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A CONVENIENT STEREOSELECTIVE SYNTHESIS OF CONJUGATED (2Z)-EN-4-YNOIC AND (2Z,4Z)- AND (2Z,4E)-DIENOIC ACID DERIVATIVES FROM PROPIOLIC ACID DERIVATIVES

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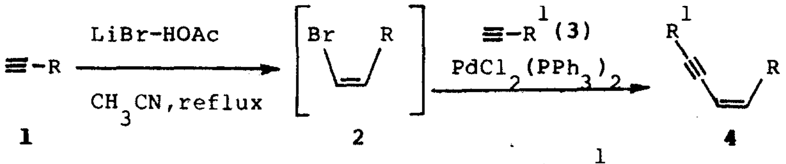
Abstract: The palladium-catalysed one-pot sequential reaction of propiolic acid derivatives with lithium halides first, and then with terminal alkynes or alkenes affords conjugated (2Z)-en-4-ynoic and (2Z,4Z)- and (2Z,4E)-dienoic acid derivatives with high stereoselectivity.

Stereodefined conjugated 2,4-dienoic acid and 2-en-4-ynoic acid derivatives[1] represent a class of important synthetic intermediates[2] and a wide variety of natural products of biological interest, such as sorbic acid, dehydromatricaria ester and arachidonic acid metabolites[3].

In recent years, many stereoselective synthetic methods for conjugated enynes and dienes have been developed[4], especially the cross-coupling reaction of vinyl halides with organometallic reagents[5]. All these methods suffer from the preparation of stereodefined vinyl halides, and organometallic reagents, which require lengthy procedures. Recently, a very convenient stereoselective method for the synthesis of 3-halo-(2Z)-propenoic acid derivatives was developed in our laboratory[6]. Based on this work, we developed a new, simple, and one-pot method for introducing a cis carbon-carbon double bond into organic molecule, i.e., the synthesis of (2Z)-en-4-ynoic and (2Z,4Z)- and (2Z,4E)-dienoic acid derivatives via palladium(0) catalysed cross-coupling reaction of propiolic acid derivatives under very mild condition with alkynes or alkenes.

For the synthesis of (2Z)-en-4-ynoic acid derivatives, a propiolic acid derivative was treated with lithium halide and acetic acid in acetonitrile first, without isolation, the mixture was allowed to undergo cross-coupling reaction with a terminal alkyne **3** in the presence of $PdCL_2(PPh_3)_2$ and CuI at rt in triethylamine[7] to afford conjugated (2Z)-en-4-ynoic acid derivatives **4**. It is noted that both lithium iodide and lithium bromide reacted smoothly, but lithium bromide was better. The coupling products showed high stereospecificity with high yields. The results are summarized in Table 1. The yields were slightly lower when $Pd(OAC)_2$, PPh_3 and Et_3N[8] were used as the catalytic system.

A typical procedure is as follows Lithium bromide(104 mg,1.2 mmol)was added to an acetonitrile(1 ml)solution of methyl propiolate(84 mg, 1 mmol) and acetic acid(66 mg,1.1 mmol). The mixture was then stirred and refluxed



1a: R=COOMe

1b $R=CONH_2$

1c: R=CN

3a: R^1=Ph

3b $R^1=n\text{-}C_4H_9$

3c $R^1=Me_3Si$

3d: $R^1=n\text{-}C_7H_{15}CH(OH)$

3e: $R^1=Me_2C(OH)$

3f $R^1=n\text{-}C_5H_{11}$

Table 1. Synthesis of (2Z)-En-4-yoic Acid Derivatives from Propiolic Acid Derivatives

1	3	Time(h)	Product	Isolated yield(%)[9]
1a	3a	6	**4aa**	85
1a	3b	6	**4ab**	84
1a	3c	6	**4ac**	77
1a	3d	5	**4ad**	80[a]
1a	3e	4	**4ae**	60[a]
1a	3f	6	**4af**	80
1b	3a	6	**4ba**	85
1b	3b	6	**4bb**	80
1b	3c	6	**4bc**	79
1b	3d	8	**4bd**	92
1b	3e	6	**4be**	82
1c	3a	8	**4ca**	90[b]

a. 2 eq Et_3N was added.

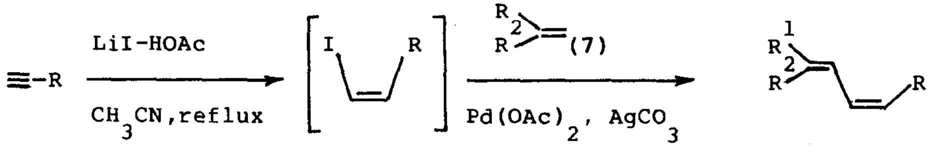
b. The reaction was carried out in a sealed tube.

for 22 h. After cooling, the mixture was purged with nitrogen, then phenylacetylene(153 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$(14 mg, 0.02 mmol), CuI(7.6 mg, 0.04 mmol)and triethylamine(4 ml) were added. The reaction was carried out at rt with stirring and monitored by TLC. After the reaction was complete, water(5 ml) was added. The mixture was extracted with ethyl acetate(3x10 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatograthy on silica gel(eluent:petroleum ether:ethyl acetate= 50:1) to afford the desired product **4aa**(160 mg, 85%).

It is worth noting that this method could also be used to synthesize (2Z)-en-4-ynamides (**4ba**-**4be**) which were rarely reported.

4 could be transformed into (2Z,4Z)-dienoic acid derivatives under suitable condition. As an example, methyl (2Z,4Z)-decadienoate 5, which was reported to show interesting biological activity[10], could be prepared by catalytic hydrogenation of methyl deca-(2Z)-en-4-ynoate **3af** over Lindlar catalyst in 87% yield[11].

From the above coupling reaction, it occurred to us that if an alkene is used instead of an alkyne, a (2Z,4E)-dienoic acid derivative might be prepared directly. Thus the intermediate 3-iodo-(2Z)-propenoic acid derivative **6** was treated with an alkene **7** in the presence of Pd(OAc)$_2$ and Ag$_2$CO$_3$[12], the reaction did give the desired product, (2Z,4E)-dienoic acid derivative **8** with high stereospecificity and high yield .



1 **6** **8**

1a R=COOMe

7a: R^1=COOMe R^2=H
7b: R^1=Ph R^2=H
7c: R^1=$COCH_3$ R^2=H
7d: R^1=CHO R^2=H
7e: R^1=COOMe R^2=CH_3

The title compouds, (2Z,4E)-dienoic acid derivatives are rarely reported. In our case, Heck's[13] and Jeffery's[4,14] catalytic systems were unsuccessful. The use of alkenyl iodides and Ag$_2$CO$_3$ as the base, which makes the reaction easier to occur at rt, might be responsible for the retaining of cis configuration from **6** to **8**. The results are shown in Table 2. Even with acrolein, which is easy to polymerize in Heck reaction[13], as an olefinic component, the reaction occurred in high yield and high stereospecificity.

Table 2. Synthesis of (2Z, 4E)-Dienoic Acid Derivatives from Propiolic Acid Derivatives[a]

1	**7**	Product	Isolated yield(%)[9]
1a	**7a**	**8aa**	81
1a	7b	8ab	94
1a	7c	8ac	75
1a	**7d**	**8ad**	89
1a	7e	**8ae**	50

a. All reactions were carried out for 24h.

A typical procedure is as follows: After preparing methyl 3-iodo-(2Z)-

propenoate(from methyl propiolate(84 mg, 1 mmol)) as described in ref. 6, the reaction mixture was purged with nitrogen, then acrolein (224 mg, 4 mmol), Ag_2CO_3 (414 mg, 1.5 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added. The reaction was carried out at rt with stirring and monitored by TLC. After the reaction was complete, the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate=15:1) to afford the desired product **8ad** (105 mg, 75%).

In conclusion, this procedure provides a method for introducing a cis carbon-carbon double bond into organic molecules with easy availability of the starting materials, simplicity of operation and high stereoselectivity, and will show its synthetic utility in organic chemistry.

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