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An unexpected aromatization reaction during the preparation of 1,2-cyclohexanedione ethers

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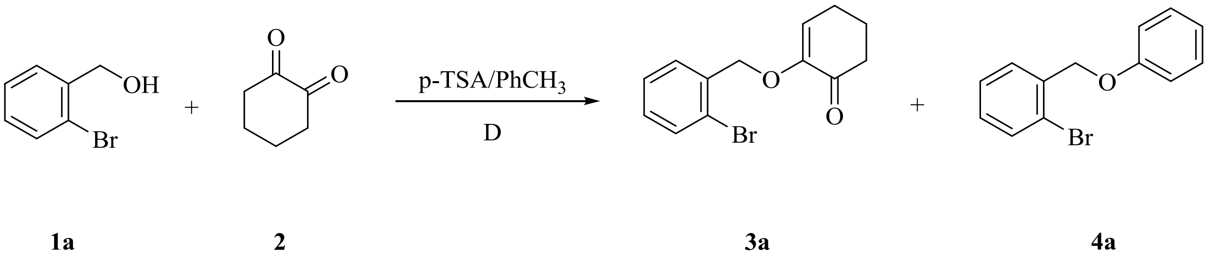
Abstract: In a heretofore-unreported reaction, 1,2-cyclohexandione reacts with a variety of alcohols under mild acid-catalyzed dehydration conditions to afford not only ethers of 1,2- cyclohexanedione but the corresponding aryl ethers as well in moderate to good yield.

Keywords: 1,2-cyclohexanedione; aromatization; aryl ethers.

1. Introduction

During the course of a synthetic methods investigation, we required the preparation of the diosphenol ether **3** from the reaction of o-bromobenzyl alcohol (**1**) and 1,2-cyclohexanedione (**2**) in accordance to a literature procedure (Scheme 1).[1] While the desired product was observed, much to our surprise we isolated the corresponding phenyl ether **4** in significant, albeit low yield. This prompted us to investigate the reaction of a variety of alcohols with 1,2-cyclohexanedione under acidic conditions.



Scheme 1. Acid-catalyzed reaction of o-bromobenzyl alcohol with 1,2-cyclohexanedione

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2. Experimental Section

2.1. Chemicals

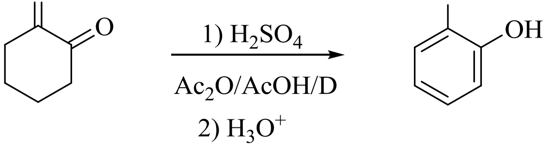
1,2-Cyclohexanedione was purchased from Ontario Chemicals and was used as received. Other chemicals were purchased from Sigma-Aldrich Chemicals. IR spectra were recorded on a Perkin-Elmer Spectrum Two Fourier Transform Infrared Spectrometers. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Biospin Ascend 400 MHz Nuclear Magnetic Resonance Spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Silica gel flash column chromatography was performed using E. Merck silica gel (230-400) and E. Merck TLC plates. Low resoultion mass spectrometry was performed on a Agilent 6890 Gas Chromatograph/5973 Quadrapole Mass Spectrometer System at 70 eV with a 7683B Autoinjector. The high-resolution mass spectrum was obtained on an Agilent LCTOF.

2.2 General method for the preparation of aryl ethers: Compounds **4a-d** and **4g-j** were synthesized by the method detailed below and their structural assignment confirmed by comparison of spectral data to that reported in the literature.

*Preparation of 1,2-dimethoxy-4-(2-phenoxyethyl)benzene (**4e**):* To a 250 mL round bottom flask equipped with a Dean-Stark tube and reflux condenser was added 1,2-cyclohexanedione (1.12 g; 10 mmol) dissolved in toluene (100 mL). 3,4 Dimethoxy-β-phenylethyl alcohol (2.28 g; 12.5 mmol) was then added to the flask, followed by the addition of *p*-TSA (170 mg; 0.98 mmol). The reaction mixture was refluxed for 24 h. The reaction was cooled to 0^o C, and an additional 125 mL of toluene was added. The mixture washed with 100 mL of 0.5 M Na_2CO_3. The organic layer was separated and washed with additional 0.5 M Na_2CO_3 (2 x 200 mL). The organics were then dried ($MgSO_4$), filtered and concentrated *in vacuo,* The crude product was purified by column chromatography on silica gel eluting with 98:2 hexanes/EtOAc to afford a **4e** as clear colorless viscous oil: (697 mg; 27%): ^{1}H NMR (400 MHz, $CDCl_3$) δ7.27-7.15 (m, 7H), 6.90-6.82 (m, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.20 (t, *J* = 7.2 Hz, 2H), 3.08 (t, *J* =7.2Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (100MHz, $CDCl_3$) δ 158.8, 149.1, 147.7, 131.1, 129.5, 120.9, 120.8, 114.6, 112.5, 111.4, 68.9, 56.0, 55 .9, 35.6. HRMS for $C_{16}H_{18}O_3$: calc'd *m/z*: 258.1256; found *m/z*: 258.1261.

3. Results and Discussion

Using a variety of aryl substituted alcohols, we found that in each case a substantial amount of aryl ether product along with the expected dione ether was formed and in several cases, the aryl ethers were the major product (**1e**, **1g-1i**). We found this interesting in light of the work of Kablaoui who has described the aromatization of 1,2-, 1,3-, and 1,4-cyclohexanediones using forcing conditions employing a strong acid/Ac_2O/AcOH system (Scheme 2) to afford pyrocatechol, resorcinol, and hydroquinone after hydrolysis of he corresponding O-acylated derivatives,[2] while Feigenbaum, *et. al.* have described the conversion of 3-aryl-1,2-cyclohexanediones to the corresponding catechols using a p-toluenesulfonyl chloride/K_2CO_3/AIBN system (Scheme 3).[3]



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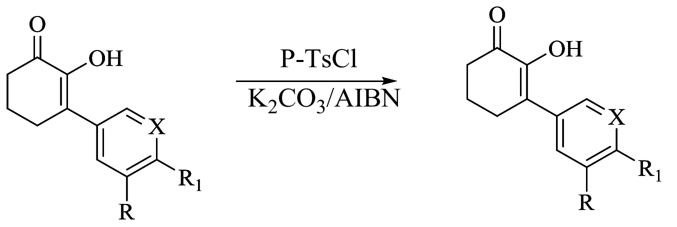
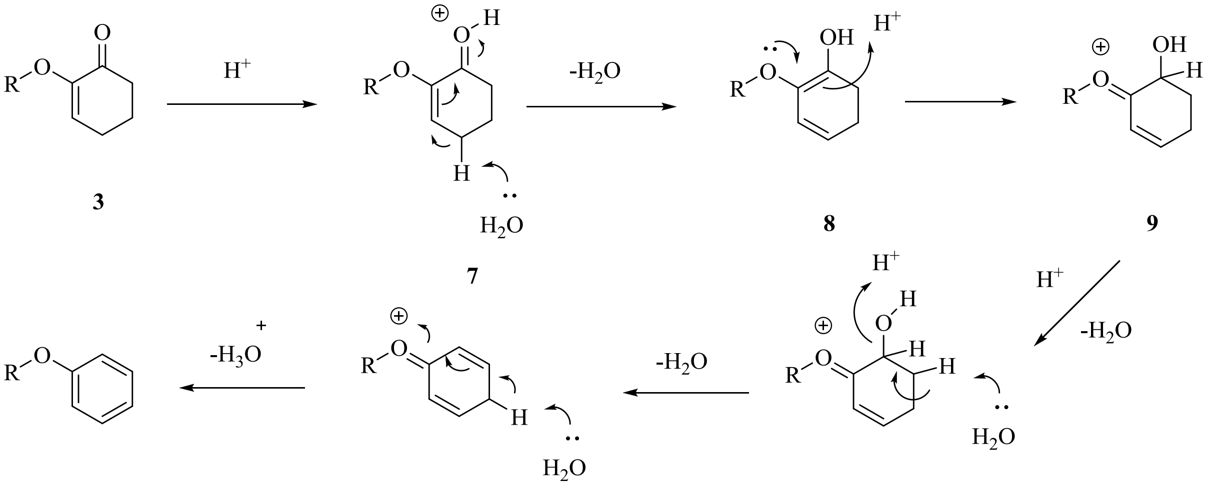
Scheme 2. Aromatization of 1,2-cyclohexanedione to catechol under acidic conditions

These reaction conditions are far more rigorous compared to those employed in this study.[4] A possible mechanism for aryl ether formation is shown below (Scheme 4).



5 **6**

Scheme 3. Aromatization of 1,2-cyclohexanedione derivatives to catechol under basic conditions



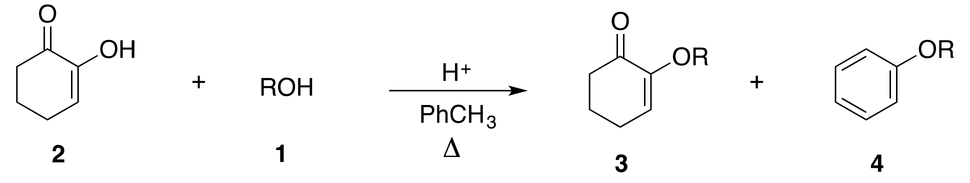
3 **7** **8** **9** **4** **11** **10**

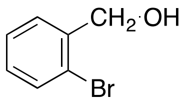
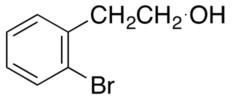
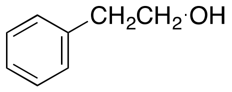
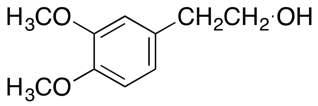
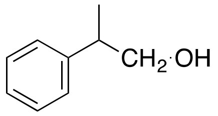
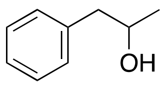
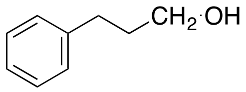
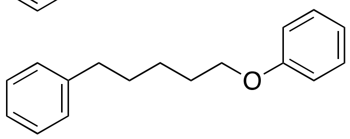
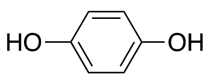
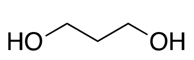
Scheme 4. Proposed mechanism for the aromatization of ethers derived from 1,2-cyclohexandione under acidic conditions

4. Conclusion

1,2-Cyclohexanedione can undergo dehydrative aromatization reactions with alcohols under relatively mild conditions. To the best of our knowledge, this type of mild aromatization reaction with 1,2-cyclohexanedione has not been reported. Future studies will focus on the scope and limitations of this chemistry.

Table 1. Synthesized Compounds



	ROH	%	%	ref.
1a		70	29	5
1b		65	24	6
1c		75	15	4,8
1d		73	27	
1e		8	77	9
1f		44	22	10
1g		17	72	11
1h		19	71	12,13
1i		29	70 (a)	14
1j		22 (b)	34 (b)	15

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[a] based on stoichiometry of 1 mole hydroquinone/1 mole 1,2-cyclohexanedione. The ether product is 4-phenoxy- phenol

[b] based on stoichiometry of 1 mole diol/2 moles 1,2-cyclohexanediol

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

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