Acid-Catalyzed Dehydration of Substituted Dienediols

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Introduction

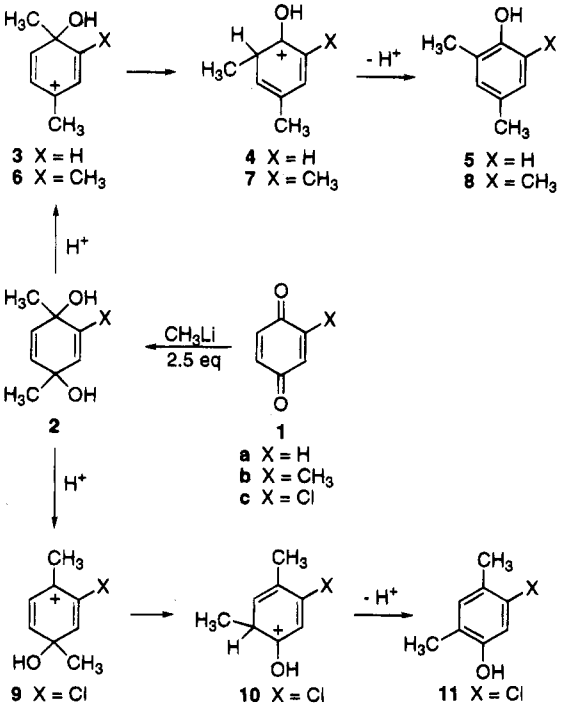
Quinones react with excess alkyllithium to give dienediols as adducts.[1,2] Recently, the acid-catalyzed dehydration of these adducts was reported as a synthetic pathway for the preparation of 2,4-dialkylphenols.[3] While this dehydration reaction has potential for regiospecific synthesis of polysubstituted phenols, which are widely used as antioxidants and stabilizers,[4] the only dienediols studied to date have been derived from benzoquinone. In this paper, we demonstrate that the products obtained from the dehydration of dienediols derived from substituted quinones vary as a function of the electronic effects and proximity of the substituents to the carbocation intermediate.

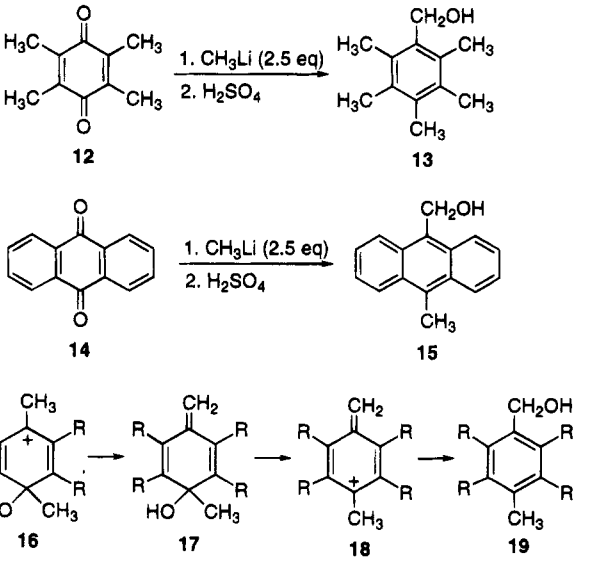
Results and Discussion

Addition of alkyllithium reagents to benzoquinone followed by addition of aqueous sulfuric acid affords 2,4-dialkylphenols. These products have been shown to arise from the acid-catalyzed dehydration of the dienediol intermediate which is the result of 1,2-additions to the quinone carbonyls.[3] The mechanism of this reaction, using methyllithium as a model organometallic, is shown in Scheme 1. Addition of a 2-fold excess of methyllithium to benzoquinone (**1a**) results in formation of the dienediol **2a**. Acid-catalyzed dehydration of **2a** affords the carbocation **3** which undergoes a 1,2-alkyl migration to give **4**. Deprotonation of **4** results in rearomatization affording 2,4-dimethylphenol (**5**) in 70% yield.

In order to determine the regiospecificity of this reaction, we studied the addition of excess methyllithium to a series of substituted quinones followed by an aqueous sulfuric acid quench. In the case of monosubstituted benzoquinones, the regiochemistry of the products is a function of the electronic effects of the substituent. Reaction of 2-methylbenzoquinone (**1b**) afforded 2,4,6-trimethylphenol (**8**) in 73% yield. The regioselectivity of this reaction is due to selective formation of the carbocation **6** which is stabilized by the hyperconjugation of the methyl group at C-2. Alkyl migration to C-6 gives **7** which upon deprotonation affords **8**. The opposite regiochemistry is observed with 2-chlorobenzoquinone (**1c**) which afforded 5-chloro-2,4-dimethylphenol (**11**) in 68% yield. In this case the electron-withdrawing effects of the chlorine substituent cause selective formation of carbocation **9**. Regiospecific alkyl migration to C-5 gives **10** which upon deprotonation affords **11** as the lone dehydration product. Presumably, migration to C-3 is hindered by the presence of the chlorine substituent at C-2, thus favoring the alkyl migration to C-5.

Scheme 1





Since migration followed by aromatization would be circumvented by substitution, we next turned to the reactions of dienediols derived from tetrasubstituted quinones. Under identical reaction conditions, tetramethylbenzoquinone (**12**) afforded pentamethylbenzyl alcohol (**13**) in 82% yield. Likewise, 9,10-anthraquinone (**14**) afforded 9-(hydroxymethyl)-10-methylanthracene (**15**) in 61% yield. Mechanistically, the formation of these benzyl alcohol derivatives can be rationalized by invoking the initial formation of carbocation **16**. Since alkyl migration cannot lead to rearomatization, elimination of the carbocation intermediate results in formation of the trienol **17**. The trienol undergoes a second dehydration affording the cation **18**. Nucleophilic addition of water at the methylene carbon gives the benzyl alcohol **19**.

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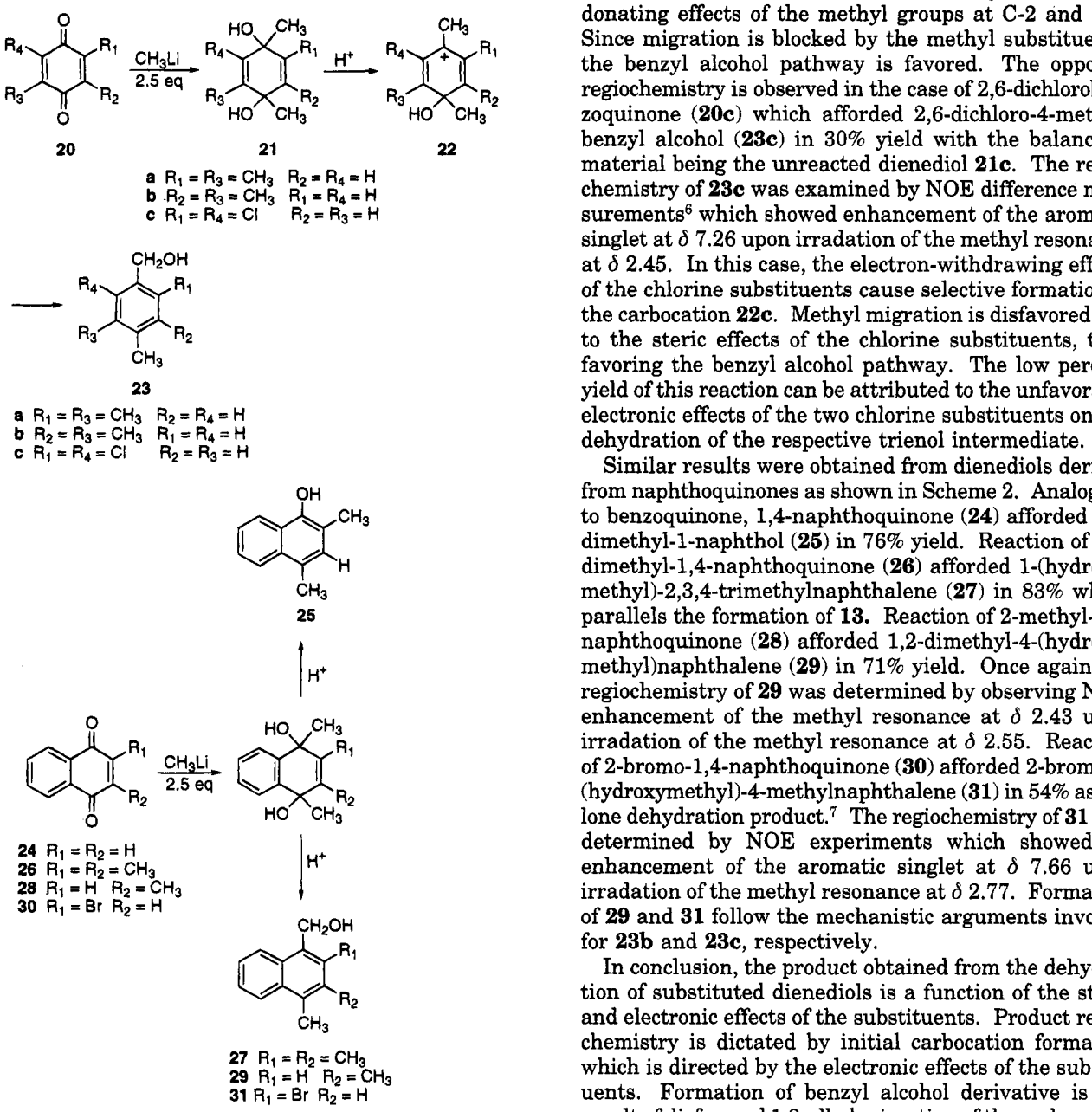
Scheme 2



To investigate the competitive nature of these reaction pathways, we turned to reactions of dienediols derived from disubstituted quinones. The benzyl alcohol pathway is preferred in the case of 2,5-disubstituted benzoquinones as shown in Scheme 2. Reaction of 2,5-dimethylbenzoquinone (**20a**) resulted in 2,4,5-trimethylbenzyl alcohol (**23a**) in 70% yield. As demonstrated in the case of **11**, alkyl migration is disfavored by the steric effects of the substituents at C-2 and C-5. Consequently, elimination followed by dehydration and addition is favored, resulting in the benzyl alcohol **23a**. Benzyl alcohol derivatives were also obtained for 2,6-disubstituted benzoquinones with the regiochemistry being a function of the electronic effects of the substituents. Reaction of 2,6-dimethylbenzoquinone (**20b**) afforded a symmetrical benzyl alcohol derivative in 68% yield which was determined to be 3,4,5-trimethylbenzyl alcohol (**23b**). The regiochemistry of the product was determined by spectral comparison with the other possible isomer, 2,4,6-trimethylbenzyl alcohol, which was synthesized by known methods.[5] Formation of **23b** can be explained on the basis of selective formation of the carbocation **22b** which is stabilized by the electron-donating effects of the methyl groups at C-2 and C-6. Since migration is blocked by the methyl substituents, the benzyl alcohol pathway is favored. The opposite regiochemistry is observed in the case of 2,6-dichlorobenzoquinone (**20c**) which afforded 2,6-dichloro-4-methylbenzyl alcohol (**23c**) in 30% yield with the balance of material being the unreacted dienediol **21c**. The regiochemistry of **23c** was examined by NOE difference measurements[6] which showed enhancement of the aromatic singlet at δ 7.26 upon irradation of the methyl resonance at δ 2.45. In this case, the electron-withdrawing effects of the chlorine substituents cause selective formation of the carbocation **22c**. Methyl migration is disfavored due to the steric effects of the chlorine substituents, thus favoring the benzyl alcohol pathway. The low percent yield of this reaction can be attributed to the unfavorable electronic effects of the two chlorine substituents on the dehydration of the respective trienol intermediate.

Similar results were obtained from dienediols derived from naphthoquinones as shown in Scheme 2. Analogous to benzoquinone, 1,4-naphthoquinone (**24**) afforded 2,4-dimethyl-1-naphthol (**25**) in 76% yield. Reaction of 2,3-dimethyl-1,4-naphthoquinone (**26**) afforded 1-(hydroxymethyl)-2,3,4-trimethylnaphthalene (**27**) in 83% which parallels the formation of **13**. Reaction of 2-methyl-1,4-naphthoquinone (**28**) afforded 1,2-dimethyl-4-(hydroxymethyl)naphthalene (**29**) in 71% yield. Once again the regiochemistry of **29** was determined by observing NOE enhancement of the methyl resonance at δ 2.43 upon irradation of the methyl resonance at δ 2.55. Reaction of 2-bromo-1,4-naphthoquinone (**30**) afforded 2-bromo-1-(hydroxymethyl)-4-methylnaphthalene (**31**) in 54% as the lone dehydration product.[7] The regiochemistry of **31** was determined by NOE experiments which showed an enhancement of the aromatic singlet at δ 7.66 upon irradation of the methyl resonance at δ 2.77. Formation of **29** and **31** follow the mechanistic arguments invoked for **23b** and **23c**, respectively.

In conclusion, the product obtained from the dehydration of substituted dienediols is a function of the steric and electronic effects of the substituents. Product regiochemistry is dictated by initial carbocation formation which is directed by the electronic effects of the substituents. Formation of benzyl alcohol derivative is the result of disfavored 1,2-alkyl migration of the carbocation intermediate due to steric effects of the substituents.

Experimental Section

Melting points were determined in unsealed capillary tubes and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer. ^{1}H (250 MHz) and ^{13}C (62.9 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm downfield from internal TMS (δ). Tetrahydrofuran was distilled under nitrogen from $LiAlH_4$. Quinones **26** and **30** were synthesized according to literature.[8,9] All other materials were obtained from commercial suppliers.

General Procedure for Addition of Methyllithium to Quinones. In a 250-mL round-bottom flask were placed

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(7) It is noteworthy to mention that, in addition to **31**, 2-bromo-3-methyl-1,4-naphthoquinone, the result of oxidative 1,4-addition, was also isolated in 30% yield from this reaction.
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quinone (5.0 mmol) and THF (100 mL) under nitrogen. The solution was cooled to −78 °C. Added to the solution was methyllithium (12.5 mmol). The resulting mixture was stirred for 1 h, allowing the temperature to rise to 20 °C. The solution was returned to −78 °C and acidified with 2 M H_2SO_4 (75 mL). The temperature was allowed to rise to 20 °C, and the reaction mixture was stirred for an additional hour. The solvent was then removed under reduced pressure and the residue extracted with dichloromethane (3 × 20 mL). The organic phase was washed with water (3 × 10 mL) and dried over $MgSO_4$. The crude products were purified by flash chromatography (silica gel, acetone/hexane).

2,4-Dimethylphenol (5). Following the general procedure, 540 mg of benzoquinone afforded **5** (428 mg, 70%): mp 26 °C (lit.[3] mp 27−28 °C); IR (KBr) 3435, 3025, 2928, 1620, 1517, 1270, 817 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.91 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 5.01 (s, 1H), 2.23 (s, 3H), 2.19 (s, 3H); ^{13}C NMR δ 151.36, 131.61, 129.91, 127.34, 123.54, 114.79, 20.36, 15.64.

2,4,6-Trimethylphenol (8). Following the general procedure, 611 mg of 2-methylbenzoquinone afforded **8** (498 mg, 73%): mp 70 °C (lit.[10] mp 71−72 °C); IR (KBr) 3387, 3013, 2916, 1608, 1481, 1197, 1016, 848 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79 (s, 2H), 4.47 (s, 1H), 2.27−2.13 (bs, 9H); ^{13}C NMR δ 149.88, 129.28, 129.10, 122.76, 20.39, 15.80.

5-Chloro-2,4-dimethylphenol (11). Following the general procedure, 713 mg of 2−chlorobenzoquinone afforded **11** (533 mg, 68%): mp 88 °C (lit.[11] mp 91 °C); IR (KBr) 3398, 2919, 1619, 1452, 1413, 1286, 1130, 1022, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79 (s, 1H), 6.49 (s, 1H), 5.02 (s, 1H), 2.24 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 154.25, 137.10, 134.97, 122,22, 119.45, 114.25, 20.74, 12.11.

2,3,4,5,6-Pentamethylbenzyl alcohol (13). Following the general procedure, 821 mg of tetramethylbenzoquinone afforded **13** (731 mg, 82%): mp 160 °C (lit.[12] mp 162−163 °C); IR (KBr) 3411, 3315, 2917, 1662, 1457, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.67 (s, 2H), 2.26 (bs, 7H), 2.15 (s, 3H), 2.14 (s, 6H); ^{13}C NMR δ 135.19, 134.05, 132.95, 127.21, 60.20, 17.00, 16.67, 16.18.

9-(Hydroxymethyl)-10-methylanthracene (15). Modifing the general procedure to include a 1.5 h reflux following methyllithium addition, 1.04 g of 9,10-anthraquinone afforded a yellow solid which was recrystallized from ethanol yielding **15** (678 mg, 61%): mp 222 °C (lit.[13] mp 222−223 °C); IR (KBr) 3406, 3074, 2904, 1390, 1077, 1029, 939, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35−8.31 (m, 4H), 7.52−7.36 (m, 4H), 5.65 (s, 2H), 3.12 (s, 3H), 1.58 (bs, 1H); ^{13}C NMR δ 131.93, 130.88, 129.91, 127.16, 125.52, 125.22, 125.06, 124.81, 64.38, 14.43.

2,4,5-Trimethylbenzyl Alcohol (23a). Following the general procedure, 680 mg of 2,5-dimethylbenzoquinone afforded **23a** (525 mg, 70%): mp 168 °C (lit.[14] mp 168 °C); IR (KBr) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (s, 1H), 6.95 (s, 1H), 4.61 (s, 2H), 2.29 (s, 3H), 2.27 (s, 1H), 2.22 (bs, 6H); ^{13}C NMR δ 135.98, 133.94, 133.34, 131.80, 129.34, 127.50, 63.33, 19.25, 19.14, 18.02.

3,4,5-Trimethylbenzyl Alcohol (23b). Following the general procedure, 680 mg of 2,6-dimethylbenzoquinone afforded **23b** (510 mg, 68%): mp 76 °C (lit.[15] mp 78 °C); IR (KBr) 3389, 3255, 2956, 1656, 1445, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (s, 2H), 4.57 (s, 2H), 4.55 (s, 1H), 2.28 (s, 6H), 2.17 (s, 3H); ^{13}C NMR δ 137.65, 136.62, 134.44, 126.38, 65.22, 20.50, 15.10.

2,6-Dichloro-4-methylbenzyl Alcohol (23c). Following the general procedure, 885 mg of 2,6-dichlorobenzoquinone afforded **23c** (287 mg, 30%): mp 69 °C; IR (KBr) 3390, 2862, 1560, 1457, 1381, 1072, 1001, 783 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (s, 2H), 4.44 (s, 2H), 2.47 (s, 1H), 2.45 (s, 3H); ^{13}C NMR δ 137.46, 135.49, 133.71, 126.81, 70.90, 17.20. Anal. Calcd for $C_8H_8Cl_2O$: C, 50.29; H, 4.22. Found: C, 50.75; H, 4.29.

2,4-Dimethyl-1-naphthol (25). Following the general procedure, 790 mg of 1,4-naphthoquinone afforded **25** (654 mg, 76%): mp 81 °C (lit.[16] mp 84 °C); IR (KBr) 3354, 3067, 2924, 1597, 1463, 1351, 1271, 1086, 864, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93−7.89 (m, 2H), 7.50 (dt, J = 7.5, 1.3 Hz, 1H), 7.37 (dt, J = 7.5, 1.5 Hz, 1H), 6.89 (s, 1H), 4.87 (s, 1H), 2.61 (s, 3H), 2.49 (s, 3H); ^{13}C NMR δ 149.84, 134.10, 133.82, 128.43, 126.05, 124.56, 123.63, 122.91, 118.45, 112.93, 19.23, 10.33.

1-(Hydroxymethyl)-2,3,4-trimethylnaphthalene (27). Following the general procedure, 931 mg of 2,3-dimethyl-1,4-naphthoquinone afforded **27** (831 mg, 83%): mp 178 °C; IR (KBr) 3448, 3074, 2893, 1692, 1602, 1451, 1343, 1059, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (d, J = 8.1 Hz,1H), 8.00 (d, J = 8.1 Hz, 1H), 7.43−7.31 (m, 2H), 5.12 (s, 2H), 2.61 (s, 3H), 2.50 (bs, 1H), 2.46 (s, 3H), 2.39 (s, 3H); ^{13}C NMR δ 135.71, 133.01, 131.71, 131.50, 128.34, 124.87, 124.57, 124.36, 124.18, 124.13, 65.67, 17.23, 17.12, 15.51. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.45; H, 7.94.

4-(Hydroxymethyl)-1,2-dimethylnaphthalene (29). Following the general procedure, 861 mg of 2-methyl-1,4-naphthoquinone afforded **29** (660 mg, 71%): mp 96 °C; IR (KBr) 3355, 2883, 1603, 1514, 1233, 1076, 992, 889, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05−8.01 (m, 2H), 7.53−7.42 (m, 2H), 7.26 (s, 1H), 5.00 (s, 2H), 2.55 (s, 3H), 2.43 (s, 3H), 2.00 (bs, 1H); ^{13}C NMR δ 133.58, 133.20, 132.52, 131.59, 129.90, 128.80, 125.67, 124.87, 124.33, 123.98, 63.59, 20.63, 14.57. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.89; H, 7.57.

2-Bromo-1-(hydroxymethyl)-4-methylnaphthalene (31). Following the general procedure, 1.185 g of 2-bromo-1,4-naphthoquinone afforded **31** (678 mg, 54%): mp 110 °C; IR (KBr) 3356, 3073, 2890, 1655, 1442, 1357, 1158, 1010, 885, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07−8.02 (m, 2H), 7.66 (s, 1H), 7.56−7.51 (m, 2H), 5.06 (s, 2H), 2.77 (s, 3H), 2.72 (bs, 1H); ^{13}C NMR δ 135.86, 133.79, 133.56, 130.12, 129.21, 126.75, 126.08, 125.11, 124.25, 124.14, 122.22, 62.92, 18.88. Anal. Calcd for $C_{12}H_{11}BrO$: C, 57.40; H, 4.42. Found: C, 57.01; H, 4.97.

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