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A *trans* diacyloxylation of indoles†

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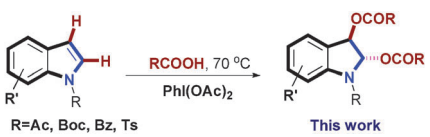
A *trans* diacyloxylation of indoles is accomplished by employing $PhI(OAc)_2$ as the oxidant. A broad range of functional groups are well tolerated. Both the electronic properties of the *N*-protecting groups of indoles and the acidity of the reaction media play important roles in the selectivity of indole acyloxylation reactions.

Indolines are structural scaffolds frequently found in important pharmaceuticals and biologically active natural compounds.[1] Inspired by Nature's efficiency of selective indole oxidation[2] and as part of our efforts in developing efficient methodologies for the functionalization of indoles,[3] we aimed to discover a convenient and versatile method towards the synthesis of 2,3-disubstituted indolines directly from the oxidation of widely available indole derivatives.[4] In this work, we describe a $PhI(OAc)_2$ promoted stereoselective diacyloxylation of indoles bearing electron deficient *N*-protecting groups. *Notably*, *only trans diacyloxylated indolines were obtained* (Scheme 1). *N*-Acetyl-2,3-diacetoxylindolines have been previously synthesized *via* electrochemical synthesis from indolines.[5] We report herein the organic synthesis of these important compounds *via* one-step diacyloxylation of indole derivatives.

Actually, dioxygenation of alkenes is an attractive transformation to make valuable compounds from widely available starting materials, among which OsO_4 catalyzed dihydroxylation is the most famous protocol.[6] During the past decade, remarkable progress has been made in the metal-facilitated olefin dioxygenation reactions including Pd,[7] Cu,[8] Ru,[9] Fe[10] and Mn.[11] However, the use of precious and/or toxic metal catalysts as well as the generation of high levels of inorganic wastes hindered the further application of these metal catalyzed processes. As a result, to explore powerful transition-metal-free procedures is an important direction.[12] Moreover, the stereo-selective dioxygenation of olefins is still challenging. The *syn* dioxygenate is usually the major product. Hence it is a significant task to achieve the *anti* dioxygenation of olefins.[13] A traditional method to synthesize *anti*-diols from alkenes is Prévost reaction, which suffers from the usage of a stoichiometric amount of silver salt.[14] Last but not the least, the dioxygenation of enamines and heterocycles containing enamine substructures has been rarely reported. All in all, this *trans* diacyloxylation of indoles reaction meets all the above-mentioned requirements for the further development of olefin dioxygenation reactions.



Scheme 1 *Trans* diacyloxylation of indoles.

We started this study by choosing 1-(1*H*-indol-1-yl)ethanone (R = Ac, R′ = H, Scheme 1) **1a** and $PhI(OAc)_2$ **2** as the model substrates to explore the behaviour of indoles bearing electron deficient *N*-protected groups in oxidative acetoxylation reactions. Noteworthily, a new product was isolated after 1 hour in 68% yield when acetic acid was used as the solvent at 70 °C. From the NMR and HRMS results, we preliminarily assigned it as the *trans*-diacetoxylated product of indole derivatives **1a**. A very similar result was also obtained for *tert*-butyl 5-methyl-1*H*-indole-1-carboxylate **1b**, and the isolated yield of the corresponding diacetoxylated product was 82% (Table 1, **3b**). Subsequently, the X-ray single crystal structures of **3a** and **3b** were obtained, which further unambiguously confirmed the structures and stereo-configuration of these products (Fig. S1, ESI†).

For this diacetoxylation reaction, the reaction conversion was dramatically influenced by acidity of the reaction media (Table S1, ESI†). The best result was obtained by using acetic acid as the sole solvent. Apart from the solvents, the *N*-protecting groups of indoles should be electron deficient groups, which was another key factor for the success of this reaction. Both indoles without any *N*-protecting groups and indoles bearing electron donating *N*-protecting groups were decomposed into unknown side-products under the standard conditions as shown in Table 1.

We then evaluated the scope of different *N*-Boc and *N*-Ac protected indoles, and the reactions of various substituted *N*-Boc and *N*-Ac protected indoles were investigated (Table 1). Regardless of the substituents, all of the reactions were carried out efficiently to afford the desired diacetoxylated indolines in good yields. The isolated yield for substrate **1g** was up to 96%. Functional groups such as chloro, bromo, methyl, benzyloxy and methoxy were well tolerated under the optimized reaction conditions (Table 1, **3a–3l**). It was worth mentioning that only *trans* diacetate products were isolated in these reactions. Moreover, the reactions of indoles bearing electron-donating

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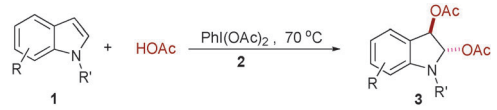
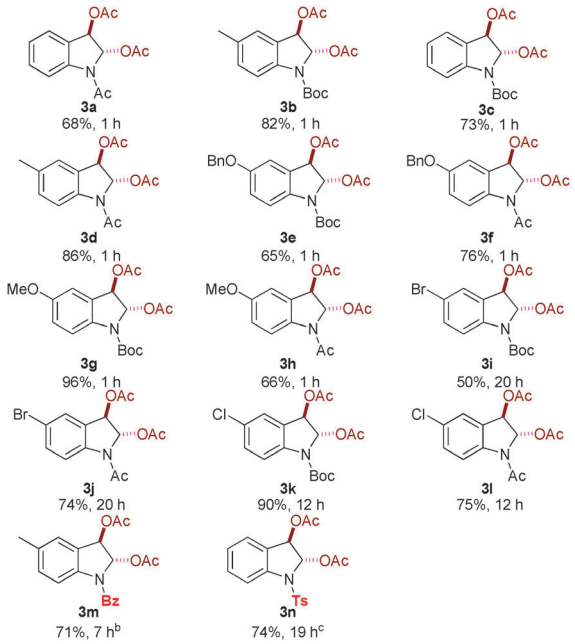
Table 1 Dearomatization/regio-selective diacetoxylation of indoles with $PhI(OAc)_2$[a]

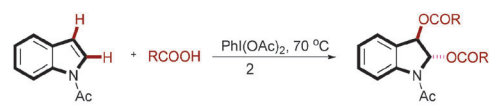




[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol) in 2 mL of HOAc at 70 °C. *trans*/*cis* > 99 : 1 for all the products determined by NMR. [b] 17% 1-benzoyl-5-methyl-1*H*-indol-3-yl acetate **4m** was also produced with 7% starting material recovered. [c] 20% starting material recovered.

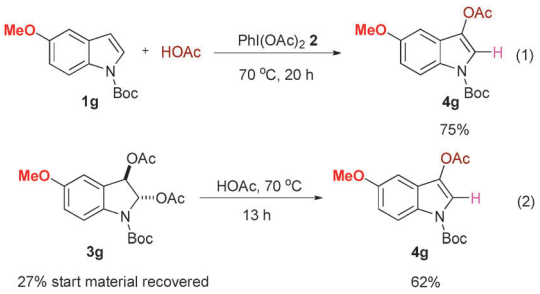
groups led to completion within 1 hour (Table 1, **3a–3h**), while those with electron-withdrawing groups required more than 12 hours (Table 1, **3i–3l**). As well as the *N*-Boc and *N*-Ac protected indoles, the reactions of both *N*-Bz and *N*-Ts protected indoles **1m** and **1n** all proceeded smoothly under the standard conditions. No *cis* diacetated products were observed for the reactions of **1m** and **1n** either.

Besides, diversified diacyloxylated indoles were prepared by simply changing the solvent from acetic acid to other acids. Employing *n*-propionic acid and *n*-octanoic acid would result in the corresponding *trans* diacylated products with the yields 63% and 50%, respectively (Scheme 2, entries 1 and 2). Interestingly, diacetoxylated indoles were not isolated because

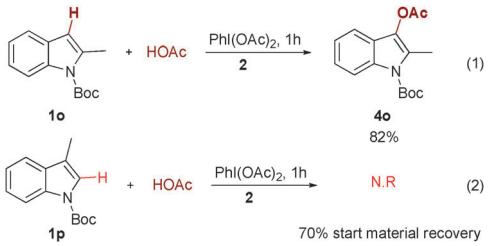


(1)	R=Et	63%	**3r**
(2)	R=C_7H_{15}	50%	**3s**
(3)	R=*t*Bu	35%	**3t**

Scheme 2 Diacyloxylation of 1-(1*H*-indol-1-yl)ethanone **1a**. *Reaction conditions*: **1b** (0.5 mmol), **2** (1 mmol) in 2 mL of RCOOH (R = Et, C_7H_{15} and *t*Bu) at 70 °C. *trans*/*cis* > 99 : 1 for all the products determined by NMR.



Scheme 3 Direct C3-acetoxylation of **1g**.



Scheme 4 Control experiments of **1o** and **1p**.

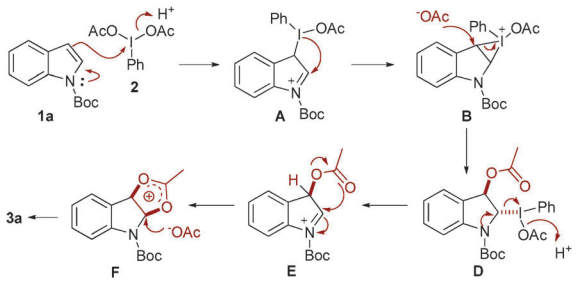
the acids as the coupling components are in large excess to **2**. However, the sterically hindered acid such as pivalic acid led to a lower yield. (Scheme 2, entry 3).

We also found that **1g** could efficiently generate *trans* diacetated product **3g** in 1 hour (Table 1, **3g**), but it was converted to C3-acetoxylated indole **4g** after 20 hours in 75% yield under the same conditions (Scheme 3, eqn (1)). When diacetate indoline **3g** was heated to 70 °C in acetic acid for 13 hours, 62% mono-acetate indole **4g** was isolated along with 27% recovered starting material (Scheme 3, eqn (2)). We therefore speculated that the thermodynamically favoured product **4g** was generated *via* elimination of acetic acid from the diacetate intermediate **3g**.

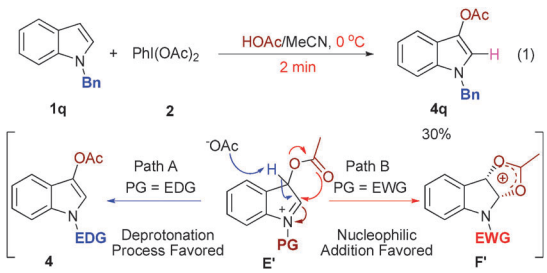
Control experiments were then performed to figure out which position (C2 or C3) on the indole ring was the initial reaction site (Scheme 4). **1o** reacted rapidly and efficiently to afford the C3-acetoxylated indole **4o** in 82% isolated yield (Scheme 4, eqn (1)). However, there was no diacetoxylation reaction upon treating **1p** under the same reaction conditions (Scheme 4, eqn (2)). The above results clarified that the reaction started by nucleophilic attack of the C3 position of indole to $PhI(OAc)_2$, which was facilitated by the acid. Very recently, Gade and Kang also reported that the proton was the catalytically active species in olefin dioxygenation with $PhI(OAc)_2$.[12c]

We propose the reaction pathways as shown in Scheme 5. Initially, intermediate **A** is generated *via* the nucleophilic attack of **1a** towards **2** promoted by the proton and further converted to the iodonium salt **B** *via* intramolecular nucleophilic attack of iodine. The acetate attacks C3 position of iodine **B** to afford *trans* intermediate **D**. The acetoxyl group attached to the iodine is then protonated and undergoes intramolecular nucleophilic attack to generate *cis* oxygen cation intermediate **F**, which determines the *trans*-selectivity of this diacetoxylation reaction. The acetate anion finally attacks from the opposite site of oxygen atoms of *cis* intermediate **F** to afford *trans diacetated* indoline **3a**.

According to the proposed mechanism, indoles bearing the electron donating *N*-protecting groups, which are more electron



Scheme 5 Direct C3-acetoxylation of **1g**.



Scheme 6 Direct C3-acetoxylation of **1q**.

rich, should undergo this process more readily. With this idea in mind, we treated **1q** with $PhI(OAc)_2$ **2** in a mixture of acetic acid and acetonitrile (1 : 1). The reaction was complete *within* 2 *minutes at* 0 °C to afford the C3-acetoxylated indole **4q** in 30% yield (Scheme 6, eqn (1)). In fact, no diacetoxylated product of **1q** was observed in this reaction. We rationalized the reaction selectivity as shown in Scheme 6. When an electron-withdrawing group was attached to the *N*-atom of indole (Scheme 6, Path B), the intramolecular nucleophilic addition of intermediate **E′** was preferred to generate the oxygen cation **F′**, which could be converted to diacetoxylated indoline finally (refer to Scheme 5). When the intermediate **E′** bears the electron donating *N*-protecting group (Scheme 6, Path A), the inter-molecular deprotonation could be favoured, which produced the more stable aromatic mono-acetoxylated product **4q**.

In conclusion, we developed an efficient diacyloxylation of indoles with $PhI(OAc)_2$ as the oxidant in the presence of carboxylic acid as the solvent. Interestingly, only *trans* diacyloxylated indolines were obtained, revealing a high stereo-selectivity. Moreover, a broad range of functional groups were well tolerated under these reaction conditions. On the basis of our observations, it is clear that both the electronic properties of the *N*-protecting groups of indoles and the acidity of the reaction media play important roles in the selectivity of this transformation. Related studies into asymmetric diacyloxylation of indoles and other heterocycles are underway in our laboratory.

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