Tetrahedron Letters,Vol.27,No.45,pp 5507-5508,1986 0040-4039/86 \$3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

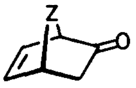
LONG-RANGE SUBSTITUENT EFFECTS. THE REGIOSELECTIVE ELECTROPHILIC ADDITIONS OF EXO-3,6-EPOXYTETRAHYDROPHTHALIDE AND ITS DERIVATIVES.

Tarcisio Ferrari and Pierre Vogel*

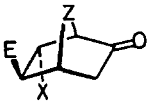
Institut de chimie organique de l'Université,
2, rue de la Barre, CH-1005 Lausanne, Switzerland.

Summary. The regioselectivity of electrophilic additions of 7-oxabicyclo[2.2.1]hept-5-enes can be controlled by carboxylate or dialkoxymethyl substituents at C(2-exo).

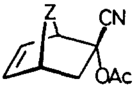
Under kinetic control, enones 1 add soft electrophiles, EX, to give the corresponding adducts 2. In contrast with 1, their synthetic precursors 3 were found to add EX with the opposite regioselectivity giving the corresponding adducts 4.[1,2] In 1 and 3 the substituents at C(2) are separated by one sp^3-hybridized carbon atom. The very high selectivities 1 → 2 and 3 → 4 suggested to us that perhaps the regioselectivity of electrophilic additions of alkenes could be controlled also by even more remote substituents. In order to test this hypothesis we have studied the electrophilic additions of the 7-oxanorbornenes derivatives 5[3,4] and 8.[4] In these molecules, the substituents are separated from the alkene moiety by two sp^3-hybridized carbon centres. Their exo configuration and the rigidity of the tricyclic skeletons prohibit them to intervene in the reaction through steric effects or/and anchimeric assistance.



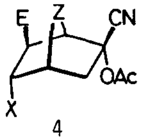
1



2

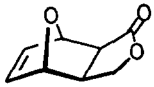


3

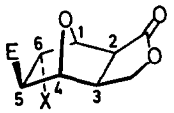


4

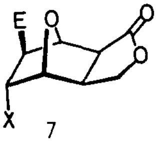
We have found that (a) Br_2 (in MeOH, -10°C), (b) PhSCl, (c) 2-NO_2-C_6H_4SCl (CH_2Cl_2/THF 7:1, - 90°C), (d) 2,4-$(NO_2)_2C_6H_3SCl$ (CH_3CN, - 40°C) and (e) PhSeCl (CH_2Cl_2, -90°C) added to 5 in an anti fashion giving the corresponding adduct mixtures 6/7 (see Table). In the major adducts 6, E substitutes the exo position at C(5) and X (= Br, Cl) the endo position at C(6) (7-oxanorborn-5-ene numbering).[5] They could be obtained pure by fractionnal crystallization



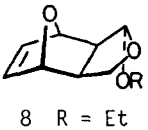
5



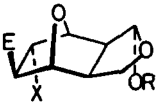
6(major)



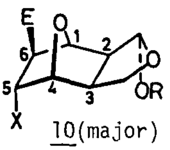
7



8 R = Et
11 R = H
12 R = menthyl



9



10(major)

Table : Product distributions

EX :	6/7	9/10
Br_2	66:34	-
PhSCl	80:20	25:75
2-$NO_2C_6H_4SCl$	84:16	28:72
2,4$(NO_2)_2C_6H_3SCl$	88:12	35:65
PhSeCl	75:25	25:75

or column chromatography on silica gel. The highest regioselectivity (ca 8:1) was observed with the most electrophilic reagent (d), thus suggesting that electronic factors intervene in the long-range substituents effects.

Under the same conditions as those of 5 + EX → 6+7, the acetal 8 added to EX giving the corresponding adduct mixtures 9/10[5] (see Table) which could be separated by chromatography. Unexpectedly, the regioselectivity of additions 8 + EX → 9+10 (as those of 11 + EX[6]) was opposite to that of 5 + EX → 6+7. We do not have yet an explanation to offer for this phenomenon. The adduct mixtures reported here were obtained under conditions of kinetic control. On heating pure 6 and 10 in MeOH containing 4% of MeONa (65°C, 1-4 h) or in THF containing 4% NaOH (45°C, 1-4 h) equilibrations to ca 1:1 mixtures of 6/7 and 9/10, respectively, were observed.

Acetal 8 can be prepared optically pure via resolution of lactol 11. On stirring a 1:1 mixture of 11 and (-)-menthol in acidic CH_2Cl_2 (TsOH, 20°C, 24 h) a mixture of the diastereomeric acetals 12[7] was obtained which was easily separated by medium pressure (Lobar) chromatography on silicagel.[6,8] Our results demonstrate the possibility to control the stereo- and regioselectivity of the functionalization of centres C(5) and C(6) in 7-oxabicyclo[2.2.1]hept-5-enes 5 and 8. Since 5[9] and 8 can be prepared optically pure, they become potential precursors for the stereoselective synthesis of natural products.

Acknowledgements. We thank Hoffmann-La Roche & Co., AG, Basel, the Fonds Herbette, Lausanne, and the Swiss National Science Foundation for generous financial support.

References and Notes.

1. P.-A. Carrupt, P. Vogel, Tetrahedron Lett. 23 (1982) 2563; 25 (1984) 2870; K.A. Black, P. Vogel, J. Org. Chem., in press.
2. For a synthetic application, see e.g.: A. Warm, P. Vogel, Tetrahedron Lett. 26 (1985) 5127; J. Org. Chem., in press.
3. S. Takano, K. Ogasawava, Synthesis (1974) 42; J.C. Grandguillot, Bull. Soc. Chim. Fr. (1979) 325.
4. T.A. Eggelte, H. de Koning, H.O. Huisman, J. Chem. Soc., Perkin Trans. I (1978) 980; Tetrahedron 29 (1973) 2445.
5. The structure of adducts 6, 7, 9, 10 were established unambigously by their elemental analyses and spectral data, in particular by 360 MHz ^{1}H-NMR with the help of double irradiation experiments and NOE's measurements. The latter were carried out by O. Desponds and G. Bodenhausen.[6] Characteristics of 6b (E = PhS, X = Cl): m.p. 148-150°C (acetone/hexane); ^{1}H-NMR ($CDCl_3$): 7,46, 7,35 (2 m, Ph); 4.98 (d, ^3J(H-C(1),H-C(6)) = 5 Hz, H-C(1)); 4.48 (t, J = 9 Hz) & 4.10 (dd, J = 9, 3.5 Hz, H_2C-C(3)); 4.43 (s, H-C(4)); 4.10 (dd, J = 5, 3.5 Hz, H-C(6)); 3.63 (d, J = 9 Hz, H-C(2)); 3.21 (d, J = 3.5 Hz, H-C(5)); 2.91 (dt, J = 9, 9, 3.5 Hz, H-C(3)). Characteristics of 10b (E = PhS, X = Cl): m.p. 142-4°C (toluene/hexane). ^{1}H-NMR ($CDCl_3$): 7.45, 7.35 (2m, Ph); 4.98 (s, H-C-OEt); 4.50 (d, J = 5 Hz, H-C(4)); 4.44 (s, H-C(1)); 4.11 (dd, J = 9, 7.5 Hz) & 3.88 (dd, J = 9, 2.3 Hz, H_2C-C(3)); 3.95 (dd, J = 5, 4 Hz, Hexo-C(5)); 3.71 & 3.43 (2m, OCH_2); 3.35 (td, J = 7.5, 2.3 Hz, H-C(3)); 3.20 (d, J = 4 Hz, Hendo-C(6)); 2.56 (d, J = 7.5 Hz, H-C(2)); 1.18 (t, CH_3).
6. Details will be given in a full paper.
7. Characteristics of (-)-12: m.p. 117-118°C, $[\alpha]_D^{25}$ = - 148°; (+)-12: m.p. 115-116°C, $[\alpha]_D^{25}$ = +70°C, C = 11 mg/mL CH_2Cl_2.
8. See also: P.W. Sprague, J.E. Heikes, J.Z. Gougoutas, M.F. Malley, D.N. Harris, R. Greenberg, J. Med. Chem. 28 (1985) 1580.
9. R. Bloch, E. Guibe-Jampel, C. Girard, Tetrahedron Lett. 26 (1985) 4087. J.B. Jones, C.J. Francis, Can. J. Chem. 62 (1984) 2578.

(Received in France 4 September 1986)