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Stereo- and regioselectivities in the epoxidation of some allylic alcohols by the dioxirane intermediate generated in the reaction of potassium caroate with acetone

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JUNE 1982

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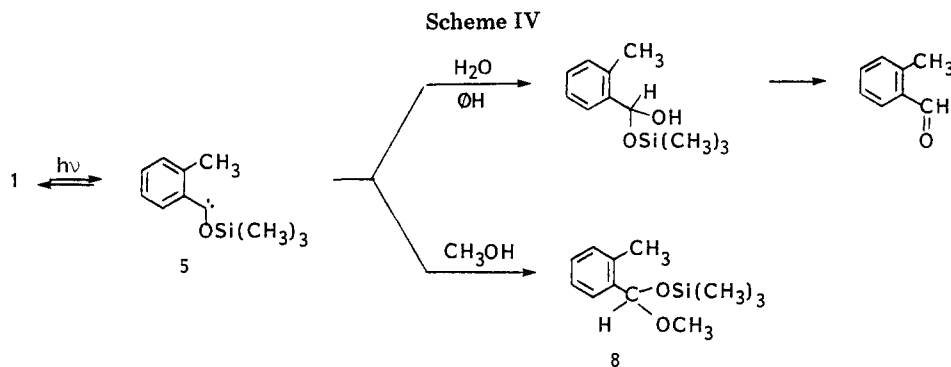


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cm column, 2% ether/petroleum ether as the eluant) gave 706 mg of **2a** which showed IR and NMR spectra identical with those reported above.

Irradiation of 1a. A solution of 60 mg of acylsilane **1a** in 5 mL of dry methanol (distilled twice from sodium) in a quartz tube was irradiated with a 450-W medium-pressure Hanovia lamp (Pyrex filter, $\lambda > 280$ nm). The reaction was completed in 15 min. The solvent was then removed in vacuo to give ca. 63 mg (90%) of clear liquid whose ^1H NMR spectrum showed that it was primarily the expected mixed acetal. This mixed acetal was further purified via preparative GLC (2 ft \times 1/8 in. column, 5% SE-30 on Chromasorb G, 120 $^\circ\text{C}$): IR (neat) 2948 (s), 1252 (s), 1124 (s), 1078 (s), 1045 (s, br), 890 (s), 876 (s), 839 (s), 748 cm^{-1} (s); ^1H NMR δ 7.52–6.97 (m, 4 H), 5.74 (s, 1 H), 3.15 (s, 3 H), 2.33 (s, 3 H), 0.10 (s, 9 H); exact mass calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Si} - \text{CH}_3$ 209.0998, obsd 209.1003.

Compound 6. To a solution of 2.0 g (16.67 mmol) of benzocyclobutenol¹³ in 5 mL of dry pyridine was added 10.76 g (66.67 mmol) of hexamethyldisilazane. To this stirred solution was added dropwise 7.23 g (66.67 mmol) of chlorotrimethylsilane; a white precipitate formed immediately. This reaction mixture was stirred at room temperature under nitrogen for 2 h and then partitioned between 200 mL of methylene chloride and 50 mL of 5% sodium bicarbonate. The organic layer was separated and washed again with 30 mL of 5% sodium bicarbonate, 20 mL of water, and finally 20 mL of saturated sodium chloride. Workup gave ~3 g of pale yellow liquid which was then passed through a 3.5 \times 15 cm silica gel column (4% ether/petroleum ether as the eluant) to give 2.2 g (69%) of silylated benzocyclobutenol as colorless liquid: IR (neat) 2955 (s), 1352 (s), 1251 (s), 1205 (s, br), 1155 (s), 1139 (s), 1118 (s), 1090 (s), 1067 (s), 905 (s), 881 (s), 838 cm^{-1} (s); NMR δ 7.20 (br s, 4 H), 5.30 (X of ABX, $J_{AX} = 2$ Hz, $J_{BX} = 4$ Hz, 1 H), 3.29 (center of AB of ABX, $\Delta\nu = 32$ Hz, $J_{AB} = 14$ Hz, $J_{AX} = 2$ Hz, $J_{BX} = 4$ Hz, 2 H), 0.20 (s, 9 H).

Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{OSi}$: C, 68.7; H, 8.4. Found: C, 68.9; H, 8.4.

2-[2-(Trideuteriomethyl)phenyl]-5,5-dimethyl-2-oxazoline.¹⁴ A solution of 8.76 g (34.5 mmol) of 2-(2-bromophenyl)-5,5-dimethyl-2-oxazoline in 90 mL of dry tetrahydrofuran was cooled to -78 $^\circ\text{C}$, and 21.7 mL (1.59 M) of *n*-butyllithium was added. The resulting anion was quenched immediately with 5 g (34.5 mmol) of perdeuteriomethyl iodide ($> 99\%$ d_3), and the reaction mixture was warmed to room temperature gradually and then stirred for another 30 min. The workup gave 7.60 g of crude product, whose NMR showed that there was ~6% of aryl coupling product in the reaction mixture. However, the coupling product was easily separated from the desired product by column chromatography on silica gel (20% ether/petroleum ether as the eluant, 3 \times 40 cm column): 0–200 mL, nil; 200–600 mL, 5.3 g (80%) of the methylated product; 600–650 mL, nil; 650–900 mL, 0.57 g (5%) of the coupling product. This material showed the following: IR (neat) 2964 (s), 1641 (s), 1035 (s), 706 cm^{-1} (s); NMR δ 7.90–7.60 (m, 1 H), 7.33–6.90 (m, 3 H), 3.90 (s, 2 H), 1.32 (s, 6 H); exact mass calcd for $\text{C}_{12}\text{H}_{12}\text{D}_3\text{NO}$ 192.1342, obsd 192.1347.

Compound 1b. The oxazoline from above was hydrolyzed¹⁴ to the carboxylic acid (5.2 g in 100 mL of 3 N hydrochloric acid),

and after the workup the crude acid was recrystallized from hexane (mp 93–95 $^\circ\text{C}$). Esterification with diazomethane afforded the crude ester which was converted to the acylsilane **1b** by the procedure of Picard.⁹ This compound was obtained as a bright yellow liquid and showed the following: IR (neat) 2958 (m), 1613 (s), 1567 (m), 1258 (s), 1204 (m), 843 (vs), 776 (m), 747 (m), 698 (m), 623 cm^{-1} (m); NMR δ 7.8–6.97 (m, 4 H), 0.27 (s, 9 H); exact mass calcd for $\text{C}_{11}\text{H}_{13}\text{D}_3\text{OSi}$ 195.1159, obsd 195.1164.

Authentic Synthesis of 2a. To a solution of 0.40 g (1.9 mmol) of **3**⁹ in 10 mL of dry tetrahydrofuran at 0 $^\circ\text{C}$ was slowly added 2.0 mL of a 1.0 M solution of borane–tetrahydrofuran complex. Gas evolution was immediate, and then the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of 5 mL of 3 N hydrochloric acid and extracted with chloroform. The workup followed by passing of the crude product through silica gel (1.5 \times 20 cm column, 10% ether/petroleum ether as the eluant) gave 312 mg (84%) of the alcohol as a colorless liquid: IR (neat) 3320 (s, br), 2954 (s), 2895 (m), 1487 (m), 1452 (m), 1416 (m), 1249 (s), 1209 (m), 1188 (m), 1155 (m), 1038 (m), 1003 (m), 845 (vs), 764 (m), 742 (m), 690 cm^{-1} (m); NMR δ 7.37–6.77 (m, 4 H), 4.45 (s, 2 H), 2.40 (br s, 1 H), 2.13 (s, 2 H), 0.02 (s, 9 H).

Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{OSi}$: C, 68.0; H, 9.3. Found: C, 68.4; H, 9.4.

A 200-mg (1.03 mmol) sample of this alcohol in 5 mL of dimethyl sulfoxide and 5 mL of dry benzene was treated with 640 mg (3.09 mmol) of dicyclohexylcarbodiimide and 66 mg of dichloroacetic acid. After being stirred for 5 h at room temperature, the reaction mixture was added to a solution of 20 mL of ethyl acetate, 5 mL of methanol, and 315 mg of oxalic acid. Removal of the urea by filtration followed by a standard workup and filtration of the crude product through silica gel (1.5 \times 20 cm column, 10% ether/petroleum ether as the eluant) gave 170 mg (86%) of **2a** identical in all respects with the pyrolysis product.

Acknowledgment. We thank the National Science Foundation for partial support of this work.

Registry No. **1a**, 65284-33-5; **1b**, 81522-27-2; **2a**, 81522-28-3; **2b**, 81522-29-4; **3**, 71435-93-3; **4**, 57754-01-5; **6**, 81522-30-7; **8**, 81522-31-8; benzocyclobutenol, 35447-99-5; 2-[2-(trideuteriomethyl)phenyl]-5,5-dimethyl-2-oxazoline, 81522-32-9; 2-(2-bromophenyl)-5,5-dimethyl-2-oxazoline, 81522-33-0; 2-(trideuteriomethyl)benzoic acid, 19137-02-1.

Stereo- and Regioselectivities in the Epoxidation of Some Allylic Alcohols by the Dioxirane Intermediate Generated in the Reaction of Potassium Caroate with Acetone

Grazia Cicala, Ruggero Curci,* Michele Fiorentino, and Onofrio Laricchiuta

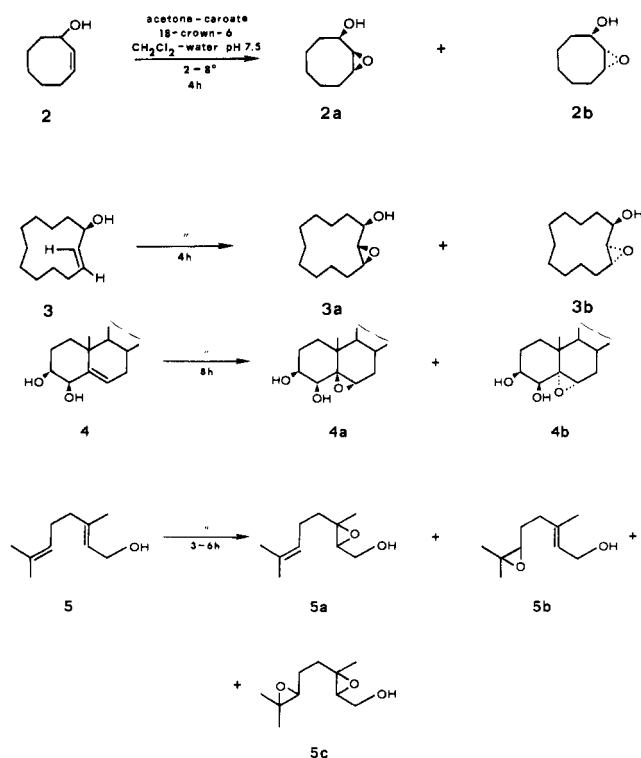
Istituto di Chimica Organica, University of Bari, via Amendola 173, Bari, 70126 Italy

We have recently reported a new process for olefin epoxidation involving peroxide reactive intermediates that arise from the reaction of potassium peroxomonosulfate (KHSO_5 , hereafter called caroate) with ketones.¹ Kinetics

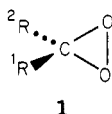
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Chart I



as well as stereochemical and ^{18}O -labeling evidence suggest that the reactive intermediates should have the dioxirane ring structure 1.¹⁻⁴



The general mechanistic features of the caraoate-ketone system have been discussed;^{1,4} it was emphasized that, in addition to the path resulting in catalysis of caraoate decomposition, the dioxirane intermediate can act as an effective oxidizer of unsaturated organic substrates.¹ The versatility of the method was shown by the excellent epoxide yields attainable in the oxidation of water-soluble alkenes carrying diversified functionalities; epoxidation of simple isolated olefins, which are practically water insoluble in most cases, could also be achieved adopting a benzene or methylene chloride buffered water (pH 7.5) biphasic system with 18-crown-6 (or $\text{Bu}_4\text{N}^+\text{HSO}_4^-$) as a phase-transfer agent.¹

Since stereo- and regioselective epoxidations of allylic alcohols often represent a key step in synthetic routes to naturally occurring substances,⁵⁻⁷ we deemed it useful to determine the selectivities attainable in the oxidation of such substrates by using the caraoate-acetone reagent. In order to compare our results with those obtained by using

Table I. Regio- and Stereoselectivity in the Acetone-Catalyzed Epoxidation of Representative Allylic Alcohols

substrate	% yield ^a	% conversion ^a	products and ratios ^{a,b}
2	96.0 ^{c,d}	95.0 ^{c,d}	2a/2b, 1:99 ^{c,d}
3	90.0 ^c	95.0 ^c	3a/3b, 29:71 ^c
4	72.0 ^e	70.0 ^e	4a/4b, 78:22 ^f
5	97.0 ^c	93.0 ^c	5a/5b/5c, 2:30:68 ^c
5	92.0 ^c	40.0 ^c	5a/5b/5c, 10:69:21 ^c

^a Unless otherwise noted, conversions and yields (based on substrate reacted) were determined after conversion of epoxy alcohols and remaining substrate into the corresponding acetates.^{8,13} ^b IR and NMR spectra of isolated epoxyacetates and/or mixture of stereomeric epoxyacetates agreed with spectral data of authentic samples obtained following literature procedures.^{8,13} ^c As determined by GLC. ^d Based on isolation of the corresponding epoxyacetates. ^e Based on isolation of the 5,6-epoxycholesterol-3 β ,4 β -diols and recovery of starting material. ^f As determined by GLC after conversion of the stereoisomeric epoxydiols into the corresponding *O,O'*-bis(trimethylsilyl) derivatives by using *N,O*-bis(trimethylsilyl)trifluoroacetamide: Chambaz, E. M.; Horning, E. C. *Analyt. Lett.* 1968, 1, 201.

the two most commonly employed epoxidation agents—namely, peroxyacids or *tert*-butyl hydroperoxide (TBHP)/vanadium(5+)^{7,8}—substrates 2–5 (Chart I) were chosen as representative.

Acetone-catalyzed epoxidations by caraoate were readily performed in a CH_2Cl_2 /buffered water (pH 7.5) biphasic system following a procedure already reported (see Experimental Section).¹ In all cases caraoate was in large excess over the stoichiometric amount required for epoxidation, due to competitive peroxide decomposition;^{1,4} little or no epoxidation was observed in the absence of acetone. The results are summarized in Table I.

Inspection of data in Table I reveals that stereoselectivities attainable by the caraoate-acetone system in the epoxidation of medium-ring allylic alcohols such as 2 and 3 resemble closely those obtained from peroxyacids.^{7,8} In fact, high stereoselectivity is observed in the conversion of (*Z*)-cyclooct-2-en-1-ol (2) into trans-epoxy alcohol 2b, which is identical with that observed in the epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 (i.e., 2a/2b = 0.5:0.95).⁸ Reaction of (*E*)-cyclododec-2-en-1-ol (3) affords a mixture of epimeric epoxy alcohols 3a and 3b, the composition of which suggests a preference for anti epoxidation akin to that exhibited by MCPBA (3a/3b 25:75).⁸

Thus, in the epoxidation of medium-ring cyclic allylic alcohols, both for peroxyacid and caraoate-acetone, the direction of stereoselectivity is mutually opposite that observed for *t*-BuOOH/V(5+), in that the vanadium system gives high *cis* selectivity whereas trans selectivity is preferred by the caraoate-acetone reagent (and by peroxyacids). Stereocontrol mechanisms have been advanced that allow one to rationalize these observations.⁷⁻¹²

The epoxidation of 4 β -hydroxycholesterol (4) provides a case where the HO—C—C=C moiety is encompassed in a more complex molecule: here, reaction with caraoate-acetone gives a ca. 3:1 mixture of the 5,6 β -oxide 4a and 5,6 α -oxide 4b, whereas epoxidation with MCPBA gives

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Table II. Significant ^{13}C NMR Chemical Shifts in Some Allylic Epoxidation Products^a

	2,3-epoxygeraniol acetate (5a') ^b	6,7-epoxygeraniol acetate (5b') ^b	2,6-diepoxygeraniol acetate (5c) ^b	5,6 β -epoxy- cholestane-3 β ,4 β -diol (4a) ^c
C ₁	63.38	61.23	63.23	36.93
C ₂	59.71	119.30	59.39, 59.90	29.67
C ₃	60.50	141.12	60.09, 60.19	71.28
C ₄	38.39	36.27	34.90, 35.33	77.27
C ₅	23.72	27.26	24.45, 24.67	65.46
C ₆	123.50	63.89	63.62, 63.77	63.93
C ₇	132.09	58.22	58.17, 58.31	32.56
C ₈ , C ₉	23.60, 17.61	24.81, 18.77	24.80, 18.71	c
C ₁₀	16.91	16.45	16.79, 17.05	c

^a In CDCl_3 , δ downfield from Me_4Si , with ^1H broad-band decoupling; most assignments confirmed by off-resonance experiments. ^b Cf. ^{13}C NMR spectrum of geraniol acetate: Bohlman, F.; Zeisberg, R.; Klein, E. *Org. Magn. Res.* 1975, 7, 426. ^c Cf. ^{13}C NMR spectra of other steroids, e.g., 5 α -cholestane-3 β ,4 β -diol: Vanantwerp, C. L.; Eggert, H.; Meakins, G. D.; Miners, J. O.; Dijerassi, C. J. *Org. Chem.* 1977, 42, 789 and references therein. Chemical shifts of other carbon atoms are all practically unchanged relative to the parent compounds and are not included.

a 2:1 mixture of the β -oxide.^{13,14} Epoxidation with *t*-BuOOH/V(5+) yields the 5,6 β -oxide exclusively.¹³

Regioselectivities were determined by using geraniol (5) as a substrate. Sharpless et al. have demonstrated that the vanadium-hydroperoxide reagent shows high regioselectivity for epoxidation of the 2,3 double bond of geraniol, whereas peroxyacids preferentially epoxidize the olefinic site ($\Delta^{6,7}$) furthest removed from the hydroxyl group,^{7,13} i.e., 5a/5b 1:2.

The last two entries in Table I illustrate the results observable by using the caroate-acetone system. At high conversions of the substrate a mixture is obtained in which the diepoxide 5c is the major product. This should be ascribed to the fact that excess oxidant is employed (see above) and to the high reactivity of the dimethyldioxirane intermediate (in $1:1\text{R} = 2\text{R} = \text{CH}_3$) generated in the reaction of caroate and acetone.^{1,3,15} At moderate conversions of 5, however, production of diepoxide 5c is considerably reduced and the 6,7-epoxide is the major product. The figures for product distributions (last two entries in Table I) suggest that diepoxide is being formed in consecutive reactions of the monoepoxidation products, mainly at the expense of 5a; this is expected since the isolated ($\Delta^{6,7}$) carbon-carbon double bond in 5a should be more electron rich and therefore more susceptible to electrophilic oxidation than the $\text{C}=\text{C}-\text{C}-\text{OH}$ moiety in 5b.⁹

In conclusion, we believe the results reported here further illustrate the fact that the caroate-acetone reagent may provide a generalized epoxidation method, representing a useful alternative to organic peroxyacids. Our work to find further useful applications of this oxidizing system in synthesis is being continued.

Experimental Section

General. Boiling points and melting points were not corrected. ^1H NMR and ^{13}C NMR spectra were run on Varian E360A and Bruker WP60 (or Varian XL200) instruments, respectively. IR spectra were taken on a Perkin-Elmer 177 instrument. GLC experiments were performed on a Hewlett-Packard 5750B (TC detector) or 5700A (FID), using either a 6 ft \times 1/4 in. 15% OV275 on Chromosorb P AW-DMCS or a 6 ft \times 1/4 in. 10% SP2100 on Supelcoport, with column temperature programming (from 80 to 250 $^\circ\text{C}$, at 8 $^\circ\text{C}/\text{min}$ in most of the cases).

Materials and Methods. Commercial potassium peroxomonosulfate (Caroat, Degussa, or Oxone, DuPont Co.) was used with no further purification; 18-crown-6 (Aldrich), *tert*-butyl hydroperoxide (TBHP, Fluka), *m*-chloroperoxybenzoic acid

(MCPBA, Aldrich), and solvents were purified by standard methods.^{17,8} (Z)-Cyclooct-2-en-1-ol (2),⁸ (E)-cyclododec-2-en-1-ol (3),⁸ and cholest-5-ene-3 β ,4 β -diol (4 β -hydroxycholesterol) (4),¹⁴ were obtained and purified by following literature procedures.^{8,14} Commercial (E)-3,7-dimethyl-2,6-octadien-1-ol (geraniol, Aldrich) (5) was purified by distillation [5, bp 93–94 $^\circ\text{C}$ (3 mm)]. *cis*-2,3-Epoxyoct-1-ol (2a), *trans*-2,3-epoxyoct-1-ol (2b), 2*c*,3*t*-epoxycyclododecan-1-ol (3a), and 2*t*,3*c*-epoxycyclododecan-1-ol (3b) were synthesized as described by Itoh et al.⁸ 5,6 β -Epoxycholestane-3 β ,4 β -diol (4a) was prepared from 4 by *t*-BuOOH/V(5+) epoxidation, as reported by Sharpless and Michaelson,^{13,14,16} mp 173–175 $^\circ\text{C}$ (Et₂O-petroleum ether); $[\alpha]_{\text{D}}^{20} + 8.9^\circ$ (c 1, CHCl_3) (lit.^{14,16} mp 173–174 $^\circ\text{C}$, $[\alpha]_{\text{D}} + 10^\circ$); IR (CHCl_3) 3600 and 3460 (OH), 1475, 1390, 1265 (epoxide C–O–C), 1060 (C–O), 980, 940, 920 cm^{-1} ; ^1H NMR (CDCl_3 , Me_4Si) δ 0.6–2.25 (41 H), 2.41 and 2.47 (br, 2, OH), 3.19 and 3.36 (br, 2, C₇H₂, AB part of ABX system), 3.60 (unresolved m, 1, C₆H, X part); ^{13}C NMR, see Table II. Authentic samples of mixture of 4a and corresponding 5,6 α -epoxycholestane-3 β ,4 β -diol (4b) were prepared by MCPBA epoxidation of 4;^{13,16} these gave satisfactory IR and NMR data. 2,3-Epoxy-3,7-dimethyl-6-octen-1-ol (5a) was obtained by *t*-BuOOH/V(5+) epoxidation of geraniol (5); treatment with $\text{Ac}_2\text{O}/\text{Py}$ afforded the corresponding acetate 5a':¹³ bp 91–92 $^\circ\text{C}$ (0.02 mm) [lit.¹³ bp 104–106 $^\circ\text{C}$ (0.025 mm)]; IR (liquid film) 2940, 1740 (C=O), 1680 (C=C), 1450, 1382, 1235, 1040, 990, 885, 845 cm^{-1} ; ^1H NMR (CCl_4 , Me_4Si) δ 1.22 (s, 3, C₁₀H₃), 1.4–1.7 (m, 2, C₄H₂), 1.55 (s, 3, C₆H₃), 1.63 (s, 3, C₅H₃), 1.8–2.2 (m, 2, C₅H₂), 1.99 (s, 3, COCH₃), 2.76 (m, 1, C₂H, X part of ABX system), 4.02 (m, 2, C₁H₂, AB part, $J_{1,2} = 6\text{ Hz}$, $J_{1,1} = 12\text{ Hz}$), 5.00 (m, 1, C₆H); ^{13}C NMR, see Table II. Reaction of 5 with MCPBA in CH_2Cl_2 at 2–8 $^\circ\text{C}$ ⁸ yielded a mixture of 5a and 6,7-epoxy-3,7-dimethyl-2-octen-1-ol (5b);^{13,17} treatment with $\text{Ac}_2\text{O}/\text{Py}$ and column chromatography separation (hexane–Et₂O) gave 5a' and 6,7-epoxy-3,7-dimethyl-2-octen-1-ol acetate 5b': bp 86–88 $^\circ\text{C}$ (0.4 mm) [lit.¹⁸ bp 113 $^\circ\text{C}$ (2 mm)]; IR (liquid film) 2980, 2940, 1745 (C=O), 1450, 1385, 1375, 1240, 1030, 960, 910, 880, 810 cm^{-1} ; ^1H NMR (CCl_4 , Me_4Si) δ 1.18 (s, 3, C₉H₃), 1.20 (s, 3, C₈H₃), 1.57 (m, 2, C₅H₂), 1.72 (s, 3, C₁₀H₃), 1.93 (s, 3, COCH₃), 2.12 (m, 2, C₄H₂), 2.50 (m, 1, C₆H, $J_{5,6} = 6\text{ Hz}$), 4.48 (d, 2, C₁H₂, $J_{1,2} = 7\text{ Hz}$), 5.32 (m, 1, C₂H, $J_{2,10} = 1\text{ Hz}$, $J_{2,4} = 0.5\text{ Hz}$); ^{13}C NMR, see Table II.

Epoxidations with Caroate-Acetone. Catalyzed (acetone and phase-transfer) epoxidations of substrates 2–5 were carried out by employing a two-phase system described in our previous article (Method B'').¹ The following procedure is representative of epoxidation of allylic alcohols: a cold solution of potassium peroxomonosulfate (27 mmol, iodometric titer)¹ in water, containing (EDTA)Na₂¹ was added dropwise (during 2 h) to a stirred biphasic mixture of CH_2Cl_2 (80 mL) and buffered (pH 7.5) water (40 mL) kept at 6–8 $^\circ\text{C}$ and containing geraniol (5, 1.54 g, 10 mmol), acetone (8 mL, 0.1 mol),¹⁹ and 18-crown-6 (0.5 g, 2 mmol).

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Upon completion of the addition, the reaction was allowed to proceed at 6–10 °C for 4 h with stirring; during the entire reaction time the apparent pH of the mixture was monitored and kept constant at pH 7.5–8 (0.5 N KOH, Metrohm E336A pH-stat).¹ Then, the CH₂Cl₂ layer was separated and the aqueous phase extracted with CH₂Cl₂ (40 mL). The combined methylene chloride extracts were dried (MgSO₄) and the solvent (and acetone) removed in vacuo, leaving a residue (2.2 g) containing 18-crown-6 and composed mainly of **5b** and 2,6-diepoxy-3,7-dimethyl-octan-1-ol (**5c**)²⁰ (¹H NMR analysis). The mixture was treated with Ac₂O/Py, affording acetylation of the alcohols; GLC analysis of the mixture of acetates allowed us to determine percent conversion, yield, and product distribution (Table I, fourth entry). Column chromatography (silica gel, petroleum ether–Et₂O) separation of the mixture afforded 0.7 g of 2,6-diepoxy-3,7-dimethyl-octan-1-ol acetate (**5c'**): bp 90–92 °C (0.02 mm); IR (liquid film) 2980, 2940, 1750 (C=O), 1380, 1240, 1125, 1042, 985, 910, 880, 850, 805 cm⁻¹; ¹H NMR (CCl₄, Me₄Si) δ 1.27 (s, 3, C₉H₃), 1.30 (s, 3, C₁₀H₃), 1.33 (d, 3 C₆H₃, J_{6,8} = 2.6 Hz), 1.55–1.90 (m, 4, C₄H₂ and C₅H₂), 2.09 (s, 3, COCH₃), 2.70 (m, 1, C₈H, J_{5,6} = 5.2 Hz), 3.15 (m, 1, C₂H, X part of ABX system), 4.20 (m, 2, C₁H₂, AB part); ¹³C NMR (Table II) nicely revealed the sample to be a diastereomeric mixture of enantiomeric couples (2*S*),3(*R*),6(*R*)-, 2(*R*),3(*S*),6(*S*)-**5c'** and 2(*S*),3(*R*),6(*S*)-, 2(*R*),3(*S*),6(*R*)-**5c'**.

Anal. Calcd for C₁₂H₂₀O₄: C, 63.13; H, 8.83. Found: C, 63.46; H, 8.86.

Acknowledgment. Financial support by the Italian National Research Council (CNR, Rome Progetto Finalizzato CFS), the NSF-CNR U.S.–Italy Cooperative Science Program and the NATO Scientific Affairs Committee is gratefully acknowledged. We also thank Professor G. Capozzi (University of Messina, Italy) and Professor O. Sciacovelli (University of Bari) for help in taking and interpreting ¹³C NMR spectra, R. A. Di Prete (American Hoechst Analytical Research Division) for technical assistance, and Degussa Co. for a gift of Caroat monopersulfate.

Registry No. 2, 14390-23-9; **2a**, 31821-36-0; **2b**, 31821-35-9; **3**, 6221-49-4; **3a**, 69798-84-1; **3b**, 69853-80-1; **4**, 17320-10-4; **4a**, 50727-96-3; **4b**, 81477-46-5; **5**, 106-24-1; **5a**, 50727-94-1; **5a'**, 50727-95-2; **5b**, 1786-07-8; **5b'**, 37715-31-4; **5c**, 62875-10-9; **5c'** (isomer 1), 81520-62-9; **5c'** (isomer 2), 81520-63-0; potassium caroate, 10058-23-8; acetone, 67-64-1.

(19) Acetone, acting as a catalyst, does not enter the reaction stoichiometry, of course; the reaction rate, however, is proportional to acetone concentration¹⁴ and therefore "excess" acetone is used in order to enhance the rate of oxidation.

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Thermal Cycloaddition of 1,3,5-Triazine with Enamines: Regiospecific Pyrimidine Annulation

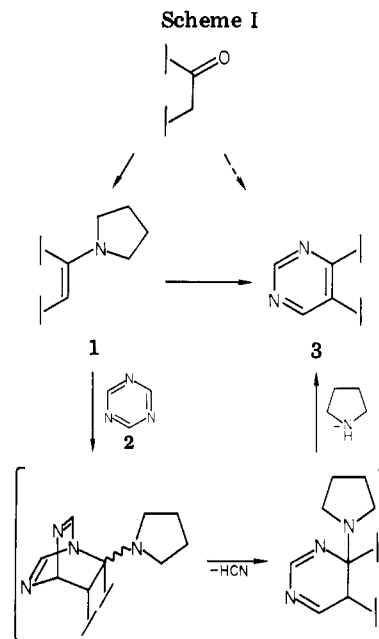
Dale L. Boger,^{*1a} Jane Schumacher, Michael D. Mullican,^{1b} Mona Patel, and James S. Panek

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045

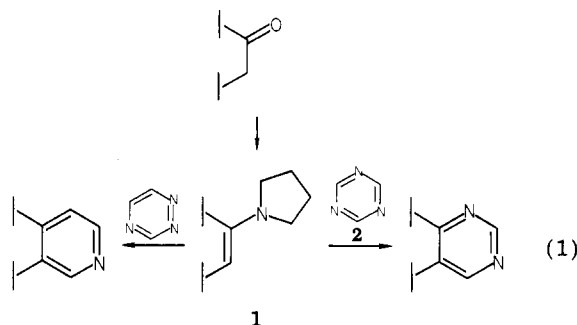
Received December 24, 1981

We have recently investigated and described a simple pyridine annulation based on the regiospecific, inverse electron demand cycloaddition reaction of pyrrolidine enamines with 1,2,4-triazine.² As a complement to this

(1) (a) Chicago Community Trust Co./Searle Scholar recipient, 1981–1984. (b) National Institutes of Health Predoctoral Fellow, 1981–1984 (Grant NIH GM 07775).



reaction we became interested in the potential of a related pyrimidine³ synthesis employing 1,3,5-triazine (**2**)⁴ as an electron-deficient diene (eq 1).



A recent study of Neunhoeffer and Bachmann has demonstrated that 1,3,5-triazine (**2**) undergoes a rapid and regiospecific cycloaddition reaction with ynamines, and the subsequent loss of hydrogen cyanide provided a simple pyrimidine synthesis.⁵ In addition, Neunhoeffer has shown that a symmetrical enamine, 1-pyrrolidinocyclopentene, participates in a similar cycloaddition reaction with **2** and affords the pyrimidine product **3b** after loss of hydrogen cyanide and pyrrolidine. This demonstrated the potential for 1,3,5-triazine to behave as a dependable, electron-deficient diene and provided the incentive for us to investigate the scope and limitations of its reaction with pyrrolidine enamines **1**³ with the expectation that this process could serve as a useful and regiospecific pyrimidine annulation (Scheme I) applicable to our current synthetic studies.

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