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Enone Synthesis via Palladium Catalyzed Reductive Carbonylation of Terminal Acetylenes

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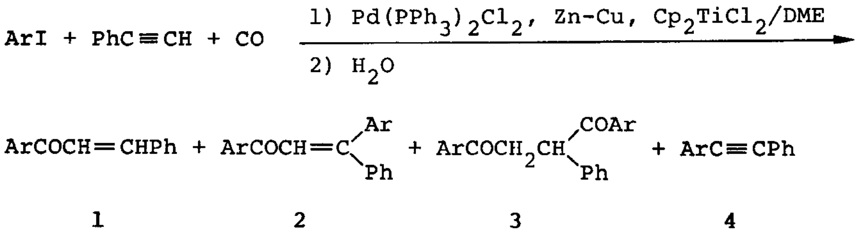
Summary: Aryl vinyl ketones are prepared by the reaction of aryl iodides and terminal acetylenes in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, Cp_2TiCl_2 and a stoichiometric amount of Zn-Cu under an atmospheric pressure of carbon monoxide.

Although there have been reported many examples of palladium catalyzed carbonylation reactions which provide carboxylic acids, esters and amides,[1] there seems to exist only a limited number of methods of ketone synthesis under carbonylation conditions.[2] Recently we developed a method of palladium catalyzed one-pot unsymmetrical ketone synthesis.[3] This reaction selectively produces alkyl aryl ketones by the coupling of alkyl iodides, aryl iodides and carbon monoxide. We have found that the above reaction, by the use of terminal acetylenes in place of alkyl iodides, also furnishes coupling products, but rather surprisingly the products were identified as aryl vinylic ketones. Here we report this novel reductive carbonylation of terminal acetylenes (eq 1 and 2).



$$\mathrm{ArI + PhC{\equiv}CH + CO} \xrightarrow[2)\ \mathrm{H_2O}]{1)\ \mathrm{Pd(PPh_3)_2Cl_2,\ Zn\text{-}Cu,\ Cp_2TiCl_2/DME}} \qquad (1)$$

$$\underset{\mathbf{1}}{\mathrm{ArCOCH{=}CHPh}} + \underset{\mathbf{2}}{\mathrm{ArCOCH{=}C}\genfrac{}{}{0pt}{}{\diagup \mathrm{Ar}}{\diagdown \mathrm{Ph}}} + \underset{\mathbf{3}}{\mathrm{ArCOCH_2CH}\genfrac{}{}{0pt}{}{\diagup \mathrm{COAr}}{\diagdown \mathrm{Ph}}} + \underset{\mathbf{4}}{\mathrm{ArC{\equiv}CPh}}$$

The carbonylation of aryl iodide and phenylacetylene was performed in the presence of catalytic amounts of bis(triphenylphosphine)palladium chloride and titanocene dichloride as well as a stoichiometric amount of zinc-copper couple. In the absence of titanocene dichloride, the reaction was slow, but gave almost the same yields and distributions of products. No acceleration of reaction was observed by the use of Cp_2ZrCl_2. Some representative results, together with the reaction conditions, are summarized in Table I. Generally, mixtures of four kinds of products, aryl styryl ketone **1**, aryl α-arylstyryl ketone **2**, 1,4-diaryl-2-phenylbutan-1,4-dione **3**, and aryl phenyl acetylene **4** were obtained. Methyl o-iodobenzoate afforded o-carbomethoxydiphenylacetylene as a sole product (46.4%), and no carbonylation products were detected. Although the selectivity among the carbonyl compounds **1**, **2**, and **3** is moderate, 4-methoxy- and 2-methylphenyl iodides furnished aryl styryl ketones in exceptionally high selectivities. Heteroaromatic compound such as 2-iodothiophene was also carbonylated to give 2-thienyl styryl ketone selectively.

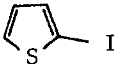
In contrast to these, the carbonylation of 1-hexyne with aryl iodides showed rather different reaction features, where aryl hexenyl ketones **5** were obtained selectively, and no carbonyl compounds corresponding to **2** and **3** were detected (eq 2). Results are summarized in Table II. Iodobenzene and 4- and 2-methyliodobenzenes provided enones **5** in respectable yields. The formation of a large amount of **6** was observed for 4-methoxyiodobenzene when reaction was quenched within 2 hours (entry 2). The amount of **6** could be reduced by conducting the reaction for a longer period of time, but this treatment did not improve the yield of **5** (entry 3). 1-Octyne reacted similarly, but methyl propiolate was unreactive and completely recovered.

$$\mathrm{ArI + BuC{\equiv}CH + CO} \xrightarrow[\text{2) } \mathrm{H_2O}]{\text{1) } \mathrm{Pd(PPh_3)_2Cl_2,\ Zn\text{-}Cu,\ Cp_2TiCl_2/DME}} \qquad (2)$$

$$\underset{\mathbf{5}}{\mathrm{ArCOCH{=}CHBu}} + \underset{\mathbf{6}}{\mathrm{ArCOC{\equiv}CBu}}$$

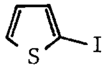
Vpc analysis of the reaction showed the increase of **1** and **5** at the expense of aryl phenylethynyl ketone and **6**, respectively. In order to get further insight into this process, the reaction mixture of entry 2 in Table I was quenched with CD_3CO_2D. Mass spectrum analysis of the resultant reaction mixture showed ca. 50 % monodeuteriation of **1** and no deuteriations of **2** and **3**. We were unable to determine the position of deuteriation in **1** spectroscopically, and hence the structure of 3-deutero-1,3-diphenyl-trans-2-propenone was determined as follows. The separated ketone **1** was reduced with $NaBH_4$ in ethanol. The structure of the thus obtained monodeuteriated alcohol was determined to be 3-deutero-1,3-diphenyl-trans-2-propenol on the basis of the disappearance of the signal

Table I. Palladium Catalyzed Reductive Carbonylation of Phenylacetylene[a]

entry	ArI	temp (°C)	time (h)	conv[b] (%)	product (% yield)[c]			
					1	2	3	4
1[d]	PhI	65	5	100	40	24	32	3
2	PhI	65	2	100	35	26	38	2
3	4-$MeOC_6H_4I$	60	3	82	81	-	-	5
4	4-MeC_6H_4I	65	2	100	41	tr	44	7
5	2-MeC_6H_4I	65	2	96	80	5	7	7
6	4-BrC_6H_4I	65	5	100	33	-	17	12
7		60	3	100	44	-	-	0

a) Usual scale is as follows: ArI (1.0 mmol), PhC≡CH (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.02 mmol), Cp_2TiCl_2 (0.04 mmol), Zn(Cu) (1.5 mmol) in 2.5 ml of dry DME under an atmospheric pressure of CO. b) Based on ArI, consumed. c) Yields are based on ArI, and hence the values in columns 7 and 8 should be devided by 2 for the comparison of molar ratios with columns 6 and 9. d) In the absence of Cp_2TiCl_2.

Table II. Palladium Catalyzed Reductive Carbonylation of 1-Hexyne[a]

entry	ArI	temp (°C)	time (h)	conv (%)	product (% yield)[b]	
					5	6
1	PhI	60	4	100	92	0
2	4-$MeOC_6H_4I$	60	2	97	50	23
3	4-$MeOC_6H_4I$	60	3	96	47	tr
4	4-MeC_6H_4I	60	4	100	69	tr
5	2-MeC_6H_4I	60	5	93	72	tr
6	4-BrC_6H_4I	60	4	100	50	0
7		60	4	100	54	7

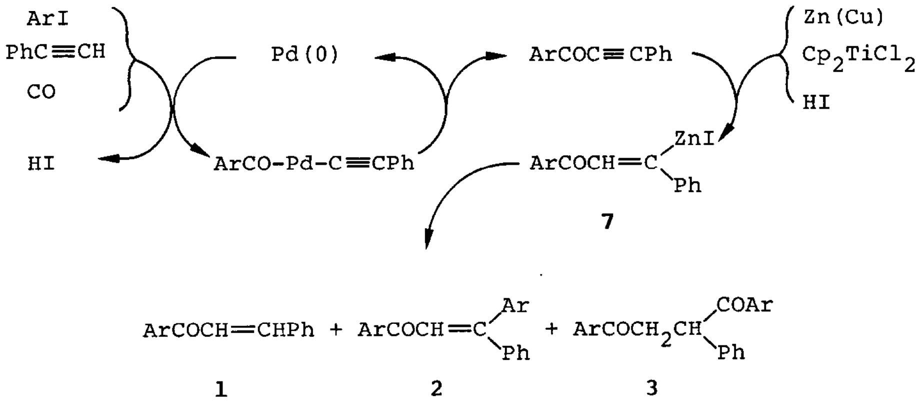
a) Usual scale is as follows: ArI (1.0 mmol), BuC≡CH (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.02 mmol), Cp_2TiCl_2 (0.04 mmol), Zn(Cu) (1.5 mmol) in 2.5 ml of dry DME under an atmospheric pressure of CO. b) Based on ArI, consumed.

corresponding to the α proton of styryl group in its ^{1}H NMR spectra. The trans structure followed from the large coupling constant (J = 16.4 Hz) as observed for the non-deuteriated alcohol.

All these observations suggest an intermediacy of vinylzinc compound 7 which might be generated via an electron transfer from Zn-Cu to aryl phenylethynyl ketone.[4] The vinylzinc 7 may afford 1 during hydrolytic workup or the monodeuteriated ketone when quenched with CD_3CO_2D. Also 7 is supposed to give 2 and 3 by the further reactions with arylpalladium complex and benzoylpalladium complex, respectively (Scheme I). We are currently investigating the utilization of this synthetically attractive vinylzinc intermediate 7.

A representative carbonylation was performed as follows: A mixture of $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), Cp_2TiCl_2 (10 mg, 0.04 mmol), and Zn-Cu (98 mg, 1.5 mmol) was purged with carbon monoxide (equipped with a CO balloon). Into this mixture was added a solution of an aryl iodide (1.0 mmol) and an acetylene (1.0 mmol) in 2.5 mL of dry dimethoxyethane via a syringe. The heterogeneous reaction mixture was immersed into an oil bath maintained at 65 °C and stirred for the period of time indicated in Tables I and II. After evaporation of the solvent, the reaction mixture was directly subjected to column chromatography (silica gel, n-hexane - ethyl acetate gradient) and products 1 - 4 and 5 - 6 were isolated in the yields shown in Tables I and II, respectively.

Scheme I



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(4) Aryl phenylethynyl ketone was reduced to phenyl styryl ketone (Zn-Cu 1.5 equiv. NH_4Cl 1.0 equiv. in THF-MeOH at 50 °C). The details will be reported shortly.

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