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Catalytic Direct Acetoxylation of Indoles

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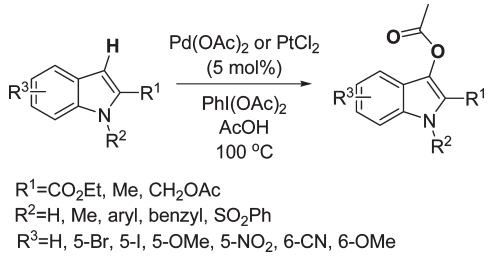

3-Acetoxyindole-2-carboxylates could be readily synthesized in a $Pd(OAc)_2$- or $PtCl_2$-catalyzed direct C-3 acetoxylation of indole-2-carboxylates using $PhI(OAc)_2$ as a terminal oxidant.

Substituted 3-oxyindoles are common scaffolds in medicinal chemistry. Thus, 3-aryloxy- and 3-alkoxyindoles have been employed in the development of COX-2 inhibitors,[1a] used as Mcl-1 inhibitors in the design of novel antitumor agents[1b] and synthesized for the treatment of respiratory disorders.[1c,d] Specifically, 3-hydroxyindole-2-carboxylates have been used as key synthetic building blocks in the development of potent PPARγ (peroxisome proliferator-activated receptor γ) modulators.[2]

3-Hydroxyindole-2-carboxylic acid esters are traditionally synthesized by Dieckmann cyclization of *N*-substituted anthranilic esters (Figure 1, route A).[3] However, this approach suffers from moderate yields and is limited by the lack of availability of properly substituted anthranilates. Alternatively, 3-alkoxyindole-2-carboxylic esters have been prepared from 3-bromoindoles by a lithiation−boronation−oxidation reaction sequence (route B)[4,5] or from 3-formylindole-2-carboxylates by a Baeyer−Villiger oxidation (route C).[6] Recently, a Pd-catalyzed alkoxylation of 3-bromoindoles has also been reported.[1b] In all cases, the syntheses are multiple-step processes and require suitably substituted starting materials. Another efficient approach to 3-hydroxy- and 3-alkoxyindole-2-carboxylates makes use of a Rh(II)-catalyzed insertion of 3-diazoindole into OH and OR bonds.[7] However, this method is restricted to *N*-unsubstituted indole-2-carboxylates. Furthermore, the poor stability of diazoindoles compromises the utility of this transformation. Finally, 3-acyloxyindole-2-carboxylic acid esters could also be accessed in poor yields (<30%) from the corresponding 1-hydroxyindoles.[8]

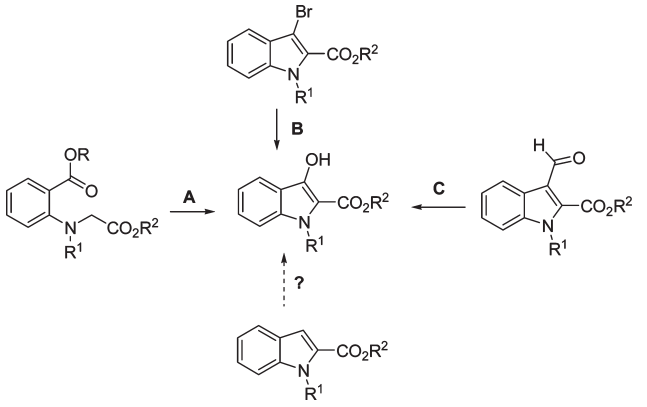

FIGURE 1. Synthetic approaches toward 3-hydroxyindole-2-carboxylates.

The most straightforward access to 3-hydroxyindole-2-carboxylates is a direct regioselective oxidation of the heterocycle. Notably, there are only scattered reports on the C-3 oxidation of the indole nucleus, and only a few of them provided 3-hydroxyindoles in synthetically useful yields. Thus, oxidation of ethyl *N*-methylindole-2-carboxylate with $Pb(OAc)_4$ furnished the corresponding 3-acetoxy derivative in 25% yield, while the *N*-unsubstituted analogue gave a dimer under the reaction conditions.[9] The use of benzoyl peroxide as an oxidant afforded *N*-methyl-3-benzyloxyindoles in moderate 50−56% yield.[10] Alternatively, Mg monoperoxyphthalate was employed in the oxidation of *N*-phenylsulfonylindole to the corresponding indol-3-one (60% yield, single example).[5] *N*-Substituted 3-acyloxyindoles were also formed as minor

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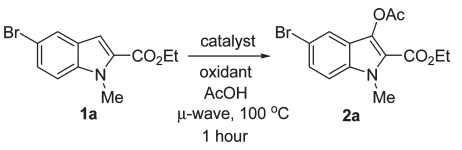
products in the synthesis of 2,3-diacetyloxyindoles by oxidation of indoles in carboxylic acid media with *N*-iodosuccinimide.[11] Clearly, an improved method for the direct regioselective oxidation of indoles would be of value.

We envisaged that the most suitable way toward 3-oxyindoles would be a Pd(II)-catalyzed C−H activation−oxidation strategy. This concept was pioneered by Henry[12] and Eberson[13] in the early 1970s and later developed by Sanford[14] into a regioselective heteroatom-directed acetoxylation of arenes. This synthetic approach is based on an electrophilic metalation of an arene with a Pd(II) species, oxidation of the resulting σ-aryl-Pd(II) intermediate, and reductive elimination of an acetyloxyarene from the Pd(IV) complex.[15] Indoles, owing to their electron-rich character, readily undergo metalation with electrophilic transition-metal salts,[16] usually Pd(II) complexes, affording C-3-[17] or C-2-cyclopalladated[18] intermediates. It has been suggested that the C-3 position is the preferred site for electrophilic palladation and that the isomeric C-2 palladium complexes form by a 1,2-migration of Pd(II) species.[19] The formation of the C-2 indolyl-Pd species is not possible in the case of *N*-substituted indole-2-carboxylates. However, electron-withdrawing C-2 ester moieties may decrease the electrophilicity of the C-3 position, rendering the indole less reactive toward palladation.[19a]

N-Methyl-5-bromoindole-2-carboxylic acid ester **1a** was chosen to test the feasibility of the C−H activation−oxidation in indoles using Pd(II) salts. We were delighted to find that the acetoxylated product **2a** was readily formed in 75% yield (Table 1, entry 1) under the conditions developed by Crabtree.[20]

In the absence of $Pd(OAc)_2$, acetoxyindole **2a** was formed in negligible amounts (< 5%) (Table 1, entry 2) ruling out the scenario of direct C-3 oxidation of indole by $PhI(OAc)_2$.[21] Notably, $PtCl_2$ turned out to be a superior catalyst to $Pd(OAc)_2$ as 3-acetoxyindole **2a** was formed in 91% yield (entry 4). However, the product **2a**, was contaminated with the corresponding 3-Cl-**2a** (< 5% GC yield). Evidently, the C−Cl bond was formed in a competing (Cl vs OAc) product-forming reductive elimination from a Pt(III) {or Pt(IV)} complex.[22] Surprisingly, $Pt(OAc)_2$[23] was considerably less efficient than $PtCl_2$ (entry 5 vs entry 4). Thus, indole **2a** was formed in only 30% yield (entry 5) together with large amounts (ca. 50%) of unidentified side products. In contrast, $PdCl_2$ was inferior to $Pd(OAc)_2$ (entry 3 vs entry 1).

TABLE 1. Evaluation of the Acetoxylation Conditions[a]



			GC yield[b] (%)	
entry	catalyst (mol %)	oxidant (equiv)	**1a**	**2a**
1	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.3)	9	75
2	none	$PhI(OAc)_2$ (1.3)	95	< 5
3	$PdCl_2$ (5)	$PhI(OAc)_2$ (1.3)	23	59[c]
4	$PtCl_2$ (5)	$PhI(OAc)_2$ (1.3)	< 1	91[c]
5	$Pt(OAc)_2$ (5)	$PhI(OAc)_2$ (1.3)	20	30[d]
6	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2.0)	99	0
7	$Pd(OAc)_2$ (5)	Oxone (1.0)	< 1	5[d]
8	$Pd(OAc)_2$ (5)	*m*-CPBA (2.0)	57	0
9	$Pd(OAc)_2$ (5)	*t*-BuOOH (2.0)	77	0
10	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (2.0)	99	0
11	$Pd(OAc)_2$ (5)	Mg peroxyphthalate (2.0)	20	18[d]

[a]Reactions were run in a sealed vessel single-mode microwave reactor using 0.5 mmol of indole **1a** in 2.0 mL of AcOH. [b]Calibrated GC yields ($C_{11}H_{24}$ as an internal standard). [c]Accompanied with ~5% of 3-chloro-**2a**. [d]Accompanied by a mixture of unidentified oxidation products.

Various alternative oxidants were also examined.[24] $K_2S_2O_8$, *m*-CPBA, *t*-BuOOH, and $Cu(OAc)_2$ were totally inefficient (0% conversion; entries 6, 8−10), while the use of Oxone resulted in an inseparable mixture of oxidation products (entry 7). High conversion (80%) was observed in the case of Mg peroxyphthalate (entry 11), but the desired **2a** was formed in poor yield (18%).

The optimal conditions from entry 1 and entry 4 (Table 1) were subsequently employed to test the scope of the method (see Table 2). Although microwave dielectric heating was employed during evaluation of the acetoxylation conditions, the conventional oil bath heating afforded the acetoxylated indoles **2** in comparable yields (entries 2, 3, 5, 17, and 21, Table 2). Consequently, both heating modes could be used with comparable efficiency.

The Pd(II)-catalyzed oxidation was found to be sensitive to the electronic nature of the substituents on both the pyrrole and the benzene rings of the indole heterocycle. Thus, electron-releasing substituents on the indole benzene ring facilitated the oxidation (entries 5−6, Table 2), presumably by increasing the electrophilicity of the C-3

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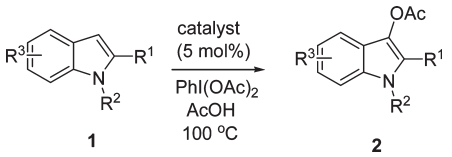
TABLE 2. Scope of the Direct 3-Acetoxylation of Indoles

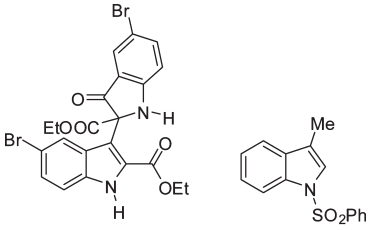


entry	indole **1**	R^1	R^2	R^3	catalyst[a]	$PhI(OAc)_2$ (equiv)	time (h)	conv (%)	yield of **2**[b] (%)
1	**a**	CO_2Et	Me	5-Br	A	1.3	2	99	77[c]
2					B	1.3	1	99	78 (82[c])
3	**b**	CO_2Et	Me	5-I	A	2.0	3	99	80 (71[c])
4					B	1.3	1	99	85[c]
5	**c**	CO_2Et	Me	5-OMe	A	1.3	2	99	75 (71[c])
6	**d**	CO_2Me	Me	6-OMe	A	1.3	0.5	99	67[c]
7	**e**	CO_2Et	Me	5-NO_2	A	2.0	16	99	63
8	**f**	CO_2Et	Me	6-CN	A	2.5	16	50	32
9					B	2.5	16	48	21
10	**g**	CO_2Et	4-Me-C_6H_4	5-Br	A	1.5	16	95	66
11	**h**	CO_2Et	3−Cl-C_6H_4	5-Br	A	1.3	2	51	44
12					A	2.0	18	99	60
13	**i**	CO_2Et	4-O_2N−C_6H_4	5-Br	A	1.3	2	34	27
14					A	2.5	16	65	48
15	**j**	CO_2Et	$PhCH_2$	5-Br	A	2.0	17	99	60
16	**k**	CO_2Et	H	5-Br	A	1.3	2	99	51[c]
17					B	1.3	1	99	67 (67[c])
18	**l**	CO_2Et	$PhSO_2$	5-Br	A	1.3	2	0	
19					B	1.3	2	0	
20	**m**	CH_3	$PhSO_2$	H	A	2.0	2	99	52[c]
21	**n**	CH_2OAc	Me	5-Br	A	1.3	2	99	76 (73[c])
22	**o**	Ph	H	H	A	1.3	2	99	0[c,d]

[a]Catalyst A: $Pd(OAc)_2$. Catalyst B: $PtCl_2$. [b]Yields refer to isolated products **2a**−**n**. [c]Microwave irradiation in a single-mode reactor was employed. [d]Unidentified mixture of products was formed.

position.[19a] On the contrary, electron-withdrawing groups substantially attenuated the reactivity (entries 7−9). Notably, the acetoxylation was found to be even more sensitive to the electronic nature of the substituents on the pyrrole ring. Thus, the time required to reach >95% conversion increased from 1−2 h to 16−18 h by switching the *N*-methyl group to the more electron-withdrawing *N*-aryl substituents (entry 1 vs entries 10,12), with *N*-(4-nitrophenyl)indole **1i** being the least reactive in the series (entry 14). The introduction of the strongly electron-withdrawing *N*-phenylsulfonyl moiety renders the indole **1l** completely unreactive (entries 18−19). Replacing the C-2 ester moiety with a methyl group (**1m**) re-established the reactivity of the indole (entry 20). Surprisingly, the *N*-benzyl-substituted indole **1j** required prolonged heating (17 h) to reach 99% conversion (entry 15 vs entry 1).

Importantly, none of the side-chain oxidation products were observed under the conditions employed (entries 20 and 21). As anticipated, neither bromo nor iodo substituents on the indole were affected under the conditions of the Pd(II)/Pd(IV) catalytic cycle (entries 1, 3, 10−16, 21)[25] or in the presence of $PtCl_2$ (entries 2, 4, 17). Acetoxylation of the *N*-unsubstituted indole **1k** was possible (entries 16 and 17). In the case of $Pd(OAc)_2$, the product **2k** was isolated in 51% yield (entry 16), accompanied by the dimeric side product **3** (~7% isolated yield).[26] Improvement of yields (up to 67%) and cleaner reactions were achieved by replacing $Pd(OAc)_2$ with $PtCl_2$ (entry 17). Interestingly, 2-phenylindole **1o** afforded a complex mixture of unidentified products under the acetoxylation conditions (entry 22).



The lack of reactivity in the case of the electron-deficient indole **1l** (entry 18) is consistent with the electrophilic C-3 palladation mechanism for the oxidation. Furthermore, none of the 2-acetoxylation products were observed when 2-unsubstituted 3-methylindole **4** was subjected to the Pd(II)-catalyzed oxidation conditions. These results reinforce the view that the formation of the σ-indolyl-Pd(II) complex occurs solely at the C-3 position.

The outcome of the 3-acetoxylation is heavily dependent on the amount of the $PhI(OAc)_2$ used. Thus, 1.3 equiv of the oxidant was sufficient to bring about the *O*-acetoxylation of electron-rich indoles (entries 1, 2, 4−6, and 21) in 67−85% yield. In contrast, the oxidation of electron-deficient indoles **1e**,**f**,**h**,**i** in the presence of 1.3 equiv of the oxidant stalled after ca. 2 h. Furthermore, the formation of Pd-black was observed, suggesting undesired reductive elimination of the products from the transient σ-indolyl-Pd(II) species, which inhibits the catalytic cycle. We speculate that reductive elim-

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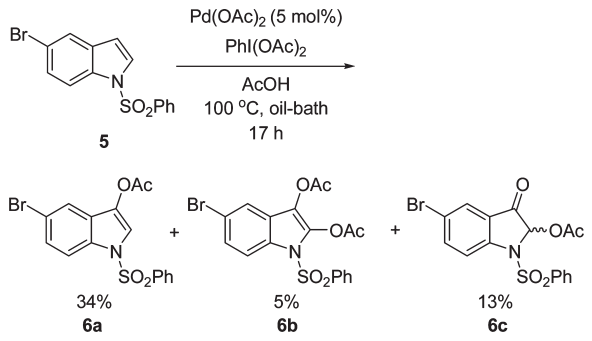
(26) The structure of the bis-indole **3** was determined by X-ray analysis.

SCHEME 1. Acetoxylation of 2,3-Unsubstituted Indole



ination is faster for Pd(II) complexes of the electronically deficient indoles **1e**,**f**,**h**,**i**,**l** as compared to the electronically sufficient analogues **1a**−**d**,**k**,**n**. This assumption is based on kinetic studies of a C−O bond-forming reductive elimination from a square planar aryl(alkoxo)Pd(II) complex.[27] The reductive elimination there was shown to be faster for aryl ligands possessing resonance-stabilizing substituents on the palladium-bound aryl group. We reasoned that the undesired reductive elimination from a σ-indolyl-Pd(II) complex could be circumvented by expediting the competitive oxidation of the transient Pd(II) complex to Pd(IV) species. Indeed, increasing the $PhI(OAc)_2$ load to 2.0−2.5 equiv improved the conversion (entries 12 and 14 vs 11 and 13, respectively) and afforded reasonable yields (entries 3, 7−10, 15, and 20).

Both $PtCl_2$ and $Pd(OAc)_2$ could be employed in the C−H activation−oxidation of indoles. Usually, the use of $PtCl_2$ gave higher or comparable yields and cleaner reactions (entry 2 vs 1, 4 vs ,3 and 17 vs 16). However, 3-Cl-indoles were always formed in $< 5\%$ yields when $PtCl_2$ was used as the catalyst. $Pd(OAc)_2$ was somewhat less efficient, although this is compensated by the lower cost of the catalyst.[28]

Finally, the $Pd(OAc)_2$-catalyzed oxidation of the 2,3-unsubstituted indole **5** was examined. As anticipated, a complex mixture of products was formed (Scheme 1). Among the major products isolated were the desired 3-acetoxyindole **6a** (34% yield), 2,3-diacetoxylated indole **6b** (5% yield), and indoxyl **6c** (13% yield).[29] The remaining material consisted of a number of unidentified minor side products. The formation of the C-2-oxidized side products **6b**,**c** evidently occurs via the C-3 to C-2 migration of the transient σ-indolyl-Pd(II) complex, followed by repeated electrophilic C-3 palladation of the intermediate C-2 acetoxyindole.

In summary, we have developed a convenient method for the direct C-3 acetoxylation of indole-2-carboxylates with $PhI(OAc)_2$ as the terminal oxidant. The oxidation could be catalyzed both by $Pd(OAc)_2$ and $PtCl_2$. The C−H activation/oxidation occurs most probably at the C-3 position as none of the 2-acetoxylation products was observed in the case of 2-unsubstituted 3-methylindole. The yields of the acetoxylation products are dependent on the electronic character of the substrate. Electron rich indoles readily undergo acetoxylation, while electron-deficient analogues require increased amounts of $PhI(OAc)_2$ (up to 2.5 equiv) and prolonged reaction times to achieve synthetically useful yields. Further studies to expand the application of the Pd(II)- and Pt(II)-catalyzed C−H activation−oxidation sequence toward the synthesis of 3-alkoxyindoles and 3-aryloxyindoles are ongoing in our laboratory.

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(28) $Pd(OAc)_2$, 98%: 92.30 euros/g; $PtCl_2$, 98% 166.00 euros/g (Aldrich Catalogue).

(29) The structure of **6c** was proven by X-ray analysis.

Experimental Section

Representative Procedure for Acetoxylation of Indoles Using $PtCl_2$. Ethyl 3-(acetyloxy)-5-bromo-1-methyl-1*H*-indole-2-carboxylate (Table 2, Entry 2). A Biotage microwave vial (2.0−5.0 mL size) equipped with a Teflon-coated stirring bar was charged with indole (0.5 mmol), $PtCl_2$ (5 mol %, 0.025 mmol, 6.7 mg), and 1.3−2.0 equiv of $PhI(OAc)_2$, and glacial acetic acid (2.0 mL) was added. The vial was closed using an aluminum open-top seal with PTFE-faced septum and heated in an oil bath at 100 °C for 1 h. After being cooled, the solution was diluted with EtOAc (50 mL), washed with water (2 × 25 mL) and brine, and dried over Na_2SO_4. Volatiles were removed (rotary evaporator), and purification of the crude product by column chromatography (40 mL silica gel, column i.d. 30 mm) using gradient elution from 4% EtOAc/petroleum ether to 15% EtOAc/petroleum ether afforded the desired product (132 mg; 78% yield); analytical TLC on silica gel, 2:5 EtOAc/petroleum ether R_f = 0.50. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 138−141 °C; colorless parallelepipeds; IR (film, cm^{-1}) 1767 (C=O), 1701 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.65 (1H, d, J = 1.8 Hz), 7.41 (1H, dd, J = 9.0, 1.8 Hz), 7.23 (1H, d, J = 9.0 Hz, overlapped with $CHCl_3$), 4.34 (2H, q, J = 7.0 Hz), 4.00 (3H, s), 2.38 (3H, s), 1.37 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.0, 160.7, 135.0, 133.1, 128.9, 121.4, 120.9, 118.8, 114.0, 112.0, 60.9, 32.0, 20.6, 14.3; GC−MS m/z (relative intensity, ion) 341 (^{81}Br, 6, M^+), 339 (^{79}Br, 6, M^+), 299 (^{81}Br, 76), 297 (^{79}Br, 76), 253 (^{81}Br, 100), 251(^{79}Br, 100) 225 (^{81}Br, 24), 223 (^{79}Br, 24), 197 (^{81}Br, 27) 195 (^{79}Br, 27). Anal. Calcd for $C_{14}H_{14}BrNO_4$: C, 49.43; H, 4.15; N, 4.12. Found: C, 49.71; H, 3.91; N, 4.02.

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Supporting Information Available: General experimental procedures for acetoxylation of indoles; full characterization data and copies of ^1H and ^{13}C NMR spectra for all compounds; X-ray crystallographic data (CIF) for **3** and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.