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SILAKETALS AS TETHERS IN INTRAMOLECULAR RADICAL CYCLISATIONS

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SUMMARY: Intramolecular radical cyclisation reactions of substrates possessing a silaketal tether proceed predominantly *via* an *endo* mode in moderate to good yield to give 7, 8 or 9 membered ring products. The products, which are protected diols, can then be deprotected using standard conditions.

In recent years there has been increasing interest in the use of silicon as a tether for the intramolecular radical cyclisation reaction[1]. A silicon tether allows a radical generated on one ligand to react with a proximal radical acceptor on a second ligand, thus providing a degree of regio- and stereochemical control. The tether may then be cleaved under a variety of conditions. Radical cyclisation reactions of tetraalkylsilanes were studied by Wilt[1a] although this technology has not (to date) found wide use in synthesis. A more practical, synthetically useful method is through the use of silyl ethers[1b-k] where one substituent is attached *via* an Si-O bond Possible drawbacks in this methodology include the need to prepare a suitably functionalised silyl ether which, for complex substrates, may prove problematical[2]. Also, after radical cyclisation the cyclic silyl ether must be further manipulated to liberate the latent functionality and conditions for this may not be compatible with other functional groups present.

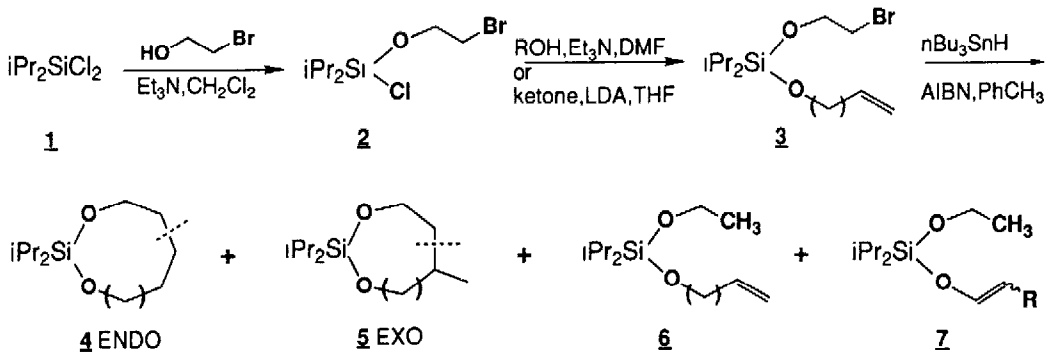
We have investigated the use of silaketals as a potential tethering unit for intramolecular reactions[3] and in this Letter we outline our results for radical cyclisations[4]. It was reasoned that (i) silaketals, eg. 3, would be readily prepared from the commercially available dialkyldichlorosilane, (ii) potentially complex substrates could be used and (iii) after the reaction the product, a protected diol, could be desilylated using a variety of standard mild conditions.

The dialkyldichlorosilane chosen for this study was the diisopropyl derivative since disubstitution is facile and the silicon acetal formed is stable to aqueous work up and chromatography on silica gel With di-tert-butyldichlorosilane the introduction of a second alcohol proved to be difficult while diphenyl or dimethylsilaketals did not survive our isolation procedures. We chose to limit this study to the use of 2-bromoethanol as the radical precursor unit and varied the radical acceptor.

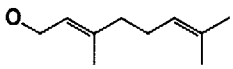
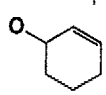
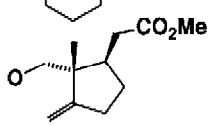
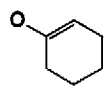
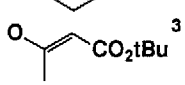
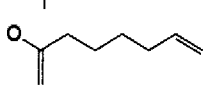
Attempts to prepare the silaketal 3 using a "one pot" process (sequential addition of 2-bromoethanol and the alcohol/enolate to 1) gave only modest yields (~30%) of the desired product at the expense of the corresponding symmetric silaketals, $iPr_2Si(OR)_2$. A more acceptable route is shown in the Scheme. Addition of 2-bromoethanol to a three-fold excess of 1 in CH_2Cl_2 gave, after a non-aqueous work up and distillation through a Vigreux column, a 60% yield of the monochlorosilane 2. Subsequent reaction of 2 with a variety of

alcohols (using Et_3N in DMF) or enolates (generated from the ketone with LDA in THF) afforded the desired silaketal 3 in good to excellent yield (67-95%, Table).

Radical cyclisation reactions were performed using nBu_3SnH and AIBN in toluene under standard



SCHEME

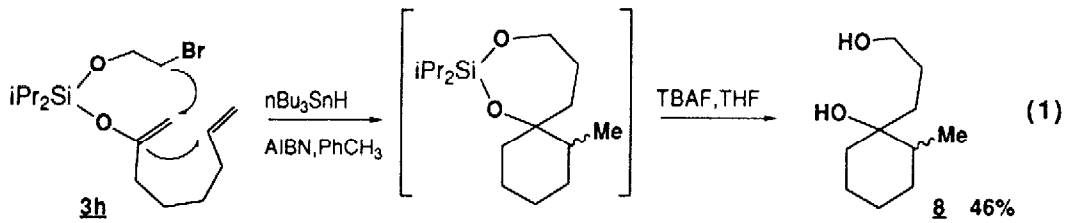
Entry	iPr2Si(O-CH2-CH2-Br)X	Yield 2→3(%)	RATIO 4 : 5	Total Yield[1] 4 + 5 (%)	Yield[1] 6(%)
3a		86	100:0	59	-
3b		67	7:93	51	3
3c		88	-	0	67
3d		82	-	0	18
3e		95	100:0	22[2]	16[2]
3f		84	100:0	50	23
3g		77	91:9	63	15
3h		76	100:0	46[4]	-

[1] Yield following column chromatography; [2] Yield after desilylation with 0.2NHCl/MeOH;
[3] Single geometric isomer (trans); [4] Yield after desilylation with TBAF/THF

TABLE

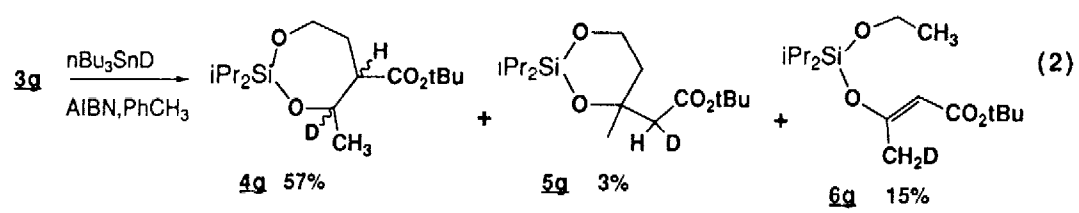
conditions[5] and the results are given in the Table[6]. Interestingly, both alkenes and enol ethers undergo preferential *endo*-trig cyclisation to produce the larger of the two possible rings Rings containing 7 (4f and 4g), 8 (4a) and even 9 (4e) atoms are readily produced by this method. It is possible to induce an *exo*-trig ring closure as in the case of substrate 3b where the presence of an α,ß-unsaturated ester makes radical attack at the ß-carbon the preferred mode of cyclisation. In contrast to this, substrate 3g which also posesses an α,ß-unsaturated ester gives predominantly the product arising from *endo*-trig cyclisation. The regiochemistry observed for these cyclisations is presumably a consequence of the relatively long Si-O bond, the large O-Si-O bond angle and also, perhaps, the "silicon anomeric effect"[7]. In addition, the presence of two oxygen atoms in the ring reduces transannular interactions thus making the formation of medium size rings more feasible.

In the case where the alkene is constrained such that *endo*-trig cyclisation is unfavoured (entry 3d) no cyclisation (*endo* or *exo*) occurred. Similarly no cyclisation was observed for the substrate derived from geraniol, 3c. Presumably substitution at the site of *endo* attack inhibits this cyclisation while the *exo*-trig mode appears to be generally disfavoured[8]. The enol-ether derived from cyclohexanone (substrate 3f) gives a 50% yield of 4f with a trans:cis ratio of 2:1. This complements results obtained by Walkup et al.[1k] where radical cyclisation of the ß-chloroethyldimethylsilylenol ether derivative of cyclohexanone afforded predominantly the cis compound.



We also investigated the possibility of performing a tandem cyclisation (eqn 1). Substrate 3h gave rise to a 2:1 mixture of diols 8 in 46% yield after deprotection. The product presumably arises *via* an *endo*-trig cyclisation onto the enol-ether and subsequent attack of the carbinol radical onto the terminal double bond

In many of the examples studied a major product is what appears to be direct reduction of the bromine atom, i.e. formation of 6 To investigate how this product arises, we repeated the reaction of substrate 3g using nBu_3SnD in place of nBu_3SnH (eqn. 2) and found, in addition to the expected products, that the reduced product contained



60% incorporation of deuterium in the allylic position. None was incorporated in the ethoxy side chain indicating that formation of the reduced product 6g is occurring *via intra*molecular H abstraction Intramolecular H abstraction is also a significant side reaction for substrates 3b,c and d as shown by the formation of the corresponding enol-ethers 7b,c and d respectively.

Finally, we addressed the question of deprotection of the products resulting from the radical ring closure. For entry 3e[9] the product was deprotected using 0.2N HCl in MeOH to give the diol in 22% overall yield. With entry 3h the product was desilylated using TBAF in THF to afford the diol 4h in 46% yield for two steps.

In conclusion, we have shown that silaketals can be readily prepared and they can act as tethers for intramolecular radical cyclisations to give products that are protected diols. Cyclisations on to alkenes or enol ethers occur exclusively or predominantly via the *endo* mode although the *exo* process may be induced. A degree of stereochemical control was observed which may prove useful in some cases and lastly, desilylation is readily achieved using standard conditions.

Acknowledgement

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2) For one recent solution to this problem see G. Stork, P F. Keitz, Tetrahedron Lett., 1989, 30, 6981.

3) This is a continuation of our work into the use of silaketals as tethers for intramolecular reactions. Our results for the silaketal tethered intramolecular Diels-Alder reaction were presented (by J.W.G.) at the PACIFICHEM '89 Meeting, Hawaii, December 1989.

4) This work was presented at the 8th International IUPAC Conference on Organic Synthesis, Helsinki, Finland, July 1990.

5) A 0.04 M solution of substrate in degassed toluene at reflux under nitrogen was treated with a 0.5 M solution (with respect to nBu_3SnH) in toluene containing 2.2 eq nBu_3SnH and 0.1 eq AIBN over 16 hr using a syringe pump. The solution was cooled, the solvent removed and the residue chromatographed on silica gel.

6) All new compounds were characterised by ir, 250 or 300 MHz NMR, micro-analysis and/or high resolution mass spectrometry.

7) A.E. Read, C. Schade, P.v.R. Schleyer, P.V. Kamath, J. Chandrasekhar, J. Chem. Soc. Chem. Commun., 1988, 67.

8) We did not observe any cyclisation at the C-6 or C-7 position of geraniol either.

9) For the preparation of the alcohol used to make 3e see J.H. Hutchinson, T. Money, S.E. Piper, Can. J. Chem., 1986, 64, 854

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