

## The Mechanism of the Clemmensen Reduction: the Substrates

James Burdon\* and Robin C. Price

Chemistry Department, The University, P.O. Box 363, Birmingham B15 2TT, U.K.

Product analysis and deuterium labelling experiments suggest that the critical intermediate in the reduction of  $\text{ArCOCH}_2\text{R}$  with  $\text{Zn}/\text{HCl}$  is a zinc-carbene; this may be protonated to give  $\text{ArCH}_2\text{CH}_2\text{R}$ , converted into  $\text{ArCH}=\text{CHR}$  by rearrangement, deprotonated to give a vinyl-zinc species, or captured by an alkene to give a cyclopropane.

Even though the Clemmensen reduction ( $>\text{C}=\text{O} \rightarrow >\text{CH}_2$  with  $\text{Zn}/\text{HCl}$ ) has been known<sup>1</sup> for over 70 years, its mechanism is far from clear. The commonly cited<sup>2,3</sup> mechanisms suffer from serious objections, and the obvious route *via* the alcohol is wrong;<sup>3</sup> alcohols are not intermediates.

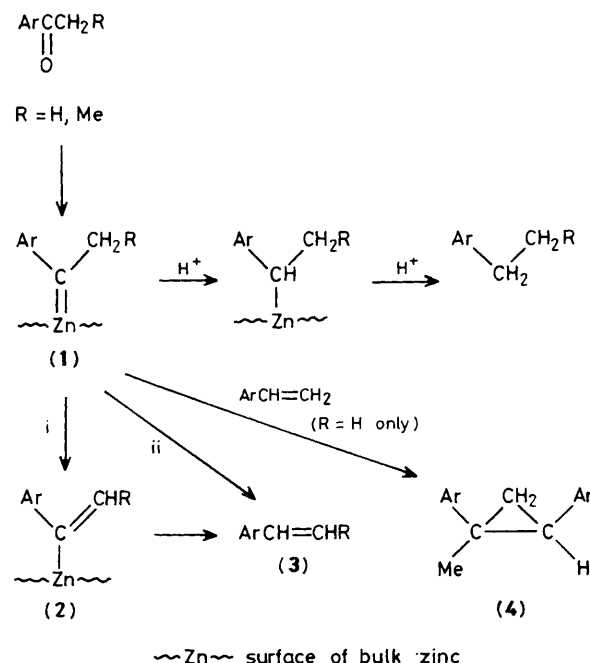
We now report some studies on acetophenone, substituted acetophenones, and propiophenone with amalgamated zinc in homogeneous† (50% aq. EtOH) solution at 20 °C and we suggest the mechanism outlined in Scheme 1. The key intermediate is a zinc-carbene (**1**) formed at the surface of bulk zinc. It is sufficient for our purposes to suppose that, whatever the nature of the bonding, the species behaves as if it were a simple carbene. Carbenes have been mentioned before<sup>2,3</sup> in connection with the Clemmensen reduction, but with little evidence and their role was not emphasised.

We regard the presence of cyclopropanes (up to 40% yield), which have not been reported before in typical Clemmensen reductions, as strong evidence for carbene intermediates (the cyclopropanes are the *cis*-diaryl isomers [e.g. (4)–(7)] with only a trace of the *trans*-isomers; both of the diphenyl isomers are known<sup>4</sup>). The capturing styrene can be either that formed in the reaction, (3), or it can be added to the reaction mixture (in a  $\text{PhCOMe}:\text{PhCH}=\text{CH}_2$  1:1 reaction, the cyclopropane yield was driven up to 75 from 35%). With ring-substituted acetophenones or with benzaldehyde the addition of styrene led to cross-coupled cyclopropanes. 4-Bromoacetophenone, for example, in the presence of styrene (1:2 molar ratio) gave the product (5) with little, if any, of the self-coupled product (6); furthermore, the yields of 4- $\text{BrC}_6\text{H}_4\text{Et}$  and 4- $\text{BrC}_6\text{H}_4\text{CH}=\text{CH}_2$  were reduced about two-fold when styrene was added, and this constitutes good evidence that ethylbenzenes, styrenes, and cyclopropanes all arise from a common intermediate: a zinc-carbene (**1**).

Attempts to capture the zinc-carbene (**1**) with alkenes other than styrenes all failed; some subtle steric factors appear to

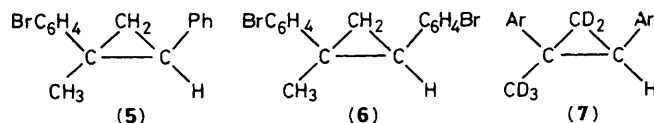
control the capture, as further evidenced by the absence of a cyclopropane in the reduction of propiophenone even when styrene was added.

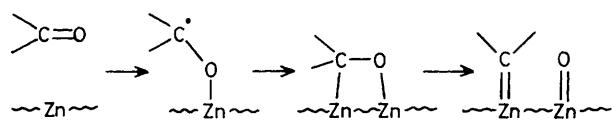
Further evidence for our mechanism comes from deuterium labelling studies.  $\text{ArCOCD}_3$  ( $\text{Ar} = 4\text{-ClC}_6\text{H}_4$ ) with  $\text{Zn}(\text{Hg})/\text{HCl}/\text{H}_2\text{O}/\text{EtOH}$  gave  $\text{ArCH}_2\text{CD}_3$  (27%),  $\text{ArCH}=\text{CD}_2$  (29%),



**Scheme 1.** i, abstraction of  $\text{H}^+$  by base ( $\text{H}_2\text{O}$ , EtOH, ketone); ii, rearrangement (1,2 H-shift). Neither i nor ii occur for  $\text{Ar} = 4\text{-MeOC}_6\text{H}_4$ .

† Preparative Clemmensen reductions are usually carried out in heterogeneous solution, e.g. water-toluene, and this drastically reduces the yields of 'dimeric' products (pinacols *etc.*); homogeneous conditions are sometimes used, however, and should not be regarded as atypical.





Scheme 2

containing  $\leq 2\%$  of  $\text{ArCD}=\text{CD}_2$ ), cyclopropane (**7**) (37%), and pinacols (7%). (Product identification and analysis here and elsewhere by g.c.-mass spectroscopy and  $^1\text{H}$  n.m.r. spectroscopy.) In this case the rearrangement route (ii, Scheme 1) is almost entirely suppressed in favour of the vinyl-zinc pathway (i). With  $\text{PhCOCD}_2\text{Me}$ , the products were  $\text{PhCH}_2\text{CD}_2\text{Me}$  (30%),  $\text{PhCD}=\text{CDMe}$  (39%),  $\text{PhCH}=\text{CDMe}$  (17%), pinacols (14%), and no cyclopropane. In this case the rearrangement route (ii) prevails over the vinyl-zinc route (i) by about 2 to 1; the trend from 4-chloroacetophenone to propiophenone is reasonable in that the carbene from the latter would be more likely to rearrange than the one from the former as evidenced by the favoured rearrangement of but-2-ylidene to but-2-ene rather than but-1-ene.<sup>5</sup>

Consistent results have been obtained from benzaldehyde, and non-deuteriated acetophenones and propiophenone, in  $\text{DCI}/\text{D}_2\text{O}/\text{EtOD}$ .

The elimination (i) and rearrangement (ii) reactions do have parallels in the literature;<sup>6</sup> an ethylidene-iron complex undergoes a reaction similar to (i) and the analogous propylidene complex one like (ii).

The rates of reduction of 4-methoxy- and 4-bromoacetophenone were much the same as acetophenone itself. The only marked change was that the 4-methoxy compound gave no styrene or cyclopropane; however, 2-methoxyacetophenone did, and we defer discussion to a full paper.

The addition of zinc chloride (45-fold molar excess over ketone) to a Clemmensen reduction had a striking effect; styrene and cyclopropane production from acetophenone and 4-bromoacetophenone was completely eliminated, while with propiophenone the yield of propenylbenzene was reduced about two-fold. All this is consistent with near suppression of the elimination route (i, Scheme 1). We tentatively ascribe this to the effective removal of the bases ( $\text{H}_2\text{O}$ ,  $\text{EtOH}$ , ketone) from the reaction mixture by solvation with zinc ions. Zinc chloride also slowed the reactions down considerably and this too can be attributed to co-ordination of the ketones.

It is not at all clear how the zinc-carbene forms from the ketone. A sequence such as that shown in Scheme 2 is plausible, with the first intermediate being perhaps responsible for the pinacols that are formed in Clemmensen reductions.

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