Palladium-catalyzed C-3 Benzylation of Indoles with Benzyltributylammonium Chloride

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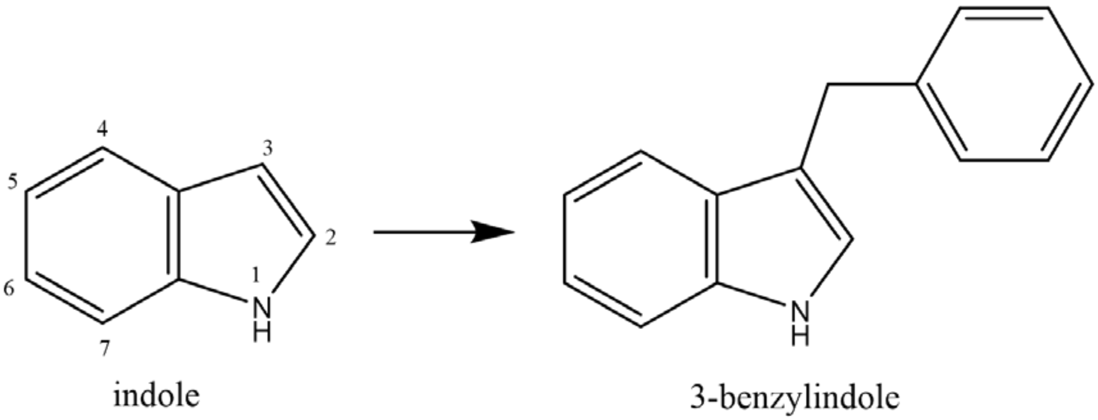
Abstract:

The indole scaffold probably represents one of the most important structural subunits for the discovery of new drug candidates. In recent years the transition metal induced-synthesis of indole compounds has gained increased popularity. However, simple alkylation of indole suffers problems such as regioselectivity at C-3, C-2, and N-1 positions.[1] The purpose of this study is to study the benzylation of indole, specifically at the C-3 position, with benzyltributylammonium chloride (Fig. 1) using palladium catalysts. Using $Pd(OAc)_2$ (II), a 40% conversion from indole to 3-benzylindole was achieved. The product was determined via GC-MS and H^1-NMR. Optimization of reaction conditions followed by using various Pd catalysts with different oxidation states which found ammonium hexachloropalladate (IV) to obtain the highest conversion of 82%. Substituted indoles were then reacted to determine C-3 regioselectivity. Percent conversion varied between substituted indoles.

Introduction:

Development of a new efficient, selective, and green synthetic method for the preparation of 3-substituted indole derivatives has drawn much attention because of their important roles as versatile building blocks for the synthesis of therapeutic and biologically active compounds, medicines, and natural products.[1] The focus on its synthesis and selective modification has been very much prevalent for many years. However, simple alkylation of indole suffers problems such as region-selectivity at C-3, C-2, and N-1 positions.[2] Alkylation reactions performed independently by both Imm and Ramachandiran show some reactivity at the C-3 position when a catalyst is present however both methods appeared to have flaws.[1,3] In the reactions performed by Imm et al., a di-indole is usually produced and is most likely due to the reaction conditions of using argon with a ruthenium catalyst. Ramachandiran used palladium (II) acetate as a catalyst at a lower temperature which resulted in di-indoles as well.

Up until recently in order to benzylate an indole, a multi-step reaction using toxic reagents was necessary. A traditional step in this process is alkylation by alkyl halides which is innately not ideal because of its poor regioselectivity. In order to achieve good regioselectivity, large amounts of acids and expensive reagents are needed and even though result in low yields. I proposed a novel method that, along with being classified as "green chemistry," results in the direct, regioselective benzylation of indole at the C-3 position using benzyltributylammonium chloride and a palladium catalyst. Optimization of reaction conditions were performed along with optimization of the palladium catalyst, after which substituted indoles were also tested for reactance.



Scheme 1. Reaction Scheme of Indole Benzylation via Benzyltributylammonium Chloride and Ammonium Hexachloropalladate(IV)

Methods:

Indole was reacted with benzyltributylammonium chloride in water at 110°C under air for 16 hours followed by the addition of the palladium catalyst, potassium carbonate and water and then heated and stirred at 110°C in a closed vessel for an additional 16 hours.

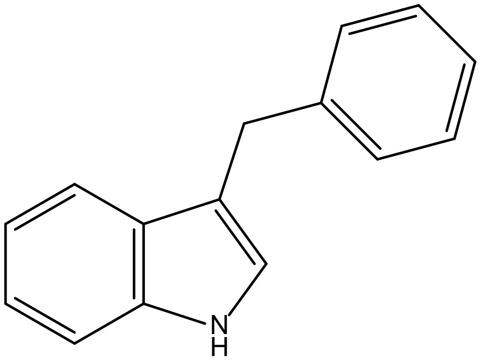
Optimization of the palladium catalyst was performed using indole under the above reaction conditions. Palladium catalysts tested had various oxidation states to see if it had any effect. Catalysts used included Pd/C (0), Bisbenzylidene Pd (0), $PdCl_2$ (II), $Pd(OAc)_2$ (II), K_2PdCl_6 (IV) and $(NH_4)_2PdCl_6$ (IV).

Optimization of reaction conditions were performed using 2-phenylindole to determine the optimal ratio of reagents to indole for the highest product conversion. The amount of starting indole was kept constant while, individually, the amount of ammonium salt, base and catalyst were varied.

Once optimized, multiple substituted indoles were used to determine the effect a substituent would have on product conversion as well as product formed. Substituted indole used in the experiment included 1-methylindole, 2-methylindole, 2-phenylindole, 5-bromoindole, 5-methoxyindole, 5-nitroindole, 7-azaindole, 7-ethylindole and 7-methoxyindole.

Results and Discussion:

Initial reaction conditions were used using indole in order to determine if the reaction worked.



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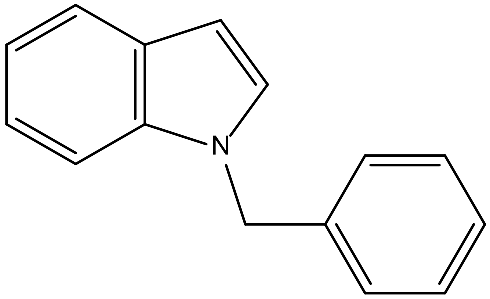

2a

After determination of a successful reaction using the initial reaction conditions, steps can be taken towards optimization of the reaction conditions in order to achieve the best possible ratio of reagents in order to achieve the highest possible conversion.

For the first aspect of optimizing the reaction conditions, various palladium catalysts with various oxidation states were tested.

GC-MS was determined to be a quick and effective method for determining the position of benzylation through the fragmentation patterns which later ^{1}H-NMR and ^{13}C-NMR results agreed with.

Table 1. Percent conversion of indole using various palladium catalysts.[a]

Palladium Catalyst	**Conversion (%)[b,c]**
Pd(0) on activated carbon	15
Bisbenzylidene Pd(0)	57
$PdCl_2$(II)	26
$Pd(OAc)_2$(II)	40
K_2PdCl_6(IV)	43
$(NH_4)_2PdCl_6$(IV)	82

[a] Reaction conditions: 7-ethylindole (1.0 mmol), $BnBu_3N^+$ (2.0 mmol), 2 ml H_2O, under air, 16 h. Addition: Pd catalyst (5 mol-%), K_2CO_3 (2.5 mmol), 5 ml H_2O, closed vessel, 16 h. [b] Based on specific indole. [c] Determined by GC-MS.

Ammonium hexachloropalladate(IV) was found to have the greatest conversion with 82%. Interestingly enough there were mixed results between the conversions of different oxidation states. Literature shows Pd(0) on activated carbon or a similar transition metal of 0 oxidation state to be the "go-to" metal as its utilization in cross-coupling reactions is well-documented. This begs the question as to why such a high conversion was found with such a high oxidation state.

Table 2. Optimization of reaction conditions.[a]

Entry	$BnBu_3N^+$ [mmol]	Catalyst [mol-%]	K_2CO_3 [mmol]	Temp. [°C]	Conv. [%][c,d]
1[b]	2	5	2.5	110	3
2	2	5	2.5	110	8
3	1	5	2.5	110	11
4	3	5	2.5	110	40
5	4	5	2.5	110	58
6	5	5	2.5	110	39
7	2	5	1.25	110	6
8	2	5	5	110	9
9	2	5	7.5	110	14
10	2	10	2.5	110	19

[a] Reaction conditions: 2-phenylindole (1.0 mmol), $BnBu_3N^+$, 2 ml H_2O, under air, 16 h. Addition: $(NH_4)_2PdCl_6$, K_2CO_3, 5 ml H_2O, closed vessel, 16 h. [b] Neat, closed vessel, 16 h. [c] Based on 2-phenylindole. [d] Determined by GC-MS.

Optimization of reaction conditions found that benzyltributylammonium chloride obtained its highest conversion in a 4:1 ratio with 2-phenylindole at 58%. At 5:1, the conversion seemed to drop which may suggest that there is a limit to the amount of ammonium salt that will react with the indole. Increasing the amount of catalyst seemed to have no effect on the overall conversion whereas increasing the amount of K_2CO_3 to a ratio of 3:1 only had a slight increase in conversion to 14%.

Table 3. Testing of indole and substituted indole under optimal* reaction conditions.[a]

Substituted indole	**Conversion [%][b,c]**
1-methylindole	6
2-methylindole	50
2-phenylindole	10
5-bromoindole	3
5-methoxyindole	16
5-nitroindole	no reaction
7-ethylindole	82
7-methoxyindole	17
Indole	91

[a] Reaction conditions: indole (1.0 mmol), $BnBu_3N^+$ (2.0 mmol), 2 ml H_2O, under air, 16 h. Addition: $(NH_4)_2PdCl_6$ (5 mol-%), K_2CO_3 (2.5 mmol), 5 ml H_2O, closed vessel, 16 h. [b] Based on specific indole. [c] Determined by GC-MS.

All tested indoles showed regioselectivity towards the C-3 position, albeit with different conversion success. Results were mostly expected with electron-donating groups helping with ring activation, and electron-withdrawing groups doing the opposite. An interesting find, however, is the low conversion success on both 5-methoxyindole and 7-methoxyindole which in aromatics are coined as electron-donating groups. The 7-methoxyindole should have at least performed somewhat close to that of 7-ethylindole. 7-azaindole was also tested and found to completely convert in a 1:1 ratio benzylation either on N-1 or N-7, N-1 benzylation shown as in **2a**.

Conclusion:

Direct benzylation of indole has eluded organic chemists in recent years with most benzylation occurring through multiple, toxic reactions. Regioselective benzylation of indole at the C-3 position using benzyltributylammonium chloride and ammonium hexachloropalladate (IV) has been successful with a high conversion using this green chemistry approach. Substituted indole for the most part all behaved as expected with the electron-donating groups promoting ring activation whereas electron-withdrawing groups having a negative effect on ring activation. Having a substituted indole at the N-1 position leads to little-to-no reaction which makes sense since ring activation in indole occurs through the N-1 position. Though conversion does vary in substituted indoles, further optimization, specific to the indole, can lead to higher conversion and thus higher yields. This novel method can lead to a “greener” approach in the design of many new substances.

References:

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