Novel "Umpolung" in C–C Bond Formation Catalyzed by Triphenylphosphine

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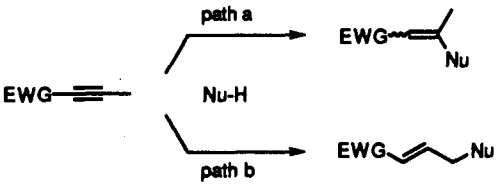
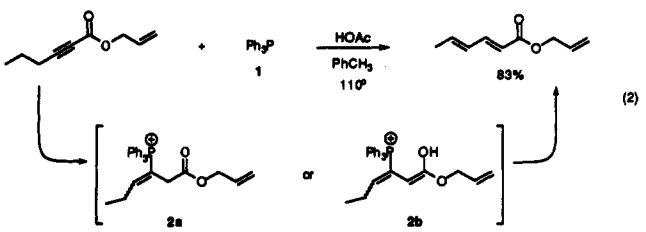
The Michael addition whereby a nucleophile adds in conjugate fashion to the α,β-unsaturated carbonyl and related compounds as illustrated in eq 1, path a, for an acetylenic acceptor constitutes one of the most important fundamental synthetic reactions in organic chemistry.[1] In contrast to the activation of the β-carbon



(1)

as an electrophile by such conjugation with an electron-withdrawing group, this same conjugation normally promotes deprotonation of the γ-carbon and thereby its behavior as a nucleophile. Our flexibility to construct complex molecules would be aided if we could effect an "umpolung" whereby the γ-carbon might also function as an electrophile. We report that just this unprecedented behavior is observed when triphenylphosphine (**1**) is used as a catalyst.[2]

We previously reported the ability of triphenylphosphine to catalyze the isomerization of ynoates to dienoates as illustrated in eq 2.[3,4] To rationalize this remarkable reaction, we hypothesized



(2)

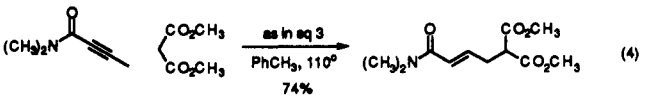
that a vinylphosphonium species such as **2a** or its enol **2b** may be involved. In such a species, the γ-carbon of the initial ynoate becomes electrophilic. If the isomerization to the diene is precluded by using a shorter alkyl chain, then such a species may be captured by a nucleophile.

Heating a 1:1 mixture of methyl 2-butynoate and dimethyl malonate in toluene with 35 mol % of **1**, 50 mol % of acetic acid, and 50 mol % of sodium acetate at 80 °C gave a 59% isolated yield of a 1:1 adduct. The spectroscopic properties clearly establish the structure of the adduct as **3**.[5] Notably, the ^{1}H NMR spectrum shows the absence of any CCH_3 groups and the presence of the (*E*)-enoate (δ 6.85, dt, J = 15.6, 7.2 Hz, 1H; δ 5.88, d, J = 15.6 Hz, 1H). While we had adopted the use of 35 mol % of **1** as our standard, we have subsequently found that 5 mol % gave a slightly higher yield (63%) in the same time period (20 h), whereas 1 mol % led to a 29% yield in the same time frame.

(3)

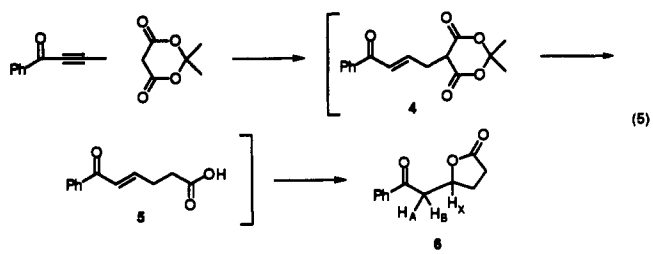
The remarkable facility of this process led us to investigate the range of pronucleophiles that may participate as shown in Scheme 1. In all cases, only the *E* olefins are observed. In general, pronucleophiles for which $pK_a < 16$ serve satisfactorily. Introducing an alkyl group on the acidic carbon of the pronucleophile compromised the yield as illustrated in the comparison of dimethyl malonate and diethyl methylmalonate. Both the lower kinetic acidity of the pronucleophile and the increased steric hindrance of the resultant nucleophile may be responsible. Increasing the kinetic acidity by using a β-keto ester and minimizing steric hindrance by using a cyclic structure as in the cases of 2-(methoxycarbonyl)cyclohexanone and 2-acetyl-γ-butyrolactone restore the yields to >70%.

Replacing the ester of the acetylenic acceptor by the less electrophilic amide led to smooth nucleophilic γ-addition of malonate anion in toluene at reflux (eq 4). On the other hand,



(4)

using a more strongly electron withdrawing group like a ketone required a kinetically more effective pronucleophile than dimethyl malonate. Indeed, 1-phenyl-2-butyn-1-one condenses with Meldrum's acid to give a product which is not a simple 1:1 adduct in 55–60% yield. Elemental composition establishes the formula as $C_{12}H_{12}O_3$. The infrared and ^{13}C NMR spectra indicate the presence of a γ-butyrolactone (1774 cm^{-1}, δ 176.6) as well as the benzoyl group (1685 cm^{-1}, δ 196.2). The ^{1}H NMR spectrum shows an ABX pattern at δ 3.25, 3.64, and 5.20 with J_{AB} = 17.4 Hz, J_{AX} = 7.5 Hz, and J_{BX} = 5.2 Hz. The data indicate the product to be the lactone **6**,[5] which derives from cleavage of the expected initial adduct **4** to the acid **5**, which cyclizes to give the thermodynamically more stable product **6**.



(5)

The ability of triphenylphosphine to impart electrophilic character to the γ-carbon of acetylene bearing an ester, amide, or ketone substituent results in a regiochemical complement of the Michael reaction. Triphenylphosphine cannot be simply serving as a base to deprotonate the pronucleophile since simple Michael addition would be expected. Scheme 2 outlines a potential mechanism in which the role of triphenylphosphine is proposed as a nucleophilic trigger.[6] Other arylphosphines like tris(2,6-dimethoxyphenyl)phosphine, tris(2-methoxyphenyl)phosphine, and 1,3-bis(diphenylphosphino)propane also function, but

(1) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Vol. 4, Chapter 1.1, pp 1–68. Lee, V. J. *Idem.*; Chapter 1.2, pp 69–138; Chapter 1.3, pp 139–168. Kozlowski, J. A. *Idem.*; Chapter 1.4, pp 169–198. Schmalz, H. G. *Idem.*; Chapter 1.5, pp 199–236. Hulce, M.; Chapdelaine, M. J. *Idem.*; Chapter 1.6, pp 237–268.

(2) Kirby, A. J. The Organic Chemistry of Phosphorus; Elsevier Pub. Co.: Amsterdam, 1967.

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

(4) Also see: Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921.

(5) This compound has been fully characterized spectroscopically and its elemental composition established by combustion analysis and/or high-resolution mass spectroscopy.

(6) Hanemoto, T.; Baba, Y.; Inanaga, J. *J. Org. Chem.* **1993**, *58*, 299. Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. Roth, F.; Gygax, P.; Frater, G. *Tetrahedron Lett.* **1992**, *33*, 1045. Also see: Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. Miyakoshi, T.; Saito, S. *Nippon Kagaku Kaishi* **1983**, 1623. Imayawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M. *Synth. Commun.* **1984**, *14*, 1267.

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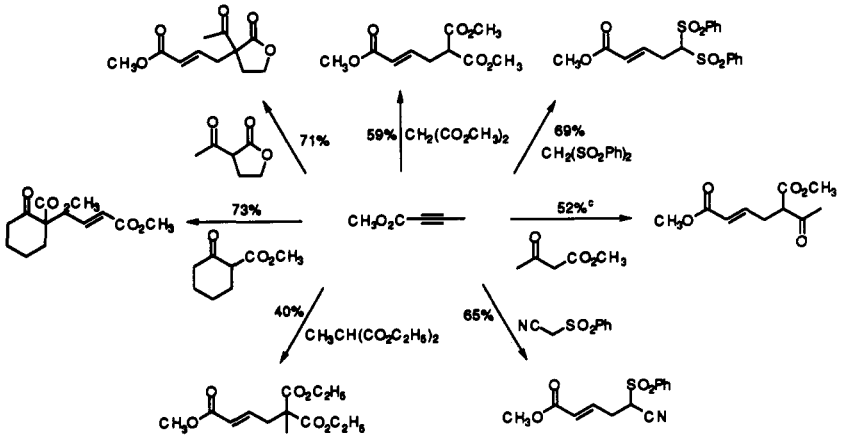
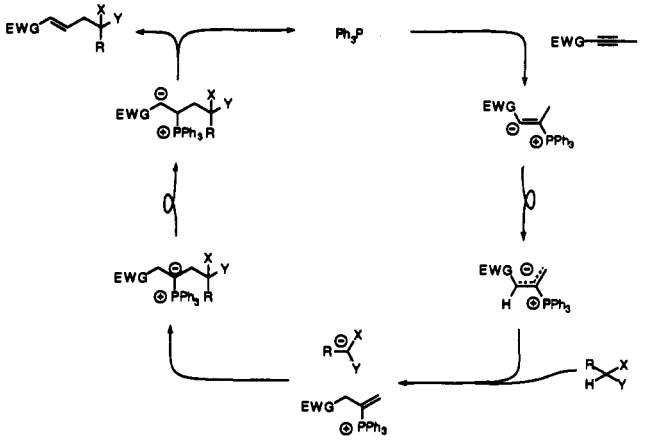
Scheme 1. γ-Addition to an Ynoate by Pronucleophiles[a,b]



[a] All reactions were run using 35 mol % of triphenylphosphine, 50 mol % of acetic acid, and 50 mol % of sodium acetate in toluene at 80 or 110 °C unless otherwise noted. [b] For all new products, see ref 5. [c] In this case, 1 equiv of sodium acetate was employed.

Scheme 2. Rationale for Nucleophilic γ-Addition to Acetylenes Bearing Electron-Withdrawing Groups



no advantage is obvious. On the other hand, the aliphatic phosphine, tri-*n*-butylphosphine, appears to be too nucleophilic and led only to uncharacterized oligomers. The requirement for protonation–deprotonation at various stages determines the pH range in which acetic acid–sodium acetate fulfills the needs. Thus, the pronucleophile must be able to serve as a nucleophile in this pH range. For carbon nucleophiles, malonic esters appear to be the upper limit. This approach to adjust the electronic nature of an electron deficient acetylene whereby nucleophilic γ-addition becomes feasible represents a new type of addition process which contributes to synthetic efficiency by providing both unprecedented regioselectivity and atom economy.

A typical experimental procedure follows: A mixture of methyl 2-butynoate (98 mg, 1.0 mmol), dimethyl malonate (132 mg, 1 mmol), triphenylphosphine (13 mg, 0.05 mmol), acetic acid (30 mg, 0.5 mmol), and sodium acetate (42 mg, 0.5 mmol) in 2 mL of toluene was heated at 80 °C for 20 h under nitrogen. Upon cooling, the reaction mixture was filtered and the solid was washed with ether. The combined organic fractions were concentrated, and the residue was purified by column chromatography (hexane/ethyl acetate, 5:1) on silica gel to give 145 mg (63% yield) of dimethyl 5-(methoxycarbonyl)-2-hexenedioate (**3**).

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Supplementary Material Available: Spectroscopic and analytical data for all products (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.