Tetrahedron Letters,Vol.30,No.49,pp 6797-6800,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STRAINED OXIRANES FROM CIS-DIOLS

Eduardo Palomino[1]*, A. Paul Schaap and Mary Jane Heeg
Department of Chemistry, Wayne State University, Detroit, MI 48201

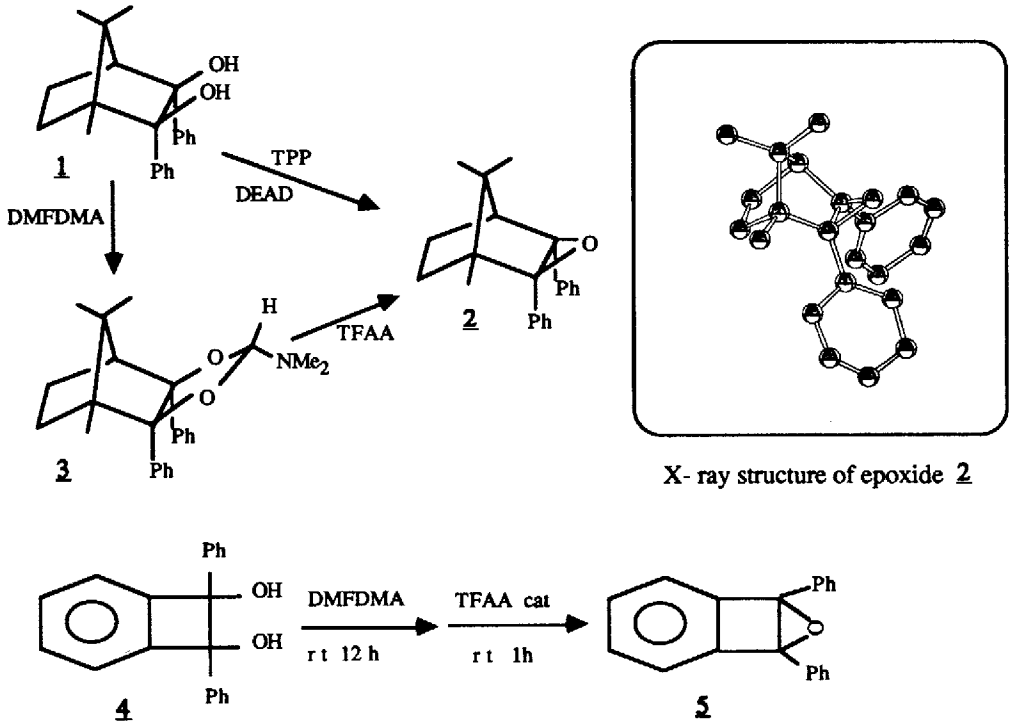
Summary: Cis-diols of some strained molecules are converted to epoxides without inversion of configuration by the use of the redox system triphenylphosphine : diethylazodicarboxylate, or by treatment of their dimethylaminodioxolane derivatives with trifluoroacetic anhydride as catalyst.

In 1974 Mitsunobu[2] and later Mengel[3] reported the preparation of a cyclic phosphorane by the reaction of a furanosyl derivative of adenine containing cis hydroxyl groups with a mixture of triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD). The reaction of the isomeric nucleoside containing trans hydroxyl groups gave, under the same conditions, a high yield of an epoxide. The use of the redox-condensation system DEAD : TPP is now well established.[2,4] The intramolecular dehydration of glycols to form epoxides under the Mitsunobu conditions has been recognized to proceed through an SN2 mechanism that requires trans-diols.

1,2-Diols have been used with success as intermediates in oxirane and alkene synthesis.[5] In these methodologies a five-membered ring intermediate is involved, the fragmentation of which, in a concerted or non-concerted fashion, gives the oxide or unsaturated compound, respectively. The 1,2 diols can be converted to the orthoformates or, preferentially, to the 2-dimethylamino-1,3-dioxolanes that are then treated with acetic anhydride at high temperature to form alkenes.[6] When the dimethylaminodioxolanes are heated directly, a fragmentation occurs with the formation of DMF and epoxides with a net inversion of configuration. The mechanism of the latter transformation involves heterolytic cleavage of the carbon-oxygen bond of the dioxolane with further backside attack by the nucleophilic oxygen.[7] Thus, meso-hydrobenzoin afforded trans stilbene oxide in 73% yield whereas d,l-hydrobenzoin was unreactive after 5 days at 102°C.

In our syntheses of oxiranes for sensitized photooxygenation studies, we have found that under conditions of skeletal strain, aromatic substituted cis-diols are transformed efficiently into epoxides without inversion of configuration. We have named this special case of conversion, unreported in the literature, the *syn* - Mitsunobu reaction. Second, via the fragmentation of the dimethylaminodioxolanes of cis-diols catalyzed by trifluoroacetic anhydride (TFAA). The two methodologies are depicted in Fig 1 for two representative examples: the diphenyl diol (1) bearing the bornane skeleton and the diphenyl benzocyclo butanediol (4), demostrating the mildness of the second procedure.

Fig 1

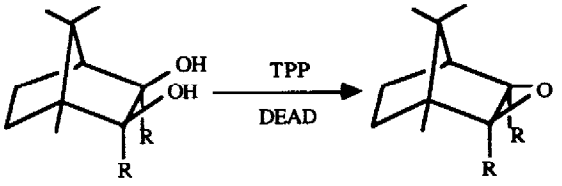


To a solution of diol **1**[8],(1.00g, 3.1 mmol) and TPP (2.00g, 7.7 mmol) in 20 ml of dry DMF were added dropwise 1.34 g (7.7mmol) of DEAD dissolved in 5 ml of DMF. After stirring for 12 h. the mixture was extracted with hexane, the hexane extracts were washed twice with water and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from ethanol afforded exo-epoxide **2**[9] in 74% yield . The stereochemistry of **2** was confirmed by X-ray crystallography (Fig 1).

Epoxide **2** was also obtained via the fragmentation of the dimethylaminodioxolane **3** (Fig 1). A dolution of diol **1** (1.00g, 3.1 mmol) in 10 ml of dimethylformamide dimethyl acetal (DMFDMA) was stirred at 60°C until no starting material was detected by TLC (ca. 1h.). After removal of the excess of reagent under vacuum, the oily residue was stirred in Na_2 with 0.1 ml (ca. 0.4 mmol) of TFAA for 1 h. Removal of the solvent under vacuum and recrystallization from ethanol afforded 98% of epoxide **2** with no traces of olefin. Following the same methodology, the colorless epoxide **5** (mp 169-70°C dec.) was prepared in 95% yield from the dimethylaminodioxolane of diol **4**[10] and TFAA (Fig 1). Epoxide **5** is stable at room temperature but rearranges irreversibly to the known yellow 1,3-diphenylisobenzofuran by heating or upon exposure to UV light.

Both methodologies show as common feature the fragmentation of a five-membered ring intermediate without inversion of configuration, a fact that suggests the involvement of stabilized carbonium ions in a somewhat similar fashion. To gain some insight into these mechanisms, the aromatic substituents were modified or replaced as shown in Table I for the syn-Mitsunobu reaction. The results seem to indicate that 1) aromatic disubstitution is required in the process and 2) electron-donating groups favor the conversion of cis diols to epoxides, but electron-withdrawers have a negative effect on the transformation.

Table 1



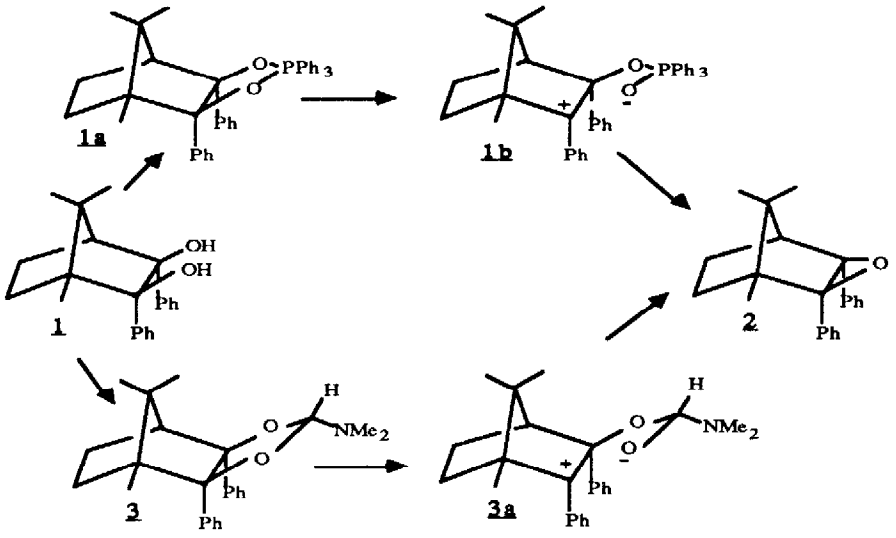
R	R	Yield epoxide (%)
Ph	Ph	74
p-$MeOC_6H_4$	p-$MeOC_6H_4$	70
m-$CF_3C_6H_4$	p-$MeOC_6H_4$	—
H	1-Naph.	—

Similar results were obtained for the fragmentation of the dimetylaminodioxolane derivatives of the diols. The influence of strain in the reaction was evidenced by the failure of both methodologies to effect the transformation of aromatic non-cyclis diols like tetraphenyl ethanediol. The mechanisms that encompass with the above observations are shown in Fig. 2.

The intermediacy of a phosphorane **1a** is assumed based on the observations of Mitsunobu[2] and Mengel.[3] Phosphorane **1a** is probably unstable due to steric constrains imposed by the rigidity of the bicyclic system and opens to the stabilized dipolar intermediate **1b**. Finally, **1b** fragments to epoxide **2** and triphenylphosphine oxide. Dipolar intermediate **3a**, on the other hand, is presumably formed from dimethylaminodioxolane **3** upon activation by trifluoroacetic anhydride.

These methodologies of epoxidation, despite the fact that are limited to strained systems and failed with aliphatic diols, represent a simple synthetic approach to oxiranes that are difficult to generate by other methods. The syn - Mitsunobu reaction, on the other hand, broadens the scope of applications and mechanistic understanding of TPP : DEAD chemistry.

Fig 2



Acknowledgement: Support from the U.S. Navy Research Program is greatly appreciated.

References and Notes

1. Current address: Department of Chemistry, Michigan Cancer Foundation, 110 E. Warren, Detroit, MI 48201.
2. Mitsunobu, O.; Hashimoto, Y.; Kimura, J. Chem. Lett. **1974**,1473.
3. Mengel, R.; Bartke, M. Angew. Chem. Int. Ed. Engl. **1978**, 17, 679.
4. Mukaiyama, T. Angew. Chem. Int. Ed. Engl. **1976**, 15, 94.
5. a). Marshall, J. A.; Lewellyn, M. E. Synth. Comm. **5**, 293, 1975.
   b). Ibid. J. Org. Chem. **42**, 1311, 1977.
6. Eastwood, F. W. Harrington, K. J. Josan, J. S. Pura, J. L. Tet. Letters **1970**, 60, 5223.
7. Neumann, H. Chimia **23**, 267, 1969.
8. Dallacker, F.; Erkens, M.; Kusumawati, S. Chem. Ber. **1978**, 111, 3191.
9. (+)-(1R, 2S, 3R, 4S)-2-endo, 3-endo-Diphenyl-2,3-epoxy bornane, **2** has m.p 178-80 °C $[\alpha]_D^{25}$ = +32.26 (c= 0.868 in CH_2Cl_2). ^{1}H-NMR($CDCl_3$) δ = 0.93 (s, CH_3), 0.94 (s, CH_3), 1.37 (s, CH_3), 1.4(m,1H), 1.7(m,1H), 1.8(m,1H), 2.0(m,1H), 2.58 (d,1H; J= 4.92 Hz), 7.0-8.0(m, 10H). $C_{22}H_{24}O$ calculated: C 86.80, H 7.94. Found C 86.56, H 7.86.
10. The unknown diol **3** (mp 200-204°C) was prepared by addition of phenyllithium to benzocyclo butanedione[11] followed by careful quenching with water; **3** is dehydrated with ease by acids with formation of the known yellow 1,3-diphenylisobenzofuran.
11. Cava J. Am. Chem. Soc. **85**, 2076, 1963.

(Received in USA 15 August 1989)