of types **1** and **2** with the reaction center at C-4 (similar to 1- and 2-naphthols) or *O*,*C*-diprotonation resulting in dications **4** with the reaction center at C-3 (similar to *N*,*C*-diprotonation of 5-amino-1-naphthol). The latter possibility seemed quite likely based on the known behavior of naphthalenediols in superacids. Indeed, when hydroxyl groups are bound to different rings of the naphthalene system, naphthalenediols undergo exclusively *O*,*C*-diprotonation in HSO_3F–SbF_5–SO_2ClF and HF–SbF_5–SO_2ClF media to produce dications **4** and **5** (X = H).[10] In addition, similar complexes **4** and **5** ($X = Al_nBr_{3n}^-$) are produced via the action of $AlBr_3$.[10b] However, *C*,*C*-diprotonated dications as stronger electrophiles[11] could react predominantly, despite their relatively low equilibrium concentration.

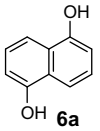
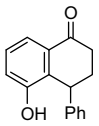
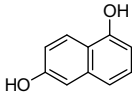
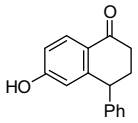
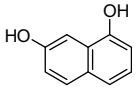
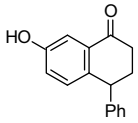
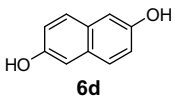
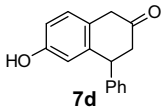
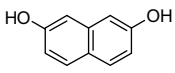
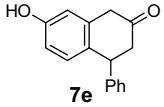


X = H or $Al_nBr_{3n}^-$

2. Results

Based on this extensive background, a study on the reactivity of isomeric 1,5-, 1,6-, 1,7-, 2,6-, and 2,7-naphthalenediols (**6a**–**e**)[12] toward benzene as a model aromatic compound is reported with the aim of synthesizing hydroxyl-containing phenyl-1- and 2-tetralones. The main aim of the work was also to determine the regioselectivity of these reactions.

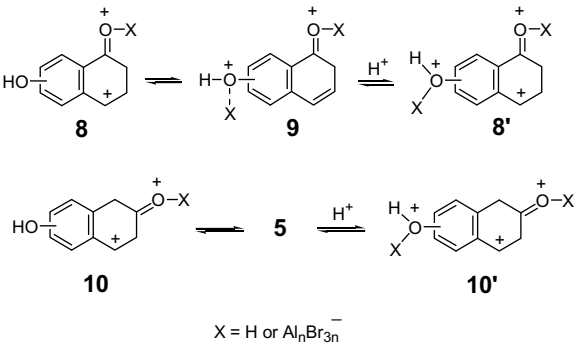
Table 1
Reactions of naphthalenediols **6a**–**e** with benzene in the presence of $AlBr_3$ at 25 °C[a]

Naphthalenediol	Reaction time (h)	Product	Yield[b] (%)
 **6a**	24	 **7a**	92
 **6b**	48	 **7b**	83
 **6c**	48	 **7c**	87
 **6d**	48	 **7d**	92
 **6e**	24	 **7e**	85

[a] The molar ratio of substrate:$AlBr_3$:benzene = 1:3.5:20, magnetic stirring.
[b] Isolated yields of purified products.

All isomers **6a**–**e** reacted smoothly with benzene in the presence of a 3.5-fold molar excess of $AlBr_3$ at room temperature to give hydroxyl-4-phenyl-1- and 2-tetralones **7a**–**e**, respectively (Table 1). Remarkably, compounds **6b** and **6c**, which may both be regarded as derivatives of 1- and 2-naphthols, reacted similarly to 1-naphthol to give 1-tetralone derivatives only. This is in accord with the analogous regioselectivity of the ionic hydrogenation of these compounds by cyclohexane (Scheme 2),[8] suggesting the participation of the same key intermediates. Likewise, no traces of hydroxyl-3-phenyl-1-tetralones (considered as possible alternative products) were detected in the reaction mixtures. The regioselectivity found indicates the predominant involvement of di- or tri-cationic intermediates **8** or **8′** as shown in Scheme 4. Although structure **9** was not detected earlier by NMR along with isomeric complexes **4** ($X = Al_nBr_{3n}^-$),[10b] the analogous complexes were generated in the case of the parent 1-naphthol and some of its other derivatives.[13]

On the basis of the recognized low reactivity (contribution) of the *O*,*C*-diprotonated dications **4**, it can be postulated that similar *O*,*C*-diprotonated dications **5** are also insufficiently strong electrophiles toward benzene. Therefore, in the case of substrates **6d** and **6e**, which represent exclusively derivatives of 2-naphthol, di- or tri-cationic species **10** and **10′** are suggested as the most probable key



Scheme 4. Proposed key intermediates.

intermediates (Scheme 4). A catalytic amount of protic superacid ($HBr–Al_nBr_{3n}$ or $H_2O–Al_nBr_{3n}$) which is required for *C*-protonation of intermediate species **9** and **5** is normally present in such reaction media due to traces of water in the starting materials. So, additional saturation of the reaction mixture with gaseous HBr, which usually accelerates similar reactions,[14] is not needed. Also, careful protection from atmospheric moisture is not necessary.

It should also be noted that a 3.5-fold molar excess of $AlBr_3$ is not essential and a decrease in the loading is possible. This, however, slows down the reaction. Moreover, the use of less than a ~2.5-fold molar excess of $AlBr_3$ does not bring about the reaction. Attempts to replace $AlBr_3$ by $AlCl_3$ were not generally successful as the reactions proceeded too slowly at room temperature. For example, reaction **6e→7e** in the presence of a 3.5-fold molar excess of $AlCl_3$ proceeded with about 50% conversion in 24 h. This is probably due to the lack of solubility of the complexes of diols **6a–e** with $AlCl_3$ in benzene. On the other hand, heating (up to 80 °C) in order to overcome this solubility problem gave rise to side reactions, which considerably decreased the yields of **7a–e**.

In conclusion, an additional approach to hydroxytetralones is elaborated. The reaction procedures using readily available naphthalenediols **6a–e** are simple and reproducible. The regioselectivity of the reactions is in contrast to that of a close derivative, 5-amino-1-naphthol. The mechanism of these reactions is interpreted in terms of key superelectrophilic intermediates **8** and **10**, analogous to *C*,*C*-diprotonated dications **1** and **2**. A study on similar condensations of **6a–e** with various derivatives of benzene is underway. In addition, their reactivity toward benzene and cyclohexane in the presence of *H*-form zeolites instead of superacids is under investigation.[15]

3. Typical procedure

3.1. 5-Hydroxy-4-phenyl-1-tetralone (**7a**)

To a solution of $AlBr_3$ (6 g, 22.5 mmol) in benzene (15 mL) was added **6a** (1 g, 6.25 mmol). The resulting solution was stirred at 25 °C for 24 h, and then poured onto ice. The resulting mixture was extracted with ether. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain the crude product, which was purified by silica gel column chromatography with benzene–acetone (5:1) to give product **7a** (1.37 g, 92%). Mp 173–174 °C (EtOH). HRMS $C_{16}H_{14}O_2$ calcd 238.0994, found 238.0989. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 2.16–2.35 (m, 1H), 2.45–2.7 (m, 3H), 4.5–4.6 (m, 1H), 7.03 (d,*J* 7.9 Hz, 1H), 7.08–7.2 (m, 2H), 7.2–7.34 (m, 4H), 7.77 (d,*J* 7.9 Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 31.0, 33.9, 38.4, 119.9, 121.2, 127.3, 128.17, 128.19, 129.0, 131.9, 134.4, 141.5, 153.5, 198.5.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.062.

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