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A Simple One-Step Synthesis of Alkylation Product from Cyclic Allylic Alcohol and Resorcinol

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Abstract □ The alkylation of resorcinol with cyclic allylic alcohol in non-aqueous acid medium gives intermolecular Friedel-Craft compounds. The products are primary alkylation products. The linkage always occurs between carbon 3 of cyclic allylic alcohol and the position 2, 4, 5 or 6 of the resorcinol.

Keywords □ Boron trifluoride etherate, cyclic allylic alcohol, resorcinol.

In recent years an increasing number of articles have appeared describing the synthesis, properties and biological activities of 5-substituted alkyl-resorcinols[1-3]. We recently reported that another development of this method, *viz* the alkylation of 5-substituted alkyl-resorcinols with monoterpenoid allylic alcohols in a modified Lewis acid reagents was a convenient source of the synthetic cannabinoids[1].

We showed that this reagent system was capable of introducing the alkylation of orcinols. In these reactions described below three products were obtained; a) substitution ortho to both the hydroxyl groups; b) substitution ortho to one of the hydroxyl groups and to methyl group; and c) double condensation (usually in a low yield).

We assumed that the postulated carbocation **4** or congeners can be produced by Lewis acid treatment of any cyclic alcohol. 2′-(1-methyl-1-cyclohexen-3-yl)-orcinol **3** obtained in this reaction may be converted to 4′-(1-methyl-1-cyclohexen-3-yl)-orcinol with BF_3-etherate by a retro Friedel-Crafts reaction, followed by recombination[2].

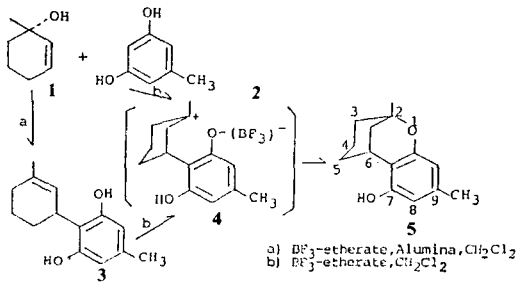
When the above described reactions are undertaken with BF_3-etherate the condensation reaction was followed by cyclization. In the above reaction (Scheme 1) a benzoxocin ring is formed. BF_3-etherate in methylene chloride initiates the ring closure which probably proceeds by the mechanism indicated through the hypothetical intermediate cation **4**. The cyclohexane ring is expected to exist predomenantly in a chair conformation.

Boron trifluoride etherate on alumina catalyses the condensation of 5-(1,1-dimethylheptyl)-resorcinol, monoalkyl-5-(1,1-dimethylheptyl)-resorcinol and 1,3-dimethyl-5-(1,1-dimethylheptyl)-resorcinol with 1-methyl-2-cyclohexen-1-ol. The products obtained was good to excellent yields[2]. The above described condensation takes place also when both phenolic groups of the resorcinols are blocked as dimethyl ether. However in this case the side chain substitution pattern does not change the yields of the reactions (ca 40%)[2].

In this paper we report a convenient single-step synthesis of the alkylation of resorcinols from cyclic allylic alcohol and resorcinol by the use of boron trifluoride etherate-on-alumina as the catalyst.

EXPERIMENTAL METHODS

IR spectra were recorded as thin film (for oil) on a Perkin-Elmer 457 grating infrared spectrometer. UV spectra were recorded on a Varian techtron 635 UV-VIS spectrometer. ^{1}H-NMR spectra were obtained on a Bruker WH-660 pulsed FT spectrometer. Chemical shifts are given in parts per million downfield from Me_4Si internal standard. Mass spectra were recorded on a LKB 2091 Gas chromatography-Mass spectrometer at 70 eV. Chromato-



Scheme 1.

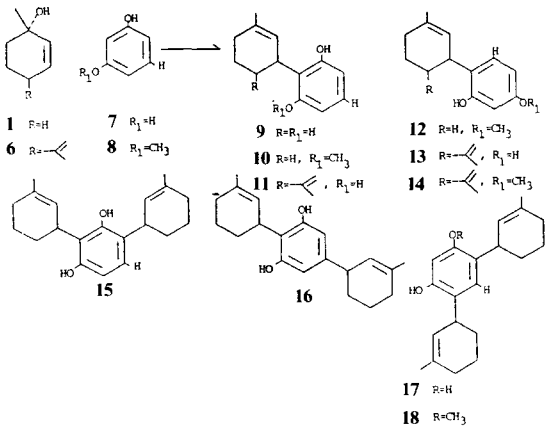
graphy; Analytical TLC was performed by using commercially available silica plates. Polygram sil N-HR/UV_{254} and the plates were visualized with fast blue phenol reagent or by charring with a solution of MeOH : H_2SO_4 (1 : 1). Column chromatography was performed by flash chromatography or medium-pressure liquid chromatography (mplc) with FMI pump on Merck Kieselgel 60 (230-400 mesh ASTM), with mixtures of ethylacetate and pertroleum ether (b.p 60-80℃).

The general procedure (A) is as follows: BF_3-etherate (0.4 m*l*) was added under nitrogen to a stirred suspension of basic aluminium oxide (Woelm, grade 1) (4.0g) in dichloromethane (20 m*l*). 1-methyl-2-cyclohexen-1-ol (2.0 mmol) and resorcinol (2.0 mmol) were added to the solution and the mixture was stirred for 5 min at room temperature. The reaction was quenched with 10% aqueous solution of sodium bicarbonate (10 m*l*). Ether (100 m*l*) and an additional portion of sodium bicarbonate solutions (100 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The reaction products were chromatographed by flash chromatography or mplc.

The general procedure (B) is as follows: BF_3-etherate (0.3 m*l*) was added under nitrogen to a stirred suspension of basic aluminum oxide (Woelm, grade I) (2g) in dry dichloromethane (20 m*l*). The mixture was stirred for 15 min at room temperature and then boiled for 1 min. (+)-cis/trans-p-mentha-2,8-dien-1-ol **6** (0.8 mmol) and resorcinol (1.0 mmol) in dichloromethane (5 m*l*) were added to the boiling suspension (40-41℃) by syringe and the reaction was quenched within 10 seconds with 10% aqueous solution of sodium bicarbonate (10 m*l*). Ether (50 m*l*) and an additional proportion of above sodium bicarbonate solution (50 m*l*) were added. The organic layer was washed brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure LC.

Preparation of compounds 9, 15, 17 and 6

Under the conditions of general procedure (A) four compounds were obtained. The first compound eluted was 2′,4′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol **15** (15 mg, 2.55%), an oil, UV_{max} (EtOH), 278 nm (ε 2205); NMR ($CDCl_3$) δ 1.77 (6H, brs, CH_3), 3.49 (1H, brd, J=7.0 Hz, C-3H), 3.96 (1H, br, C-3H), 5.54 (1H, brs, C-2H), 5.64 (1H, brs, 2-H), 6.46 (1H, d, J=8.0 Hz, arom H), 6.82 (1H, d, J=8.0 Hz, arom H); MS (20°), *m/e* 2998 (M^+, 100), 255 (39); IR (film), 3410, 1600, cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 2′,4′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol dimethyl ether **15a** quantitatively, an oil, NMR ($CDCl_3$) δ 1.26 (6H, brs, CH_3), 33.75 (3H, s, OCH_3), 3.81 (3H, d, J=3.0 Hz, OCH_3), 5.34 (2H, brs, C-2H), 6.45 (1H, brs, arom H), 6.95 (1H, m, arom H); MS (20°), *m/e* 326 (M^+, 100), 231 (55); IR (film), 1630, 1590 cm^{-1}. The second compound eluted was 2′,5′-bis-(1-methyl-1-cyclohexen-3-yl) resorcinol **16** (20 mg, 3%), an oil, UV_{max} (EtOH), 274 (ε 2516), 280 nm (2433); NMR ($CDCl_3$) δ 1.80 (6H, brs, CH_3), 3.52 (1H, d, J=6.0 Hz, C-3H), 3.97 (1H, br, C-3H), 5.69 (2H, brs, C-2H), 6.31 (1H, d, J=6.0 Hz, C-3H), 3.97 (1H, br, C-3H), 5.69 (2H, brs, C-2H), 6.31 (1H, d, J=1.0 Hz, arom H), 6.997 (1H, dd, J=6.0 Hz, arom H); MS (20°), *m/e* 298 (M^+, 14), 204 (90), 161 (100); IR (film), 3430, 1595 cm^{-1}. The third compound eluted was 4′,6′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol **17** (130 mg, 32%), an oil, UV_{max} (EtOH), 284 nm (ε 3379); 1.76 (6H, brs, CH_3), 3.20 (2H, br, C-3H), 5.56 (2H, brs, C-2H), 6.30 (1H, s, arom H), 6.72 (1H, s, arom H); MS (20°), *m/e* 298 (M^+, 100), 255 (446); IR (film), 3440, 1615, 1505 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 4′,6′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol dimethyl ether **17a** quantitatively, an oil, NMR ($CDCl_3$) δ 1.72 (6H, brs, CH_3), 3.85 (6H, s, OCH_3), 5..35 (2H brs, C-2H), 6.47 (1H, brs, arom H), 6.92 (1H, brs, arom H); MS (20°), *m/e* 326 (M^+, 100), 237 (40); IR (film), 1590, 1570 cm^{-1}. The forth compound eluted was 2′-(1-methyl-1-cyclohexen-3-yl)-resorcinol **9** (162 mg, 40%) as the major product, an oil, UV_{max} (EtOH), 282 nm (ε 3829); NMR ($CDCl_3$) δ 1.74 (3H, brs, CH_3), 3.44 (1H, m, C-3H), 5.52 (1H,



Scheme 2.

brs, C-2H), 6.22 (1H, d, J=2.0 Hz, arom H), 6.38 (1H, d, J=2.0 Hz, arom H), 6.87 (1H, s, arom H); MS (20°), *m/e* 204 (M^+, 98), 189 (49), 161 (100); IR (film), 3400, 1614, 1590 cm^{-1}. Acetylation acetic anhydride in pyridine led to 2-(1-methyl-cyclohexen-3-yl)-resorcinol diacetate **9a**, an oil, NMR ($CDCl_3$) δ 1.73 (3H, brs, CH_3), 2.63 (6H, s, OCH_3), 3.49 (1H, br, C-3H), 5.32 (1H, brs, C-2H), 6.85 (1H, d, J=1.0 Hz, arom H), 6.9 (1H, d, J=2.0 Hz, arom H), 7.18 (1H, brs, arom H); MS (20°), *m/e* 288 (M^+, 9), 244 (54), 204 (100); IR (film), 1760, 1614, 1590 cm^{-1}.

Preparation of compounds 10, 12 and 18

Under the conditions of general procedure (A) three compounds were obtained. The first compound eluted 2′-(1-methyl-1-cyclohexen-3-yl)-resorcinol **10** (15 mg, 7%), an oil, UV_{max} (EtOH) 225 sh (ε 3741), 278 (4360), 285 sh nm (3726); NMR, ($CDCl_3$) δ 1.77 (3H, brs, CH_3), 3.44 ((1H, br, C-3H), 3.75 ((3H, s, OCH_3), 5.54 (1H, brs, C-2H), 6.41 (1H, t, J=2.0 Hz arom H), 6.69 (1H, d, J=2.0 Hz, arom H), 6.89 (11H, s, arom H); MS (20°), *m/e* 218 (M^+, 100), 175 (91); IR (film), 3425, 1615, 1595 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 2′-(1-cyclohexen-3-yl)-resorcinol dimethyl ether **10a** quantitatively, an oil, NMR ($CDCl_3$) δ 1.74 (3H, brs, CH_3), 3.79 (3H, s, CH_3), 3.80 (6H, s, OCH_3), 5.36 (1H, br, C-2H), 6.37 (1H, s, arom H), 6.46 (1H, d, J=2.0 Hz, arom H), 7.13 (1H, s, arom H); MS (20°), *m/e* 232 (M^+, 100), 18 (49); IR (film), 1614, 1586 cm^{-1}. The second compound eluted was 4′,6′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol **18** (60 mg, 10%), an oil, UV_{max} (EtOH), 227 sh (ε 1619), 2282 nm (605); NMR ($CDCl_3$) δ 1.75 6H, brs, CH_3), 3.76 (3H, s, OCH_3), 5.35 (1H, brs, C-2H), 5.63 (1H, s, C-2H), 6.37 (1H, s, arom H), 6.77 (1H, s, arom H); MS (20°), *m/e* 312 (M^+, 100), 2997 (43); IR (film), 3460, 1594 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 4′,5′-bis-(1-methyl-1-cyclohexen-3-yl)-resorcinol dimethyl ether **17a** quantitatively. The third compound eluted was 6′-(1-methyl-1-cyclohexen-3-yl)-resorcinol **12** (132 mg, 30%), as the major product, an oil, UV_{max} (EtOH), 272 (ε 1858), 279 nm (174); NMR ($CDCl_3$) δ 1.78 (3H, brs, CH_3), 3.78 (3H, s, OCH_3), 3.98 (1H, br, C-3H), 55.60 (1H, brs, C-2H), 6.38 (1H, brs, arom H), 6.51 (1H, d, J=2.0 Hz, arom H), 7.20, 7.06, 6.93 (1H, s, arom H); MS (20°), *m/e* 218 (M^+, 99), 175 (100); IR (film), 3430, 1585 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 6′-(1-methyl-1-cyclohexen-3-yl)-resorcinol dimethyl ether **12a** quantitatively, an oil, NMR ($CDCl_3$) δ 1.26 (3H, brs, CH_3), 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.27 (1H, brs, C-2H), 6.52 (1H, brs, arom H), 6.60 (1H, brs, arom H), 7.13 (1H, t, arom H); MS (20°), *m/e* 232 (M^+, 100), 164 (53); IR (film), 1630, 1520 cm^{-1}.

Preparation of compounds 11 and 13

Under the conditions of procedure (B) we obtained two compounds. The less polar one was shown to be 2′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol **11** (68 mg, 35%), an oil, $[\alpha]_D$; −87° (MeOH); UV_{max} (MeOH), 309 nm (ε 401); NMR ($CDCl_3$) δ 1.68 and 1.81 (2×3H, s, CH_3), 3.87 (1H, br, C-3H), 4.50 and 4.60 (2×1H, brs, C-9H), 5.47 (1H, brs, C-2H), 6.31 (1H, brs, arom H), 6.45 (1H, brs, arom H), 7.20 (1H, t, J=8.0 Hz, arom H); MS (20°), *m/e* 244 (M^+, 57), 176 (43), 161 (100); IR (film), 3395, 1615, 1585, 882 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 2′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol diacetate **11a** (50 mg, 62%), an oil, NMR ($CDCl_3$) δ, 1.58 (3H, s, CH_3), 1.68 (3H, brs , CH_3), 2.22 (2×3 H, s, $COCH_3$), 3.46 (1H, br, C-3H), 4.44 (2H, brd, J=5.0 Hz, C-9H), 5.16 (1H, brs, C-2H), 6.74 (1H, d, J=2.0 Hz, arom H), 6.95 (1H, brs, arom H), 7.15 (1H, d, J=6.0 Hz, arom H); MS (20°), *m/e* 328 (M^+, 52), 218 (57), 176(81), 161 (100);; IR (Nujol), 1750, 1645, 1585, 890 cm^{-1}. The more polar product was 4′-(3-3,4-trans-p-methadien-1,8-yl)-resorcinol **13** (53 mg, 27%), an oil, $[\alpha]_D$; −99° (EtOH); UV_{max} (EtOH),

280 nm (ε 3070); NMR ($CDCl_3$) δ, 1.58 (3H, brs, CH_3), 1.77 ((3H, brs, CH_3), 3.23 (1H, br, C-3H), 4.56 ((1H, brs, C-9H), 4.60 (1H, d, J=1.0 Hz, C-9H), 5.49 (1H, brs, C-2H), 6.13 (1H, t, J=2.0 Hz, arom H), 6.34 (1H, t, J=3.0 Hz, arom H), 6.74 (1H, q, J=3.0 Hz, arom H); MS (20°), *m/e* 244 (M^+, 33), 176 (92), 162 (100); IR (film), 3360, 1600, 880 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 4′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol diacetate **13a**, an oil, NMR ($CDCl_3$) δ, 1.55 (3H, brs, CH_3), 1.67 (3H, brs, CH_3), 2.19 (3H, s, $COCH_3$), 2.21 (3H, s, $COCH_3$), 3.48 (1H, br, C-3H), 4.46 (1H, brs, C-9H), 4.56 (1H, brd, J=2.0 Hzz, C-99H), 5.21 (1H, brs, C-2H), 6.82 (1H, d, J=1.0 Hz, arom H), 6.99 (1H, d, J=3.0 Hz, arom H), 7.08 (1H, brs, arom H); MS (20°), *m/e* 328 (M^+, 11), 218 (86), 177 (100); IR (film), 1761, 1642, 1588, 887 cm^{-1}.

Preparation of 4′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol monoether 14

Under the conditions of general procedure (B) we obtained compound **14** (mg, 40%), an oil, $[10a]_D$; −82.6° (EtOH); UV_{max} (EtOH), 278 nm (ε 262); NMR δ ($CDCl_3$), 1.60 (3H, s, CH_3), 1.89 (3H, s, CH_3), 3.27 (1H, br, C-3H), 3.75 (3H, s, OCH_3), 4.57 (1H, brs, C-9H), 4.66 (1H, d, J=2.0 Hz, C-9H), 5.47 (1H, br, C-2H), 6.40 (2H, m, arom H), 6.86 1H, d, J=8.0 Hz, arom H); MS (20°), *m/e* 258 (M^+, 50), 190 (100); IR (film), 3440, 1618, 1440, 884 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 4′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol dimethylether **14a**, an oil, NMR ($CDCl_3$), 1.26 (3H, s, CH_3), 1.66 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.47 (1H, brs, C-H), 4.54 (1H, d, J=2.0 Hz, C-9H), 6.40 (2H, m, arom H), 7.03 (1H, d, J=8.0 Hz, arom H); MS (20°), *m/e* 272 (M^+, 20), 204 (100); IR (film), 1612, 1500, 885 cm^{-1}.

RESULTS AND DISCUSSION

Recent work from our laboratories[2] has resulted in a facile synthesis of 5-alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol derivatives in good yield by reaction of cyclic allylic alcohol and 5-substitutedalkyl-resorcinol catalyzed by boron trifluoride etherate-on-alumina.

We report now that the same reagent system may be used to prepare the alkylation of resorcinols. The primary alkylation products is readily separated by Flash chromatography and mplc. The linkage occurs always between carbon 3 of cyclic allylic alcohol moiety and **2**, **4**, **5** or **6** of the resorcinol. It is of interest to point out that, by contrast, while alkylation of monomethyl-resorcinol take place mostly at the C-4 position, alkylation of resorcinols take place preferentially at the C-2 position.

The condensation of 1-methyl-2-cyclohexen-1-ol with resorcinol gave four compounds under the conditions of general procedures; 2′-(1-methyl-cyclohexen-3-yl)-resorcinol **9** as the major product in 40% yield and the products of double condensation **15**, **17** and **16** in 2.6%, 32% and 3% yield.

In the four compounds the UV spectra show the absence of conjugation with the benzene ring, and as an olefinic methyl group seen in the NMR spectra the double bond is at the C-1 position (see experimental section). These findings are compatible with structures **9**, **15**, **17** and **16**.

The BF_3-etherate on alumina catalysed condensation reaction take place also with monomethyl resorcinol. The condensation of 1-methyl-2-cyclohexen-1-ol with monomethyl resorcinol gave three compounds; 2′-(1-methyl-1-cyclohexen-3-yl)-3′-methyl resorcinol **10** as the minor product in 7% yield, an corresponding isomer **12** as the major product in 30% yield[2] and the product of double condensation **18** in 10% yield. Compound **10** is less polar than the product of double condensation **18**.

We show that when BF_3-etherate on alumina is used as condensing reagent the reaction of (+)-cis/trans-p-mentha-2,8-dien-1-ol **6** with resorcinol. **7** on a 0.8 mmole scale, leads to 2′-(3-3,4-trans-p-menthadien-1,8-yl)-resorcinol **11**, cannabidiol-like compound) as the major product, in 35% yield as chromatographically pure oil. No cyclizations were observed and as the rest of the products were much more polar (13.27% yield) than **11**.

In none of the above described reaction intramolecular cycilzations were not observed by the addition of one of the hydroxyl groups to a suitably placed double bond. This is undoubtedly due to the "mildness" of the BF_3-etherate on alumina reagent which catalyses a Friedel-Crafts type reaction but apparently does not attack olefins (or attacks them at a low rate) to form a cationic center[4].

The noncyclized products (e.g 9) contain double bond which are on the cyclohexene ring. As the ultraviolet spectra eliminate the possibility of con-

jugation with either the double bond or the aromatic ring, the cyclohexen double bond has to occupy position C-1. This position is supported additional indicated that it is deshielded by both the double bond and the aromatic ring. Such an effect is possible only if the double bond occupied the C-1 position[2]. When the reactions delineated in Scheme 2 were performed in the absence of alumina the yields obtained were either low, or the desired products could not be isolated at all, due to cyclization reaction.

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