

Observations on the Scope of an Intramolecular Directed Aldol Condensation. A New Synthesis of Eight-membered Rings†

G. Stuart Cockerill and Philip Kocienski*

Department of Organic Chemistry, The University, Leeds LS2 9JT, U.K.

The TiCl_4 -catalysed intramolecular directed aldol condensation of silyl enol ethers and acetals can be used to make 6-, 7-, and 8-membered rings; a template effect of Ti is invoked to explain the formation of medium rings.

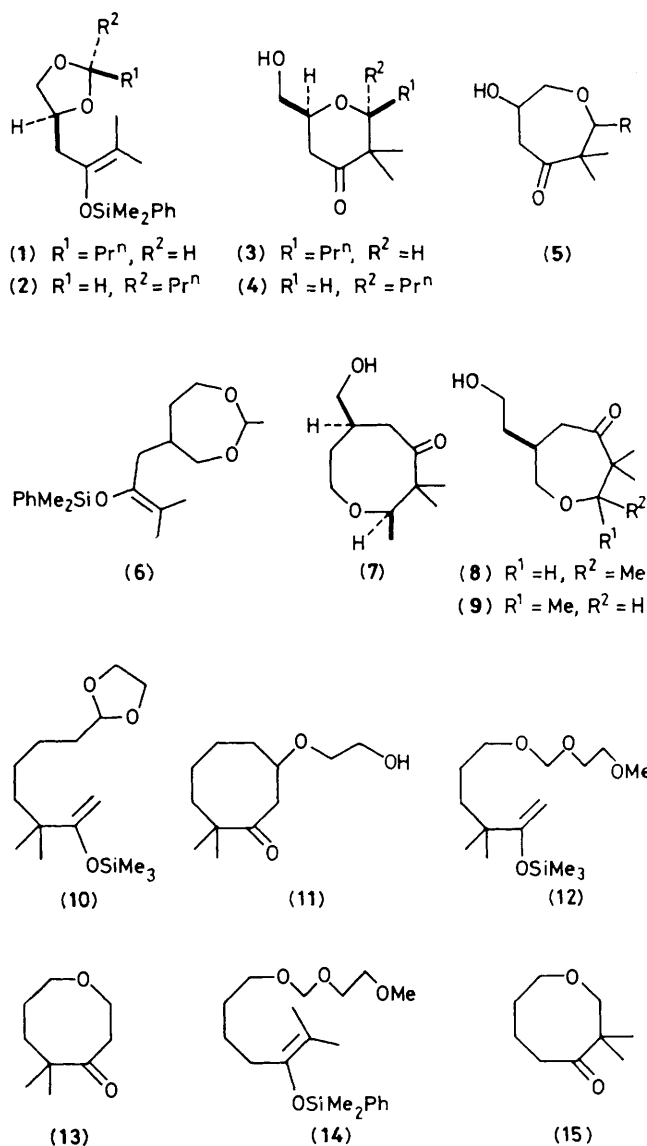
The construction of medium rings in general and 8-membered rings in particular by C-C annulation poses a significant synthetic problem for which there are comparatively few solutions. We now report a new synthesis of 8-membered rings based on a TiCl_4 -catalysed intramolecular directed aldol condensation of silyl enol ethers with acetals¹ (the Mukaiyama reaction²), the intramolecular variant of which has received only scant attention.³⁻⁸

In an attempt to control the stereoselectivity of the intramolecular Mukaiyama reaction which served as the key step in our recent synthesis of pederol dibenzoate,⁹ we examined the cyclisation of the model dioxolane derivatives (1) and (2) under a variety of conditions. There were two surprising results. First, treatment of *cis*-dioxolane (1) with 1–2 equiv. of TiCl_4 in CH_2Cl_2 at -78°C gave the *cis*-tetrahydropyran-4-one (3) exclusively in 65% yield whereas similar reactions of the *trans*-dioxolane (2) gave a 1:1 mixture of (3) and (4) in 72% yield.‡ Secondly, treatment of either of the dioxolanes (1) or (2) with trimethylsilyl trifluoromethanesulphonate⁹ or $(\text{Pr}^i\text{O})_2\text{TiCl}_2\text{-CH}_2\text{Cl}_2$ gave only the *cis*-tetrahydropyran-4-one (3) in ca. 42% yield. No cyclisation products were obtained with SiCl_4 or ZnCl_2 . Thus the stereochemistry of the reaction depended on the stereochemistry of the precursors (1) and (2) only when TiCl_4 was used as catalyst. The absence of the oxepan-4-one (5) indicates that electrophilic cleavage of the acetal group in (1) and (2) was regioselective.

The reaction of the acetal (6) (1:1 mixture of chromatographically inseparable diastereoisomers) with TiCl_4 gave (7), (8), and (9) (88% combined yield) in a ratio of 2:3:3 respectively.‡ Therefore cleavage of the acetal (6) was not regioselective and a mixture of 7- and 8-membered rings corresponding to alternative modes of acetal cleavage was obtained. Once again TiCl_4 was unique in its effect on the course of the reaction for treatment of (6) with other electrophiles did not yield significant amounts of the oxocan-4-one. For example, with SnCl_4 , a 33% yield of a 1:1 mixture of (8) and (9) was obtained and h.p.l.c. analysis revealed only traces of (7).

The formation of an eight-membered ring by directed aldol condensation *without the need for high dilution conditions* is unprecedented and noteworthy since eight- and nine-membered rings are the most difficult to construct by any method of ring closure.¹⁰ Further examples include the conversion of the dioxolane (10) and the (2-methoxyethoxy)methyl ethers (12) and (14) into the eight-membered ring products (11), (13), and (15) in 44, 40, and 30% yields respectively. The cyclisation reactions reported herein represent a significant extension of the scope of the Mukaiyama reaction which has heretofore been applied only to the synthesis of seven- and eleven-membered rings.^{3,5,7}

We propose that the formation of eight-membered rings and the unique effect of Ti on the stereo- and regio-chemistry of



the cyclisations of (1), (2), and (6) are related and attributable to a template effect resulting from steric constraints imposed on intermediates in which the silyl enol ether and acetal oxygens are *both* co-ordinated to the Ti catalyst. Template effects have been previously proposed in transition metal chemistry in order to rationalise, for example, the stereochemistry of a zirconium-mediated intermolecular directed aldol condensation¹¹ and to explain the formation of medium rings in the intramolecular alkylation of π -allyl palladium complexes¹² and the dimerisation of bis(π -allyl)nickel complexes.¹³

† All compounds reported are racemic.

‡ Yields refer to chromatographically purified products. Relative composition of mixtures was determined by h.p.l.c. analysis of the corresponding 3,5-dinitrobenzoate esters.

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