

(C₁₅H₁₇O₂N) calcd 243.1259, found 243.1237. This product was identical in all respects with an authentic sample prepared from 2-hydroxy-1-naphthalenecarboxylic acid.

***N,N*-Diethyl-2-(hydroxymethyl)benzamide (3g).** A 152-mg sample (0.800 mmol) of *o*-toluamide **1g** was subjected to the standard procedure. The crude product mixture was treated with 30 mg of NaBH₄ in 5 mL of THF to reduce overoxidized material. Flash chromatography (EtOAc/hexane = 1/1 followed by EtOAc) then gave 80 mg (49%) of a colorless oil: NMR (60 MHz, CDCl₃/Me₄Si) 0.97–1.33 (m, 6 H), 3.20 (q, *J* = 7 Hz, 2 H), 3.53 (q, *J* = 7 Hz, 2 H), 3.94 (s, 1 H, exchangeable in D₂O), 4.53 (s, 2 H), 7.20–7.33 (m, 4 H); IR (CHCl₃) 3400, 1600, 1285, 1010 cm⁻¹; M⁺ (C₁₂H₁₇O₂N) calcd 207.1259, found 207.1254.

***N,N*-Diethyl-2-hydroxy-3,4,5-trimethoxybenzamide (3h).** Trimethoxybenzamide **1h** (410 mg, 1.53 mmol) was treated according to the standard procedure. The crude product was purified on a Chromatotron (eluent EtOAc/hexane = 1/1) to afford 210 mg (48%) of a white solid. Reduced pressure distillation [130 °C (0.5 mm)] gave crystals: mp 87–88 °C; NMR (250 MHz, CDCl₃/Me₄Si) 1.24 (t, *J* = 7 Hz, 6 H), 3.46 (q, *J* = 7 Hz, 4 H), 3.77 (s, 3 H), 3.95 (s, 6 H), 6.54 (s, 1 H), 6.95 (br s, 1 H, exchangeable in D₂O); IR (CHCl₃) 3505, 1620, 1580, 1210, 1110 cm⁻¹; M⁺ (C₁₄H₂₁O₅N) calcd 283.1419, found 283.1406.

***N,N*-Diethyl-2,3,4,5-tetramethoxybenzamide (4).** A two-phase system consisting of 90 mg (0.32 mmol) of benzamide **3h**, 0.20 mL (2.1 mmol) of dimethyl sulfate, 160 mg (0.500 mmol) of *n*-Bu₄NBr, and 29 mg (0.72 mmol) of NaOH in 6 mL of CH₂Cl₂ and 6 mL of water was stirred overnight. After acidification with dilute HCl the phases were separated, and the aqueous phase was extracted (3×) with EtOAc. The combined organic solution was washed with brine, dried over Na₂SO₄, and concentrated. Elution of the product from a Chromatotron with EtOAc/hexane (1/1) gave 60 mg (63%) of a colorless oil. This was distilled at 125–127 °C (0.7 mm): NMR (60 MHz, CDCl₃/Me₄Si) 0.96–1.35 (m, 6 H), 3.03–3.50 (m, 4 H), 3.86 (s, 6 H), 3.90 (s, 3 H), 3.97 (s, 3 H), 6.50 (s, 1 H); IR (CHCl₃) 3030, 1608, 1570, 1110, 1065 cm⁻¹; M⁺ (C₁₅H₂₃O₅N) calcd 297.1576, found 297.1587.

***N,N*-Diethyl-2-hydroxy-3,4,5,6-tetramethoxybenzamide (3i).** Hydroxylamine of 36 mg (0.12 mmol) of amide **4** gave material which was purified on a Chromatotron. Elution with EtOAc/hexane (1/1) afforded 15 mg (43%) of a colorless oil: NMR (60 MHz, CDCl₃/Me₄Si) 1.15 (t, *J* = 7 Hz, 6 H), 3.02–3.47 (m, 4 H), 3.76 (s, 6 H), 3.83 (s, 3 H), 3.90 (s, 3 H); IR (CHCl₃) 3500, 1620, 1120, 1035 cm⁻¹.

***N,N*-Diethyl-2-acetoxy-3,4,5,6-tetramethoxybenzamide (5).** A 10-mg sample (0.030 mmol) of amide **3i** and 0.06 mL (0.6 mmol) of acetic anhydride were dissolved in 0.5 mL (0.6 mmol) of pyridine. The reaction mixture stirred at room temperature overnight. Then water was added, stirring was continued for 1 h, and the reaction mixture was extracted (3×) with EtOAc. The combined organic solution was washed with aqueous NaHCO₃ and with brine, dried over Na₂SO₄, and concentrated. The product, purified on a Chromatotron (eluent EtOAc/hexane = 1/1) was isolated as a colorless oil (8 mg, 75%). An analytical sample was obtained by reduced pressure distillation [150 °C (0.8 mm)]: NMR (250 MHz, CDCl₃/Me₄Si) 1.07 (t, *J* = 7 Hz, 3 H), 1.20 (t, *J* = 7 Hz, 3 H), 2.25 (s, 3 H), 3.09–3.25 (m, 2 H), 3.40–3.72 (m, 2 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H); IR (CH₂Cl₂) 2905, 1730, 1615, 1450, 1110, 1038 cm⁻¹; M⁺ (C₁₇H₂₅O₇N) calcd 355.1631, found 355.1619.

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Registry No. **1a**, 1696-17-9; **1b**, 62924-93-0; **1c**, 135-77-3; **1d**, 51674-10-3; **1e**, 105518-12-5; **1f**, 5454-10-4; **1g**, 2728-04-3; **1h**, 5470-42-8; **3a**, 19311-91-2; **3b**, 19351-20-3; **3c**, 90539-42-7; **3d**, 85630-30-4; **3e**, 106114-62-9; **3f**, 106114-63-0; **3g**, 103258-38-4; **3h**, 106114-64-1; **3i**, 106114-65-2; **4**, 106114-66-3; **5**, 106114-67-4.

Degenerate Cope Rearrangement of 4-Vinylcyclopentene

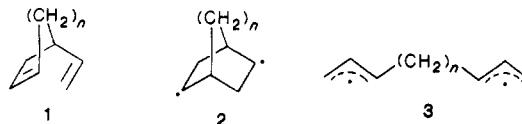
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Cope rearrangements of hydrocarbons having a 1,5-hexadiene moiety take place through a variety of mechanistic paths and span an enormous range of reactivities.² Near one extreme, the degenerate valence isomerization shown by semibullvalene has Δ*G*[‡] equal to 5.5 kcal/mol at -140 °C;³ at the other, systems like bicyclo[3.3.0]octa-2,6-diene fail to show appreciable rearrangement even under extreme thermal conditions.⁴

4-Vinylcycloalkenes (**1**) offer the prospect of correlating systematic homologous structural variations with Cope rearrangement reactivities, for the -(CH₂)_{*n*}- bridge between C3 and C6 of the 1,5-hexadiene unit provides geometrical restrictions of graded severity on ground- and transition-state structures (**2**) if C1–C6 bond making is then well advanced. If, on the other hand, C3–C4 cleavage were well ahead of C1–C6 bond formation in the transition state, no ring-strain effects on transition state structures (**3**) would be seen.



The degenerate Cope rearrangement of 4-vinylcyclohexene and several competitive thermal rearrangements shown by this hydrocarbon have been studied in great detail,^{5,6} but Cope rearrangements of other 4-vinylcycloalkenes are unreported. Thus no comparative considerations of reactivity differences for even two different members of the series have been possible.

3-Vinylcyclobutene, **1** (*n* = 0), reacts thermally to form *trans*-1,3,5-hexatriene so fast that, presumably, a degenerate Cope process may never be seen for it experimentally.⁷ We have followed the Cope rearrangement of 4-vinylcyclopentene, the next lowest member of the homologous series of dienes **1**, one subject to substantial geometrical constraints in transition-state structure **2**.

Results

Condensation of cyclopentene-4-carbaldehyde (**4**) with (dideuteriomethylene)triphenylphosphorane in Me₂SO-*d*₆/THF gave 4-(ethenyl-2,2-*d*₂)cyclopentene. At 360 MHz, the ¹H NMR spectrum showed two 2 H multiplets at 2.10 and at 2.48 ppm for the diastereomeric C3,5' and C3',5' protons, the H-C4 multiplet at 2.85 ppm, C1,2 olefinic protons as a singlet at 5.67 ppm, and the ethenyl-C1 proton

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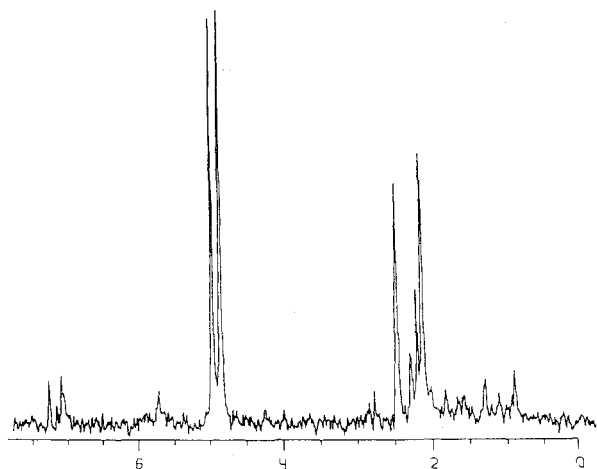
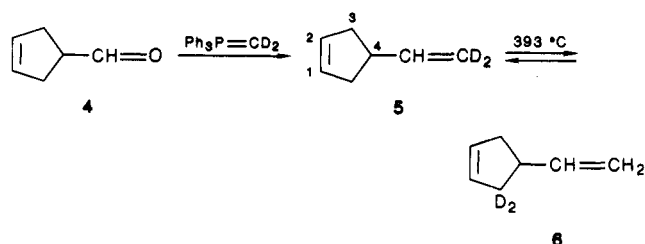


Figure 1. Deuterium NMR spectrum of a thermolysis reaction mixture from diene **5** with hexanes as a bath gas after 1261 min at 393.1 °C.

at 5.88 ppm. Residual protons at ethenyl-C2 gave extremely weak doublets from coupling with ethenyl-C1-H at 4.87 and 4.97 ppm; deuterium incorporation was estimated to be better than 95% at ethenyl-C2. The ^2H NMR spectrum with ^1H decoupling gave sharp singlets of equal intensity, at 4.9 and 5.0 ppm.

Thermolysis of the deuterium-labeled diene **5** at 393.1 °C in the gas phase with hexanes as a bath gas for times between 8 and 50 h gave reaction mixtures characterized by ^2H NMR at 360 MHz and by analytical gas chromatography. A representative NMR spectrum of a mixture is shown in Figure 1. The pair of ^2H singlets of starting material **5** at 4.9 and 5.0 ppm and the pair of singlets at



2.1 and 2.5 ppm characteristic of **6** are apparent in the spectrum; the absorptions near 0.9 and 1.3 ppm are natural abundance ^2H signals from the hexanes, and other deuterium signals are ascribed to various decomposition products. According to chromatographic analyses, this product mixture contained 75% of the 4-vinylcyclohexenes **5** and **6** and 25% of other hydrocarbons, notably toluene, cycloheptadiene, and cycloheptatriene. At long reaction times, deuterium-labeled toluene predominated.

For the degenerate first-order Cope rearrangement $\mathbf{5} \rightarrow \mathbf{6}$ with rate constant k and $\mathbf{6} \rightarrow \mathbf{5}$ with rate constant $(k/2)$, the differential equations may be readily solved to give the integrated expression $\ln((3[5] - 1)/2) = -(3/2)kt$, where $[5]$ is expressed as a mole fraction; $[5] + [6] = 1.0$. The ^2H NMR integration data gave a fair linear plot based on this equation ($r = 0.998$) with $k = 0.75 \times 10^{-5} \text{ s}^{-1}$ ($\Delta G^\ddagger = 55.7 \text{ kcal/mol}$).

Discussion

For the Cope rearrangement of 4-vinylcyclohexene as followed by deuterium label equilibration between C3 methylene and vinylic methylene positions at 393.1 °C, $k = 4.9 \times 10^{-5} \text{ s}^{-1}$ ($\Delta G^\ddagger 53.2 \text{ kcal/mol}$).⁵

The two rearrangements, then, have $k_{\text{rel}} = 6.5$ and $\Delta\Delta G^\ddagger 2.5 \text{ kcal/mol}$ at 393 °C, with 4-vinylcyclohexene showing

the faster Cope process. More precisely, one should state $k_{\text{rel}} \geq 6.5$ and $\Delta\Delta G^\ddagger \geq 2.5 \text{ kcal/mol}$, since the observed equilibration between **5** and **6** might arise by way of an alternative mechanism involving 6,6-dideuterio-1,4-cycloheptadiene as an intermediate;⁸ this diene might possibly revert to 4-vinylcyclopentene at rates competitive with concerted thermal elimination of hydrogen to give cycloheptatriene⁹ and eventually toluene.^{10,11}

Thermochemical analyses for the two Cope rearrangements imply that the relevant transition-state structures cannot both be construed as bis-allylic diradicals **3**. If they could then, since **3** ($n = 1$) is 5 kcal/mol more energetic than **3** ($n = 2$),¹² and since ΔH°_f for 4-vinylcyclopentene is about 8.8 kcal/mol higher than that for 4-vinylcyclohexene,^{13,14} k_{rel} should be about 8×10^{-2} : 4-vinylcyclohexene should react *slower* than 4-vinylcyclopentene. In contrast, the 1,4-diyl energetic models for transition-state structures give a fair account of the observed rate difference. If **2** ($n = 1$) and **2** ($n = 2$) are separated by an 11.3 kcal/mol gap in ΔH°_f , as are bicyclo[2.2.1]heptane¹² and bicyclo[2.2.2]octane,^{15,16} then 4-vinylcyclopentene, according to the model, should react more slowly, with $\Delta\Delta G^\ddagger 2.5 \text{ kcal/mol}$, or $k_{\text{rel}} = 6.6$.

The thermochemical model based on the 1,4-diyl structures **2** even gives a fair energetic agreement absolutely. For 4-vinylcyclohexene, ΔH°_f (gas) = 16.6 kcal/mol;¹⁷ for bicyclo[2.2.2]octane, ΔH°_f is -23.7 ;^{15,16} for the conversion $\text{CH}_3\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CHCH}_3$, $\Delta\Delta H^\circ_f = +44.8$.¹⁸ Hence the thermochemical estimate of ΔH°_f for **2** ($n = 2$) from the observed kinetics, $16.6 + 53.2 = 69.8 \text{ kcal/mol}$, is close to $-23.7 + 2(44.8) = 65.9$. The parallel analysis for $\mathbf{1} \rightarrow \mathbf{2}$ ($n = 1$) gives similar results: $(8.8 + 16.6) + 55.7 = 81.1$ compared with $-12.4 + 2(44.8) = 77.2$. In both systems, the discrepancies are 3.9 kcal/mol, with the kinetically projected energies for the 1,4-diyl structures above the values based on the bicyclo[2.2.n]hydrocarbons and the $\text{CH}_3\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CHCH}_3$ process; regrettably, experimental ΔH°_f values for 2-bicyclo[2.2.1]heptyl and 2-bicyclo[2.2.2]octyl radicals do not seem to be available.

A similar thermochemical model for Cope rearrangements of 1,4-bis(methylene)cyclohexane and 1,4-bis(methylene)cycloheptane has been employed effectively by Doering and Troise;¹⁶ there too the 1,4-diyl diradical structures, bicyclo[2.2.2]octa-1,4-diyl and bicyclo[3.2.2]nona-1,5-diyl, are serviceable enthalpic models for the transition-state structures associated with high-energy degenerate Cope rearrangements.

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Experimental Section

Both ^1H and ^2H NMR spectra were recorded on a Nicolet NT 360-MHz instrument. Gas chromatographic preparative collections and analyses were done on Varian Aerograph A 90-P3, Varian 1520, and Hewlett Packard 5792A instruments.

4-Formylcyclopentene was prepared in five steps by using procedures drawn from the literature. Diethyl cyclopentene-4,4-dicarboxylate, from diethyl malonate, 2 equiv of NaH, and (*Z*)-1,4-dichloro-2-butene, was hydrolyzed and decarboxylated at 180 °C to afford 4-carboxycyclopentene.¹⁹ Reduction of the acid with LiAlH_4 in ether gave the alcohol;^{20,21} oxidation with CrO_3 in CH_2Cl_2 -pyridine provided the desired aldehyde 4 having ^1H NMR spectral characteristics in full agreement with prior observations.²¹

4-(Ethenyl-2,2- d_2)cyclopentene. Into a flame-dried, three-necked flask was placed a stir bar, 33 mL of tetrahydrofuran (freshly distilled from sodium and sodium benzophenone ketyl), and 3.00 g (8.3 mmol) of (trideuteriomethyl)triphenylphosphonium bromide. The flask was capped with a septum through which a needle was inserted to provide a nitrogen source. Then 5.7 mL of methylolithium in ether (1.5 M, 8.6 mmol, low in halide) was added to yield an orange solution which was stirred for 1 h. To this was added 33 mL of dimethyl- d_6 sulfoxide, which was freshly distilled from calcium hydride; a precipitate soon formed but then dissolved with further stirring. After the aldehyde was added (0.80 g, 8.33 mmol) and stirring was continued for another hour, the orange solution was treated with 1 mL of deuterium oxide and the product solution was poured into 400 mL of water; the dark orange phase which formed on top was removed with a Pasteur pipet and placed into 200 mL of water. Again, the upper orange phase was removed, then placed with 90 mL of water in a separatory funnel and shaken vigorously. The upper orange organic layer now amounted to about 0.5 mL; it was isolated with a small pipet, and further purification of the desired diolefin was achieved by using preparative gas chromatography on a 20% 1,2,3-tris(2-cyanoethoxy)propane (TCEP) on 50/80 mesh Chromosorb P column at 120 °C. It was identified by direct NMR comparisons with a spectrum of authentic 4-vinylcyclopentene provided by Professor P. K. Freeman.²²

Thermolyses of 4-(ethenyl-2,2- d_2)cyclopentene were conducted by using a well-seasoned 300-mL Pyrex bulb and kinetics bath.²³ Temperature measurements employed a Hewlett-Packard Model 2802A digital thermometer; hexanes served as a bath gas. After each run at 393.1 °C, hydrocarbons were condensed from bulb to the vacuum line and examined by ^2H NMR spectroscopy and by analytical gas chromatography. Integrated ^2H absorption intensities for 5 and 6 led to estimates of mole fractions of 5: 0.83 (at 500 min), 0.72 (810 min), and 0.62 (1261 min; Figure 1), and hence $k = 0.75 \times 10^{-5} \text{ s}^{-1}$ (ΔG^\ddagger 55.7 kcal/mol).

An earlier estimate of the rate of this degenerate rearrangement based on a less completely deuterated sample of 5, thermolyses in a 1-L quartz bulb at 409.6 °C, and analyses of product mixtures by ^1H NMR (Varian XL-100) gave an estimate of $k = 1.26 \times 10^{-5} \text{ s}^{-1}$ (ΔG^\ddagger 56.4 kcal/mol) for the rate constant $5 \rightarrow 6$.

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Stabse-Protected 2-Chloroallylamine: A Useful Synthon for Primary Allylic Amines via Nickel-Catalyzed Cross-Coupling

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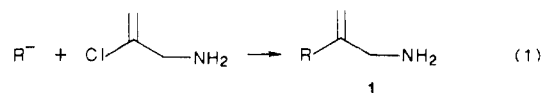
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Primary allylic amines have been receiving enough attention as enzyme inhibitors¹ and natural products that methods for their synthesis have been reviewed recently.² New synthesis methods continue to be devised.³

We needed an efficient synthesis of 2-substituted allylamines in connection with our studies of mechanism-based inhibition of dopamine β -hydroxylase.⁴ Many diverse and imaginative synthesis methods for primary allylic amines have been described;² however, nearly all require starting with a complete carbon skeleton and forming a carbon-nitrogen bond in the key step. All methodologies require multistep transformations. We wish to report a simple, one-step procedure for preparation of 2-substituted allylamines from readily available precursors by means of transition-metal-catalyzed carbon-carbon bond formation.

The most direct synthesis of a 2-substituted allylamine that we could imagine would be the coupling of a carbanion with 2-chloroallylamine⁵ (eq 1). In recent years, general



solutions to the problem of nucleophilic vinylic substitution of unactivated olefins have been reported.⁶ We were attracted to the nickel-catalyzed cross-coupling reaction of vinylic and aromatic halides with Grignard reagents.⁷ Kumda and co-workers have thoroughly investigated the scope of this reaction;⁸ however, there are few examples

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