# 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 methoxyvinyllithium 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.

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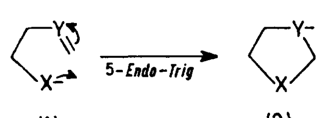
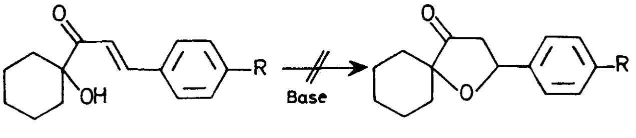
† All new compounds have given spectroscopic and analytical data in accord with their structures.

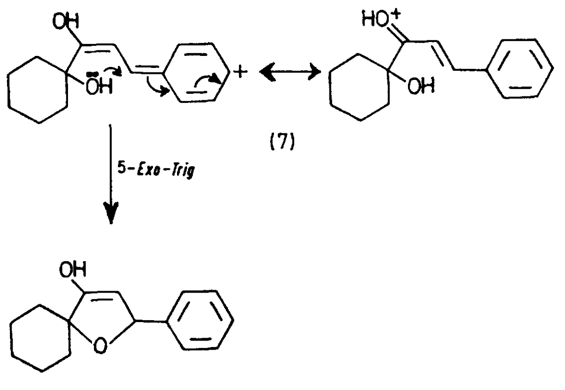


(1) (2)



(3) R = H
(4) R = OMe

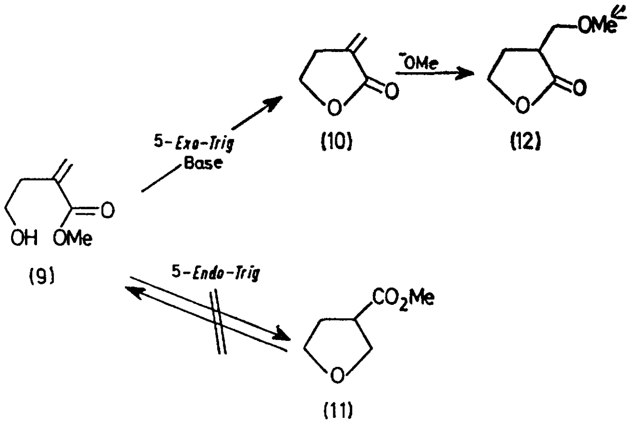
(5) R = H
(6) R = OMe



(7)

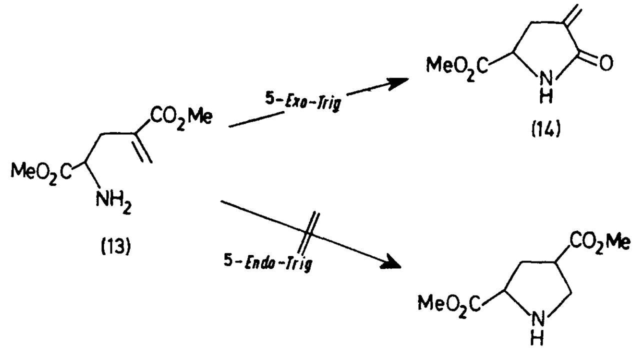
(8)

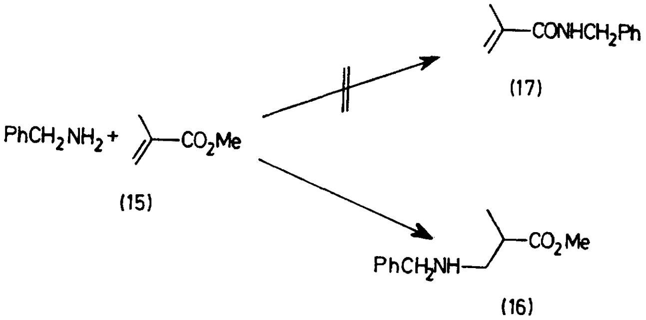
With these ring-closed products in hand, we have shown that they rapidly and efficiently exchange both their α-hydrogen atoms under the same basic conditions, *i.e.*, sodium methoxide in deuteriated methanol at 65 °C, in which (**3**) and (**4**) are *not* converted into (**5**) and (**6**), respectively. 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 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.



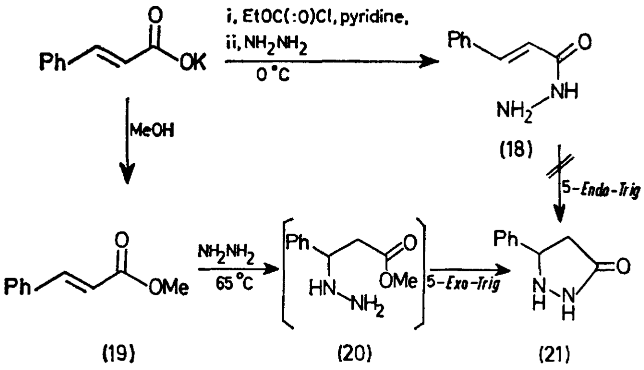
Scheme 1

Thus the alcohol (**9**), {obtained by opening [$Ba(OH)_2$] and methylation ($CH_2N_2$) 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

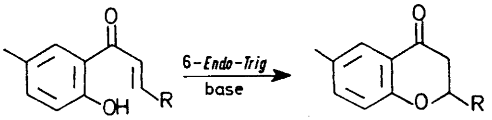


Scheme 2

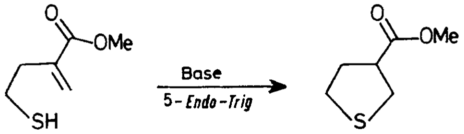
α-substituted acrylamides, (**15**) to (**17**).[5] Thus the conversion of (**13**) into the lactam (**14**) shows that the normally preferred 1,4-addition is disfavoured with respect to the 5-*Exo-Trig* transacylation.

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 αβ-unsaturated ketones (**22**) which upon treatment with methanolic sodium methoxide smoothly closed to the 4-chromanones (**23**).[7]

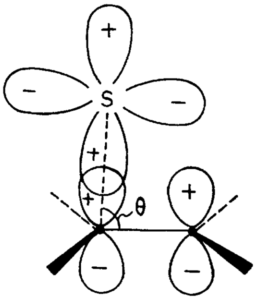


(22) (23)



(24) (25)

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 3*d*-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.



(26)

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.

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