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Rules for Ring Closure. Stereoelectronic Control in the Endocyclic Alkylation of Ketone Enolates

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Summary Endocyclic alkylation of ketone enolates is shown to depend critically upon the size of the so formed ring and six- but not five-membered cyclic ketones can be synthesized in this way; a rationale for this difference is presented. stereoelectronic grounds that 5-Endo-Trigonal processes, (6), were disfavoured, whereas 6-Endo-Trigonal closures, (7), were favoured ring closures. Since the Endo-alkylation, (3) to (5), is stereoelectronically similar to the processes (6) and (7) it was possible to predict that the Endo-alkylation of a ketone to a 5-membered ring would be disfavoured, whereas the formation of a 6-membered cyclic ketone, by analogy with the 6-Endo-Trig process (7), in this way would be favoured. We now present evidence that this is true. Thus inverse Markownikov addition of hydrogen bromide to the ketone (8)³ gave (90%) the ketobromide (9), b.p. 130 °C at 25 mmHg; v (neat) 3000m and 1705s cm⁻¹; δ (CDCl₃) 1·2 (s, 6H), 2·2 (s, 3H), and 2·2 and 3·35 (A₂B₂ m, 4H total), which was converted into both potassium and lithium enolates (10, M = K or Li) with potassium

KETONIC substances of the general type (1) can be deprotonated to the isomeric enolates (2) or (3) which, in principle, may be intramolecularly alkylated (when Y is a leaving group) to the ring structures (4) or (5). Since these alkylations proceed by breakage of the enolate double bond in either exocyclic or endocyclic modes, we refer to them as *Exo* and *Endo* alkylations, respectively. Recently, in a general treatment of ring closures,^{1,2} we suggested on

t-butoxide (1.5 equiv.) in t-butyl alcohol-ether and lithium di-isopropylamide (1.25 equiv.) in ether at 25 °C. In both cases the sole reaction product was the enol ether (11) (>70% isolated), ν (neat) 3000s, 1670s, 1220s, 1060s, and 820s cm⁻¹; δ (CDCl₃) 1.2 (s, 6H), 1.80 (t, J 7 Hz, 2H), 3.75 cm⁻¹; δ (CDCl₃) 1.2 (s, 6H), 1.80 (t, J 7 Hz, 2H), 3.75

and 4.05 (ABq, J 2 Hz, 2H), and 4.0 (t, J 7 Hz, 2H), which was very sensitive to hydrolysis and therefore converted into the 2,4-dinitrophenylhydrazone of (13), m.p. 102–103.5 °C.† Spectroscopic analysis of the reaction mixture from (10) showed the absence (<3%) of the cyclopentanone (12).



In contrast to this result, conversion of the ketone $(14)^4$ into the bromide (15), b.p. 100 °C at 5 mmHg, ν (neat) 2950 m and 1705s cm⁻¹; δ (CDCl₃) 1.05 (s, 6H), 1.65 (m, 4H), 2.1 (s, 3H), and 3.35 (m, 2H), and thence into the enolates (16,

M = K or Li) under the same conditions as before gave only the cyclohexanone (17),⁵ (>95% by n.m.r.), converted into the known 2,4-dinitrophenylhydrazone, m.p. 136—138 °C.⁶

The remarkable difference between these two cyclizations results from stereoelectronic control of the alkylation of the ambident nucleophile, *i.e.* the enolate ion. For such an ion, (19), carbon alkylation requires approach of the electrophile perpendicular to the plane of the enolate, whereas oxygen alkylation requires approach in the plane of the enolate. Consequently, in the five-membered ring case approach of the alkylating centre to the carbon site in the reasonable O-metallated species, existing as *s*-cis and *strans* forms shown in planar form (20), is sterically difficult‡ compared to its approach in the plane to the oxygen site, (20) to (22), yielding the observed enol ether product. On



† All new crystalline compounds have given adequate combustion data.

[‡] This difficulty has the same stereoelectronic origin as the disfavouredness of 5-Endo-Trig ring closures (ref. 1). These results indicate that the remaining direction for approach of an electrophile to the oxygen atom, *i.e.* perpendicular to the plane in (19), is in some way disfavoured relative to the in-plane approaches.

the other hand, in the six-membered precursor (21) the carbon alkylation is sterically possible, for the same reasons as those by which 6-Endo-Trig processes for ring closure are favoured,^{1,2} namely that the extra bond length in (21)enables a near perpendicular approach to the enolate and hence carbon alkylation.7

The natural extension of these ideas to the four- and three-membered cases for Endo-alkylation predicts, following the Rules of Ring Closure,¹ is that processes described by (23) and (24) would be disfavoured. In the fourmembered case, evidence has been presented that enol ether formation and participation of dipole (25) are the major

- ¹ J. E. Baldwin, J.C.S. Chem. Comm., 1976, 734. ² J. E. Baldwin, J. Cutting, W. Dupont, L. I. Kruse, L. Silberman, and R. C. Thomas, J.C.S. Chem. Comm., 1976, 736.

³ Prepared by method of M. A. Schexnayder and P. S. Engel, J. Amer. Chem. Soc., 1975, 97, 4825.

- ⁴ R. Gelin, S. Gelin, and C. Deshayes, Bull. Soc. chim. France, 1973, 2153.
- ⁵ R. E. Ireland and J. A. Marshall, J. Org. Chem., 1962, 27, 1615.
- ⁶S. Julia and C. Gueremy, Bull. Soc. chim. France, 1965, 2994.

⁷ The literature contains two cases wherein attempted closures of enolates of the type (10) led only to enol ether products: G. Baddeley, E. K. Baylis, and B. G. Heaton, Proc. Chem. Soc., 1961, 451; D. Taub, R. D. Hoffsommer, and N. L. Wendler, J. Org. Chem., 1964, 29, 3486. We thank Professor P. Grieco for bringing these results to our attention. A case of a 6-Endo-alkylation has been

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10 H. O. House and G. A. Frank, J. Org. Chem., 1965, 30, 2948; F. G. Bordwell, R. C. Scamehorn, and W. R. Springer, J. Amer. Chem. Soc., 1969, 91, 2087. ¹¹ H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, California, 1972, p. 492.

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processes.⁸ The three-membered case, which is involved in the classical Faworskii rearrangement,9 may similarly involve the favoured product enol ether $(\mathbf{27})$ or the dipole (28).¹⁰ In contrast to these limitations on *Endo*-alkylations, in accord with the Rules,¹ the Exo-alkylations, (2) to (4), are all favoured processes with many literature precedents for forming rings from 3 to 7 members.¹¹

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