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Organic Synthesis with Trialkylphosphine Catalysts. Conjugate Addition of Alcohols to α,β-Unsaturated Alkynic Acid Esters

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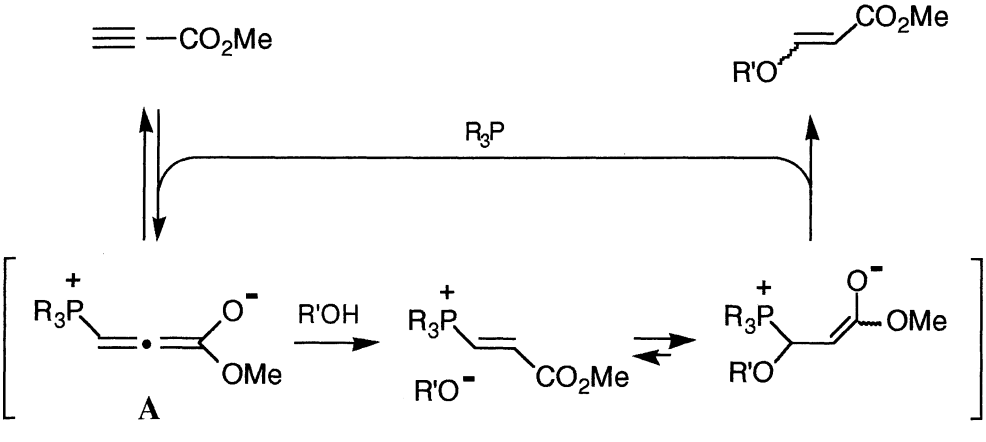
The conjugate addition of alcohols to α,β-unsaturated alkynic acid esters proceeds under neutral conditions in the presence of a catalytic amount of trialkylphosphine to give the corresponding β-alkoxy-α,β-unsaturated alkenic acid esters in good to excellent yields.

Although organophosphorus compounds have been widely used in organic synthesis as useful reagents (e.g., in Wittig and related reactions and in some deoxygenation reactions) as well as effective ligands of a number of transition metal catalysts, there are few reactions in which organophosphorus(III) species work as catalysts.[1] We report here an efficient trialkylphosphine-catalyzed addition of alcohols to α,β-unsaturated alkynic acid esters.[2,3]

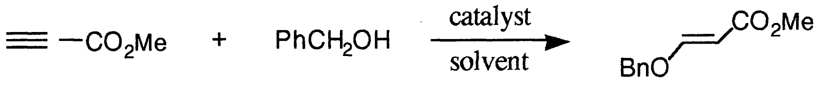
As shown in Scheme 1, we assumed that when a trialkylphosphine attacked the β-carbon of methyl propiolate to give the phosphonium enolate intermediate (A),[4] it then abstracted protons from alcohols (R'OH) to form the corresponding phosphonium alkoxides. Conjugate addition of the alkoxy anions to the β-trialkylphosphonium acrylate counterpart followed by elimination of the phosphine to be recycled as a catalyst would afford the 3-alkoxyacrylates as the final products.



Scheme 1.

According to the above working hypothesis, the reaction of methyl propiolate with benzyl alcohol was first examined on the catalytic activity of a series of organophosphorus(III) compounds in various solvents.[5] The results are listed in Table 1. Among the catalysts examined, tributylphosphine gave the best results as expected from its high nucleophilicity. The reactions were completed within 10 min at room temperature to afford methyl 3-benzyloxyacrylate almost quantitatively in perfect *E*-stereoselectivity (Entries 6 and 7). No considerable solvent-effect was observed as far as tributylphosphine was employed as a catalyst.

Table 1. Examination of Catalysts and Solvents [a)]



Entry	Catalyst [b)]	Solvent	Time	Yield[c)]/%	*E* / *Z* [c)]
1	PPh_3	PhH	8 h	86	3 / 1
2	PPh_3	CH_2Cl_2	8 h	85	5 / 1
3	PPh_3	THF	8 h	62	3 / 1
4	PPh_3	CH_3CN	8 h	>98	5 / 1
5	PBu_3	PhH	10 min	83	*E*
6	PBu_3	CH_2Cl_2	10 min	>98	*E*
7	PBu_3	THF	10 min	>98	*E*
8	PBu_3	CH_3CN	10 min	>98	99 / 1
9	$P(c\text{-Hex})_3$	CH_3CN	2 h	66	7 / 1
10	$P(OMe)_3$	CH_3CN	8 h	N.R.	

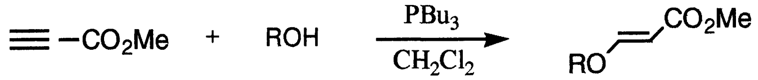
a) The reactions were performed at room temperature. b) The catalyst (0.1 equiv.) was used.
c) Determined by ^1H NMR (400 MHz) analysis.

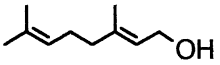
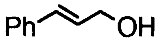
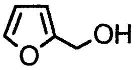
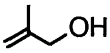
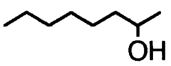
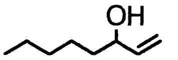
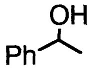
A variety of alcohols were found to react with methyl propiolate under the optimized conditions as summarized in Table 2. The reaction with primary, secondary allylic, benzylic, and homoallylic alcohols completed within 10 min at room temperature to give the corresponding 3-alkoxyacrylates in good to excellent yields. A thiol also reacted rapidly. However, saturated secondary alcohols and tertiary alcohols hardly reacted. Some attempts to make a carbon-carbon bond by using dimethyl malonate or related compounds as possible carbon nucleophiles in place of alcohols failed under similar conditions. These results seem to indicate that nucleophiles having suitable acidity and small steric requirement are essential to accomplish this catalytic reaction.

A β-substituted alkynic acid ester also reacted with benzyl alcohol to give the corresponding trisubstituted olefin with *E*-geometry (Eq. 1). In this case, trimethylphosphine was found to be a better catalyst probably because of its smaller steric requirement.

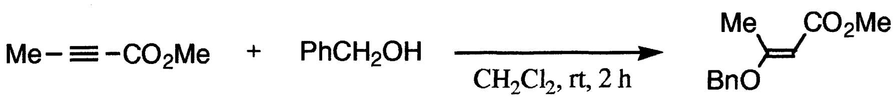
There have been three precedents concerning the conjugate addition of alcohols to propiolates, in which N-methylmorphorine,[3a)] sodium cyanide,[3b)] or copper(I) triflate[3c)] was employed as the catalyst, respectively. However, they require longer reaction time (20 h – 4 days) and/or the use of stoichiometric amount of the catalysts.

Table 2. PBu_3-Catalyzed Conjugate Addition of Alcohols to Methyl Propiolatea)



Entry	ROH	Time / min	Yieldb)/%	E / Zc)
1		10	>98	11 / 1
2		3	91	*E*
3		5	90	*E*
4		5	>98	*E*
5d)		10	96	*E*
6d)	$\equiv$-CH_2OH	10	95	*E*
7		30	14	*E*
8		10	53	*E*
9		10	96c)	*E*
10e)	Cholesterol	10	82	*E*
11	n-$C_{18}H_{37}SH$	3	95	*E*

a) The reactions were carried out at room temperature in CH_2Cl_2 (2 mL) under argon by using methyl propiolate (0.2 mmol), alcohols (0.2 mmol), and PBu_3 (0.03 mmol) unless otherwise stated. b) Isolated yield. c) Determined by ^1H NMR (400 MHz) analysis. d) PBu_3 (0.2 equiv.) was used. e) PBu_3 (0.5 equiv.) was used.

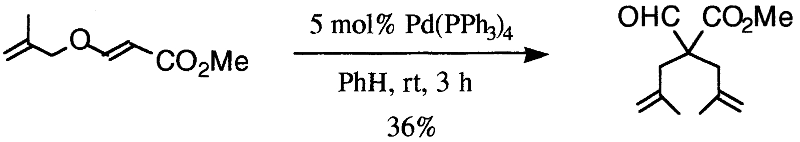
 (1)

PBu_3 (0.2 equiv.) 67%

PMe_3 (0.2 equiv.) 76%

The present method seems superior to the precedents in terms of mildness, gererality, and efficiency of the reaction.

3-Alkoxyacrylate derivatives thus obtained are potentially useful synthetic intermediates because they possess the contiguous three carbon unit with different oxidation states. Actually, one of them (methyl 3-methoxyacrylate) has been used for the synthesis of a variety of heterocyclic compounds in the field of chemical industry.6) As another application, a palladium-catalyzed reaction of methyl 3-methallylacrylate is shown in Eq. 2.7)



(2)

Since phosphonium enolates are readily obtainable from α,β-unsaturated carbonyl compounds and trialkylphosphine catalysts under neutral conditions, they should find further application as useful synthetic intermediates.8)

References

1) For the dimerization of acrylates in the presence of a organophosphorus(III) catalyst, see: F. Myman, Brit. Patent 1100350 (1965), *Chem. Abstr.*, **69**, 10093w (1968); S. Kitazume, *Japan Kokai*, 77, 105, 115 (1977), *Chem. Abstr.*, **88**, 89131f (1978); J. W. Nemec, R. B. Wuchter, U. S. Patent 4145559 (1979), *Chem. Abstr.*, **91**, 4960q (1979); H. Amri and M. Rambaud, J. Villieras, *Tetrahedron Lett.*, **30**, 7381 (1989).

2) A part of this work was presented at the 59th National Meeting of Chemical Society of Japan, Yokohama, April 1990, Abstr., No. 4D816.

3) For similar transformations, see a) E. Winterfeldt, *Chem. Ber.*, **97**, 1952 (1964); E. Winterfeldt and H. Preuss, *ibid.*, **99**, 450 (1966); b) J. S. Walia and A. S. Walia, *J. Org. Chem.*, **41**, 3765 (1976); c) S. H. Bertz, G. Dabbagh, and P. Cotte, *ibid.*, **47**, 2216 (1982).

4) H. Hoffmann and H. J. Diehr, *Chem. Ber.*, **98**, 363 (1965); M. A. Shaw, J. C. Tebby, R. S. Ward, and D. H. Williams, *J. Chem. Soc., C*, **1968**, 2795.

5) Some other trivalent compounds of 15th group elements were also tested. While triphenylantimony and triphenylbismuth did not show catalytic acitivity, some amines such as DMAP, pyridine, triethylamine, and diisopropylethylamine did catalyze the reaction in some extent: DMAP (8 h, 98%), Py (10 h, 45%), Et_3N (1 h, 73%), $(i\text{-}Pr)_2NEt$ (15 h, 13%), and DBU (15 h, 0%). The results strongly support the working hypothesis shown in Scheme 1; i.e., the catalyst works as a nucleophile to produce the corresponding phosphonium (or ammonium) enolate, but not simply as a base to promote the formation of the alkoxide.

6) Industrially, methyl 3-methoxyacrylate is synthesized from methyl acrylate, methanol, and oxygen in the presence of palladium and methyl nitrite catalysts via the formation of 3,3-dimethoxypropionate. We thank Mr. M. Yamashita (Ube Industries, Ltd.) for the above information.

7) A palladium-catalyzed intramolecular rearrangement of similar systems has been reported. B. M. Trost, T. A. Runge, and L. N. Jungheim, *J. Am. Chem. Soc.*, **102**, 2840 (1980).

8) For phosphoniosilylation of enones and related reactions, see A. P. Kozikowski and S. H. Jung, *J. Org. Chem.*, **51**, 3400 (1986); S. Kim and P. H. Lee, *Tetrahedron Lett.*, **29**, 5413 (1988); T. Takanami, K. Suda, and H. Ohmori, *ibid.*, **31**, 677 (1990) and references cited therein.

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