Construction of 3-oxyindoles *via* hypervalent iodine mediated tandem cyclization–acetoxylation of *o*-acyl anilines†

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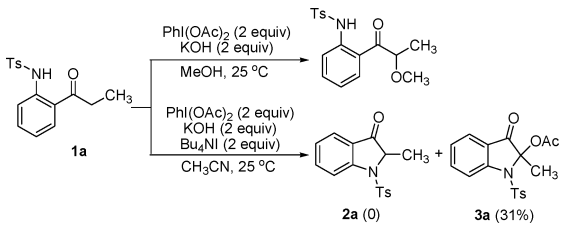
Received 16th June 2010, Accepted 6th July 2010
DOI: 10.1039/c0cc01911a

An efficient tandem cyclization–acetoxylation of *o*-acyl anilines mediated by the combination of iodobenzene diacetate with tetrabutylammonium iodide provides a new convenient and useful route to 2-acetoxy indolin-3-ones, which are ready to be converted into other 2-substituted 3-oxyindole derivatives.

In past decades, the versatility of hypervalent iodine organic compounds has been well recognized, and attracted especially active interest due to their benign environmental character and ready availability.[1] In addition to the very useful oxidizing properties, a notable feature of the hypervalent iodine compounds is their capability to undergo ligand exchange and reductive elimination reactions like transition metals. For example, Moriarty and co-workers have reported the use of the combination of $PhI(OAc)_2$/KOH/MeOH in the synthesis of a wide range of heterocycle structures.[1f] The process involves the ligand exchange reaction of the hypervalent iodine compound with the corresponding substrate and a subsequent reductive elimination of PhI and the generation of desired carbon–carbon, hetero–heteroatom, or carbon–heteroatom bonds without extra chemical transformations.[2]

As important heterocyclic compounds, 3-oxyindoles are widely distributed in natural products and synthetic compounds.[3] Possessing a variety of biological activities, they have found applications as COX-2 inhibitors[4a] and Mcl-1 inhibitors in the design of novel antitumor agents.[4b] Meanwhile, they are key building blocks for the potent peroxisome proliferator-activated receptor γ modulators.[4c] Despite the considerable amount of effort that has been expended in the preparation of 3-oxyindoles,[5] new and straightforward methods to access these heterocycles are always highly desirable. Fistulosin, which was isolated from the root of the Welsh onion by Tomita's group in 1999, exhibits antifungal activities against the wilt-producing fungus *Fusarium oxysporum*.[6] Nishida and co-workers reported the first synthesis of fistulosin using the ruthenium catalyzed cycloisomerization of a diene as a key step.[7] Recently, we have investigated hypervalent iodine mediated oxidative cyclizations and have developed a practical method for the synthesis of a variety of cyclic compounds.[8] We envisioned that the indolin-3-one structure of fistulosin might be constructed *via* iodine(III) mediated oxidative cyclization of the corresponding *o*-acyl aniline derivatives.

To test our hypothesis, we selected 4-methyl-*N*-(2-propionylphenyl)benzenesulfonamide **1a** as the model substrate for reaction condition screening. Our earlier examination of the iodine(III)-mediated oxidative cyclization of **1a** employing the reaction system of $PhI(OAc)_2$/KOH/MeOH was unsuccessful (Scheme 1). α-Methoxylation of the phenyl ketone was observed. When the reaction was conducted in polar or nonpolar aprotic solvents, although α-methoxylation was inhibited, no cyclization product was obtained. To generate a more reactive hypervalent iodine species, some salts were added.[9] While the introduction of Bu_4NBr, KBr, or KI had no effect on the reaction, the reaction with Bu_4NI afforded a major product.[10] However, the ^1H NMR spectrum indicated that the isolated product was not the expected compound **2a**, but 2-methyl-3-oxo-1-tosylindolin-2-yl acetate **3a**. As control experiments, replacements of $PhI(OAc)_2$ by PhIO and $PhI(OCOCF_3)_2$ resulted in complicated reactions, and no cyclized product was obtained. When Bu_4NI was introduced into the reaction with $PhI(OAc)_2$/KOH/MeOH, only the α-methoxylation product was isolated. When the α-methoxylation product was treated with the combination of $PhI(OAc)_2$/Bu_4NI/NaOAc, no reaction occurred.



Scheme 1

Product **3a** has the same core structure as fistulosin. Meanwhile, its acetal structure provides a possibility to access some other indolin-3-one derivatives. Motivated by the synthetic potential of the method, the reaction was further optimized by examining various reaction conditions. To promote the possible α-acetoxylation, KOH was replaced by NaOAc, and the yield of product **3a** was improved to 50%. In the control experiment without AcONa, the yield decreased to 17%. The best ratio of substrate, $PhI(OAc)_2$, Bu_4NI, and NaOAc was 1 : 3 : 2.5 : 1, with which the yield increased to 62%. The screening of solvents revealed dioxane as the best choice, in which product **3a** was formed in 89% yield after 1 h.‡ A higher temperature (40 °C) resulted in a complicated reaction, while the reaction proceeded sluggishly at 0 °C.

Further investigation indicated that *N*-Ts protection for *o*-acyl aniline was essential to the oxidative cyclization (Table 1, entries 1–6). This reaction was evaluated using different *o*-acyl aniline derivatives. Either electron-donating or -withdrawing substituted *o*-propionyl anilines were successfully converted to the cyclized products in good to excellent

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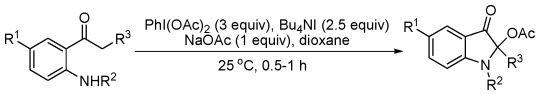
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, copies of ^1H NMR and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c0cc01911a

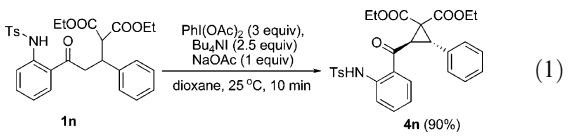
Table 1 $PhI(OAc)_2/Bu_4NI$ mediated oxidative cyclization of *o*-acyl anilines



Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	H	Ts	CH_3	**3a**	89
2	H	CH_3SO_2	CH_3	**3b**	0
3	H	CF_3CO	CH_3	**3c**	0
4	H	CH_3CO	CH_3	**3d**	0
5	H	PhCO	CH_3	**3e**	0
6	H	$PhCH_2$	CH_3	**3f**	0
7	CH_3	Ts	CH_3	**3g**	86
8	$(CH_3)_2CH$	Ts	CH_3	**3h**	92
9	CH_3O	Ts	CH_3	**3i**	88
10	Cl	Ts	CH_3	**3j**	90
11	Br	Ts	CH_3	**3k**	90
12	H	Ts	H	**3l**	50
13	CH_3	Ts	CH_2Ph	**3m**	75

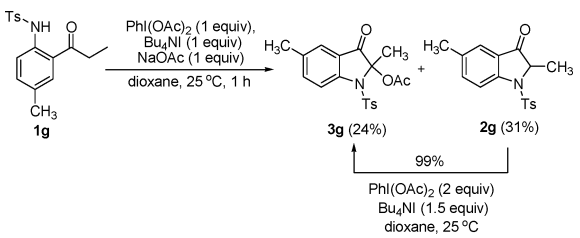
[a] Isolated yield based on **1**.

yields (Table 1, entries 7–11). With respect to the acyl moiety, acetyl and phenylpropanoyl derivatives were also found to be suitable substrates, and the corresponding products were isolated in moderate to good yields (Table 1, entries 12 and 13). When compound **1n** was employed as the substrate, no desired 2-acetoxy indolin-3-one derivative was formed, but a cyclopropanation product **4n** was isolated in 90% yield.[8c]

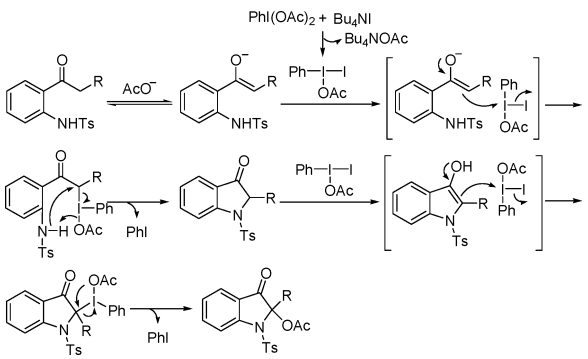


(1)

To gain insight into the mechanism, a reaction was carried out with 1 equivalent of $PhI(OAc)_2$ and Bu_4NI. While 35% of substrate **1g** was recovered after 1 h, the reaction afforded α-acetoxy indolin-3-one **3g** and indolin-3-one **2g** in 24% and 31% yield. When indolin-3-one **2g** was treated with $PhI(OAc)_2$ and Bu_4NI again, it was converted into 2-acetoxy indolin-3-one **3g** quantitatively (Scheme 2).



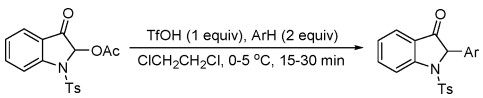
Scheme 2



Scheme 3 Hypothesized reaction pathway.

On the basis of this observation and the literature evidence,[11] the following plausible mechanism can be formulated (Scheme 3). Under the basic conditions, the enolate of the substrate reacts with the generated highly reactive iodine(III)

Table 2 Friedel–Crafts reaction of α-acetoxy indolin-3-one



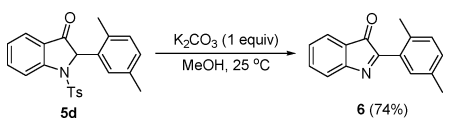
Entry	Product	Yield (%)[a]
1	**5a**	84
2	**5b-1** **5b-2**	85 (37 : 63)[b]
3	**5c-1** **5c-2**	91 (33 : 67)[b]
4	**5d**	85
5	**5e**	80
6	**5f-1** **5f-2**	82 (20 : 80)[b]
7	**5g**	81
8	**5h**	84
9	**5i**	84
10	**5j**	86
11	**5k-1** **5k-2**	52 (33 : 67)[b]

[a] Isolated yield based on **3l**. [b] The ratio was determined by ^1H NMR spectroscopy.

species to form an α-hyperiodination intermediate, which is ready to undergo an intramolecular attack by the nitrogen atom to yield indolin-3-one **2** accompanied by the reductive elimination of PhI. After the second α-hyperiodination and subsequent reductive elimination, α-acetoxy indolin-3-one **3** is formed. The generation of the unreactive I_2 from the reaction of $PhI(OAc)_2$ with Bu_4NI makes it necessary to use 3 equivalents of $PhI(OAc)_2$ and 2.5 equivalents of Bu_4NI.

To explore the use of the resultant 2-acetoxy indolin-3-one, we next investigated its Friedel–Crafts reaction. To activate the acetal structure, a variety of Lewis and Brønsted acids were examined. Trifluoromethanesulfonic acid (TfOH) was finally found to be the best catalyst for the Friedel–Crafts reaction of α-acetoxy indolin-3-one **3l** with benzene. In the presence of 1 equivalent of TfOH, the reaction completed in 15 min at 0 °C and afforded product **5a** in 84% yield (Table 2, entry 1). The scope of the Friedel–Crafts reaction with respect to the aromatic compound was then investigated. Reactions of electron-rich aromatic compounds with alkoxy or alkyl substitutions proceeded smoothly, and gave rise to the corresponding 2-aryl indolin-3-ones **5** in good to excellent yields (Table 2, entries 2–10). The electron-poor chlorobenzene was also a suitable substrate, albeit that a moderate yield of the product was obtained.

When 2-aryl indolin-3-one **5d** was treated with a catalytic amount of K_2CO_3 in MeOH, it was converted into the corresponding 3*H*-indol-3-one **6** in 74% yield (eqn (1)). The *N*-oxides of 3*H*-indol-3-one have been found to have useful biological activities against a range of bacteria, mycobacteria and fungi.[12]



(2)

In conclusion, we have developed an efficient method for the construction of 2-acetoxy indolin-3-ones *via* a tandem oxidative cyclization–acetoxylation of *o*-acyl anilines using the combination of $PhI(OAc)_2/Bu_4NI/AcONa$. The resultant 2-acetoxy indolin-3-one is ready to be converted into other 2-substituted 3-oxyindole derivatives. The current direction for future research is aimed at extending the scope and potential synthesis applications.

Financial support from the National Natural Science Foundation of China (20702006) is gratefully acknowledged.

Notes and references

‡ Representative experimental procedure: a mixture of **1a** (61 mg, 0.2 mmol), $PhI(OAc)_2$ (193 mg, 0.6 mmol), and NaOAc (16 mg, 0.2 mmol) in dioxane (1 mL) was treated with Bu_4NI (185 mg, 0.5 mmol). The reaction was allowed to stir at 25 °C for 1 h. Upon completion by TLC, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (25 mL), and extracted using ethyl acetate (25 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to provide 2-methyl-3-oxo-1-tosylindolin-2-yl acetate **3a** in 89% yield.

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