Tetrahedron Letters, Vol.31, No.42, pp 6081-6084, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

SINGLE ELECTRON TRANSFERS IN ZINC-PROMOTED REACTIONS. THE MECHANISMS OF THE CLEMMENSEN REDUCTION AND RELATED REACTIONS.

M.L.Di Vona, B.Floris, L.Luchetti, and V.Rosnati*

Dipartimento di Scienze e Tecnologie Chimiche, II Universita' di Roma, "Tor Vergata", Via Orazio Raimondo, 00173, ROMA (Italy).

A parallel study of the Clemmensen reaction of benzophenone, **1**, benzhydryl chloride, **2**, and dichlorodiphenylmethane, **3**, suggests new hypotheses about the mechanism of this reduction of diarylketones. Two main pathways have been recognized, both involving ionic and non-ionic reactions. The devised mechanisms provide a tool for interpreting literature data not understood hitherto, concerning Clemmensen-type as well as other zinc-promoted reactions.

In spite of several contributions, so far little is known about the mechanism of the Clemmensen reduction, the literature data being so contradictory, that no conclusion can be drawn.[1] The generally accepted view points to carbon-zinc bond formation.

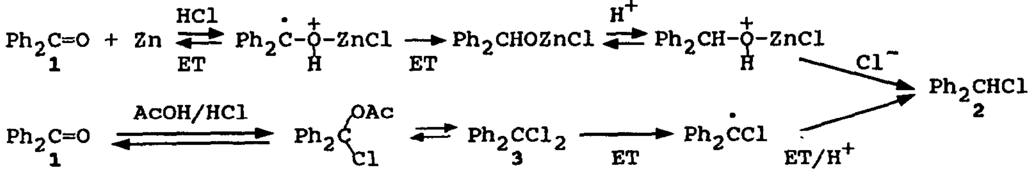
In order to contribute to the understanding of the mechanism, we have extensively studied the Clemmensen reduction of benzophenone, **1**, benzhydryl chloride, **2**, and dichlorodiphenylmethane, **3**, using anhydrous AcOH as the solvent, in the presence of a strong mineral (HCl) or organic acid (TFA with added LiCl as a source of chloride ions).

TABLE. Product distribution in the Clemmensen reduction of **1**, **2**, and **3**, in different reaction systems (2 h at 114°C).

COMPD.	REACTION SYSTEM	CONVERSION %	PRODUCTS				
			Ph_2CHOAc	Ph_2CH_2	$(Ph_2CH)_2$	Ph_3CCOPh	$Ph_2C{=}CPh_2$
1	Zn/AcOH	52	42	3	6	1	-
1	Zn/AcOH/HCl	100	4	23	3	65	5
1	Zn/AcOH/TFA/LiCl	100	-	21	-	52	27
2	Zn/AcOH	100	3	71	24	1	1
2	Zn/AcOH/HCl	100	-	58	38	3	1
3	Zn/AcOH/HCl	100	-	47	3	21	29
3	Zn/AcOH	100	-	46	2	13	39

All the results, a selection of which are reported in the Table, point to the conclusion that this complex reductive process proceeds through two pathways, involving ionic and non-ionic reactions, with benzhydryl chloride as a common intermediate (Scheme 1).

SCHEME 1



Benzhydryl chloride, actually, represents the final neutral intermediate in the reaction sequence leading to diphenylmethane.

The product distribution, obtained by working in different reaction systems and reaction conditions, indicates that in the presence of HCl **3** is also an intermediate in the reaction, being responsible for high yield of dimeric products. Indeed, dimer formation, while practically absent in the reduction performed in neat AcOH, represents an important event in the presence of chloride ions.

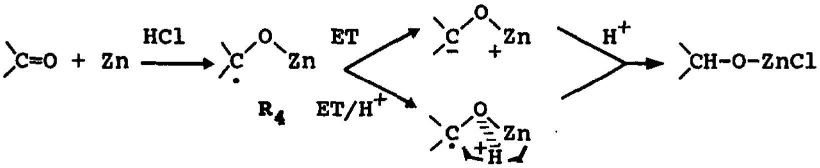
The reduction of **2** and **3** can be interpreted according as follows:

$$\underset{\mathbf{2}}{Ph_2CHCl} \xrightarrow{e} [Ph_2CHCl]^{\cdot-} \xrightarrow[Cl^-]{} \underset{R_1}{Ph_2\dot{C}H} \xrightarrow{e/H^+} Ph_2CH_2$$

$$\underset{\mathbf{3}}{Ph_2CCl_2} \xrightarrow{e} [Ph_2CCl_2]^{\cdot-} \xrightarrow[Cl^-]{} \underset{R_2}{Ph_2\dot{C}Cl} \xrightarrow{e/H^+} Ph_2CHCl$$

Dimeric products, such as 1,2-diphenylethane, benzopinacolone, and tetraphenylethene, clearly originate from coupling reactions, involving radical species, such as R_1, R_2, and $Ph_2C^{\cdot}OH$ (R_3), that are likely formed through electron transfers (ETs) from the metal zinc to **1**, **2**, and **3**, respectively. The molecules resulting from coupling reactions can be converted into the products through known ionic reactions. Experiments performed with the usual Clemmensen reagent, amalgamated zinc, gave results similar to those reported in the Table.

Altogether, the results point to a reaction mechanism initiated by an ET from zinc metal to the substrate, ultimately resulting in the carbon radical R_4. The latter species may then be reduced directly by zinc (either bound or free), or through the intermediacy of a coordinated proton in a four-membered, cyclic transition state:

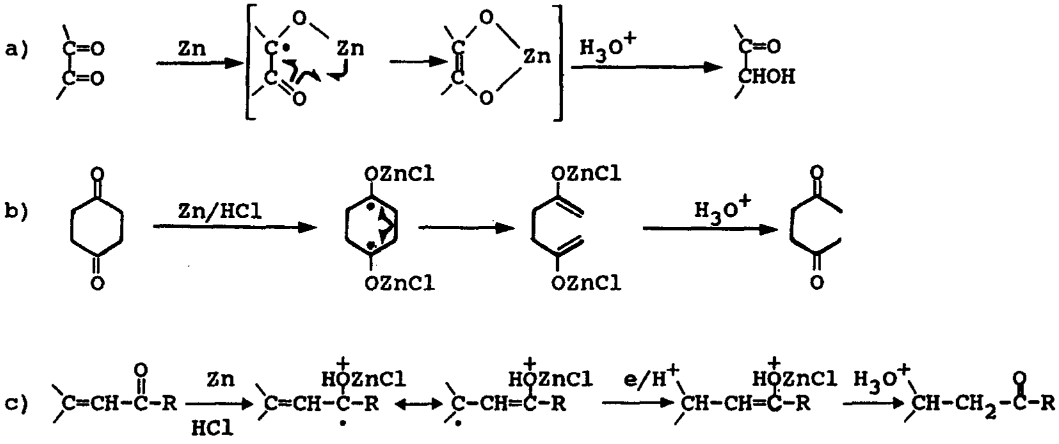


In this context, it is important to emphasize that benzophenone is not reduced by amalgamated zinc in anhydrous DMF, whereas it is reduced very slowly in the DMF/H_2O system, in the absence of HCl.

The reduction of Ph_2CDCl, resulting only in Ph_2CDH, indicates that carbenes, which were sometimes invoked, are not intermediates, at least as far as the reduction of R_1 is concerned. Furthermore, reduction experiments in the presence of styrene as a scavenger prove that carbene formation is not relevant: the insertion product, 1,1,2-triphenylcyclopropane, was formed in 9%, 5%, and 3% yields, starting from 1, 2, and 3, respectively.

According to this mechanistic picture, a number of Clemmensen reductions of specific substrates (e.g., 1,2-, 1,3-, 1,4-diketones, and α,β-unsaturated ketones[2]), all of which result in a *ketonic* product, can now be correlated and easily interpreted (see Scheme 2).

SCHEME 2

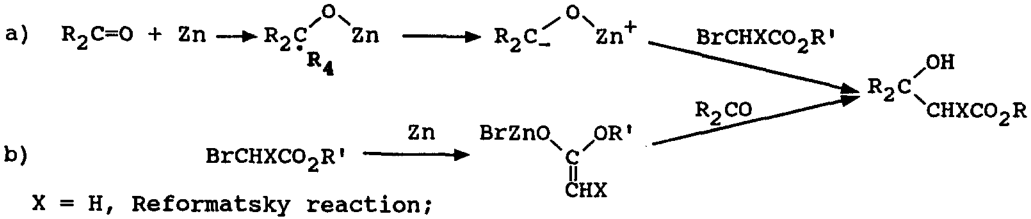


So far, the preservation of the carbonyl function during these reactions has found no rationale whatsoever. Known reductions of 1,3- and 1,4- cyclic and acyclic diketones, involving ring-opening, ring contraction, and/or rearrangement, can also be interpreted according to our basic postulates, as it will be shown in forthcoming papers.

The above mechanistic picture also sheds light on the mechanisms of other zinc-promoted reactions, resulting in carbon-carbon, instead of carbon-hydrogen, bonds. Among these, the Reformatsky reaction is of particular relevance, since until recently it has been the object of long debate, as to whether reaction occurs through a dimeric "Reformatsky reagent", a zinc enolate or a Grignard-like precursor.[3] Indeed, whatever the interaction between zinc metal and a generic ketone may be, the destiny of an organozinc radical, like initially formed R_4, appears to be dependent on the experimental conditions. Thus, the further reaction course, leading to reduction, depends on the H^+ concentration, while the possibility of diverting the reaction from reduction towards a new carbon-carbon bond formation depends on the presence of a suitable co-reagent, usually an α-halo carbonyl compound. Accordingly, by working in aprotic solvents and in non-acidic media, in the presence of a co-reagent such as those typical of the Reformatsky[4] and the related Darzens synthesis,[5] the drift of the reaction is shifted towards the carbon-

carbon bond formation. Pathways (a) and (b) in Scheme 3, both of which involve ionic and non-ionic reactions, may be operating as alternatives or concurrently, depending on the experimental conditions employed.

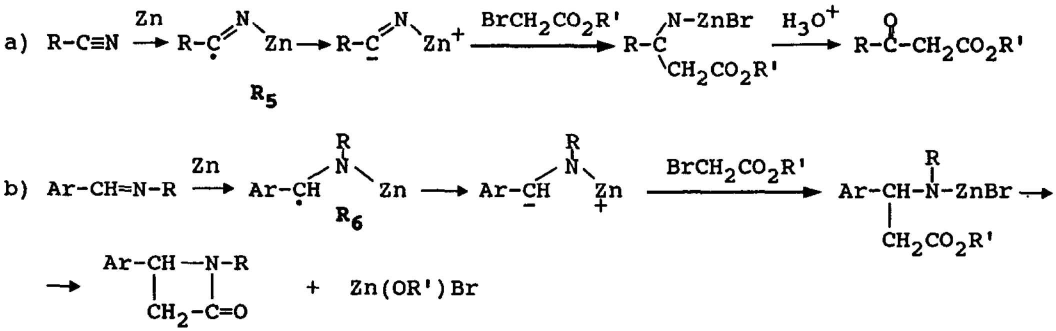
SCHEME 3



X = H, Reformatsky reaction;
X = halogen, Darzens reaction.

The reaction of zinc and an α-bromo ester with a nitrile (the Blaise synthesis of β-ketoesters)[6] or a Schiff base (the Gilman-Speeter synthesis of β-lactams)[7] can be interpreted in analogous fashion, according to Scheme 4.

SCHEME 4



Finally, it is possible that R_4, R_5, and R_6 react directly with the α-halo carbonyl compound in a solvent cage, through a purely radical mechanism. Research is in progress to evaluate the above mechanistic hypotheses.

REFERENCES

1. J.March, "*Advanced Organic Chemistry*",3rd Ed.,J.Wiley, New York,1985.
2. E.Vedejs, "*Organic Reactions*", **22**, 401 (1975).
3. J.Dekker, A.Schouten, P.H.M.Budzelaar, J.Boersma, G.J.M.van der Kerk, A.L.Spek, and A.J.M.Duisenberg, *J.Organomet.Chem.*, **320**, 1 (1987).
4. M.W.Rathke, "*Organic Reactions*", **22**, 423 (1975).
5. M.S.Newman and B.J.Magerlein, "*Organic Reactions*", **5**, 426 (1949).
6. S.M. Hannick and Y.Kishi, *J.Org.Chem.*, **48**, 3833 (1983).
7. H.Gilman and M.Speeter, *J.Am.Chem.Soc.*, **65**, 2255 (1943).

(Received in UK 22 August 1990)