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A FACILE CHEMO AND REGIOSELECTIVE REDUCTIVE OPENING OF 1,2 EPOXIDES VIA FREE RADICAL REACTION

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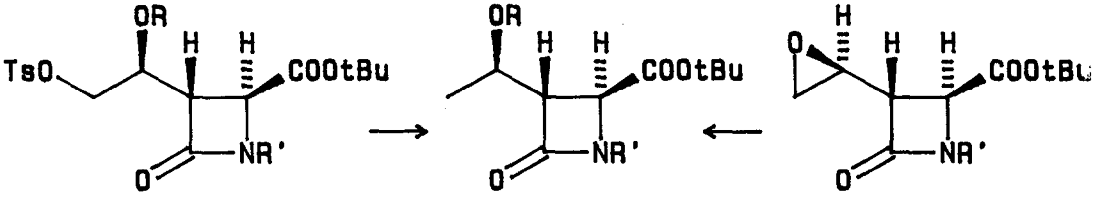
Summary: a free radical reaction has been applied to several 1,2 epoxides; the regio and chemoselective reduction of the epoxy ring to afford secondary alcohols occours, in presence of NaI and nBu$_3$SnH in DME at 80°C, in rather good yield.

The mechanistic aspects of the free radical reactions have been extensively studied since 1960's[1], but only recently some useful applications to organic synthesis have started to appear more frequently[2] ; the high chemoselectivety and specificity of the radical process has been often used in the total synthesis of several complex organic molecules[3], where the coexisting presence of several reactive groups could be an unsoluble problem for many organic transformations.

In 1975 Barton[4] discovered a useful deoxygenation reaction of secondary hydroxyl groups via free radicals; nevertheless, because of the instability of the intermediate primary radical, this method cannot be applied to primary alcohols. More recently Ueno et al.[5] have demonstrated the possibility to reduduce a primary hydroxyl group via its tosyl derivative, by free radical reaction (NaI, nBu$_3$SnH in DME).

Considering our studies in the synthesis of 2-azetidinones[6], key intermediates in the synthesis of important β-lactam antibiotics, we have applied the Ueno procedure on compound 1[7] to obtain 2, with the reaction favourably proceeding in 24 h., with 75% yield and complete chemoselectivity. In the preceding paper in this issue we have shown the obtaining of the same product 2 by reductive opening of the epoxide 3 and successive protection of the secondary hydroxyl group, employing the same reaction conditions used by Ueno: in this case 2 was obtained as the only product, with 85% yield after purification, in 2 h. at 80·C. Comparing the two methodologies we have obtained 2 in higher overall yield and shorter time: it is also noteworthy the complete regioselectivety obtained for this particular and interesting compound.



1 2 3

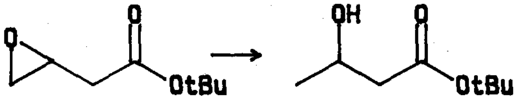
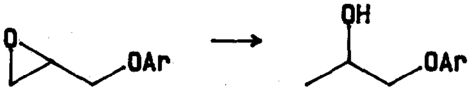
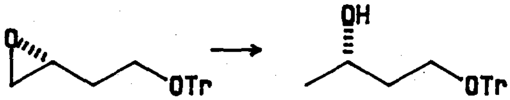
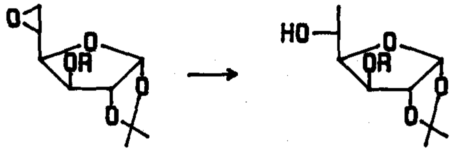
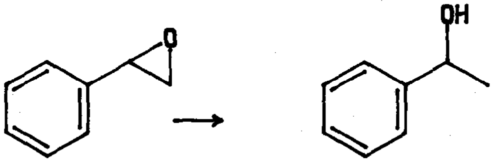
To test the flexibility and the usefulness of our reaction we have extended it to a series of different 1,2 epoxides as shown in the table.

The chosen examples are spread from simple (entries 1,3 and 5) to some chiral epoxides (entries 2 and 4) of significant importance in asymmetric synthesis. Apart from the rather good yield (79-95%) it seems that the regioselectivity of the reaction may be related, in some way, to the steric hindrance of the substituent of the epoxy ring.

In a typical procedure the epoxide (1 eq), diluted in anhydr. DME under a nitrogen atmosphere, is added of NaI (2.5 eq.), nBu$_3$SnH (2.5 eq.) and AIBN, and then allowed to stand at 80·C for 1-6 h. After the reaction is completed and quenched with MeOH at room temp., silica gel is added and the mixture stirred for 10 min. The solvent is then evaporated under vacuum and the residue poured on a silica gel column and chromatographed. The crude product, dissolved in CH$_3$CN is washed three times with hexane; the CH$_3$CN phase is concentrated in vacuo affording the product almost pure , free of tin organic compounds.

We are now investigating an extension of a similar procedure to α,β-epoxy esters and acids, and a possible utilization of the radical process

TABLE

entry		yield[1]	ratio[2]	time	temp.
1[3]		77%	99: 1	1h	70'C
2[4]		92%	99: 1	2h	80'C
3[5]		95%	15: 1	6h	80'C
4[6]			8: 1	4h	80'C
5[4]		88%	6: 1	1h	70'C

1. yields are based on purified products and have not been optimized
2. ratio is referred to the secondary alcohols vs primary ones, and have been determined by HPLC
3. prepared according to: S.G. Boots and M.R. Boots, J. Pharmacological Sciences, 64, 262 (1975)
4. commercially available products
5. prepared from R-(+)-malic acid: R. Di Fabio and A. Misiti, unpublished results
6. prepared in four steps from diacetone-D-glucose (Aldrich)

to obtain intra and intermolecular C-C bond formation; moreover the mechanism will be also investigated, with respect to a possible intermediate iodohydrin and a successive radical process.

References and notes

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1) For a recent book on free radical mechanism see: D.C. Nonhebal, J.M. Tedder and J.C. Walton " Radicals ", Cambridge University Press, Cambridge 1979.

2) For some monographs on the use of free radical reactions in synthesis see: D.I. Davies and M.J. Parrott " Free radicals in Organic Synthesis ", Springer-Verlag, New York 1978; B. Giese " Radicals in Organic Synthesis-Formation of carbon-carbon bonds " Pergamon Press, New York 1986.

3) For some recent and elegant syntheses via free radicals see: G. Stork, P.M. Sher and H. Chen, J.Am.Chem.Soc., 108, 6384 (1986); S.J. Danishefsky and J.S. Ponek, ibidem, 109, 917 (1987); K.C. Nicolau, D.G. McGarry, P.K. Somers, C.A. Veale and G.T. Furst, ibidem, 109, 2504 (1987); G. Stork and R. Mook Jr., ibidem, 109, 2829 (1987).

4) D.H.R. Barton and S.W. McCombie, J.Chem.Soc. Perkin I, 1574 (1975).

5) Y. Ueno, C. Tanaka and M. Okawara, Chem. Letters, 795 (1983).

6) C. Bonini and R. Di Fabio, Tetrahedron Lett., preceding paper in this issue.

7) Compound 1 has been easily obtained from the corresponding 1,2 diol prepared as described in ref.6.

8) All compounds gave satisfactory ^{1}H-NMR and MS data.

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