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Synthesis of 4,7-Difunctionalized Indoles via Imino Exchange and Sulfinyl Migration

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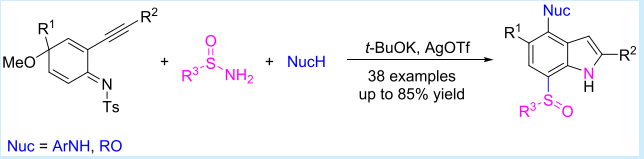
ABSTRACT: A process that rapidly assembles 4,7-difunctionalized indoles from 2-alkynycyclohexadienimines, sulfinamides, and nucleophiles (amines or alcohols) was developed. The process involves imino exchange, cascade cyclization/1,4-nucleophilic addition/aromatization, and 1,3-migration of the sulfinyl group. The 7-sulfinyl group is easy to convert into the sulfonyl or the thioether group through a simple oxidation and reduction reaction.



Among the family of indoles, a wide variety of biologically active indole derivatives contain substituents in the benzenoid moiety of the indole nucleus.[1] However, access to benzenoid ring functionalized indoles through direct electrophilic aromatic substitution reaction is difficult because the C4−C7 positions are not preferred reaction sites.[2] Therefore, in recent decades, organic chemists have devoted great effort to explore protocols for accessing the 4-, 5-, 6-, or 7-functionalized indoles. The Reissert,[3] Fischer,[4] and Batcho−Leimgruber[5] indole syntheses, the metal−halogen exchange[6] or the transition-metal-catalyzed cross-coupling reaction of 4,7-haloindoles,[7] and the nucleophilic addition or cycloaddition of indolyne[8] have been developed as the primary methods for the synthesis of benzenoid ring functionalized indoles. However, in some cases, the syntheses might suffer from difficulties in multistep synthesis of precursors, rather harsh conditions, and low efficiency in yield, for example, the synthesis of 4,7-difunctionalized indoles (for the structure, see Figure 1).

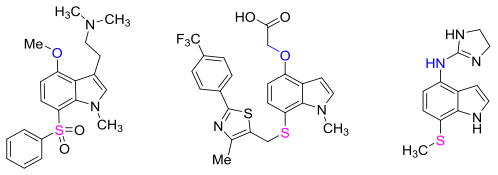


Figure 1. Biologically active 4,7-difunctionalized indoles.

4,7-Difunctionalized indoles are highly valuable synthetic targets owing to their remarkable biological activities as serotonin receptor modulators, α-2 adrenoceptor agonists, or PPAR modulators.[9] However, there are some limitations for their conventional synthesis, for example, the multistep synthesis of 4-amino- or 4-alkoxy-substituted indoles as precursors, the competition of the C3 or the C5 position with the C7 position in electrophilic halogenation reaction,[10] and the deactivation of catalyst by the sulfur atom in transition-metal-catalyzed cross-coupling with sulfur compounds. The limitations of synthetic methods heavily impede their biological studies of such compounds as the active pharmaceutical ingredients. To address this challenge, we sought a way to rapid assemble 4,7-difunctionalized indoles from readily available starting materials, possibly via the reaction of 2-alkynycyclohexadienimines.

2-Alkynycyclohexadienimines, the oxidative dearomatization product of 2-alkynylanilines, are attractive starting materials in the synthesis of functionalized indoles because of their high reactivity, multiple functionality, and ready availability.[11] We conceived that the target 4,7-difunctionalized indoles can be assembled from the reaction of 2-alkynycyclohexadienimines with sulfinamides and nucleophiles through simple conversions. The underlying principle of the process is depicted in Scheme 1. Sulfinamides are used as the source of sulfinyl group and are incorporated into the structure of 2-alkynycyclohexadienimines through an imino exchange reaction. Subsequent cascade cyclization/1,4-nucleophilic addition/aromatization reaction generates 4-amino- or 4-alkoxyl-substituted indoles. The conjugated electron-donating effect of the C4 substituent promotes an intramolecular nucleophlic attack of the C7 carbon atom to the sulfinamide group leading to a 1,3-migration of the sulfinyl group to provide 7-sulfinyl-substituted free (NH) indoles. The 7-sulfinyl group might be easily converted into the sulfonyl or the thioether group through simple oxidation and reduction reaction. Herein, we report the investigation along this line.

In an initial test, 2-alkynycyclohexadienimine, *tert*-butylsulfinamide, and *p*-toluidine are used as the standard substrates for

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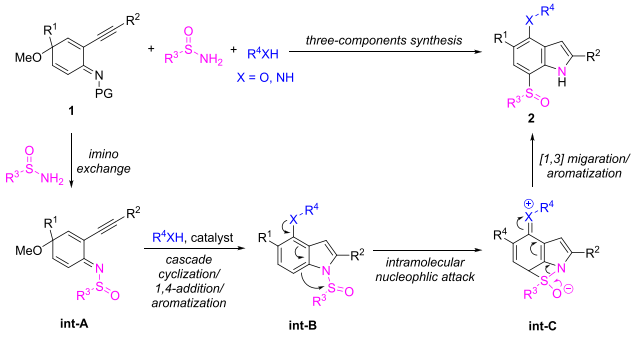
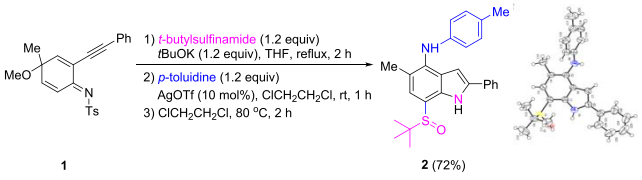
Scheme 1. Proposed Pathway for the Synthesis of 4,7-Difunctionalized indoles



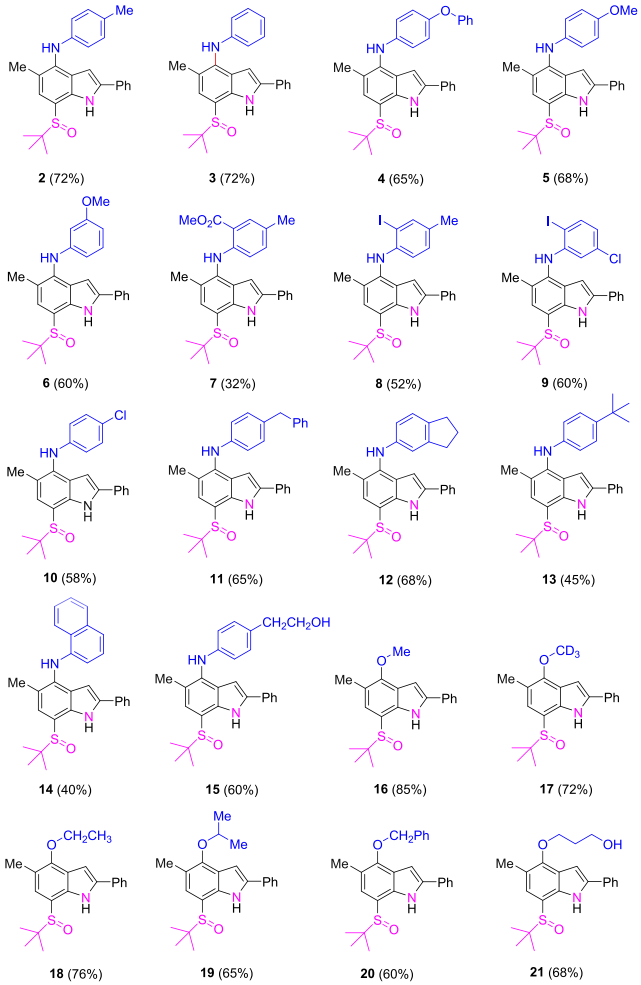
searching for potential catalysts and suitable reaction conditions. The reaction of 2-alkynycyclohexadienimine with *tert*-butylsulfinamide in THF at refluxing temperature in the presence of 1 equiv of potassium *tert*-butoxide gave rise to the imino exchange product in 92% isolated yield. Among a variety of metal salts, silver trifluoromethanesulfonate proved to be the best catalyst for the cascade cyclization/1,4-nucleophilic addition/aromatization reaction. No catalyst was required for subsequent 1,3-migration of the sulfinyl group. Heating of the resulting 4-aminoindole in dichloroethane at 80 °C for 2 h led to the formation of 4-amino-7-sulfinylindole **2** in 88% yield. The structure of **2** was confirmed by single-crystal X-ray diffraction analysis. Because the excess *tert*-butylsulfinamide might act as the nucleophilic competitor of the nucleophiles in the 1,4-nucleophilic addition reaction and 1,3-migration reaction in the presence of AgOTf was complex, the three-component reaction was carried out in a stepwise manner and gave rise to **2** in 72% yield (Scheme 2). When the reaction was conducted on a 1 mmol scale, compound **2** was isolated in 69% yield.

Scheme 2. Three-Component Synthesis of 4-Amino-7-sulfinylindole



With the optimal reaction conditions in hand, the scope of this three-component synthesis was investigated by systematically varying the nucleophiles, the 2-alkynylcyclohexadienimines, and the sulfinamides. A variety of aromatic amines were examined (Scheme 3). An electronic effect was observed for aromatic amines with different substituents. With electron-rich substituents such as a methoxyl group, phenoxy, or benzyl group, aromatic amines gave higher yields than those bearing electron-deficient groups such as chloro, iodo, and ester group. The reactions of 4-*tert*-butylaniline or naphthalen-1-amine provided the corresponding products in moderate yields due to steric factors. When 2-(4-aminophenyl)ethan-1-ol was employed, the reaction gave rise to the nitrogen-addition product **15** in 60% yield. When benzylamine or *n*-butylamine was used as nucleophile, the formation of 4-aminoindoles was not observed. When alcohols were used as the cosolvent of the cascade cyclization/1,4-nucleophilic addition/aromatization

Scheme 3. Scope of Nucleophiles



reaction, the reaction proceeded smoothly leading to the formation of 4-alkoxy-7-sulfinyl indoles **16**–**21** in good yields.

The reaction was also found to tolerate a range of functional groups on 2-alkynylcyclohexadienimines (Scheme 4). For example, substrates bearing an alkyl, alkoxy, halogen, acetyl, trifluoromethyl, and thienyl group proceeded smoothly, no matter whether the substituent is an electron-donating or an electron-withdrawing group. A steric effect of the alkynyl substituents was observed. For example, substrates bearing a *p*-chlorophenyl group gave a higher yield than those bearing a *m*-chloro or *o*-chlorophenyl group. The *para*-substituent in 2-alkynylcyclohexadienimines could also be an ethyl, *n*-butyl, or isopropyl group.

When propane-1-sulfinamide, propane-2-sulfinamide, or cyclohexanesulfinamide was used instead of *t*-butylsulfinamide, the corresponding 7-sulfinyl indoles were formed in moderate yields (Scheme 5). When benzenesulfinamide was employed, the imino exchange reaction did not occur, even when using *N*-4-nitrobenzenesulfonyl protected 2-alkynylcyclohexadienimine as a substrate.

The sulfinyl group in the product is ready to be transformed into the sulfonyl or the thioether group through simple oxidation and reduction reaction. As shown in Scheme 6, treatment of **2** with PPh_3 in the presence of TiCl4 or with *m*-CPBA gave rise to compound **41** and **42** in 62% and 93% yield, respectively.

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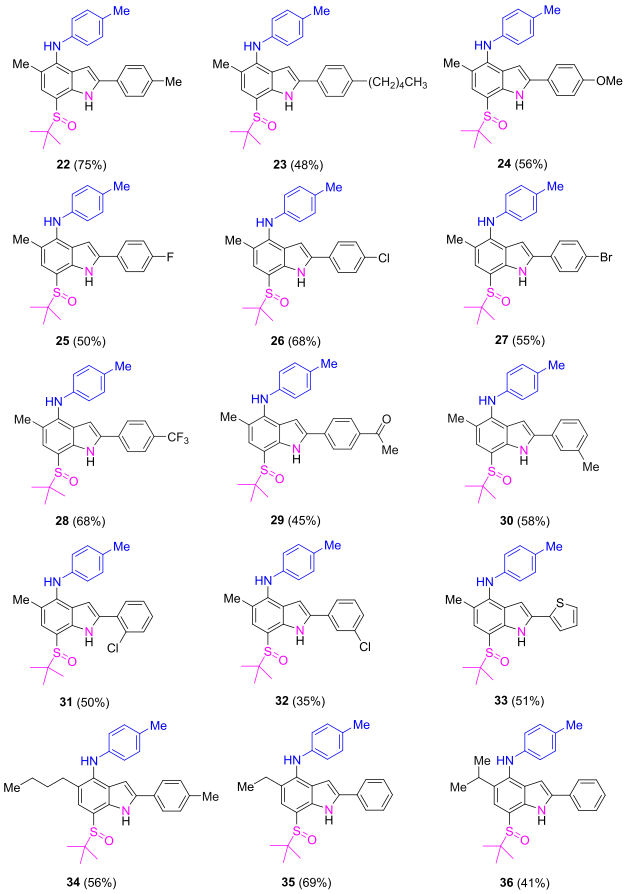
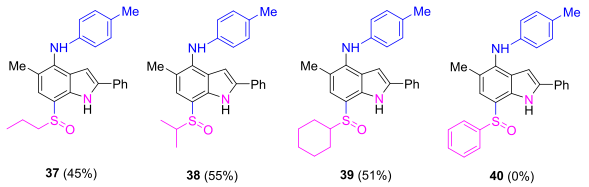
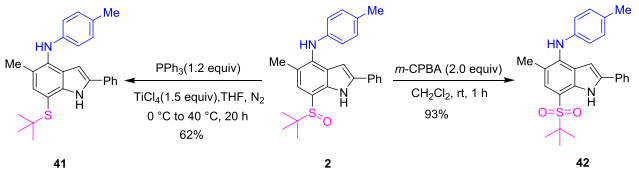
Scheme 4. Scope of 2-Alkynylcyclohexadienimines



Scheme 5. Scope of Sulfinamides

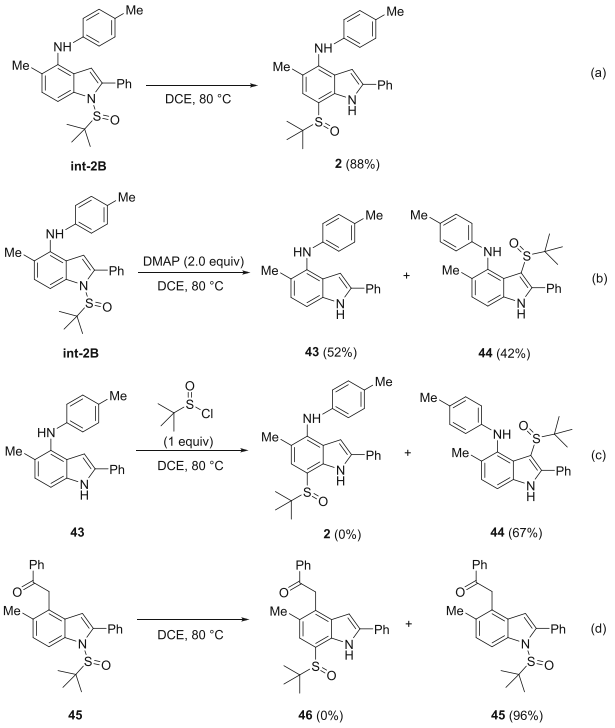


Scheme 6. Transformation of the 7-Sulfinyl Group



To gain insight into the reaction, some control experiments were conducted (Scheme 7). The 4-substituted intermediate **int-2B** was isolated, and it can be converted into compound **2** under the standard conditions (Scheme 7a). When **int-2B** was treated with 2 equiv of DMAP, the formation of **2** was not observed but NH-free indole **43** and 3-sulfinyl-substituted indole **44** were isolated instead (Scheme 7b). It is proposed that DMAP might act as a nucleophilic reagent to attack the sulfinamide group of **int-2B** to promote the cleavage of the C−S bond leading to the formation of N−H free indole **43** and an active sulfinylpyridinium DMAP-SOBu-*t*. Because the C7 position is not a preferred reaction site for electrophilic substitution reaction, the NH free indole **43** reacts with the

Scheme 7. Control Experiments



sulfinylpyridinium to afford the 3-sulfinyl-substituted indole **44**. Treatment with compound **43** with 1 equiv of *t*-butylsulfinyl chloride produced provided **44** as the major product (Scheme 7b). These results indicated that the migration of the sulfinyl group might occur via an intramolecular addition−elimination process. Moreover, under the standard conditions, the sulfinyl migration of compound **45**, which bears a carbon substitution at the C4 position, did not occur (Scheme 7c). It revealed that the conjugated electron-donating effect of the C4 substituent might be essential to the sulfinyl migration.

In conclusion, we developed a method to rapid assemble 4,7-difunctionalized from three readily available starting materials. The process involves an imino exchange of 2-alkynycyclohexadienimines with sulfinamides, a cascade cyclization/1,4-nucleophilic addition/aromatization reaction, and a 1,3-migration of the sulfinyl group. Development of an extension of this strategy to other multifunctionalized indoles and investigation of the biological activities of 4,7-difunctionalized indoles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04257.

General experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

Accession Codes

CCDC 1968017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

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Notes

The authors declare no competing financial interest.

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