References and Notes

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Rate Acceleration of the Intramolecular Ene Reactions of 1,6- and 1,7-Enynes by Electron-Withdrawing Substituents

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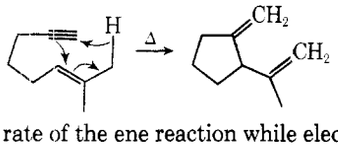
The intramolecular ene reactions of 1,6- and 1,7-enynes containing a hydrogen, methyl, or carbomethoxy substituent of the acetylene have been investigated. Since the acetylene is acting as the enophile, the methyl substituent retards the reaction while the carbomethoxy group significantly accelerates it. A terminal 1,6-enyne, **1**, cyclizes at 210 °C while the carbomethoxy enyne **2** cyclizes at 135 °C. The cyclization of 1,7-enynes has been shown to be slow, typically requiring temperatures 100 °C higher than the corresponding 1,6-enyne. The acetylene **10** activated by both ketone and a carbomethoxy group cyclizes cleanly at 90 °C.

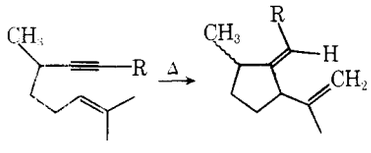
The intramolecular ene reaction of 1,6-enynes (eq 1) has recently been shown to be a useful method for the synthesis of complex molecules,[1] including chiral acetic acid[1h] and prostaglandins.[1i] For terminal acetylenes this reaction typically takes place in 1–5 h at 220 °C. In this intramolecular ene reaction the triple bond is functioning as the enophile so that electron-withdrawing substituents on the acetylene should



(1)

accelerate the rate of the ene reaction while electron-donating or bulky substituents on the acetylene should retard the reaction. We were interested in examining the magnitude of these effects and the extension of this ene reaction to 1,7- and 1,8-enynes. We report here that the addition of electron-withdrawing substituents to 1,6- and 1,7-enynes drastically lowers the temperature required for the intramolecular ene reaction and makes it a mild, general route for the formation of both five- and six-membered rings.

Enynes **1**–**3** were chosen for initial study because of their accessibility from the noraldehyde using the procedure of



1, R = H
2, R = CO_2CH_3
3, R = CH_3

4, R = H
5, R = CO_2CH_3
6, R = CH_3

Corey and Fuchs.[2] Reaction of 2,6-dimethyl-5-heptenal[3] with dibromomethylenetriphenylphosphorane affords 1,1-dibromo-3,7-dimethyl-1,6-octadiene. Treatment of this dibromide with 2 equiv of butyllithium yields the lithium salt of 3,7-dimethyl-6-octen-1-yne.[2] Addition of water, methyl chloroformate, or methyl iodide yields **1**,[4] **2**, or **3**, respectively. Pyrolysis of **1** in toluene for 62 h at 210 °C gives the ene adduct **4** in greater than 95% yield as a ca. 1:1 mixture of diastereomers. These conditions are similar to those reported for similar systems.[1] Adduct **4** contains the skeleton of the iridoid monoterpenes with appropriate functionality for conversion to a variety of iridodiols.[5] Enyne **3**, a methyl acetylene, cyclizes more slowly than **1**. Pyrolysis of **3** for 48 h at 225 °C gives 15% conversion to **6**. At higher temperatures or longer reaction times a variety of unidentified products are formed. A previous study has shown that *trans*-6-octen-1-yne (**7**) cyclizes 5.7 times faster than the homologous methylacetylene, *trans*-7-nonen-2-yne (**8**), at 382 °C in the vapor phase.[1b,1c] While these results are not strictly comparable to our solution studies, they are consistent with our results. Huntsman found that the terminal acetylene **7** cyclizes cleanly to the expected ene adduct, while the methyl acetylene **8** gives two products. The expected ene adduct is obtained in 80% yield and 2-ethyl-1-vinylidenecyclopentane (**9**) is formed in 10% yield. The allene **9** is derived from the double bond functioning as the enophile. *cis*-7-Nonen-2-yne gives only **9** and recovered starting material.[1b,cc]

Substitution of the terminal hydrogen of **1** with a carbomethoxy group was expected to lower the temperature required for the ene reaction. Pyrolysis of the alkenynoate **2** for 24 h at 135 °C results in conversion to the ene adduct **5** in

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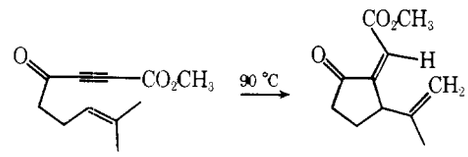
greater than 95% yield. Spectroscopic and gas chromatographic analysis indicate that **5** is a mixture of diastereomers but that only one double bond isomer is formed. The mild conditions required and stereospecific formation of the α,β-unsaturated ester make this a useful synthetic procedure. We have recently found that with aluminum chloride catalysis the ene reaction of methyl propiolate and a variety of alkenes occurs at 25 °C. However, treatment of **2** with aluminum chloride in benzene at 25 °C gives only recovered starting material.

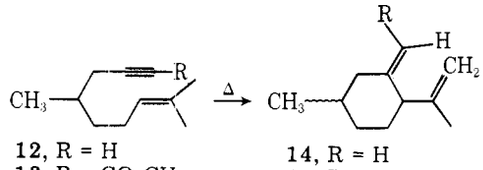
To investigate the effect of additional electron-withdrawing groups on the rate of the ene reaction, the ene reaction of keto ester **10** was studied. Treatment of 5-methyl-4-hexenoyl chloride with the silver salt of methyl propiolate in methylene chloride affords **10** in good yield.[6] Heating **10** in benzene for



10 **11**

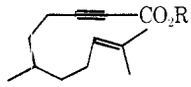
12 h at 90 °C gives complete conversion to the ene adduct **11** as a single isomer. At higher temperatures partial isomerization about the conjugated double bond occurs. This cyclopentanone synthesis is clearly applicable to the synthesis of prostaglandins.

To the best of our knowledge, ene reactions of 1,7 enynes have not been reported previously.[7] In order to determine the usefulness of this reaction for the synthesis of six-membered rings we have examined the cyclization of **12** and **13**, the homologues of **1** and **2**. These compounds were prepared from citronellal using the previously described procedures.[2] Pyrolysis of **12** in toluene for 48 h at 255 °C gives 17% conversion to the ene adduct **14**. At higher temperatures extensive de-



12, R = H
13, R = CO_2CH_3

14, R = H
15, R = CO_2CH_3



16, R = CH_3
17, R = H

composition occurs. On the other hand, pyrolysis of the ester **13** for 62 h at 225 °C gives ene adduct **15** in 85% yield.

The 1,8-alkynoate **16** was investigated to determine the ability of the intramolecular ene reaction to form cycloheptanes. Treatment of citronellyl bromide with dilithium propiolate[8] gives **17** in 18% yield. Esterification with methanol and sulfuric acid gives **16** in 50% yield. Pyrolysis of **16** in toluene at 270 °C gives slow decomposition to several unidentified products. No ene adduct could be isolated. This observation is consistent with the slow rates of other intramolecular reactions which form seven-membered rings.

Our results indicate that the electron-withdrawing carbomethoxy group vastly increases the rate of these intramolecular ene reactions. This allows formation of cyclopentanes under mild conditions and allows the extension of this reaction to the synthesis of cyclohexanes. In a previous study of related intramolecular ene reactions, Huntsman has shown that methyl 5,9-dimethyl-2,8-decadienoate cyclizes in a flow system at 400 °C while the hydrocarbon 8-methyl-1,7-nonadiene cyclizes at 490 °C in a flow system.[9,10]

Our studies have shown that while intramolecular ene reactions are facile for 1,6-enynes to give cyclopentanes, they proceed efficiently only for activated 1,7-enynes to give cyclohexanes and they cannot be used to produce cycloheptanes. Conia, in studies of ene reactions of the enols of unsaturated ketones, found little preference for the formation of five- rather than six-membered rings.[11] Huntsman, in studies of intramolecular ene reactions of 1,6- and 1,7-dienes, found that 7-methyl-1,6-octadiene cyclizes in a flow system at 450 °C,[12] while 8-methyl-1,7-octadiene requires 490 °C for a similar reaction.[9] This rate difference is in the same direction though much less pronounced than the difference between **2** and **13**.

The intramolecular ene reactions of alkenynoates provide efficient routes to both five- and six-membered rings. We are currently exploring applications of these reactions to total synthesis of natural products.

Experimental Section

All boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 283 infrared spectrometer. NMR spectra were determined on a Varian A-60 spectrometer. The mass spectra were obtained with an AEI MS9 mass spectrometer. GC analyses were performed on a Perkin-Elmer 3920 gas chromatograph. THF was purified by distillation from sodium benzophenone ketyl.

1,1-Dibromo-3,7-dimethyl-1,6-octadiene.[2] To 500 mL of CH_2Cl_2 containing 26.2 g (0.1 mol) of triphenylphosphine, 33.2 g (0.1 mol) of carbon tetrabromide, and 6.54 g (0.1 mol) of zinc powder was added 7.01 g (0.05 mol) of freshly distilled 2,6-dimethyl-5-heptenal. The reaction mixture was stirred at room temperature overnight. Workup, consisting of diluting the reaction mixture to 2.5 L with pentane, filtering the precipitate, dissolving the precipitate in 200 mL of fresh CH_2Cl_2, reprecipitating the precipitate with 1.5 L of pentane, refiltering the precipitate, and evaporating the combined pentane fractions, afforded 13.9 g of crude product. Distillation yielded 4.78 g (0.0162 mol, 32% yield) of pure dibromide: bp 73–85 °C (0.05 mm); NMR ($CDCl_3$) δ 6.16 (d, 1, J = 9 Hz, CH=CBr_2), 5.08 (bd t, 1, J = 7 Hz, C**H**=$C(CH_3)_2$), 2.9 to 1.15 (m, 11), and 0.98 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2964, 2926, 2868, 2851, 1616, 1451, 1375, 1260, 846, and 779 cm^{-1}.

1,1-Dibromo-4,8-dimethyl-1,7-nonadiene.[2] The previous procedure was used to treat 66.4 g (0.2 mol) of carbon tetrabromide, 52.4 g (0.2 mol) of triphenylphosphine, and 13 g (0.2 mol) of zinc powder with 15.2 g (0.098 mol) of freshly distilled citronellal in 500 mL of CH_2Cl_2 yielding 16.94 g of crude product. Distillation afforded 9.05 g (0.0292 mol, 30% yield) of pure dibromide: bp 90–110 °C (0.10–0.15 mm); NMR ($CDCl_3$) δ 6.43 (t, 1, J = 7 Hz, CH=CBr_2), 5.12 (bd t, 1, J = 7 Hz, C**H**=$C(CH_3)_2$), 2.3–1.0 (m, 13), and 0.9 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2962, 2915, 2852, 2726, 1618, 1453, 1378, 1347, 1117, 891, 863, 827, and 779 cm^{-1}.

Lithium Salt of 3,7-Dimethyl-6-octen-1-yne.[2] n-Butyllithium in hexane (6.2 mL, 2.3 M, 14.3 mmol) was added to a solution containing 1.77 g (5.97 mmol) of 1,1-dibromo-3,7-dimethyl-1,6-octadiene in 20 mL of anhydrous THF at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then 1 h at room temperature. This solution of lithium acetylide was immediately used in the following reactions.

Lithium Salt of 4,8-Dimethyl-7-nonen-1-yne.[2] In a manner similar to the above, 6 mL of 2.1 M n-butyllithium in hexane (12.6 mmol) was added to 1.78 g (6 mmol) of 1,1-dibromo-4,8-dimethyl-1,7-nonadiene and this solution was immediately used in the following reactions.

3,7-Dimethyl-6-octen-1-yne (1). To the above solution of the lithium salt of 3,7-dimethyl-6-octen-1-yne in 20 mL of THF at 0 °C was added 5.0 mL of water. Warming to room temperature, followed by extraction with 3 × 10 mL of pentane, drying of the extracts ($MgSO_4$), and evaporation of solvent afforded 0.9365 g of product contaminated with octane. Preparative GC on a 6 ft × 0.25 in. 5% DEGS column at 80 °C (T_r = 9 min) afforded pure 3,7-dimethyl-6-octen-1-yne: NMR ($CDCl_3$) δ 5.1 (t, 1, J = 7 Hz, C**H**=$C(CH_3)_2$), 2.0 (d, 1, J = 2 Hz, C≡CH), 2.7–1.25 (m, 11), and 1.15 (d, 3, J = 7 Hz, $CHCH_3$); IR (neat) 3310, 2970, 2925, 2875, 2855, 2105 (w), 1450, and 1375 cm^{-1}.

Methyl 4,8-Dimethyl-7-nonen-2-ynoate (2). To a solution containing 0.852 g (6 mmol) of the lithium salt of 3,7-dimethyl-6-octen-1-yne in 20 mL of THF at −30 °C was added 0.683 g (7 mmol) of methyl chloroformate. The reaction mixture was stirred at room temperature for 1 h, diluted to 75 mL with pentane, washed with 3

× 50 mL of H_2O, dried ($MgSO_4$), and evaporated. The crude product (0.973 g, 84% yield) was purified by preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C (T_r = 8.5 min): NMR $CDCl_3$) δ 5.12 (t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 3.75 (s, 3, OCH_3), 2.61 (m, 1), 2.4–1.4 (m, 10, CH_2 and C=C(CH_3)$_2$), and 1.23 (d, 3, J = 7 Hz, $CHCH_3$); IR (neat) 2968, 2950, 2928, 2871, 2855, 2232 (s), 1719, 1434, 1376, 1258, 1204, 1128, 1075, 1032, and 751 cm^{-1}.

4,8-Dimethyl-7-nonen-2-yne (3). To a THF solution of the lithium salt derived from 2.37 g (8 mmol) of 1,1-dibromo-3,7-dimethyl-1,6-octadiene at −78 °C was added 1.35 g (9.5 mmol) of methyl iodide. The reaction mixture was stirred at room temperature overnight and then diluted to 50 mL with pentane, washed with 3 × 25 mL of H_2O, dried ($MgSO_4$), and evaporated giving 1.44 g of crude product. Preparative gas chromatography on 4 ft × 0.25 in. 20% DEGS column at 80 °C afforded pure 3 (T_r = 6.8 min): NMR ($CDCl_3$) δ 5.10 (bd t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 2.4–1.2 (m with d at 1.71, J = 2 Hz, 14, CH_2, CH, C≡CCH_3), and 1.05 (d, 3, J = 7 Hz, $CHCH_3$); IR (neat) 2955, 2926, 2859, 1456, 1377, 1261, 1108, and 737 cm^{-1}.

4,8-Dimethyl-7-nonen-1-yne (12). 1,1-Dibromo-4,8-dimethyl-1,7-nonadiene (1.24 g, 4 mmol) was converted to **12** as previously described giving 0.975 g of crude product which was purified by GC on a 4 ft × 0.25 in. 20% DEGS column at 70 °C (T_r = 9 min): NMR ($CDCl_3$) δ 5.11 (bd t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 2.3–1.2 (m with d at 1.96, J = 2 Hz, 14, C≡CH), and 1.01 (d, 3, J = 7 Hz, $CHCH_3$); IR (neat) 3313, 2966, 2921, 2856, 2117 (w), 1454, 1378, and 1112 cm^{-1}.

Methyl 5,9-Dimethyl-8-decen-2-ynoate (13). 1,1-Dibromo-4,8-dimethyl-1,7-nonadiene (1.68 g, 5.4 mmol) was converted to **13** as described for **2** yielding 0.9876 g of crude product. Column chromatography on 50 g of silica gel using 15% ether in pentane as eluant yielded 0.3153 g (1.52 mmol, 28% yield) of pure **13:** NMR ($CDCl_3$) δ 5.08 (bd t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 3.72 (s, 3, OCH_3), 2.5–1.15 (m, 13), and 1.00 (d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2960, 2920, 2875, 2855, 2235 (s), 1718, 1450, 1432, 1380, 1255, 1075, 818, 751, and 735 cm^{-1}.

Methyl 6,10-Dimethyl-9-undecen-2-ynoate (16). The dilithium salt of propiolic acid (1.57 g, 22.5 mmol) was prepared by the method of Carlson and Oyler[12] and treated with 4.93 g (22.5 mmol) of 1-bromo-3,7-dimethyl-6-octene in 24 mL of 1:1 THF–HMPA at −45 °C. The slurry was stirred at −10 °C for 2 h and then at room temperature for 72 h. Workup, consisting of diluting the reaction mixture to 100 mL with Et_2O, washing with 3 × 30 mL of saturated $NaHCO_3$, acidifying the basic layer (5% HCl) and extracting it with 3 × 20 mL of Et_2O, drying the Et_2O extracts ($MgSO_4$), and evaporating the solvent afforded 0.7735 g of acid **17** (4 mmol, 18% yield).

To 0.54 g of acid **17** in 25 mL of methanol was added 45 μL of concentrated H_2SO_4 and the solution was stirred at room temperature overnight. Workup, consisting of diluting the reaction mixture to 75 mL with Et_2O, washing the mixture with 3 × 100 mL of saturated $NaHCO_3$ and 3 × 70 mL of H_2O, drying the mixture ($MgSO_4$), and evaporating the solvent afforded 0.270 g of crude ester. Chromatography on 10 g of silica gel using 10% ether in benzene as eluant yielded 0.089 g of pure **16:** NMR ($CDCl_3$) δ 5.10 (bd t, 1, J = 7 Hz, CH=C(CH_3)$_2$), 3.72 (s, 3, OCH_3), 2.5–1.05 (m, 15), and 0.9 (distorted d, 3, J = 6 Hz, $CHCH_3$); IR (neat) 2960, 2925, 2875, 2860, 2243, 1720, 1450, 1436, 1380, 1257, 1075, 752, and 735 cm^{-1}.

Methyl 8-Methyl-4-oxo-7-nonen-2-ynoate (10). To a 20-mL THF suspension of 0.557 g of NaH (50% dispersion, 12 mmol) was added 1.42 g (11 mmol) of 5-methyl-4-hexenoic acid followed by 1.68 g (13.2 mmol) of oxalyl chloride and the reaction mixture was stirred overnight. The acid chloride solution was filtered through celite and evaporated yielding 1.06 g of acid chloride which was used immediately in the following reaction. The acid chloride was added to a 20-mL CH_2Cl_2 suspension of methyl propiolate silver salt[6] and stirred in the dark for 4 days. Filtration through celite and evaporation of solvent afforded 1.11 g of crude keto ester, contaminated with anhydride. Chromatography of 0.577 g of crude product on 30 g of silica gel using 8% ether in pentane as eluant yielded 0.372 g (65% yield) of pure **10:** NMR ($CDCl_3$) δ 5.08 (bd t, 1, J = 6 Hz, CH=C(CH_3)$_2$), 3.33 (s, 3, OCH_3), 2.85–2.10 (m, 4, CH_2), and 1.67 (m, 6, C=C(CH_3)$_2$); IR (neat) 2961, 2921, 1727, 1691, 1436, 1257, 1122, 986, and 748 cm^{-1}.

Thermal Reactions of Enynes. General Procedure. A pyridine washed NMR or resealable tube was charged with between 0.5 and 1.5 mL of toluene containing 0.9 to 1.5 mmol of enyne. The tube was then flushed with N_2, cooled to −78 °C, evacuated to 0.1 mm Hg, and sealed. The sealed tubes were immersed to ~⅔ their length and heated in a thermostatically controlled oil bath (DC-710H fluid). Upon completion of reaction (which was monitored by NMR) the tubes were opened and the products were separated by preparative gas chromatography.

Ene Reaction of 3,7-Dimethyl-6-octen-1-yne (1). A solution of 0.098 g of **1** in 0.5 mL of toluene in a sealed NMR tube was heated to 205–215 °C for 62 h. Preparative gas chromatography on a 6 ft × 0.25 in. SE-30 column at 80 °C (T_r = 14 min) afforded **4** as an isomeric mixture: NMR ($CDCl_3$) δ 4.75 (m, 4, C=CH_2), 3.18 (m, 1, C=C-CHC=C), 2.85–1.2 (m, 8), 1.08 and 1.05 (2 doublets, 3, J = 6 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3073, 2954, 2914, 2866, 1643, 1441, 1380, 1372, and 889 cm^{-1}; mass spectrum m/e 136 (M^+), 121, 95, and 93.

Ene Reaction of Methyl 4,8-Dimethyl-7-nonen-2-ynoate (2). Heating 0.054 g of ester **2** in 0.5 mL of toluene at 130–140 °C for 24 h as described above followed by preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C (T_r = 19.2 min) gave **5** as an isomeric mixture: NMR ($CDCl_3$) δ 5.61 (m, 1, C=CHCO_2Me), 4.85 (m, 2, C=CH_2), 3.70 (s, 3, OCH_3), 3.38 (m, 1, C=CCHC=C), 2.2–1.3 (m, 8), 1.13 and 1.10 (2 doublets, 3, J = 7 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3080, 2958, 2875, 1721, 1651, 1465, 1452, 1436, 1375, 1355, 1302, 1206, 1176, 1134, 1030, 898, and 876 cm^{-1}; mass spectrum m/e 194 (M^+), 179, 163, 135, 119, and 93.

Ene Reaction of 4,8-Dimethyl-7-nonen-2-yne (3). Heating a 0.8-mL toluene solution containing 0.060 g of **3** at 220–230 °C for 48 h followed by preparative gas chromatography on a 5 ft × 0.25 in. 5% DEGS column at 80 °C yielded a complex mixture containing 15% of **6** (T_r = 2 min): NMR ($CDCl_3$) δ 4.69 (m, 3, C=CH_2, CH=C), 2.67 (m, 1, C=CCHC=C), 2.45–0.75 (m, 14); IR ($CHCl_3$) 3075, 2962, 2930, 2873, 1642, 1460, 1375, and 892 cm^{-1}; mass spectrum m/e 150 (M^+), 135, 121, 109, 107, 95, 93, and 91.

Ene Reaction of 4,8-Dimethyl-7-nonen-1-yne (12). A solution containing 0.15 g of **12** in 1.5 mL of toluene was heated to 250–260 °C for 48 h. Preparative gas chromatography on an 8 ft × 0.25 in 5% DEGS column at 80 °C gave **14** as an isomeric mixture in 17% yield (T_r = 14.8 min): NMR ($CDCl_3$) δ 4.65 (m, 4, C=CH_2), 2.8–1.0 (m, 11), and 0.9 (m, 3, $CHCH_3$); IR ($CHCl_3$) 3078, 2948, 2929, 2869, 1644, 1454, 1374, and 891 cm^{-1}; mass spectrum m/e 150 (M^+), 135, 121, 107, and 93.

Ene Reaction of Methyl 5,9-Dimethyl-8-decen-2-ynoate (13). A solution of 0.8 mL of toluene containing 0.13 g of ester **13** was heated to 215–230 °C for 62 h. Preparative gas chromatography on a 4 ft × 0.25 in. 20% DEGS column at 160 °C gave **15** as an isomeric mixture in 85% yield (T_r = 8.1 min): NMR ($CDCl_3$) δ 5.7 and 5.53 (m, 1, C=CHCO_2Me), 5.0 and 4.8 (m, 2, isomeric C=CH_2), 4.0–1.1 with singlet at 3.66 (m, 13), and 1.0 and 0.95 (2 doublets, 3, J = 5 Hz, isomeric $CHCH_3$); IR ($CHCl_3$) 3085, 2945, 2922, 2865, 1718, 1642, 1455, 1445, 1432, 1375, 1258, 1205, 1156, 892, and 871 cm^{-1}; mass spectrum m/e 208 (M^+), 193, 177, and 149.

Ene Reaction of Methyl 8-Methyl-4-oxo-7-nonen-2-ynoate (10). A solution containing 0.081 g of keto ester **10** in 0.5 mL of toluene was heated to 87–95 °C for 20 h in a sealed tube and then cooled and evaporated to yield 0.080 g of pure **11:** NMR ($CDCl_3$) δ 5.93 (d, 1, J = 3 Hz, C=CHCO_2Me), 4.96 (m, 2, C=CH_2), 3.82 (s, 3, OCH_3), 3.8–3.4 (m, 1), and 2.6–1.5 (m, 7); IR ($CHCl_3$) 3080, 2955, 2920, 1730, 1645, 1600, 1435, 1340, 1160, 1025, and 897 cm^{-1}; mass spectrum m/e 194 (M^+), 166, 163, 162, 147, 134, and 119.

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Registry No.—**1**, 18791-15-6; 1 Li salt, 65890-28-0; **2**, 65890-29-1; **3**, 65890-30-4; *cis*-**4**, 65890-31-5; *trans*-**4**, 65890-32-6; *cis*-**5**, 65890-33-7; *trans*-**5**, 65890-34-8; **6**, 65890-35-9; **10**, 65915-86-8; **11**, 65890-36-0; **12**, 65890-37-1; **13**, 65890-38-2; *cis*-**14**, 65890-39-3; *trans*-**14**, 65890-40-6; *cis*-**15**, 65890-41-7; *trans*-**15**, 65890-42-8; **16**, 65890-43-9; **17**, 65890-44-0; 1,1-dibromo-3,7-dimethyl-1,6-octadiene, 65890-45-1; 2,6-dimethyl-5-heptenal, 106-72-9; 1,1-dibromo-4,8-dimethyl-1,7-nonadiene, 65890-46-2; citronellal, 106-23-0; 4,8-dimethyl-7-nonen-1-yne lithium salt, 65890-47-3; propiolic acid dilithium salt, 65890-27-9; 1-bromo-3,7-dimethyl-6-octene, 4895-14-1; 5-methyl-4-hexenoic acid, 5636-65-7; 5-methyl-4-hexenoyl chloride, 65890-48-4; methyl propiolate silver salt, 57031-37-5.

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trans-1-*N*-Acylamino-1,3-dienes: Preparation from Dienoic Acids

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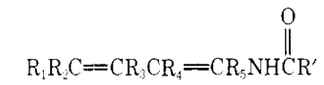
The convenient preparation of *trans* 1-*N*-acylamino-1,3-dienes from conjugated dienoic acids by a modified Curtius procedure is reported. This procedure is specifically illustrated by the preparation of the 1,3-butadiene and 1,3-pentadiene carbamates, thiocarbamates, and ureas (**4–13**) in yields of 44–80%. The ^{13}C NMR spectra of these acylamino-1,3-dienes have been determined, and the shift assignments are discussed.

Dienamides are extremely useful components for Diels–Alder synthesis.[2] The application of *N*-acyl-*N*-alkyl-1-amino-1,3-butadienes for the intramolecular Diels–Alder elaboration of natural products has been impressively demonstrated by Oppolzer and co-workers,[3] while recent reports from our laboratory have clearly demonstrated the utility of *N*-acyl-1-amino-1,3-dienes, and intermolecular Diels–Alder strategies, for solving stereochemical problems in the area of alkaloid total synthesis.[4]

A recent report from our laboratory described a versatile synthetic route to both *N*-trichloroacetyl-1-amino-1,3-dienes (**1**, R′ = CCl_3) and *N*-trichloroacetyl-2-amino-1,3-dienes.[5]

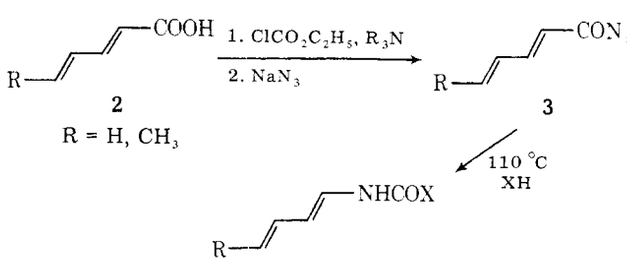


1

Synthetic applications of these dienes were limited to a certain extent, however, by their moderate Diels–Alder reactivity, a property attributed to the electron-withdrawing nature of the trichloroacetyl substituent. In this paper we report[6] that a variety of *trans*-1-*N*-acylamino-1,3-dienes can be conveniently prepared, on large scales, from dienoic acids using a modified Curtius sequence.[7] This route provides a general entry to the more reactive dienamides **1**[8] which have heteroatom acyl substituents (R′ = OR, SR, NR_2).

Results

Preparation. Dienoic acids **2** were converted, via their mixed anhydrides, into the azide derivatives **3.** The acyl azides were not isolated but instead extracted into toluene and added directly to a refluxing toluene solution containing the free-radical inhibitor 4-*tert*-butylcatechol. The diene isocyanate thus produced was either trapped as it was formed (procedure A) or cooled to room temperature before the trapping agent was added (procedure B). Concentration of the toluene solution and filtration through silica gel afforded the pure crystalline *trans*-1-*N*-acylamino-1,3-dienes **4–13** in overall yields of 44–80%. It is critical that the crude dienamides be purified immediately, as yields were dramatically reduced if the concentrated toluene solution was stored for several days before purification. Results are summarized in Table I.



2
R = H, CH_3

3

4, R = H; X = $OCH_2C_6H_5$
5, R = H; X = $OC(CH_3)_3$
6, R = H; X = OC_2H_5
7, R = H; X = OC_6H_5
8, R = H; X = SC_6H_5
9, R = H; X = $N(CH_2)_4$
10, R = CH_3; X = OC_2H_5
11, R = CH_3; X = OC_6H_5
12, R = CH_3; X = SC_6H_5
13, R = CH_3; X = $N(CH_2)_4$

The in situ trapping procedure (procedure A) is preferred for the preparation of diene carbamates, but it was markedly inferior for the preparation of diene ureas. The latter result is likely due to decomposition of the more reactive diene ureas in refluxing toluene. The amount of trapping reagent used was dictated by its ease of removal from the product dienamide. When a trapping reagent was employed which was not significantly more reactive than ethanol (e.g., *tert*-butyl alcohol or benzyl alcohol), the ethanol produced from the mixed anhydride condensation had to be removed in order to avoid the formation of contaminating amounts of the ethyl carbamate **6.** This is most easily done by concentrating the acyl azide solution to one-half its volume on a rotary evaporator, with ethanol being removed as a toluene azeotrope. In our early experiments we experienced significant problems with reproducibility. After convincing ourselves that this did not derive from the source or purity of the sodium azide employed,[9] we looked in greater detail at the mixed anhydride formation step. In our hands the reaction of *trans*-2,4-pentadienoic acid and ethyl chloroformate was not reproducible using standard conditions.[7] However, this reaction was totally reliable when *N,N*-diisopropylethylamine was substituted for triethylamine as the acid scavenger.

Properties. Dienamides **4–13** are reasonably stable crystalline solids which, when pure, can be stored in a freezer (but not at room temperature) for several months with little decomposition. The only exceptions are the phenyl thiocarbamates **8** and **12,** which decompose in a freezer within days with the loss of thiophenol.

The ^{13}C NMR spectra for the acylamino-1,3-dienes prepared in this study, and for *trans*-1-trichloroacetamido-1,3-butadiene (**14**),[5] are summarized in Table II.[10] For the butadienes the assignment for the terminal methylene carbon

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