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VERSATILE SYNTHESIS OF 2,2-DISUBSTITUTED INDOLINONES *VIA* PROTECTED INDOLONES GENERATED BY ONE-POT MULTI-OXIDATION OF 2-SUBSTITUTED INDOLES

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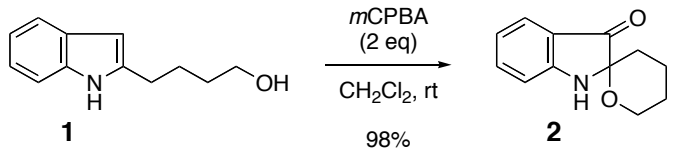
Abstract –The discovery of expeditious multi-oxidation of indoles to masked indolones led us to the development of a versatile synthetic method to access a variety of 2,2-disubstituted indolinones bearing two different substituents.

Oxidation of 2,3-disubstituted indole followed by alkyl group migration is a well-known method to obtain indolin-3-one, i.e., indoxyl.[1] The migration step is stereospecific in terms of the stereochemistry of the initial oxidation and, in addition, it should be noted that it is usually successful in the case of ring contraction reaction to form spiro-indolin-3-one (spiro-indoxyl). Kishi performed the elegant application of this method in his total synthesis of austamide.[2] Recently, McWhorter showed Grignard addition to 2-phenylindolone to form 2,2-disubstituted indolinone[3] and its application to total synthesis of (±)-8-desbromohinckdentine A.[4] Also, Fukuyama showed the utility of CuI-mediated intramolecular amination[5] to form chiral 2,2-disubstituted indolinone in the course of total synthesis of duocarmycins.[6] Despite enormous efforts by synthetic organic chemists during the last five decades, the development of an expeditious and versatile synthesis of indolinones is still an issue to be solved. The advent of such a methodology could increase the utility of indolinones as a synthetic building block for both natural product synthesis and pharmaceutical applications. Herein, we report the discovery of a novel one-pot oxidation method of indoles to give masked indolones, and their utility as versatile precursors to obtain a variety of 2,2-disubstituted indolinones with two different substituents.

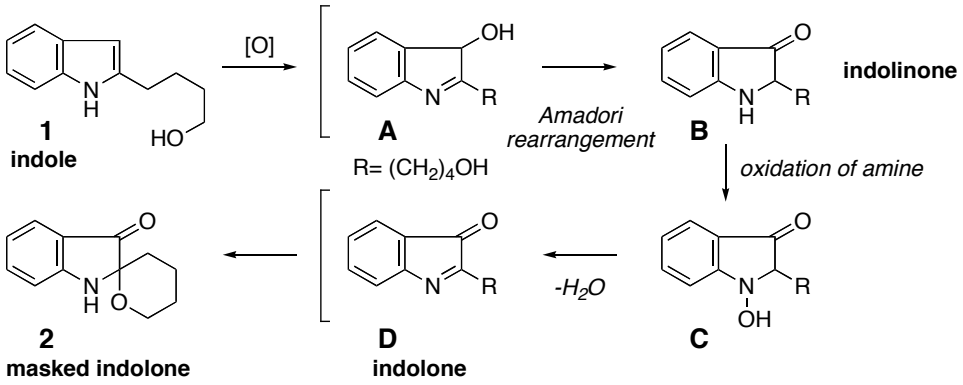
In the course of synthetic studies towards lundurine A,[7] we discovered that oxidation of 2-(4-hydroxylbutyl)indole (**1**) with two equivalents of *m*CPBA in CH_2Cl_2 furnished indolinone spiro-*N,O*-ketal **2** in excellent yield (Scheme 1).[8] Under the same conditions, 2-(3-hydroxylpropyl)indole gave the

corresponding ketal in 76% yield (not shown). Both of the indolinone ketals were stable for purification by SiO_2 column chromatography.



Scheme 1. Oxidation of 2-Substututed Indole with *m*CPBA to Form Masked Indolone

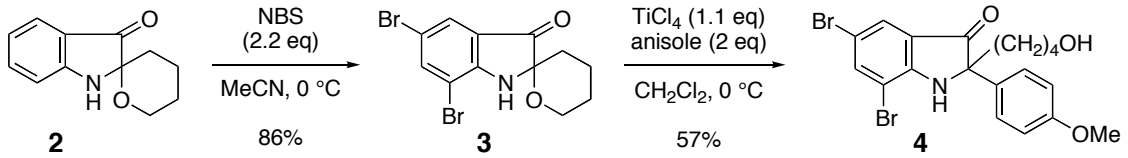
A possible reaction mechanism of the one-pot oxidation could be as follows (Scheme 2). After initial oxidation of indole **1** with *m*CPBA, facile Amadori rearrangement[9] of 3-hydroxylindolenine **A** gave mono-substituted indolinone **B**. The lack of a substituent at the 3-position could avoid the undesired oxidative cleavage due to this rearrangement. The resulting indolinone **B** was oxidized to **C** by excess *m*CPBA and then dehydrated to give 2-substituted indolone **D**. Finally, the butanol side chain at the 2-position of indolone **D** trapped the imine to form the indolinone *N,O*-ketal **2** without isomerization to an exocyclic unsaturated isomer. We assume it is protected from further oxidation of nitrogen due to steric bulk of the adjacent quarternary center and electronic effect (*N,O*-ketal). The same reaction of 2-(4-acetoxybutyl)indole furnished a nitrone derived from indolone **D** without spiro-ketal formation. This supports the suggested intermediates in our proposed reaction mechanism. The potential of these compounds as masked indolones was quickly realized, because the reactive indolones can be regenerated by Lewis acid treatment in the presence of appropriate nucleophiles to afford 2,2-disubstiuted indolinones.



Scheme 2. Possible Mechanism of the Oxidation of Indole to Form the Masked Indolone

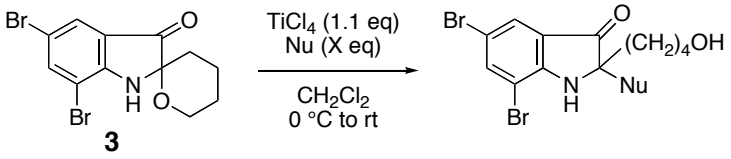
With the masked indolones in hand, we proceeded to investigate the nucleophilic introduction of the second substituent. The Lewis acid mediated Friedel-Crafts reaction of the masked indolone **2** with anisole gave the desired compound in only low yield (9%) with a lot of unidentified polymers. We realized polymerization might occur due to nucleophilicity of the aniline aromatic ring of both the substrate and the product. To prevent this undesired side reaction, the reactivity of the aromatic ring was

attenuated by bromination at the 5- and 7-positions with NBS (86%, Scheme 3). After this modification, the Lewis-acid mediated Friedel-Crafts reaction of **3** with 2 equivalents of anisole proceeded smoothly to afford the desired single isomer **4** in 57% yield. The two bromides allow further potential elaboration by Pd-mediated coupling reactions to introduce substituents on the aromatic ring.



Scheme 3. Friedel-Crafts Reaction of Masked Indolone with Anisole to give Indolinone

To explore the utility of this methodology, we decided to screen the Lewis acid mediated coupling reaction to introduce a substituent at the 2-position by using this masked dibromoindolone **3** (Table 1). Due to high reactivity of the activated intermediate α-ketoimine, it was expected a variety of coupling reactions would be applicable. Indeed, in addition to the Friedel-Crafts reaction mentioned above (Entry 1), allylation with allyltrimethylsilane (**5a**, Entry 2), Petasis condensation with boronic acid[10] (**6**, Entry 3), and aza-Prins reaction with alkene (**7**, Entry 4) worked under the same condition with good yields. The dibromination is not always necessary, as the allylation of the indolinone ketal **2** with allyltrimethylsilane gave the desired product **5b** in 69% yield (Entry 2, X = H).



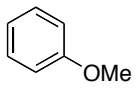
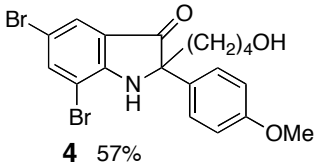
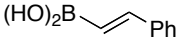
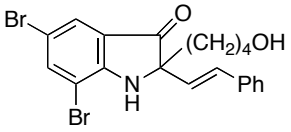
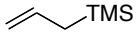
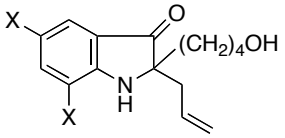
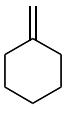
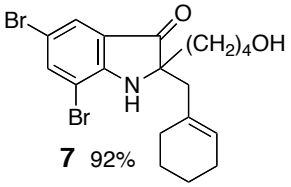
Entry	Nucleophile	Product/Yield	Entry	Nucleophile	Product/Yield
1	 (2 eq)	 **4** 57%	3	 (5 eq)	 **6** 47%
2	 (2 eq)	 **5a** 74% (X = Br) **5b** 69% (X = H)	4	 (5 eq)	 **7** 92%

Table 1. Lewis Acid Mediated Synthesis of 2,2-Disubstituted Indolinone

Herein, we reported a versatile synthetic method to obtain 2,2-disubstituted indolinones via stable masked indolones generated by multi-oxidation of 2-substituted indoles. The stable masked indolones were prepared in one-pot by *m*CPBA oxidation of readily available 2-(hydroxylalkyl)indoles. The Lewis acid mediated coupling reaction of the indolone with nucleophiles gave a variety of 2,2-disubstituted

indolinones after the attenuation by dibromination. Currently we are investigating the enantioselective synthesis of 2,2-disubstituted indolinone, and its application to total synthesis of natural product hinckdentine A as a key coupling reaction. The progress in our laboratory will be reported in due course.

ACKNOWLEDGEMENTS

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