

THE REACTION OF ALKYL 4-HYDROXY-2-ALKYNOATES AND 4-HYDROXY-2-ALKYN-1-ONES WITH PALLADIUM  
TRIBUTYLAMMONIUM FORMATE AND WITH TRIBUTYLAMINE: PREPARATION OF 1,4-DICARBONYL COMPOUNDS

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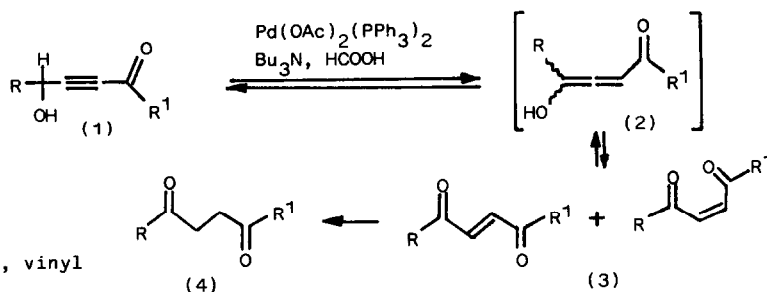
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**Summary** - Ethyl 4-oxo-2-alkenoates and 1,4-dioxo-2-alkenes are easily prepared by treating ethyl 4-hydroxy-2-alkynoates and 4-hydroxy-2-alkyn-1-ones with *n*-tributylamine. Treatment of ethyl 4-hydroxy-2-alkynoates and 4-hydroxy-2-alkyn-1-ones with palladium-tributylammonium formate produces ethyl 4-oxo-alkanoates and 1,4-alkandiones in good to high yield through a novel one-pot isomerization/hydrogenation reaction.

1,4-Dicarbonyl compounds are valuable intermediates in organic synthesis<sup>1</sup>. Moreover, 4-oxo-2-enoates and 1,4-dioxo-2-enes are important features of many naturally occurring macrocycles such as Vermiculine<sup>2</sup>, Pyrenophorin<sup>2</sup>, Cytochalasins A<sup>3</sup>, K<sup>4</sup>, L<sup>4</sup> and Aspochalasin B<sup>5</sup>.

Several methods for the synthesis of these compounds have been developed<sup>6</sup>. Many of them, however, follow lengthy procedures and/or use expensive chemicals and/or need starting materials not easy to prepare.

During our studies on the palladium-catalysed hydroarylation<sup>7,8</sup> and hydrogenation<sup>8</sup> of carbon-carbon multiple bonds in the presence of cheap formic acid and tributylamine we have found that easily available alkyl 4-hydroxy-2-alkynoates<sup>8-10</sup> and 4-hydroxy-2-alkyn-1-ones<sup>11</sup> (1) undergo facile isomerization/hydrogenation to give 1,4-dicarbonyl derivatives (4) (Table 1) most likely according to the following scheme:

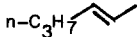
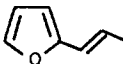

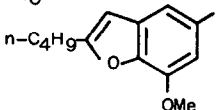

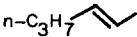


Scheme 1

Compounds (1) undergo base catalysed isomerization to an E/Z mixture of (3) through the allenyl alcohol (2) faster than palladium-catalysed hydrogenation of the carbon-carbon triple bond<sup>8,13</sup>. Then, palladium-catalysed hydrogenation of (3) produces saturated 1,4-dicarbonyl derivatives (4). When R is a vinyl group, hydrogenation occurs regioselectively on the carbon-carbon double bond between the carbonyl groups (Table 1, entries e,f,m).

Support to the scheme 1 is given by the isolation of the E/Z mixture of (3) after treating (1) with only tributylamine (Table 2). To our knowledge this very simple and mild reaction

Table 1 - Preparation of Ethyl 4-Oxo-alkanoates and Alkan-1,4-diones (4)

	Ethyl-4-hydroxy-2-alkynoates and 4-hydroxy-2-alkyn-1-ones (1)		Reaction time (h)	Yield % of (4) <sup>a,b</sup>
	R	R <sup>1</sup>		
a	Ph-	-OEt	5	65
b	4-Br-C <sub>6</sub> H <sub>4</sub> -	"	5	79
c	4-Me <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -	"	5	50
d	4-Me-C <sub>6</sub> H <sub>4</sub> -	"	3	79
e		"	3	71
f		"	3	74
g		"	4	82
h		"	5	62
i		-Ph	4	46
l	4-Me-C <sub>6</sub> H <sub>4</sub> -	"	4	61
m		"	2	41

a) Yields refer to single non-optimized runs, are calculated on the starting compounds (1) and are for pure, isolated products; b) All of new products gave spectroscopic data in agreement with proposed structures and satisfactory microanalyses.


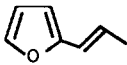
provides a novel entry into this important class of compounds. Trans-ethyl 4-oxo-4-phenyl-2-butenoate, easily available from benzaldehyde (Table 2), has been recently used as starting material in the synthesis of N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanine, a portion of many biologically active molecules.<sup>14</sup>

Furthermore, treatment of compounds (3) with palladium-tributylammonium formate under usual conditions affords compounds (4). As an example of this two-step process, the E/Z mixture (3b), isolated as described above, was subjected to palladium-catalysed hydrogenation to give the corresponding 1,4-dicarbonyl derivative (4b) in 90 % yield.

In some cases the equilibrium constant for transformation of (1) to (3) appears to be very low. However, palladium-catalysed reduction of (3) in the next step allows starting material flowing to (4) in good yield. This is the case of (1d) which gives very poor amounts of (3d) in the presence of tributylamine but reacts with palladium-tributylammonium formate producing (4d) in 79% yield.

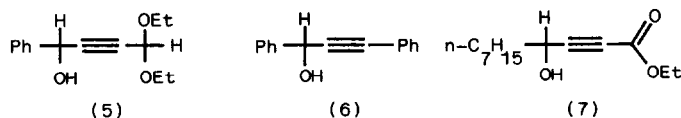
The presence of both carbonyl and aryl/heteroaryl/vinyl groups in the starting material has been proved necessary for the success of the reaction. Otherwise base catalysed isomerization of the propargylic system is prevented and usual hydrogenation of carbon-carbon triple bond can be observed. Compounds (5), (6) and (7) were recovered essentially unchanged after treatment with tributylamine and reaction of (7) with palladium-tributylammonium formate produced the

Table 2 - Preparation of Ethyl 4-Oxo-2-alkenoates and 1,4-Dioxo-2-alkenes (3)<sup>a</sup>

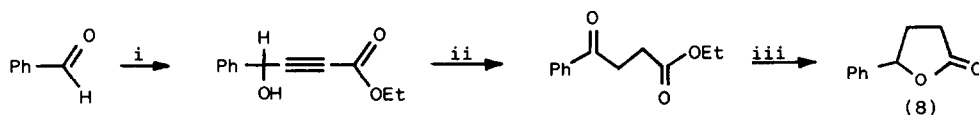
	Ethyl 4-hydroxy-2-alkynoates and 4-hydroxy-2-alkyn-1-ones (1)		Yield % of (3) <sup>b,c</sup>	
	R	R <sup>1</sup>	E isomer	Z isomer
a	Ph-	-OEt	67	8
b	4-Br-C <sub>6</sub> H <sub>4</sub> -	"	54	25
d <sup>d</sup>	4-Me-C <sub>6</sub> H <sub>4</sub> -	-Ph	12	4
f		-OEt	57	38
g		"	34	28

a) Reaction mixtures were usually worked-up after 0.5-1 h. b) Yields refer to single non-optimized runs, are calculated on the starting compounds (1) and are for pure isolated products. c) All of new products gave spectroscopic data in agreement with the proposed structures and satisfactory microanalyses. d) The starting material has been recovered in 67 % yield.

corresponding butenolide and/or saturated  $\gamma$ -lactone derivative through a one-pot reduction/cyclization process depending on the excess of formic acid<sup>8</sup>.



Application of our procedure to the synthesis of  $\gamma$ -phenyl- $\gamma$ -butyrolactone (8)<sup>15</sup> starting from benzaldehyde produced the target compound in 34 % overall yield<sup>16</sup>.



Scheme 2

In conclusion, the present method offers a new and, within its limitations, convenient access to 1,4-dicarbonyl compounds. Main features are the use of easily available starting materials, mild reaction conditions and safe and cheap reagents.

A typical procedure for the synthesis of (4) is as follows: to a stirred solution of 1f (0.252 g, 1.14 mmol), Bu<sub>3</sub>N (1.36 ml, 5.72 mmol), and Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.017 g, 0.023 mmol) in DMF (1 ml), HCOOH (0.17 ml, 4.44 mmol) was added all at once. The reaction mixture was stirred at 60°C for 3 h under argon. Then diethyl ether and 0.1 N HCl were added, the organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. Chromatography of the residue on silica gel (n-hexane/AcOEt 95/5 as eluant) gave (4f) (0.188 g, 74 % yield); mp = oil; IR (liquid film) 1730, 1670, 1620, 1070, 780 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  7.55 (m, 1H), 7.41 (A part of an AB system, J=16.5 Hz, 1H) 6.68 (B part of an AB system, J = 16.5 Hz, 1H), 6.73-6.46 (m, 2H), 4.17 (q, J = 7.5 Hz, 2H), 3.10-2.87 (m, 4H), 1.23 (t, J=7.5Hz, 3H); MS (m/e) 222, 177, 121.

A typical procedure for the synthesis of (3) is as follows: a solution of (1b) (0.5 g, 1.77

mmol) and  $\text{Bu}_3\text{N}$  (0.42 ml, 1.77 mmol) in DMF (1 ml) was stirred at room temperature for 0.5 h. Then diethyl ether and 0.1 N HCl were added, the organic layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated. Chromatography of the residue on silica gel (n-hexane/AcOEt, 90/10 as eluant) gave 0.271 g (54 % yield) of (3b), E isomer, and 0.127 g (25 % yield) of (3b), Z isomer. E isomer: mp = 59–61°C; IR (KBr): 1710, 1650, 1610, 820  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.91 (d,  $J=15.7$  Hz, 1H), 7.81 (AA'BB' system, 4H), 6.91 (d,  $J=15.7$  Hz, 1H), 4.32 (q,  $J=7.5$  Hz, 2H), 1.34 (t,  $J=7.5$  Hz, 3H); MS (m/e): 284, 282, 185, 183, 157, 155. Z isomer: mp = oil; IR (liquid film) 1725, 1680, 1590, 820  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.77 (AA'BB' system, 4H), 6.86 (d,  $J=12$  Hz, 1H), 6.30 (d,  $J=12$  Hz, 1H), 4.08 (q,  $J = 7.5$  Hz, 2H), 1.09 (t,  $J=7.5$  Hz, 3H); MS (m/e): 284, 282, 185, 183, 157, 155.

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