Unusual regioselectivity in a Diels—Alder reaction of isoprene with levoglucosenone

M. S. Miftakhov,* I. N. Gaisina, and F. A. Valeev

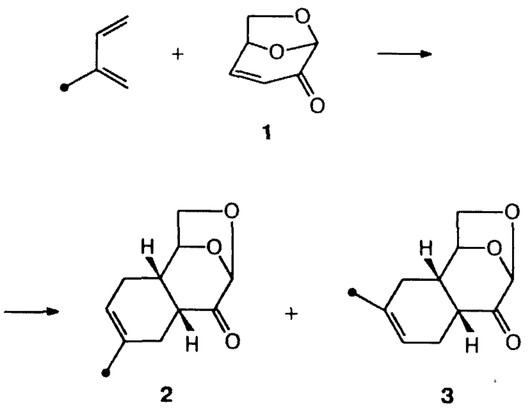
*Institute of Organic Chemistry, Ufa Reseach Center of the Russian Academy of Sciences,
71 prosp. Oktyabrya, 450054 Ufa, Russian Federation.
Fax: +7 (347 2) 35 6066*

The $ZnCl_2$-catalyzed [4+2]-cycloaddition of isoprene with levoglucosenone is highly regio- and stereoselective.

Key words: isoprene, Diels—Alder reaction, levoglucosenone, transition state, stereocontrol.

Condensations of isoprene with asymmetric dienophiles (alkyl acrylates,[1—3] methacrylates,[4] α-ethylacrylates,[5] acrolein,[6] styrene,[7] dichlorovinylroborane,[8] methyl vinyl ketone,[9] acrylonitrile,[10] *etc.*) result in cyclohexene derivatives, which are regioisomeric with respect to the position of the methyl group at the double bond. The ratio of regioisomers is usually[8] from 3 : 2 to 9 : 1, whereas in reactions catalyzed by $LiClO_4$ [11] and $AlCl_3$,[12] the corresponding ratio is 19 : 1. Similar results have been obtained in reactions of isoprene with phenylmaleic anhydride,[13] indene,[14] and 2-substituted derivatives of dichlorovinylborane.[8] The observed regioselectivity of the reactions was successfully explained by the frontier molecular orbital theory.[15] According to CNDO/2 [16] and *ab initio*[17] calculations of the electronic structure of isoprene, the negative charge at C(1) is somewhat higher than that at C(4) (the charges at C(1) and C(4) in the *S-cis* form of isoprene are −0.14 and −0.13, respectively). Therefore, in the transition state of cycloaddition involving enones, a bond is preferably formed between C(1) and the more electropositive β-carbon atom of the activated double bond. In the examples given, irrespective of the nature of the reagents and the reaction conditions, the above-noted electronic control of the reaction is realized to a certain extent, although in some cases, steric factors predominate.[18] Nevertheless, stereocontrol does not play a major role for isoprene, because the methyl group is small and remote from the reacting centers in the transition state. Effective steric control of the regiochemistry of [4+2]-cycloaddition of isoprene is probably possible only for specific dienophiles, which can "feel and differentiate" steric hindrance created in the transition state by the methyl group of isoprene. In the present work, we studied the reaction of isoprene with one of dienophiles of this kind, *viz*., levoglucosenone (1)[19] (Scheme 1).

Scheme 1



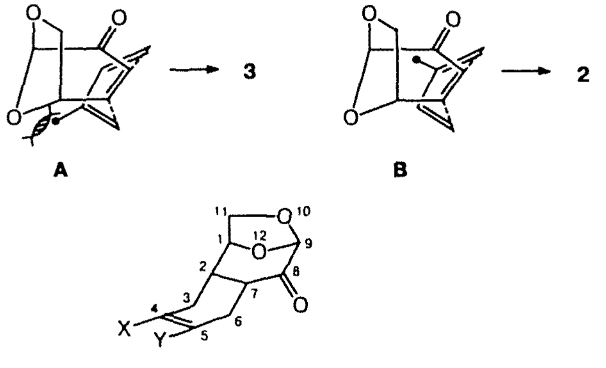
It was shown[20] that this reaction catalyzed by $ZnCl_2$ in CH_2Cl_2 at ~20 °C occurs smoothly and regioselectively with the preferential formation of adduct **2**; the fraction of the "electronically controlled" adduct **3** in the reaction mixture is 5—7 %, and the overall yield of regioisomers is 75—80 %. Conversely, the thermal reaction of isoprene with enone **1** (toluene, 160 °C) is not regioselective, as *endo* adducts **2** and **3** are formed in a 6 : 4 ratio and in an 80 % overall yield.

The preferential formation of isomer **2** in the catalytic reaction is evidently caused by steric control, which, however, does not imply the control of product formation,[21] *i.e.*, thermodynamic stability of the end products **2** and **3**. It was shown in a separate experiment that the pure isomer **2** does not change under the conditions of the thermal reaction (toluene, 160 °C, 5 h). This suggests that neither interconversions **2** $\rightleftharpoons$ **3** according to the retrodiene scheme nor epimerization at C(7) occur. The C(3)—C(6) fragments of the cyclohexene moiety in the boat conformation in the molecules of isomers **2** and **3** as well as in the similar adduct **4** [22] are *exo*-oriented with respect to the pyranose ring and do not manifest noticeable differences in the spatial shielding of the Me

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 2047—2049, August, 1996.

group. Hence, steric control apparently occurs in the transition state and is kinetic in nature. For example, the *endo* orientation of the diene in pre-complex **A** leading to adduct **3**, which is required at the transition state,[22,23] is unfavorable due to steric interaction of the methyl group with the acetal O atom, whereas there is no such hindrance in pre-complex **B** (Scheme 2).

Scheme 2



2–4

2: X = H, Y = Me
3: X = Me, Y = H
4: X = H, Y = H

The assignment of isomers **2** and **3** was based on a comparative study of ^{13}C NMR spectra and their comparison with the data for adduct **4**.[22,24] The diagnostic chemical shifts are those of allylic carbon atoms, C(3) and C(6), for which a distinct (+)-β-effect of the methyl group[25] (~4 ppm) is observed on going from adduct **4** to isomers **2** and **3**. These chemical shifts for compounds **2**—**4** are 20.65, 24.41, 20.35 ppm (C(3)) and 28.85, 24.97, 24.05 ppm (C(6)), respectively.

Experimental

^1H and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (300 and 75.47 MHz, respectively) using $SiMe_4$ as the internal standard. TLC was performed on Silufol chromatographic plates (Czech Republic). Optical rotations were measured on a Perkin Elmer-141 instrument. Mass spectra were recorded on an MX-1306 instrument (ionization energy 70 eV, temperature of the ionization chamber 30 to 50 °C).

Synthesis of tricyclic enones 2 and 3. *A.* A mixture of levoglucosenone **1** (1.84 g, 14.6 mmol), isoprene (3.0 mL), and toluene (15 mL) was heated for 5 h at 160 °C in a sealed Pyrex tube. The tube was opened, the solvent was removed on a rotary evaporator, and the residue was chromatographed on silica gel using ethyl acetate—hexane (1 : 9) as the eluent to give 2.25 g (80 %) of a mixture of adducts **2** and **3** in a 6 : 4 ratio, which was difficult to separate.

B. One crystal of anhydrous $ZnCl_2$ was added with stirring to a solution of levoglucosenone **1** (5.0 g, 3.9 mmol) and isoprene (4.1 g, 6.0 mmol) in CH_2Cl_2 (20 mL), and the mixture was kept for 16 h. The mixture was then washed with water and saturated NaCl, dried with $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using ethyl acetate—pentane (1 : 9) as the eluent to give 5.8 g (75 %) of adduct **2**.

(1*S*,2*S*,7*R*,9*R*)-5-Methyl-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-en-8-one (2). R_f = 0.66 (ethyl acetate—hexane, 1 : 1), m.p. 103—105 °C (ether—hexane, 1 : 9), $[\alpha]_D^{21}$ −39.1° (*c* 1.0, $CHCl_3$). Found (%): C, 68.20; H, 7.25. $C_{11}H_{14}O_3$. Calculated (%): C, 68.06; H, 7.20. ^1H NMR, δ: 1.65 (s, 3 H, Me); 1.84—2.70 (m, 5 H, CH, CH_2); 3.12 (t, 1 H, C(7)H, $J_{6,7}$ = 7.0 Hz); 4.03 (dd, 1 H, C(11)—H(*endo*), J_{gem} = 7.4 Hz, $J_{11,1}$ = 5.0 Hz); 4.2 (d, 1 H, C(11)—H(*exo*)); 4.48 (d, 1 H, C(1)H, $J_{11,1}$ = 5.0 Hz); 5.12 (s, 1 H, C(9)H); 5.38 (m, 1 H, C(4)H). ^{13}C NMR, δ: 20.63 (C(3)); 23.52 (Me); 28.85 (C(6)); 37.55 (C(2)); 40.99 (C(7)); 67.19 (C(11)); 77.15 (C(1)); 101.61 (C(9)); 117.86 (C(4)); 131.51 (C(5)); 202.28 (C(8)). MS, *m/z* (I_{rel} (%)): 194 $[M]^+$ (71), 120 $[M-C_3H_6O_2]^+$ (45), 166 $[M-CO]^+$ (36), 148 $[M-CHO-OH]^+$ (39), 130 $[M-CHO-OH-H_2O]^+$ (28).

(1*S*,2*S*,7*R*,9*R*)-4-Methyl-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-en-8-one (3). ^1H NMR, δ (in a mixture with isomer **2**): 1.86 (s, 3 H, Me); 3.20 (t, 1 H, C(7)H, $J_{6,7}$ = 7.0 Hz); 5.12 (s, 1 H, C(9)H); 5.38 (m, 1 H, C(4)H). ^{13}C NMR, δ: 23.23 (Me); 24.41 (C(3)); 24.97 (C(6)); 38.68 (C(2)); 40.27 (C(7)); 67.19 (C(11)); 77.15 (C(1)); 101.61 (C(9)); 118.71 (C(4)); 130.91 (C(5)); 202.28 (C(8)).

(1*S*,2*S*,7*R*,9*R*)-10,12-Dioxatricyclo[7.2.1.0^{2,7}]dodec-4-en-8-one (4). ^{13}C NMR [24] (*cf.* Ref. 22): 20.35 (C(3)); 24.04 (C(6)); 38.04 (C(2)); 40.53 (C(7)); 67.25 (C(11)); 77.24 (C(1)); 101.62 (C(9)); 123.95 (C(4)); 124.61 (C(5)); 202.19 (C(8)).

References

1. K. Alder and W. Vogt, *Lieb. Ann.*, 1949, **564**, 120.
2. I. N. Nazarov, A. I. Kuznetsova, and N. V. Kuznetsov, *Zh. Obshch. Khim.*, 1955, **25**, 88 [*J. Gen. Chem. USSR*, 1955, **25** (Engl. Transl.)].
3. I. N. Nazarov, Yu. A. Titov, and A. I. Kuznetsova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*], 1959, 1412 (in Russian).
4. J. Meinwald and H. C. Hwang, *J. Am. Chem. Soc.*, 1957, **79**, 2910.
5. R. Pummerer, F. Aldebert, and H. Sperber, *Lieb. Ann.*, 1953, **583**, 191.
6. A. A. Petrov and N. P. Sopov, *Zh. Obshch. Khim.*, 1957, **27**, 795 [*J. Gen. Chem. USSR*, 1957, **27** (Engl. Transl.)].
7. J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Am. Chem. Soc.*, 1952, **74**, 2667.
8. N. Noirett, A. Youssofi, B. Carboni, and M. Wanltier, *J. Chem. Soc., Chem. Commun.*, 1992, 1105.
9. J. N. Babler, D. O. Olsen, and W. H. Arnold, *J. Org. Chem.*, 1974, **39**, 1656.
10. A. A. Petrov and A. F. Sapozhnikov, *Zh. Obshch. Khim.*, 1948, **18**, 424 [*J. Gen. Chem. USSR*, 1948, **18** (Engl. Transl.)].
11. R. M. Pagni, G. W. Kabalka, S. Bains, M. Plesko, J. Wilson, and J. Bartmess, *J. Org. Chem.*, 1993, **58**, 3130.
12. T. Inunkai and T. Kojima, *J. Chem. Soc., Chem. Commun.*, 1969, **7**, 1334.
13. L. E. Miller and D. J. Mann, *J. Am. Chem. Soc.*, 1950, **72**, 1484.
14. E. D. Bergmann, *Bull. Res. Council Israel 5A*, 1956, 147; *Chem. Abstr.*, 1956, **50**, 15493.

15. K. N. Houk, *J. Am. Chem. Soc.*, 1973, **95**, 4092; I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley and Sons, New York, 1976.
16. Yu. E. Eizner and B. L. Erusalimskii, in *Elektronnyi aspekt reaktsii polimerizatsii* [*An Electronic Aspect of the Polymerization Reaction*], Nauka, Leningrad, 1978, 56 (in Russian).
17. G. N. Bondarenko, D. Sc. Thesis (Chemistry), Moscow, 1992 (in Russian).
18. W. Carruthers, *Cycloaddition Reactions in Organic Synthesis* in *Tetrahedron Organic Chemistry Series*, Eds. J. E. Baldwin and P. D. Mangus, Pergamon Press, New York, 1990, **8**, 1.
19. V. Halpern, R. Riffer, and A. Broido, *J. Org. Chem.*, 1973, **38**, 204.
20. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, 1973, **95**, 4094.
21. S. Chandrasekhar, *Chem. Soc. Rev.*, 1987, **16**, 313.
22. D. Ward and F. Shafizadeh, *Carbohydr. Res.*, 1981, **95**, 155.
23. P. Bhat and D. Horton, *Carbohydr. Res.*, 1983, **122**, 189; F. Shafizadeh and M. G. Essig, *Carbohydr. Res.*, 1983, **114**, 71.
24. F. A. Valeev, I. N. Gaisina, M. S. Miftakhov, and G. A. Tolstikov, *Zh. Org. Khim.*, 1993, **29**, 205 [*Russ. J. Org. Chem.*, 1993, **29** (Engl. Transl.)].
25. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *YaMR-spektroskopiya v organicheskoi khimii* [*NMR Spectroscopy in Organic Chemistry*], Khimiya, Leningrad, 1983 (in Russian).

Received November 17, 1995;
in revised form April 4, 1996