Triphenylphosphine-Catalyzed Isomerizations of Enynes to (*E,E,E*)-Trienes: Phenol as a Cocatalyst

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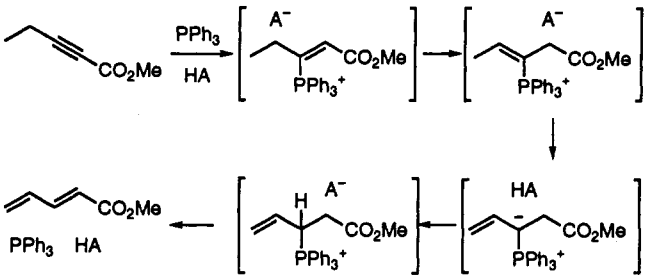
Trost and Kazmaier recently reported that PPh_3 catalyzes the isomerization of alkynyl ketones, esters, and amides to the corresponding (*E,E*)-dienes.[2,3] This simple isomerization promises to be an attractive alternative to more conventional preparations of dienes and other polyenes.[4] Our interest in the synthesis of polyene macrolide antibiotics led us to consider extending this method to the preparation of higher alkenes. We now report the isomerization of enyne esters to (*E,E,E*)-triene esters using an improved catalytic system.

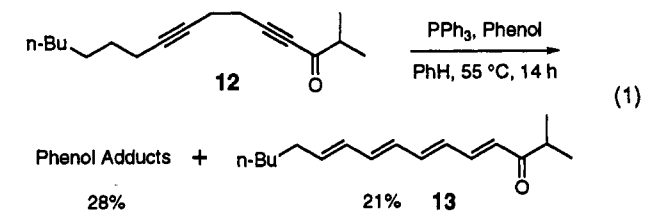
Isomerization of the enyne ester **1** to triene ester **7** was initially examined.[5] Trost had shown that PPh_3 and acetic acid were necessary to isomerize alkynyl esters, whereas PPh_3 alone was sufficient to isomerize the more reactive alkynyl ketones. Treatment of **1** with PPh_3 and acetic acid in refluxing xylenes (140 °C) led to a very slow isomerization to **7** accompanied by decomposition. Substituting triflic acid for acetic acid shut the reaction down completely! Consideration of the reaction mechanism led to the series of possible intermediates shown in Scheme 1. The acid (HA) would be expected to facilitate the initial addition of PPh_3 to the alkyne, while a strong conjugate base (A) would be expected to promote the subsequent proton transfer reactions. Triflic acid was ineffective as a cocatalyst because the triflate anion is not a strong enough base. A series of weak acids (strong conjugate bases) were screened in the isomerization reaction. Phenol was found to be a very effective cocatalyst with PPh_3 for the isomerization of enyne **1** to triene **7**. A number of substituted phenols were also examined as cocatalysts,[6] but none was superior to phenol.

Scheme 1



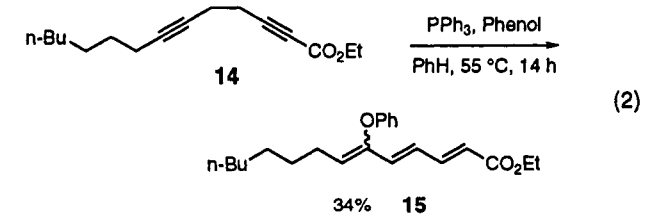
Several examples of this isomerization reaction are shown in Table 1. The reaction rates show a strong concentration dependence, and so all of the examples in Table 1 (except entry 6) were run using the standard concentrations: 1 M substrate, 1 M PPh_3, and 1 M phenol in benzene. The enyne esters **1–4** isomerized at 55 °C to give the (*E,E,E*)-triene esters **7–9** in good yield (entries 1–4).[7] Each of the trienes **7–9** was found to have the *E,E,E* geometry by NMR spectroscopy. The isomerization conditions are nearly neutral and should be compatible with most protecting groups. The alkyne esters **5** and **6** were also examined and found to isomerize at 25 °C to give the (*E,E*)-diene esters **10** and **11**, respectively, in good yield (entries 5 and 7).[7] When the alkyne **5** was treated with acetic acid instead of phenol under the same reaction conditions, only 17% of diene **10** was detected along with the recovered starting material.

The isomerization of dialkynes to tetraenes was investigated using PPh_3 and phenol. The dialkyne ketone **12** was isomerized at 55 °C under standard conditions to give the tetraene ketone **13** in 21% yield, eq 1. A major side



(1)

reaction was conjugate addition of the phenol to the unsaturated ketone. A mixture of phenol adducts was isolated in 28% yield. A similar attempt to isomerize the dialkyne ester **14** to the corresponding tetraene was unsuccessful. The major product was the phenol adduct **15** which was isolated in 34% yield. The unexpected



(2)

regiochemistry presumably arises from conjugate addition of phenoxide to a vinyl phosphonium intermediate. The combination of phenol and PPh_3 leads to conjugate additions with diyne esters, but it is a mild and effective

(1) Alfred P. Sloan Research Fellow 1992–1994.

(2) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935.

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(4) (a) Pommer, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 423–429. (b) Wadsworth, W. S. *Org. React. (N.Y.)* **1977**, *25*, 73–253. (c) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717–720. (d) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, 4991–4994. (e) Hayashi, T.; Oishi, T. *Chem. Lett.* **1985**, 413–416. (f) Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1985**, *26*, 4891–4894. (g) Shi, L.; Xia, W.; Yang, J.; Wen, X.; Huang, Y.-Z. *Tetrahedron Lett.* **1987**, *28*, 2155–2158. (h) Duhamel, L.; Ple, G.; Ramondenc, Y. *Tetrahedron Lett.* **1989**, *30*, 7377–7380. (i) Kann, N.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5312-5323. (j) Nozoe, S.; Kikuchi, K.; Ishii, N.; Ohta, T. *Tetrahedron Lett.* **1992**, *33*, 7551–7552. (k) Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *Synth. Lett.* **1993**, 435–436.

(5) Enyne esters **1** and **2** were prepared from 1-decyne by the following sequence and separated by chromatography: (i) *n*-BuLi, CH_2O (68%); (ii) Swern oxidation (100%); (iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2 (72%). Enyne esters **3** and **4** were prepared by analogous routes. Alkynyl esters **5** and **6** were prepared by treating the corresponding terminal alkyne with *n*-BuLi and ethyl chloroformate.

(6) A series of reactions were run for 10 h at 140 °C in xylenes using 0.2 M **1**, 0.2 M PPh_3, and 0.1 M substituted phenol. The products were analyzed by GC against an internal standard. Phenol and 2,6-difluorophenol catalyzed the reaction at comparable rates. The 2,6-dichlorophenol and 2,4,6-trichlorophenol did not catalyze the reaction as rapidly. Acetic acid and 2,6-di-*tert*-butyl-4-nitrophenol were the least effective catalysts, returning unreacted starting material.

(7) The (*E,E,E*)-triene ester was the major alkene isomer formed in each case with ≥10:1 selectivity by ^1H NMR spectroscopy. Similarly, the (*E,E*)-diene was the major alkene isomer formed in each case with ≥20:1 selectivity.

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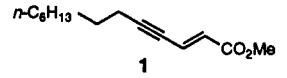
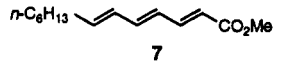
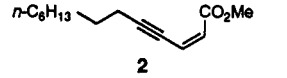
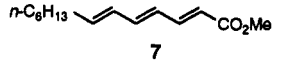
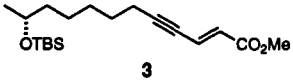
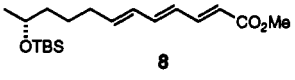
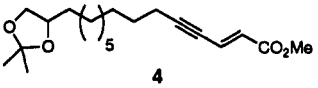
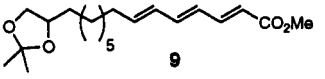
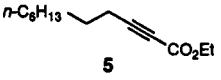
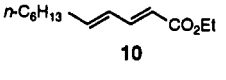
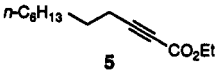
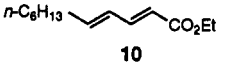
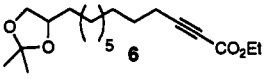
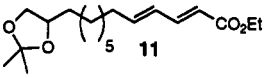
Table 1. Isomerizations of Alkynes with PPh_3 and Phenol

entry	starting material	reagents	T (°C)/time (h)	product	yield (%)
1	 1	PPh_3/PhOH	55/12	 7	70
2	 2	PPh_3/PhOH	55/12	 7	74
3	 3	PPh_3/PhOH	55/14	 8	75
4	 4	PPh_3/PhOH	55/14	 9	88
5	 5	PPh_3/PhOH	25/14	 10	85
6	 5	PPh_3/AcOH	25/14	 10	17 + SM
7	 6	PPh_3/PhOH	25/14	 11	80

catalytic system for the isomerizations of enyne esters to (*E,E,E*)-triene esters.

Experimental Section

General Experimental Details. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230–400 mesh).[8] Commercial CH_2Cl_2 was distilled from CaH_2 under N_2. Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals the number of carbon atoms are given in parentheses.

Methyl (2*E*,4*E*,6*E*)-Trideca-2,4,6-trienoate (7). Ester 1 (200 mg, 0.90 mmol) was dissolved in 0.90 mL of benzene. PPh_3 (236 mg, 0.90 mmol) and phenol (85 mg, 0.90 mmol) were added to this solution. The mixture was warmed to 55 °C and stirred for 12 h. The solution was cooled to ambient temperature and diluted with ether and 1 N NaOH. The layers were separated, and the aqueous layer was extracted with ether (2×). The combined organic layers were washed (water, brine) and dried ($MgSO_4$). The solution was filtered, concentrated under reduced pressure, and purified by flash chromatography (SiO_2, 5% EtOAc/hexanes) to give 140 mg (0.63 mmol, 70%) of the product as a yellow oil: IR (neat) 1719, 1618, 1004 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 15.3, 11.5 Hz, 1 H), 6.53 (dd, *J* = 14.7, 10.6 Hz, 1 H), 6.22 (dd, *J* = 15.0, 11.5 Hz, 1 H), 6.19 (dd, *J* = 15.0, 10.6 Hz, 1 H), 5.93 (dt, *J* = 14.4, 7.1 Hz, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 3.81 (s, 3 H), 2.10 (dt, *J* = 14.1, 7.0 Hz, 2 H), 1.46–1.21 (m, 8 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 167.6; *C*H 145.1, 141.4, 140.8, 132.6, 129.8, 127.7; CH_2 33.0, 31.7, 30.0, 28.9, 22.6; CH_3 51.4, 14.1; HRMS (CI-NH_3) calcd for $C_{14}H_{22}O_2$ (M + H^+) 223.1698, found 223.1696.

Methyl (2*E*,4*E*,6*E*,11*R*)-11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]dodeca-2,4,6-trienoate (8): yield 75%; IR (neat) 1719, 1645, 1619, 1004, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 15.3, 11.3 Hz, 1 H), 6.12 (dd, *J* = 15.3, 11.0 Hz, 1 H), 5.91–5.82 (m, 3 H), 5.54 (dt, *J* = 14.5, 7.0 Hz, 1 H), 3.61 (m, 1 H), 3.38 (s, 3 H), 1.88 (m, 2 H), 1.38 (m, 2 H), 1.25 (m, 2 H), 1.12 (d, *J* = 6 Hz, 3 H) 0.97 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) δ *C* 166.9, 18.2; *C*H 144.9, 140.9, 139.7, 130.3, 128.2, 120.3, 68.5; CH_2 39.4, 33.1, 25.3; CH_3 26.0, 23.9, −4.3, −4.6; HRMS (EI-CH_4) calcd for $C_{19}H_{34}O_3Si$ (M^+) 338.2277, found 338.2278. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12. Found: C, 67.17; H, 10.00.

(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Methyl (2*E*,4*E*,6*E*)-14-(2,2-dimethyl-1,3-dioxolan-4-yl)tetradeca-2,4,6-trienoate (9): yield 88%; IR (neat) 1709, 1619, 1007 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.49 (dd, *J* = 15.3, 11.3 Hz, 1 H), 6.20 (dd, *J* = 15.1, 10.7 Hz, 1 H), 5.97-5.89 (m, 3 H), 5.59 (dt, *J* = 14.3, 6.6 Hz, 1 H), 3.91–3.90 (m, 1 H), 3.84–3.80 (m, 1 H), 3.46 (s, 3 H), 3.41–3.33 (m, 2 H), 1.95–1.82 (m, 2 H), 1.52 (m, 1 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.29–1.05 (m, 10 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) δ *C* 166.8, 108.4; *C*H 145.1, 141.2, 140.0, 130.4, 128.4, 120.4, 76.3; CH_2 69.8, 34.1, 33.2, 29.9, 29.8, 29.5, 29.3, 26.3; CH_3 51.0, 27.4, 26.1; HRMS (CI-CH_4) calcd for $C_{20}H_{32}O_4$ (M + H^+) 337.2379, found 337.2369. Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.44.

Ethyl (2*E*,4*E*)-Undeca-2,4-dienoate (10). Ester 4 (200 mg, 0.95 mmol) was dissolved in 0.95 mL of benzene. PPh_3 (249 mg, 0.95 mmol) and phenol (89 mg, 0.95 mmol) were added to this solution. After being stirred for 14 h at ambient temperature, the solution was diluted with ether and 1 N NaOH. The layers were separated, and the aqueous layer was extracted with ether (2×). The combined organic layers were washed (water, brine) and dried ($MgSO_4$). The solution was filtered, concentrated under reduced pressure, and purified by flash chromatography (SiO_2, 2% EtOAc/hexanes) to give 170 mg (0.81 mmol, 85%) of the product as a yellow oil: IR (neat) 1715, 1644, 1000 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.50 (dd, *J* = 15.3, 10.9 Hz, 1 H), 5.94–5.86 (m, 2 H), 5.68 (dt, *J* = 14.1, 7.0 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 1.82–1.80 (m, 2 H), 1.22–1.13 (m, 8 H), 1.01 (t, *J* = 7.1 Hz, 3 H), 0.88 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) δ *C* 167.2; *C*H 145.0, 144.7, 128.3, 119.1; CH_2 60.1, 33.0, 31.6, 28.8, 28.6, 22.5; CH_3 14.3, 14.0; HRMS (CI-CH_4) calcd for $C_{13}H_{22}O_2$(M + H^+) 211.1698, found 211.1713. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.12; H, 10.33.

Ethyl (2*E*,4*E*)-14-(2,2-dimethyl-1,3-dioxolan-4-yl)tetradeca-2,4-dienoate (11): yield 80%; IR (neat) 1715, 1643, 1617, 1001 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.49 (dd, *J* = 15.3, 10.9 Hz, 1 H), 5.96–5.88 (m, 2 H), 5.70 (dt, *J* = 14.3, 6.9 Hz, 1 H), 4.07 (q, *J* = 7.1 Hz, 2 H), 3.95–3.87 (m, 2 H), 3.82 (dd, *J* = 7.6 Hz, 1 H), 3.36 (dd, *J* = 7.6 Hz, 1 H), 1.84–1.79 (m, 2 H), 1.54–1.50 (m, 1 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 1.29–1.03 (m, 10 H), 1.01 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) δ *C* 166.7, 108.7; *C*H 145.0, 144.0, 128.7, 119.9, 76.2; CH_2 69.7, 60.0, 33.9, 33.0, 29.8, 29.6, 29.2, 28.6, 26.2; CH_3 27.3, 26.0, 14.3. Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.15; H, 9.79.

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