

Sonochemical Reduction of α,β -Epoxy Ketones and α' -Oxygenated Analogs by Aluminium Amalgam

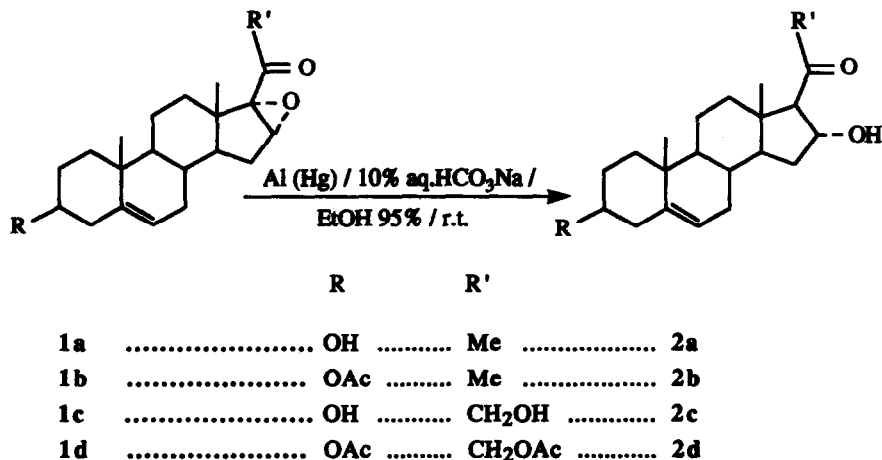
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Abstract: The sonochemical reductive opening of α,β -epoxy ketones and their α' -oxygenated (-OH or -OAc) analogs by aluminium amalgam allows shorter reaction times, better yields of the respective β -hydroxy ketones and minimization of by-products. The rates of these reactions are affected by the intensity of the acoustic waves and by temperature.

Reductions of α,β -epoxy ketones to the corresponding β -hydroxy ketones are of great interest in the synthesis of a variety of important natural products and several procedures have been reported for this selective reduction¹. Our improved method with aluminium amalgam², when performed on steroids such as 16 $\alpha,17\alpha$ -epoxy-20-oxopregnenes, affords good yields of 16 α -hydroxy-20-ketones without formation of 16-en-20-ones as by-products, however long reaction times (28-32 hours) were required to process 2-3 mmoles of substrate. 21-Oxygenated (-OH or -OAc) 16 $\alpha,17\alpha$ -epoxy ketones, a type of compound which has not been previously subjected to reduction with aluminium amalgam, gave, in quite poor yields, the corresponding 16 α -hydroxy ketones, therefore limiting the use of this low cost reagent.

Following our previous work in sonochemistry³, a burgeoning research field⁴, we now report the successful application of ultrasound to heterogeneous reductions with aluminium amalgam. The study includes the evaluation of acoustic waves intensity and temperature during the experiments as well as mechanistic consi-



Scheme 1

Table 1. Comparative study under ultrasonic and classical conditions

Substrate	Reaction Conditions ^{a)}	β -Hydroxy ketone ^{b)} %	By-products ^{b)} %
1a	6 h /)))	82	—
	6 h / (↻)	63	—
1b	6 h /)))	80	17
	6 h / (↻)	54	15
1c	20 min. /)))	80	14
	20 min. / (↻)	23	4
	60 min. /)))	65	30
	60 min. / (↻)	50	28
1d	60 min. /)))	63	15
	60 min. / (↻)	40	10

a) Reaction time / ultrasound ())) or magnetic stirring [(↻)]

b) Quantified by HPLC and identified ^{5,6} by ¹H and ¹³C NMR

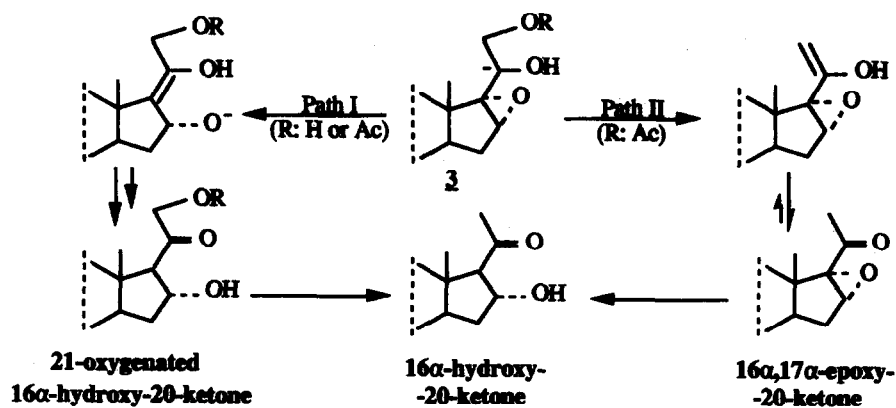
derations about the products generated by reaction of α' -oxygenated α,β -epoxy ketones.

The classical conditions² (Scheme 1) were applied to the α,β -epoxy ketones 1a-1d (0.15mmoles) and the heterogenous mixtures submitted to ultrasonic irradiation using an ultrasonic cleaning bath (40 KHz). The experiments performed showed a significant improvement in such sonicated reductions, which allow better yields and faster reactions for all the 16 α ,17 α -epoxy-20-oxopregnenes studied (Table 1).

Ultrasound has a marked effect on the reaction rates. Even when substrates 1a and 1b were processed on a larger scale (3mmoles) the reactions were 4 times faster. Under the alkaline conditions used to perform these reactions, the β -hydroxy ketone 2b was partially hydrolysed (at C-3) with subsequent formation of the corresponding 3 β ,16 α -dihydroxy-20-ketone as a by-product.

The 21-oxygenated epoxy ketones 1c and 1d reacted much faster than their non functionalized counterparts 1a and 1b. However, the reaction times had to be carefully controlled to avoid increase of unwanted by-products, which are mainly due to reductive C-O fission at C-21. The substrate 1c after 20 minutes of sonicated reaction afforded the best yield of 16 α ,21-dihydroxy-20-ketone 2c (Table 1). More prolonged reaction (60 minutes) led to conversion of 2c into the corresponding 16 α -hydroxy-20-ketone. Such a result may indicate that the reduction of the 21-OH group occurs after the reductive opening of the epoxide. Two by-products also accompany the formation of the 21-acetoxy-16 α -hydroxy-20-ketone 2d, the 16 α -acetoxy-21-hydroxy-20-ketone resulting from an internal transesterification of 2d and the 16 α ,17 α -epoxy-20-ketone. The presence of the latter from the beginning of the reaction suggests a reductive fission, as aforementioned for 2c, but in this case, of the starting material 1d and is a competitive reaction for the epoxide reductive opening.

The mechanism proposed for the reduction of ketones⁷, α,β -epoxy ketones⁸ and α -heterosubstituted ketones⁹ leads us to suggest the formation of 3 (Scheme 2) by reaction of substrates 1c and 1d with aluminium amalgam. The carbanion 3 can then either induce the ring-opening of the epoxide (path I) or the elimination of the group at C-21 (path II) with production of 21-oxygenated 16 α -hydroxy-20-ketones and 16 α ,17 α -epoxy-20-ketones, respectively. Since aluminium amalgam was used in large excess, further conversion of both compounds into 16 α -hydroxy ketones will proceed (Scheme 2). According to our results, path II was only



Scheme 2

significant for the 21-acetoxy-16 α ,17 α -epoxy-20-ketone **1d**, where a good leaving group is present. We wish to emphasize that the limitations mentioned for the reduction of α -oxygenated substrates **1c** and **1d** were greatly overcome by ultrasonic irradiation which made possible yields unavailable under classical conditions and also shorter reaction times.

Sonochemistry is reported to be affected by several factors⁴ and, as a first approach, we have decided to study the influence of acoustic intensity and temperature on reactions with the epoxy ketones (0.3mmoles) **1a**

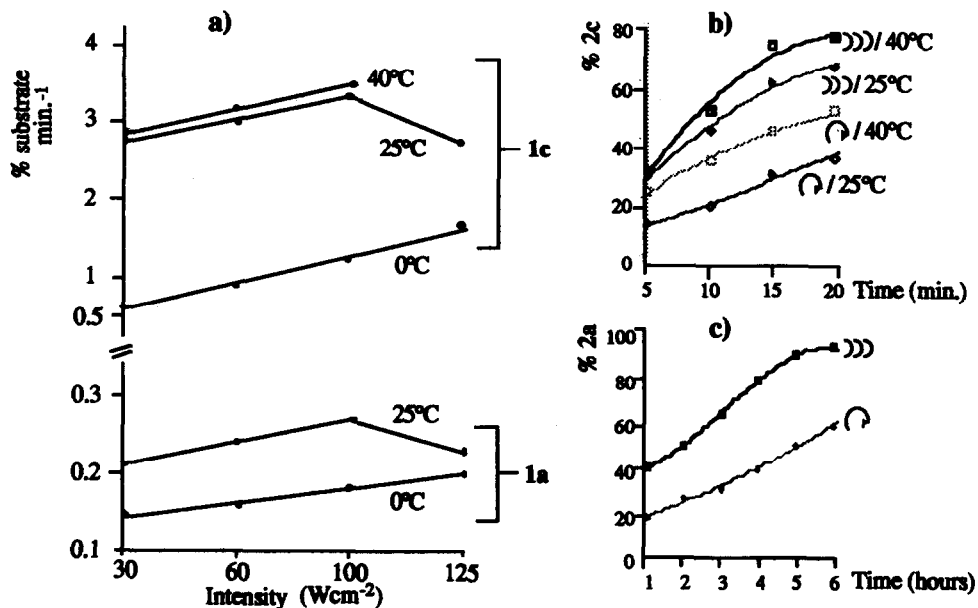


Figure 1. a) % of substrates (**1a** and **1c**) converted *per* minute vs acoustic intensity for reactions performed at different temperatures; b) yield (%) of product **2c** vs reaction time for 25°C and 40°C, under magnetic stirring and ultrasound (100Wcm⁻²); c) yield (%) of product **2a** vs reaction time for 25°C, under magnetic stirring and ultrasound (100Wcm⁻²)

and 1c. The experiments were performed in aluminium cells with an immersion titanium horn (variable acoustic potency up to 250W, equipped with a flat tip, 12.7 mm diameter at the irradiating surface) and the temperature was kept constant using a thermostated bath with stirring.

For reactions at 0°C a correlation between the acoustic intensities studied and the amount of substrate converted *per* minute was observed (Fig.1a). However, for reactions performed at 25°C, the highest amount of substrate consumed was detected when 100 Wcm⁻² were applied. Further increase of the ultrasonic intensity to 125 Wcm⁻² resulted in slower reactions (Fig.1a) which indicates that the optimum acoustic intensity for these reductions is 100 Wcm⁻². These findings are in agreement with previous observations on other heterogeneous reactions¹⁰, and are rationalized by a loss of the cavitation efficiency. Under the reported optimized ultrasonic conditions the reductions were much faster than under magnetic stirring at the same temperature (Fig.1b and 1c).

For an acoustic intensity of 100 Wcm⁻² a further increase in temperature to 40°C improved the reaction rates (Fig.1a and 1b). This thermal activation, also seen when reactions were performed under magnetic stirring (Fig.1b), suggests a mass transport dependence for the described reductions, although the erosive effects at the metal surface as well as the fracture of the protective oxide coating promoted by ultrasound should also have profound bearing on the course of the sonochemical reactions.

Further experiments will be undertaken to evaluate the effect of temperature on the reactions and to apply sonochemical reduction by aluminium amalgam to other epoxy ketones.

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5. 2a: in agreement with the reported data in ref. 2a.
6. 2b: ¹H NMR (200MHz, CDCl₃) δ 2.17 (s, 21-H₃), 2.90 (d, J 5.9 Hz, 17 α -H), 4.85 (m, w_{1/2} 15.5 Hz, 16 β -H); ¹³C NMR (50MHz, CDCl₃) δ 74.26 (C-16), 208.69 (C-20); 2c: ¹H NMR (200MHz, C₅D₅N) δ 2.71 (d, J 8 Hz, 17 α -H), 4.35 (ABq, J 20 Hz, 21-H₂), 5.05 (m, w_{1/2} 14.5 Hz, 16 β -H); ¹³C NMR (50MHz, C₅D₅N) δ 71.10 (C-21), 71.84 (C-16), 208.51 (C-20); 2d: ¹H NMR (200MHz, CDCl₃) δ 2.17 (s, 21-OCOCH₃), 2.52 (d, J 7 Hz, 17 α -H), 4.65 (ABq, δ_A 4.59, δ_B 4.72, J 17.2 Hz, 21-H₂), 4.84 (m, w_{1/2} 17 Hz, 16 β -H).
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