δ 2.15 (s, 3 H, CH_3), 5.15 (d, J = 4.5 Hz, 1 H, H_A), 6.03 (dd, J = 4.5, 3 Hz, 1 H, H_B), 6.42 (d, J = 3 Hz, 1 H, H_C), 7.1–7.7 (s, 10 H, Ar H).

4-Hydrazino-2,6-diphenyl-4*H*-thiopyran 1,1-Dioxide (5). To a solution of 0.89 g (3 mmol) of **3** in 50 mL of ethanol was added 3 mL (1 equiv) of a solution of 1.0 M of hydrazine in ethanol. The reaction mixture, which turned from yellow to orange, was heated at 50 °C overnight. The solvent was removed under vacuum, and the residue was recrystallized from methanol to give 0.26 g (28%) of pure **5**: mp 162–163 °C; ^1H NMR (Me_2SO-d_6) δ 3.4 (br s, 2 H, NH_2), 6.96, 6.97 (s, s, 2 H, olefinic), 7.3–7.85 (m, 10 H, Ar H). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.8; H, 4.5; N, 9.0; S, 10.3. Found: C, 64.7; H, 4.5; N, 9.1; S, 10.6.

2,4-Dihydrazino-2,6-diphenylthiopyran 1,1-Dioxide (12). A mixture of 0.89 g (3 mmol) of **3** and 2 equiv of hydrazine in 40 mL of ethanol was heated at 50 °C for 12 h. The reaction mixture was concentrated on a rotary evaporator to ~20 mL, and 200 mL of ether was added dropwise. The precipitated white solid was collected and washed with ether to give 0.63 g (60%) of **12**: mp 158–160 °C dec (gas evolution); ^1H NMR (Me_2SO-d_6) δ 3.4 (br s, NH_x), 6.38 (s, 1 H, olefinic), 6.8 (s, 1 H, olefinic), 7.25–7.85 (m, 10 H, Ar H). On addition of D_2O, the ^1H NMR spectrum of **12** reverted quickly to that of **5**. Anal. Calcd for $C_{17}H_{18}N_4O_2S$: C, 59.6; H, 5.3; N, 16.4; S, 9.4. Found: C, 59.5; H, 5.3; N, 16.3; S, 9.7.

Crystal Structure Determination. Six-sided brownish yellow needles were grown by slow evaporation from ethanol. Data were collected on an Enraf-Nonius CAD4 diffractometer.[9] Unit cell data and other pertinent crystallographic data are given in the crystal data table as supplementary material. Choice of space group $Pn2_1a$ over $Pnma$ was confirmed by the successful structure refinement. Data were corrected for a 30% decrease in intensities over the data collection period, as determined by hourly monitoring of three standard reflections. The structure was solved by direct methods (MULTAN 11/82) and refined by the full-matrix least-squares method. Anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogens were applied in the final cycles of refinement.

Registry No. **2**, 41068-60-4; **3**, 103438-51-3; **5**, 103438-56-8; **6**, 103438-54-6; **7**, 103438-53-5; **9**, 66510-40-5; **10**, 103438-52-4; **12**, 103438-57-9; **14**, 103438-55-7; *p*-toluenesulfonohydrazide, 1576-35-8.

Supplementary Material Available: Tables of crystal data and positional and thermal parameters (6 pages). Ordering information is given on any current masthead page.

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[9] Programs were from the Structure Determination Package SDP-PLUS V1.1, 1983, Enraf-Nonius Corp., Delft, Holland.

An Intramolecular Immonium Ion Variation of the Diels–Alder Reaction: Synthesis of (±)-Dihydrocannivonine

Paul A. Grieco* and Scott D. Larsen

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

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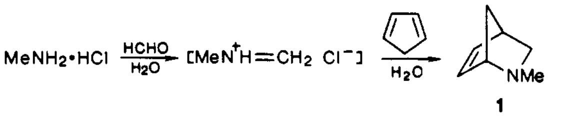
During studies on the intermolecular cycloaddition of dienes with simple unactivated immonium salts in aqueous medium, we found that the reaction of cyclopentadiene with methylmethyleneammonium chloride in water at ambient temperature gives rise to an 82% yield of bicyclic amine **1** after 3 h (cf. eq 1).[1] This result is particularly striking in view of the negligible concentration of methylmethyleneammonium chloride in water. In contrast the less reactive cyclohexadiene upon reaction with either methyl- or benzylmethyleneammonium chloride gives rise after long reaction times and elevated temperatures to only modest yields of Diels–Alder adducts. For example, cyclocondensation of benzylmethyleneammonium chloride with cyclohexadiene in water required 42 h at 55 °C in order to realize a 35% yield of bicyclic amine **2** (cf. eq 2).



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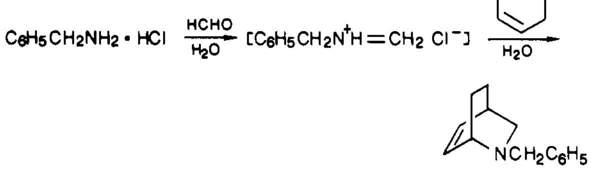
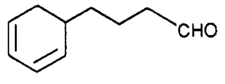


2 (2)

In order to further probe reactions employing cyclohexadiene we set out to examine a system wherein an aldehyde unit was directly incorporated into a cyclohexadiene system. Detailed below is the synthesis of cyclohexadiene **3** and its transformation via an intramolecular immonium ion Diels–Alder reaction into racemic dihydrocannivonine **4**.



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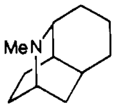

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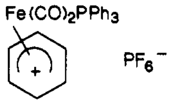
The synthesis of substituted cyclohexadiene **3** follows from methodology recently developed by Pearson.[2] Treatment of dicarbonyl(cyclohexadiene) (triphenylphosphine)iron complex **5**[3] with the Grignard reagent derived from 4-bromobutyl tetrahydropyranyl ether (**6**) gave rise to the (cyclohexadiene)iron complex **7** as the sole product in 90% isolated yield. Simultaneous demetalation of complex **7** and cleavage of the tetrahydropyranyl ether proceeded smoothly upon exposure of **7** to copper(II) chloride in ethanol[4] at room temperature, giving rise after 5 h to 4-(5-cyclohexadienyl)butanol (**8**) in 63% isolated yield. The actual decomplexation of **7** occurs immediately whereas deprotection of the alcohol requires several hours. Swern oxidation of **8** provided access to aldehyde **3** which



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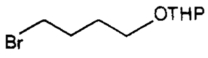

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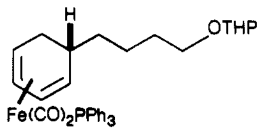

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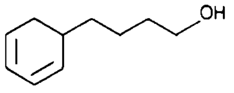

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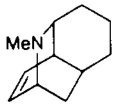

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0022-3263/86/1951-3553$01.50/0

set the stage for the intramolecular immonium ion Diels–Alder reaction.

Initial attempts to carry out the intramolecular immonium ion Diels–Alder reaction with dienyl aldehyde **3** and monomethylamine hydrochloride by rapid addition of **3** to a homogeneous solution of the amine hydrochloride in water or aqueous ethanol gave rise to poor yields (<10%). Yields could be dramatically improved by slowly adding substrate over 20–30 h to a 1–2 M solution of amine hydrochloride (excess) in water/ethanol (1:1) at ca. 70 °C. Indeed slow addition of a solution of dienyl aldehyde **3** in ethanol to monomethylamine hydrochloride in aqueous ethanol at 70 °C provided tricyclic amine **9** in 66% yield. The spectral data for **9** were completely in accord with the assigned structure (see Experimental Section). Subsequent catalytic hydrogenation of **9** afforded racemic dihydrocannivonine **4**[5].

Experimental Section

4-Bromobutyl Tetrahydropyranyl Ether (6). Dihydropyran (7.0 mL, 77 mmol) was added via syringe to a cooled solution (0 °C) of 4-bromobutanol[6] (8.95 g, 58.5 mmol) in 60 mL of anhydrous ether containing 20 mg of *p*-toluenesulfonic acid. After 1 h at ambient temperature, the reaction mixture was washed with saturated sodium bicarbonate solution (2 × 40 mL) and brine (1 × 40 mL). The organic layer was dried over anhydrous potassium carbonate. The solution was filtered, and the solvent was removed in vacuo, providing 14.4 g (96%) of bromide **6** as a colorless oil, [IR (neat) 2950, 2875, 1440, 1385, 1370, 1355, 1345, 1325, 1260, 1200, 1185, 1135, 1120, 1070, 1030, 1020, 985, 970, 905, 870, 815 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.58 (m, 1 H), 3.75–3.90 (m, 2 H), 3.40–3.60 (m, 4 H), 1.9–2.1 (m, 2 H), 1.65–1.90 (m, 4 H), 1.50–1.65 (m, 4 H); MS, M$^+$ 236.0407 (calcd for $C_9H_{17}BrO_2$ 236.0401)] which was used directly in the next reaction.

Dicarbonyl[5-(((4-tetrahydropyranyl)oxy)butyl)cyclohexadiene](triphenylphosphine)iron (7). To a suspension of magnesium turnings (470 mg, 19.4 mmol) in 15 mL of dry tetrahydrofuran was added a single crystal of iodine. To this mixture under argon was added 0.60 mL (3.2 mmol) of bromide **6**. The mixture was stirred and heated until reaction was initiated, at which time the remaining bromide (3.0 mL, 16.1 mmol) was added dropwise via syringe over 5 min while the reaction temperature was maintained at 45 °C. After 1 h at ca. 40 °C, the Grignard reagent was added dropwise via syringe over 10 min to a solution of dicarbonyl(cyclohexadiene)(triphenylphosphine)iron complex **5**[3] (8.91 g, 14.9 mmol) in 100 mL of dry methylene chloride cooled to −78 °C. The reaction turned a deep reddish brown color. After being stirred 2 h at −78 °C, the reaction was warmed to 0 °C, where stirring was continued for 5 min. The reaction was quenched by pouring into 100 mL of water. The organic layer was separated, and the aqueous layer was extracted with 50 mL of methylene chloride and (2 × 50 mL) ether. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified on 210 g of silica gel. Elution with 25% ether–hexane → 50% ether–hexane provided 8.19 g (90%) of **7** as an amber viscous oil [R_f 0.67, 1:1 ether–hexane; IR (film) 3060, 2930, 2860, 1965, 1905, 1480, 1435, 1350, 1260, 1200, 1185, 1120, 1080, 1025, 980, 910, 870, 815, 745, 695 cm^{-1}], which was immediately demetalated in the next reaction.

4-(5-Cyclohexadienyl)butanol (8). The complex (8.16 g, 13.4 mmol) from the above experiment was dissolved over 30 min in 180 mL of absolute ethanol. Solid cupric chloride (16.8 g, 125 mmol) was added over a 5-min period, resulting in a mildly exothermic reaction (care must be taken since foaming results). The reaction temperature was maintained at ca. 25 °C by use of a water bath. The reaction color went from deep red to brown to green. The reaction was stirred at 25 °C for 5 h to ensure complete cleavage of the tetrahydropyranyl ether. The reaction was quenched by pouring into 250 mL of water. The product was isolated by extraction (4 × 75 mL) with ether–hexane (1:1). The combined organic extracts were dried on anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure provided the crude product, which was purified on 100 g of silica gel. Elution with 40% ether–hexane gave 1.29 g (63%) of pure alcohol **8** as a colorless oil: R_f 0.42 (1:1 ether–hexane); IR (CHCl$_3$) 3630, 3450, 3050 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 5.88 (m, 2 H), 5.78 (m, 1 H), 5.70 (m, 1 H), 3.65 (t, 2 H, J = 7 Hz), 2.2–2.4 (m, 2 H), 1.95 (m, 1 H), 1.3–1.7 (m, 7 H); MS, M$^+$ 152.1202 (calcd for $C_{10}H_{16}O$ 152.1197).

4-(5-Cyclohexadienyl)butanal (3). To a solution of oxalyl chloride (1.42 mL, 16.4 mmol) in 25 mL of methylene chloride cooled to −78 °C was added 2.37 mL (33 mmol) of dry dimethyl sulfoxide in 2.0 mL of methylene chloride. After 15 min at −78 °C, a solution of alcohol **8** (1.25 g, 8.22 mmol) in 12 mL of methylene chloride was added dropwise. Stirring was continued for 45 min prior to the dropwise addition of 11.5 mL (66 mmol) of diisopropylethylamine. After an additional 30 min, the reaction mixture was warmed to room temperature, where stirring was continued for 30 min. The reaction was quenched by pouring into 200 mL of pentane, and the mixture was washed with 80 mL of water, 75 mL of ice cold 1 M aqueous hydrochloric acid solution, 80 mL of water, and finally with 80 mL of a saturated sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude aldehyde was purified on 80 g of silica gel. Elution with ether–hexane (1:9) followed by ether–hexane (1:5) provided 789 mg (64%) of pure aldehyde **3** as a pale yellow, volatile oil: R_f 0.33 (1:9 ether–hexane); IR (CHCl$_3$) 3040, 2735, 1720 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.77 (t, 1 H, J = 1.8 Hz), 5.90 (m, 2 H), 5.78 (m, 1 H), 5.69 (m, 1 H), 2.44 (td, 2 H, J = 1.8, 7.2 Hz), 2.30 (m, 2 H, 1.97 (m, 1 H), 1.68 (m, 2 H), 1.3–1.6 (m, 2 H); MS; M$^+$ 150.1044 (calcd for $C_{10}H_{14}O$ 150.1041).

***N*-Methyl-2-azatricyclo[5.3.1.$0^{3,8}$]undec-9-ene (9).** A solution of monomethylamine hydrochloride (440 mg, 6.5 mmol) in 7.0 mL of water–ethanol (1:1) was degassed by being cooled to 0 °C and subjected it to five cycles of evacuation and argon purging. To this solution at ca. 70 °C was added a solution of the diene aldehyde **3** (150 mg, 1.0 mmol) in 200 μL of ethanol over a 29-h period by employing a 500-μL gas-tight syringe and a syringe pump. Stirring at ca. 70 °C was continued for 10 h after addition was complete. The reaction was cooled, diluted with 15 mL of water, and washed with ether (4 × 5.0 mL). The aqueous phase was cooled to 0 °C, and made basic with solid potassium hydroxide. The product was isolated by extraction (2 × 7.0 mL) with methylene chloride. The extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 107 mg (66%) of **9**, which was pure by ^{1}H NMR analysis: R_f 0.33 (85:15:1 chloroform–methanol–29% aqueous NH$_3$); IR (CHCl$_3$) 3050, 2940, 2860, 2700, 1450, 1365, 1275, 1145, 1125, 1040 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.41 (ddd, 1 H, J = 1.4, 6.9, 7.9 Hz), 6.22 (ddd, 1 H, J = 0.7, 5.0, 6.9 Hz), 3.30 (m, 1 H), 2.19 (s, 3 H), 2.05 (m, 1 H), 1.96 (m, 1 H), 1.15–1.90 (m, 9 H); MS; M$^+$ 163.1354 (calcd for $C_{11}H_{17}N$ 163.1361).

***N*-Methyl-2-azatricyclo[5.3.1.$0^{3,8}$]undecane (4).** A solution of **9** (25 mg, 0.15 mmol) in 2.0 mL of ethanol was added to a suspension of 10% Pd/C (12 mg) in 1.0 mL of ethanol under an atmosphere of hydrogen. After 5 min, the reaction was filtered through Celite, and 5 drops of acetic acid were added. The solvent was removed in vacuo, leaving 34 mg of a residue, which was dissolved in methylene chloride, washed with 0.5 M potassium carbonate solution, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure provided 15 mg (60%) of the known dihydrocannivonine **4** as a pale yellow oil. Unequivocal proof of structure came from comparison of the ^{13}C NMR data of synthetic **9** with that (in parentheses) reported by Evans:[5] ^{13}C NMR δ 60.6 (60.8), 50.7 (50.8), 42.6 (42.6), 34.3 (34.1), 33.3 (33.3), 31.8 (31.8), 31.0 (30.9), 29.2 (29.2), 25.9 (25.8), 18.0 (18.1), 15.9 (15.9).

Acknowledgment. This investigation was supported by a grant from the National Science Foundation. The 300-MHz NMR instrument (Varian XL-300) used in the above studies was purchased with funds provided by the

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National Institutes of Health (Grant RR-1882).

Registry No. (±)-3, 103564-29-0; (±)-4, 69100-18-1; **5**, 89589-68-4; **6**, 31608-22-7; **7**, 103564-32-5; (±)-**8**, 103564-30-3; (±)-**9**, 103564-31-4; dihydropyran, 110-87-2; 4-bromobutanol, 33036-62-3.

Cation-Anion Combination Reactions. 25.[1] Reactivity of Carbonate Ion

C. D. Ritchie* and Yongchun Tang

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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Carbonate–bicarbonate buffers are frequently used for the pH range around 10. Neither the carbonate nor bicarbonate ions are considered to be very reactive twoard organic electrophiles, although Swain[2] has reported a nucleophilicity parameter for bicarbonate ion in water.

In the course of other work, we have observed a reaction of carbonate ion with (*p*-methoxyphenyl)tropylium cation in water and have been able to measure both rate and equilibrium constants for this reaction.

Experimental Section

The (*p*-methoxyphenyl)tropylium perchlorate was available from an earlier study.[3] The stop–flow spectrophotometer used for the entire study was the single wavelength instrument described previously[4] and was thermostatted at 25.0 °C. Absorbance was measured at the wavelength of maximum absorbance of the cation, 425 nm.

A master solution of the (*p*-methoxyphenyl)tropylium perchlorate in acetonitrile, ca. 10^{-2} M, was diluted into very dilute aqueous acid to give a reaction solution having a cation concentration of ca. 6×10^{-5} M. This solution was mixed with the carbonate/bicarbonate buffer solutions in the stop–flow apparatus.

Two series of experiments, one with a buffer ratio, $(HCO_3^-)/(CO)_3^{2-})$, of 1.34 (pH 10.0), and the other with a buffer ratio of 4.0 (pH 9.5), were carried out.

Results

Upon mixing the solution of the cation with the carbonate buffer solution, the absorbance of the cation disappears in two clearly distinguishable stages, each following good first-order kinetics. The rate and extent of the first stage of reaction depends on the concentration of carbonate ion, but is independent of the buffer ratio. The second, slow, stage of reaction shows a dependence on the extent of the first stage as expected for the reaction scheme

$$\mathrm{R^+ + CO_3^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ROCO_2^-} \tag{1}$$

$$\mathrm{R^+ + OH^- \text{ or } H_2O \xrightarrow{k_2} ROH} \tag{2}$$

where the first reaction reaches equilibrium faster than the second reaction.

Table I. Reaction of Carbonate Ion with (*p*-Methoxyphenyl)tropylium Ion in Water at 25.0 °C

$10^2 I$,[a] M	$10^3 a_{CO_3}$[b]	$(A_0 - A_\infty)/A_\infty$[c]	$10^{-2}k_{fast}$[d]	$10^{-3}K_{eq}$[e]	$10^{-4}k_1$[f]
		at pH 10.0			
0.93	1.44	1.37	0.68	0.95	2.7
1.40	2.00	2.01	0.77	1.00	2.6
1.86	2.53	2.33	0.93	0.92	2.6
2.32	2.98	2.72	1.04	0.91	2.6
2.78	3.42	2.90	1.09	0.85	2.4
3.25	3.83	3.62	1.23	0.95	2.5
3.70	4.23	4.09	1.34	0.97	2.5
		at pH 9.5			
0.70	0.70	0.66	0.38	0.93	2.1
1.75	1.49	1.20	0.70	0.80	2.6
3.50	2.51	2.10	0.97	0.84	2.6
5.25	3.35	2.76	1.11	0.82	2.4
7.00	4.08	3.43	1.22	0.84	2.3
			avg	0.90	2.5

[a] Ionic strength. [b] Activity of carbonate ion, calculated using the activity coefficient given by: $-\log \gamma = 2.046I^{1/2}/(1 + 1.481I^{1/2})$. [c] A_0 is the absorbance at zero time, and A_∞ is the absorbance when the fast stage of reaction has reached equilibrium. [d] Pseudo-first-order rate constant for fast stage. [e] Calculated from $(A_0 - A_\infty)/(A_\infty \times a_{CO_3^{2-}})$. [f] Second-order rate constant in units of $M^{-1}\ s^{-1}$ for reaction 1.

The experimental data allowing the evaluation of the rate and equilibrium constants for reaction 1 are shown in Table I.

The pseudo-first-order rate constants for the slow stage of reaction allow the evaluation[5] of the pseudo-first-order rate constants for reaction 2. At pH of 10.0, we obtain $k_2 = 6.1\ s^{-1}$, and, at pH 9.5, we find $k_2 = 2.1\ s^{-1}$. Neither constant varies significantly with buffer concentration. The values are slightly higher than those we calculate (k_2 = 4.3 and 1.7, respectively) from the rate constants for reactions of water and hydroxide ion at 23 °C which were reported earlier.[3]

Discussion

The rate constant for reaction of hydroxide ion with (*p*-methoxyphenyl)tropylium cation, at 23 °C, is only slightly greater than that for reaction of carbonate ion: $k_{OH}/k_{CO_3} = 4.0 \times 10^4/2.5 \times 10^4 = 1.7$. The ratio of equilibrium constants is much greater, $K_{OH}/K_{CO_3} = 2.0 \times 10^5$. In terms of the exchange equilibrium

$$\mathrm{ROH + HCO_3^- \rightleftarrows RCO_3^- + HOH} \tag{3}$$

of the type suggested by Hine[6] and recently discussed by us for a variety of nucleophiles and cations,[7] we can evaluate $K = 1.3$ using pK_a of 15.7 for water and 10.3 for HCO_3^-. This value is much closer to unity than those for most nucleophiles and cations. For reactions in which R^+ is the Pyronin-Y cation (3,6-bis(dimethylamino)-xanthylium cation) or (*p*-(dimethylamino)phenyl)tropylium cation, all nucleophiles studied, with the exception of the one alkoxide ion studied, give equilibrium constants much greater than unity for the exchange reactions analogous to eq 3. Even peroxide ion, an oxygen nucleophile, has $K \approx 10^4$ for the exchange reaction.

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