Zinc-Promoted Reactions. 2. Ionic and Nonionic Pathways in the Reduction of Acetophenone and 2,2-Dimethyl-1-phenylpropan-1-one

Luciana Luchetti and Vittorio Rosnati*

Dipartimento di Scienze e Tecnologie Chimiche, II Università di Roma, Tor Vergata, Via Orazio Raimondo, 00173 Roma, Italy

Received February 6, 1991

The Clemmensen reduction of acetophenone and related substrates ($PhCHXCH_3$, X = Cl, OH, OAc) was investigated in anhyd AcOH and in the presence of LiCl, HCl, or TFA. Ethylbenzene, 1-acetoxy-1-phenylethane, 2,3-diphenyl-2,3-butanediol, and 2,3-diphenyl-2-butene were formed in yields strongly dependent on the experimental conditions. The formation of the hydrocarbon was favored in neat AcOH and in AcOH/HCl/LiCl. Ionic and nonionic pathways were recognized. In the presence of Cl^-, the proposed mechanism involves the intermediacy of $PhCH(CH_3)Cl$. The process may proceed via $[PhCOCH_3]^{\bullet-}$ and the carbon radical $PhC^{\bullet}(CH_3)OZnX$. The second SET may lead to a carbanion, quenched by the acid to give $PhCH(CH_3)OZnX$, a precursor of $PhCHXCH_3$ (X = OAc, Cl). Coupling reactions, involving different radical species, account for the formation of the dimeric compounds. In the reduction of 2,2-dimethyl-1-phenylpropan-1-one, the preponderance of addition reactions, mainly involving Cl^-, can be explained by the difficult approach of zinc metal to the hindered carbonyl group. Only traces of neopentylbenzene were obtained, the main product being 2-methyl-3-phenyl-2-butene. The proposed mechanism requires that the first SET occurs on adduct $PhCCl(OH)C(CH_3)_3$ to produce 2,2-dimethyl-1-phenylpropan-1-ol, the precursor of the alkene.

The mechanisms at work in the Clemmensen reduction of alkyl aryl ketones have not yet been elucidated in spite of the efforts of several authors, who studied the reaction of simple substrates such as acetophenone (**1**), and 2,2-dimethyl-1-phenylpropan-1-one (**2**).

The first mechanism was proposed by Brewster,[1] who suggested that in the Clemmensen reduction the carbonyl compound might coordinate to the metal surface to form a carbon–metal bond or an oxygen–metal bond, according to the structure of the substrate. Nakabayashi,[2] by investigating the kinetics and the electrochemical reduction of **1**, concluded that the electrochemical process could not be related to the Clemmensen reduction. He also suggested that the chemical process might occur through the intermediacy of a carbonium ion and the formation of a zinc–carbon bond. The intermediacy of a zinc carbene has also been proposed.[3] The hypothesis that 1-chloro-1-phenylethane (**3a**) is an intermediate in the reduction of **1** was also put forward.[4,5] Horner and Schmitt[6] showed that (i) 3,3-diphenylbutan-2-one (**4**) and 2,3-diphenyl-2,3-butanediol (**5**) were formed from **1** along with ethylbenzene and 2-methyl-1,2-diphenylpropan-1-one; (ii) styrene and 1-phenylethanol could partially be converted into ethylbenzene; (iii) the Clemmensen reduction of **1** could not be simulated by a parallel electrochemical experiment, either at constant voltage or at constant current density; and (iv) the nature and the concentration of the acid as well as temperature were among the determining factors. Investigations on the reduction of **2** were reported by Nakabayashi[2] and Brewster and co-workers.[7]

The above literature data, which obviously refer to various sets of experimental conditions, are occasionally contradictory and by no means conclusive. Therefore, on the basis of our previous work on the reduction of diaryl ketones,[8,9] we have reinvestigated the reduction of **1** and **2** under several sets of experimental conditions, properly selected to afford information about the blend of mechanisms involved. The zinc-promoted reduction of 1-chloro-1-phenylethane (**3a**), 1-phenylethanol (**3b**), and 1-acetoxy-1-phenylethane (**3c**) have also been investigated.

Results

The reduction of **1** with amalgamated zinc was generally performed in AcOH at 25 °C for 2 h in different systems. The results presented in Table I show that selective reduction to ethylbenzene was obtained in anhyd AcOH, albeit with low conversion (30%). Prolonged reaction times did not lead to complete reduction; the hydrocarbon yield increased to 47%, with a 6% yield of **3c** after 3 days. In 60% aqueous AcOH, 63% of **1** was converted into essentially equal amounts of ethylbenzene and **3c**.

In the presence of HCl or TFA, the ethylbenzene yield was lower than in anhyd AcOH, acetolysis being an important side reaction. 2,3-Diphenyl-2-butene (**6**) was only obtained in reactions performed in the presence of Cl^-, from either HCl or LiCl. However, **6** did not form when an excess of Cl^- was present, as in the case of the reduction performed in AcOH/HCl/LiCl. Minor amounts of 1-methyl-1,2-diphenylcyclopropane (**7**) and 2-acetoxy-3-hydroxy-2,3-diphenylbutane (**8**) were occasionally detected in the reaction mixtures and identified by MS only.

Table II reports the figures of Table I normalized, in order to show the relative contribution of the pathways occurring under the selected experimental conditions.

The reduction of **3a** was studied at 25 °C for 2 h in various systems. The relative product distributions are reported in Table III. The data show that (i) an efficient reduction occurred even in neat AcOH; (ii) solvolysis was an important process except in the reactions performed in the presence of LiCl; and (iii) styrene was always a minor product.

In the reduction of **3b**, the data of Table III show that esterification, rather than reduction, occurred in neat

(1) Brewster, J. H. *J. Am. Chem. Soc.* **1954**, *76*, 6360–6308.
(2) Nakabayashi, T. *J. Am. Chem. Soc.* **1960**, *82*, 3900–3906, 3906–3908, 3909–3913.
(3) Burdon, J.; Price, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 893–894.
(4) Steinkopf, W.; Wolfram, A. *Justus Liebigs Ann. Chem.* **1923**, *430*, 113–161.
(5) Poutsma, M.; Wolthuis, E. *J. Org. Chem.* **1959**, *24*, 875–877.
(6) Horner, L.; Schmitt, E. *Justus Liebigs Ann. Chem.* **1978**, 1617–1633.
(7) Brewster, J. H.; Patterson, J.; Fidler, D. A. *J. Am. Chem. Soc.* **1954**, *76*, 6368–6371.
(8) Di Vona, M. L.; Floris, B.; Luchetti, L.; Rosnati, V. *Tetrahedron Lett.* **1990**, *31*, 6081–6084.
(9) Di Vona, M. L.; Rosnati, V. *J. Org. Chem.* **1991**, *56*, 4269–4273.

0022-3263/91/1956-6836$02.50/0

Table I. Product Distribution in the Reduction of Acetophenone (1)[a]

solvent/ additive(s)	conversn, %	products, %					
		$PhCH_2CH_3$	$PhCH{=}CH_2$	$PhCH(OAc)CH_3$, 3c	$CH_3COC(Ph)_2CH_3$, 4	$PhC(OH)(CH_3)$-$C(OH)(CH_3)Ph$, 5	$Ph(CH_3)C{=}C(CH_3)Ph$, 6
AcOH	30	30					
AcOH[b]	63	33		30			
AcOH/TFA	43[c]	7	1	32		1	
AcOH/HCl	57[d]	18	4	15	2		15[e]
AcOH/LiCl	67[c]	9	8	25		5	18[e]
AcOH/TFA/ LiCl	58	15	3	5	2	14	19[e]
AcOH/HCl/ LiCl	98	67	2	29			

[a] Experimental conditions: 2 h at 25 °C. [b] Reaction performed in 80% AcOH. [c] Two percent of 8 was also detected. [d] Three percent of 7 was also detected. [e] Mixture of *E* and *Z* isomers.

Table II. Relative Weight of the Pathways in the Reduction of Acetophenone (1)[a]

solvent/additive(s)	process			
	% reductn (to $PhCH_2CH_3$)	% acetolysis	% coupling reactions (to 4–6)	% eliminatn (to $PhCH{=}CH_2$)
AcOH	100			
AcOH/H_2O	52	48		
AcOH/LiCl	14	38	36	12
AcOH/TFA	16	75	7	2
AcOH/TFA/LiCl	26	9	60	5
AcOH/HCl	32	26	35	7
AcOH/HCl/LiCl	68	30		2

[a] The table reports normalized data from Table I.

Table III. Product Distribution in the Reduction of 1-Chloro-1-phenylethane (3a) and 1-Phenylethanol (3b)[a]

substrate	solvent/additive(s)	conversn, %	products, %		
			$PhCH_2CH_3$	$PhCH{=}CH_2$	$PhCH(OAc)CH_3$, 3c
3a	AcOH	92	46	2	44
3a	AcOH/LiCl	46	40	4	2
3a	AcOH/TFA	100	23	1	76[b]
3a	AcOH/TFA/LiCl	57	27	9	21[c]
3a	AcOH/HCl	100	35	1	64
3a	AcOH/HCl/LiCl	49	38	9	2
3b	AcOH	2	1		1
3b	AcOH[d]	58	4		54
3b	AcOH/TFA	15		1	14[e]
3b	AcOH/HCl	100	49		51
3b	AcOH/HCl/LiCl	19[f]	9	1	6

[a] Experimental conditions: 2 h at 25 °C. [b] This includes 10% of 1-phenyl-1-(trifluoroacetoxy)ethane (3d). [c] This includes 1% of 3d. [d] Reaction run for 2 h at refluxing temperature. [e] This includes 4% of 3d. [f] Three percent of 3a was also detected.

Table IV. Product Distribution in the Reduction of 2,2-Dimethyl-1-phenylpropan-1-one (2)[a]

solvent/additive(s)	conversn, %	products, %		
		$PhCH_2C(CH_3)_3$	$Ph(CH_3)C{=}C(CH_3)_2$, 9	$PhCH(OH)C(CH_3)_3$, 10
AcOH/TFA	11		11	
AcOH/HCl	46	2	32	12
AcOH/HCl[b]	43		40	3
AcOH/LiCl	42		42	
AcOH/TFA/LiCl	57	4	40	13

[a] Experimental conditions: 2 h at 25 °C. [b] Reaction run for 2 h at refluxing temperature.

AcOH, as well as in the presence of TFA. On the other hand, reduction and solvolysis were equally important in AcOH/HCl. In the presence of LiCl some **3a** was detected among the products.

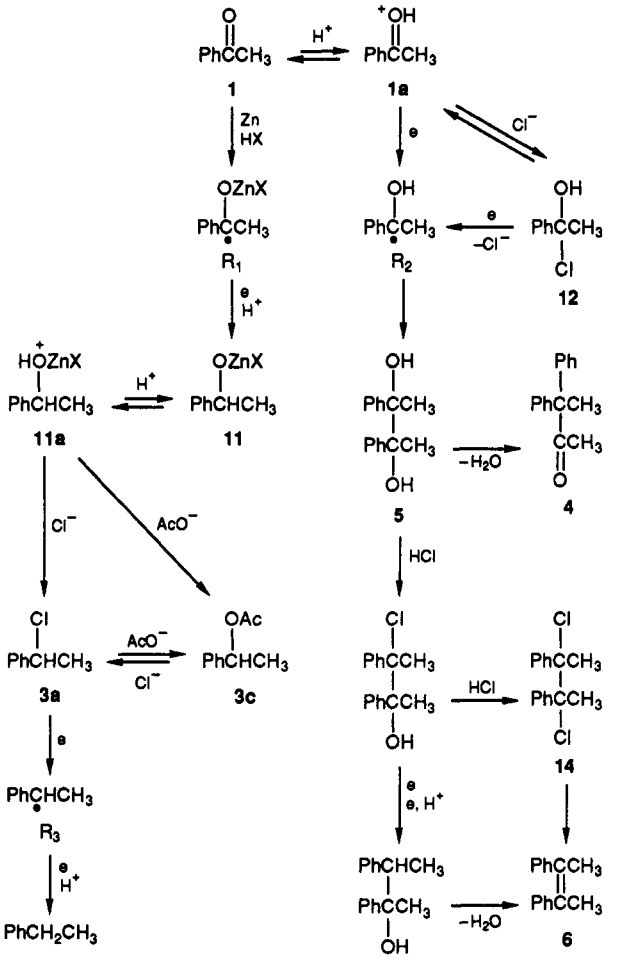
Acetate **3c** was not reduced to ethylbenzene, unless Cl^- was present (see Experimental Section). At 25 °C **3a** was formed (14%) with minor amounts of ethylbenzene (7%). The reduction was more efficient (36%) in refluxing AcOH/HCl.

The results obtained from the reduction of **2** are reported in Table IV. They show that in every case the main product was trimethylphenylethene (**9**). Neopentylbenzene, when formed, was only a byproduct, while 2,2-dimethyl-1-phenylpropan-1-ol (**10**) was observed in significant amounts only occasionally.

Discussion

The results obtained from the zinc-promoted reduction of **1** and related substrates **3a–c** point to a mechanistic picture in line with that recently put forward for the reduction of benzophenone.[8,9] In its essence, the reduction of **1** may involve a series of SETs from the metal to the substrate, or its conjugate acid, and to other species formed as intermediates. Benzylic radicals are believed to take part in the reduction. Also, a series of ionic reactions (acid–base equilibria, acid-catalyzed addition, solvolysis, and nucleophilic displacements) participate in the reduc-

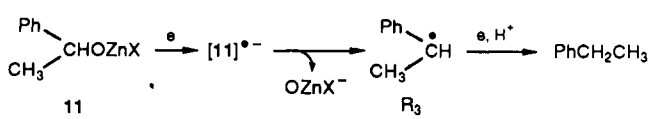
Scheme I. Electron Transfers and Ionic Reactions Involved in the Zinc-Promoted Reduction of Acetophenone in Different Solvents and under Different Conditions



tive process. Scheme I reports the pathways leading to ethylbenzene, along with **3a**, **3c**, **4**, **5**, and **6**.

The reaction is initiated by a SET from the zinc to the substrate, leading to radical anion $[PhCOCH_3]^{\bullet-}$. This anion may evolve to benzylic radical R_1 having a divalent zinc atom bound to the carbonyl oxygen, with its positive charge neutralized by a counterion ($CH_3CO_2^-$, $CF_3CO_2^-$, or Cl^-, depending on the reaction medium). A SET from the zinc to radical R_1 may result in the formation of zinc alkoxide **11**, the first neutral intermediate in the process leading to ethylbenzene. Subsequently, ionic reactions can lead to chloride **3a**, a precursor of ethylbenzene and acetate **3c**. The experimental conditions, and particularly the nature and the concentration of the acid, may significantly influence the equilibrium between **1** and its conjugate acid **1a**. The latter, having a lower reduction potential, should undergo reduction more easily than the ketone. Hence, the occurrence of carbon radical R_2, deriving from **1a**, must intervene in reductions performed in strongly acidic media. As for R_3, there is little doubt that such a radical is the final precursor of ethylbenzene.

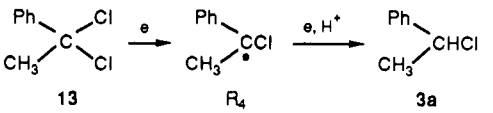
The reduction in the absence of Cl^- requires a mechanism slightly different from that illustrated in Scheme I. Since in AcOH and AcOH/TFA **3a** cannot form, the formation of ethylbenzene may be explained in terms of direct reduction of **11** (X = $OCOCH_3$, $OCOCF_3$):



Protonation of **11** is certainly a more efficient process in the presence of TFA than in neat AcOH. Consequently, acetolysis easily occurs even at room temperature, via **11a**. It is worthwhile to emphasize that R_3 did not dimerize, as the intermediate diphenylmethyl radical did in the reduction of benzophenone.[9]

The absence of dimeric compounds in AcOH and AcOH/TFA and, by contrast, their formation in AcOH/HCl cannot be ascribed to a different protonating ability of the two acids, which have comparable pK_a values in AcOH.[10,11] In AcOH/HCl and AcOH/TFA/LiCl, the dimeric compounds can form through adduct **12**, undergoing reduction to give radical R_2. The coupling of radical R_2 accounts for the formation of dimeric compounds **4–6**, while the pathways involving R_1 and R_3 are responsible for the formation of ethylbenzene, styrene, and acetate **3c**.

The formation of 1-methyl-1,2-diphenylcyclopropane (**7**) most probably requires the intermediacy of a carbenoid species, undergoing C insertion into a styrene molecule.[9] Under our experimental conditions, methylphenylcarbene might form either by dehydrochlorination of **3a** or by dechlorination of 1,1-dichloro-1-phenylethane (**13**). The former possibility, however, is unlikely, since no cyclopropane derivative was formed after prolonged heating of styrene and chloride **3a** in AcOH. The occurrence of the *gem*-dichloride **13** finds its parallel in the benzophenone reduction.[9] Besides being a possible precursor of the carbene, **13** might undergo reduction to chloride **3a** and eventually to ethylbenzene via radical R_4.



At first sight, the pattern of the reduction products in the presence of LiCl seems contradictory. As shown by Table II, the acetolysis was enhanced in AcOH/LiCl (0 → 38%), strongly depressed in AcOH/TFA/LiCl (75 → 9%), and slightly affected in AcOH/HCl/LiCl (26 → 30%). Furthermore, dimer formation increased in AcOH/LiCl (0 → 36%) and in AcOH/TFA/LiCl (7 → 60%), but decreased dramatically in AcOH/HCl/LiCl (35 → 0%).

The manifold role played by LiCl may find its rationale if the concurrence and the interference of the ionic pathways with the SETs are considered. The lower yield of ethylbenzene induced by LiCl in AcOH can be due to the formation of adduct **12**, the precursor of the dimers through coupling reactions of R_2. On the other hand, the enhanced yield of acetate **3c** may be tentatively explained in terms of the greater ionic strength of the medium and the easier solvolysis of **11** when X is Cl rather than AcO.

The largely prevailing formation of acetate **3c** in AcOH/TFA may be due to the fact that the equilibrium **11** ⇄ **11a** is shifted to the right by the stronger acid. This allows acetate **3c** to accumulate, since it is not reduced in the absence of Cl^-. In AcOH/TFA/LiCl the strongly depressed solvolysis can be a consequence of the increased competition of the pathways through adduct **12**, leading to the dimers. The higher yield of ethylbenzene is ascribed to the formation of chloride **3a** through nucleophilic substitution by LiCl on **11a**. In AcOH/HCl/LiCl the salt affects mostly reduction and coupling reactions. This may be due to the increased production of **3a** resulting in an increased yield of ethylbenzene, with the reaction pro-

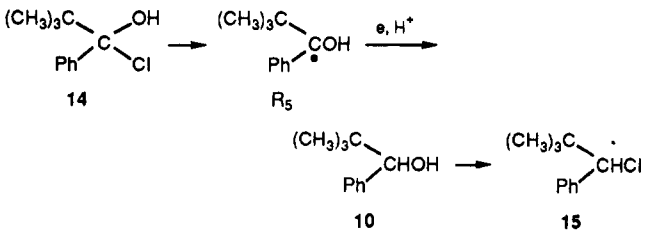
(10) Shkodim, A. M.; Karkuzaki, L. I. *Zh. Fiz. Khim.* **1959**, *33*, 2795–2801.
(11) Fialkov, Yu. Ya.; Borovikov, Yu. Ya. *Ukr. Khim. Zh.* **1964**, *30*, 119–125.

ceeding mainly through R_1. The suppression of dimer formation in AcOH/HCl/LiCl is rather difficult to explain. However, the very fact that no dimeric compounds were formed under those conditions clearly indicates that the reaction proceeds exclusively through the pathway involving R_1.

It was already mentioned that in neat AcOH the reduction of 1 might also occur exclusively via R_1 and 11 (X = OAc). The low conversion (30%) can be ascribed to the formation of an AcOH adduct, which did not undergo reduction and therefore gave back 1 during the final workup. This is supported by the reduction in 80% aqueous AcOH, which resulted in a higher conversion (63%).

The results obtained in the reduction of **3a–c** are in line with our mechanistic picture. Thus, **3a** underwent reduction to ethylbenzene and solvolysis, the former accounting for 78% of the reaction in AcOH/HCl/LiCl. Alcohol **3b** and acetate **3c** were efficiently reduced only in AcOH/HCl, i.e., when they could be converted into the chloride.

The reduction of **2** presents a much simpler picture and resembles that of benzopinacolone.[9] Due to steric hindrance, the carbonyl of **2** cannot be easily approached by the zinc, and protonation of the substrate, ultimately resulting in HCl addition, becomes the predominant process. Adduct **14** may undergo reduction to alcohol **10** through the intermediacy of radical R_5.



Alkene **9** may derive from chloride **15** through an acid-catalyzed rearrangement, probably involving an ion pair. The reduction of **15** may lead to neopentylbenzene, formed only in the presence of Cl^-, from either HCl or LiCl.

The mechanistic picture depicted so far is indirectly supported by the fact that cyclohexanone and nonan-5-one do not undergo reduction with amalgamated zinc in neat AcOH. This can be ascribed to the tertiary alkyl radicals which may form through the first SET. These radicals are much less stable than the corresponding benzhydryl or benzyl radicals, ones which are involved in the reduction of diaryl and alkyl aryl ketones.

The present investigation has shown that the zinc-promoted reduction of alkyl aryl ketones and related compounds in AcOH is a rather complex process with radical and ionic pathways. Working in the presence of coreagents such as LiCl, HCl, and TFA, which can influence the ionic reactions, allows the reductive process to be partially diverted from deoxygenation to carbon–carbon bond formation.

Experimental Section

GC and GC/MS analyses were carried out as described in the previous paper.[9]

Materials. Anhyd AcOH was prepared according to a standard procedure. Solutions of approximately 0.3 M anhyd HCl in AcOH were prepared by bubbling HCl gas into the solvent. TFA (Aldrich) was used without further purification at 10% concentration. Substrates **1**, **2**, and **3b** are commercially available (Aldrich) at 99% purity. Chloride **3a** was prepared by reacting **3b** with $SOCl_2$. Acetate **3c** was obtained by acetylation of **3b** with AcCl.

General Procedure for the Reduction. The reactions were generally performed at 25 °C, and occasionally at refluxing temperature, in AcOH (anhyd or 80%) in different systems (see Tables I–IV), following the procedure previously reported.[9] GC and GC/MS analyses were performed on the residue and the product distributions determined. The GC data were corrected according to response factors obtained from pure samples of the products. The data represent the average of two or more experiments. Isolation of the products, when necessary, was accomplished by known procedures. Their identification was made on the basis of GC/MS and ^1H NMR studies and comparison with authentic samples, either purchased or synthesized (**4**,[12] **6**,[13] **7**,[14] **9**,[15]).

Reduction of 3c. The reduction of **3c** for 2 h at 25 °C afforded ethylbenzene (4%) in AcOH/TFA/LiCl and ethylbenzene (7%) and **3a** (14%) in AcOH/HCl; in AcOH/HCl at refluxing temperature, the product distribution was 36% ethylbenzene, 5% styrene.

Reduction of Cyclohexanone and Nonan-5-one. The reactions were performed in anhyd AcOH at 25 °C with amalgamated zinc. After 2 h, only starting material was recovered.

Acknowledgment. This work was supported by the Consiglio Nazionale delle Ricerche (CNR) and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

Registry No. 1, 98-86-2; 2, 938-16-9; **3a**, 672-65-1; **3b**, 98-85-1; **3c**, 93-92-5; cyclohexanone, 108-94-1; 5-nonanone, 502-56-7.

Supplementary Material Available: Complete mass spectral data for the products (1 page). Ordering information is given on any current masthead page.

(12) Markgraf, J. H.; Newton, T. A. *J. Chem. Educ.* **1979**, *56*, 334.
(13) Furstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729–1734.
(14) Landgrebe, J. A.; Kirk, A. G. *J. Org. Chem.* **1967**, *32*, 3499–3506.
(15) Marxmeier, H.; Pfeil, E. *Chem. Ber.* **1964**, *97*, 815–826.