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# Ultrasound Assisted Zinc Reactions in Synthesis 2. A New Clemmensen-type Reduction

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**Abstract:** A mild and efficient method is described for the reduction of carbonyls to methylene groups. Under ultrasonic irradiation, deoxygenation of 3-oxosteroids with zinc dust in acetic acid or acetic acid / water was achieved in 15 minutes. The observed selectivity at C-3 in the presence of 17- and 20-oxo groups is discussed.

Clemmensen reduction is a powerful method widely used in synthesis to convert carbonyls to methylenes[1]. Quite recently a reaction performed in an ultrasonic laboratory cleaner has been reported[2].However the vigorous conditions usually employed make it unsuitable for the reduction of acid--sensitive and polyfunctional compounds.Following our experience with zinc reduction of α,β-unsaturated ketones, high-intensity ultrasound was applied to 3-oxosteroids under the same rather mild conditions described in the previous note[3].

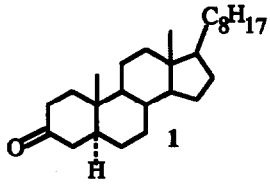
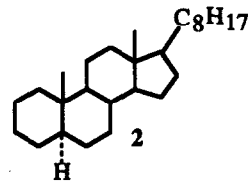
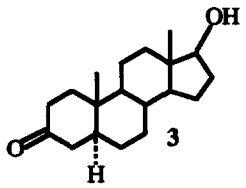
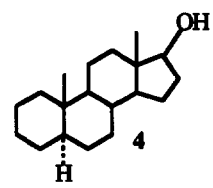
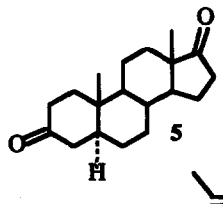
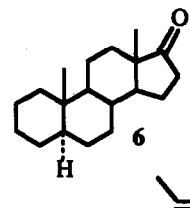
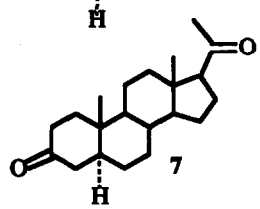
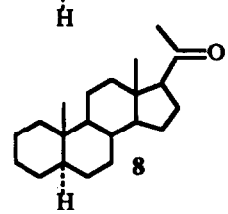
Steroids from different series such as 5α-cholestan-3-one **1**, 17β-hydroxy-5α-androstan-3-one **3**, 5α-androstane-3,17-dione **5** and 5α-pregnane-3,20-dione **7** have been evaluated. All the reactions were completed in 15 minutes and the results are summarized in Table 1.

Ultrasonic irradiation greatly enhances the rates of these heterogenous reactions, leading to complete absence of by-products and good yields of pure 3-deoxysteroids **2**, **4**, **6** and **8**[4,5] were achieved. Furthermore, as a result of the application of ultrasound to the reaction, commercially available zinc without any previous activation (sonic or chemical) could be used. This simplification as well as the mild conditions required (AcOH or AcOH:$H_2O$ ; room temperature), renders this procedure a very convenient method to perform a Clemmensen reaction.

Selectivity of reduction for the 3-oxo group in the presence of 17- and 20-oxo groups in the androstane **5** and the pregnane **7** respectively was found and confirmed by treatment of 3β-hydroxy-5α--androstan-17-one and 3β-hydroxy-5α-pregnan-20-one under the same conditions previously used. After 30 minutes any reaction has occurred. This is in agreement with results reported by Yamamura *et al.* for reactions performed on steroids under different mild conditions[6]. The observed lack of reactivity is consistent with the known susceptibility of the Clemmensen reductions to steric hindrance[7] and makes this mild sonochemical process even more valuable for synthetic purposes.

Investigations to evaluate the mildness of the method towards functionalities, such as cyano, amido and acetoxy are in progress.

Table 1. Zinc reduction of 3-oxosteroids under ultrasonic irradiation

| Substrates[a] | Solvent | Temp. (°C) | Products | Yield(%)[b] |
|---|---|---|---|---|
|  1 | AcOH | 15 |  2 | 89 |
|  3 | AcOH<br>AcOH:$H_2O$ 2:1 | " |  4 | 90 |
|  5 | AcOH | " |  6 | 87 |
|  7 | AcOH | 25 |  8 | 90 |

[a] The reactions were performed with 5g of zinc dust ( 5μm; Aldrich) per 500mg of 3-oxosteroid.

[b] The yields are reported for 15 minutes of reaction and refer to crystalline products.

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REFERENCES AND NOTES

1. Vedejs, E. *Org. React.*, **1975** , 22, 401-422.
2. Reeves, W.P.; Murry, A.J.; Willoughby, D.W.; Friedrich, W.J., *Synth. Commun.*, **1988**, 18, 1961-1966.
3. See the typical procedure described in previous note: Salvador, J.A.R.; Sá e Melo, M.L. ; Campos Neves, A.S., *Tetrahedron. Lett.*
4. $^1$H NMR (CDCl3, 200MHz) : **2** δ 0.64 ( s, 18-H3), 0.78 ( s , 19-H3 ), 0.86 (d, J=8Hz , 21-H3), 0.90 (d, J=8Hz , 26-H3 e 27-H3); **4** δ 0.73 (s, 18-H3), 0.79 ( s, 19-H3 ), 3.63 (m, 17α-H) **6** δ 0.80 ( s, 18-H3) ,0.86 (s, 19-H3 ) **8** δ 0.59 (s, 18-H3), 0.77 (s, 19-H3 ), 2.10 (s, 21-H3), 2.51 (t, J = 8Hz, 17α-H ).
5. $^{13}$C NMR data for **2**, **4** and **6** are in agreement with:Blunt, J.W.; Stothers,J.B.,*Org. Magn. Reson.*,**1977**, 9, 439-464; selected data for **8** (CDCl3, 50 MHz) δ 209.4 ($C_{20}$).
6. Yamamura, S.; Toda, M.; Hirata , Y., *Org.Synth.Coll.*, **1988**, 6, 289-292.
7. Yamamura, S., *Chem. Commun.*, **1968**, 1494-1495.

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