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Tetrahydrofuran, Tetrahydropyran and Oxepane Formation by Cobaloxime π -Cation Cyclizations

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Abstract. Studies are reported on the cyclization of $(\omega$ -hydroxy- β -hydroxyalkyl)cobaloximes (1, 2 and 3) to form 5, 6 and 7-membered ring cyclic ethers (4, 5 and 6). Reversible cyclization and eventual irreversible alkene decomplexation (to form 7, 8 and 9) varied as a function of ring size. The practical consequence is that cyclizations to form 5 and 6 membered rings are feasible whereas formation of a 7 membered ring is not. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Cobalt and compounds; Carbonium ions, Cyclization, Ethers

New and improved methods for the synthesis of 5-, 6-, 7-, 8- and 9-membered ring cyclic ethers have been developed in studies on the synthesis of polyether natural products [1]. In this paper we report studies on a new approach to cyclic ether formation by acid-catalyzed cyclizations of $(\omega$ -hydroxy- β -hydroxyalkyl)cobaloximes as shown in Scheme 1.



We recently reported that treatment of 1 with mild acid (pH 6.0-6.8/H₂O:CH₃OH; 10 min, room temp) followed by filtration through silica gel produced tetrahydrofuran 4 as a slightly air and light sensitive orange powder in 70% isolated yield [2]. The cyclization of 1 to 4 was regiospecific, as shown, and was stereospecific with complete retention of configuration.

To examine the formation of a tetrahydropyran by the same method, racemic cobaloxime 11 was prepared from racemic 10 [3] as shown in Scheme 2 [4]. Treatment of 11 with K_2CO_3 (0.5 equiv) in CH₃OH at room temp for 4-5 h formed 2 in situ. Treatment of the solution of 2 with pyridinium *p*-toluenesulfonate (PPTS; 2 equiv) for 20 min followed by filtration through silica gel provided tetrahydropyran 5 as a slightly air and light sensitive orange solid in 69% isolated yield. When this reaction was carried out in an NMR tube in CD₃OD, ¹H NMR analysis showed that the reaction went to completion immediately upon addition of PPTS. The formation of 5 was regiospecific as shown.

Attempts to perform the same type of cyclization on cobaloxime 3 [5] to form 6 failed (Scheme 3). Despite several attempts to isolate 6, only low yields of impure 6 were obtained.

0040-4039/98/\$19.00 © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)00601-7 When this reaction was carried out in an NMR tube in CDCl₃ using PPTS (2 equiv), ¹H NMR analysis showed that 6 was formed rapidly but alkene 9 was the major final product.



that there are significant differences in the stabilities of 4, 5 and 6. Compounds 4, 5 and 6 were prepared as shown in Scheme 4. Acid catalyzed conversions



of 4, 5 and 6 to 7, 8 and 9 (2 equiv PPTS/CDCl₃) were studied by ¹H NMR. Clean conversions of cobaloximes to alkenes were observed. The approximate rates of each reaction are as follows: cyclic cobaloxime \rightarrow alkene (approximate half life in hours), $4 \rightarrow 7$ (30 h), $5 \rightarrow 8$ (11 h), $6 \rightarrow 9$ (2-4 h). It is unclear why oxepane cobaloxime 6 is so labile compared to tetrahydrofuran cobaloxime 4 and tetrahydropyran cobaloxime 5.

In summary, these exploratory studies indicate that cyclization of $(\omega$ -hydroxy- β -hydroxyalkyl)cobaloximes may be a useful new method for the regio- and stereospecific formation of tetrahydrofurans and tetrahydropyrans but not for the formation of oxepanes.

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References and Notes

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- [3] Compound 10 was prepared from racemic 1,2,6-hexanetriol as follows: (a) acetone, p-TsOH (76%). (b) Ac₂O, DMAP, Py, Et₂O (90%). (c) MeOH/HCl, 24 h (37%).
- [4] All new compounds were characterized by ¹H NMR, ¹³C NMR, IR and HRMS.
- [5] Racemic 12 was prepared from 1,6-hexanediol as follows: (a) (i) NaH/THF (ii) 1 equiv TBDMSCl (63%).
 (b) oxalyl chloride, DMSO, Et₃N/CH₂Cl₂ (92%). (c) (i) (O-*i*-Pr)Me₂SiCH₂MgCl/THF (ii) KF, KHCO₃, H₂O₂, MeOH/THF (60%). (d) (MeO)₂CMe₂, CH₂Cl₂, PPTS (93%). (e) Bu₄NF, THF (83%). (f) Ac₂O, Py, DMAP/Et₂O (91%). (g) H⁺ (various conditions; ~50%).