Boron Trifluoride Etherate on Alumina-A Modified Lewis Acid Reagent (II). Alkylation of 5-(1,1-dimethylheptyl)-Resorcinols

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Boron trifluoride etherate on alumina catalyses the condensation 5-(1,1-dimethylheptyl)-resorcinol, monoalkyl-5-(1,1-dimethylheptyl)-resorcinol and 5-(1,1-dimethylheptyl)-resorcinol dimethyl ether with 1-methyl-2-cyclohexen-1-ol. The products obtained was good to excellent yields.

Introduction

We recently reported that simplified cyclohexenyl derivatives (nor-isopropenyl canabidiols) had anticonvulsant activity in rats. Nor-isopropenyl cannabidiols were slightly more potent than cannabidiol. In general compounds having a 1,1-dimethylheptyl side chain were more potent in both audiogenic seizure and rotorod neurotoxicity tests than *n*-amyl homologs.[1]

The alkylation of 5-alkylresorcinols with monoterpenoid allylic alcohols in modified Lewis acid reagent has received some attention in the recent years. Both inter and intramolecular alkylations are observed to proceed in moderate yields. These investigations have been promoted by proposals of mechanism for the synthetic cannabinoids, and they have been aimed to perform the alkylation in mild media.[2]

In this paper we wish to report a simple and fast procedure for preparing the alkylation of 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-resorcinols from 1-methyl-2-cyclohexen-1-ol and 5-(1,1-dimethylheptyl)-resorcinols.[3] The decision to synthesize these 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-resorcinols bases on the known anticonvulsant activity in the cyclohexenyl derivatives.

Experimental

Unless otherwise stated the following apply. Mass spectra were recorded on a LKB 2091 Gas chromatograph-Mass Spectrometer at 70 eV. IR spectra were recorded as thin films (for oils) on a Perkin-Elmer grating infrared spectrophotometer, model 457. UV spectra were taken in ethanol solution on a Varian UV-Vis spectrophotometer, model 635. ^{1}H-NMR spectra were determined at 60 MHz on a Bruker W.P. 60 or at 300 MHz on a Bruker W.H. 300 instrument. Column chormatography was performed by medium-pressure liquid chormatography (m.p.l.c.) with an FMI pump on Merck Kieselge 60, 230-400 mesh ASTI, with a mixed solvent of diethyl ether and light petroleum (b.p. 60-80℃) in the ratio 2:98.

General procedure. BF_3-etherater (0.2 m*l*) was added under nitrogen to a stirred suspension of basic aluminum oxide (Woelm, grade I) (2 g) in dichloromethane (10 m*l*). 1-Methyl-2-cyclohexen-1-ol (1 mmol) and 5-(1,1-dimethylheptyl)-resorcinols (1 mmol) in dichloromethane (3 m*l*) were added to the solution via syringe 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 (50 m*l*) and an additional portion of sodium bicarbonate solution (50 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure liquid chromatography.

Preparation of 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-resorcinol (3). Under the conditions of general procedure we obtained (3) (580 mg, 88%), an oil, UV_{max} (EtOH), 273 (ε1840), 280 nm (1760); NMR ($CDCl_3$) δ 0.84 (3H, t, CH_3), 1.20 (2×3H, s, CH_3), 1.78 (3H, brs, CH_3), 3.76 (1H, br, C-3H), 5.65 (1H, brs, CH_3), 3.76 (1H, br, C-3H), 5.65 (1H, brs, C-2H), 6.34 (2H, s, arom H); MS (20°), m/e 330 (M^+, 25), 287 (11), 260 (13), 246 (100); IR (film), 3440, 2970, 1628, 1580, 1435 cm^{-1}.

Preparation of 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-1′-methyl resorcinol (4). Under the conditions of general procedure we obtained (4) (1370 mg, 80%), an oil, UV_{max} (EtOH), 272 (ε1560), 279 nm (1470); NMR ($CDCl_3$) δ 0.84 (3H, t, CH_3), 1.24 (2×3H, s, CH_3), 1.77 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 3.95 (1H, br, C-3H), 5.62 (1H, brs, C-2H), 6.40 (1H, s, arom H), 6.44 (1H, d, J=1 Hz, arom H); MS (20°), m/e 344 (M^+, 30), 301 (13), 288 (9), 274 (11), 260 (100); IR (film), 3446, 2910, 2853, 1612, 1574, 1436 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-resorcinol dimethyl ether (6) quantitatively.

Preparation of 2′-(1-methyl-1-cyclohexen-3-yl)-3′-ethyl-5′-(1,1-dimethylheptyl)-resorcinol (5). Under the conditions of general procedure we obtained (5) (498 mg, 70%), an oil, UVmax (EtOH), 272 (ε1240), 278 nm (1170); NMR ($CDCl_3$) δ 0.84 (3H, t, CH_3), 1.37 (2×3H, s, CH_3), 1.59 (3H, t, J=6 Hz, CH_3), 2.02 (3H, brs, CH_3), 3.95 (2H, q, J=7 Hz, methylene H), 5.61 (1H, brs, C-2H), 6.15 (1H, brs, arom H), 6.41 (1H, brs, arom H); MS (20°), m/e 358 (M^+, 40), 329 (6), 315 (14), 302 (21), 288 (12), 274 (100); IR (film), 3470, 2950, 2888, 1625, 1582, 1436 cm^{-1}.

Ethylation with ethyliodide and potassium carbonate in DMF led to 2′-(1-methyl-1-cyclohexen-3-yl)-5′-(1,1-dimethylheptyl)-resorcinol diethyl ether (**5a**) quantitatively, an oil, NMR ($CDCl_3$) δ 0.84 (3H, t, CH_3), 1.24 (2×3H, t, J=10 Hz, CH_3), 1.65 (3H, brs, CH_3), 3.94 (2×2H, q, J=10 Hz, methylene H), 5.28 (1H, brs, C-2H), 6.47 (2H, s, arom H); MS

(20°), m/e 386 (M^+, 100), 271 (9), 358 (33), 343 (9), 330 (7); IR (film), 2908, 2854, 1569, 1414 cm^{-1}.

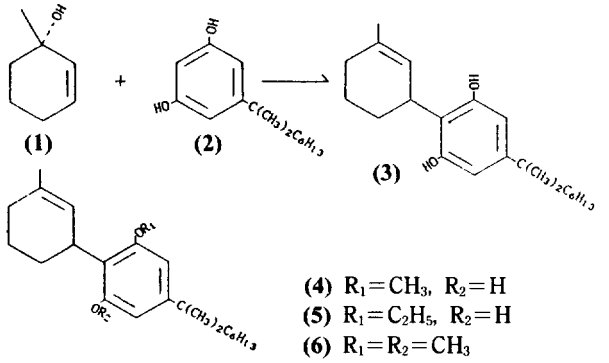
Preparation of 2'-(1-methyl-1-cyclohexen-3-yl)-5'-(1,1-dimethylheptyl)-resorcinol dimethyl ether (6). Under the conditions of general procedure we obtained (6) (296 mg, 41%), an oil, UV_{max} (EtOH), 206 (ε89500), 232 sh nm (25590); NMR ($CDCl_3$) δ 0.84 (3H, t, CH_3), 1.25 (2×3H, brs, CH_3), 1.64 (3H, brs, CH_3), 3.30 (1H, brd, J=5 Hz, C-3H), 4.15 (2×3H, s, OCH_3), 5.27 (1H, brs, C-2H), 6.48 (2H, brs, arom H); MS (20°), m/e 358 (M^+, 100), 343 (24), 330 (39), 290 (33), 274 (69); IR (film), 2940, 2870, 1613, 1580, 1455 cm^{-1}.

Results and Discussion

We report that when BF_3-etherate on alumina is used as condensing reagent the reaction of 1-methyl-2-cyclohexen-1-ol (1) with 5-(1,1-dimethylheptyl) resorcinol (2) on a 1.0 mmole scale, leads to 2'-(1-methyl-1-cyclohexen-3-yl)-5'-(1,1-dimethylheptyl)-resorcinol (3) as the major product, in 88% yield as chromatographically pure oil. The NMR spectrum shows the presence of three aliphatic methyl group and of one olefinic methyl group. The two aromatic hydrogen atoms are magnetically equivalent. These findings are compatible with structure (3).

The BF_3-etherate on alumina catalysed condensation reaction takes place also with monoalkyl resorcinols.

Monomethyl resorcinol undergoes condensation with 1-methyl-2-cyclohexen-1-ol leading to the expected product (4). This compound is obtained in an excellent yield (80%). The NMR spectrum shows the presence of three aliphatic methyl group and of one olefinic methyl group.



(1) (2) (3)

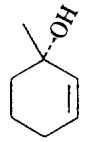
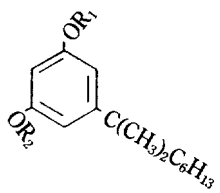
(4) R_1=CH_3, R_2=H
(5) R_1=C_2H_5, R_2=H
(6) R_1=R_2=CH_3

Methylation on compound (4), 2'-(1-methyl-1-cyclohexen-3-yl)-5'-(1,1-dimethylheptyl) resorcinol dimethyl ether (6) was obtained. As expected, the aromatic protons (at δ=6.48 ppm) and the aromatic methoxy groups (at δ=4.15 ppm) (6) are magnetically equivalent.

Reactions with monoethyl ether resorcinol was also undertaken to yield (5). Ethylation on compound (5), 2'-(1-methylcyclohexen-3-yl)-5'-(1,1-dimethylheptyl)-resorcinol diethyl ether (5a) was obtained. As shown, the aromatic protons (at δ= 6.47 ppm) are magnetically equivalent. Structures of (4) and (5) are thus established by spectroscopic and chemical correlations.

The above described condensation takes place also when both phenolic groups of the resorcinols are blocked as dimethyl ether (6). However in this case the side chain substitution pattern does not change the yields of the reactions (*ca.* 40%).[4,5]

Table 1. Condensation of 1-methyl-2-cyclohexen-1-ol with 5-(1,1-dimethylheptyl)-resorcinols by Catalysis with BF_3-etherate on Alumina

1-methyl-2-cyclohexen-1-ol	5-(1,1-dimethylheptyl)-resorcinol		product yied (%)
 (1)			
as above	R_1=R_2=H	(3)	88
as above	R_1=CH_3, R_2=H	(4)	80
as above	R_1=C_2H_5, R_2=H	(5)	70
as above	R_1=R_2=CH_3	(6)	41

When 5-(1,1-dimethylheptyl)-resorcinols are alkylated with 1-methyl-2-cyclohexen-1-ol in the presence of boron trifluoride etherate on alumina, no isomers are detected in any product under the reaction conditions used in the investigation. It is interest to point out that, by contrast, while alkylation of 5-methylresorcinol take place mostly at the C-4 position,[5] alkylation of 5-(1,1-dimethylheptyl)-resorcinols take place preferentially at the C-2 position because of steric effect.

When the reactions delineated in Table 1 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.[2a]

All unknown reaction products described in the Table 1 are identified by comparison of their physical data (MS, ^{1}H-NMR and IR)

In conclusion we have developed a simple and convenient procedure for preparing the alkylation of 5-(1,1-dimethylheptyl)-resorcinols from 1-methyl-2-cyclohexen-1-ol and resorcinols. The present synthesis has led to the desired products in good to excellent yields.

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