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The Intramolecular Silyl Modified Sakurai (ISMS) Reaction. A Novel and Highly Convergent Synthesis of Oxocenes

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Abstract: *By employing the intramolecular version of the SMS reaction, oxocenes, including spiroethers and spiroketals, can be prepared in a highly convergent, one-step operation.*

In the preceding communication[1], we have described our initial findings on a novel and powerful methodology - The Silyl Modified Sakurai (SMS) reaction - for the preparation of homoallylic ethers **directly** from carbonyl derivatives. We envisioned that the intramolecular variant of the SMS reaction might provide a simple and efficient route towards the synthesis of spiroethers and spiroketals[2]. In this Letter, we report some of our results on the successful realisation of this objective.

TMSOTf-catalysed condensation of TMS ether **2** - readily prepared from the commercially available alcohol[3] - with an aldehyde or a ketone **1** gives smoothly the oxonium cation **3** which is intramolecularly intercepted by the nucleophilic π-system[4] of the olefin, affording the six-membered ring heterocycle **4** (Figure 1). A few representative examples of this methodology are collected in Table 1.

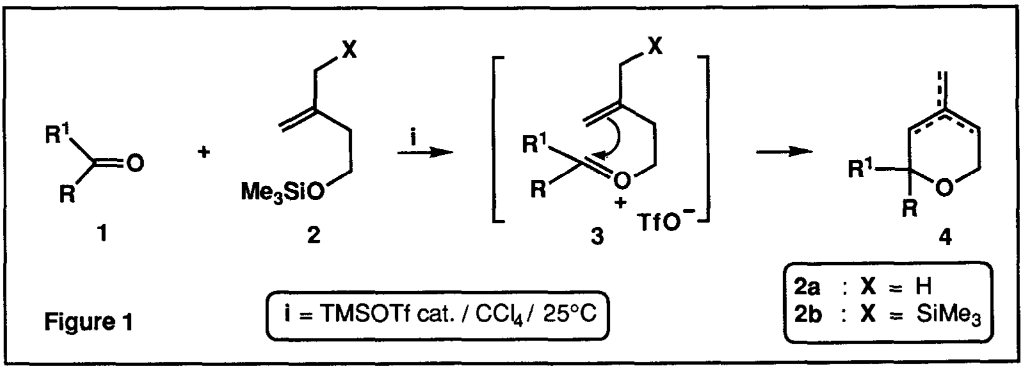
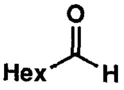
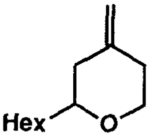
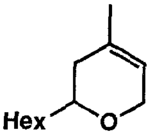
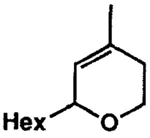
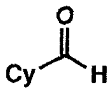
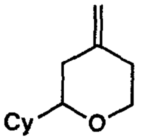
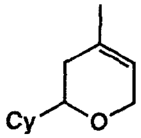
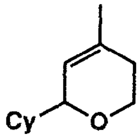
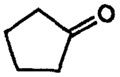
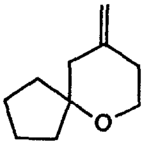
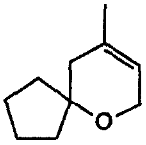
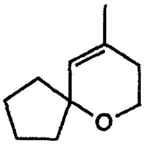
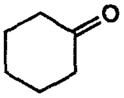
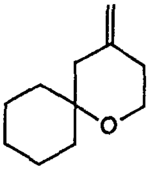
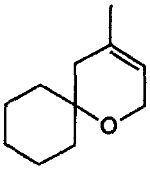
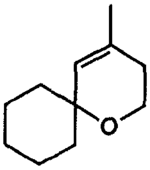


Figure 1

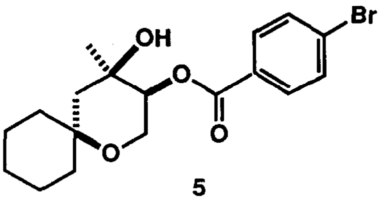
As can be seen, the reaction is successful for both aldehydes and ketones, leading to monosubstituted and spiroethers (Entries 1 - 4). When using the silyl ether **2a**, a mixture of the three regioisomeric olefins is typically produced [Table 1, condition (a)], with the $\Delta^{3,4}$ isomer being the major one[5]. Upon longer exposure to the reaction conditions, the exocyclic isomer is converted quantitatively into the $\Delta^{2,3}$ and $\Delta^{3,4}$ isomers [Table 1, condition (b)]. The ratio of these *endo*-isomers is not altered by the reaction time and always favours the $\Delta^{3,4}$ isomer.

Table 1 : ISMS Reaction of Carbonyl Derivatives

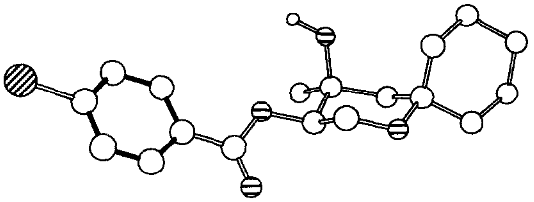
Entry	Substrate	Reagent	Products					Yields
1				+		+		
		2a[(a)]	7	:	10	:	4	(91%)
		2a[(b)]	-	:	16	:	6	(90%)
		2b[(c)]	16	:	3	:	2	(88%)
2				+		+		
		2a[(a)]	2	:	5	:	3	(90%)
		2a[(b)]	-	:	18	:	8	(88%)
3				+		+		
		2a[(b)]	3	:	18	:	10	(92%)
		2b[(c)]	31	:	9	:	4	(94%)
4				+		+		
		2a[(a)]	-	:	12	:	11	(93%)
		2b[(c)]	12	:	1	:	1	(97%)
		2b[(d)]	-	:	1	:	1	(94%)

Hex = hexyl; **Cy** = cyclohexyl; (a) = the reaction was stopped immediately after the disappearance of the starting material; (b) = the reaction mixture was stirred another 30 min; (c) = the reaction was performed at -15°C; (d) = the reaction was carried out at 20°C.

By employing reagent **2b** and Condition (c), the exocyclic isomer becomes the major one [Table 1, condition (c)] though isolation by conventional techniques proved sometimes difficult, owing to rapid isomerisation into the endocyclic systems[6]. For example, cyclohexanone gave an *exo* : *endo* ratio of 6 : 1 **provided the reaction was performed at -15°C. At room temperature** [Condition (d)], **only the *endo*-isomers were produced** (Entry 4). The structure of the $\Delta^{3,4}$ *endo*-isomer was unambiguously established by X-Ray diffraction analysis of the monoprotected diol **5** [7] (Figure 2).

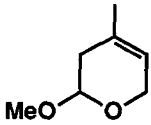
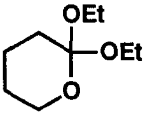
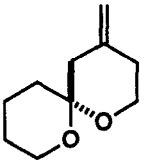
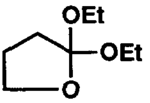
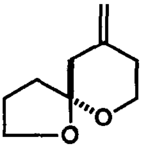


5



Interestingly, orthoesters were found to participate in this unique process. Thus, ISMS reaction between trimethyl orthoformate and the silyl ether **2a** gave the expected cyclic acetal in good yield (Table 2). Finally, a simple and highly convergent synthesis of spiroketals - the basic component of pheromones and other important natural products[2] - is provided by the condensation of reagent **2b** with ortholactones[8] (Table 2, entries 2 and 3). In these latter cases, only the exocyclic isomer is produced.

Table 2 : ISMS Reaction of Orthoesters

Entry	Substrate	Reagent	Products	Yields
1	$HC(OMe)_3$	2a		67% [(a)]
2[(b)]		2b		83%
3[(b)]		2b		80%

(a) = contains less than 10% of the regioisomeric *endo*-olefin; (b) = the orthoesters were prepared according to reference 9.

In summary, we have shown that the ISMS reaction is a powerful strategy for the construction of oxocenes, including spiroethers and spiroketals. Further work on delineating the scope and synthetic applications of this novel methodology, as well as on controlling the position of the double bond in the final products, is being actively pursued in this laboratory and will be reported in due course.

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References and Notes

[a] University of Sheffield, X-ray Crystallographic Analysis.

1. Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.*, preceding communication
2. Perron, F.; Albizati, K. M. *Chem. Rev.*, **1989**, *89*, 1617 and references cited therein.
3. The monosilylated derivative **2a** was prepared from the commercially-available alcohol using TMSCl / Et_3N. The bis-silylated reagent **2b** was synthesised according to: Trost, B. M.; Chan, D. M. T.; Nanninga, N. *Org. Synth.*, **1984**, *62*, 58.
4. **a.** Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *Tetrahedron*, **1990**, *46*, 1757. **b.** Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.*, **1989**, *54*, 5695. **c.** Nussbaumer, C.; Fráter, G. *J. Org. Chem.*, **1987**, *52*, 2096. **d.** Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.*, **1986**, *86*, 857. **e.** Cockerill, G.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans I*, **1985**, 2093. **f.** Nishiyama, H.; Itoh, K. *J. Org. Chem.*, **1982**, *47*, 2496. **g.** Schulte-Elte, K. H.; Hawer, A.; Ohloff, G. *Helv. Chim. Acta*, **1979**, *62*, 2673. **h.** Johnson, W. S. *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 9. For the formation of tetrahydropyrans and oxepanes from allyltrimethylsilane and aldehydes, see: **a.** Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.*, **1988**, *53*, 911. **b.** Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.*, **1987**, *28*, 973. **c.** Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.*, **1987**, *28*, 3441.
5. The preferential formation of this isomer probably indicates its greater stability (lesser $A^{1,3}$ strain) as compared to the sterically more crowded $\Delta^{2,3}$ one.
6. This isomerisation is almost certainly triggered by traces of triflic acid that accompanies or is generated by partial hydrolysis of the TMSOTf catalyst. It is noteworthy that, if the ISMS reaction is run **in the presence of collidine** - with the intention of quenching the triflic acid - **the exocyclic isomer is formed exclusively**. Adding a catalytic amount of triflic acid leads rapidly to the formation of the *endo*-isomers. The generality of this observation has to be fully investigated.
7. Although the two regioisomeric *endo*-olefins are often difficult to separate, the corresponding diols - obtained by catalytic osmylation (OsO_4/NMO/acetone/H_2O/20°C) - can be easily differentiated. Indeed, only the $\Delta^{2,3}$ derived diol is acylated rapidly (BrC_6H_4COCl/Et_3N/CH_2Cl_2/20°C). The regioisomeric diol is sterically more hindered and the acylation reaction proceeds extremely slowly.
8. The ortholactones are readily prepared by treating the lactones with Meerwein salt followed by sodium ethoxide: Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc. Perkin Trans. I*, **1987**, 2171. The ISMS reaction can be performed on the lactones themselves but the yields are lower.

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