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ALKALOID ASSISTED ASYMMETRIC SYNTHESIS IV¹

Additional routes to chiral epoxides

Jan C. Hummelen and Hans Wynberg

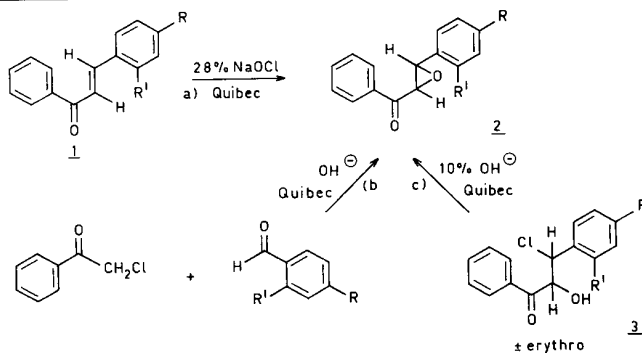
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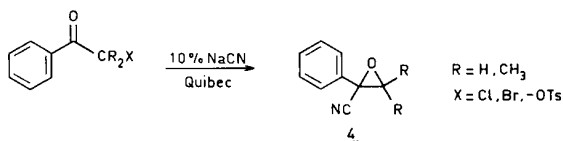
In order to increase the scope² of our recent synthesis of optically active epoxides³ we have studied alternate routes to this class of compounds. Optically active epoxides were obtained as products from the following reactions (Scheme I and II):

- The epoxidation of α,β -unsaturated ketones using 28% sodium hypochlorite;
- The Darzens condensation of chloroketones and aromatic aldehydes;
- The ring closure of racemic halohydrins;
- The addition of cyanide to α -haloketones and to an α -ketotosylate.

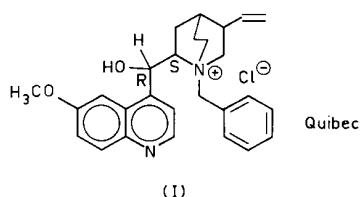
scheme I



scheme II



All of the four reactions summarized (1-4) were conducted under phase-transfer conditions⁴, using quininium benzylchloride (I = QUIBEC) as chiral catalyst³:



a) *Sodium hypochlorite*

The advantages of the use of hypochlorite ion in the preparation of racemic epoxides has been recorded⁵. We have found 28% sodiumhypochlorite, using QUIBEC to be an effective reagent in the synthesis of chiral epoxides. Several unsaturated ketones could be epoxidised which failed to yield products under previously described conditions³. Note that the chalcone 1 (R=R'=H) gave the epoxide 2 (R=R'=H) of opposite configuration when 28% NaOCl was used instead of 30% H₂O₂ (e.e. appears to be the same, however).

In a typical experiment 4 mmoles benzalacetophenone (1, R=R'=H) was treated with 8 ml of a 1:1 mixture of toluene and 28% NaOCl (with two additions 1.4 ml portions of 28% NaOCl after 2 hrs and 46 hrs) and 50 mg QUIBEC at room temperature with vigorous stirring for 72 hrs. The corresponding epoxide (2, R=R'=H) was formed in 66% yield^{6,7} with $[\alpha]_{578}^{25} = +53.1^\circ$ (c = 3.15, CH₂Cl₂), optical purity 25±5%⁸. Other epoxides were obtained in the same manner⁹.

b) *The Darzens condensation*

The reaction of *p*-chlorobenzaldehyde and phenacylchloride (2.5 mmoles of both in a mixture of 2.5 ml 10% NaOH and 2.5 ml toluene, stirred for three hours at room temperature with 6 mole percent catalyst QUIBEC) furnished the epoxyketone 2 (R=Cl, R'=H) in 68% yield with $[\alpha]_{578}^{25} = -24^\circ$ (c = 6.10, CH₂Cl₂)⁶, optical purity 8±1%.

The same epoxide prepared by using 28% NaOCl was found to have an optical purity of 15±2%. When less reactive aldehydes (*i.e.* benzaldehyde and piperonal) were treated with phenacylchloride under these conditions, selfcondensation of the latter lowered the yield of the desired epoxyketone.

c) *Ring closure of halohydrins*

Since all of the base catalysed epoxidations appear to involve the ringclosure of the initial 1,4-adduct it appeared worthwhile to attempt kinetic resolution on an α -halohydrin. When the \pm erythro chlorohydrin 3 (R=R'=H) derived from racemic *trans*-benzalacetophenone oxide 2 (R=R'=H)¹⁰, was treated with 10% NaOH in a H₂O/toluene mixture (1:1) with 6 mole percent QUIBEC for ten minutes at room temperature, the *trans*-epoxide 2 (R=R'=H) was produced in 90% yield with $[\alpha]_{578}^{25} = -12.5^\circ$ (c = 2.14, CH₂Cl₂)⁶, optical purity 6±1%. This appears to be a classical example of a kinetic resolution. Racemic epoxide was stable under these conditions.

d) Epoxynitriles

Finally, it was found that another class of chiral epoxides, namely epoxynitriles, could be prepared by the following method (Scheme II):

α -bromoisobutyrophenone (2 mmoles) was stirred in a mixture of 2 ml 10% NaCN and 2 ml toluene with 50 mg QUIBEC for 18 hours at room temperature¹¹. The epoxynitrile 4 (R=CH₃) was formed in 94% yield⁶ with $[\alpha]_{578}^{RT} = -3.0^\circ$ (c = 3.25, CH₂Cl₂). The optical purity of the epoxynitrile could be ascertained neither with the shift reagent Eu(dcm)₃ nor with Eu(tfc)₃.

DISCUSSION

The present and previous³ data shows clearly that both enantiomers of a variety of chiral epoxides are accessible using cinchona alkaloid salts under phase-transfer condition. Optimization experiments¹² have shown that the best route to chalcone epoxides thusfar utilizes essentially our earlier³ conditions: an enantiomeric excess of 55±2% was achieved in some cases (6b in ref. 3) when the reaction was carried out at 3° for 90 hours.

By itself it is remarkable that one chiral catalyst (quinine or QUIBEC) is capable of introducing a considerable degree of asymmetry into products from many different reactions, to wit: the Michael reaction¹³, Darzens condensation^{14,15}, epoxidation by H₂O₂³, *t*-BuOOH³, the thioladdition to α,β -unsaturated ketones^{1,16}, halohydrin ringclosure¹⁵ and cyanide addition to α -haloketones¹⁵.

NOTES AND REFERENCES

1. R. Helder, R. Arends, H. Hiemstra, W. Bolt and H. Wynberg, *Tetrahedron Lett.*, 2181 (1977) is Part III.
2. a) Initial attempts to prepare optically active terreic acid^b using our phase-transfer technique³ failed, presumably due to the high solubility of terreic acid in the aqueous phase;
b) J.C. Sheehan, W.B. Lawson and R.J. Gaul, *J. Am. Chem. Soc.*, **80**, 5536 (1958).
3. R. Helder, J.C. Hummelen, R.W.P.M. Laane, J.S. Wiering and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976).
4. For a recent review of the use of optically active catalysts in phase-transfer reactions see E.V. Dehmlov, *Angew. Chem. Int. Ed.*, **16**, 493 (1977).
5. Topics in stereochemistry, N.L. Allinger and E.L. Eliel, Vol. 7, page 185; Wiley, 1973.
6. All reactions were worked up in the same manner: 50 ml 1:1 toluene/ethylacetate was added, the layers were separated, the organic layer was washed three times with 50 ml water, the solvent was removed at an evaporator and the residue was chromatographed on a silicagel column, using CH₂Cl₂ as eluting solvent.
7. Higher chemical yields have been obtained, but the rotation of the product then tended to be lower.

8. In most cases the enantiomeric excess was determined, using $\text{Eu}(\text{dcm})_3$ in CCl_4 , for samples having a slightly different rotation from that reported here. Thus, the use of optical purity instead of enantiomeric excess.
9. Epoxidation by 28% NaOCl gave the following compounds from the corresponding α,β -unsaturated ketones: 2-benzylidenecyclohexanone-1-oxide, chemical yield 40%, $[\alpha]_{578}^{25} = -10.6^\circ$ ($c = 2.50$, CH_2Cl_2) (absolute configuration (R, S): J. Muzart and I.P. Pète, *Tetrahedron Lett.*, 303 (1977)), isophorone oxide, chemical yield 23%, $[\alpha]_{578}^{25} = -4.0^\circ$ ($c = 1.54$, CH_2Cl_2) and 1,2-styrylbenzoyl-oxirane, chemical yield 78%, $[\alpha]_{578}^{25} = +17.6^\circ$ ($c = 2.17$, CH_2Cl_2).
10. H.O. House, *J. Org. Chem.*, 21, 1306 (1956); O. Widman, *Ber.* 49, 477 (1916).
11. Under similar conditions epoxy nitrile 4 (R=H) could be prepared:
 - a) from phenacylchloride, reaction time 21 hrs, in 40% yield, $[\alpha]_{578}^{25} = -1.2^\circ$ ($c = 3.4$, CH_2Cl_2) and
 - b) from phenacyltosylate, reaction time 6 hrs, in 55% yield, $[\alpha]_{578}^{25} = -2.3^\circ$ ($c = 1.6$, CH_2Cl_2).Phenacyltosylate was prepared by the method of A.L. Growther and G. Holt, *J. Chem. Soc.*, 2818 (1963).
12. H. Wynberg and B. Greijdanus, manuscript in preparation.
13. H. Wynberg and R. Helder, *Tetrahedron Lett.*, 4057 (1975).
14. a) S. Colonna, R. Fornasier and U. Pfeiffer, accepted for publication in *J. Chem. Soc., Perkin I*;
b) S. Colonna and R. Fornasier, unpublished results.
15. This study.
16. H. Pracejus, F.W. Wilcke and K. Hanemann, *J. Prakt. Chem.*, 319, 219 (1977).