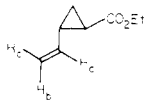
0.72; UV (hexane) λ_{max} 203 nm (ϵ 4450); IR 2990, 1728, 1640, 905 cm^{-1}.

^1H NMR analysis suggested the presence of 14/15 in a ratio of 3:7. Selective decoupling experiments permitted assignments of certain resonances to the appropriate isomer: NMR ($CDCl_3$) δ 1.11 (m, 1), 1.27 (dt, 3, $COCH_2CH_3$), 1.31 (s, cis CH_3), 1.34 (s, trans CH_3), 1.43 (m, 1), 4.15 (dq, 3, $COCH_2CH_3$), 4.97-5.21 (m, 2, CH_2=CH), 5.46 (dd, 1, trans CH_2=CH, J_{trans} = 16 Hz, J_{cis} = 10 Hz), 5.96 (dd, 1, cis CH_2=CH, J_{trans} = 16 Hz, J_{cis} = 10 Hz).

Addition of 0.5 molar equiv of $Eu(thd)_3$ to the $CDCl_3$ solution of 14/15 shifted the ^1H NMR resonances of the *trans*-CH_2=CH to 5.47 ppm while the *cis*-CH_2=CH was moved to 6.04 ppm.

Ethyl *trans*-2-Vinylcyclopropanecarboxylate (16). Wittig reaction of 284 mg (2 mmol) of 10/11 with methylidenetriphenylphosphorane prepared as above provided a crude oil. Column chromatography with $CHCl_3$/MeOH (99:1) elution afforded 225 mg (80%) of 16: TLC ($CHCl_3$/MeOH, 10:1) R_f 0.71; UV (hexane) λ_{max} 207 nm (ϵ 4960); IR 2990, 1729, 1640, 910 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (m, 1), 1.26 (t, 3, $CO_2CH_2CH_3$), 1.38 (m, 1), 1.64 (m, 1), 2.01 (m, 1), 4.14 (q, 2, $CO_2CH_2CH_3$), 4.99 (d, 1, H_b, J = 10 Hz), 5.16 (d, 1, H_c, J = 16 Hz), 5.44 (dd, 1, H_a, J_{trans} = 16 Hz, J_{cis} = 10 Hz).



Acknowledgment. We gratefully acknowledge the assistance of Mr. Mel Micke in obtaining mass spectra and Ms. Pat Mings for manuscript preparation. R.W.C., Jr., deeply appreciates the financial support in the form of a National Cancer Institute Fellowship.

Registry No. (11*E*)-3, 89827-98-5; (11*Z*)-3, 89887-36-5; (11*E*)-4, 89887-37-6; (11*Z*)-4, 89887-38-7; (11*E*)-5, 89827-99-6; (11*Z*)-5, 89887-39-8; (11*E*)-6, 89887-40-1; (11*Z*)-6, 89887-41-2; 7, 62285-98-7; 8, 13950-14-6; 9, 13949-97-8; 10, 13950-12-4; 11, 13949-93-4; 12, 79-77-6; 13, 31821-03-1; 14, 52345-63-8; 15, 52345-60-5; 16, 2183-90-6; CH_2=CHBr, 593-60-2.

A Study of the Stereoselectivity of Cyclopropanation of Some α,β-Unsaturated Aldehydes by Ethyl (Dimethylsulfuranylidene)acetate

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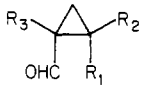
Received October 3, 1983

The effect of aprotic solvent polarity on the stereoselectivity of cyclopropanation of the α,β-unsaturated aldehydes methacrolein and acrolein by ethyl (dimethylsulfuranylidene)acetate has been investigated. The proportion of less favored cis cyclopropane isomer was found to increase linearly with the log of the solvent dielectric constant. This effect of solvent on stereoselectivity was much more pronounced with the more sterically demanding substrate methacrolein. Stability and kinetic studies suggest that this effect is due to an increased reaction rate in the more polar solvents. A general mechanism for the reaction is proposed that seems to account for the experimental observations.

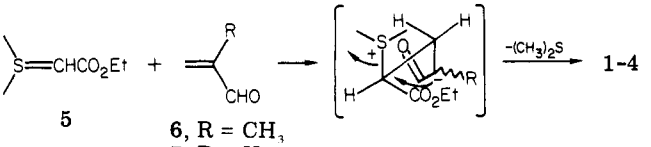
During the course of synthesis of some analogues of *all-trans*- and 13-*cis*-retinoic acid,[2] we required useful quantities of the four 2-formylcyclopropanecarboxylates 1-4. These formyl esters were prepared by Payne[3] by the



1, R_1 = CO_2Et; R_2 = H; R_3 = CH_3
2, R_1 = H; R_2 = CO_2Et; R_3 = CH_3
3, R_1 = CO_2Et; R_2 = H; R_3 = H
4, R_1 = H; R_2 = CO_2Et; R_3 = H

reaction of the stabilized sulfur ylide 5 with the appropriate α,β-unsaturated aldehydes, presumably through a dipolar intermediate as shown in Scheme I.[4,5] With both methacrolein (6) and acrolein (7) as substrate, predominantly trans cyclopropanation to give 2 and 4, respectively (GLC analysis), was observed under the reported conditions.[3] Since we desired essentially equal quantities of 1-4, an examination of the effect of solvent polarity on product cis/trans isomer ratios seemed warranted for this cyclopropanation. This was of especial interest since aprotic solvent polarity markedly influences reaction stereose-

Scheme I



5 6, R = CH_3 7, R = H

Table I. Effect of Solvent Polarity on Cyclopropane Stereochemistry[a]

substrate	solvent	dielectric constant,[b] 20 °C	products,[c] rel % cis	products,[c] rel % trans	lit. cis/trans[d]
6	C_6H_6	2.28	30 (9.37)	70 (8.87)	32:68
6	THF	7.58	35	65	
6	CH_2Cl_2	9.08	41	59	
6	Me_2CO	20.70	45	55	
6	CH_3CN	37.50	48	52	
7	C_6H_6	2.28	8.5 (9.35)	91.5 (9.31)	
7	Me_2CO	20.70	14.5	85.5	17:83

[a] All reactions were run for 18 h at 25 °C under an Ar atmosphere. [b] Schneider, R. L. *Eastman Org. Chem. Bull.* **1975**, *47*, 1-12. [c] Determined by HPLC analysis and integration of the ^1H NMR spectrum after purification. δ values in parentheses are the chemical shifts of the aldehydic protons ($CDCl_3$). [d] See ref 3.

(1) (a) National Cancer Institute Fellow, 1982-1984. (b) Program Project Grant No. AM-14881 from the National Institutes of Health.
(2) Curley, R. W., Jr.; DeLuca, H. F. *J. Org. Chem.* previous paper in this issue.
(3) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351-3355.
(4) Johnson, A. W.; Hruby, V. L.; Williams, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 918-922.
(5) Trost, B. M. *J. Am. Chem. Soc.* **1967**, *89*, 138-142.

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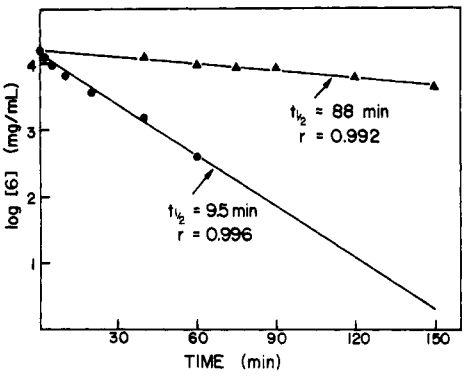


Figure 1. Effect of solvent polarity on reaction of 6 vs. time: ●, acetone; ▲, benzene. Correlation coefficient (r) derived from least-squares linear regression analysis.

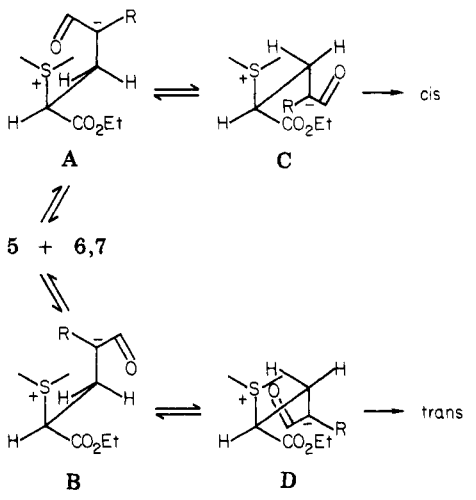
lectivity in related processes such as the Michael-type cyclopropanation[6] and the Wittig reaction.[7]

As can be seen in Table I, cyclopropanation of **6** in benzene gave virtually the same ratio of *cis*-**1** to *trans*-**2** as was observed previously when determined by integration of the areas under the trans aldehydic (δ 8.87) and cis aldehydic (δ 9.33) proton resonances in the ^{1}H NMR spectrum (90 MHz). These isomer ratios were confirmed by HPLC analysis, and identity was established by isolation of **2** and conversion by oxidation/hydrolysis to the known *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid.[8,9] Although chemical yields were comparable (80–90%), when the polarity of the solvent was progressively increased (as evidenced by dielectric constant; ε) there was an attendant increase in the ratio of **1/2**. Over the solvent range investigated, this increase was proportional to log ε and the ratio of **1/2** approached unity when the reaction was performed in acetonitrile, the most polar, aprotic solvent employed (Table I).

When cyclopropanation of **7** was performed in acetone, Payne observed a stronger bias for the trans product **4** than that observed in reactions with **6**.[3] Therefore, as might be expected, we were unable to substantially improve on the ratio of **3/4** by varying solvent polarity as had been done for reaction with **6**. Nevertheless, a slight but measureable difference in the ratio of **3/4** was observed when this slightly lower yield reaction (60–65%) was performed in benzene and acetone (Table I). In the case of mixtures of **3** and **4**, integration of the high-resolution ^{1}H NMR spectrum (200 MHz) was required to resolve the aldehydic proton resonance doublets for the trans (**4**, δ 9.31) and cis (**3**, δ 9.35) products.

The influence of solvent polarity on reaction stereoselectivity was not quite as dramatic as in the related cases cited above.[6,7] However, it is clear that at least in the case of the more sterically demanding 2-methyl-substituted acrolein **6**, significant variation in the stereoselectivity of cyclopropanation can be affected by solvent polarity changes with no significant influence on yields. That this greater cis/trans ratio with increase in solvent polarity may be due to the preferential formation of a "kinetic product" is suggested by the observation that these mixtures of **1/2** are equilibrated to a 10:90 cis/trans ratio when exposed to a solution of NaOMe/MeOH. Additional direct evidence that the influence of a polar aprotic solvent on stereoselectivity may be due to an effect on reaction rate

Scheme II



was obtained by measuring the extent of reaction of methacrolein (**6**) with ylide **5** over time in the high-resolution FT-NMR. In both benzene-d_6 and acetone-d_6 the methacrolein concentration showed a first-order decline over time with concomitant formation of the appropriate cyclopropane product mixture (Figure 1). Regression analysis of the data showed the half-life of **6** to be about 9.5 min in the polar solvent acetone and 88 min in the nonpolar benzene.

By analogy with many studies of the Wittig olefination,[7] the mechanism proposed in Scheme II seems reasonable to account for the observed results. Electrostatic interactions should favor initial formation of the eclipsed betaines A and B.[10] Subsequent collapse to cyclopropanes via anti conformers C and D[4,5] is apparently retarded in solvents of low dielectric constant less capable of shielding the proposed internal ion-pair attraction. This would promote relatively greater equilibration of A and B, resulting in preferential formation of the favored trans product. In solvents of increasing dielectric constant the rate of cyclopropane formation may become much more competitive with betaine equilibration, resulting in increasing proportions of cis cyclopropane. Finally, despite the limited number of substrates investigated, it seems reasonable that the more sterically demanding the 2-position substituent of the α,β-unsaturated aldehyde, the greater would be the ability of a polar, aprotic solvent to promote cis cyclopropane formation via the anti conformer C.

Experimental Section

All melting points, determined with a Thomas-Hoover capillary apparatus, and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390, Nicolet NMC-200, or Bruker WH-270 spectrometer with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer 567 grating infrared spectrophotometer as liquid films. UV spectra were recorded with a Beckman Model 24 spectrophotometer. TLC was performed on silica gel 60 F_{254} precoated aluminum-backed plates from EM Reagents. Column chromatography was performed on silica gel 60, 70–230 mesh from EM Reagents. HPLC was carried out on a Beckman 332 gradient liquid chromatograph equipped with a Beckman 160 UV detector on two columns: DuPont Zorbax-Sil, 4.6 mm × 25 cm (flow rate 2 mL/min), and Waters μPorasil, 7.8 mm × 30 cm (flow rate 4 mL/min). Commercial Ar was dried by bubbling through concentrated H_2SO_4. All organic solvents

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(8) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568–6572.
(9) Ingold, C. K. *J. Chem. Soc.* **1925**, *127*, 387–398.
(10) Johnson, A. W. "Ylid Chemistry"; Academic Press: New York, 1966.

were appropriate dried prior to use.

General Procedure. To a magnetically stirred solution of α,β-unsaturated aldehyde (1.7 mmol) in 1.5 mL of dry solvent, in a round-bottomed flask equipped with an Ar inlet and $CaSO_4$ drying tube, was added ylide **5**[3,11] (1.7 mmol) all at once. Stirring was continued for 18 h at room temperature. The solution was concentrated under reduced pressure to give the formylcyclopropanecarboxylates as crude oils, which were purified by distillation under reduced pressure or by column chromatography.

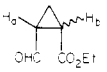
Ethyl 2-Methyl-2-formylcyclopropanecarboxylates (1 and 2). To 5.4 g (77 mmol) of **6** in 50 mL of acetone was added 11.4 g (77 mmol) of ylide **5**. Workup as above afforded 10.9 g of crude **1/2** as an oil. Short-path vacuum distillation afforded 10.0 g (83%) of **1/2** as a clear oil: bp 51-53 °C (0.3 mmHg) [lit.[3] bp 45 °C (<1 mmHg)]; TLC (hexanes/EtOAc 3:1) R_f 0.35; IR 2990, 1721 (br) cm^{-1}; UV (95% EtOH) λ_{max} 210 nm (ϵ 1828), 280 nm (ϵ 56).

The two isomers were separated by HPLC (Zorbax-Sil; CH_2Cl_2/hexane, 52:48) to give *cis*-**1** [t_R 22.5 min; NMR ($CDCl_3$) δ 1.26 (s, 3, CH_3), 1.27 (t, 3, CH_2CH_3, J = 7.5 Hz), 1.41 (m, 1, H_c), 2.08 (br s, 1, H_b), 2.10 (m, 1, H_a), 4.17 (q, 2, $COCH_2$, J = 7.5 Hz), 9.37 (s, 1, CHO)] and *trans*-**2** [t_R 17.5 min; NMR ($CDCl_3$) δ 1.40 (s, 3, CH_3), 1.30 (t, 3, CH_2CH_3, J = 7.5 Hz), 1.50-1.58 (m, 2, H_b and H_c), 2.24 (s, 1, H_a), 4.20 (q, 2, $COCH_2$, J = 7.5 Hz), 8.87 (s, 1, CHO)].

A sample of *trans*-**2** was readily air-oxidized in dilute $CHCl_3$ solution to cleanly give the trans acid ester which was hydrolyzed (1 N HCl) to provide crude *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid. Two crystallizations from CH_3CN afforded clean diacid: mp 169-171 °C (lit.[9] mp 168 °C).

Ethyl 2-Formylcyclopropanecarboxylates (3 and 4). To 95 mg (1.7 mmol) of **7** in 1.5 mL of acetone was added 250 mg (1.7 mmol) of ylide **5**. Workup as above provided crude **3/4** as a viscous red oil. Column chromatography with $CHCl_3$/MeOH (99:1) elution afforded 155 mg (65%) of **3/4** as a clear oil: TLC ($CHCl_3$/MeOH 10:1) R_f 0.72; IR 2994, 1720 (br) cm^{-1}; UV (hexane) λ_{max} 203 nm (ϵ 1126), 284 (ϵ 27).

The two isomers were separated by HPLC (Zorbax-Sil; CH_2Cl_2/hexane, 41:59) to give *cis*-**3** [t_R 22 min; NMR ($CDCl_3$) δ 1.28 (t, 3, CH_3, J = 7.5 Hz), 1.54 (m, 2, CH_2), 1.94 (m, 1, H_b), 2.06 (m, 1, H_a), 4.28 (q, 2, $COCH_2$, J = 7.5 Hz), 9.35 (d, 1, CHO, J = 4 Hz)] and *trans*-**4**: [t_R 19 min; NMR ($CDCl_3$) δ 1.29 (t, 3, CH_3, J = 7.5 Hz), 1.53 (m, 2, CH_2), 2.26 (m, 1, H_b), 2.45 (m, 1, H_a), 4.29 (q, 2, $COCH_2$, J = 7.5 Hz), 9.31 (d, 1, CHO, J = 3.5 Hz).



Kinetic Studies. In an Ar-flushed 178 mm × 5 mm o.d. NMR tube was dissolved 16 mg (0.23 mmol) of **6** in 0.5 mL of benzene-d_6 or acetone-d_6. Base-line spectra were recorded by FT-NMR at 270 MHz, then 36 mg (0.24 mmol) of ylide **5** in 0.5 mL of the appropriate d_6 solvent was added. Spectra were collected for 25 s at appropriate intervals, and the relative amounts of **6** and product (**1/2**) were determined by integration of the aldehydic proton region where there was no overlap of resonances for the three species in either solvent.

Acknowledgment. We thank the National Cancer Institute for the financial support of R.W.C., Jr., in the form of a fellowship. Helpful discussions on ^1H NMR interpretations with Dr. Brad Helmer are acknowledged. We also express our gratitude to Ms. Pat Mings for the preparation of this manuscript.

Registry No. *cis*-**1**, 13950-14-6; *trans*-**2**, 13949-97-8; *cis*-**3**, 13950-12-4; *trans*-**4**, 13949-93-4; **5**, 7380-81-6; **6**, 78-85-3; **7**, 107-02-8; *trans*-1-methyl-1,2-cyclopropanedicarboxylic acid, 697-49-4.

(11) The sulfur ylide was prepared in high yield according to Payne[3] and was found to be stable for 2-4 weeks under Ar at -20 °C while protected from light. However, this compound was rapidly destroyed when exposed to short-wavelength UV light.

The Oxime Rearrangement Cyclization. Synthesis of Alkylidene-Δ^1-pyrrolines

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Received January 18, 1984

Appropriately functionalized alkenyl oximes cyclize to Δ^1-pyrrolines when treated with trimethylsilyl polyphosphate (PPSE) in refluxing CCl_4. The reaction is stereospecific, and the reaction conditions do not cause oxime isomerization at a rate comparable to rearrangement cyclization. Terminators found to be compatible with PPSE are trisubstituted olefins and styryl groups; some vinyl chlorides may be used under more forcing conditions (P_2O_5/CCl_4/reflux). Alkenyl amides also cyclize under the stated conditions via a nitrilium ion transition state.

Introduction

The field of cationic cyclizations as a tool for organic synthesis has blossomed in recent years largely due to the pioneering work of the Johnson group. Johnson has concluded that the only two good initiators for cationic cyclizations in the carbocycle series are stabilized ions derived from acetals and allylic alcohols. Thus, much of the work in recent years has been in the development of efficient cyclization terminators.[1] These studies have had several objectives in common, among which are assistance (i.e., rate enhancement) in the cyclization, minimization of product multiplicity arising from carbonium ion rearrangements, random deprotonations, etc., and manipulation of ring size. Both olefinic[2] and acetylenic/allenic[3] terminators have

(1) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51-98; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9-17.

(2) Other than unfunctionalized alkenes, the following sp^2-hybridized nucleophiles have been shown to be efficient cationic cyclization terminators. **Enol ethers**: (a) Felkin, H.; Lion, C. *Tetrahedron* **1971**, *27*, 1387-1401, 1403-1408; *Chem. Commun.* **1968**, 60-61. **Chloro olefins**: (b) Lansbury, P. T. *Acc. Chem. Res.* **1972**, *5*, 311-320. **Fluoro olefins**: (c) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800-7802. **Allylsilanes**: (d) Hughes, L. R.; Schmid, R.; Johnson, W. S. *Bioorg. Chem.* **1979**, *8*, 513-518. (e) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182-183. (f) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251-255. **Vinylsilanes**: (g) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851-1853. (h) Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297-5300. **Styrenes**: (i) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281-1282. (j) Closson, W. D.; Roman, S. A. *Tetrahedron Lett.* **1966**, 6015-6020. (k) Garst, M. E., Cheung, Y.-F.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *101*, 4404-4406.

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