

5-Endo-Trigonal Reactions: a Disfavoured Ring Closure

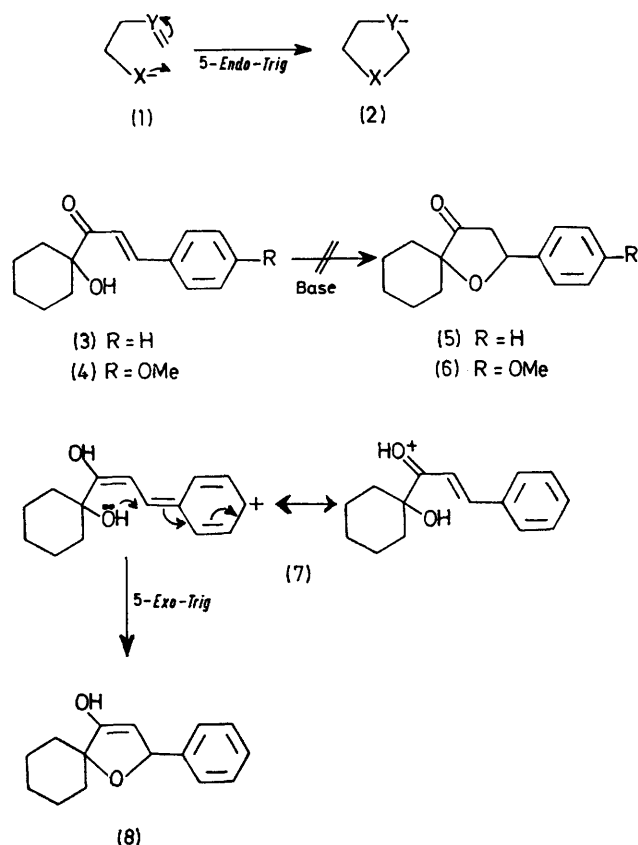
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Summary A number of polyfunctional molecules have been examined as substrates for the 5-Endo-Trigonal ring-forming reaction, and it has been found that for first-row elements this is a disfavoured process, alternative reactions of type 5-Exo-Trig generally taking precedence; one case of a 5-Endo-Trig closure for a second-row element, sulphur, has been found.

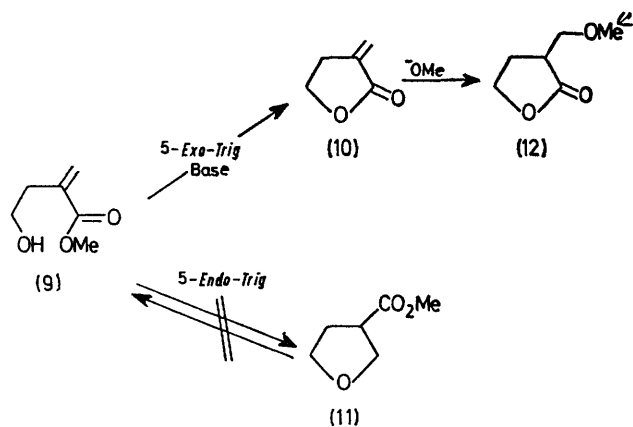
IN connection with a general treatment of ring-forming reactions, we have investigated examples of the 5-Endo-Trigonal process (1) to (2), since it was suggested that this is a geometrically disfavoured reaction.¹ We report here results which are in accord with this view.

Firstly, we synthesized the ketols (3) and (4) by condensation of the methylketone, made from methoxyvinyl-lithium and cyclohexanone,² with benzaldehyde or *p*-methoxybenzaldehyde. Under a variety of basic conditions, *e.g.* sodium methoxide-methanol, sodium hydride-tetrahydrofuran (temperature range 0–65 °C) we have been unable to close this substance to the furanones (5) or (6),† through a 5-Endo-Trigonal process. However, on acid catalysis (toluene-*p*-sulphonic acid in benzene at 80 °C) (3) and (4) were efficiently closed to the ketones (5) and (6) respectively. We believe this successful closure is the result of contributions from structures of type (7),³ which now permit the favoured 5-Exo-Trig mode of closure.

† All new compounds have given spectroscopic and analytical data in accord with their structures.



With these ring-closed products in hand, we have shown that they rapidly and efficiently exchange both their α -hydrogen atoms under the same basic conditions, *i.e.*, sodium methoxide in deuteriated methanol at 65 °C, in which (3) and (4) are *not* converted into (5) and (6), respectively. This proves that the lack of ring closure or ring opening is a result of a kinetic rather than a thermodynamic barrier. We conclude this is evidence for the existence of the steric barrier previously suggested.¹ Since this disfavoured 5-Endo-Trigonal reaction involves formation of the enolate [derived from (8)] which contains two trigonal

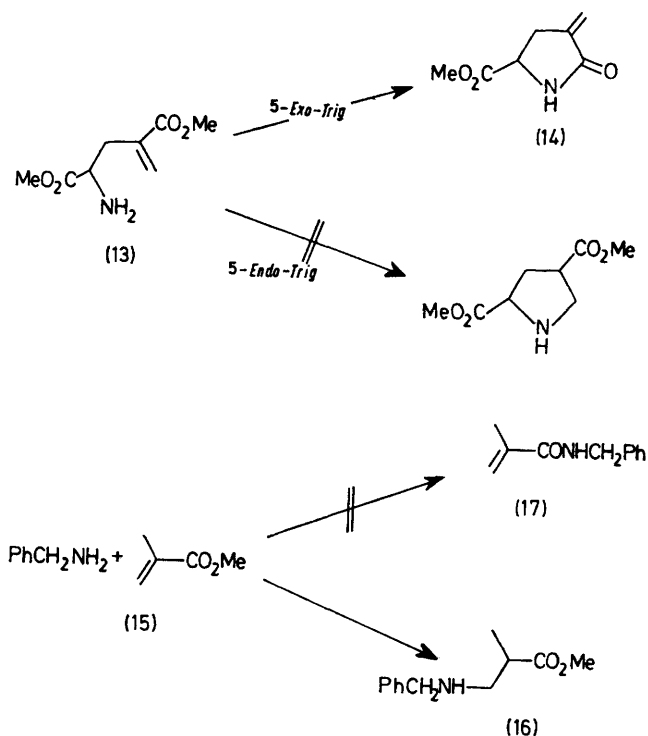


SCHEME 1

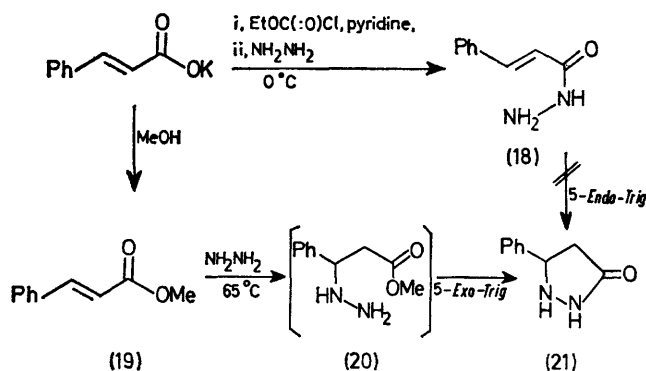
atoms in the five-membered ring and therefore may be an extreme test of the disfavoured nature of this process, we

chose to study the competition between 5-Endo-Trig and 5-Exo-Trig processes in a simpler system. The results of this investigation are summarized in Scheme 1.

Thus the alcohol (9), {obtained by opening [Ba(OH)₂] and methylation (CH₂N₂) of the known lactone (10)⁴} upon treatment with a variety of bases closed efficiently and cleanly to the lactone (10) (5-Exo-Trig process), with no trace of (11) (5-Endo-Trig process). Also (10) smoothly added methoxide to yield the ether (12), showing that the double bond is very susceptible to Michael-type addition. Again the ester (11) exchanged its α -hydrogen atom under the conditions of conversion of (9) into (10) with no reversion to (9).



A nitrogen analogue of (9) was prepared. Thus the amino-diester (13), upon release from its stable hydrochloride salt rapidly closed at 25 °C to the lactam (14) (100%) *via* the favoured 5-Exo-Trig pathway. It is known that primary amines add 1,4 to α -substituted acrylic esters (15) to (16) more rapidly than they are transacylated to

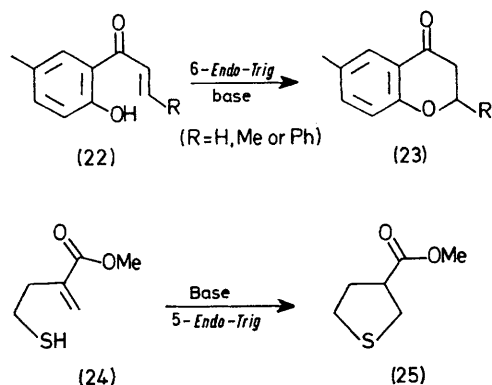


SCHEME 2

α -substituted acrylamides, (15) to (17).⁵ Thus the conversion of (13) into the lactam (14) shows that the normally preferred 1,4-addition is disfavoured with respect to the 5-*Exo-Trig* transacylation.

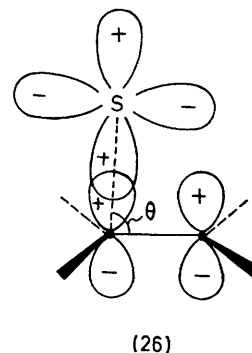
The reactions of cinnamic acid derivatives with hydrazine are also in accord with these ideas. Thus, Scheme 2 illustrates this situation. The hydrazide (18) cannot, even at 200 °C, be converted into the pyrazolone (21) (5-*Endo-Trig* process); however, the ester (19) reacts with hydrazine at 65 °C to give cleanly (21), by way of the 1,4-adduct (20), followed by the favoured 5-*Exo-Trig* closure.⁶

In contrast to the difficulty of ring closure by 5-*Endo-Trig* pathways the 6-*Endo-Trig* reaction occurs readily. This was exemplified by the synthesis of the $\alpha\beta$ -unsaturated ketones (22) which upon treatment with methanolic sodium methoxide smoothly closed to the 4-chromanones (23).⁷



Finally we have found that a second-row element in some circumstances facilitates the normally disfavoured 5-*Endo-Trig* process. Thus the thiol ester (24) reacted at 65 °C

with sodium methoxide-methanol to yield the sulphide (25), identical with authentic material.⁸ It seems likely that this may be a general phenomenon for second-row elements since their larger radii and bond lengths allow them to obtain conformations which are difficult for the corresponding first-row elements. A complementary, molecular orbital, explanation of this process may be found in the presence in a second-row atom of unoccupied 3d-orbitals which can thereby receive electrons (back donation) from the occupied π -orbitals of the double bond. Such bonding interactions as (26) would reduce the angle θ from the



first-row value of *ca.* 109° to more nearly 90° or less, thereby reducing the geometric constraint for an endocyclic ring closure.

We are pursuing this area in the hope of defining closer limits for these rules.

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¹ J. E. Baldwin, preceding communication.

² J. E. Baldwin, G. Höfle, and O. W. Lever, Jr., *J. Amer. Chem. Soc.*, 1974, **96**, 7126.

³ J. E. Baldwin, following communication.

⁴ P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, 1974, **39**, 1958.

⁵ (a) E. Rouvier, J. C. Giacomoni, and A. Cambon, *Bull. Soc. chim. France*, 1971, 1717; (b) Similar preferred 5-*Exo-Trig* closures have been noted previously, *cf.* D. L. Lee, C. J. Morrow and H. Rapoport, *J. Org. Chem.*, 1974, **39**, 893.

⁶ Similar observations have been made previously, although without explanation, *cf.* W. O. Godtfredson and S. Vangedal, *Acta. Chem. Scand.*, 1955, **9**, 1498.

⁷ K. von Auwers and E. Lämmerhirt, *Annalen*, 1920, **421**, 30.

⁸ G. Claeson and H.-G. Jonsson, *Arkiv. Kemi*, 1968, **28**, 174.