Metal Enolates as Protecting Groups for Ketones During Metal Hydride Reduction

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Summary Selective conversion of a ketone into a metal enolate is a convenient and efficient means of protecting such functions during metal hydride reductions.

SELECTIVE reduction of a specific carbonyl group in a molecule which bears a number of such functions is a problem frequently met in natural products chemistry. Although metal hydrides display differential reactivity with carbonyls in varying environments,[1] the most common approach has been the use of masking groups such as acetals, enamines, *etc.*, to protect selectively certain carbonyl functions.[2]

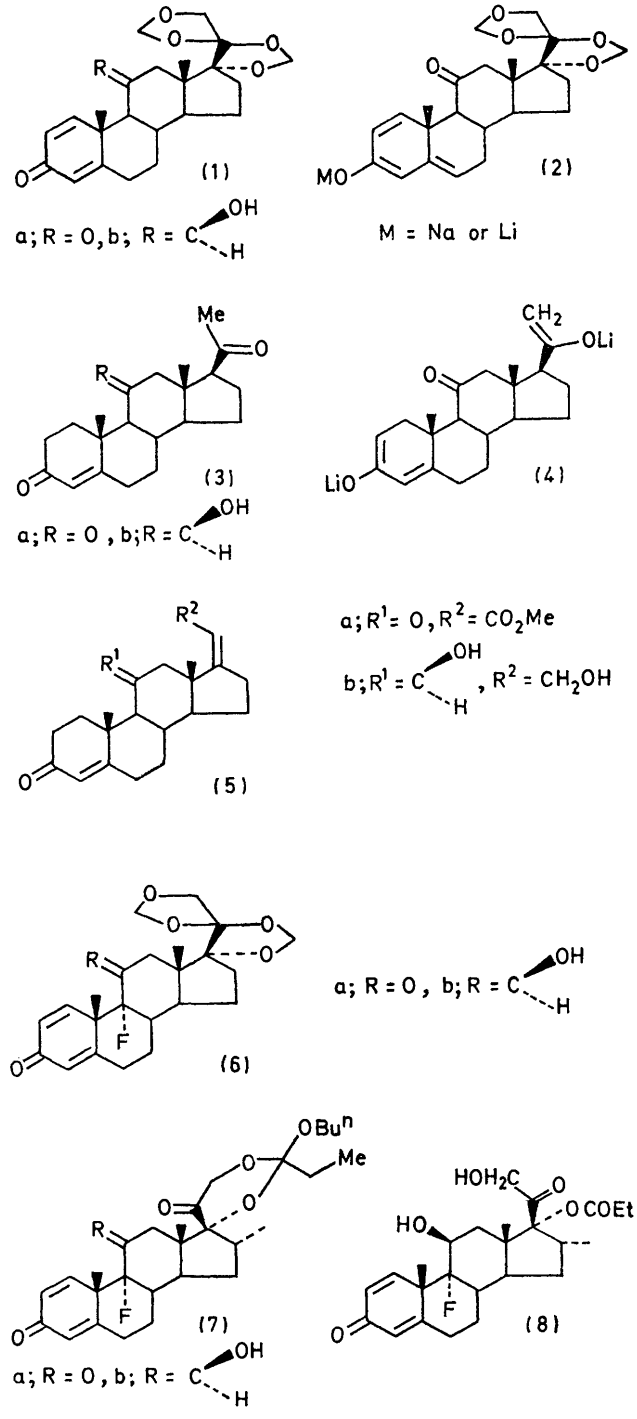
Recent studies have demonstrated the possibility of the selective conversion of steroidal ketones into metal enolates[3] which might be expected to be inert to metal hydride reduction (*cf.* ref. 4). We now report that the selective conversion of specific ketones into metal enolates is a reliable and convenient means of protecting such functions during metal hydride reductions.

Prednisone BMD (**1a**) may be converted into the corresponding 1,3,5-trien-3-olate (**2**) by sodium or lithium bistrimethylsilylamide[5] or trityl-lithium.[6] These enolates may be reduced *in situ* with metal hydride to give good yields of prednisolone BMD (**1b**). Better yields are obtained with Ph_3CLi than with sodium or lithium bistrimethylsilylamide. The visible colour-change attending the protonolysis of Ph_3CLi is an added advantage of the use of this reagent. Studies of the stability of lithium enolates, particularly reactive bis enolates such as (**4**) derived from (**3a**), indicate that these intermediates decay rather rapidly when stored in solution at room temperature ($t_{\frac{1}{2}}$ *ca.* 3 h). Thus the reaction was carried out at −78°. The formation of the bis enolates derived from (**3a**) and (**7a**) did not reach completion quickly at −78°. In this case, it was necessary to allow the enolate reaction to warm to 0°. Following enolate formation the solution was then cooled to −78° and the reducing agent added.

Reduction was carried out with $LiAlH_4$ and the excess was destroyed with gaseous NH_3. Compounds **1a**, **3a**, **5a**—**7a** were converted by this method into **1b**, **3b**, **5b**—**7b** respectively (40—75%). The conversion of (**5a**) into (**5b**) normally entails the reduction of an ester function as well as a ketone in the presence of a "masked" α,β-unsaturated ketone *via* three steps as in the commercial synthesis of hydrocortisone.[7] The reduction of (**7a**) into (**7b**), which involves the protection of the corticosteroid side chain as an enolized 17,21-orthoester, is of significance as such orthoesters are normal intermediates in the synthesis of the commercially important 17-acyloxy- or 17,20-bisacyloxy-corticosteroid analogues.[8]

The conversion of (**6a**) into (**6b**) completes an alternative synthesis[9] of the medicinally important 9α-fluoro-11β-hydroxy steroids avoiding the 9(11)-ene and 9β,11β-epoxide as intermediates.

The major complication in the use of metal enolates as protecting groups is the tendency of enolized α,β-un-



saturated ketones to undergo protonation at the α-carbon atom[10] to give the unconjugated isomer.

All reactions were carried out under argon in THF using 4—10 hydride equiv. of $LiAlH_4$ per mole of of substrate.

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[1] (a) P. J. Neustaedter in 'Steroid Reactions,' ed. C. Djerassi, Holden-Day, San Francisco, 1963, pp. 135—148; (b) D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 135—143.
[2] H. J. E. Loewenthal, *Tetrahedron*, 1959, **6**, 269; J. F. W. Keana, ref. 1(a), pp. 2—65.
[3] D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Comm.*, 1969, 1497: M. Tanabe and D. F. Crowe, *ibid.*, p. 1498.
[4] N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, 1968, **90**, 2927.
[5] V. Wannagat and H. Niederprum, *Chem. Ber.*, 1961, **94**, 1540.
[6] H. O. House and V. Kramer, *J. Org. Chem.*, 1963, **28**, 3362.
[7] J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Amer. Chem. Soc.*, 1955, **77**, 4436.
[8] Glaxo Group Ltd., Netherland Patent No. 6608763 (June 27, 1966), *Chem. Abs.*, 1967, **67**, 82326f.
[9] D. H. R. Barton, R. H. Hesse, M. M. Pechet, G. Tarzia, H. T. Toh, and N. D. Westcott, *Chem. Comm.*, 1972, 122, and references cited.
[10] G. Kruger, *J. Org. Chem.*, 1968, **33**, 1750 and references cited.
[11] R. E. Beyer, F. Hoffman, R. M. Moriarty, and L. H. Sarrett, *J. Org. Chem.*, 1961, **26**, 2421.
[12] B. J. Magerlein and R. H. Levin, *J. Amer. Chem. Soc.*, 1953, **75**, 3654.