

A Novel Synthesis of Seven-membered Ring Cyclic Ethers

Prabhat Arya and Tak-Hang Chan*

Department of Chemistry, McGill University, Montreal, P.Q. H3A 2K6, Canada

Silyl ethers of homopropynyl alcohols condense with α -alkyl-substituted aldehydes under Lewis acid conditions to give functionalised oxepanes.

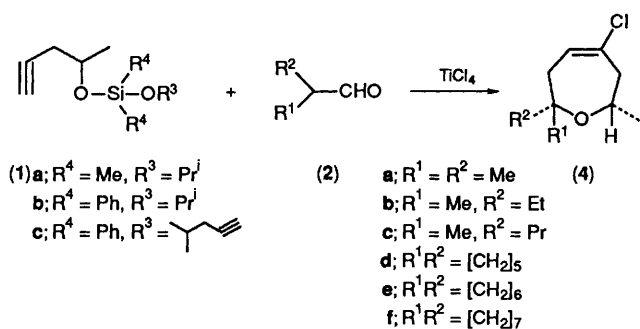
Seven-membered ring cyclic ethers have been found as structural units in an increasing number of natural products.¹ Many of them are derived from marine sources,^{2,3} and possess interesting biological activities.^{3,4} It is not surprising that a number of new methods have recently been developed for the synthesis of the oxepane skeleton. These approaches usually involve intramolecular reactions of some type: *e.g.* acetal formation of a hydroxy-ketone;⁵ regioselective opening of an epoxy-alcohol;⁶ regioselective opening of an epoxy-ether by allylstannane or allylsilane;⁷ or a Prins cyclization of an alkenyl-acetal.⁸ We report here a novel and unexpected synthesis of functionalized oxepanes by an intermolecular condensation reaction.

Recently, the electrophilic condensation of silyl ethers of homopropynyl alcohols (**1**) with aliphatic aldehydes (**2**) ($R^1 = \text{alkyl}$, $R^2 = \text{H}$) under TiCl_4 conditions was found to give regioselectively the dihydropyrans (**3**) with *cis*-stereochemistry.⁹ When we tried to extend the reaction to α -alkyl-substituted aldehydes, the course of the reaction was dramatically altered depending on the nature of substituents on the silyl group of (**1**). The isopropoxy-dimethylsilyl ether (**1a**)

Table 1. Electrophilic condensation of silyl ether (**1**) and aldehyde (**2**).

Silyl ether (mmol)	Aldehyde (mmol)	TiCl_4 /mmol	Conditions ^a	Isolated yield (%)	
				(4)	(8)
(1b) (1.2)	(2a) (1.5)	1.5	(A)	50	12
(1b) (1.2)	(2b) (1.5)	1.5	(A)	51	8 ^b
(1b) (1.2)	(2c) (1.5)	1.5	(A)	55	
(1b) (1.5)	(2d) (3)	2.5	(A)	58	
(1b) (1.5)	(2e) (3)	2.5	(A)	49	
(1b) (1.5)	(2f) (3)	2.5	(A)	45	
(1c) (1.2)	(2a) (1.5)	1.5	(B)	56	21
(1c) (1.2)	(2b) (1.5)	1.5	(B)	63	15 ^b
(1c) (1.2)	(2c) (1.5)	1.5	(B)	62	5 ^b
(1c) (1.5)	(2d) (3)	2.5	(B)	71	5
(1c) (1.5)	(2e) (3)	2.5	(B)	64	8
(1c) (1.5)	(2f) (3)	2.5	(B)	52	11

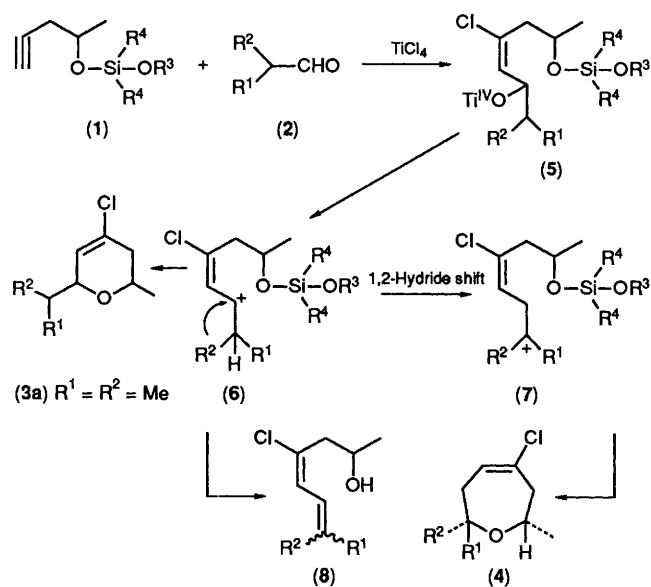
^a (A): -78°C for 1 h, then -40°C for 1.5 h; (B): -78°C for 0.5 h, then -35°C for 1 h. ^b Isolated as mixture of two geometrical isomers.



condensed with isobutyraldehyde (**2a**; $\text{R}^1 = \text{R}^2 = \text{Me}$) in the presence of TiCl_4 to give the dihydroxyran (**3a**) as reported.⁹ However, the isopropoxydiphenylsilyl ether (**1b**) reacted with (**2a**) under identical reaction conditions to give 4-chloro-2,7,7-trimethyl-4,5-dehydro-oxepane (**4a**) as the major product with very little of (**3a**). Similarly, the diphenylsilyl acetal (**1c**) reacted with (**2a**) to give (**4a**), again with little or no (**3a**). Other α -alkyl-substituted aldehydes reacted with either (**1b**) or (**1c**) to give the corresponding oxepanes (**4**).[†]

In cases where the two alkyl groups on the α -carbon of aldehyde, (**2b**) or (**2c**), were different, only one stereoisomer of (**4**) was obtained. The stereochemistry of (**4b**) or (**4c**) was determined by nuclear Overhauser enhancement techniques which showed that the C-2-hydrogen was *cis* to the methyl group on C-7. Similar reactions can be applied to various cycloalkancarbaldehydes (**2d–e**) to give the corresponding spiro compounds (**4d–e**) in reasonable isolated yields (Table 1).

The formation of the oxepane (**4**) can be rationalised according to the mechanism in Scheme 1. Under TiCl_4 conditions, (**1**) condenses with (**2**) to give the intermediate (**5**) which ionises to give the carbocation (**6**). In the case of (**1a**), cyclisation of (**6**) gives the dihydroxyran (**3**). In the case of (**1b**) or (**1c**), the cyclisation process is slower because of the bulkier substituents on silicon. 1,2-Hydride shift intervenes to



Scheme 1

give the cation (**7**), which cyclises to the oxepane (**4**). Alternatively, proton elimination can occur from either (**6**) or (**7**) to give the diene (**8**). Indeed, the dienes (**8**) could be isolated from the reaction mixtures as minor reaction products.

In conclusion, the present reaction offers a novel synthesis of seven-membered ring cyclic ethers. The double bond and the chloro substituent in (**4**) can be further transformed, if necessary, to other functionalised oxepanes.

Received, 6th March 1990; Com. 0/01005G

References

- D. J. Faulkner, *Nat. Prod. Rep.*, 1986, **3**, 1; 1984, **1**, 251,551.
- 'Marine Natural Products,' ed. P. J. Scheuer, Academic Press, New York, 1978, vol. 1; 1983, vol. 5.
- M. Murata, A. M. Legrand, and T. Yasumoto, *Tetrahedron Lett.*, 1989, **30**, 3793.
- A. Fukuzawa and T. Masamune, *Tetrahedron Lett.*, 1981, **22**, 4081.
- H. Kotsuki, I. Kadota, and M. Ochi, *Tetrahedron Lett.*, 1989, **30**, 1281; H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, *J. Org. Chem.*, 1989, **54**, 5153.
- K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, and C. K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 5335.
- G. A. Molander and S. W. Andrews, *J. Org. Chem.*, 1989, **54**, 3114.
- A. Castaneda, D. J. Kucera, and L. E. Overman, *J. Org. Chem.*, 1989, **54**, 5695.
- T. H. Chan and P. Arya, *Tetrahedron Lett.*, 1989, **30**, 4065.

[†] *General procedure:* to a solution of TiCl_4 (1.5 ml; 1 M in CH_2Cl_2) in CH_2Cl_2 (5 ml) at -78°C was added dropwise a solution of the aldehyde (**2**) (1.5 mmol) in CH_2Cl_2 (4.0 ml). After 10 min, the silyl ether (**1**) (1.2 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise. The mixture was stirred at -78°C for 1 h and then at -40°C for a further 1.5 h. The mixture was quenched at -40°C with buffer solution (pH 7) and extracted with CH_2Cl_2 . The organic layer was dried and evaporated to give the product which was purified by flash column chromatography using ethyl acetate–hexane (1:5) as eluant.