

ORGANOCOPPER REACTIONS I. REDUCTION OF STEROIDAL  
 $\alpha$ -EPOXY-KETONES WITH LITHIUM DIMETHYLCUPRATE

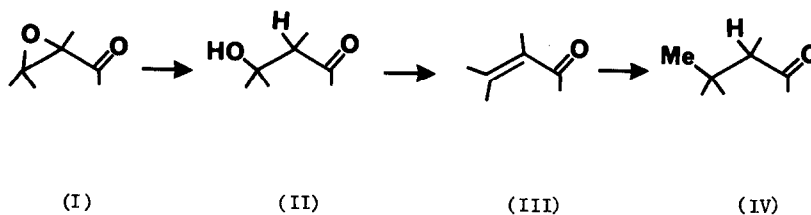
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In the short period of time since it was recognised<sup>1</sup> that discrete alkylcopper species promote regioselectivity of conjugate alkylation of  $\alpha, \beta$ -unsaturated carbonyl compounds, these reagents have assumed an increasingly important role in synthesis.<sup>2,3</sup> Although the mechanism of conjugate alkylation and related reactions using organocopper is not beyond dispute, the concept<sup>4</sup> of initial electron transfer to the substrate has not been seriously challenged. In this respect the analogy with alkali metal-ammonia<sup>5</sup> and chromium(II)<sup>6</sup> systems is obvious, and it follows that the choice of substrates to which an alkyl transfer from organocopper is not possible, might afford reduction products.

Although lithium dimethylcuprate adds readily to simple oxirans,<sup>7</sup> it is reasonable to suppose that in an  $\alpha$ -epoxy-ketone moiety, the intervention of a reductive process *via* electron transfer to the carbonyl group, would be strongly competitive. This expectation was realised in a series of experiments carried out on steroidal  $\alpha$ -epoxy-ketones(I). The substrate (I) in ether was added dropwise to ethereal lithium dimethylcuprate at 0° under nitrogen. The reactions proceeded rapidly, as evidenced by TLC monitoring for the consumption of starting material, and preparative experiments were stopped after 5 min by the addition of aqueous NH<sub>4</sub>Cl. No products ascribable to direct alkylation of the epoxy-group were detected; instead

TABLE. Reaction of  $\text{LiMe}_2\text{Cu}$  with  $\alpha$ -epoxy-ketones.<sup>a</sup>

Starting Material (I)	Products (% isolated) <sup>c</sup>		
	(II)	(III)	(IV)
4 $\beta$ ,5 $\beta$ -Epoxy-3-one <sup>8</sup>	5 $\beta$ -OH-3-one (67)	$\Delta^4$ -3-one (30)	-
4 $\beta$ ,5 $\beta$ -Epoxy-6-one <sup>9</sup>	4 $\beta$ -OH-6-one (25)	$\Delta^4$ -6-one (60)	4 $\beta$ -Me-6-one (11)
4 $\alpha$ ,5 $\alpha$ -Epoxy-6-one <sup>10</sup>	4 $\alpha$ -OH-6-one (85) <sup>d</sup>	$\Delta^4$ -6-one ( 5)	4 $\beta$ -Me-6-one ( 2)
5 $\beta$ ,6 $\beta$ -Epoxy-4-one <sup>9</sup>	6 $\beta$ -OH-4-one ( 9)	$\Delta^5$ -4-one (65)	6 $\beta$ -Me-4-one (18) <sup>d</sup>
5 $\alpha$ ,6 $\alpha$ -Epoxy-4-one <sup>11</sup>	6 $\alpha$ -OH-4-one (90) <sup>d</sup>	$\Delta^5$ -4-one ( 5)	-

<sup>a</sup> Reaction with 2 mol. equiv.  $\text{LiMe}_2\text{Cu}$  at  $0^\circ$  for 5 min.

<sup>b</sup> Cholestane series, prepared according to literature (refs. in Table).

<sup>c</sup> Identified by comparison with authentic material or literature data. The preparation of the 4-hydroxy-6- and 6-hydroxy-4-ketones is described in ref. 12, and the  $\beta$ -methyl ketones in ref. 13.

<sup>d</sup> Isolated as mixtures of 5 $\alpha$ - and 5 $\beta$ -isomers as shown by TLC/MS, and by equilibration (cf. ref. 13).

the primary products of a reductive process, *viz.*  $\beta$ -hydroxy-ketones(II), were obtained together with variable amounts of the corresponding  $\alpha,\beta$ -unsaturated ketones(III) and  $\beta$ -methyl ketones(IV) as consecutively derived artefacts (Table).

The yield of III was greater in those cases where the hydroxy-group of the primary product (II) was axial, owing to the resultant ease of  $\beta$ -elimination. It is probable that both secondary products (III) and (IV) were formed during the addition of  $\text{NH}_4\text{Cl}$  and indeed, the formation of IV could be suppressed by the less convenient procedure of quenching the reaction in a reverse manner to that described above. This did not appreciably affect the resultant yield of III.

The synthetic utility of the method was assessed by treating the  $\alpha$ -epoxy-ketones(I) with lithium in liquid ammonia and quenching the reactions with solid  $\text{NH}_4\text{Cl}$ . Rigorous exclusion of moisture afforded slightly higher yields of II than were obtained using lithium dimethylcuprate, but III still occurred as a significant impurity together with traces of further reduced material (MS). It appears that the organocopper method suffers no serious disadvantage, and would be superior for selective reduction of  $\alpha$ -epoxy-ketones containing unprotected carbonyl groups elsewhere in the molecule. Although direct comparison was not made with  $\text{Cr(II)}$  salts<sup>6,14</sup> the rapidity of reduction under mild conditions and the ease of work-up of the organocopper method may be advantageous.

The results described here provide additional support for an electron transfer step in organocopper alkylations. Furthermore the reductive pathway should extend to other  $\alpha$ -functionalised ketones capable of reduction by dissolving metals. Preliminary experiments on  $\alpha$ -acyloxy- and  $\alpha$ -halo-ketones confirm that reduction to the parent ketones proceeds rapidly in certain cases. These will be reported in a forthcoming communication.

REFERENCES

1. H.O. House, W.L. Respass, and G.M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
2. J.F. Normant, *Synthesis*, 63 (1972).
3. G.H. Posner in 'Organic Reactions' Vol. 19, John Wiley & Sons Inc., 1972, ch. 1.
4. H.O. House and M.J. Umen, *J. Amer. Chem. Soc.*, **94**, 5495 (1972) and refs. cited.
5. H.O. House, 'Modern Synthetic Reactions' 2nd Edn., W.A. Benjamin Inc., 1972, ch. 3.
6. J.R. Hanson and E. Premuzic, *Angew. Chem. Internat. Edn.*, **7**, 247 (1968).
7. R.W. Herr, D.W. Wieland, and C.R. Johnson, *J. Amer. Chem. Soc.*, **92**, 3813 (1970).
8. P.A. Plattner, H. Heusser, and A.B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).
9. J.R. Bull, *Tetrahedron Letters*, 5959 (1968).
10. S. Greenfield, E. Glotter, D. Lavie, and Y. Kashman, *J. Chem. Soc.(C)*, 1460 (1967).
11. D. Lavie, Y. Kashman, and E. Glotter, *Tetrahedron*, **22**, 1103 (1966).
12. J.-P. Pete and M.-L. Viriot-Villaume, *Bull. Soc. Chim. Fr.*, 3699 (1971).
13. J.R. Bull, *J. Chem. Soc.(C)*, 1128 (1969).
14. C.H. Robinson & R. Henderson, *J. Org. Chem.*, **37**, 565 (1972).