

Ultrasound Assisted Zinc Reactions in Synthesis 1. Efficient Reduction of Enones

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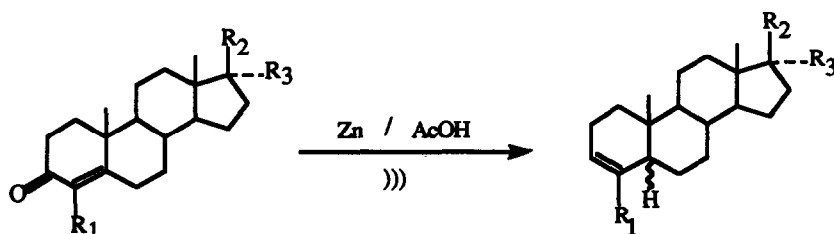
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Abstract: Zinc reduction of α,β -unsaturated ketones in acetic acid has been efficiently accomplished under sonochemical conditions. Different α -enone systems give two kinds of products: olefins and allylic alcohols. Regio- and stereoselectivities are reported.

Reduction of α,β -unsaturated ketones is used to afford isolated double bonds, particularly in the synthesis of common steroid olefin systems. Among several methods found in the literature¹, zinc in acetic acid at room temperature is reported as a selective reductive process for the enone system in the presence of isolated ketones². Migration of the double bond to the carbon atom which originally carried the oxygen is the usual feature of this partial reduction.

The use of ultrasound to enhance the chemical reactivity of metal powders in heterogenous solid-liquid systems is well established³. Our experience in sonochemistry⁴ and in particular the use of ultrasonic irradiation to activate zinc powder to perform the Reformatsky reaction⁵, prompted us to apply sonochemical conditions to assist the reduction of α,β -unsaturated ketones.

We find that steroids with the common 4-en-3-one system are efficiently reduced to Δ^3 -steroids, as illustrated in Scheme 1.



1 R₁=H; R₂=OAc; R₃=H

2 R₁=H; R₂=OAc; R₃=H

3 R₁=Cl; R₂=OAc; R₃=H

4 R₁=Cl; R₂=OAc; R₃=H

5 R₁=H; R₂,R₃=O

6 R₁=H; R₂,R₃=O

7 R₁=H; R₂=COCH₃; R₃=H

8 R₁=H; R₂=COCH₃; R₃=H

Scheme 1

In a typical procedure, 3-oxoandrost-4-en-17 β -yl acetate 1(500mg) in a glass Rosette cell was dissolved in AcOH (30ml). Zinc dust (5 μ m, Aldrich) (4g) was added and the reaction mixture irradiated with an immersion probe system (Sonics & Materials, Inc. Mod.VC, 600Watts, 20KHz, 1/2inch probe, 95W/cm⁻²) at 15°C. After 15 minutes the reaction was complete (tlc monitoring). The solution was evaporated under reduced pressure after filtration of the zinc and the residue extracted with ether.

The steroidal 4-en-3-ones 1, 3, 5 and 7 yielded almost quantitatively mixtures of the 5 α - and 5 β -3-olefins 2⁶, 4⁷, 6⁸, and 8⁹ (Table 1). The lack of reactivity of the isolated carbonyl groups present at 5 and 7 towards this reaction was confirmed by ir, ¹H and ¹³C nmr.

Variable ratios were found for the epimeric mixtures (Table 1). The stereoelectronic features of the substrates probably affect the approach of the reagents to the β -carbon on the postulated allylic radical at C-5 formed in the course of the reaction^{10,11}.

Table 1. Zinc reduction of 4-en-3-ones under ultrasonic irradiation

Substrates (500mg)	Zinc dust (g)	Solvent	Temperature (°C)	Time (min.)	Products	Epimeric ratio ^a (5 α :5 β)
1	4	AcOH	15	15	2	0.9:1
1	"	AcOH:H ₂ O (1:1)	"	"	2	"
3	4	AcOH	15	15	4	1.7:1
3	"	AcOH:H ₂ O (1:1)	"	"	4	"
5	6	AcOH	15	15	6	0.8:1
7	5	AcOH	25	10	8	1.5:1

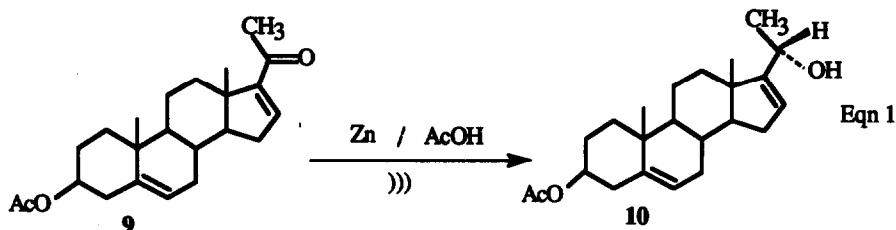
^a Calculated by integration of the 3-H signals in crude samples.

The ultrasound- assisted zinc reduction in acetic acid is complete in a very short time (15 minutes *versus* 1-5 hours for silent reactions^{2,10}). Furthermore a significant decrease of the amount of zinc needed to perform the reactions and the complete absence of by-products (apart from steroid 3 where traces of a dimer were found) makes this sonochemical process very efficient. These results corroborate the known effectiveness of ultrasonic irradiation to increase greatly the reactivity of metal powders.

The same results were also obtained for reactions conducted under milder solvent conditions, as

reported in Table 1.

Another α,β -unsaturated carbonyl system, the 16-en-20-one present in pregnane **9**, a readily available material for steroid synthesis, under the same conditions but at 25°C for 1h, gave the pure 16-en-20(R)-ol **10**¹² quantitatively (Eqn 1).



This result suggests a different mechanism pathway involved in its formation, probably through acetolysis of the O-Zn bond as suggested by McKenna *et al.*².

A reference to this type of reduction has been made previously for a steroid with a 16-en-20-one system when treated with Zn/AcOH/H₂O under different conditions¹³.

The chemoselectivity observed in the reduction of 4-en-3-ones in the presence of isolated carbonyl groups and the good stereoselectivity of the reduction of a 16-en-20-one, renders these sonochemical reactions of interest for synthetic purposes.

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6. IR (KBr) : 3020 cm^{-1} (=C-H), 1645 cm^{-1} (C=C) ; ^1H NMR (CDCl_3 , 200MHz) 5 α isomer: δ 0.78 (s, 18-H₃) , 0.80 (s, 19-H₃) , 5.28 (m, 4-H) , 5.54 (m, 3-H) ; 5 β isomer: δ 0.78 (s, 18-H₃) , 0.95 (s, 19-H₃) , 5.29 (m, 4-H) , 5.65 (m, 3-H); ^{13}C NMR (CDCl_3 , 50MHz) 5 α isomer: δ 125.34 (C₃), 131.12 (C₄) ; 5 β isomer: δ 127.00 (C₃) , 131.99 (C₄).
7. Spectroscopic data are in agreement with those reported in ref. 10.
8. IR (KBR) : 3020 cm^{-1} (=C-H), 1735 cm^{-1} (C=O); ^1H NMR (CDCl_3 , 200MHz) 5 α isomer: δ 0.79 (s, 19-H₃) , 0.87 (s, 18-H₃) , 5.29 (m, 4-H) , 5.54 (m, 3-H) ; 5 β isomer: δ 0.88 (s, 18-H₃) , 0.98 (s, 19-H₃) , 5.31 (m, 4-H) , 5.64 (m, 3-H) ; ^{13}C NMR (CDCl_3 , 50MHz) 5 α isomer: δ 125.47 (C₃) , 130.81 (C₄) , 217.24 (C₁₇) ; 5 β isomer: δ 127.10 (C₃), 131.85 (C₄), 217.24 (C₁₇).
9. IR(KBR): 3020 cm^{-1} (=C-H) , 1705 cm^{-1} (C=O); ^1H NMR (CDCl_3 , 200MHz), 5 α isomer: δ 0.61(s, 18-H₃) , 0.77 (s, 19-H₃) , 2.10 (s, 21-H₃) , 5.30 (m, 4-H) , 5.54 (m, 3-H); 5 β isomer: δ 0.62 (s, 18-H₃), 0.95 (s, 19-H₃) , 2.11 (s, 21-H₃) , 5.31 (m, 4-H) , 5.64 (m, 3-H); ^{13}C NMR (CDCl_3 , 50MHz) 5 α isomer: δ 125.42 (C₃) , 131.21 (C₄) , 209.51 (C₂₀); 5 β isomer: δ 127.99 (C₃) , 132.22 (C₄) , 209.51 (C₂₀) .
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12. IR(KBR): 3300-3500 cm^{-1} (OH) ; ^1H NMR (CDCl_3 , 200MHz), 5 α isomer: δ 0.92 (s, 18-H₃) , 1.06 (s, 19-H₃), 1.33 (d, J=6Hz, 21-H₃) , 4.36 (q, J=6Hz, 20 β -H), 5.65 (m, 16-H) ; ^{13}C NMR (CDCl_3 , 50MHz), δ 123.05 (C₁₆) , 159.66 (C₁₇) , 73.93 (C₂₀).
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