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STEREOSELECTIVE PETERSON ALKOXYCARBONYLMETHYLENATION REACTION OF SUBSTITUTED CYCLOHEXANONES

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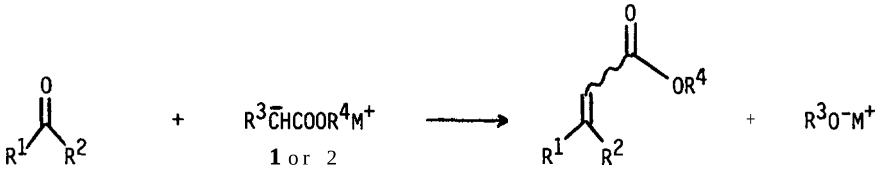
Summary: In contrast to previous results the Peterson olefination reaction of substituted cyclohexanones with metallotrimethylsilylacetates (1) affords moderate to high stereoselectivity.

In recent years the Peterson olefination reaction has become an increasingly important alternative to the Wittig reaction, especially for the preparation of conjugated olefinic compounds'. Its recognized advantages over the Wittig approach are twofold: (i) the stabilized α-silyl carbanions are generally more reactive than the corresponding phosphorus ylids, and (ii) the workup step is not complicated by the presence of phosphorus compounds. Unfortunately, prior experience has led to the generally accepted view that the Peterson reaction exhibits little or no stereoselectivity. Thus, in the reactions of metallotrimethylsilylacetate derivatives **1a** and **1b** with a variety of unsymmetrical carbonyl compounds either a roughly equimolar mixture of E- and Z-isomers, or a slight preference toward formation of the E-isomer, have been reported*. In one case studied, an increase in steric bulk of the alkyl group in **1** (reagent **1c**) gave rise to predominant Z-stereoselectivity[3]. We have also reported[4] an example of preferential formation of the Z-isomer upon treatment of a 2,3-epoxycyclohexanone with ethyl lithiotrimethylsilylacetate **(1b)**.



1 or 2

Peterson reagents **1**

R^3 = Me$_3$Si-

1a M = Li, R^4 = Li
1b M = Li R^4 = Et
1c M = Li ', R^4 = tert-Bu
1d M = K , R^4 = Et

Horner-Emmons reagents 2

R^3 = (EtO)$_2$P(O)-

*a M = Na, R^4 = Et
2b M = Li, R^4 = Et

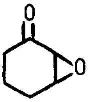
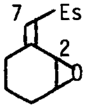
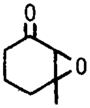
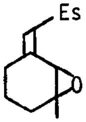
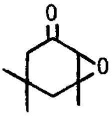
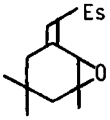
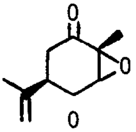
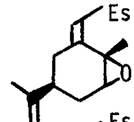
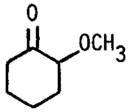
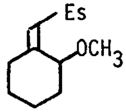
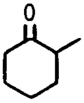
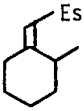
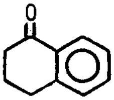
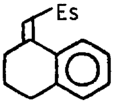
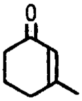
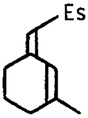
The current quest for stereoselective Peterson reactions[1,5] prompts us to describe the most recent results of our continuing study of stereoselective olefinations of 2-substituted cyclohexanones with silyl ester carbanions **1**[6]. The data are summarized in Table 1 and reveal marked Z-stereosectivity[7] in contrast to the companion results obtained for the corresponding Horner-Emmons olefinations[8].

As it can be seen from entries 1-7 in Table 1, the Peterson reaction is stereoselective regardless of substituent type at position 2 in the starting cyclohexanone, with the configuration (Z) of the alkoxycarbonyl group nearest the most sterically hindered site of the ring strongly favored. The olefinations of 3-methyl-2-cyclohexen-1-one (entry 8) also provide no exceptions to this observation. In the latter case the E-isomer, which is the major product, actually has the *cis*-orientation of the more sterically bulky groups.

Our studies indicate that the degree of the stereoselectivity is markedly influenced by the reagent. For the selected reagents studied, the reaction stereoselectivity generally falls in the following order: **1d**> **1c**> **1b**. Unfortunately, the total yields of the olefination products increase in the opposite order. This is apparently the result of increased ketone enolization by the more sterically hindered reagents, ethyl potassio-(trimethylsilyl)acetate (**1d**) and *tert*-butyl lithio(trimethylsilyl)acetate (**1c**). Ethyl lithio(trimethylsilyl)acetate (**1b**) would appear to be the reagent of choice for stereoselective Z-olefination of cyclohexanones, since it shows relatively high selectivity and affords the highest absolute yield of the product. Since the first step of the Peterson olefination reaction involves irreversible addition[1] of the reagent to the carbonyl group, the reactions described here seem to be governed strictly by steric interactions, acting under kinetic control. However, further mechanistic studies are required in order to better understand the varying degrees of stereoselectivity exhibited by the three reagents **1b**-**1d**.

In the case of the Horner-Emmons reactions it is well known that reaction between a carbonyl compound and a stabilized phosphonate carbanion is reversible and the ease of elimination usually favors the E-product[9]. Indeed, the olefination of carvone oxide in entry 4 with triethyl sodiophosphonoacetate (**2a**) gave rise to the E-isomer in a good yield. Nonetheless, in striking contrast to this single example, other epoxyketones could be olefinated under the Horner-Emmons conditions with only modest selectivity. In one case (entry 3) a change of the counter ion from sodium to lithium in reagent **2** had no effect on the selectivity.

Table 1. Peterson and Horner-Emmons olefination reactions

Entry	Ketone	Reagent	Product (Z shown)	Z:E	Overall Yield, %	^{1}H-NMR chemical shifts (δ, $CDCl_3$/TMS) indicative of the configuration[a] (Data for Z-isomers shown first) 7-H	2-H	$2\text{-}CH_3$
1		**1c**		78:22	60	5.98	4.70	
		1d		92:8	60	6.02	3.42	
		2a		50:50	70			
2		**1b**		78:22	78	5.93	4.57	
		1c		83:17	77	6.03	3.20	
		1d		89:11	70			
		2a		45:55	82			
3		**1b**		90:10	87	5.95	4.77	
		1c		90:10	82	6.12	3.22	
		2a		58:42[b]	85			
		2b		58:42	85			
4		**1b**		90:10	90	5.88		1.59
		2a		10:90	85	6.11		1.47
5		**1b**		72:28	84	5.78	5.26	3.26
		1c		87:13	63	5.82	3.58	3.31
6		**1b**		89:11	86	5.55	4.03	1.15
						5.58	2.20	1.07
7		**1b**		67:33	82	5.79		
		1c		82:18	56	6.33		
8		**1b**		45:55	85	5.32	7.31	
		1d		44:56	5	5.42	5.82	

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[a] Data for ethyl esters; *t*-butyl derivatives showed similar values within 0.2 ppm. See refs. 7 for the configurational assignments by NMR.

[b] Z:E Ratio of 3:2 has been reported for the reaction with trimethyl sodiophosphonoacetate (ref. 7b).

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References and Notes

1. For a review see: D.J. Ager, **Synthesis**, 384 (1984).

2. (a) P. A. Grieco, C.-L.J. Wang, and S.D. Burke, **J. Chem. Soc., Chem. Commun.**, 537 (1975); (b) A.E. Asato, A. Kini, M. Denny, and R.S.H. Liu, **J. Am. Chem. Soc., 105**, 2923 (1983); (c) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, **J. Am. Chem. Soc., 96**, 1620 (1974); (d) H. Taguchi, K. Shimoji, H. Yamamoto, and H. Nozaki, **Bull. Chem. Soc. Japan, 47**, 2529 (1974).

3. M. Larcheveque, C. Leguet, A. Debal, and J.Y. Lallemand, **Tetrahedron Lett.**, 22, 1595 (1981).

4. M. Visnick, L. Strekowski, and M.A. Battiste, **Synthesis**, 284 (1983).

5. A.R. Bassindale, R.J. Ellis, and P.G. Taylor, **Tetrahedron Lett.**, **25**, 2705 (1984).

6. To our best knowledge, ethyl potassio(trimethylsilyl)acetate (**1d**) has not been previously reported. **Generation of 1d**: A solution of potassium bis(trimethylsilyl)amide [C.A. Brown, **J. Org. Chem.**, **39**, 3913 (1974)], prepared from potassium hydride (35% dispersion in mineral oil, 1.38 g, 12 mmol), hexamethyldisilazane (3.2 ml, 15 mmol), and tetrahydrofuran (10 ml), was cooled to -78° C and treated dropwise with ethyl trimethylsilylacetate (2.2 ml, 12 mmol). The resultant solution was stirred at -78°C for 10 min. **Peterson olefinations**: See refs. 1 and 4. The isomers were separated on a silica gel column eluting with ethyl acetate-pentane (3:97).

7. For the E-Z configurational assignments in these types of compounds by ^{1}H-NMR spectroscopy see: (a) M. Rouillard, S. Geribaldi, and M. Azzaro, **Org. Magn. Res., 16**, 94 (1981); (b) N. Bensel, H. Marchall, and P. Weyerstahl, **Tetrahedron Lett.**, 2293 (1976); (c) Refs. 2c, 2d, and 4.

8. See ref. 4 for the experimental procedure.

9. F.A. Carey and R. J. Sundberg, **Advanced Organic Chemistry**, part B, p. 57, Plenum Press, New York, 1977; and references cited therein.

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