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Boron Trifluoride Etherate-Catalyzed Formation of Resorcinols: Synthesis of 3,4,5,6-Tetrahydro-7-hydroxy-2 methyl-9-alkyl-2,6-methano-2H-1-benzoxocins

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Abstract □3,4,5,6-Tetrahydro-7-hydroxy-2-methyl-9-alkyl-2,6-methano-2H-1-benzoxocins are readily prepared by boron trifluoride etherate-catalyzed cyclization of resorcinols with cyclic allylic alcohol.

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

Benzoxocin derivatives are of considerable inherent interest and synthetic utility because of their interesting biological activities[1,2].

Dzurilla *et al*[3,4] have reported that boron trifluoride is a good catalyst for cyclization of *O*-alkyl-N-(3-phenylpropenoyl)-thiocarbamates.

Recently, a series of work for the synthesis of 3,4,5,6-tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-9-alkyl-2,6-methano-2H-1-benzoxocins has been initiated in our laboratory[5].

We here report a much more efficient preparation of the desired resorcinol derivatives by the use of boron trifluoride etherate as a catalyst[6].

EXPERIMENTAL

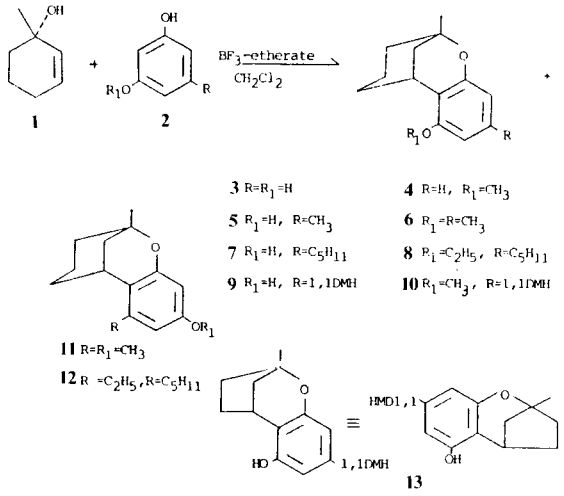
IR spectra were recorded as thin film (for oils) and in Nujol mulls on a Perkin-Elmer 457 grating infrared spectromer. UV spectra were recorded on a Varian techtron 635 UV-VIS spectrometer. ^{1}H-NMR spectra were obtained on a Bruker WH-60 and WH-300 pulsed FT spectrometer. Chemical shifts are given in parts per million down Me_4Si as internal standard. Mass spectra were recorded on a LKB 2091 Gas chromatography-Mass spectrometer at 70 eV.

MP is uncorrected and was measured in closed capillaries in a Thomas-Hoover instrument. Chromatography: 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 with FMI pump on Merck Kieselgel 60, 230-240 mesh ASTM, with mixtures of ethylacetate and pertroleum ether (b.p 60-89). Microanalysis was done in house.

In a typical reaction a mixture of 1-methyl-2-cyclohexen-1-ol (1.0 mmole) **1** and 5-(1.1-dimethylheptyl)-resorcinol (1.0 mmole) **5** was added sufficient anhydrous dichloromethane. Then BF_3-etherate (0.2 m*l*) was added under nitrogen to the solution *via* syringe and the mixture was stirred for 5 min at room temperature, and was then worked up. The reaction product was purified by medium pressure liquid chromatography on a silica-gel-column (elution with 2 : 98, ethyl acetate to petroleum b.p 60-80℃).

Preparation of 3,4,5,6-tetrahydro-7-hydroxy-2-methyl-9-pentyl-2H-1-benzoxocin, 7

Under the conditions of general procedure we obtained **7** (165 mg, 60%), an oil, UV_{max} (EtOH), 274 (ε 1250), 281 nm (1240); NMR δ ($CDCl_3$), 0.88 (3H, t, CH_3), 1.34 (3H, s, CH_3), 2.46 (2H, t, benzylic H), 3.31 (1H, br, C-6H), 4.91 (1H, s, OH), 6.12 (1H,



Scheme 1

d, J=2.0 Hz, arom H), 6.27 (1H, brs, arom H); MS (20°), *m/e* 274 (M^+, 54), 218 (100); IR (film), 3350, 1616 cm^{-1}.

Preparation of compounds 8 and 12

Under the conditions of general procedure we obtained two tricyclic compounds. The first compound eluted was 3,4,5,6-tetrahydro-7-ethoxy-2-methyl-9-pentyl-2,6-methano-2H-1-benzoxocin **8** (175 mg, 58%), an oil, UV_{max} (EtOH), 274 (ε 2490), 280 nm (2200); NMR δ ($CDCl_3$), 0.87 (3H, t, CH_3), 1.31 (3H, t, CH_3), 1.72 (3H, d, J=3.0 Hzz, CH_3), 2.49 (2H, t, benzylic H), 3.37 (1H, br, C_6-H), 3.99 (2H, q, J=7.0 Hz, methylene H), 6.18 (1H, brs, arom H), 6.26 (1H, brs, arom H); MS (20°), *m/e* 302 (M^+, 89), 246 (100); IR (film) 2940, 1620 cm^{-1}. The second compound eluted was an isomer (12) (15 mg, 5%),

Table 1. 3,4,5,6-Tetrahydro-7-hydroxy-2-methyl-9-alkyl-2,6-methano-2H-1-benzoxocins

Product	3	4	5	6	7	8	9	10	11	12	13
Yield (%)	32	65	37	60	60	58	80	84	34	5	90
Ref.	8	8	2	2			8	8	2		8

1, 1 DMH indicates 1,1-dimethylheptyl

an oil, UV_{max} (EtOH), 278 sh (ε 3100), 285 nm (3240); NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 1.37 (3H, t, J=2.0 Hz, CH_3), 1.75 (3H, d, J=3.0 Hz, CH_3), 2.50 (1H, brd, J=4.0 Hz, benzylic H), 2.40 (1H, d, J=1.0 Hz, benzylic, H), 3.18 (1H, br, C-6H), 3.92 (2H, q, J=7.0 Hz, methylene H) 6.22 (H, d, J=3.0 Hz, arom H), 6.30 (1H, d, J=3.0 Hz, arom H); MS (20°), *m/e* 302 (M^+, 100); IR (film), 2930, 1588 cm^{-1}.

RESULTS AND DISCUSSION

When 1-methyl-2-cyclohexen-1-ol was condensed with resorcinol derivatives under the conditions of procedure above described, we obtained the expected products (**3**,**5**,**7** and **9**). In these series we observed a definite qualitative correlation between the size of the side chain of the reacting resorcinol and the position of the alkylation by the 1-methyl-2-cyclohexen-1-ol. The yield of the product increases; 32% **3**, 37% **5**, 60% **7** and 80% **9**. The yield is the highest with 5-(1,1-dimethylheptyl) resorcinol presumably because of steric effects. Their formation depends on the nature of the alkyl group. The strucutres of **3**, **5**, **7** and **9** were established on the basis of their molecular weight (mass spectra) and NMR spectra.

The above described condensation takes place also when monoalkyl ether resorcinol is blocked. However, in this case the side chain substitution pattern does not change the yields of the reactions (ca 60%) with the exception of 5-(1,1-dimethylheptyl)-resorcinol. When 5-(1,1-dimethylheptyl)-resorcinol participates in the reaction the corresponding isomer is not observed at all.

When the above described reactions are undertaken with BF_3-etherate the condensation reaction was followed by cyclization[7]. In the above reaction 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. The cyclohexane ring is expected to exist predominantly in a chair conformation[2].

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