ORGANIC LETTERS

2003
Vol. 5, No. 3
289−291

Palladium-Catalyzed Reaction of Aryl Iodides with Acetic Anhydride. A Carbon Monoxide-Free Synthesis of Acetophenones

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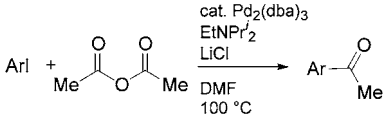
Received November 6, 2002

ABSTRACT

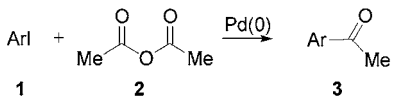


The palladium-catalyzed reaction of aryl iodides with acetic anhydride provides a straightforward and experimentally simple carbon monoxide-free route to acetophenones. The reaction tolerates a wide range of functionalized aryl iodides. Acetophenones are isolated in excellent yield with a variety of neutral, slightly electron-rich, and slightly electron-poor aryl iodides, whereas moderate yields are obtained with aryl iodides containing strongly electron-withdrawing substituents.

The reaction of aryl- and vinylpalladium complexes with carbon−heteroatom multiple bonds is emerging as a stimulating new frontier in palladium catalysis. In fact, recent reports have shown that aryl- and vinylpalladium complexes can undergo intramolecular reactions with aldehyde,[1,2] ketone,[3] and nitrile[4] functionalities to afford indenone and indanone derivatives and other cyclic alcohols and ketones. The success of these reactions appears to be strongly dependent on their intramolecular character.

We now report that the reaction of arylpalladium complexes with carbonyl compounds can also occur *intermolecularly*. In particular, the palladium-catalyzed reaction of aryl iodides with acetic anhydride provides a straightforward and experimentally simple new route to acetophenones (Scheme 1), common structural units of a variety of biologically active compounds and useful intermediates for the preparation of significant pharmaceuticals.[5]

Scheme 1



1 **2** **3**

During our studies directed toward finding new methods for the palladium-catalyzed formation of C−C bonds, we have discovered that subjecting *p*-iodoanisole to acetic anhydride in the presence of 1.25 mol % $Pd_2(dba)_3$ and 2 equiv of Et_3N in DMF at 80 °C gives the corresponding acetophenone product in 54% yield (the corresponding biaryl was obtained in 43% yield).

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10.1021/ol027243b CCC: $25.00
Published on Web 01/11/2003

To the best of our knowledge, the behavior of acetic anhydride as an acetyl donor in a palladium-catalyzed reaction of this type has never been reported.

This result prompted us to search for optimal reaction conditions for this substrate. A survey of reactions with a variety of bases ($EtNPr^i_2$, DABCO, pyridine, K_2CO_3) and solvents (DMA, DMSO, THF, toluene) showed that the best results can be obtained by using 1.25 mol % $Pd_2(dba)_3$ and a 0.427 M solution of *p*-iodoanisole with a 1:5:2 molar ratio of *p*-iodoanisole:acetic anhydride:$EtNPr^i_2$ in DMF at 100 °C for 15 h. Under these conditions, *p*-methoxyacetophenone was isolated in 70% yield and only trace amounts of the biaryl byproduct were observed. Interestingly, though a lower reaction rate was observed, the reaction can be successfully carried out in the presence of 2.5 mol % 5% palladium on charcoal (Table 1, entry 2).

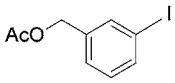
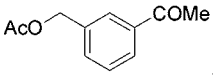
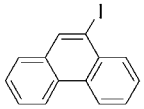
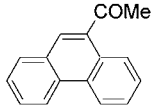
Using the same conditions, we found that ethyl *p*-iodobenzoate, a model electron-poor aryl iodide, gave the biaryl derivative as the main reaction product: acetophenone and biaryl products were isolated in 34 and 57% yields, respectively. Utilization of phosphine ligands [PPh_3, P(*o*-tol)$_3$, P(2-furyl)$_3$, tris(*p*-chlorophenyl)phosphine, tris(2,4,6-trimethoxyphenyl)phosphine] did not have any beneficial effect on the reaction course. On the contrary, their employment tends to lower the yields of ethyl *p*-acetylbenzoate by favoring the formation of the biaryl byproduct. The amount of biaryl was found to decrease by adding LiCl and diluting the reaction mixture. Indeed, in the presence of 5 equiv of LiCl and with a 0.142 M solution of ethyl *p*-iodobenzoate, acetophenone and biphenyl products were isolated in 70 and 10% yields, respectively. It was observed that LiCl is more effective than $^nBu_4NCl$ and $^nBu_4NBr$ in limiting the formation of biaryls.

After observing the beneficial effect of LiCl and dilution in limiting the formation of biaryls with ethyl *p*-iodobenzoate, LiCl and 0.142 M solutions of aryl iodides were employed in all the experiments we carried out, independent of the nature of the aryl iodide. In practice, the conditions we used when the procedure was extended to include other aryl iodides are as follows: aryl iodide (1 equiv, 0.142 M), $Pd_2(dba)_3$ (0.0125 equiv), $EtNPr^i_2$ (2 equiv), acetic anhydride (5 equiv), LiCl (5 equiv) in DMF at 100 °C.

Under these conditions the reaction proceeds very smoothly and, as shown in Table 1, appears to tolerate a wide range of functionalized aryl iodides, including those containing ether, ketone, ester, and nitro groups. The presence of *ortho* substituents does not seem to hamper the reaction (Table 1, entry 6). Acetophenones were isolated in excellent yield with a variety of neutral, slightly electron-rich, and slightly electron-poor aryl iodides, whereas moderate yields were obtained with aryl iodides containing strongly electron-withdrawing substituents. With the latter substrates, biaryl byproducts were isolated in significant yield, even in the presence of LiCl (Table 1, entries 16 and 17).

Only *o*-iodoanisole, among the substrates that we have investigated, produced a complex reaction mixture containing the desired acetophenone derivative, phenoxyacetone **4**, and other compounds we have not further investigated (Scheme 2). The formation of **4** is interesting. Presumably, it involves the intermediacy of a five-membered ring, oxygen-containing palladacycle, as suggested by Dyker in the palladium-catalyzed C−H activation at methoxy groups,[6] and its conversion into a phenoxymethylpalladium complex that subsequently reacts with acetic anhydride according to the present procedure.

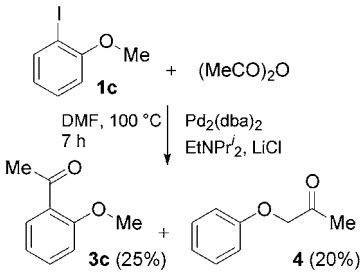
Table 1. Palladium-Catalyzed Synthesis of Acetophenones from Aryl Iodides and Acetic Anhydride[a]

entry	substrate		time (h)	product		yield %[b]
1	*p*-MeO-C_6H_4-I	**1a**	7	*p*-MeO-C_6H_4-COMe	**3a**	70[c]
2	*p*-MeO-C_6H_4-I	**1a**	110	*p*-MeO-C_6H_4-COMe	**3a**	51[c,d]
3	*m*-MeO-C_6H_4-I	**1b**	24	*m*-MeO-C_6H_4-COMe	**3b**	67
4	*o*-MeO-C_6H_4-I	**1c**	7	*o*-MeO-C_6H_4-COMe	**3c**	25[e]
5	*p*-Me-C_6H_4-I	**1d**	4.5	*p*-Me-C_6H_4-COMe	**3d**	88
6	*o*-Me-C_6H_4-I	**1e**	24	*o*-Me-C_6H_4-COMe	**3e**	77
7	3,5-Me_2-C_6H_4-I	**1f**	30	3,5-Me_2-C_6H_4-COMe	**3f**	70
8		**1g**	3		**3g**	77
9	PhI	**1h**	8.5	PhCOMe	**3h**	74
10		**1i**	6		**3i**	80
11	*p*-F-C_6H_4-I	**1j**	6	*p*-F-C_6H_4-COMe	**3j**	90
12	*o*-F-C_6H_4-I	**1k**	8.5	*o*-F-C_6H_4-COMe	**3k**	74
13	*m*-CF_3-C_6H_4-I	**1l**	5	*m*-CF_3-C_6H_4-COMe	**3l**	94
14	*p*-Cl-C_6H_4-I	**1m**	8	*p*-Cl-C_6H_4-COMe	**3n**	80
15	*p*-EtOOC-C_6H_4-I	**1n**	1.45	*p*-EtOOC-C_6H_4-COMe	**3n**	70
16	*p*-MeCO-C_6H_4-I	**1o**	4	*p*-MeCO-C_6H_4-COMe	**3o**	30[f] (47)[g]
17	*p*-NO_2-C_6H_4-I	**1p**	6	*p*-NO_2-C_6H_4-COMe	**3p**	50[h]

[a] Unless otherwise stated, reactions were run in DMF at 100 °C by using 0.142 M solutions of **1** with the following molar ratios: **1**:**2**:$EtNPr^i_2$:LiCl:$Pd_2(dba)_3$ = 1:5:2:5:0.0125. [b] All products gave appropriate ^1H and ^{13}C NMR and IR spectra and elemental analytical data. [c] Iodoanisole 0.427 M. In the absence of LiCl. [d] In the presence 0.025 equiv of 5% Pd/C. [e] Complex reaction mixture was obtained, containing about 20% **4** and other unidentified products. [f] Corresponding biaryl was isolated in 20% yield. [g] **1**:**2**:$EtNPr^i_2$:LiCl:$Pd_2(dba)_3$ = 1:3:2:7:0.025. Corresponding biaryl was isolated in 15% yield. [h] Corresponding biaryl was isolated in 25% yield.

The extension of the procedure to other anhydrides has been briefly explored. The reaction of *p*-iodoanisole with propionic acid anhydride and hexanoic acid anhydride (24

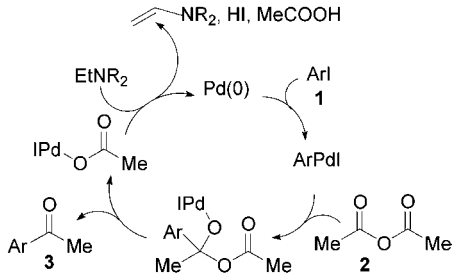
Scheme 2



h) afforded the corresponding aromatic ketone products in 38 and 37% yields, respectively (the biaryl byproduct was isolated in 7 and 9% yields, respectively). No benzophenone derivative was observed with benzoic acid anhydride.

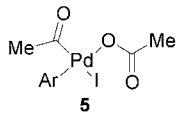
A possible reaction mechanism accounting for the observed unprecedented palladium-catalyzed formation of acetophenones from aryl iodides and acetic anhydride is as follows (Scheme 3): (a) oxidative addition of aryl iodide to

Scheme 3



Pd(0), (b) addition of the resultant arylpalladium intermediate to the carbonyl group of the anhydride to give an alkoxypalladium intermediate, (c) formation of the acetophenone product by β-elimination of an acetoxypalladium species, and (d) regeneration of the Pd(0) catalyst by reduction. Presumably, the reduction step is effected by the tertiary amine.[7] A similar mechanism, involving the intramolecular addition of a C−Pd bond of aryl- and vinylpalladium intermediates across the C═O bond of aldehyde and ketone groups, has been proposed by Yamamoto for the palladium-catalyzed synthesis of indenols,[2,3a] indanols,[3b] and other cyclic alcohols.[3b]

Another possible mechanism, related to that proposed by Larock for the formation of indenones from *o*-iodobenzaldehyde and internal alkynes,[1] involves an oxidative insertion of the arylpalladium complex into the anhydride CO−O bond to form the palladium(IV) intermediate **5** that could generate the acetophenone product via reductive elimination. Intermediate **5** could also form via oxidative addition of acetic anhydride to Pd(0)[8] followed by the oxidative insertion of the resultant acetylpalladium complex into the aryl C−I bond.



In conclusion, we have demonstrated the first examples of the palladium-catalyzed intermolecular reaction between aryl iodides and carbonyl compounds. The reaction tolerates important functional groups and could open up new and exciting synthetic pathways. It compares well with most common palladium-based procedures for the preparation of acetophenones from aryl iodides (relying on the palladium-catalyzed reaction of aryl iodides with tetramethylstannane[9] or methyl zinc[10] in the presence of carbon monoxide, with vinyl ether,[7j,11] and with zinc salts of enol ether anions)[9] and is particularly applicable to small-scale reactions where direct use of carbon monoxide is impractical as in the synthesis of compound libraries.[12]

Research on the scope and limitations of this chemistry are actively underway in our laboratory.

Acknowledgment. This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Università degli Studi "La Sapienza".

Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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