ORGANIC LETTERS

2000
Vol. 2, No. 1
69−72

Palladium-Catalyzed Arylation of α-Methylene-γ-butyrolactone: 3-Benzylfuran-2(5*H*)-ones vs (*Z*)-Benzylidene-γ-butyrolactones and Their Reduction to 3-Benzyl-γ-butyrolactones

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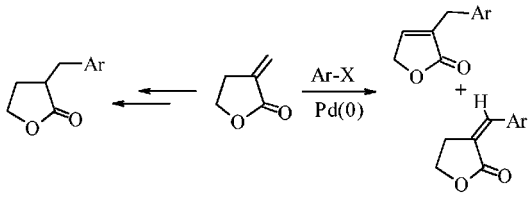
Received November 3, 1999

ABSTRACT



The palladium-catalyzed arylation of the α-methylene-γ-butyrolactone proceeds in good yields and may be directed toward the synthesis of 3-benzylfuran-2(5*H*)-ones when the starting aryl iodides contain strongly electron-withdrawing groups. The combined palladium-catalyzed arylation/hydrogenation of the α-methylene-γ-butyrolactone represents a new simple entry into functionalized α-benzyl-γ-butyrolactones.

Recently, a growing amount of attention has been paid to the synthesis of 5*H*-furan-2-ones[1] and α-benzylidene-γ-butyrolactones.[2] Some of these derivatives exhibit interesting biological activities.[3] Moreover, they are useful synthetic intermediates.[4] In connection with our interest in developing new synthetic strategies for the construction of heterocycles involving palladium catalysis,[5] we report that α-methylene-γ-butyrolactone **1** may represent a suitable building block precursor for the synthesis of 5*H*-furan-2-ones **3** and stereodefined α-benzylidene-γ-butyrolactones **4**. Among the several methods for the synthesis of these latter derivatives it is worth noting, owing to its simplicity, the synthesis of

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10.1021/ol9912130 CCC: $19.00
Published on Web 12/17/1999

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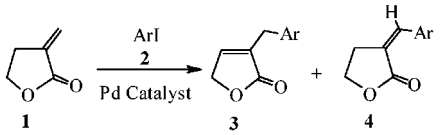
substituted α-benzylidene-γ-butyrolacones (*E* + *Z* steroisomers) in excellent yields through the palladium-catalyzed reaction of arenediazonium salts (Heck-type reaction) with **1**.[6]

On the basis of the stereochemical trend of the vinylic substitution observed with a variety of reactions of unsaturated halides/triflates with α-acetamido acrylic acid derivatives and methyl α-methyl acrylic acid derivatives,[7] we decided to investigate the palladium-catalyzed arylation of **1** using aryl iodides **2** as arylating agents with the aim of achieving a stereoselective synthesis of substituted α-benzylidene-γ-butyrolactones. Sterodefined α-benzylidene-γ-lactones are useful intermediates for the synthesis of podophyllotoxin[8] and optically active α-spirocyclopropyllactones.[9]

4-Iodoacetophenone was selected as the model aryl iodide, and the preparation of the corresponding α-benzylidene-γ-butyrolactone was attempted under a variety of conditions to evaluate the influence of the catalytic system, bases, and **1**/**2** ratio on the reaction outcome (Scheme 1 and Table 1).

Scheme 1



With the use of Et_3N as base in the presence of catalytic amounts of $Pd(OAc)_2[Pd(o\text{-tolyl})_3]_2$ in DMF at 80 °C, the corresponding α-benzylidene-γ-butyrolactone **3** was isolated as single (*Z*) steroisomer after 8 h in 21% yield (Table 1, entry 1).

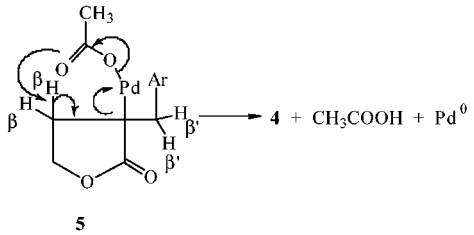
Table 1. Experimental Conditions for the Synthesis of **3** + **4**[a,b] from **1** and 4-Iodoacetophenone

					3 + **4**	
entry	base	solvent	catalyst	*t* (h)	% yield	(**4**:**3**)
1	Et_3N	DMF	$Pd(OAc)_2/P(o\text{-tol})_3$	8	63	2
2	Et_3N	DMF	$Pd(OAc)_2$	20	60	1.3
3	AcOK	DMF	$Pd(OAc)_2$	9	54	24
4	AcOK[c]	DMF	$Pd(OAc)_2$	48	53	5.6
5	AcOK[d]	DMF	$Pd(OAc)_2$	4	54	25
6	AcOK	NMP	$Pd(OAc)_2$	21	45	28
7	AcOK	DMA	$Pd(OAc)_2$	23	32	30
8	AcOK + Et_3N	DMF	$Pd(OAc)_2$	9	66	11
9	AcOK + K_2CO_3	DMF	$Pd(OAc)_2$	5	–	
10	AcOTl	DMF	$Pd(OAc)_2(PPh_3)_2$	24	33	8.5
11	AcOTl	DMF	$Pd(OAc)_2$	8	55	7.1

[a] Unless otherwise started, reactions were carried out at 80 °C under a nitrogen atmosphere using the following molar ratios: **1**:**2**:catalyst:base = 1:1.5:0.05:3. [b] Yields refer to single runs and are given for pure isolated products. [c] Temperature 40 °C. [d] Reaction was carried out at 80 °C under a nitrogen atmosphere using the following molar ratios: **1**:**2**:catalyst:TBACl:base = 1:1.5:0.05:1:3.

Assignment of the olefin geometry was unambiguously done by using T-ROESY NMR experiments. Surprisingly, the reaction showed a very low selectivity in the β-elimination step and the 3-benzylfuran-2(5*H*)-one **4**, derived from endocyclic elimination of hydridopalladium species from the addition intermediate **5**, was isolated in 42% yield (Scheme 2). To our knowledge, this is the first example of butenolide

Scheme 2



derivative formation starting from **1**. Omitting the ligand (Table 1, entry 2) produced only minor modifications of the reactivity and/or selectivity, at least from a synthetic point of view. Switching to AcOK, in the presence of catalytic amounts of $Pd(OAc)_2$ in DMF at 80 °C produced chemoselectively **4** in 54% yield (Table 1, entry 3). The addition of *n*-Bu_4NCl increased the reaction rate without modification in the selectivity (Table 1, entry 5).[10] With *N*-methyl-2-pyrrolidone and *N*,*N*-dimethylacetamide as solvents, a very similar trend was observed; however, lower conversions of the starting materials than in DMF took place (Table 1, entries 6 and 7). The role of the base for directing the β-palladium hydride elimination step is even demonstrated by the lower selectivity obtained using a mixed system AcOK/Et_3N (Table 1, entry 8). Finally, we used AcOTl in place of AcOK, to make sure that the formation of **4** was not a consequence of the migration of the double bond of the initially formed **3**. Tl(I)[11] salts are reported to eliminate the isomerization of the double bond caused by β-palladium hydride elimination/readdition/elimination sequence. The isolation of **4** as the main product, also in the presence of

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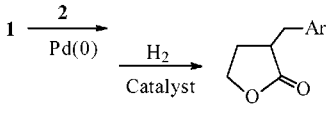
AcOTl (Table 1, entries 10 and 11) clearly rules out that isomerization occurs. With regard to the effect of the acetate anion on the reaction course, an explanation based on the formation of a σ-alkylpalladium acetate intermediate **5** and its decomposition through basic intramolecular attack of the acetate moiety on the β-hydrogen[12a] could account for the regioselective β-elimination observed in the presence of favorable electronic effects (the presence of the electron-withdrawing acyl group in the aromatic ring makes the β'-hydridopalladium elimination more difficult) (Scheme 2).

Related mechanisms involving a seven-membered cyclic transition state containing palladium have been reported.[12]

According to that, when the system was extended to other aryl iodides the chemoselective formation of the butenolide derivatives has been accomplished only in the presence of strongly electron-withdrawing substitutents in the aromatic ring.[13]

The stereochemistry of the α-benzylidene-γ-butyrolactones was always found to be *Z*. It must be emphasized that variable amounts of biaryl derivatives were observed in all the reactions, and better results were usually obtained using a 1.5 molar excess of the α-methylene-γ-butyrolactone over the halide. Even if the selectivity of the β-hydropalladium elimination is limited, the mixtures of **3** + **4** can be hydrogenated to the corresponding α-benzyl-γ-butyrolactones **6** in high yield. A one-pot arylation/hydrogenation reaction to give **6** derivative has, also, been accomplished (Scheme 3).[14] The importance of these results is further stressed by

Scheme 3



6

the observation that we failed to obtain the corresponding **6** derivative through the palladium-catalyzed conjugate addition of α-methylene-γ-butyrolactone with 4-iodoacephenone[15] (**3** + **4** were isolated in 75% yield; **3**:**4** ratio = 1).

The results obtained are summarized in Table 2.

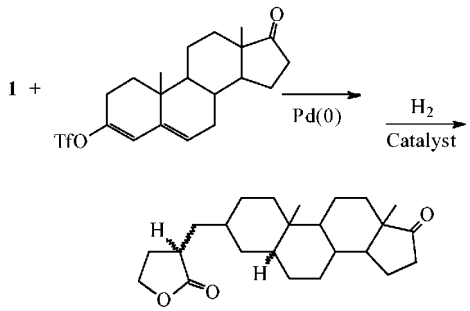
Interestingly, one application of this synthetic methodology (Scheme 4), by using the androsten-3,5-dienyl-17-one 3-triflate as σ-donor in the palladium-catalyzed Heck-type

Table 2. Experimental Condition for the Synthesis of (**3** + **4**)[a,b] and 6 Derivatives

entry	**2**	**3** + **4** % yield (4:3)	**6** % yield
1	4-CH_3CO-C_6H_4-I	64 (8)	95[c,d]
2	4-CH_3OOC-C_6H_4-I	60 (20)	95[c]
3	4-CH_3OOC-C_6H_4-I		57[e]
4	2-CH_3OOC-C_6H_4-I	81 (1.2)	96[c]
5	2-CH_3OOC-C_6H_4-I		78[e]
6	4-CH_3O-C_6H_4-I	73 (0.6)	96[c]
7	4-CH_3O-C_6H_4-I	82 (0.6)[f]	
8	4-CH_3O-C_6H_4-I	63 (0.5)[g]	
9	4-CH_3O-C_6H_4-I	74 (0.6)[h]	
10	4-CH_3O-C_6H_4-I		70[e]
11	1-iodonaphthalene	62 (0.7)	95[c]
12	1-iodonaphthalene		59[e]
13	3-CF_3-C_6H_4-I	81 (0.7)	96[c]
14	3-CF_3-C_6H_4-I		78[e]

[a] Unless otherwise stated, reactions were carried out at 80 °C in DMF in the presence of an excess of AcOK under a nitrogen atmosphere using the following molar ratios: **1**:**2**:$Pd(OAc)_2$:AcOK = 1.5:1:0.05:3. [b] Yields refer to single runs, are given for pure isolated products, and are based on **2**. [c] Yields refer to reduced products derived from hydrogenation of isolated **3** and **4**. [d] Yield refer to 3-(4′-ethybenzyl)furan-2(5*H*)-one. [e] Yields refer to isolated reduced products of the one-pot procedure. [f] Reaction was carried out at 80 °C in DMF in the presence of an excess of AcOK under a nitrogen atmosphere using the following molar ratios: **1**:**2**:$Pd(OAc)_2$:ddpf:AcOK = 1.5:1:0.05:0.05:3. [g] Reaction was carried out at 80 °C in DMF in the presence of an excess of Et_3N under a nitrogen atmosphere using the following molar ratios: **1**:**2**:$Pd(OAc)_2$:Et_3N = 1.5:1:0.05:4. [h] Reaction was carried out at 80 °C in DMF in the presence of an excess of Et_3N under a nitrogen atmosphere using the following molar ratios: **1**:**2**:$Pd(OAc)_2$:ddpf:Et_3N = 1.5:1:0.05:0.05:4.

Scheme 4



reaction, gives special prominence to the possibility of stereocontrol in the formation of the new sterocenters.

The steroidal substituted γ-lactone **7** was isolated in high de (80%). No attempts were made to determine the config-

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(13) **General Procedure.** A total of 2 mmol of aryl iodide, 3 mmol of α-methylene-γ- butyrolactone, 6 mmol of AcOK, and 0.1 mmol of $Pd(OAc)_2$ were dissoved in 3 mL of DMF, and the mixture was stirred under nitrogen at 80 °C for 3 h. After it was cooled, the reaction mixture was washed with a mixture ethyl acetate and saturated aqueous $NaHCO_3$. The phases were separated, and the combined organic phases were dried over Na_2SO_4. After removal of the solvent, the crude was purified by flash chromatography. All products were identified by ^1H and ^{13}C NMR and mass spectroscopy.

(14) **General Procedure.** A total of 2 mmol of aryl iodide, 3 mmol of α-methylene-γ- butyrolactone, 6 mmol of AcOK, and 0.1 mmol of $Pd(OAc)_2$ were dissoved in 3 mL of DMF, and the mixture was stirred under nitrogen at 80 °C for 3 h. After it was cooled, the reaction mixture was washed with a mixture of ethyl acetate and saturated aqueous $NaHCO_3$. The phases were separated, and the combined organic phases were dried over Na_2SO_4. After removal of the solvent, the crude product was dissolved in ethyl acetate and was hydrogenated in the presence of Pd/C (5%) at atmospheric pressure. After the completion of the hydrogenation the catalyst was filtered, the solvent was evaporated and the crude product purified by chromatography (silica gel, $CHCl_3$/petroleum ether).

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uration of the new chiral centers. Further work is in progress to evaluate the scope and the limitations of this synthetic methodology with triflates.

In conclusion, the palladium-catalyzed arylation of the α-methylene-γ-butyrolactone may give 3- benzylfuran-2(5*H*)-ones when the starting aryl iodides contain strongly electron-withdrawing groups in the aromatic rings while the combined arylation/hydrogenation reaction of the α-methylene-γ-butyrolactone represent a new simple entry into functionalized α-benzyl-γ-butyrolactones.

Acknowledgment. We thank the CNR and MURST, as well as OTKA (T023525) for providing financial support.

OL9912130