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$LiAlH_4$ Promoted Reductive Deoxygenation of Hydroxybenzyl Alcohols *via* Benzoquinone Methide Intermediates.

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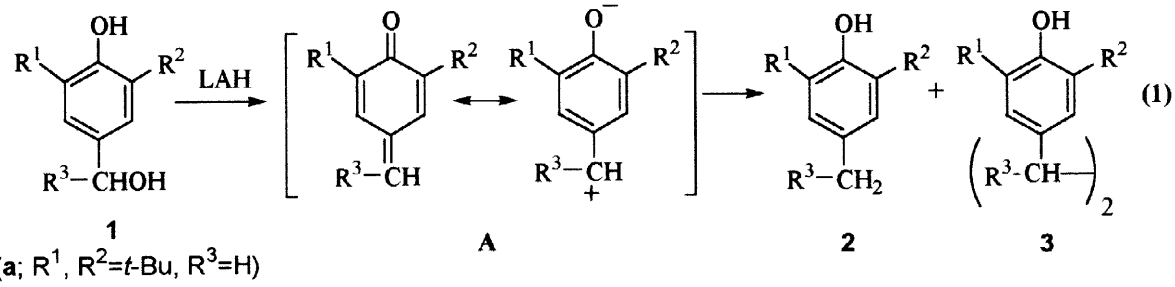
Abstract: Primary and secondary hydroxybenzyl alcohols react with $LiAlH_4$ in chlorobenzene to give the corresponding alkylphenols. The reaction proceeds through the formation of benzoquinone methide as an intermediate. An example of [4+2] cycloaddition of benzoquinone methide is also reported.

Benzoquinone methides of resonance hybrids **(A)** play an important role as the reactive intermediates in the oxidation of phenols.[1] In general, *p*-benzoquinone methide with substituents on the terminal methylene and cyclohexadiene framework are isolable and stable.[2] The electrophilic character of the exocyclic alkylidene carbon has been widely exploited in the reactions with nucleophiles.[3] However, in the case of simple benzoquinone methide (R_1, R_2, R_3=H), or benzoquinone methide without a substituent on the terminal methylene (R_3=H), isolation is impossible and the utility of these transient intermediates is limited because of their instability and method of generation.[2] Practically, benzoquinone methides are prepared *in situ* by several methods.[1-6] In the course of our study on the transient intermediates, such as 2,6-di-*tert*-butyl-*p*-benzoquinone methide, the intermolecular nucleophilic addition and Diels-Alder reaction have been investigated[4] since they appeared worthwhile for the application to synthetic methodology. This paper describes an entirely new synthetic method for the preparation of benzoquinone methide intermediate which appears to proceed through the reductive dehydroxylation of hydroxybenzyl alcohols.

3,5-Di-*tert*-butyl-4-hydroxybenzyl alcohol **1a**, when treated with $LiAlH_4$ in chlorobenzene at 120 °C, gave 2,6-di-*tert*-butyl-4-methylphenol **2a**, benzoquinone methide **A** and a trace amount of dimer **3a** (eq 1).



(1)

1 (a; R^1, R^2=*t*-Bu, R^3=H) **A** **2** **3**

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To optimize the reaction conditions, several common solvents and metal hydride reagents were examined with 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol **1a** as the model compound. With 1.2 mol equiv of $LiAlH_4$, chlorobenzene (or chlorobenzene/THF = 1:1) provided the best yield of **2a** (77%, entry 3). Other solvents examined (THF, ether, or toluene) gave unsatisfactory results. With 0.5 mol equiv of $LiAlH_4$ in chlorobenzene, 33% of **A**, 56% of **2a** and a trace of **3a** were produced and 7% of **1a** was recovered (entry 2). When using other metal hydrides (Table 1, entries 5-7), ~5% of **2a** and 11~34% of **A** were obtained and 64~86% of **1a** was recovered. In most cases, we observed the formation of transient intermediate 2,6-di-*tert*-butylbenzoquinone methide **A** during the transformation of **1a** to **2a**.

Table 1. Effects of Reducing Agents on the Dehydroxylation of **1a**.[a]

entry	reducing agent (equiv)	time (h)	yield, %[b]		
			2a	**A**	**(1a)**
1	$LiAlH_4$, 0.15	4.0	3	30	66
2	$LiAlH_4$, 0.5	7.0	56	33	7
3	**$LiAlH_4$, 1.2**	**4.0**	**77**	**1**	**0**
4	$LiAlH_4$, 2.0	2.0	74	1	0
5	$NaBH_4$, 1.2	8.0	1.2	34	64
6	CaH_2, 1.2	5.0	3	22	74
7	KH, 1.2	5.0	2	11	86

[a]Reactions were performed by using of **1a** (1.0 mmol) with reducing agent in 10 mL of chlorobenzene. [b]The product distribution were determined by GLC with internal standard.

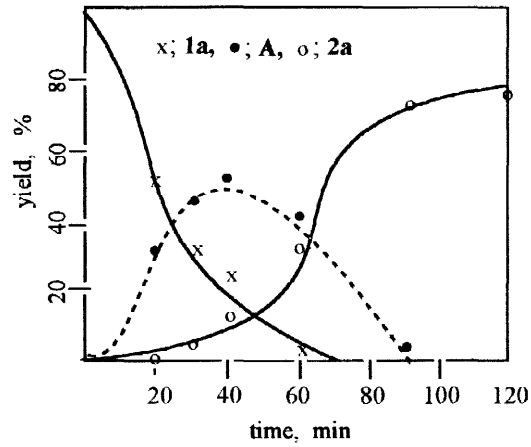
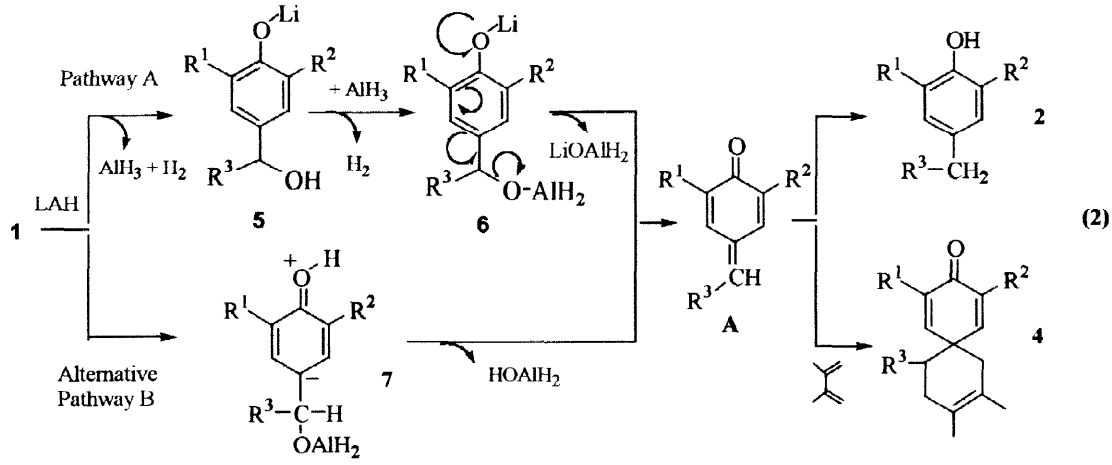


Figure. Time/Course profile for the reaction of **1a** (0.1M) and $LiAlH_4$ (0.12M) in chlorobenzene.

Evidence for the formation of **A** in the reaction of **1a** with $LiAlH_4$ is presented in Figure. The decrease of **1a** is counterbalanced by appearance of **A** and **2a** whose concentrations increase steadily until a certain period of time. After ~50% of **A** was generated *in situ* in solution, the rate for the formation of **2a** was suddenly accelerated to complete the reaction. Other direct evidence for the existence of intermediate **A** is provided by a diene trapping experiment.[4,6] With the background of previous work, it was decided to concentrate on the interception of **A** generated *in situ* from **1a** by reaction with $LiAlH_4$ and diene. Thus, under the same conditions treatment of 2,3-dimethylbutadiene leads to the formation of spiroketone **4a** in 75% yield (eq 2).

In fact, the hydrogenolysis of aminobenzyl alcohols and aminobenzoic acids with $LiAlH_4$ to the corresponding methyl anilines had been reported by Conover and Tarbell[7] as early as 1950. They claimed, however, the hydroxy compounds examined (*p*-hydroxybenzoic acid, ethyl *p*-hydroxybenzoate, and 2,4-dihydroxybenzladehyde) showed no detectable amount of the expected cresol derivatives. Later, chroloaluminum hydride prepared from $LiAlH_4$ and $AlCl_3$ received attention for the hydrogenolysis of 2°-benzylic alcohols.[8] Interestingly it was reported that the simple 1°-benzyl alcohols failed to react with $LiAlH_4$ or chroloaluminum hydride.[8a] Meanwhile, benzylic alcohols treated with $LiAlH_4/TiCl_3$ coupled to give bibenzyls *via* dimerization of benzylic radicals.[9] Unfortunately, the reductive dehydroxylation of hydroxybenzyl alcohols has not been extensively studied with $LiAlH_4$.

From our results, the reactive intermediate benzoquinone methide **A** must be generated from its complex with aluminum, **6** (eq 2). The phenolic hydrogen is more acidic than the benzylic hydrogen, thus the mechanism would involve the deprotonation of the phenolic hydrogen to give complex **5**. Complex **5** then reacts with AlH_3 furnished by LAH to form **6**. The stabilized benzoquinone methide formed by loss of $LiOAlH_2$ would readily pick up a hydride ion from the reducing agent or be trapped by diene. In the alternative pathway B, the formation of the complex **7** may be involved followed by loss of $HOAlH_2$ to give the benzoquinone methide **A**. In fact, it has been reported that the mechanism for the hydrogenolysis of *p*-aminoaryl carbinols by LAH involves the formation of *p*-$^{+}H_2N{=}C_6H_4[CH(R)(OAlH_2)]^{-}$, which is similar to **7**.[7] This process would readily lead to C-O bond cleavage to form the resonance stabilized carbonium ion, *p*-$^{+}H_2N{=}C_6H_4$-$CH(R)^{+}$. Since the observations of benzoquinone methide by GC-MSD and the trapping experiment with diene suggest its existence in solution, our reaction does not proceed via carbonium ion.



(2)

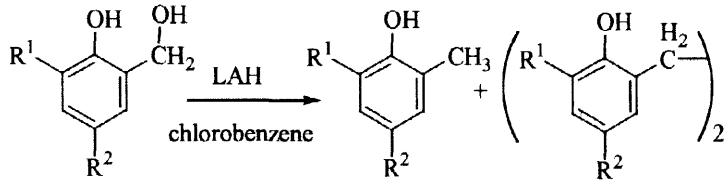
Other *p*-hydroxybenzyl alcohols with $LiAlH_4$ were also studied. All of the dehydroxylations were successful under the similar conditions and provided the corresponding *p*-methylphenols in reasonable yields (Table 2).

Table 2. Reductive Dehydroxylation of *p*-Hydroxybenzyl Alcohols **1** by $LiAlH_4$

entry	*p*-hydroxybenzyl alcohols				conditions		yield (%)
	1	**R¹**	**R²**	**R³**	$LiAlH_4$ (equiv)	time (h)	**2**
1	**1a**	*t*-Bu	*t*-Bu	H	1.2	4	77
2	**1b**	OMe	OMe	H	3.0	2	61
3	**1c**	Ph	Ph	H	3.0	8	80
4	**1d**	*i*-Pr	*i*-Pr	H	3.0	8	97
5	**1e**	Me	Me	H	2.0	5	66
6	**1f**	OMe	H	H	3.0	3	87
7	**1g**	H	H	H	3.0	5	90
8	**1h**	*t*-Bu	*t*-Bu	Me	1.2	1	70
9	**1i**	*t*-Bu	*t*-Bu	Et	1.2	3	74

In particular, dehydroxygenation of simple and unsymmetrical *p*-hydroxybenzyl alcohols **1f** and **1g** also gave *p*-methylphenols in high yields (~90 %). If one focuses attention on the isolable benzoquinone methide with

a substituent on the methine, it is worth commenting that 2° *p*-hydroxybenzyl alcohols **1h** and **1i** were also reduced to give the expected products in good yields. Furthermore, isolated benzoquinone methide generated from **1h** by known method[2a] also proceeded to react with the hydride from $LiAlH_4$ (1 mol equiv) to give the product **2h** in 87 % yield. We extended the dehydroxylation with $LiAlH_4$ to *o*-hydroxybenzyl alcohols **8**. Even though the formation of dehydroxylated product **9** was the major reaction pathway, the dimerization of *o*-benzoquinone methides also occurred to a significant degree.



8 **9** **10**

	8		$LiAlH_4$	Yield, %	
	R^1	R^2	(equiv)	**9**	**10**
8a	*t*-Bu	*t*-Bu	1.2	68	16
8a	*t*-Bu	*t*-Bu	2.0	10	66
8b	Me	Me	3.0	58	17
8c	H	H	3.0	71	7

In summary, we have developed an efficient method for performing the reductive deoxygenation of hydroxybenzyl alcohols to give the corresponding alkyl phenols. The mechanism proceeds by way of a benzoquinone methide intermediate that is generated *in situ*.

Experimental details are as follows: $LiAlH_4$ (1.2 mmol, 0.046g) was added to a solution of **1a** (1.0 mmol, 0.236g) in chlorobenzene (5 mL) and THF (5 mL) at room temperature. The mixture was stirred for 4 h at reflux. Addition of water, followed by separation of the organic layer in conjunction with usual aqueous work up gave 0.19g of crude mixture. The crude mixture was purified by column chromatography on silica gel using hexane/EtOAc (8:2) as the eluent.

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