Boron Trifluoride Etherate-Catalyzed Formation of 3,4,5,6-Tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-9-alkyl-2,6-methano-2H-1-benzoxocin Derivatives

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3,4,5,6-Tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-9-alkyl-2,6-methano-2H-1-benzoxocin derivatives are readily prepared by boron trifluoride etherate-catalyzed formation of 5-alkylresorcinols with 1-thioxolanyl-2-cyclohexenol. The yield is the highest with 5-(1,1-dimethylheptyl)resorcinol. The one with 5-pentylresorcinol is higher than with 5-methylresorcinol and resorcinol apparently because of steric effects. The yields of the product increase; 3a(7%), , 3b(22%), 3c(38%) and 3d(50%).

Introduction

The alkylation of orcinols was performed in BF₃-etherate on alumina reagent or in the absence of alumina. Both inter and intramolecular Friedel-Crafts alkylations were observed to proceed in moderate yields.[1]

Recently Dzurilla et al.[2,3] have reported that boron trifluoride is a good catalyst for cyclization of O-alkyl-N-(3-phenylpropenoyl) thiocarbamates.

We here report a much more efficient preparation of the desired Benzoxocin derivatives by the use of boron trifluoride etherate as the catalyst. The decision to synthesize these particular homologs bases on the known structure-activity relationship in the benzoxocin series.[4]

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. ¹H-NMR spectra were obtained on a Bruker WH-200, and WH-300 pulsed FT spectrometer. Chemical shifts are given in parts per million down field from Me₄Si internal standard. Mass spectra were recorded on a Varian Mat, CH-5 mass spectrometer. Chromatography; Analytical TLC were performed by using Commercially available silica plates. Polygram sil N-HR/UV₂₅₄ and the plates were visualized with fast blue phenol reagent or by charring with a solution of MeOH : H₂SO₄(1 : 1). Medium pressure liquid chromatography was performed by ALTEX glass column, 1 meter long, internal diameter 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 m*l*/min.

Preparation of 3,4,5,6-Tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-2,6-methano-2H-1-benzoxocin (3a). BF₃-etherate (1.5 m*l*) was dissolved in dry dichloromethane (100 m*l*) under nitrogen. The mixture was stirred for 5 min at room temperature and boiled for 1 min. 1-Thioxolanyl-2-cyclohexenol (1) (864 mg, 4.0 mmol) and resorcinol (2a) (550 mg, 5 mmol) in dichloromethane (20 m*l*) were added to the boiling suspension via syringe and the reaction mixture was

quenched within 10 sec with 10% aqueous solution of sodium bicarbonate (10 m*l*). Ether (150 m*l*) and an additional portion of the above sodium bicarbonate solution (250 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 ethylacetate to petroleum ether (5 : 95) gave (3a) (85 mg, 7%), an oil, NMR δ (CDCl₃), 2.94(4H, q, *J*=4.0 Hz, 2SCH₂), 4.00(1H, m, C-6H), 4.60(1H, s, SCHS), 5.40(1H, brs, OH), 6.24(1H, d, *J*=8.0 Hz, arom H), 6.39(1H, d, *J*=8.0 Hz, arom H), 6.90(1H, q, *J*=7.0 Hz, arom H); IR (neat), 3350, 1596, 1450 cm⁻¹. The product was acetylated in the usual way and the resulting oil was chromatographed on TLC platers (elunt 30% ethyl acetate in petroleum ether b.p. 60-80°) to yield 3,4,5,6-tetrahydro-7-acetoxy-2-(1,3-dithian-2-yl)-2,6-methano-2H-1-benzoxocin (4a) (59 mg, 62%), an oil, NMR δ (CDCl₃), 2.29(3H, s, COCH₃), 2.58-2.82(4H, m, 2SCH₂), 3.66(1H, m, C-6H), 4.75(1H, br, SCHS), 6.69(1H, d, *J*=1.5 Hz, arom H), 6.73 (1H, d, *J*=3.0 Hz, arom H), 7.2(1 H, q, *J*=9.0 Hz, arom H); MS(100°), m/e 350(M⁺, 100), 243 (56), 2.33(30), 201(74); IR(neat), 1763, 1597, 1500, 1450 cm⁻¹.

Preparation of 3,4,5,6-tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-9-methyl-2-,6-methano-2H-1-benzoxocin (3b). Under the conditions of procedure (3a) compound (3b) was obtained in 22% (282 mg) yield, an oil, UV max (EtOH), 275(ε 1910), 280 nm (1930); NMR δ (CDCl₃), 2.18(3H, t, CH₃), 2.92(4H, q, *J*=4.0 Hz, 2SCH₂), 4.00(1H, br, C-6H), 4.58(1H, brs, SCHS), 5.13(1H, br, OH), 6.13(1H, brs, arom H), 6.21(1H, brs, arom H); MS (20°), m/e 322(M⁺, 100), 270 (25), 214(36), 199(35); IR (neat), 3460, 1585, 1425 cm⁻¹.

Acetylation with acetic anhydride in pyridine led to 3,4,5,6-tetrahydro-7-acetoxy-2-(1,3-dithian-2-yl)-9-methyl-2,6-methano-2H-1-benzoxocin (4b) (176 mg, 68%), an oil, NMR δ (CDCl³), 1.19(3H, s, CH₃), 2.31(3H, s, COCH₃), 2.89(4H, q, *J*=4.0 Hz, 2SCH₂), 4.62(1H, brs, SCHS), 6.10(1H, brs, arom H), 6.37(1H, brs, arom H); MS (20°), m/e 364(M⁺, a), 236(29), 181(11), 161(100); IR (Nujol), 1745, 1580, 1439 cm⁻¹.
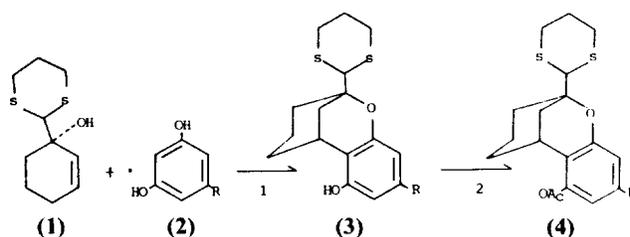
Preparation of 3,4,5,6-tetrahydro-7-hydroxy-2-(1,3-dithian-2-yl)-9-pentyl-2,6-methano-2H-1-benzoxocin (3c). BF₃ etherate (0.4 m*l*) was dissolved in dry dichloromethane (20 m*l*) under nitrogen. The mixture was stirred for 5 min at room temperature. Compound (1) (1296 mg,

6 mmol) and olivetol (360 mg, 2 mmol) were added to the solution via syringe. After 5 min, the reaction mixture was worked up, ether (50 m*l*) and 10% sodium bicarbonate solution (150 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The residue was separated by medium pressure L.C. Elution with ethylacetate to petroleum ether (2.5 : 97.5) gave (3c) (280 mg, 38 %), an oi, UV max (EtOH), 272(2520), 279(2570); NMR δ (CDCl₃), 0.88(3H, t, CH₃), 2.31(2H, t, benzylic H), 2.91(4H, q, *J*=4.0 Hz, 2SCH₂), 3.52(1H, s, SCHS), 6.12(1H, brs, arom H), 6.23(1H, brs, arom H); MS (150°), m/e 378(29), 272(58), 199(32); IR (neat), 330, 1585, 1430 cm⁻¹. Compound (3c) was actylated in the usual way and the resulting oil was chromatographed on TLC plates (eluent 25% ethyl acetate in petroleum ether b.p. 60-80°) to yield 3,4,5,6-tetrahydro-7-acetoxy-2-(1,3-dithian-2-yl)-9-pentyl-2,6-methano-2H-1-benzoxocin (4c) (60 mg, 60%), an oil, NMR δ (CDCl₃) 0.87(3H, t, CH₃), 2.29(3 H, s, COCH₃), 2.51(2H, t, benzylic H), 2.87(4H, brq, *J*=4.0 Hz, 2SCH₂), 4.56(1H, brs, SCHS), 6.73(2H, s, arom H); MS (220°), m/e 420(M⁺, 30), 376(20), 271(50), 119(110); IR (neat), 1765, 1575, 1425 cm⁻¹.

Preparation of 3,4,5,6-tetrahydro-7-acetoxy-2-(1,3-dithian-2-yl)-9-(1,1-dimethyl heptyl)-2,6-methano-2H-1-benzoxocin (3d). Under the conditions of procedure (3c) compound (3d) was obtained in 50% (215 mg) yield, an oil, NMR δ(CDCl₃), 0.89(3H, t, CH₃), 1.20(6H, s, CH₃), 2.90(4H, q, *J*=8.0 Hz, 2SCH₂), 3.46(1H, t, *J*=3.0 Hz, C-6H), 4.59(1H, s, SCHS), 5.24(1H, s, OH), 6.35(1H, sm, arom H), 6.66(1H, s, arom H). The product was acetylated in the usual way and the resulting oil was chromatographed on silica. Elution with 2.5% ethyl acetate in petroleum ether (b.p. 60-80°) gave 3,4,5,6-tetrahydro-7-acetoxy-2-(1,3-dithian-2-yl)-9-(1,1-dimethylheptyl)-2,6-methano-2H-1-benzoxocin (4d) (150 mg, 63%), an oil NMR δ (CDCl₃), 0.84(3H, t, CH₃), 1.24(6H, brs, CH₃), 2.32(3H, s, COCH₃), 2.78(4H, t, *J*=5.0 Hz, 2SCH₂), 4.59 (1H, s, SCHS), 6.77(1H, s, arom H), 6.82(1H, s, arom H); MS (180°), m/e 476(M⁺, 97), 475(100); IR (neat), 1766, 1625, 1416 cm⁻¹.

Results and Discussion

M. Dzurilla *et al.*[2,3] reported the preparation of 1,3-thiazin-2,4-diones in moderate yield by reaction of O-alkyl-N-(3-phenylpropenoyl)monothiocarbamates catalyzed by boron trifluoride. However, the reaction was slow and tedious. We here report that the condensation between 1-thioxolanyl-2-cyclohexenol (1) and 5-alkylresorcinols (2) proceeds smoothly without further cyclization when BF₃ etherate on alumina is used as a catalyst.[5] However, cyclizations do take place in the absence of alumina. In the sulfur diphenol compounds (5) the olefinic proton appears as a broad singlet at 5.38-5.52 ppm region,[5] however, in the sulfur analogs of the cyclised products (3) no double bond is observed.[6] It is of interest to compare the chemical shift of the C-3 allylic benzylic proton in the noncyclized series (5) with the corresponding C-6 proton in the cyclized compounds (3).[7,8] The C-3 proton in the former is deshielded as compared to the C-6 one in the latter. In the noncyclized products (5), the aromatic ring, which can rotate freely, is most probably in the same plane as the C-3 hydrogen, which is therefore deshielded.[7]

(1)   (2)   (3)   (4)

a) R=H	a) R=H	a) R=H
b) R=CH₃	b) R=CH₃	b) R=CH₃
c) R=C₅H₁₁	c) R=C₅H₁₁	c) R=C₅H₁₁
d) R=C(CH₃)₂C₆H₁₃	d) R=C(CH₃)₂C₆H₁₃	d) R=C(CH₃)₂C₆H₁₃

1) BF₃-etherater, CH₂Cl₂
2) acetic anhydride, pyridine

(5)
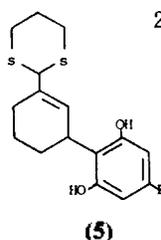
As expected, the aromatic protons in the cyclized compounds (3) are not magnetically equivalent. In the above reaction a benzoxocin ring is formed. BF₃-etherate in methylenechloride initiates the ring closure which probably proceeds by the mechanism indicated through the hypothetical intermediate cation. The cyclohexane ring is expected to exist predominantly in a chair conformation.[9a] 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-thioxolanyl-2-cyclohexenol. Their formation depends on the nature of the alkyl group. The yield is highest with 5-(1,1-dimethylheptyl) resorcinol.[9b] The one with 5-pentylrosorcinol is higher than with 5-methylresorcinol and resorcinol apparently because of steric effects. The yields of the products incresses: 3a (7%), 3b(22%), 3c (38)and 3b(50%).

References

1. S. H. Baek, *Bull. Korean Chem. Soc.*, **9**, 71 (1988).
2. M. Dzurilla, P. Kutschy, D. Koscik, and S. Toma, *Collect. Czech. Chem. Commun.*, **55**, 710 (1990).
3. M. Dzurilla, P. Kutschy, and P. Kristian, *Synthesis*, 933 (1985).
4. S. Houry, R. Mechoulam, P. J. Fowler, E. Macko, and B. Loev, *J. Med. Chem.*, **17**, 287 (1974).
5. S. H. Baek, Boron trifluoride etherate on alumina-A modified Lewis acid reagent (III). Synthesis of 5-alkyl-3-(1-thioxolanyl-cyclohexenyl) resorcinol derivatives, synthesis, in manuscript.
6. R. Adams and coworkors, *J. Am. Chem. Soc.*, **62**, 2566 (1940).

Methanethiolate on Silver Surface

Bull. Korean Chem. Soc., Vol. 12, No. 6, 1991 635

7. Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, 93, 217 (1972).

8. B. Cardillo, L. Merlini, and S. Servi, *Tetrahedron Lett.*, 945 (1972).

9. (a) R. K. Razdan, H. C. Dalzell, nd G. R. Handrick, *J. Am. Chem. Soc.*, 96, 5860 (1974); (b) S. J. Dominiani, C. W. Ryan, and C. N. Dearmitt, *J. Org. Chem.*, 42, 344 (1977).

The Electronic Structure of Methanethiol Adsorbed on Silver Surface: An Extended Hückel Study

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The adsorption of methanethiol on a Ag(100) surface has been studied with Extended Hückel calculation in the cluster approximation of the substrate. Since it has been known that methanethiol is chemisorbed dissociatively on silver surface by rupture of S-H bond, the methanethiolate radical is taken as adsorbate. Of the various adsorption sites, the 4-fold hollow site is preferred. The methanethiolate radical is mainly adsorbed *via* its $2e$ orbital. The charge transfer from metal to this level leads to the C-S bond weakening, which is consistent with the red shift of C-S stretching mode in surface enhanced Raman (SER) spectrum.

Introduction

Understanding the interactions between thiols and various metals has been of a great concern in catalytic chemistry.[1-15] The thiol adsorption on noble metals has been a subject of much investigation since thiols show the surface-enhanced Raman scattering (SERS) phenomena. Among the various noble metals, silver is extensively studied.[1-8]

We carried out Extended Hückel (EH) calculation on some aliphatic thiols-methanethiol, ethanethiol, 1-propanethiol, and 1-buthanethiol- and found that they have similar energy and nature of HOMO, which is considered to play a central role in bonding to metal surfaces. Details are given in the Appendix. Thus the survey of the adsorption of methanethiol, which is the simplest thiol, on silver surface is motivated to understand the nature of the adsorption of thiol compounds on silver surface.

The adsorption of methanethiol on the transition metal surfaces has been a subject for numerous experimental investigations. The SERS experiment of methanethiol (CH_3SH) adsorbed on silver showed that the adsorbate is chemisorbed dissociatively on metal surface by rupture of its S-H bond.[1-7] From the high-resolution electron energy loss (HREELS) and near-edge X-ray fine structure (NEXAFS) spectrum, Koestner found that the dehydrogenation of the adsorbate on a Pt(111) surface results in formation (CH_3S) and that the thiomethoxy is adsorbed with a highly tilted S-C bond (45± 10°).[9] The dissociative adsorption mechanism was confirmed from the EELS and thermal desorption (TDS) experiments on a Cu(100) surface.[10] Angle resolved ultraviolet photoelectron spectroscopy (ARUPS) and NEXAFS revealed that the C-S bond of CH_3S is tilted about 30° from the surface normal on a Cu(111) surface.[11]

In present EH calculation for the methanethiol on silver surface, the experimental results described above are used in fixing the adsorption geometry.

We use a cluster model to represent metal surface. Since the chemisorption is regarded as a local phnomenon, *i.e.*, an adsorbate is essentially coupled to only a small number of neighbouring metal atoms, our cluster approach is logically reasonable.[15,16] Moreover, since the SERS phenomena has been known to occur on the rough suface[17-19] or the colloid of a finite dimension,[1-8] the cluster model calculation is adequate to describe the chemistry of the SERS properties than the band calculation. But the results using the cluster model do not seem to converge rapidly with its size increasing and we take as large silver clusters as possible.[15,16]

In the present work, we concentrate on a Ag(100) plane. However, some results on the (110) and (111) planes are presented. Since the higher Miller planes can be described by the combination of the simple Miller planes, this work can be generalized, with some modification, to the higher Miller indices. Although the EH formalism is not very quantitative in nature, it still retains its computational simplicity, ease of interpretation of result, and reasonable computationl time for the calculations on large molecules.

We carry out the fragment orbital (FMO) analysis to see the change of MO of adsorbate due to adsorption. In the FMO analysis, as the basis of the composite system (adsorbate-substrate), AO of each atom is transformed into MO of each fragment (adsorbate and substrate before adsorption). The fragment orbitals serve as the basis of the adsorbate-substrate system.

We also apply consistently the language and formalism of simple perturbation theory, in particular the second-order expression for the interaction of two levels:[20]

$$\Delta E = \frac{|H_{ij}|^2}{E_i^\circ - E_j^\circ}$$

Computational Details

We model the silver metal substrate by a cluster of three layers of atoms. The three layer model has been shown to