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A Palladium - Catalyzed Domino Reaction of 3-Acetyl-5-hexyn-2-one with Aryl Iodides under Carbon Monoxide.

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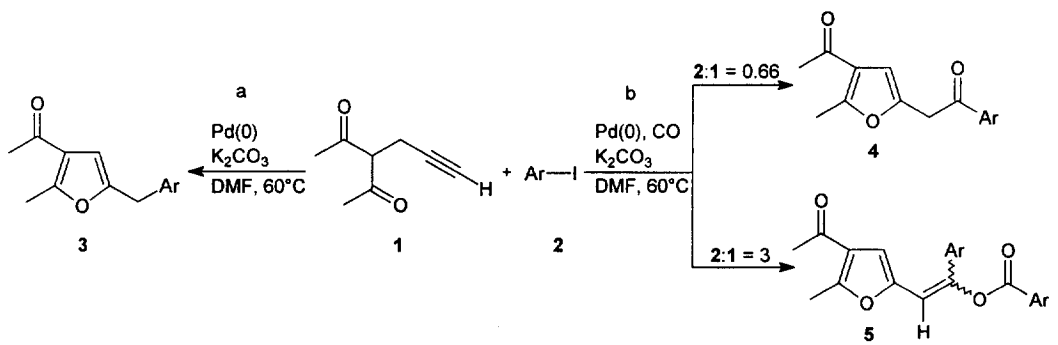
Abstract: The palladium-catalyzed reaction of 3-acetyl-5-hexyn-2-one with aryl iodides under a carbon monoxide atmosphere produces different 2,3,5-trisubstituted furans depending on the alkyne/aryl iodide ratio. Copyright © 1996 Published by Elsevier Science Ltd

The domino reactions are of increasing importance in synthetic organic chemistry[1] because they are more environmentally friendly than stepwise reactions in that they minimize production waste, energy and cost. The ability of triple bonds to undergo palladium-catalyzed additions affording intermediates capable of forming further **C-C** or **C-X** bonds according to the domino priciple, is emerging as a valuable tool in organic synthesis. Our continued interest in this area allowed us to develop new synthetic approaches to heterocycles through *in situ* hydroarylation(hydrovinylation)/cyclization reactions, [2] and through annulation reactions promoted by σ- vinyl, σ-aryl- [3] and σ-acylpalladium complexes. [4] Different sequential palladium-catalyzed reactions of compounds containing multiple **C-C** bonds with unsaturated halides/ triflates under a carbon monoxide atmosphere have been described.[5] Based on the results obtained in the palladium-catalyzed synthesis of 2,3,5-trisubstituted furans[3c] from the easily available[6] 3-acetyl-5-hexyn-2-one **1** with unsaturated triflates/halides in the presence of palladium (0) complexes and K_2CO_3 (Scheme 1a), we preliminary report that the same reaction under carbon monoxide could represent a versatile synthetic methodology to the synthesis of 2,3,5-substituted furans **4** (Scheme 1b).



Scheme 1

On the basis of the results obtained in the palladium-catalyzed synthesis of 2-subtituted-3-acylindoles and 2-substituted-3-acyl-benzo[b]furans, [4] we investigated the possible influence of ligands, temperature and 3-acetyl-5-hexyn-2-one **1**/ *p*-chlorophenyl iodide **2a** ratio (Table 1) on the reaction outcome.

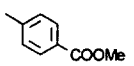
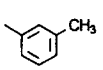
In essence, palladium complexes with weakly coordinated ligands gave satisfactory results. The use of $Pd(OAc)_2/P(0\text{-}tol)_3$, as a catalytic system, in acetonitrile, under a carbon monoxide atmophere at 60 °C and a **2/1** ratio = 0.66 (procedure A)[7] made possible the chemoselective synthesis of **4** (Table 2, entries a, c, j, l).

Table 1. Palladium-catalyzed Synthesis of 2,3,5-Trisubstituted Furans **4a** from **1** and **2a**.

entry	catalyst (palladium:ligand ratio)	Temp. (°C)	2:1 ratio	recovered **3** (% yield)[a]	recovered **4** (% yield)[a]	recovered **5** (% yield)[a]
a	$Pd(Ph_3)_4$	45	1.2	23	19	-
b	$Pd(OAc)_2$	45	1.2	2	54	-
c	$(C_6H_5CN)_2PdCl_2$	60	0.66	-	69	-
d	$Pd(dba)_2/P(o\text{-}tol)_3$ (1:4)	45	1.2	-	22	-
e	$Pd(OAc)_2/P(o\text{-}tol)_3$ (1:4)	45	1.2	-	33	-
f	"	r.t.	1.2	-	3	-
g	"	60	2	-	-	51
h	"	45	2	-	12	34
i	"	60	1.2	-	30	19
j	"	60	0.66	-	64	-
k	$Pd(OAc)_2/P(p\text{-}tol)_3$ (1:4)	60	0.66	20	17	-
l	$Pd(OAc)_2$/dppf (1:2)	60	0.66	21	18	-
m	$Pd(OAc)_2$/dppp (1:2)	60	0.66	-	33	-
n	$Pd(DIPHOS)_2$	60	0.66	23	47	-

[a] Unless otherwise stated, reactions were carried out in MeCN; yields referred to single runs and are for pure, isolated products.

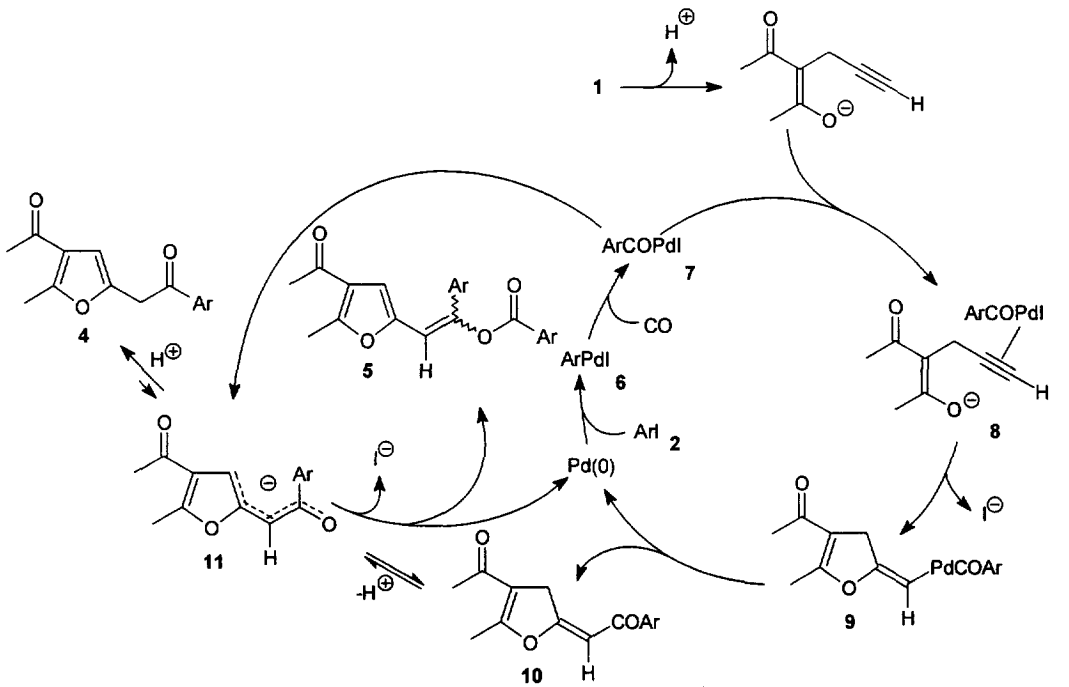
Table 2. Palladium-catalyzed Synthesis of Furans **4** and **5**.

entry	procedure	Ar	recovered **3** (% yield)	recovered **4** (% yield)	recovered **5** (% yield)
a	A		-	64	-
b	B	//	-	-	51
c	A		-	55	-
d	B	//	-	-	54[d]
e	A		21	33	-
f[a]	A	//	15	53	-
g[b]	A	//	4	41	-
h[c]	A	//	-	45	-
i	B	//	-	-	54
j	A	Ph	-	60	-
k	B	Ph	-	-	58[e]
l	A		-	60	-
m	B	//	-	-	57[f]

[a]pCO=1.5 atm. [b]pCO=2.0 atm. [c]2/1 ratio=0.5, pCO=2.0 atm.[d]E/Z=90:10. [e]E/Z=77:23. [f]E/Z=68:32.

The catalyst was prepared *in situ* from $Pd(OAc)_2$ and P(*o*-tol)$_3$ in a 1/4 ratio. We are uncertain, however, about the nature of the active catalyst and we have not investigated the effect of the Pd/P ratio on the course of the reaction. Both $Pd(OAc)_2$ and $(C_6H_5CN)_2PdCl_2$, in the absence of phosphine ligands, were, also, effective catalysts (Table 1, entries b,c), but their accidental precipitation may preclude the reproducibility of the results. Palladium complexes with more strongly coordinated ligands led to disappointing results, at least from a synthetic point of view and competitive non-carbonylative cyclization (Scheme 1a) was found to be a significant side reaction. In some case (Table 2, entries e,f,g) a slight increase of the pressure of carbon monoxide and a further lowering of **2/1** ratio (Table 2, entry h) is needed to achieve a higher chemoselectivity.

Mechanistically, the cyclization of 3-acetyl-5-hexyn-2-one **1** can be rationalized according to the following sequence: a) formation of the oxidative addition complex **6** from **2** and palladium (0) species generated *in situ*,[8] b) carbonylation of **6** to give the σ-acylpalladium intermediate **7**, c) generation of the π-alkynylpalladium complex **8**, d) generation of the σ-vinylpalladium complex **9** via regioselective trans addition of the oxygen and palladium across the carbon-carbon triple bond (*exo-dig* process), e)reductive elimination of Pd(0) to give **10**, and isomerization of **10** to **4** (Scheme 2). Upon changing the **2/1** ratio from 0.66 to 3 (Procedure B)[9] the further O-acylation[10] of **11** makes possible the formation, as the main reaction product, of enol esters **5** (Table 2, entries b, d, i, k, m) derived by the capture of acylpalladium intermediates **7**. To shed light on this point, **4a** was reacted with **2a** in acetonitrile, under a balloon of carbon monoxide, in the presence of the palladium catalyst and K_2CO_3, leading to the formation of **5a**.



Scheme 2

Enol esters **5** were mainly isolated as E isomers. The structure of compound **5** was assigned on the basis of spectroscopic data.[11] Vinyl protons in the E isomers are down field from vinyl protons in the Z isomers.

Further work is in progress to define the scope and limitations of these reactions.

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7. A typical procedure A is as follows: to a solution of **1**(0.2 g, 1.45 mmol) in anhydrous acetonitrile were added 4-chlorophenyl iodide **2a** (0.23 g, 0.96 mmol), K_2CO_3 (0.67 g, 4.82 mmol), $P(o\text{-}tol)_3$ (0.059 g, 0.19 mmol) and $Pd(OAc)_2$ (0.011 g, 0.05 mmol). The flask was purged with carbon monoxide for few seconds and connected to a balloon of carbon monoxide. The reaction mixture was stirred at 60 °C overnight and poured in a separatory funnel containing 0.1 HCl and ethyl acetate. The organic layer was separated and aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with 85/15 n-hexane/EtOAc mixture to give 0.169 g (64% yield) of **4a**: mp 109-110 °C; IR (Kbr) 1730, 1710 cm^{-1}; ^1H NMR δ 7.93 (AA' part of an AA'BB' system, J = 8.5 Hz, 2 H), 7.43 (BB' part of an AA'BB' system, J = 8.9 Hz, 2 H), 6.49 (s, 1 H), 4.25 (s, 2 H), 2.54 (s, 3 H), 2,37 (s, 3 H); ^{13}C NMR δ 193.9, 193.3, 156.0, 145.8, 140.1, 134.3, 129.9, 128.1, 122.4, 109.2, 37.8, 28.1, 14.3,; Ms m/e (relative intensiy) 276 (M^+, 4), 139 (100).
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9. A typical procedure B is as follows: to a solution of **1**(0.21 g, 1.52 mmol) in anhydrous acetonitrile were added 4-chlorophenyl iodide **2a** (0.0.724 g, 3.04 mmol), K_2CO_3 (1.05 g, 7.60 mmol), $P(o\text{-}tol)_3$ (0.092 g, 0.30 mmol) and $Pd(OAc)_2$ (0.017 g, 0.08 mmol). The flask was purged with carbon monoxide for few seconds and connected to a balloon of carbon monoxide. The reaction mixture was stirred at 60 °C overnight and poured in a separatory funnel containing 0.1 HCl and ethyl acetate. The organic layer was separated and aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatogrphy on silica gel eluting with 85/15 n-hexane/EtOAc mixture to give 0.32 g (51% yield) of **5a**: mp 133-135 °C; IR (Kbr) 1740, 1690 cm^{-1}; ^1H NMR δ 8.19 (AA' part of an AA'BB' system, J = 8.1 Hz, 2 H), 7.52 (BB' part of an AA'BB' system, J = 8.1 Hz, 2 H), 7.45 (AA' part of an AA'BB' system, J= 9.2 Hz, 2 H), 7.28 (BB' part of an AA'BB' system, J = 9.2 Hz, 2 H), 6.66 (s, 1 H), 6.60 (s, 1 H), 2.29 (s, 3 H), 2,24 (s, 3 H); ^{13}C NMR δ 193.4, 163.5, 156.4, 147.2, 140.5, 134.7, 132.7, 129.1, 128.9, 127.5, 125.6, 122.9, 111.4, 105.2, 28.8, 14.21; Ms m/e (relative intensiy) 414 (M^+, 27), 139 (100).
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