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

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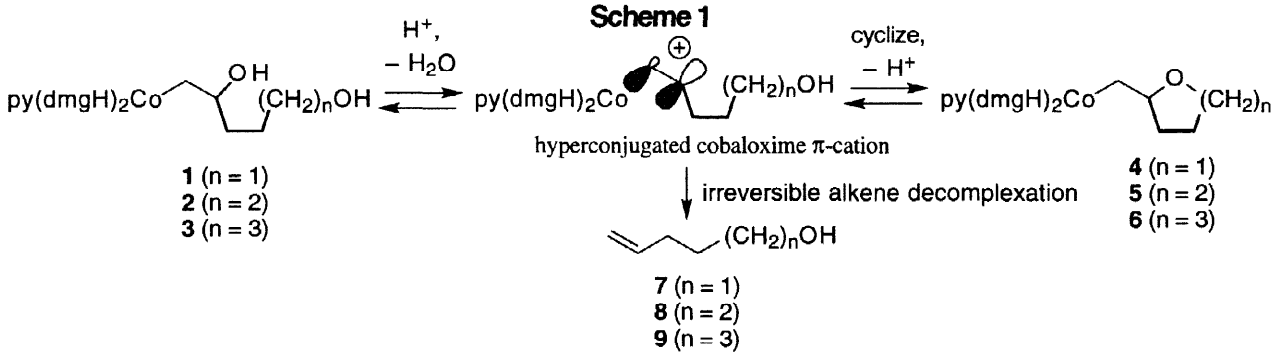
Abstract. Studies are reported on the cyclization of (ω-hydroxy-β-hydroxyalkyl)cobaloximes (**1**, **2** and **3**) to form 5, 6 and 7-membered ring cyclic ethers (**4**, **5** and **6**). Reversible cyclization and eventual irreversible alkene decomplexation (to form **7**, **8** and **9**) varied as 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.

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 (ω-hydroxy-β-hydroxyalkyl)cobaloximes as shown in Scheme 1.

Scheme 1



We recently reported that treatment of **1** with mild acid (pH 6.0-6.8/H_2O:CH_3OH; 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 CH_3OH 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 CD_3OD, ^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.

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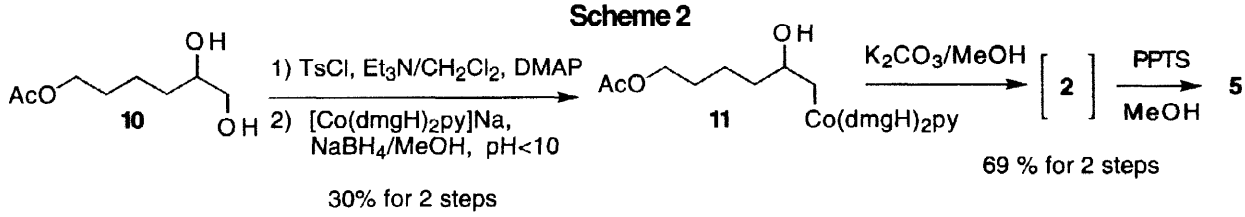
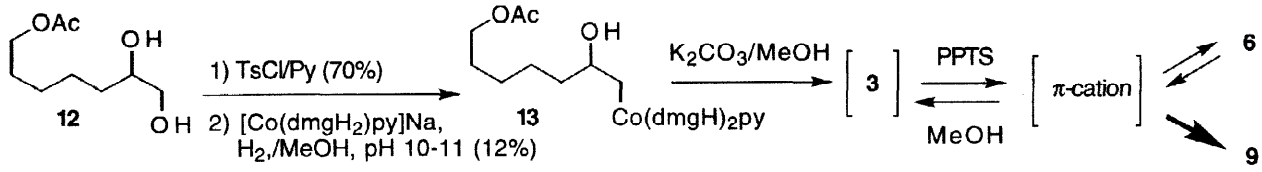
When this reaction was carried out in an NMR tube in $CDCl_3$ using PPTS (2 equiv), ^1H NMR analysis showed that **6** was formed rapidly but alkene **9** was the major final product.

Scheme 2

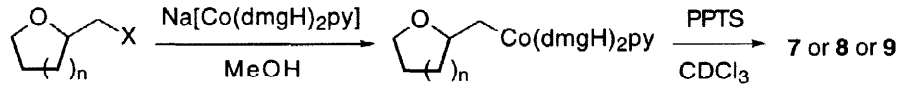


Scheme 3



These results indicate 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/$CDCl_3$) were studied by ^1H NMR. Clean conversions of cobaloximes to alkenes were observed. The approximate rates of each reaction are as follows: cyclic cobaloxime → alkene (approximate half life in hours), **4** → **7** (30 h), **5** → **8** (11 h), **6** → **9** (2-4 h). It is unclear why oxepane cobaloxime **6** is so labile compared to tetrahydrofuran cobaloxime **4** and tetrahydropyran cobaloxime **5**.

Scheme 4



14 (n = 1, X = Br)
15 (n = 2, X = Br)
16 (n = 3, X = I)

4 (n = 1)
5 (n = 2)
6 (n = 3)

In summary, these exploratory studies indicate that cyclization of (ω-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

[1] Useful (but not comprehensive) leading references: (a) Pietra, F. *Nat. Prod. Reports* **1997**, 453-464. (b) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499-7504. (c) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483-7498. (d) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446-2452. (e) Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 589-607. (f) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953-1980. (g) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Reports* **1995**, 165-181. (h) Faulkner, D. J. *Nat. Prod. Reports* **1995**, 223-269.

[2] Grubb, L. M.; Branchaud, B. P. *J. Org. Chem.* **1997**, *62*, 242-243.

[3] Compound **10** was prepared from racemic 1,2,6-hexanetriol as follows: (a) acetone, *p*-TsOH (76%). (b) Ac_2O, DMAP, Py, Et_2O (90%). (c) MeOH/HCl, 24 h (37%).

[4] All new compounds were characterized by ^1H NMR, ^{13}C 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, Et_3N/CH_2Cl_2 (92%). (c) (i) (O-*i*-Pr)Me_2SiCH_2MgCl/THF (ii) KF, $KHCO_3$, H_2O_2, MeOH/THF (60%). (d) $(MeO)_2CMe_2$, CH_2Cl_2, PPTS (93%). (e) Bu_4NF, THF (83%). (f) Ac_2O, Py, DMAP/Et_2O (91%). (g) H^+ (various conditions; ~50%).