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SOLVENT EFFECTS ON REGIOSELECTION IN $4+3 \rightarrow 7$ CYCLIZATIONS. A STEPWISE REACTION OF TRANS-1,3-PENTADIENE.[1]

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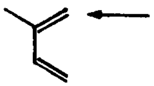
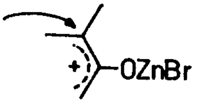
In the light of current theories, it is surprising that the $4+3 \rightarrow 7$ cyclization of 2-methylbutadiene (4) with 1,1-dimethyloxyallyl cation (5) can lead principally to the known constituent of hop oil, 2,2,5-trimethylcyclohept-4-enone (karahanaenone, 1), rather than the isomeric 2,2,4-trimethylcyclohept-4-enone (2).[1] 2-Methylbutadiene (4) is clearly most susceptible to electrophilic attack at carbon C-1, whereas nucleophilic attack of a 1,1-dimethyloxyallyl cation 5 in ionizing solvents is expected preferentially at the tertiary terminus and has been shown to occur exclusively so.[3] On this simple argument, which can be rephrased with greater precision and generality in HOMO-LUMO terminology,[4] the predominant 2,2,5-trimethylcyclohept-4-enone (1) is the wrongly oriented regioisomer.[5] We now show that a change from isopentane or benzene to a more polar solvent reverses regioselection to yield 2,2,4-trimethylcyclohept-4-enone (2) as the major isomer and, at the same time, reduces the relative amount of $3+2 \rightarrow 5$ product.



preferred site
of electrophilic
attack

4

preferred site
of nucleophilic
attack



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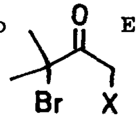
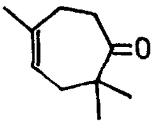
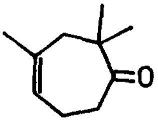
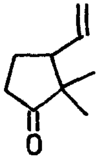
A typical experiment is as follows. Into a 50 ml 3-necked flask containing a large bar magnet and fitted with a low temperature thermometer as well as a 25 ml pressure equilibrating dropping funnel, is introduced zinc-copper couple (2.10 g, 0.03 g atom Zn), isoprene (2.73 g, 0.04 mol) and acetonitrile (10 ml) under nitrogen. A solution of 1,3-dibromo-3-methyl-2-butanone[3b] (2.44 g, 0.01 mol) in dimethoxyethane (DME) (1.35 g, 0.015 mol) and acetonitrile (5 ml) is added dropwise over a period of 90 min under vigorous stirring, the reaction flask being cooled to 6-8° by immersion into ice. At the end of the addition, the temperature is allowed to reach 23° and stirring is continued for a further 12 hr. The green product oil is isolated by the aqueous work up described previously[1] (for preparative glc work) and also by nonaqueous work up (for glc-ms examinations) via the liquid-liquid extraction technique using isopentane at -30°.[7] Our results and also earlier experiments, all carried out several times, are summarized in Table 1.

Experiments No. 1 and 2, which involve zinc and iron oxyallyl as electrophilic intermediates in solvent benzene and isopentane, should be contrasted with No. 3 and 4, which are considered to involve zinc oxyallyl and sodium oxyallyl, respectively, but now in a more polar solvent. The reversal of regioselectivity brought about merely by a change in solvent polarity is unusual and in point of fact, seems not to exist for what may appear to be related reactions, namely 1,3-dipolar and Diels-Alder additions. Our experiments show that ion pairing of the electrophilic intermediate(s) has an important bearing on the product distribution, no matter whether the combination of allyl cation and diene is stepwise or concerted.

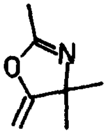
In extending the work on isoprene we studied the cyclizations involving trans-1,3-pentadiene and butadiene (Table 2). Apparently, leakage into cyclopentanones depends on several factors. Aside from the possible temperature effect noted previously[1] the structure of the diene seems important, e.g. the propenylcyclopentanone 7a derived from trans-1,3-pentadiene has a more stable precursor 10 (Scheme 1) and will be formed more readily than the vinylcyclopentanone 9 derived from parent butadiene. Consistently, the only or the major cyclopentanone isomer formed from each of the three dienes investigated is the crowded one, as expected for a stepwise reaction in which the two most stabilized termini combine in the final stage. We also note that the proportion of five-membered ring is increased at the expense of seven-membered ring in nonpolar solvents such as benzene and isopentane.

Table 1. Cycloadducts from the Reaction of 2-Methylbutadiene with Oxyallyl Intermediates Generated from 1,3-Dihalogeno-3-methyl-2-butanone under Various Conditions

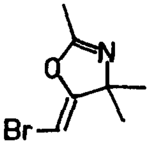
No		Experimental	Cycloadducts [%]*			% Yield	Ratio of Regioisomers 1 : 2
							
1	X=I	Zn/Cu (column method), isopentane,[a] benzene	1 (53.9)	2 (23.5)	3 (22.6)	12	74 : 26[b] 70 : 30
2	X=I	Fe$_2$(CO)$_9$, benzene, 57-80[a]					66 : 34 72 : 28
3	X=Br,I	Zn/Cu (one flask reaction), 10°, 24 hr, MeCN-DME	42.4	48.3	9.3	5	47 : 53[c]
4	X=Br,I	NaI, MeCN, Hg (Cu)[d]				2	46 : 54[b,e]

[a] See ref. 1. [b] H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., 12, 819 (1973); see in particular pp. 824 and 834. [c] This inverted ratio was reproduced consistently. A change from X=Br to X=I as the leaving group had no significant effect on the isomer distribution. [d] Dehalogenation in homogeneous conditions; Hg and also Cu, which was used in later experiments, merely serve to trap molecular iodine liberated during the reaction. See also footnote b and G. Fierz, R. Chidgey and H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., 13, 410 (1974). [e] We thank Dr. B. Willhalm for analyzing the small amount of product by high resolution glc-ms.

*Competing reactions: Debromination of 1,3-dibromo-3-methyl-2-butanone in acetonitrile with Zn-Cu couple as well as with NaI-Cu below 25° produces linear 1,4-diketones; see C. Chassin, E. A. Schmidt and H. M. R. Hoffmann, J. Am. Chem. Soc., 96, 606 (1974). Dehalogenation of the dihaloketone with Zn-Cu couple in MeCN-DME produces also two novel cycloadducts, i. e. 2,4,4-trimethyl-5-methylene-2-oxazoline (A) and bromine substituted B [For a related addition to DMF, see H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt and R. H. Smithers, J. Am. Chem. Soc., 94, 3201 (1972). Review on oxazolines: J. A. Frump, Chem. Rev., 71, 483 (1971)].

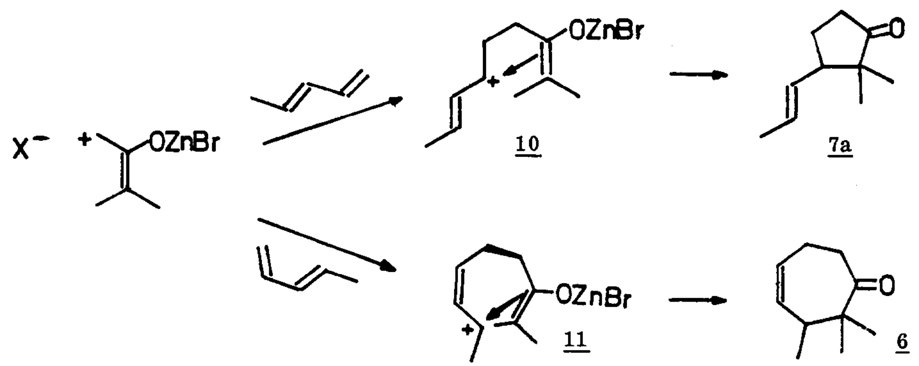


A



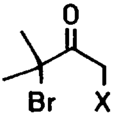
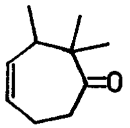
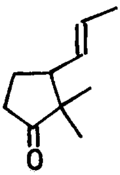
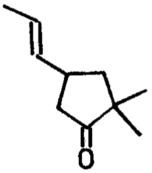
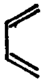
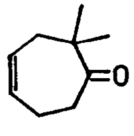
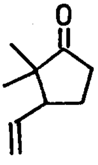
B

Perhaps the most interesting result is the predominant formation of regioisomer 6, which once again, is the wrongly oriented product and unlike 1, arises in both polar and nonpolar conditions. In our opinion, the experimental findings are best rationalized by a stepwise process, in which one σ bond is made well ahead of the other (Scheme 1). Of the four intermediates that can be envisaged a priori, given the formation of any four σ bonds in the first step, π complex 11 arises by coupling of the two sterically most accessible termini. Accordingly, 11 enjoys maximum stabilization, the positive charge interacting intramolecularly with the most alkylated double bond. Cyclization to the observed seven-membered ring 6 is completed by covalent collapse, the crowded σ bond being formed in the final step similar to the formation of crowded vinylcyclopentanones discussed above.



Scheme 1

Table 2. Seven- and Five-membered Rings from the Zinc-induced Dehalogenation of 1,3-Dihalogeno-3-methyl-2-butanone in the Presence of trans-1,3-Pentadiene and Butadiene

Diene		Experimental Conditions	Cycloadducts			Ratio of 7-membered ring to 5-membered ring	% Yield
			4-Cycloheptenones	Vinylcyclopentanones			
	4b; X=I	Zn-Cu isopentane, column method	 6[a] (26%)	 7a[b] (65%)	 7b[c] (9%)	26:74	10-20
	4a; X=Br	MeCN-DME, 10° for 1.5 hr, then rt, 24 hr	62%	38%		62:38	8
	4a; X=Br	MeCN-DME	 8[c] (93%)	 9[c] (7%)		91:9	1[d]

[a] Nmr δ(TMS, CCl_4, 100 MHz) 0.95 (s,3H), 1.05 (s,3H), 1.02 (d,J=7Hz,3H), 2.19-2.47(m,3H), 2.69-3.01 (m,1H), 3.03-3.37 (m,1H), 5.09-5.59 (m,2H); in benzene solvent the methyl signals are clearly resolved, the diastereotopic gem-dimethyls appearing at 0.86 and 1.06, the methyl doublet at 0.77 ppm. The marked chemical shift difference of the gem-dimethyl protons (which are adjacent to the chiral centre), and the complexity of the nmr signals for the methylene protons α to the carbonyl group establish 6 as the crowded regioisomer. Ir (CCl_4, cm^{-1}) 1709 (s). Mass spectrum (20 eV, rel. intensities, glc-ms) $C_{10}H_{16}O$ m/e 152 (90) (M^+), 137 (19), 123 (11), 109 (54), 96 (29), 95 (100), 81 (65), 70 (98), 68 (38), 67 (71), 55 (44), 53 (21), 43 (62), 42 (38), 41 (82). Anal. Calcd. for $C_{10}H_{16}O$: C, 78.9; H, 10.6. Found: C, 79.5; H, 10.5. Using different preparative and glc procedures compound 6 was isolated six times in a purity range of 90-95%, estimated by analytical glc. An impurity with nmr peaks at δ 1.0-1.35, 1.99-2.19 ppm could not be removed. See also ref 6. [b] 2,2-Dimethyl-3-(1'-propenyl)-cyclopentanone (7a); nmr δ (TMS, CCl_4, 100 MHz) 0.76 (s,3H), 0.95 (s,3H), 1.72 (d,J=5Hz,3H), 1.84-2.74 (m,5H), 5.2-5.7 (m,2H), Ir (CCl_4, cm^{-1}) 1742 (s); ms 152 (86) (M^+), 137 (18), 123 (11), 109 (47), 97 (11), 96 (34), 95 (60), 81 (87) [$(M-C_2H_4-CO-CH_3)^+$ and $(M-C_5H_{11})^+$], 70 (100), 69 (34), 68 (47), 67 (60), 55 (47), 43 (50), 41 (80). See also ref 6. [c] Satisfactory spectral data were obtained for these compounds. [d] Experimental conditions for the reaction with butadiene were -10 to 0° for 1 hour, rising gradually to 22° over a period of 5 hours and then 10 hours' stirring at 22°.

Acknowledgments. We thank Professor D. N. Kevill for a discussion and the Science Research Council as well as NATO for support of this work.

References and Notes

(1) The Allyl Cation Route to Seven-Membered Rings, 16. Part 15 R. Chidgey and H. M. R. Hoffmann, Tetrahedron Lett., 2633 (1977).

(2) Present address: Institut für Organische Chemie der Technischen Universität, Schneiderberg 1 B, 3000 Hannover, Germany.

(3) (a) Methanol as solvent and nucleophile: H. M. R. Hoffmann, T. A. Nour and R. H. Smithers, J. C. S Chem. Comm., 963 (1972); (b) Dimethylformamide: H. M. R. Hoffmann, K. E. Clemens, E. A. Schn and R. H. Smithers, J. Am. Chem. Soc., 94, 3201 (1972).

(4) Assuming that the HOMO of the diene interacts most strongly with the LUMO of the allyl cation, w expect preferential bonding between carbon C-1 of 2-methylbutadiene (4) and the tertiary terminus the allylic cation (5), i. e., between the two termini with the greatest coefficients in the nearest pa of frontier orbitals. See I. Fleming, Frontier Orbitals and Organic Chemical Reactions, J. Wiley Sons, London 1976 for a recent survey and the names of the pioneers in this field. Cf. also O. Eis stein, J. M. Lefour, N. T. Anh and R. F. Hudson, Tetrahedron, 33, 523 (1977).

(5) Alternatively karahanaenone (1) can be regarded as the product of anti-Markownikoff cyclization of neryl pyrophosphate; see ref. 6.

(6) S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., 99, 4192

(7) The low temperature reactor-extractor developed by Dr. E. A. Schmidt was used; see ref. 3 (b).

Note added in proof: In a recent communication R. Noyori et al., J. Am. Chem. Soc., 99, 5196 (1977) h concluded that "the [3+4] cycloaddition involving 2-oxyallyls is occurring in a concerted manner, and b the primary and secondary frontier MO interactions are equally important in determining the regiosele vity". Experimentally this work was based on studies with substituted furans as diene component, a single solvent, namely benzene being used. As we have already found that regioselectivities of substit furans are also solvent dependent, the mechanistic discussion of these authors should be viewed with reserve.