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Palladium-Catalyzed Carbonylation of Haloindoles: No Need for Protecting Groups

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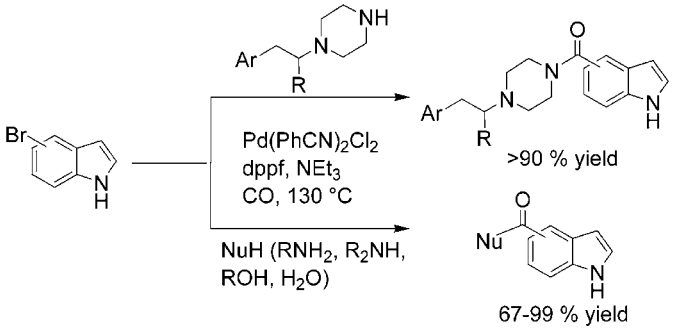
ABSTRACT



For the first time, palladium-catalyzed carbonylations of unprotected bromoindoles have been performed successfully with different N- and O-nucleophiles. Various indole carboxylic acid derivatives are accessible in excellent yield. For example, aminocarbonylation of 4-, 5-, 6-, or 7-bromoindole with arylethylpiperazines provides a direct one-step synthesis for CNS active amphetamine derivatives.

The introduction of carboxylic acid groups into arenes using carbonylation reactions is an interesting method among the array of catalytic conversions of aryl halides performed by palladium complexes.[1] "Classic" syntheses of aromatic esters or amides generally require a carboxylic acid precursor. Alternatively, arene carboxylic acid derivatives can be prepared through palladium-catalyzed carbonylation of the corresponding aryl halides in the presence of a suitable nucleophile.[2] Advantages of this method include the broad availability of substrates and the high tolerance of palladium catalysts against a variety of functional groups. Therefore, this route has become a useful tool for the preparation of substituted benzoic acid derivatives.[3]

For some time, we have been involved in the development of more efficient palladium catalysts for carbonylation of aryl bromides and chlorides.[4] Due to their importance as building blocks for pharmaceuticals and agrochemicals, we became especially interested in the carbonylation of heteroaryl chlorides. For example, we have performed alkoxy-

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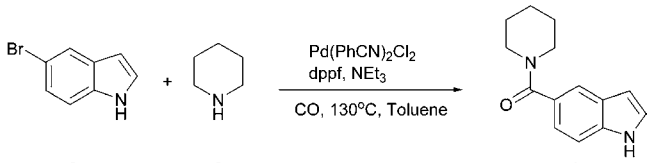
Table 1. Aminocarbonylation of 5-Bromoindole with Piperidine: A Model Reaction



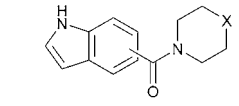
2 3 4

entry	Pd	ligand	Pd/L [mol %]	solvent	temp [°C]	time [h]	*p*CO [bar]	conversion[a] [%]	yield[a] [%]
1	$Pd(PhCN)_2Cl_2$	dppb	1:3	toluene	130	20	25	29	23
2	$Pd(PhCN)_2Cl_2$	PPh_3	1:6	toluene	130	12	25	24	10
3	**$Pd(PhCN)_2Cl_2$**	**dppf**	**1:3**	**toluene**	**130**	**20**	**25**	**92**	**81**
4	$Pd(PhCN)_2Cl_2$	dppf	1:3	NMP	130	12	25	11	0
5	$Pd(PhCN)_2Cl_2$	dppf	1:3	dioxane	130	12	25	53	38
6	$Pd(PhCN)_2Cl_2$	dppf	0.1:0.3	toluene	130	12	25	9	0
7	$Pd(PhCN)_2Cl_2$	dppf	1:3	toluene	110	12	25	20	3
8	$Pd(PhCN)_2Cl_2$	dppf	1:3	toluene	130	12	10	17	2
9	$Pd(PPh_3)_2Cl_2$	dppf	1:3	toluene	130	20	25	31	28

[a] Based on 5-bromoindole; determined by GC (hexadecane as internal standard). Reaction conditions: 5-bromoindole (1.0 mmol), piperidine (1.5 mmol), NEt_3 (1.5 mmol), solvent (10 mL) in a 25 mL autoclave.

carbonylations of pyridines, pyrazines, quinolines, and pyrimidines in the past.[5]

More recently, we turned our attention to carbonylations of haloindoles. In particular, we were attracted by the possibility of synthesizing indole carboxylic amides as shown in Figure 1, in a straightforward manner. The resulting



(1)

CNS active, 5-HT_{2A} receptor antagonists

X = NMe, CH_2, $NCHRCH_2Ar$
R = H, Me
Ar = Ph, 4-F-Ph, 4-MeOPh

Figure 1. Bioactive Indole Derivatives.

products are known to be potent ligands for the serotonin (5-HT) subtype 2A receptor and therefore constitute potential CNS active compounds.[6]

However, a literature survey regarding carbonylation reactions of indoles revealed that, despite the usefulness of carboxylated indoles, there was no such reaction of easily available bromoindoles reported. Also, other types of palladium-catalyzed coupling reactions of unprotected haloindoles are rare.[7] One of the possible reasons for the lack of these reactions is the presence of the acidic NH proton and the possibility of the haloindole to oligomerize or polymerize in the presence of a palladium catalyst. In addition, it seems difficult to introduce other amines, alcohols, or water as nucleophiles in the presence of the free indole nitrogen.

Nevertheless, we started our investigation using the reaction of 5-bromoindole with piperidine as a model system. Selected results are shown in Table 1. From our previous work in palladium-catalyzed carbonylations of aryl halides, it is known that bidentate ligands lead to good selectivities and improved activities compared to monodentate ligands.[4,5] Therefore, we performed initial reactions using 1,4-bis(diphenylphosphino)butane (dppb) as a ligand in the presence of bis(benzonitrile)palladium(II) dichloride (Pd/ligand 1:3).

As shown in Table 1 (entry 1), even at 130 °C (20 h, 25 bar of CO pressure), only 23% yield of 5-(*N*-piperidylcarbonyl)indole (**4**) was obtained. Despite the disappointingly low yield, this result was somewhat encouraging because a high chemoselectivity (79%) was observed. Hence, attack of 5-bromoindole on the acylpalladium complex is significantly slower compared to the reaction of piperidine. Under similar reaction conditions, the use of triphenylphosphine as a ligand, expectedly, yielded an even smaller amount of the desired product (entry 2). Fortunately, using 1,1′-bis(diphenylphosphino)ferrocene (dppf) as a ligand with $Pd(PhCN)_2Cl_2$ (Pd/L 1:3) (entry 3) afforded a significant

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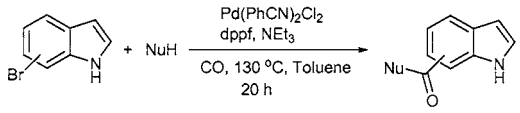
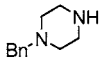
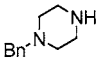
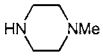
Table 2. Pd-Catalyzed Carbonylation of Bromoindoles with Nucleophiles



Entry	2	5	Conv.[a] [%]	Yield[b] [%]
1	4-Br		100	**6a** (91)
2	7-Br		100	**6b** (94)
3	5-Br		100	**6c** (99)
4[c]	4-Br		100	**6d** (93)
5	6-Br	nBuNH$_2$	100	**6e** (95)
6[d]	4-Br	EtOH	100	**6f** (98)
7	7-Br	H_2O	80	**6g** (67)

[a] Based on bromoindole, determined by GC. [b] Isolated yield. [c] Pd/L 5/15 mol %. [d] EtOH (10 mL) was used as a solvent. Reaction conditions: bromoindole (1.2 mmol), nucleophile (1.0 mmol), $Pd(PhCN)_2Cl_2$ (1 mol %), dppf (3 mol %), NEt_3 (1.2 mmol), toluene (10 mL).

increase in the catalyst activity. Testing different solvents revealed that toluene gives the best yield for this model reaction. However, at lower temperatures (110 °C) or at lower carbon monoxide gas pressures (10 bar), only a negligible amount of product **4** was obtained (Table 1, entries 7 and 8). Interestingly, using a mixture of phosphines ($Pd(PPh_3)_2Cl_2$ and dppf) produced **4** in only 28% yield (Table 1, entry 9).

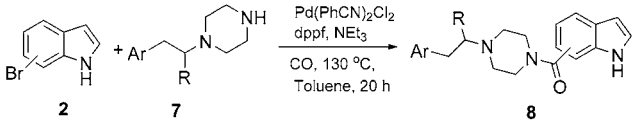
Next, the optimal reaction conditions found in the model reaction were employed for the carbonylation of four different bromoindoles with six different nucleophiles (Table 2). Due to their potential biological activity, our main interest was focused on the use of different piperazine derivatives as nucleophiles. *N*-Benzyl piperazine reacted well with 4-bromo and 7-bromoindole to give 4-benzylpiperazin-1-yl-(1*H*-indol-4-yl)methanone (**6a**) and 4-benzylpiperazin-1-yl-(1*H*-indol-7-yl)methanone (**6b**) in very good isolated yields (91 and 94% yields, respectively) (entries 1 and 2).

Similarly, the aminocarbonylation of 5-bromoindole with *N*-methylpiperazine gave the corresponding indole amide (**6c**) in excellent yield (99%) (entry 3). Next, we explored the potential of this method for the synthesis of other interesting indole derivatives. In Table 2 (entries 4−7), a few examples are shown demonstrating the generality of this reaction in indole chemistry. Thiomorpholine was coupled smoothly to give **6d** in 93% yield at somewhat higher catalyst concentration (5 mol %). 6-Bromoindole also underwent selective aminocarbonylation with primary amines. Here, *n*-butylamine gave **6e** in 95% yield. Using ethanol as a solvent and nucleophile, ethoxycarbonylation was realized, forming an indole carboxylic ester[8] in 98% yield. This ester is an important synthetic intermediate for the synthesis of many bioactive molecules.[9] Interestingly, the free indole carboxylic acid (**6g**)[10] was also directly accessible. However, product purification was more difficult; thus, the yield was somewhat lower (67%) in this case.

Finally, we applied our successful method to synthesize the new CNS active amphetamine deriviatives.[11] Here, three different arylethylpiperazines were used as nucleophiles in the aminocarbonylation of bromoindoles. The utilized 2-arylethylpiperazines are easily accessible by base-catalyzed hydroamination of the corresponding styrenes with *N*-benzylpiperazine[12,13] and subsequent palladium-catalyzed debenzylation. In general, aminocarbonylation of bromoindoles with arylethylpiperazines produced the amphetamine derivatives **8a**−**e** in excellent isolated yields (92−99%).

For example, 2-(4-fluorophenyl)ethylpiperazine reacted well with 7- and 6-bromoindole (Table 3, entries 1 and 2)

Table 3. Pd-Catalyzed Carbonylation of Bromoindoles with 2-Arylethylpiperazines



entry	2	Ar	R	conversion[a] [%]	yield[b] [%]
1[c]	7-Br	4-F−Ph	H	100	**8a** (99)
2[c]	6-Br	4-F−Ph	H	100	**8b** (92)
3	4-Br	Ph	Me	100	**8c** (96)
4	5-Br	Ph	Me	100	**8d** (96)
5	7-Br	Ph	H	100	**8e** (94)

[a] Based on bromoindole, determined by GC. [b] Isolated yield. [c] Amine used as double HCl salt, and 3.5 mmol of NEt_3 was used. Reaction conditions: bromoindole (1.2 mmol), nucleophile (1.0 mmol), $Pd(PhCN)_2Cl_2$ (1 mol %), dppf (3 mol %), NEt_3 (1.2 mmol), toluene (10 mL).

to yield exclusively the carbonylation products **8a** and **8b**. No simple amination product without CO insertion or indole oligomerization was observed in these reactions.

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In addition, 2-phenethylpiperazine and 1-methyl-2-phenylethylpiperazine also yielded the aminocarbonylation products of indoles in high yields (Table 3, entries 3−5).

In conclusion, we have developed an easy and general protocol for the direct synthesis of various indole carboxylic acid derivatives. In addition, we have shown that palladium-catalyzed carbonylation of different bromoindoles in the presence of dppf as a ligand and Et_3N as a base gave potentially bioactive amphetamine analogues in excellent yield. To the best of our knowledge, this is the first example for the carbonylation of unprotected bromoindoles with various nucleophiles involving cyclic and acyclic amines, alcohols, and water.

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Supporting Information Available: Complete experimental details along with spectroscopic data for all new molecules synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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