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Stereoselective synthesis of hex-2-(*E*)-en-4-yn-1,6-dioates and *E*,*Z*-muconic acid diesters via organo-catalyzed self-coupling of propiolates

P. Veeraraghavan Ramachandran,* Michael T. Rudd and M. Venkat Ram Reddy

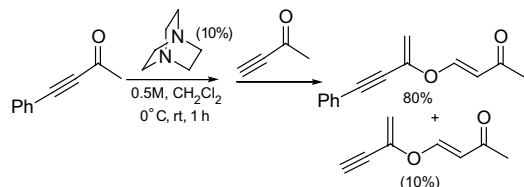*Department of Chemistry, 560 Oval Drive, Purdue University, West Lafayette, IN 47907-2084, USA*

Abstract—Alkyl propiolate couples with itself in the presence of catalytic DABCO under very mild conditions to provide a quantitative yield of *E*-hex-2-en-4-yne dioates. Hydrogenation of these enyne dioates using Lindlar catalyst provides the corresponding *E*,*Z*-diene dioate, a common structural motif found in an array of natural products.
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We had reported that, while attempting a Baylis–Hillman reaction of ethyl acrylate with α-acetylenic ketones, we stumbled upon a novel 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed coupling of acetylenic ketones via a carbon–oxygen bond yielding divinyl ethers.[1] This organo-catalysis reaction is feasible only when the terminus of the acetylene is free. We could extend this reaction to include the cross-condensation of terminal and internal acetylenic ketones under carefully controlled conditions (Scheme 1).[1]
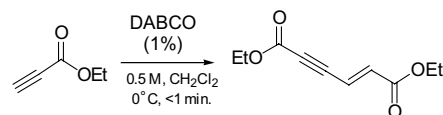
When we undertook to cross couple 4-phenyl-3-butyn-2-one with ethyl propiolate, we encountered an instantaneous, quantitative, and stereodefined self-condensation of the ester via a carbon–carbon bond to form diethyl *E*-2-en-4-yn-1,6-dioate (Scheme 2).

Scheme 2.

These types of conjugated *E*-enyne diesters and the corresponding *E*,*E*- or *E*,*Z*-diene diesters or their derivatives are part of several natural products.[2] For example, muconic acid ester is a precursor for the synthesis of macrocyclic trichothecane esters, a class of compounds belonging to potent cytostatic materials with known antibiotic, antifungal, antiviral, and antitumor properties. One such compound, verrucarin A is shown in Figure 1.[2] Apart from their synthetic potential, the corresponding diacids have been reported to exhibit bacteriostatic activity against *Bacillus subtilis*
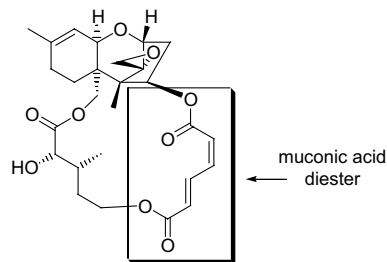

Scheme 1.

* Corresponding author. Tel.: +1 765 494 5303; fax: +1 765 494 0239; e-mail: chandran@purdue.edu

Figure 1. Verrucarin A.

and *Saccharomyces cerevisiae* at concentrations >0.2%.[3] These diacids are also useful as cross-linking agents for OH-containing materials, such as cellulose, and as intermediates for insecticides.[3] Accordingly, several syntheses of muconic acid diesters have been reported.[4]

A literature search revealed a stoichiometric reaction of methyl propiolate with triethylamine, *N*-methylpiperidine, or *N*-methylpyrrolidine to form the enyne dioate in moderate to high yields.[5] A patent also disclosed the dimerization of propiolate esters in the presence of 10% of a tertiary amine at temperatures ranging from −10 to 100 °C for several hours.[3,6] Numerous amines, including DABCO, pyridine and picoline were reported to be effective. It is surprising that there has been no earlier reference to this patent, although several applications of muconic acid esters have since been reported.

Our experiments established that long reaction times and extreme conditions are not necessary for the coupling. This study focused on the limitations of the instantaneous and catalyzed reaction. No influence of solvents was observed. Various amines, aromatic and aliphatic, were tested as organic catalysts. Differing from the claim in the patent, pyridine and picoline were ineffective for catalysis. TMEDA compares well with the efficacy of DABCO. However, DBU failed to catalyze the reaction (Table 1).

Examination of the catalytic turnover revealed that 0.1 mol % of DABCO is sufficient to catalyze the reac-

tion. Decreasing the catalyst further results in an incomplete reaction. We chose 1% catalyst at 0 °C as the standard condition for the reaction with the catalyst being removed at the end of the reaction by filtration through a pad of silica. We prepared a series of aromatic and aliphatic propiolate esters via DCC mediated esterification of propiolic acid, including esters from chiral alcohols. In all of the cases, we experienced no difficulty in forming the enyne diesters (Scheme 3). In fact, the reactions of aromatic esters were highly instantaneous and exothermic and were carried out under controlled conditions at low temperature.
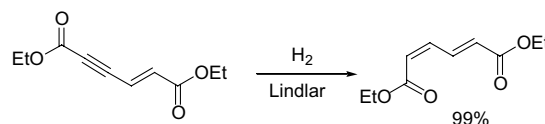
The proposed mechanism of the catalytic cycle is as follows (Scheme 4).

We converted a representative enyne diester, diethyl 2*E*-en-4-yn-1,6-dioate, to (*E*,*Z*)-muconic acid diester (Scheme 5). Hydrogenation using Lindlar catalyst provided the corresponding *E*,*Z*-diene dioate. Selective enzymatic hydrolysis of the *E*,*Z*-diester and conversion to various other difunctionalized dienes is known.[7] This diene has also been applied in Diels–Alder reactions.[8]
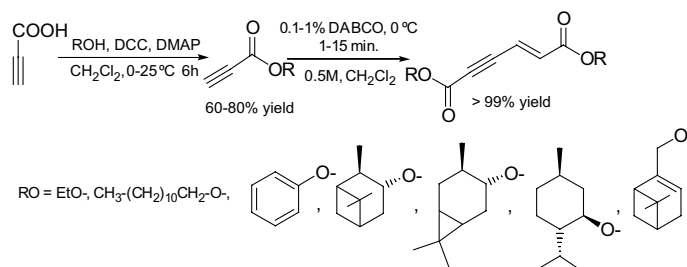
A typical experimental procedure for the preparation of diisopinocampheyl hex-2-(*E*)-en-4-yn-1,6-dioate and the corresponding *E*,*Z*-dienoate is as follows. To a solution

Table 1. Amine-catalyzed coupling of propiolates

Entry	Catalyst	% Catalyst	Solvent	Reaction time	% Conversion
1	DABCO	10	CH_2Cl_2	<1 min	99
2	DABCO	10	Hexane	<1 min	99
3	DABCO	10	EtOAc	<1 min	99
4	DABCO	10	CH_3CN	<1 min	99
5	DABCO	10	Toluene	<1 min	99
6	DABCO	10	THF	<1 min	99
7	Et_3N	10	CH_2Cl_2	<1 min	70
8	TMEDA	10	CH_2Cl_2	<1 min	90
9	DBU	10	CH_2Cl_2	1 h	0
10	Pyridine	10	CH_2Cl_2	1 h	0
11	Picoline	10	CH_2Cl_2	1 h	0
12	DABCO	1	CH_2Cl_2	<1 min	99
13	DABCO	0.1	CH_2Cl_2	15 min	96
14	DABCO	0.01	THF	24 h	80
15	DABCO	0.001	THF	24 h	20

Scheme 4.

Scheme 5.

RO = EtO-, CH_3-$(CH_2)_{10}CH_2$-O-,

Scheme 3.

of isopinocampheol (1.56 g, 10 mmol) and propiolic acid (0.65 g, 9.25 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a combined solution of DCC (1.91 g, 9.25 mmol) and DMAP (0.011 g, 0.0925 mmol) in CH_2Cl_2 (5 mL) over a period of 1 h. The reaction was stirred for an additional 5 h. The reaction mixture was then filtered, and washed with ether. Following evaporation of the solvents, the crude product was purified by silica gel chromatography (95/5 hexanes/ethyl acetate) to yield 1.44 g (75%) of the propynoate product. To a solution of isopinocampheyl propiolate (1.03 g, 5 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added DABCO (0.0056 g, 0.05 mmol). The reaction immediately turned dark, and was stirred for 15 min. The volatiles were then evaporated, and the crude reaction mixture was purified by silica gel chromatography (95/5 hexanes/ethyl acetate) to yield 1.02 g (99%) of the corresponding enyne product. To a stirred solution of enyne dioate (1.02 g, 2.5 mmol) and hexanes (5 mL) was added Lindlar catalyst (0.04 g), and quinoline (0.1 mL). The reaction flask was exposed to H_2(g) and the uptake of hydrogen was monitored. When the reduction was complete, the volatiles were evaporated, and the crude reaction mixture was purified by silica gel chromatography (95/5 hexanes/ethyl acetate) to yield 0.83 g (80%) of the corresponding diene product.

In conclusion, we have found that alkyl propiolates couple with themselves in the presence of 0.1 M equiv of DABCO under very mild conditions to provide a quantitative yield of *E*-hex-2-en-4-yne dioates. Hydrogenation of these enyne dioates using Lindlar catalyst provides the corresponding *E,Z*-diene dioate. We believe that this procedure will find applications in organic synthesis.

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