ORGANIC LETTERS

2008
Vol. 10, No. 21
4899−4901

Tandem Palladium-Catalyzed N,C-Coupling/Carbonylation Sequence for the Synthesis of 2-Carboxyindoles

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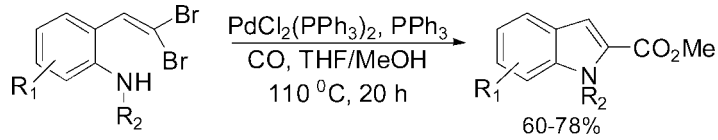
Received August 25, 2008

ABSTRACT



Tandem palladium-catalyzed N,C-coupling/carbonylation, under 10 atm of carbon monoxide and at 110 °C, is a novel and efficient method for the preparation of 2-carboxyindoles. The catalyst system tolerates a variety of functional groups, and the noted indoles were obtained in good isolated yields.

The indole moiety is one of the most widely distributed heterocyclic systems in nature, and its myriad of derivatives continue to attract significant attention, especially in the pharmaceutical sector.[1] Several indoles display substantial biological activity; in nature, the indole skeleton is present in key molecules such as tryptophan and serotonin. Vincristine, indomethacin, and pindolol are good examples of commercial drugs based on this heterocyclic system. As pharmaceutical intermediates, most of the indoles are accessed in large-scale production through the classical "Fischer indole" synthesis;[2] however, a number of other interesting methods, based on metal catalysis, have recently emerged in the literature.[3,4]

2-Carboxyindole alkaloids are inhibitors toward hyaluronidase,[5] tubulin polymerization,[6] HIV-1 integrase,[7] human cytosolic phosphorilase $A_2\alpha$,[8] and factor Xa,[9] just to name a few. There are some efficient methods to prepare these compounds,[10] and the protocol published by Driver and coworkers,[10a] which is based on a rhodium-catalyzed intramolecular C−H amination reaction, deserves special mention. This methodology involves the use of azides.

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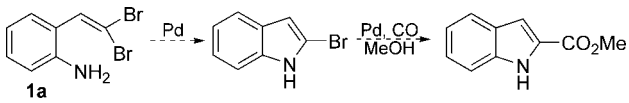
10.1021/ol801985q CCC: $40.75
Published on Web 10/01/2008

Tandem reactions are particularly appealing, as they can enhance the efficiency of reaching the target molecules. They also avoid the separation of intermediates, as it saves the number of steps, and in principle reducing the amount of waste. The versatility of the catalyst can also be exploited, through a number of different reactions occurring in the same flask.[11] Our research group has published alternative protocols for the synthesis of nitrogen containing heterocycles, based on transition metal-mediated carbonylation reactions.[12] We now describe a tandem palladium-catalyzed N,C-coupling/carbonylation sequence as a route to 2-carboxyindoles (Scheme 1).

Scheme 1. Strategic Approach to the Synthesis of 2-Carboxyindoles



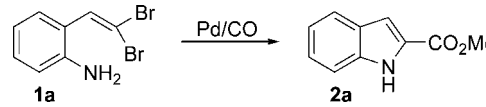
The 2-(2,2-dibromovinyl)phenylamine **1a**, easily prepared in two steps from 2-nitrobenzaldehyde, was chosen as the model compound to investigate the viability of the strategy. Table 1 provides the results of a series of optimization experiments. These results show that the $PdCl_2(PPh_3)_2$ is the catalyst system of choice for this reaction. Thus, using DIPEA as the base, a 1:1 mixture of THF/MeOH as the solvent, under 10 atm of CO, and at 110 °C, the desired indole **2a** could be isolated in 70% yield (entry 9). While methanol is a good solvent for the reaction, and THF is not, a mixture of the two results in increased yield of **2a** (compare entries 8 and 10). When ethanol was used as the cosolvent, the ethyl ester **3a** could be obtained, but in slightly lower isolated yield (entry 11).

Using the conditions described in entry 9, the tandem N,C-coupling/carbonylation protocol was extended to other substrates substituted with different groups in the aromatic ring, and the target indoles were isolated in good yields (60−78%), as shown in Scheme 1. This method tolerates halogen, such as chlorine and fluorine substituents, as well as other electron donating and withdrawing groups.

We have also used substrates substituted at the nitrogen, and the desired indoles, including the tricyclic **2n**, could also be obtained according to the same protocol in good isolated yields (Scheme 3).

In an attempt to further exploit the versatility of the catalytic system, the tribromide **1b** was subjected to the aforementioned conditions. The indole **2h** was isolated in 65% yield, proving that three steps (N,C-coupling and two consecutive carbonylations) can take place in the same autoclave, using the same catalyst (Scheme 4).

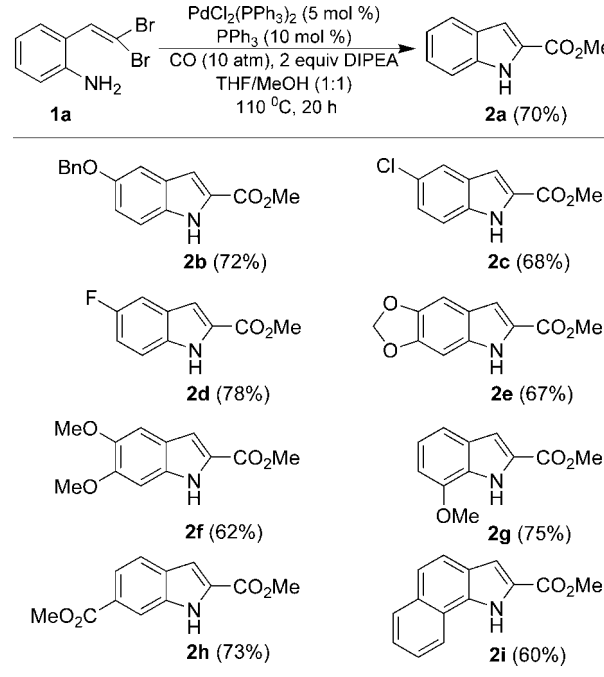
Table 1. Selected Screening for the Tandem N/C-Coupling−Carbonylation of **1a**[a]



entry	catalyst	base	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$	DIPEA	dioxane	20
2	$Pd(PPh_3)_4$	DIPEA	toluene	27
3	$Pd(PPh_3)_4$	DIPEA	MeOH	41
4	$Pd(PPh_3)_4$	Et_3N	MeOH	31
5	$Pd(PPh_3)_4$	DBU	MeOH	23
6	$Pd(PPh_3)_4$	DMAP	MeOH	35
7	Pd(dppe)	DIPEA	MeOH	NR
8	$PdCl_2(PPh_3)_2/PPh_3$	DIPEA	MeOH	57
9	$PdCl_2(PPh_3)_2/PPh_3$	DIPEA	THF/MeOH	70
10	$PdCl_2(PPh_3)_2/PPh_3$	DIPEA	THF	--[c]
11	$PdCl_2(PPh_3)_2/PPh_3$	DIPEA	THF/EtOH	61[d]

[a] All reactions were carried out with 1 mmol of **1a**, 5 mol % of the catalyst, 2 equiv of base, 8 mL of solvent, at 110 °C, under 30 atm (10 atm for entries 8−11) of CO, for 16 h (20 h for entries 8−11); 0.5 mL of MeOH was added to reactions not performed in this solvent. [b] Isolated yield. [c] Less than 40% conversion. [d] The ethyl ester **3a** was isolated instead.

Scheme 2. Synthesis of Indoles Substituted with Different Groups



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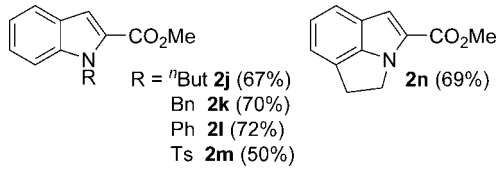
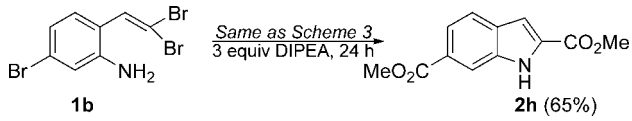
Scheme 3. Synthesis of Indoles Substituted at the Nitrogen



In conclusion, this research has led to a novel and efficient protocol for the synthesis of 2-carboxyindoles, through a one-pot palladium-catalyzed N,C-arylation/carbonylation sequence. The CO pressure employed is moderate,[13] and the isolated yields are good. The reaction applies to indoles bearing different patterns of substitution at the aromatic ring, as well as at the nitrogen atom. The present approach opens new opportunities for the synthesis of the pharmacologically important indole moieties.

Scheme 4



Acknowledgment. We are indebted to SASOL Technology and to the Natural Sciences and Engineering Research Council of Canada for financial support of our research.

Supporting Information Available: Full experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for all synthesized indoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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