Tetrahedron Letters, Vol. 33, No. 47, pp. 7205-7206, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

A NOVEL REGIO- AND STEREO-SPECIFIC HYDROACETOXYLATION REACTION OF 2-ALKYNOIC ACID DERIVATIVES

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Abstract: 2-Alkynoic acid derivatives were hydroacetoxylated regio- and stereospecifically by reaction with lithium acetate in HOAc at rt under the catalysis of palladium acetate to afford 3-acetoxy-2(Z)-alkenoic acid derivatives.

The high reactivity of the carbon-carbon triple bond toward nucleophilic reagents is of great significance in many synthetic reactions.[1] Usually such addition reaction occurred non-stereoselectively. Recently, we reported a novel regio- and stereospecific hydrohalogenation reaction of 2-propynoic acid and its derivatives.[2] The nucleophility of acetate anion is similar to that of chloride anion.[3] The discovery of the stereospecific hydrohalogenation reaction of 2-propynoic acid derivatives attracts our interest to study the corresponding hydroacetoxylation reaction. On the other hand, the pure geometrical isomers of enol esters are very important precursors in stereoselective synthesis.[4,5] Herein, we wish to report a regio- and stereo-specific hydroacetoxylation reaction of 2-alkynoic acid derivatives with lithium acetate in HOAc in the presence of palladium acetate at rt to afford the thermodynamically unfavorable Z-enol acetates.

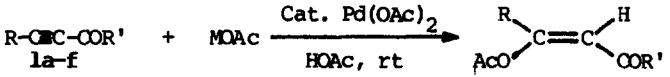
A general procedure is as follows: To a solution of alkynoate(1 mmol) and LiOAc(1 mmol) in HOAc(1 mL), $Pd(OAc)_2$(0.05 mmol) was added under stirring. The reaction mixture was stirred at rt until the alkynoate disappeared as monitored by TLC. Water(5 mL) was added, and the mixture was neutralized with solid K_2CO_3, extracted with ether and dried($MgSO_4$). The product 2 was isolated by preparative TLC on silica gel using petroleum ether/ethyl acetate as the solvent.

The results are summarized in the **Table.** The configuration of carbon-carbon double bond in the product was determined by ^1H NMR spectra, because the vinyl proton of the E-isomer appears at further downfield than that of the Z-isomer due to the deshielding effect of the cis acetoxy group.[6,7]

When the reaction between methyl 2-heptynoate (**1c**) and LiOAc was carried out in CF_3COOH in the presence of $Pd(OAc)_2$, only methyl 3-oxoheptanate(3) was obtained (entry 6). This may be due to the high acidity of CF_3COOH, which catalyzed the hydrolysis of the initial product 3-acetoxy-2-heptenoate(**2e**). 2-Butynamide could also react with NaOAc stereospecifically (entry 10). Complex reaction occurred from unsubstituted 2-propynoates and LiOAc in the same condition.

Reaction of acetic acid-d with benzyl 2-butynoate(**1a**) in the presence of two equivalents of LiOAc and a catalytic amount of $Pd(OAc)_2$ at rt for 14 h, afforded benzyl 3-acetoxy-2(Z)-2-d-butenoate in 87% yield, indicating that the vinylic hydrogen comes from the acid.

Table. Reaction of 2-Alkynoic Acid Derivatives



1a-f

2a-f

Entry	1			M	Time	Product	Isolated Yield
	No.	R	R'		(h)		(%)
1	**1a**	Me	OBn	Li	8.5	**2a**	78
2	1b	Me	OMe	Li	15	**2b**[a]	83
3	1b	Me	OMe	Na	2	**2b**	82.5
4	1c	n-Bu	OMe	Li	20	**2c**	83
5	**1c**	n-Bu	OMe	Na	12	**2c**	78
6[b]	**1c**	n-Bu	OMe	Li	5	3[c]	76
7	**1d**	Ph	OMe	Li	22	**2d**[d]	83
8	**1d**	Ph	OMe	Na	24	**2d**[d]	82
9	**1e**	Me	R'[e]	Li	30	**2e**	56
10	**1f**	Me	NH_2	Na	4.5	**2f**[a]	79

a. The configuration of double bond was assigned by comparing the ^1H NMR data with the literature value;[8] b. CF_3COOH was used as the solvent; c. Compound 3 is $n\text{-}C_4H_9COCH_2COOCH_3$. d. Z:E > 97:3; e. R'= $OCH_2CH{=}CHCH_2OH$.

The regio- and stereo-selective formation of the alkenylpalladium intermediate by trans attack of acetate anion at the coordinated carbon-carbon triple bond was postulated as the key step in this hydroacetoxylation.[9] The intermediate was trapped by proton with the retention of the configuration of the double bond to afford the product stereospecifically.

Acknowledgement: We thank the National Natural Science Foundation of China and The Laboratory of Orgmetallic Chemistry, Academia Sinica for financial support.

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(Received in China 20 July 1992)