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Boron Trifluoride Etherate on Alumina-Modified Lewis Acid Reagent(III): Synthesis of 5-Alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol Derivatives

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Abstract □ 5-Alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol derivatives are readily prepared by boron trifluoride-on-alumina-catalyzed formation of 5-alkylresorcinols with 1-thioxolanyl-2-cyclohexenol; their formation depends on the nature of the alkylgroup. The yield is the highest with 5-(1,1-dimethylheptyl)-resorcinol. The one with 5-pentylresorcinol is higher than 5-methylresorcinol and resorcinol apparently because of steric effects. The yields of the products increases; **3a** (10%), **3b** (20%), **3c** (48%) and **3d** (77%).

Keywords □ 5-Alkylresorcinols, 1-thioxolanyl-2-cyclohexenol.

Recently we reported that simplitied cannabidiol derivatives lacking the isopropenyl (nor-isopropenyl CBSs) were slightly more potent than cannabidiol (CBD). A nor-isopropenyl CBD having a 1-acetoxy group had potent antiaudiogenic seizure activity and a favorable protective index.

Structure-anticonvulsant activity relationship studies on this system revealed that 5-alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol derivatives as a key intermadiate are essential for biological activity[1].

The alkylation of 5-alkylresorcinols with monoterpenoid allyic alcohols was performed in BF_3-etherate on alumina reagent or in the absence of alumina. Both inter and intra-molecular Friedel-Crafts alkylations were observed to proceed in moderate yields[2].

We here report a much more efficient preparation of the desired 5-alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol derivatives by the use of boron trifluoride etherate-on-alumina as the catalyst.

EXPERIMENTAL

UV spectra were recorded on a Varian techtron 635 UV-VIS spectrophotometer. IR spectra were recorded on a Perkin-Elmer 457 grating infrared spectrophotometer. H-NMR spectra were obtained on a Bruker WH-200, and WH-300 pulsed FT spectrometer. Chemical shifts are given in parts per million downfield from Me_4Si internal standard. Mass spectra were recorded on a Varian Mat. CH-5 mass spectromether. Chromatography; Analytical TLC were performed by using commercially available silica plates. Polygram sil N-HR/VU_{254} and the plates were visualized with fast blue phenol reagent or by charring with a solution of MeOH : H_2SO_4 (1 : 1). Medium pressure liquid chromatography was perfomed by ALTEX glass column, 1 meter long, internal diamether 9 mm using FMI pump and silica gel 60 (230-400 mesh) purchased from Merck, collective fraction with LKB 2070 or LKB 7000 fraction collectors of 2-10 ml/min.

Preparation of 1-thioxolanyl-2-cyclohexenol, 1[5,6]

To a solution of 1,3-dithiane (6.0 g, 50 mmol) dissolved in dry THF (100 ml) at −78℃ under nitrogen, *n*-butyl-lithium (55 mmol, 8.6 ml of a solution in hexane) is added dropwise. After 1 hr at −25℃ to −15℃, 2-cyclohexenone (4.8 g, 50 mmol) in THF-hexane (1 : 1) is added dropwise at −78℃. After 1-5 min the reaction mixture is quenched by the addition of saturated aquous ammonium chloride (250 ml), washed with two times with ether, once with a saturated salt solution, and dried with magnesium sulfate. After filtration and removal of the volatiles, the product is isolated on a medium pressure L.

C. Elution with ethyl acetate to petroleum ether (20 : 80) give **1** (9.88 g, 92%), an oil, NMR δ ($CDCl_3$), 1.72-2.11 (8H, m, $(CH_2)_3$, of the cyclohexene ring and CH_2CH_2S), 2.23 (1H, s, SCHS), 5.82 (1H, brd, J=10 Hz, C-2H), 5.91 (d, J=3 Hz), 6.09 (brs), (1H, C-3H); MS (20°), *m/e* 216 (M^+, 2), 1.88 (3), 169 (1), 119 (100); IR (film), 3440, 2930, 1424 cm^{-1}.

Preparation of 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-resorcinol, 3a

BF_3-etherate (1.2 m*l*) was added under nitrogen to a stirred suspension of basic aluminum oxide (Woelm, grade I) (8 g) in dry dichloromethane (80 m*l*). The mixture was stirred for 15 min at room temperature and then boiled for 1 min. Compound **1** (691 mg, 3.2 mmol) and resorcinol (440 mg, 4 mmol) in dichloromethane (20 m*l*) were added to the boiling suspension by syringe and the reaction was quenched within 10 sec with 10% aqueous solution of sodium bicarbonate (10 m*l*). Ether (200 m*l*) and an additional portion of the above sodium bicarbonate solution (200 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure L. C. Elution with ethyl acetate to petroleum ether (5 : 95) **3a** (96 mg, 10%), an oil, UV_{max} (EtOH), 275 (ε 1770), 280 nm (1810); NMR δ ($CDCl_3$), 2.88 (4H, brt, J=4 Hz, $2SCH_2$), 3.79-4.28 (1H, m, C-3H), 4.59 (1H, s, SCHS), 5.47 (1H, brs, C-2H), 6.12 (1H, d, J=9 Hz, arom H), 6.37 (1H, d, J=8 Hz, arom H), 6.82 (1H, q, J=7 Hz, arom H); MS (20°), *m/e* 308 (M^+, 100), 270 (23), 250 (30), 119 (38); IR (film), 3460, 1590, 1465, 1386 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-resorcinol diacetate (70 mg, 62%), an oil, UV_{max} (EtOH), 209 (ε 27830), 250 sh nm (1180); NMR δ ($CDCl_3$), 2.29 (2×3H, s, $COCH_3$), 2.90 (4H, q, J=4 Hz, $2SCH_2$), 3.56 (1H, br, C-3H), 4.63 (1H, s, SCHS), 5.76 (1H, brs, C-2H), 6.82 (1H, d, J=3 Hz, atom H), 7.04 (1H, d, J=9 Hz, arom H), 7.30 (1H, d, J=10 Hz, arom H); MS (20°), *m/e* 392 (M^+, 100), 349 (26), 201 (14); IR (film), 2930, 1610, 1590 cm^{-1}.

Preparation of 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5'-methylresorcinol, 3b

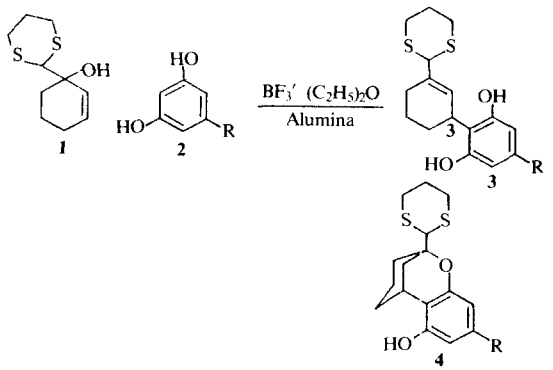
Under the conditions of procedure **3a** compound **3b** was obtained in 20% (153 mg) yield, m.p. 73-75℃; UV_{max} (EtOH), 273 (ε 1380), 280 nm (1430); NMR δ ($CDCl_3$), 2.19 (3H, s, CH_3), 2.89 (4H, t, J=4 Hz, $2SCH_2$), 4.07 (1H, br, C-3H), 4.59 (1H, s, SCHS), 5.52 (1H, brs, C-2H), 6.23 (2H, s, arom H); MS (170°), *m/e* 322 (M^+, 100), 270 (17), 216 (45); IR (KBr), 3460, 1625, 1585, 1425 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5'-methylresorcinol diacetate (98 mg, 65%) yield, an oil, NMR δ ($CDCl_3$), 2.29 (2×3H, s, $COCH_3$), 2.88 (4H, t, J=Hz, $2SCH_2$), 3.48 (1H, brd, J=7 Hz, C-3H), 4.64 (1H, brs, SCHS), 5.77 (1H, br, C-2H), 6.74 (2H, brs, arom H); MS (20°), *m/e* 406 (M^+, 100), 362 (24); IR (film), 2933, 1768, 1625, 1585 cm^{-1}.

Preparation of 2'-(1-(1,3-dithian-2-yl)-cyclohene-3-yl)-5'-pentylresorcinol, 3c

BF_3-etherate (0.6 m*l*) was added under nitrogen to a stirred suspension of basic aluminum oxide (woelm, grade I) (6 g) in dry dichloromethane (60 m*l*). Compound **1** (1.944 g, 9 mmol) and olivetol (540 mg, 3.0 mmol) in dichloromethane (5 m*l*) were added to the solution *via* syringe. After 5 min, the reaction mixture was worked up. Ether (100 m*l*) and 10% sodium bicarbonate solution (200 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure L. C. Elution with ethyl acetate to petroleum (2.5 : 97.5) gave **3c** (550 mg, 48%), an oil, UV_{max} (EtOH), 273 (ε 1030), 281 nm (1000); NMR δ ($CDCl_3$), 0.88 (3H, t, CH_3), 2.43 (2H, t, benzylic H), 2.89 (4H, t, J=4 Hz, $2SCH_2$), 3.99 (1H, br, C-3H), 4.59 (1H, brs, SCHS), 5.44 (1H, brs, C-2H), 6.23 (2H, s, arom H); MS (20°), *m/e* (M^+, 9), 378 (11), 270 (28), 205 (100); IR (film), 3460, 1623, 1580, 1435 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 2'-(1-(1,3-dithian-2-yl)-cyclohene-3-yl)-5'-pentylresorcinol diacetate (370 mg, 61%) yield, an oil, NMR δ ($CDCl_3$), 0.87 (3H, t, CH_3), 2.28 (2×3H, s, $COCH_3$), 2.52 (2H, t, benzylic H), 2.86 (4H, t, J=4 Hz, $2SCH_2$), 4.62 (1H, brs, SCHS), 5.72 (1H, brs, C-2H), 6.73 (2H, s, arom H); MS (200°), *m/e* 461 (M^+, 100, 429 (32), 271 (11); IR (film), 2933, 1754, 1622, 1596 cm^{-1}.

Preparation of 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5'-(1,1-dimethylheptyl)-resorcinol, 3d

Under the conditions of procedure **3c** compound **3d** was obtained in 77% (1.01 g) yield, an oil, UV_{max} (EtOH), 274 (ε 810), 279 nm (780); NMR δ ($CDCl_3$),



R=H, CH_3, C_5H_{11}, $C(CH_3)_2C_6H_{13}$

0.85 (3H, t, CH_3), 1.20 (2×3H, brs, CH_3), 2.90 (4H, t, J=4 Hz, $2SCH_2$), 3.96 (1H, br, C-3H), 4.59 (1H, brs, SCHS), 5.38 (1H, brs, C-2H), 6.35 (2H, s, arom H); MS (180°), *m/e* 434 (M^+, 100), 360 (20), 243 (33); IR (film), 3360, 1625, 1580, 1420 cm^{-1}. Acetylation with acetic anhydride in pyridine led to 2'-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5-(1,1-dimethylheptyl)-resorcinol diacetate (874 mg, 67%) yield, an oil, UV_{max} (EtOH), 280 sh (ε 510), 317 nm (1570); NMR δ ($CDCl_3$), 0.84 (3H, t, CH_3), 1.23 (2×3H, brs, CH_3), 2.30 (2×3H, s, $COCH_3$), 2.87 (4H, t, J=4 Hz, $2SCH_2$), 3.40 (1H, br, C-3H), 4.69 (1H, brs, SCHS), 5.80 (1H, br, C-2H), 6.84 (2H, s, arom H); MS (180°, *m/e* 518 (M^+, 100), 433 (14); IR (film), 2930, 1765, 1625, 1416 cm^{-1}.

RESULTS AND DISCUSSION

We report that when BF_3-etherate on alumina is used as condensing agent the condensation between 1-thioxolanyl-2-cyclohexenol **1** and 5-alkyl-resorcinols **2** proceeds smoothly without further cyclization. In the sulfur diphenol compounds **3** the olefinic proton appears as a broad singlet at 5.38-5.52 ppm region, however, in the sulfur analogs of the cyclised products **4** no double bond is observed[3]. It is of interest to compare the chemical shift of the C-3 allylic benzylic proton in the noncyclized series **3** with the corresponding C-6 proton in the cyclized compounds **4**. The C-3 proton in the former is deshieled as compared to the C-6 one in the latter.

In the noncyclized products **3**, the aromatic ring, which can rotate freely, is most probably in the same plane as the C-3 hydrogen, which is therefore deshielded[4].

In the above reaction intramolecular cyclizations were not observed by the addition of one of the hydroxyxl groups to a suitably placed double bond. This is undoubtedly due to the "mildness" of 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.

In these series we observed a definite qualitative correlation between the size of the side chain of the reaction 5-alkylresorcinol and the position of the alkylation by the 1-thioxolayl-2-cyclohexenol. Their formation depends on the nature of the alkyl group.

The yield is the highest with 5-(1,1-dimethylheptyl)-resorcinol. The one with 5-pentylresorcinol is higher than with 5-methylresorcinol apparently because of steric effects. The structures of the products were deduced from the analytical and spectroscopic data.

We can conclude that boron trifluoride etherate is a superior catalyst for effecting rapid formation of 5-alkyl-3-(1-thioxolanyl-cyclohexenyl)-resorcinol derivatives in moderate yields using ethyl acetate-petroleum ether (b.p. 60-80°) as the solvent.

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