Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8349-8350, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01900-4

A novel highly effective and stereoselective epoxidation of allylic and homoallylic alcohols using chloral hydrate and hydrogen peroxide

Helmut Kasch
Hans-Knöll-Institute of Natural Products Research, Beutenbergstr.11, D - 07745 Jena, Germany

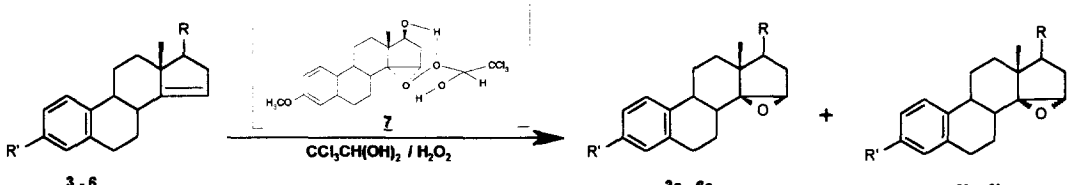
Abstract: A mixture of chloral hydrate (1) and hydrogen peroxide (2) was developed as a novel effective epoxidation reagent. Its efficacy was tested with steroid structures. It is a moderate oxidant superior to peracids and other hydrogen peroxide / catalyst combinations due to its higher regio- and stereoselectivity. Allylic and homoallylic alcohols (3, 4) are more rapidly epoxidized by neighbouring group participation of the corresponding hydroxyl groups than those with isolated olefinic double bonds. Copyright © 1996 Elsevier Science Ltd

Epoxidations of isolated and conjugated olefinic double bonds have frequently been done. Stereoselective reactions resulting from epoxidation with peracids[1], tert.butyl-hydroperoxide[2] or hydrogen peroxide (2) in combination with a catalyst[3, 4] are of special interest . While combinations of 2 with ketones have been used for epoxidation, this reaction has failed for aldehydes until now. One reason was the well known oxidation of aldehydes to the corresponding acids or their rearrangement to esters by Baeyer-Villiger reaction.

We tested ketones and aldehydes which are capable of forming stable hydrates as catalysts, such as ninhydrine, alloxan, and 1 in the aim of finding suitable substrates which are faster epoxidized than the catalyst is oxidized. When alloxan and ninhydrine were used, low yields of epoxidation were found.

Surprisingly, a combination of 1 and 2 was found to be a very efficient epoxidation reagent. It offers the possibility for selective epoxidation and oxidation of different substrates mainly with double bonds.

In this paper the epoxidation of steroid alkenes 3 and 4 with a neighbouring hydroxyl group is described.



No	3	4	5	6
R	17α-OH	17ß-OH	17ß-OAc	17-one
R'	CH_3O			

No	3 a/b	4 a/b	5 a/b	6 a/b
R	17α-OH	17ß-OH	17ß-OAc	17-one
R'	CH_3O			

Scheme 1.

Usually, 30 percent of 2 , Na_2HPO_4 and / or Na_2CO_3 (anhydrous) and 1 are added as a reagent to the steroid olefin (3, 4) dissolved in methylene chloride, chloroform, 1,2-dichloroethane, toluene or benzene, respectively. After a moderate reaction time, the workup is carried out by the reduction of 2 , and finally the steroid is isolated by extraction. The procedure is a very mild one, and opening of epoxides by acid catalysis, as is often observed in the presence of peracids, was not found. If starting materials with sensitive acid hydrolizable groups were employed the usage of Na_2CO_3 instead of Na_2HPO_4 was more advantageous.

The parent compound should be an activated, but not sterically hindered alkene. On one side the activation can proceed by another double bond like 5(10),9(11)-estra-dienes and on the other side by neighbouring hydroxyl groups such as in 3-methoxy-1,3,5(10),14-tetraen-17-ols (3, 4). The syn direction of the epoxidation of 3 and 4 is energetically favoured[5] in comparison with olefins without a neighbouring hydroxyl group. Two variants, the peracid oxidation[6] and the new method, were compared (table 1.) to demonstrate the syn directing effect on different substrates 3 - 6 . Only in cases where an epoxidation under neighbouring

group participation took place good selectivity was determined (3 and 4) and high reaction rates were reached. The latter effect was used for regioselective epoxidations. With 5 and 6 the directing effect of the 17-oxygen decreased, and the attack on the Δ^{14}-double bond was influenced by the steroid skeleton. The epoxidation mechanism can be explained in analogy to that proposed by Bartlett[7] or by Heggs and Ganem,[8] where a cyclic non polar intermediate 7 seems to be preferred.

Table 1. Selectivity in epoxidation by different substrats and methods

Compounds	Peracid[6] [%]		Chloral hydrate-method [%]	
	α-Epoxide	ß-Epoxide	α-Epoxide	ß-Epoxide
3 (17α-OH)	3b 88	3a 12	3b 95	3a -
4 (17ß-OH)	4b 35	4a 65	4b -	4a 95
5 (17ß-OAc)	5b 75	5a 25	5b 50	5a 50
6 (17-oxo)	6b 34	6a 66	6b 33	6a 67

The chloral hydroperoxide hydrate should be the initial epoxidation reagent. However, the presence of a hydroperoxide adduct derived from the rearranged hydroperoxide hydrate (trichloromethylformiate) can not be excluded. Thus the trichloromethylformiate was determined as the main product by ^{1}H NMR of a mixture of the reagent in the absence of olefins. The rearranged product can be attributed to a Baeyer-Villiger[10] reaction. Acid derivatives such as trichloroacetic acid were minor products, which are normally observed in reactions of aldehydes with hexafluoroacetone hydroperoxide hydrate.[8,9]

The epoxidation reagent should be fixed on the hydroxyl group by H bridges as demonstrated for 7 (scheme 1.). Apparently, the reaction is not favoured if stable hemiacetals of chloral are formed. The cleavage of intermediatly occurring acetals is a prerequisite to achieve high yields. We could demonstrate that in some cases the "catalyst" was only needed in catalytic amounts. Normally, more than the stoichiometric amounts are necessary in the presence of weakly activated olefins[11] because the rearrangement of the reagent will occur as side reaction.

This novel epoxidation procedure is not restricted to steroids.

Acknowledgements: I wish to thank Mrs. Röhrig for technical assistance, Dr. Hobe and Prof. Gräfe for general discussions.

References and Notes

1. Ponsold, K.; .Schubert, G; .Wunderwald, M.; Tresselt; D. *J.prakt.Chem.* **1981**, *323*, 819-821.
2. Baily, M.; Marko, I.E.; Ollis, W.D. *Tetrahedron.Lett.* **1991**, *32*, 2687 - 2690.
3. Ratcliffe, C.T.; Hardin, C.V.; Anderson, L.R.; Fox; W.B. *J.Chem.Soc.,Chem.Commun.* **1971**, 784.
4. Nickisch, K.; Arnold, H.; Rohde, R. *EP* 0298020; DE 3722486 **1988**, *ref.C.A.* **1989**, *111*, 39670.
5. Henbest, H.B.; Wilson;R.A.L. *J.Chem.Soc.* **1957**, 1958 - 1965.
6. Schubert,G.; Ponsold, K. *Pharmazie* **1979**, *34*, 323 - 325.
7. Bartlett, P.D., *Record.Chem.Progr.* **1950**, *11*, 47. Kirk, D.N.; Hartshorn, M.P. *in Steroid Reaction Mechanism, Elsevier Publishing Co.* **1968**, 71 - 77, and references therein. *1*, 2484 - 2486.
8. Heggs, R.P.; Ganem, B. *J.Amer.Chem.Soc.* **1979**, *101*, 2484 - 2486.
9. Kim, L., U.S. *Patent Appl.* 171.743, *ref. C.A.* **1973**, *78*, 159400n.
10. Kirk, D.N.; Hartshorn, M.P. in *Steroid Reaction Mechanism, Elsevier Publishing Co.* **1968**, 345 - 349.
11. A representive procedure is given for 17ß-hydroxy-3-methoxy-14ß,15ß-oxido-1,3,5(10)-estratriene (4a):
    0.125 g (0.326 mmol) 17ß-Hydroxy-3-methoxy-1,3,5(10),14-estratetraene (4) were dissolved in 5 ml methylene chloride, and after adding of 0.250 g (1.76 mmol) Na_2HPO_4 , 0.125 g (1.18 mmol) Na_2CO_3 and 0.3 ml (3.3 mmol) H_2O_2 (2 ,30 percent) the mixture was stirred for 15 min. Thereafter, 0.250 g (1.51 mmol) chloral hydrate (1) were added at once to the mixture and stirring was continued 10 h. For working up, the reaction mixture was treated with aqueous $Na_2S_2O_3$ solution. The organic layer was washed to neutral with saturated aqueous Na_2CO_3 solution and water. The extract was dried over Na_2SO_4, the solvent was removed, and the residue was crystallized from methylene chloride / methanol (yield 90%). Mp. 158 - 160 °C. ^{13}C NMR [500MHz] in $CDCl_3$ (ppm): 1C 126.5; 2C 11.5; 3C 157.5; 4C 113.8; 5C 137.5; 6C 29.3; 7C 26.3; 8C 36.4; 9C 43.3; 10C 131.2; 11C 22.3; 12C 34.6; 13C 45.4; 14C 74.5; 15C 59.5; 16C 35.9; 17C 77.6; 18C 13.4; 19C 55.1. ^{1}H NMR [500 mHz] $CDCl_3$(ppm): 7.21 d (1-H); 6.74 q (2-H, $J_{2H\text{-}1H}$= 8.6 Hz; $J_{2H\text{-}4H}$=2.6 Hz); 6.65 d (4-H); 3.78 s (3-OCH_3); 3.55 s (15-H); 3.52 t (17α-H); 2.84 m (6-H); 2.43 m (9α-H); 1.16 s (13-CH_3).

(*Received in Germany* 31 *May* 1996; *revised* 19 *September* 1996; *accepted* 23 *September* 1996)