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ORGANOCOPPER REACTIONS-II.[1] REDUCTION OF STEROIDAL α-ACETOXY- AND α-BROMO-KETONES WITH LITHIUM DIMETHYLCUPRATE

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It was recently shown[1] that lithium dimethylcuprate is an efficient and mild reductant for α-epoxy-ketones. The inference that electron transfer[2] to such substrates is very rapid, led to speculation that other α-functionalised ketones might also be susceptible to reduction; accordingly a series of experiments was carried out on steroidal α-acetoxy- and α-bromo-ketones.

When an ethereal solution of 2α-acetoxy-5α-cholestan-3-one[3] (1) was added to lithium dimethylcuprate (2 mol. equiv.) in ether at 0° under N_2, a rapid reaction took place and the mixture was worked up after 4 min and filtered through silica with benzene to give the 3-ketone (2) (82%). A similar result was obtained with the 2β-acetoxy-3-ketone (3), and in either case the reaction could be quenched with Ac_2O to give the Δ^2-enol acetate of 3.

The reduction method was further tested on two cucurbitacin derivatives which had resisted other possible methods[4] for selective 2-deacetoxylation. Thus, brief treatment of the 2,16-diacetate[4] (4) in dry THF with ethereal lithium dimethylcuprate at 0°, followed by mild alkaline treatment to eliminate the 16-acetoxyl group, afforded the Δ^{16}-3,11,20-trione[5] (6) (50%). A similar procedure on the 2,16,19-triacetate[4] (5) was less successful, but the 2-deacetoxyl compound (7) was obtained in 26% yield. These results demonstrate the value of this method for polyfunctional systems; further work is in progress to optimise yields.

In striking contrast to the reaction rate of 2-acetoxy-3-ketones, the reduction of 5-acetoxy-5α-cholestan-6-one (8) with lithium dimethylcuprate proceeded very slowly. After 18 h at 0°, starting material was no longer present, and the expected 6-ketone (9) was obtained (50%) together with a more polar product (35%), m.p. 255°, for which the hydroxy-lactone structure (10) was deduced from spectroscopic data. This was verified by treating the

acetoxy-ketone (8) with $NaNH_2$ in liquid NH_3-Et_2O to give 10 in quantitative yield.[6] The reason for slow reduction of 8 to 9 is not clear, but this evidently permitted the intervention of a proton abstraction step by Me_2Cu^- or a related base, leading to intramolecular condensation. The possibility of an intramolecular proton transfer to explain the necessary formation of the more basic ester-enolate, from a Δ^6-enolate anion, cannot be excluded.

Similar experiments were carried out on two steroidal α-bromo-ketones; the reaction of the 5α-bromo-6-ketone (11) with lithium dimethylcuprate in ether at 0° was complete within 2 min and afforded the debrominated product (12) (95%). A similar reaction on the 2α-bromo-3-ketone proceeded as rapidly and gave after chromatography the 3-ketone (2) (80%) together with the 2α-methyl-3-ketone (14) (12%). Mixed fractions revealed traces of further products which were not identified. The formation of the 2α-isomer (14) is not mechanistically significant since the reaction and isolation conditions allowed adequate opportunity for equilibration.

Although the conversion of α-bromo- to α-alkyl-ketones by lithium dialkylcuprates has been documented,[7] it was recently reported[8] that 2-bromocyclododecanone is reduced under these conditions. It is evident that the factors determining which of the competitive reaction pathways is followed, are not yet understood. Further work is in progress on this aspect of the problem. It is clear however, that lithium dimethylcuprate is a potentially useful reagent for the selective reduction of certain α-functionalised ketones, and that it may be the reagent of choice for converting secondary α-acetoxy-ketones to the parent ketones.

REFERENCES AND FOOTNOTES

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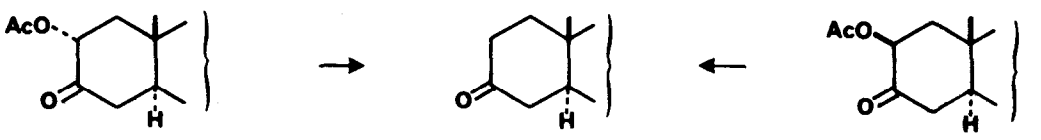
3. All starting materials were prepared according to standard literature methods; reaction products were fully characterised and were identified by comparison with authentic material, where appropriate. All partial formulae in the Scheme refer to the cholestane skeleton.



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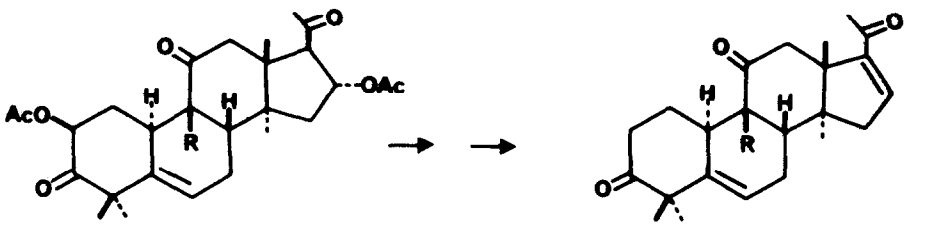
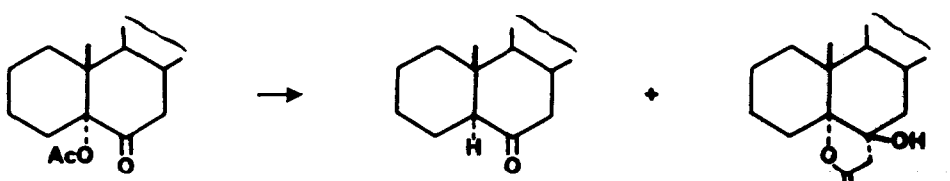


4 R = CH_3

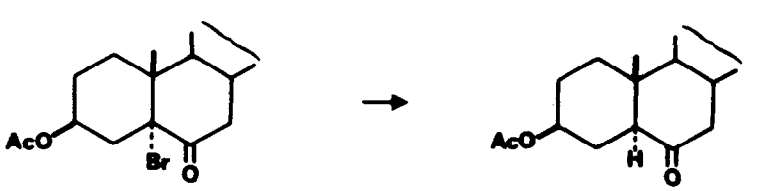
5 R = CH_2OAc

6 R = CH_3

7 R = CH_2OH



8 9 10



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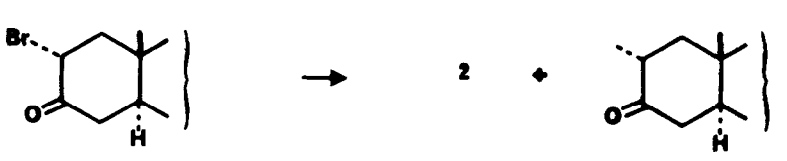

13 2 14

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