Tetrahedron Letters,Vol.25,No.47,pp 5387-5388,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

DIELS-ALDER STEREO- AND REGIOSELECTIVITY CONTROLLED BY REMOTE SUBSTITUENTS AND SOLVENT. CYCLOADDITIONS OF 1-(DIMETHOXYMETHYL)-2,3-BIS(METHYLENE)-7-OXABICYCLO[2.2.1]HEPTANE

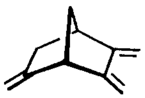
Jean-Luc Métral and Pierre Vogel*

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

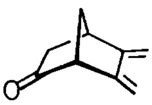
Summary. *The regioselectivity of the* $EtAlCl_2$*-catalyzed addition of methyl vinyl ketone to the title diene can be reversed by solvent modification.*

The chemical properties of the diene moieties in 2,3-bis(methylene)bicyclo[2.2.1]alkanes can be affected by remote substitution at C(5) and C(6).[1] For example, the Diels-Alder additions of 1[2] and 2[3] are "para" regioselective, whereas those of 3[2] and 4[4] are "meta" regioselective. This type of long-range substituent effect has been applied in the synthesis of anthracyclinones.[1,2] We report here the cycloadditions of diene 5 whose stereo- and regioselectivities is controlled by the dimethyl acetal group. Most interesting was the observation that a small change in the nature of the solvent can reverse the regioselectivity of the $EtAlCl_2$-catalyzed reactions.

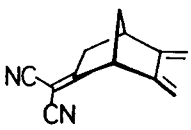
The diene 5 was readily prepared from the Diels-Alder adduct of maleic anhydride with dimethyl acetal of furfural.[5] This adduct was reduced with $LiAlH_4$ (THF, 0 °C), then hydrogenated (H_2/PtC/AcOEt, 0 °C) to give 6. Esterification (MsCl, pyr) gave 7 which afforded 5 on treatment with tBuOK in DMF/HMPT at 0 °C. On heating 5 with an excess of methyl vinyl ketone (MVK) in C_6H_6 to 100 °C, a 2.3:1:2.3:1 mixture of 8/9/10/11 was obtained in 90 % yield. Better ste-



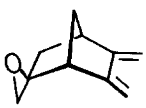
1



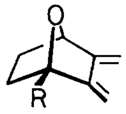
2



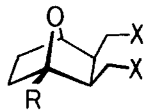
3



4



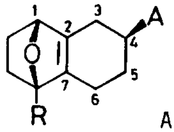
5



R = $CH(OMe)_2$

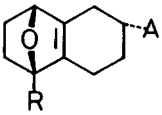
6 : X = OH

7 : X = OMs

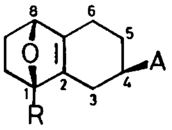


A = COMe

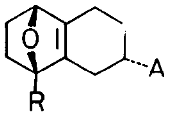
8 : "para"-β



9 : "para"-α



10 : "meta"-β



11 : "meta"-α

reo- and regioselectivities were observed under Lewis acid catalyzed conditions. Reaction of 5 with MVK precomplexed with BF_3-Et_2O in CH_2Cl_2 (- 85 °C, 20 min.) gave a 13.5:1:2.5:1.25 mixture of 8/9/10/11 (94 %). The major adduct 8 was isolated by HPLC.[6] Similarly, reaction of 5 with MVK precomplexed with $EtAlCl_2$ in 5:1 CH_2Cl_2/hexane (- 90 °C, 1 h.) gave a 32.5:1:3:2 mixture of 8/9/10/11 (95 %). When the solvent mixture contained higher proportions of hexane, the "para" regioselectivity was found to decrease and the "meta" regioisomer 10 became the favoured adduct. The best "meta" regioselectivity was observed in 1.5:1 CH_2Cl_2/hexane which led to 10:1:24:1 mixture of 8/9/10/11. An adverce effect of increasing the hexane content is that the reaction becomes sluggish due to the decreased solubility of the reactants. Nevertheless, the overall yield was 67 % and the major product 10 was isolated by HPLC.[6]

The reversal of Diels-Alder regioselectivity by a change of Lewis acid has been observed several times.[7] To our knowledge, however, the solvent effect reported here is unprecedented. Further work is required to give an explanation. It is possible, however, that the "meta" regioselectivity arises from co-coordination[8] of $EtAlCl_2$ with MVK and the acetal group in 5. This is favoured in an uncoordinating solvent such as hexane. In the presence of a coordinating solvent such as CH_2Cl_2, the latter competes with 5 for coordination to $EtAlCl_2$ and consequently "para" attack is favoured for reasons of steric hindrance. This hypothesis implies exo face selectivity for the cycloadditions of 5, as found for other dienes grafted on 7-oxanorbornane systems.[9,10]

Acknowledgments. We are grateful to Hoffmann- La Roche and Co., Basel, to the "Swiss National Science foundation" and to "Fonds Herbette", Lausanne, for financial support.

References and Notes.

1. P. Vogel, in "Stereochemistry and Reactivity of Systems Containing π Electrons", W.H. Watson, Ed., Verlag Chemie International, Deerfield Beach, Florida (1983) p. 147-195.
2. J. Tamariz, L. Schwager, J.H.A. Stibbard and P. Vogel, Tetrahedron Lett. 24, 1497 (1983).
3. M. Avenati, P.-A. Carrupt, D. Quarroz and P. Vogel, Helv. Chim. Acta 65, 188 (1982).
4. C. Mahaim, L. Schwager, P.-A. Carrupt and P. Vogel, Tetrahedron Lett. 24, 3603 (1983).
5. L. Mavoungou-Gomès, Bull. Soc. Chim. France, 1753 (1967).
6. a) Structure established by 360 MHz ^{1}H-NMR spectroscopy by Prof. J. Lauterwein, University of Lausanne. Recognition of protons at C(3,4,5,6) based on ^5J(H-1, H-6β) = 1.2 Hz in 8, ^5J(H-8, H-3β) = 1.2 Hz in 10.[9] 8 and 10 were equilibrated with 9 and 11, respectively, in the presence of MeONa in MeOH; b) details will be given in a full paper.
7. Z. Stojanac, R.A. Dickinson, N. Stojanac, R.J. Woznow and Z. Valenta, Can. J. Chem. 53, 616 (1975); J. Das, R. Kubela, G.A. MacAlpine, Z. Stojanac and Z. Valenta, Ibid. 57, 3308 (1979); T.R. Kelly and M. Montury, Tetrahedron Lett., 4311 (1978); R.C. Gupta, D.A. Jackson and R.J. Stoodley, J. Chem. Soc., Chem. Commun., 929 (1982).
8. T. Takebayaski, N. Iwasawa, T. Mukaiyama and T. Hata, Bull. Chem. Soc. Jpn., 56, 1669 (1983); B.B. Snider and G.B. Phillips, J. Am. Chem. Soc., 104, 1113 (1982).
9. C. Mahaim and P. Vogel, Helv. Chim. Acta 65, 866 (1982).
10. Regioselective cycloaddition of 5 to butynone is also observed.[6b]

(Received in France 15 September 1984)