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

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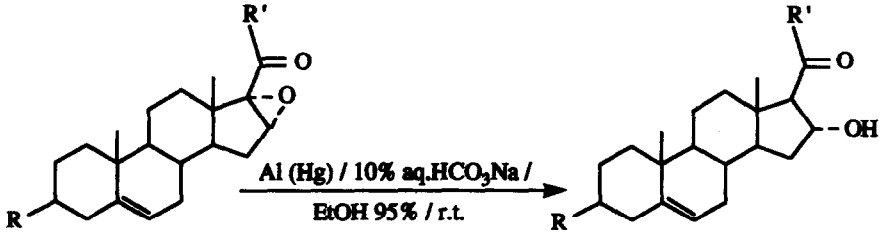
Abstract: The sonochemical reductive opening of α,β-epoxy ketones and their α'-oxygenated (-OH or -OAc) analogs by aluminium amalgam allows shorter reaction times, better yields of the respective β-hydroxy ketones and minimization of by-products. The rates of these reactions are affected by the intensity 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 reduction[1]. Our improved method with aluminium amalgam[2], when performed on steroids such as 16α,17α--epoxy-20-oxopregnenes, affords good yields of 16α-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) 16α,17α-epoxy ketones, a type of compound which has not been previously subjected to reduction with aluminium amalgam, gave, in quite poor yields, the corresponding 16α-hydroxy ketones, therefore limiting the use of this low cost reagent.

Following our previous work in sonochemistry[3], a burgeoning research field[4], we now report the sucessful 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-



	R	R'	
1a	OH	Me	2a
1b	OAc	Me	2b
1c	OH	CH_2OH	2c
1d	OAc	CH_2OAc	2d

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 ^{1}H and ^{13}C NMR

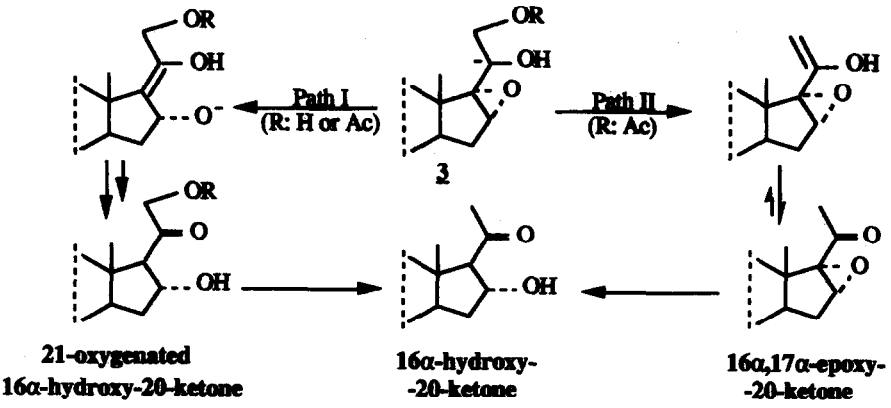
derations about the products generated by reaction of α'- oxygenated α,β-epoxy ketones.

The classical conditions[2] (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 16α,17α-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 3β,16α-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 16α,21-dihydroxy-20-ketone **2c** (Table 1). More prolonged reaction (60 minutes) led to conversion of **2c** into the corresponding 16α-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-16α-hydroxy-20-ketone **2d**, the 16α-acetoxy-21-hydroxy-20-ketone resulting from an internal transesterification of **2d** and the 16α,17α-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 ketones[7], α,β-epoxy ketones[8] and α-heterosubstituted ketones[9] 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 16α-hydroxy-20-ketones and 16α,17α-epoxy-20-ketones, respectively. Since aluminium amalgam was used in large excess, further conversion of both compounds into 16α-hydroxy ketones will proceed (Scheme 2). According to our results, path II was only



Scheme 2

significant for the 21-acetoxy-16α,17α-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 factors[4] 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

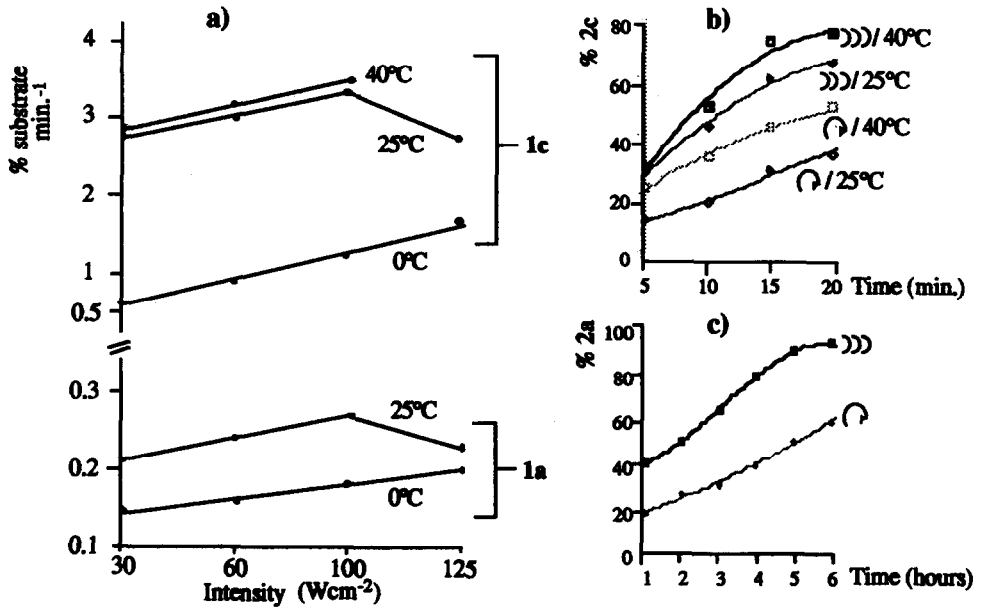


Figura 1. a) % of substrates (1a and 1c) converted *per* minute *vs* acoustic intensity for reactions performed at different temperatures; b) yield (%) of product 2c *vs* reaction time for 25°C and 40°C, under magnetic stirring and ultrasound (100Wcm^{-2}); c) yield (%) of product 2a *vs* reaction time 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 reactions[10], 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 applly 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, $CDCl_3$) δ 2.17 (s, 21-H_3), 2.90 (d, J 5.9 Hz, 17α-H), 4.85 (m, $w_{1/2}$ 15.5 Hz, 16β-H); ^{13}C NMR (50MHz, $CDCl_3$) δ 74.26 (C-16), 208.69 (C-20); **2c**: ^1H NMR (200MHz, C_5D_5N) δ 2.71 (d, J 8 Hz,17α-H), 4.35 (ABq, J 20 Hz, 21-H_2), 5.05 (m, $w_{1/2}$ 14.5 Hz, 16β-H); ^{13}C NMR (50MHz, C_5D_5N) δ 71.10 (C-21), 71.84 (C-16), 208.51 (C-20); **2d**: ^1H NMR (200MHz, $CDCl_3$) δ 2.17 (s, 21-OCOCH_3), 2.52 (d, J 7 Hz, 17α-H), 4.65 (ABq, δ_A 4.59, δ_B 4.72, J 17.2 Hz, 21-H_2), 4.84 (m, $w_{1/2}$ 17 Hz, 16β-H).
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