Zinc-Promoted Reactions. Part 5. The Behaviour of Alkyl Substituted 1,3-Diketones

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Abstract. The zinc-promoted reaction of 2,4-pentanedione and related β-dicarbonyl substrates have been investigated under a variety of conditions. The results were explained according to a general mechanism, involving ionic and nonionic pathways.

The zinc-promoted reduction of 2,4-pentanedione and related β-dicarbonyl compounds was previously investigated under the classical Clemmensen conditions, (aqueous HCl [1]), and in different solvents, (HCl in acetic anhydride and diethyl ether [2]). Complex mixtures of products were obtained, in yields from low to moderate. The mechanism of the reaction, however, has not been elucidated. In particular, no explanation has been offered for the fact that in most cases products with one carbonyl group retained were obtained. Product distribution was discussed in terms of mechanism [3]; although an electron transfer from the zinc to the carbonyl oxygen was described, the simple, consequent formation of zinc alkoxides was not considered and the usual organometallic intermediates, with C-Zn bonds, were drawn.

The results obtained in our investigation on the mechanism of zinc-promoted reductions of diaryl- [4, 5], aryl alkyl [6], and α,β-unsaturated ketones [7] in anhydrous acetic acid indicated that we may have at hand a mechanistic tool to interpret the reaction of β-dicarbonyl compounds. In fact, a variety of zinc-promoted processes leading to carbon-carbon bond formation or cleavage in dicarbonyl derivatives were explained accordingly [8].

We report here the results of an investigation on the behaviour of alkyl substituted 1,3-dicarbonyl compounds with zinc, in conditions comparable to those of our previous reports. The examined substrates were chosen in order to have enolizable and non enolizable compounds, the latter being acyclic and cyclic, with the aim to elucidate any importance of structural features in directing the reaction course.

Results and Discussion

2,4-Pentanedione (acetylacetone) was treated with zinc powder or amalgamated zinc, under a variety of conditions, chosen on the basis of previous results with diaryl [5] and aryl alkyl [6] ketones. Thus, trifluoroacetic acid (TFA) replaced HCl as the proton source and LiCl was the origin of Cl⁻. Results are shown in Table 1. No substantial difference emerged between reactions carried out with zinc powder and those with amalgamated zinc. No reaction at all was observed in neat acetic acid and low conversions were found in the presence of LiCl or TFA. Only when both the proton (TFA) and the chloride ion (LiCl) sources were present, were significant conversion percents obtained. On the contrary, quantitative conversions were attained under conditions similar to those of the classical Clemmensen reactions. This points at the importance of HCl in the addition reaction to the keto moiety, before the reduction occurs. 2-Pentanone, 1, and 3- methyl-2-butanone, 2, were the products, with a general prevalence of the former, with few exceptions, in the reaction in 1:1 v/v aqueous HCl-AcOH. Interestingly, 2-pentanone was not amongst the products identified in the literature [1]. We obtained no direct evidence of cyclopropane intermediates, although the presence of the rearranged ketone, 3-methyl-2- butanone, is an indirect one. The low conversions might, *inter alia*, be related to a deactivation of zinc surface of some sort. As a matter of fact, one experiment performed in a sonicator yielded a conversion of 27% (instead of the usual 7% of the non sonicated reaction), other conditions being equal (Table 1).

3-Methyl-2,4-pentanedione was even less reactive than the unsubstituted substrate (Table 2). The product, in low amount, was 3-methyl-2-pentanone, 3, sometimes accompanied by 4-hydroxy-3-methyl-2-pentanone, 4. Of course, any rearrangement of cyclopropane intermediates gives the same product, *i.e.*, 3- methyl-2-pentanone.

In order to show the possible importance of enol species in the behaviour of β-dicarbonyl compounds, 3,3-dimethyl-2,4- pentanedione was treated with zinc powder or amalgamated zinc, in acetic acid, under a variety of conditions. Unfortunately, the scarce reactivity was accompanied by demethylation reaction(s), which occurred also in the absence of zinc. Thus, the product distribution obtained from 3,3-dimethyl-2,4-pentanedione (Table 2) came, in fact, by reduction of demethylated species.

Enol-type derivatives were taken into consideration, in order to assess the importance of enol species in the reductive process. However, no conclusive result was obtained, because the enol ether 4-methoxy-3-penten-2-one underwent

## Table 1. REACTION OF 2,4-PENTANEDIONE WITH ZINC IN ANHYDROUS ACETIC ACID
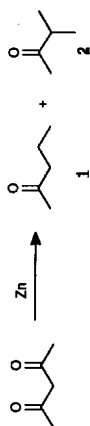
Entry	Co-reagent	Reaction time, h	Temperature °C	with Zn Conversion[a] %	% **1**	% **2**	with amalgamated Zn Conversion[a] %	% **1**	% **2**
1	-	48	r.t.	0	-	-	0	-	-
2	-	2	reflux	2	2	-	9	9	traces
3	LiCl	2	r.t.	5	5	-	7[b]	6.5	0.5
4	LiCl	24	r.t.	5	3	2	8	6	2
5	LiCl	2	reflux	12	11	1	30	29	1
6	TFA	2	r.t.	0	-	-	0	-	-
7	TFA	48	r.t.	2	2	-	18	16	2
8	TFA	2	reflux	13	12	1	15	8	7
9	TFA, LiCl	48	r.t.	11	7	4	8	3	5
10	HCl(g)	24	r.t.	9	5	4	29	20	9
11	HCl(g)	2	reflux	16	13	3	100	6	94
12	HCl aq[c]	2	r.t.	83	19	64	100	3	97
13	HCl aq[c]	2	reflux	100	21	79			

(a) Relative to diphenylmethane as the internal standard.
(b) Sonicated, 27% conversion, 21% **1**, 6% **2**.
(c) 1:1 v/v AcOH/ concentrated HCl.

Table 2. REACTION OF 3-METHYL-2,4-PENTANEDIONE AND 3,3-DIMETHYL-2,4-PENTANEDIONE WITH ZINC IN ANHYDROUS ACETIC ACID AT REFLUX TEMPERATURE
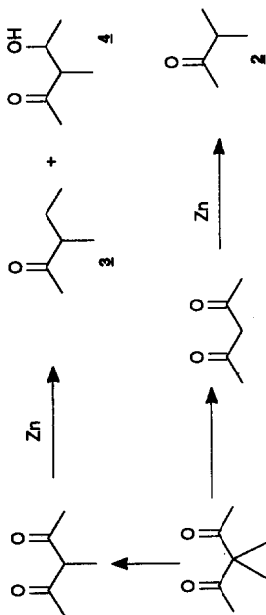
Substrate	Co-reagent	Reaction time, h	with Zn				with amalgamated Zn			
			Conversion% (a)	% 2	% 3	% 4	Conversion% (a)	% 2	% 3	% 4
3-methyl-2,4-pentane-dione	LiCl	2	1		1	-	15		11	4
	TFA	2	0		-	-	<1		traces	traces
	HCl(g)	2	2(c)		2	-	18		9	9
	HCl aq (b)	2	38(c)		20	11	100(d)		49	18
3,3-di-methyl-2,4-pentane-dione (e)	-	2	2	0.3	1	-	1	0.1	0.4	-
	LiCl	2	3		1	-	8	1.0	1.4	1.3
	TFA	2	3	1.0	1	-	3	1.0	1.0	-
	HCl(g)	2					7	2.0	1.0	3.0
	HCl aq (b)	16	3	1.6	1	-	23	6.7	0.6	12.6

(a) Relative to diphenylmethane as the internal standard.
(b) 1:1 v/v AcOH/concentrated HCl.
(c) 7% 2,4-Pentanedione.
(d) 33% 2,4-Pentanedione.
(e) Conversion not accounted for refer to demethylated products, 3-mthyl-2,4-pentanedione and 2,4-pentanedione. Demethylation was observed in blank experiments performed without zinc under otherwise identical conditions.
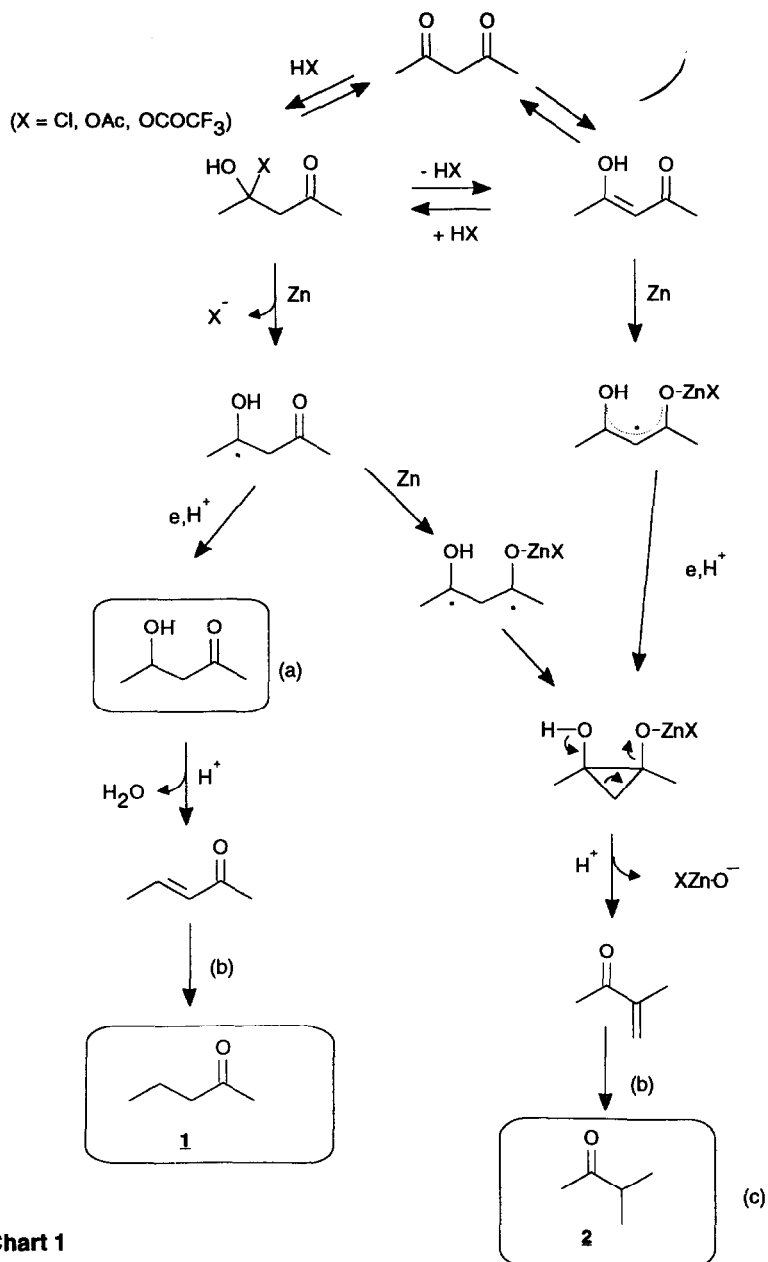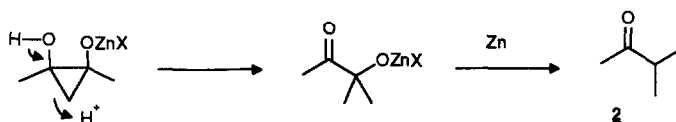
Chart 1

(a) The ketol, 3-methyl-4-hydroxy-2-pentanone, **4**, was found among the products from 3-methyl-2,4-pentanedione. (b) Reaction pathways of α,β-unsaturated ketones [7].
(c) According to a referee's suggestion, an alternative mechanism for the formation of ketone **2** might be:

demethylation reaction, with formation of acetylacetone, even under mild conditions (see Experimental). On the other hand, the enol ester, 4-acetoxy-3-penten-2-one could not be isolated as a pure compound. Its formation was identified in the reaction mixture (GC/MS experiments), but any attempt to distill the enol ester failed, yielding 2,4-pentanedione and a brown tarry residue. Analogously, 4-acetoxy-3-methyl-3-pentene-2-one was present in the crude mixture from the reaction of 3-methyl-2,4-pentanedione with acetic anhydride, but attempted distillation gave 3-methyl- 2,4-pentanedione only, with a dark brown sticky residue.

From the experimental picture it is not possible to distinguish between pathways involving the enol and the keto (*via* adduct) forms. A simplified reaction scheme may be drawn as in Chart 1. The fact that one carbonyl function is retained is easily explained by the intermediacy of α,β- unsaturated ketones, which were shown to undergo reduction of the carbon-carbon double bond *via* the formation of zinc enolates [7].

A related substrate, tetramethylcyclobutane-1,3-dione, was investigated, because it has no enolizable proton and is a rigid system, which was reported to undergo ring-opening reaction in the Clemmensen reduction [9]. Under our experimental conditions, this cyclic β-diketone was quite unreactive (Table 3), unless high temperature and concentrated HCl were used. Generally, only two products were obtained; 2,4-dimethyl-3-pentanone, 5, and 2,5-dimethyl-3-hexanone, 6, in line with previous findings [9]. However, it must be noted that 5, the ketone with one carbon atom less than the starting material, was formed quantitatively by refluxing tetramethylcyclobutane-1,3-dione in aqueous HCl/AcOH <u>without</u> zinc.

The reactivity of tetramethylcyclobutane-1,3-dione with zinc in aqueous HBr was lower than that in aqueous HCl and the latter acid in methanol or in water
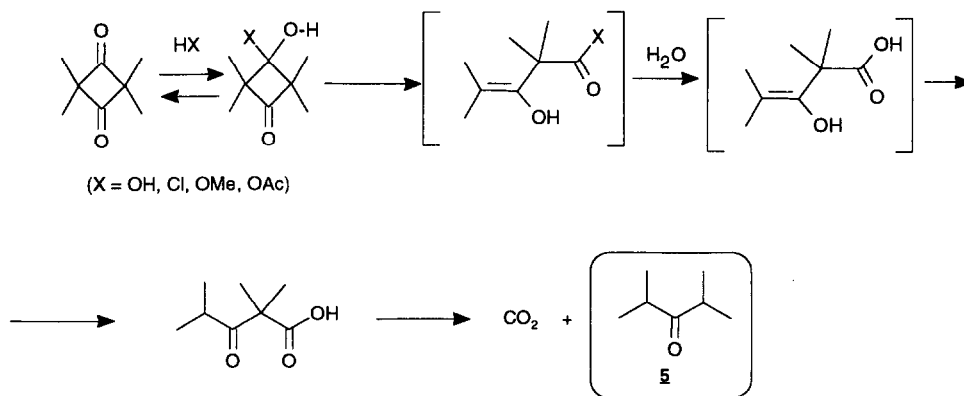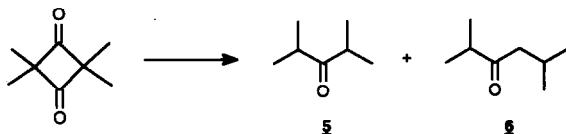

(X = OH, Cl, OMe, OAc)

Chart 2

Table 3. REACTION OF TETRAMETHYLCYCLOBUTANE-1,3-DIONE WITH ZINC IN DIFFERENT MEDIA

Solvent	Co-reagent	Reaction time, h	Temperature °C	Conversion % [a]	% **5**	% **6**
AcOH	-	3	r.t.	0	-	-
AcOH	HCl(g)	3	r.t.	0	-	-
AcOH	HCl aq[b]	24	r.t.	10	5	2
		5	reflux	67	43	20
		5 [c]	reflux	98	56	19
		5 [d]	reflux	100	100	-
AcOH	HBr aq[e]	24	r.t.			
		5	reflux			
MeOH	HCl aq [f]	70	r.t.	<1	traces	-
H2O	HCl aq [g]	72	r.t.	4	1	-

[a] Relative to diphenylmethane as the internal standard. Conversion percents not accounted for refer to a number of unidentified peaks, less than 1% each.
[b] AcOH/concentrated HCl 1:1 v/v.
[c] With amalgamated zinc.
[d] With no zinc added.
[e] AcOH/concentrated HBr 1:1 v/v.
[f] MeOH/concentrated HCl 4:1 v/v.
[g] 7 M aqueous HCl.

was less effective than in AcOH (Table 3).

The slow hydrolytic cleavage of tetramethylcyclobutane-1,3-dione can be explained in terms of a multi-step process, starting with a nucleophilic addition to one of the carbonyl group, by any of the possible reagent present in the reaction mixture (H_2O, HCl, MeOH). A subsequent ring cleavage will lead - directly or after hydrolysis - to an easily decarboxylating β-ketoacid (Chart 2).

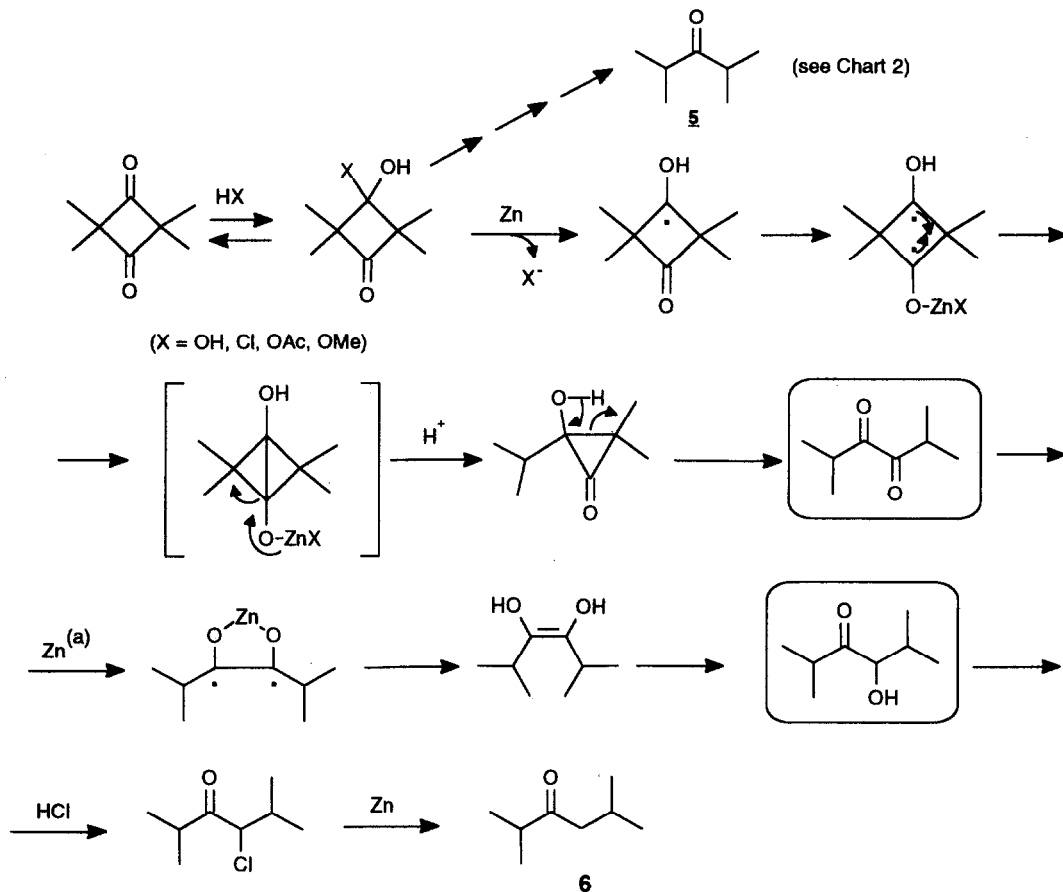Two indications emerge clearly from the results in Table 3, the inevitable

Chart 3

(a) Reaction pathway of 1,2-diketones [8].

concurrency of hydrolytic cleavage and the necessity of an acid-catalyzed nucleophilic addition prior to reduction. A possible mechanistic pathway in agreement with observations may be drawn for the zinc-promoted reaction of tetramethylcyclobutane-1,3-dione, as in Chart 3. The carbon-carbon bond formation, yielding a cyclopropane ring, is not unusual [8]. Of course, the intermediate with two condensed cyclopropyl rings may be not completely formed, the C-C bond breaking being possibly concerted with the C-C bond formation. The intermediacy of the α-diketone, 2,5-dimethylhexane-3,4-dione, and of the α-ketol, 4-hydroxy-2,5-dimethylhexane-3-one (evidentiated with boxes in Chart 3), was confirmed by reacting each of these compounds independently with zinc in HCl/AcOH (see Experimental).

In conclusion, the previously formulated hypothesis, that the zinc-promoted reduction in acetic acid is a complex process with radical and ionic processes [4-7], seems to hold also with alkyl substituted 1,3-diketones, the behaviour of which can be explained according to the general mechanism.

Experimental

Gas chromatographic analyses were performed with a Carlo Erba HRGC 5300 Mega Series instrument, using a SPB-35, 30m x 0.25 mm capillary glass column. GC/MS experiments were carried out with a Hewlett-Packard Model 5830A apparatus, equipped with a 0.5 m 2% OV-17 Chromosorb GAW-DMLS column. ^{1}H NMR spectra were recorded on a Bruker WP-80 spectrometer, with $CDCl_3$ as the solvent and Me_4Si as the internal standards.

Materials. 2,4-Pentanedione, tetramethylcyclobutane-1,3-dione, and 4-hydroxy-2,5-dimethylhexane-3-one were commercially available reagent grade compounds and were used as received, after checking their purity. 3-Methyl-2,4-pentane- dione [10] and 3,3-dimethyl- 2,4-pentanedione [2] were prepared according to literature and also purchased. 4-Methoxy-3-pentene-2-one [11] and 2,5-dimethylhexane-3,4-dione [12] were synthesized as reported in the literature.

Ethanoic acid (AcOH) was dehydrated by refluxing with its anhydride [6]. Solutions of ca. 0.3 M anhydrous HCl in AcOH were prepared by bubbling HCl gas into anhydrous AcOH.

Amalgamated zinc was prepared immediately prior to use, by stirring zinc powder with $HgCl_2$ in acid aqueous solution [13], washing with water and with the solvent to be used in the reaction.

Reduction Experiments. Different reaction conditions were used, as reported in the Tables, together with the corresponding results. In a typical reaction, 0.3 mmol β-diketone in 10 ml AcOH were treated with a two- or three-fold excess

zinc or amalgamated zinc. The reaction was stopped, generally after 2 h, the mixture poured into water containing sodium acetate and extracted several times with CH_2Cl_2. The organic extracts were reunited, washed with water to neutrality, dried over anhydrous Na_2SO_4, and evaporated. In order to detect any loss of unreacted volatile species, diphenylmethane was used as an internal standard and blank experiments were performed.

Reaction products were identified on the basis of their mass and ^{1}H NMR spectra, as compared with those of authentic samples.

Reduction of 2,5-dimethylhexane-3,4-dione. 0.7 Mmol α-diketone were treated with zinc in AcOH/HCl. After 2 days stirring at room temperature, all the starting material disappeared, yielding, after usual work-up, 97% 4-hydroxy-3,4- dimethyl-hexane-3-one and 3% 2,5-dimetyl-3-hexanone, 6.

Reduction of 4-hydroxy-2,5-dimethylhexane-3-one. When 2 mmol α-ketol were treated with zinc in AcOH, after 24 h at room temperature and usual work-up, 43% unreacted starting material was recovered, together with 57% α-diol, 2,5-dimethylhexane-3,4-diol, identified on the basis of the mass spectrum, as compared with an authentic sample. When the reaction was performed in AcOH/HCl, unreacted starting material was recovered together with 5% of 6. This confirms the importance of HCl in generating chloro-derivatives along the reduction pathway.

Reaction of 4-methoxy-3-pentene-2-one. 1 Mmol substrate, treated with 2 equivalent zinc, underwent demethylation to 2,4-pentanedione in AcOH (58%, after 20 h at room temperature), in AcOH/HCl (almost quantitatively under the same conditions), and even in tetrahydrofuran, although more slowly.

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