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$PtCl_4$-catalyzed cyclization of *N*-acetyl-2-alkynylanilines: A mild and efficient synthesis of *N*-acetyl-2-substituted indoles

Nattawadee Chaisan [a], Wilailak Kaewsri [a], Charnsak Thongsornkleeb [a,b,*], Jumreang Tummatorn [a,c], Somsak Ruchirawat [a,c]

[a] Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology (EHT), Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand
[b] Laboratory of Organic Synthesis, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand
[c] Laboratory of Medicinal Chemistry, Chulabhorn Research Institute, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand

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ABSTRACT

An efficient synthesis of *N*-acetyl-2-substituted indole derivatives *via* direct intramolecular hydroamination of *N*-acetyl-2-alkynylaniline derivatives was developed. The reaction could be applied to a wide range of substrates employing only 1–2 mol% of $PtCl_4$ as the catalyst to furnish the desired indole products in moderate to excellent yields. The current protocol is efficient, reliable and scalable, and could serve as an important tool for convenient and rapid access to this important class of *N*-heterocyclic skeleton from readily available substrates.

Introduction

It would be very difficult to overemphasize the importance of indoles in compounds of biological, pharmacological and medicinal significance. The realm of natural products, marketed drugs and compounds in clinical trials is filled with molecules containing indole nucleus in their structures as exemplified in Fig. 1.[1] In fact, indole can be referred as a privileged structure of significant medicinal values. As a result, many chemists are still actively investigating strategies and methods for efficient generation of this essential nucleus as evidenced in the literature.[2]

Several strategies and methods for the preparation of indole derivatives have been described starting from a variety of substrates.[2b,c] One of the most common and reliable strategies focuses on the direct intramolecular hydroamination of 2-alkynylaniline derivatives employing bases,[3a,b] electrochemical method,[3c] and a wide variety of transition metal catalysts.[4] In addition, 2-alkynylaniline derivatives have also been employed in tandem intramolecular cyclization-functionalization to provide indole scaffold with the incorporation of different functional handles.[5] For the method employing transition metal catalysts, the most prevalent catalysts utilized were based on palladium,[4a,b] indium[4e] and gold complexes.[4d,f,h] However, some of the reactions carried out using these catalysts suffer from high catalyst loading (5–10 mol %), high reaction temperatures (50–110 °C), and/or long reaction time (up to 24 h in some systems).[4] In addition, most of these methods seemed to work well only with the 2-alkynylaniline substrates containing free amino group (–NH_2) while there were only few published methods of *N*-protected 2-alkynylaniline substrates undergoing the cyclization. For examples, $PdCl_2(CH_3CN)_2$ (13 mol %) in refluxing acetonitrile[4b] and $InBr_3$ (5 mol%) in refluxing toluene[4e] were utilized in the cyclization of *N*-acetyl-2-alkynyl anilines to provide the corresponding *N*-acetyl indole products in relatively moderate yields of 69% and 71%, respectively (Scheme 1). To expand the repertoire of methods available in the synthetic toolbox for the construction of this very important class of heterocyclic skeleton, we wish to report $PtCl_4$ as a mild and very efficient catalyst for the conversion of *N*-acetyl-2-alkynylanilines to *N*-acetyl-2-substituted indoles. The current procedure is highlighted by low catalyst loading, low reaction temperature, and applicability to a wide range of substrates.

* Corresponding author at: Program on Chemical Biology, Chulabhorn Graduate Institute, Center of Excellence on Environmental Health and Toxicology (EHT), Ministry of Education, 54 Kamphaeng Phet 6, Laksi, Bangkok 10210, Thailand.
E-mail address: charnsak@cri.or.th (C. Thongsornkleeb).

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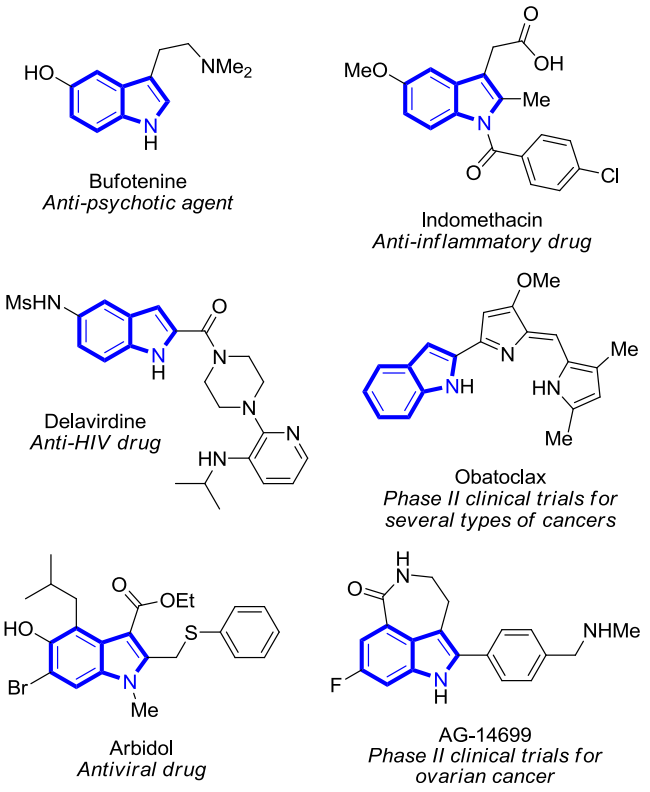
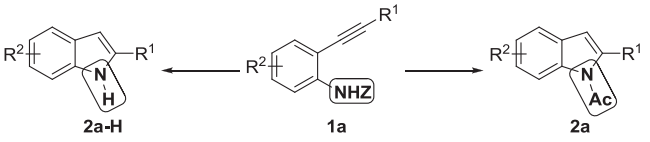


Fig. 1. Examples of natural products, marketed drugs and compounds in clinical trials containing indole scaffolds.

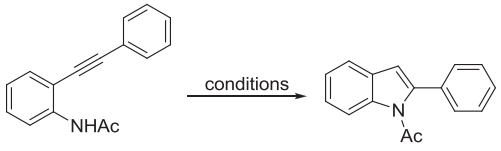


Scheme 1. Methods for the construction of indole derivatives *via* hydroamination of 2-alkynylanilines.

Results and discussion

To commence the investigation, substrate **1a** was constructed[6] and employed in the optimization study. We subjected compound **1a** to conditions as summarized in Table 1. We focused on screening the reaction with platinum catalysts for the cyclization of substrate **1a**. As summarized in Table 1, when 10 mol% of K_2PtCl_6 was utilized in DCM, the conversion of alkynylaniline **1a** to the corresponding indole **2a** was effected in 86% yield after stirring the reaction mixture at room temperature overnight (entry 1). $PtCl_2$ was next investigated; at 10 mol% in DCM at room temperature overnight, compound **1a** was smoothly converted to indole **2a** with excellent efficiency (98%, entry 2). However, in an attempt to lower the catalyst loading to 2 mol% of $PtCl_2$, product **2a** was obtained in only 37% yield (entry 3). $PtCl_4$ was next investigated, first at 10 mol %. At this amount, the reaction was complete within 3 h and the desired product was obtained in 96% yield (entry 4). When the amount of $PtCl_4$ was lowered to 5 mol%, the reaction took longer to complete (5 h), however, the desired product **2a** was obtained with comparable efficiency (99%, entry 5). In an attempt to study the effect of different solvents, the cyclization was conducted with 5 mol% of $PtCl_4$ in acetonitrile and DMF at room temperature for 4 h and 3 h, respectively, to find that the reactions produced no product, but only recovered starting material **1a** (entries 6–7). This result was in a stark contrast to the previous report that $PdCl_2$ could effect the same conversion in refluxing acetonitrile,[4b] while $PtCl_4$ in our reaction seemed to be shut down in acetonitrile. From these results, it was sufficient to conclude that DCM was the solvent of choice for this transformation. In lowering the amount of $PtCl_4$ catalyst even further, it was found that 2 mol% of the catalyst could fully convert compound **1a** to the corresponding indole **2a** in excellent yield upon stirring at room temperature in DCM overnight (entry 8). A comparable yield (97%, entry 9) of product **2a** was obtained when the reaction was conducted with 1 mol% of $PtCl_4$. Finally, the reaction with the catalyst loading as low as 0.5 mol% was attempted (entry 10). Under these conditions, the reaction became significantly more sluggish and even after allowing the reaction to stir at room temperature overnight, only 8% yield of the desired indole product was obtained with the recovery of all remaining starting material. We suspected that at such extremely low catalyst loading, the reaction required much longer time to initiate and

Table 1
Optimization of cyclization of compound **1a** to indole **2a**.



Entry	Catalyst	Equiv	Solvent	Temp	Time	Yield[a]
1	K_2PtCl_6	10 mol%	DCM	rt	Overnight	86%
2	$PtCl_2$	10 mol%	DCM	rt	Overnight	98%
3	$PtCl_2$	2 mol%	DCM	rt	Overnight	37%
4	$PtCl_4$	10 mol%	DCM	rt	3 h	96%
5	$PtCl_4$	5 mol%	DCM	rt	5 h	99%
6	$PtCl_4$	5 mol%	CH_3CN	rt	4 h	NR
7	$PtCl_4$	5 mol%	DMF	rt	3 h	NR
8	**$PtCl_4$**	**2 mol%**	**DCM**	**rt**	**Overnight**	**99%**
9	$PtCl_4$	1 mol%	DCM	rt	Overnight	97%
10	$PtCl_4$	0.5 mol%	DCM	rt	Overnight	8%

[a] Isolated yields.