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Iodine-Mediated α-Acetoxylation of 2,3-Disubstituted Indoles

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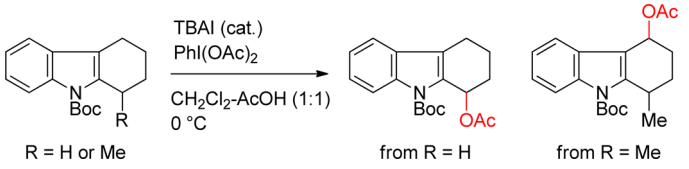
ABSTRACT



A new method for direct α-functionalization of 2,3-disubstituted indoles has been developed. The present reaction provides α-acetoxy indole derivatives regioselectively under mild conditions using commercially available and nontoxic iodine reagents. This reaction is a useful synthetic tool because obtained α-acetoxy products can be transformed into various functionalized indoles by substitution reactions with nucleophiles.

Indoles are compounds that have very versatile properties in chemistry and biology. Indole components are found in many natural products and pharmaceutical agents.[1] Therefore, many chemical methods for synthesis and functionalization of indole compounds have been developed.[2] Among these methodologies, direct functionalization of side chains of 2,3-disubstituted indole compounds via an oxidation process serves for preparation of a variety of indole derivatives.[3] Chloroindolenines generated by the reaction of indoles with *tert*-butyl hypochlorite are typical intermediates for α-functionalization of 2,3-disubstututed indoles.[3a] Various oxidants such as bromine,[3b] iodine pentoxide (I_2O_5),[3c] selenium dioxide (SeO_2),[3d] oxygen (O_2)/silver acetate (AgOAc),[3e] lead(IV) acetate ($Pb(OAc)_4$),[3f] azide reagents,[3g] and Vilsmeier reagents[3h] can be used for activation of 2,3-disubstituted indoles. Another method is regioselective α-alkylation of 2,3-disubstituted indoles using strong bases.[3i] However, these methods often involve unavoidable problems such as a relatively narrow scope of substrates, harsh reaction conditions, and the use of hazardous reagents. Recently, useful C−H functionalization reactions that can provide a shortcut to complex molecules from easily available materials have attracted much interest,[4] and development of practical methods for C−H functionalization of side chains of indoles is also among these important subjects.[5]

In the course of our progressive synthetic study of an indole alkaloid, we applied the Suárez method using iodine (I_2) and iodoxybenzene diacetate ($PhI(OAc)_2$), which is typically used to generate alkoxy radicals,[6] to a 2,3-disubstituted indole compound at room temperature. After identification of products of this reaction by NMR and

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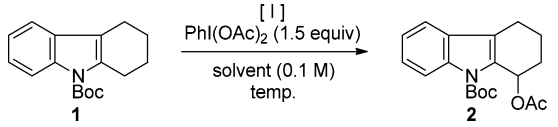
10.1021/ol302983t

mass spectrometric analysis, we noticed that an acetoxy group was introduced into a C2α position of this indole compound. This fact surprised us because this indole derivative was apparently in an unactivated form by an electron-withdrawing *tert*-butoxycarbonyl (Boc) group on a nitrogen atom. Since iodine compounds are attractive as economical and environmentally friendly reagents,[7,8] this observation led to the discovery of a practical α-functionalization of 2,3-disubstituted indole compounds.

Table 1. Optimization of Reaction Conditions



entry	[I](equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	I_2 (0.75)	CH_2Cl_2	rt	2	38
2	– (0)	CH_2Cl_2	rt	24	0
3[b]	I_2 (0.75)	CH_2Cl_2	rt	24	0
4	I_2 (0.1)	CH_2Cl_2	rt	3	50
5	I_2 (0.1)	AcOH	rt	3	73
6	TBAI (0.2)	AcOH	rt	1	78
7	TBAI (0.2)	CH_2Cl_2–AcOH (1:1)	rt	0.5	74
8	TBAI (0.2)	CH_2Cl_2–AcOH (1:1)	0	2	83
9	TBAI (0.2)	CH_2Cl_2–AcOH (1:1)	−20	18	50

[a] Isolated yield. [b] Without $PhI(OAc)_2$.

Initially, we set out to optimize reaction conditions by using protected 1,2,3,4-tetrahydrocarbazole **1** as a model substrate (Table 1). When compound **1** was treated with iodine (0.75 equiv) and $PhI(OAc)_2$ (1.5 equiv) in CH_2Cl_2 at room temperature, the reaction was completed after 2 h but gave 2α-acetoxylated product **2** in only 38% yield (entry 1).[9] Interestingly, no 3α-acetoxylated product was detected from this reaction mixture.[9] The absence of iodine or $PhI(OAc)_2$ did not provide acetoxylated product **2** at all (entries 2 and 3). The former reaction (entry 2) gave a complex mixture and a small amount of unreacted **1** (10%), whereas the latter one (entry 3) just gave unreacted **1** and deprotected tetrahydrocarbazole in 50% and 19% yields, respectively. These results indicate that acetyl hypoiodite (AcOI) generated from two reagents seems to mediate this reaction and, hence, iodine should work as a reproducible iodide source (I^-).[10,11] Actually, when iodine was reduced to a catalytic amount (0.1 equiv), the yield of product **2** was improved (entry 4). Next, we found that replacement of dichloromethane by acetic acid gave **2** in a better yield (73%) (entry 5). Tetrabutylammonium iodide (TBAI) was likely to work as a more effective iodide source than iodine because it gave **2** in a similar yield (78%) in a shorter reaction time (1 h) (entry 6).[12] The use of acetic acid as a cosolvent of dichloromethane (v/v, 1:1) resulted in completion of the reaction in only 30 min (entry 7). Two solvents seem to cooperate to elevate reactivity in this reaction. Therefore, we performed the reaction at a low temperature (0 °C) and succeeded in obtaining **2** in excellent yield after 2 h (entry 8). However, a lower temperature (−20 °C) made the reaction sluggish (entry 9).

Since the optimum reaction conditions were determined (Table 1, entry 8), we next applied the reaction conditions to α-acetoxylation of various indole derivatives (Figure 1). Reactions of 6-chloro or methoxytetrahydrocarbazole derivatives smoothly proceeded to give the corresponding 2α-acetoxylated products **3** and **4** in good yields. Incidentally, the reaction of the 6-chlorotetrahydrocarbazole derivative in AcOH at room temperature (the conditions in Table 1, entry 6) gave **3** in only 49% yield after 24 h. This result also supports the positive effect elicited by using two solvents in the present reaction. A tetrahydrocarbazole derivative protected by a *p*-toluenesulfonyl (Ts) group instead of the Boc group was also transformed into 2α-acetoxylated product **5** in good yield, whereas the yield of 2α-acetoxylated **6** bearing a benzyl (Bn) group was moderate. This reaction and electron-rich indoles seem to be incompatible.[13] However, since nitrogen atoms of indole derivatives are often protected by electron-withdrawing groups such as Ts or Boc groups at the early stage in synthetic studies of complex molecules, this reaction might be synthetically convenient in such cases. Cyclic systems having different ring sizes also gave the corresponding 2α-acetoxylated products **7** and **9**, but the corresponding alcohol **8** was isolated along with **7** in the case of a five-membered ring derivative. A 3-phenyltetrahydrocarbazole derivative underwent stereoselective acetoxylation to give *trans*-isomer **10** in a diastereoselective manner. Interestingly, when 1-methyl tetrahydrocarbazole derivative was subjected to the acetoxylation conditions, the regioselectivity of this reaction was switched to the less hindered 3α position of the indole to give **11** with high diaseteroselectivity. Apparently, the regioselectivity seems to be controlled kinetically rather

(6) (a) Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953–1956. Reviews: (b) Suárez, E.; Rodríguez, M. S. β-Fragmentation of Alkoxy Radicals: Synthetic Applications. In *Radicals in Organic Synthesis* Vol. 2; Renaud, P., Sibi, M. P., Eds.; WILEY-VCH: Weinheim, 2001; pp 440–454. (c) Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581.

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(9) In 1,2,3,4-tetrahydrocarbazoles, "2α" and "3α" correspond to C1 and C4 positions, respectively.

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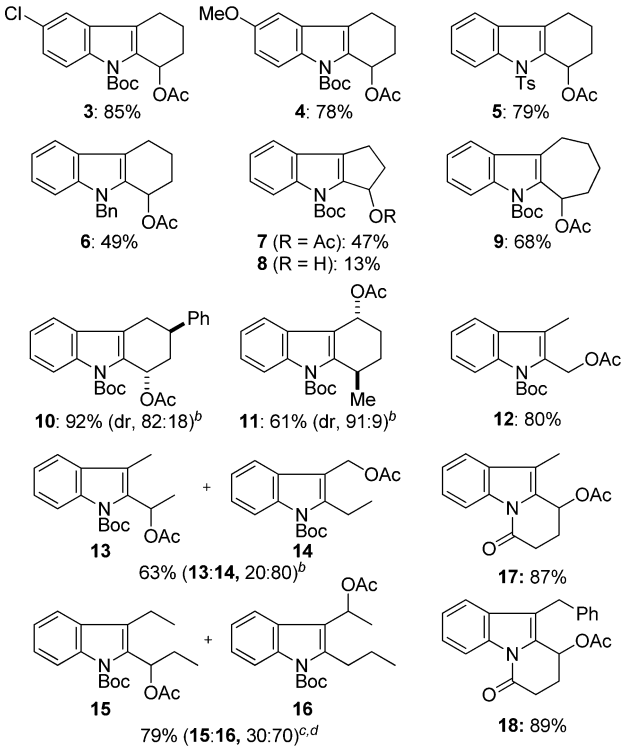
(12) Recent examples of α-functionalization of carbonyl compounds using $PhI(OAc)_2$/TBAI: (a) Fan, R.; Sun, Y.; Ye, Y. *Org. Lett.* **2009**, *11*, 5174–5177. (b) Lu, S.-C.; Zheng, P.-R.; Liu, G. *J. Org. Chem.* **2012**, *77*, 7711–7717.

(13) Tetrahydrocarbazole without a protecting group did not provide the corresponding α-acetoxylated product.

Figure 1. α-Acetoxylation of various indole derivatives.



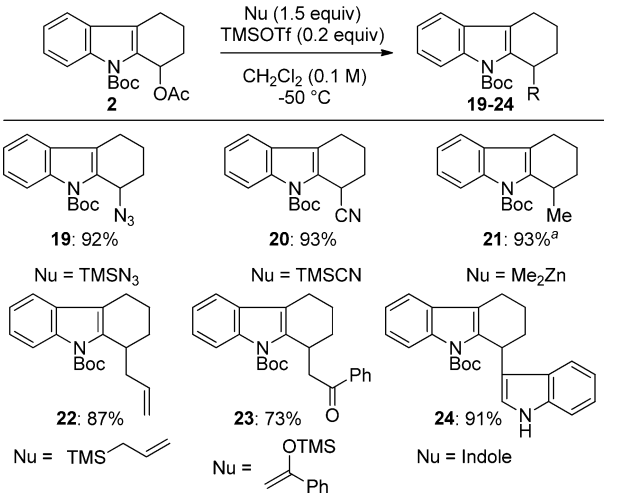
[a]Same conditions as Table 1, entry 8. [b]Ratios were determined by ^{1}H NMR analysis. [c]Yields and ratios were determined by ^{1}H NMR analysis using an internal standard (mesitylene). [d]0.4 equiv of TBAI and 2.0 equiv of $PhI(OAc)_2$ were used at room temperature.

than thermodynamically. A 2,3-dimethylindole derivative gave only 2α-acetoxylated product **12** similarly, whereas a 2-ethyl-3-methylindole derivative underwent selective acetoxylation onto the less hindered 3α methyl group to give **14** along with a small amount of 2α product **13**. Unexpectedly, the reaction of a 2-propyl-3-ethylindole derivative gave a mixture of two regioisomers **15** and **16**, and 3α isomer **16** was major. When 10-substituted-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one derivatives were used as substrates, acetoxylation exclusively took place at cyclic sites to give **17** and **18** in good yields.

The α-acetoxy indole products prepared by the present reaction turned out to be synthetically useful intermediates because we could gain a variety of derivatives by reactions of **2** with nucleophiles with the aid of trimethylsilyl trifluoromethansulfonate (TMSOTf) at −50 °C (Figure 2). The use of trimethylsilyl azide ($TMSN_3$) and trimethyl cyanide (TMSCN) as nucleophiles provided azide **19** and nitrile **20** from **2** in 92 and 93% yields, respectively. The reaction of **2** with dimethyl zinc afforded methylated product **21** in 93% yield. As a representative example, it has been illustrated that a sequence of α-acetoxylation followed by alkylation using organozinc reagents serves as a method for alkylation of the α-position of indoles. Similarly, reactions with allyltrimethylsilane or a trimethylsilyl enol ether[14] provided the corresponding allylated compound **22** and carbonyl derivative **23** via formation of new C−C bonds. In addition, the coupling reaction with indole smoothly proceeded to give bisindole derivative **24** in excellent yield.

Flexible functionalization of tetrahydrocarbazole derivative **1** using the characteristic regioselectivity of this acetoxylation reaction is illustrated in Scheme 1. Methylation to obtain **21** could be conducted without purification by silica gel chromatography after acetoxylation of **1**. As

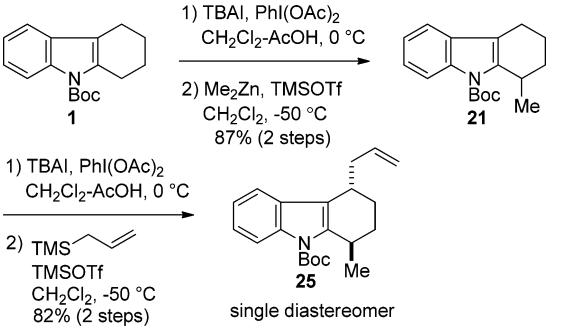
Figure 2. Reactions of **2** with nucleophiles.



[a]1.5 equiv of TMSOTf was used.

above (Figure 1), acetoxylation of **21** exclusively occurred at the 3α-position to give **11**, and subsequent allylation gave *trans*-dialkylated product **25** as a single diastereomer. At this point, we noticed that product **11** acetoxylated from **21** was partially decomposed in the course of purification by silica gel chromatography, and back-to-back allylation of the crude product without purification was effective for obtaining a good yield (82%) of **25** like the first alkylation of **1**. Eventually, we succeeded in obtaining the difunctionalized tetrahydrocarbazole derivative in four steps involving two purification operations.

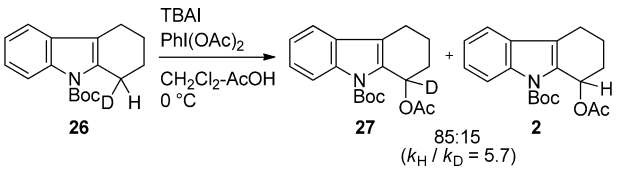
Scheme 1. Regioselective Functionalization of **1**



(14) Fu, T.-h.; Bonaparte, A.; Martin, S. F. *Tetrahedron Lett.* **2009**, *50*, 3253–3257.

We examined the reaction of deuterated substrate **26** to obtain information about a reaction pathway (Scheme 2). The obtained product was a mixture of deuterated compound **27** and normal compound **2**, and the ratio was estimated to be 85:15 by ^{1}H NMR analysis. This clear isotope effect suggests that the rate of deprotonation at the α-position of indoles is sensitive to slight differences in molecules.

Scheme 2. Kinetic Isotope Effects



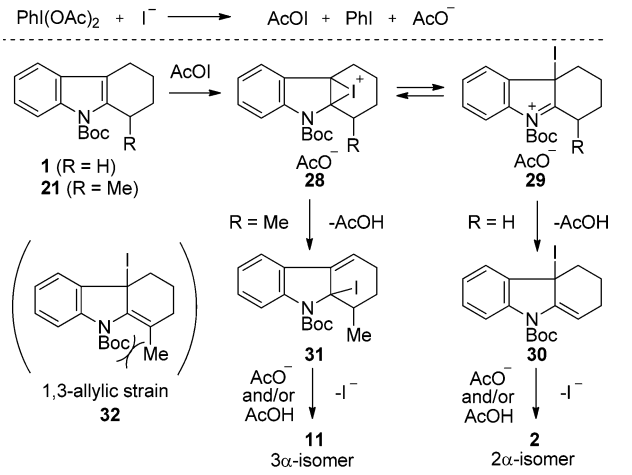
A plausible mechanism for this acetoxylation reaction is shown in Scheme 3. As mentioned above, AcOI was surely generated by the reaction between $PhI(OAc)_2$ and iodide ion.[10] This could work as a strong electrophile against tetrahydrocarbazole derivatives and give iodonium ion intermediate **28**.[15] Electron-pushing from a nitrogen atom would rapidly transform **28** into iminium intermediate **29** via ring-opening. In the case of nonsubstituted tetrahydrocarbazole (R = H), elimination of the hydrogen atom at the 2α-position provides dearomatized indole form **30**. Both of S_N1 and S_N2' mechanisms are possible in the step that introduces an acetoxy group into **30** to give **2**.[16] In either mechanism, the diastereoselective production of **10** and **11** might be attributed to the axial attack of the reactive species (*e.g.* AcOI or AcO^-) from the opposite side of a substituted group. The eliminated iodide ion from **30** would be reoxidized into AcOI by $PhI(OAc)_2$.

The kinetic isotope effect indicated that the rate of elimination step from **29** (R = H) to **30** was significantly variable depending on structures of substrates (Scheme 2). Therefore, a switching point of the regioselectivity in 2α-substituted indole substrates should be there. If iminium intermediate **29** (R = Me) is formed from 2α-substituted indole derivatives **21**, it is presumed that the following elimination of a 2α-hydrogen atom is kinetically unfavorable due to a 1,3-allylic strain in the transition state

(15) Acetoxy radical (AcO•), that may be formed from AcOI, is unlikely to participate in this reaction because the high regioselectivity in this reaction cannot be explained by the radical mechanism reasonably. Especially, the radical mechanism would not give compounds **11**, **14**, and **18** as major products because C-H abstraction by radical species should occur at positions where resultant radicals are stabilized, such as more substituted (secondary or tertiary) or benzylic positions.

(16) When the reaction of **1** was performed in the presence of $TsNH_2$, an 2α-amination product was detected along with **2**. This supports the S_N1 mechanism, though the competitive S_N2' mechanism cannot be ruled out yet.

Scheme 3. Proposed Mechanism



(For convenience, **32** is shown as an eliminated form). Probably, formation of **29** would be fast but would be reversible, and elimination at the 3α-position of **28** (R = Me) affords another dearomatized indole intermediate **31** followed by the attack by acetate ion and/or acetic acid to provide 3α-acetoxylated product **11**. The regioselectivity in the reaction affording **15** and **16** can be similarly explained by the 1,3-allylic strain of eliminated intermediates. When elimination occurrs at the 2α-position of the 3-ethyl-2-propylindole derivative, the resultant intermediate can potentially cause 1,3-allylic strain against both of a C3 ethyl group and the Boc group and would kill the predominance of this route.

In conclusion, we have developed a new method for C−H acetoxylation at the α-position of 2,3-disubstituted indole derivatives. This reaction proceeds under mild conditions without metallic reagents and follows the characteristic regioselective manner. In addition, it allowed for access to broad indole derivatives through substitution reactions of the α-acetoxylated product with various nucleophiles. We anticipate that the present reaction will serve for the synthesis of complex indole natural products and the search for potential lead compounds of medicines.

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Supporting Information Available. Expermental detail and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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