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Synthesis of 4-Alkylindoles from 2-Alkynylanilines via Dearomatization- and Aromatization-Triggered Alkyl Migration

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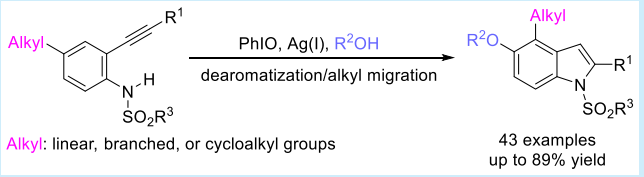
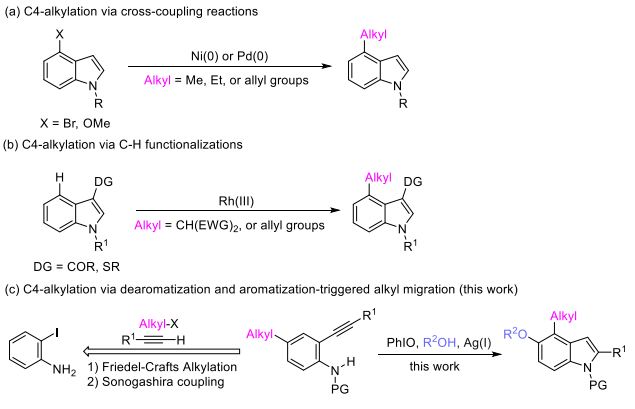
ABSTRACT: A simple method for rapid synthesis of 4-alkylindoles from 2-alkynylanilines was reported. The protocol involves an oxidative dearomatization and an aromatization triggered regioselective alkyl migration. A range of alkyl groups including linear, branched, or cycloalkyl groups can be introduced into the C4 position of indole.



4-Alkylindoles constitute a very important class of compounds because of their existence as core structures in a range of alkaloids such as agroclavine, ergoline, serotobenine, trikentrins, and penitrems.[1] Because the C4 position of indoles is not a preferred site for electrophilic alkylation, a variety of methods, including intramolecular Claisen rearrangement,[2] Cope rearrangement,[3] Witkop photocyclization,[4] or iodine(III)-mediated [3 + 2] cycloaddition,[5] have been developed for introducing the C4 alkyl substituents in the synthesis of various indole alkaloids. Recently, transition metals such as nickel- or palladium-catalyzed cross-coupling reactions of 4-halo- or 4-methoxyindoles with methyl tosylate,[6] allylic alcohols,[7] triethylaluminum,[8] or boronic acids[9] have been explored to access 4-alkylindoles (Scheme 1a).[10] Additionally, the groups

Scheme 1. Routes to 4-Alkylindoles

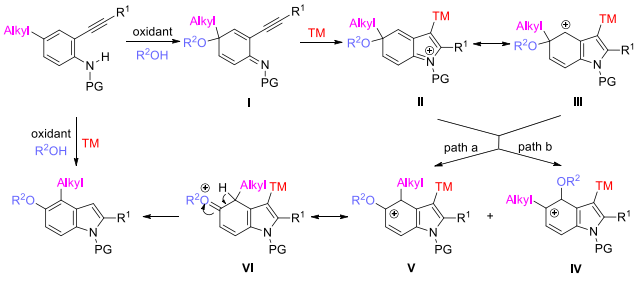


of Li,[11] Punniyamurthy,[12] and Miura[13] have reported the rhodium- or the iridium-catalyzed regioselective C−H functionalization reactions directed by the C3 carbonyl or thioether groups to install the C4 alkyl groups (Scheme 1b). Despite these elegant advances, in some cases, these methods might suffer from the limited scope of the alkyl groups, harsh reaction conditions, and the difficulty in the multistep synthesis of precursors. Driven by their remarkable importance as active pharmaceutical ingredients, the development of an efficient method to prepare 4-alkylindoles from simple and available starting materials under mild conditions is still highly valuable.

2-Alkynylanilines have found widespread use in the synthesis of various indoles via cyclization or cascade cyclization/coupling reactions.[14] In this paper, we report a process that converts 4-alkyl-2-alkynylanilines to 4-alkylindoles via an oxidative dearomatization and an aromatization-triggered selective alkyl migration (Scheme 1c). 4-Alkyl-2-alkynylanilines are easily prepared from 2-iodoaniline via alkylation and Sonogashira coupling reactions.

The underlying principle is shown in Scheme 2. Oxidative dearomatization might transform the electron-rich 4-alkyl-2-alkynylanilines to the electron-deficient cyclohexadienimines I.[15] In the presence of a transition metal (π acid), the nucleophilic cyclization might generate an iminium inter-

Scheme 2. Tentative Pathway for the Formation of 4-Alkylindoles from 4-Alkyl-2-alkynylanilines



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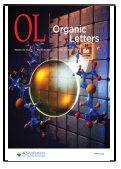

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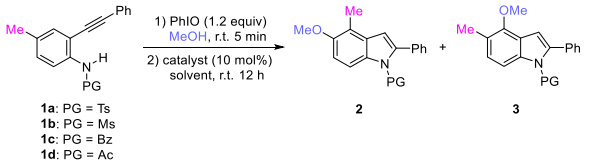
mediate **II** or a carbocation intermediate **III**. Aromatization to restore the aromaticity to form the indole system might be a great driving force to trigger a group migration from the C5 position to the C4 position. The group migration might proceed via two pathways, the alkyl migration (path a) or the alkoxy migration (path b), to generate intermediates **V** and **IV**, respectively. Because the positive charge in the intermediate **V** can be stabilized by the oxygen atom of the alkoxy group (intermediate **VI**), the group migration via path a is preferred leading to the formation of 4-alkylindoles. Herein, we report the investigation along this line.

In an initial test, a catalytic amount of silver triflate was added to the reaction mixture after dearomatization reaction of *N*-Ts-4-methyl-2-(phenylethynyl)aniline **1** with 1.1 equiv of iodosobenzene in methanol. The reaction provided 4-methoxyindole **3a** as the major product (Table 1, entry 1).

Table 1. Evaluation of Catalysts and Conditions[a]



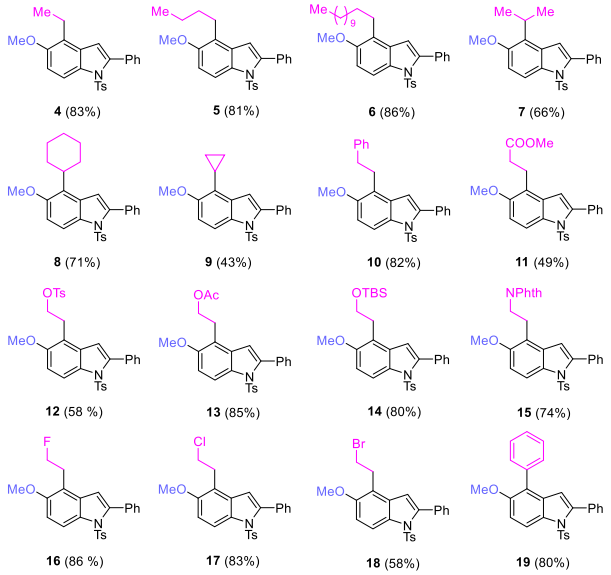
entry	PG	catalyst	solvent	yield[b] (%)	2/3[c]
1	Ts	AgOTf	MeOH	65	1:20
2	Ts	AgOTf	CH_2Cl_2	64	6:1
3	Ts	AgOTf	CF_3CH_2OH	68	4:1
4	Ts	AgOTf	CH_3CN	74	9:1
5	Ts	AgOTf	acetone	79	12:1
6	Ts	AgOTf	THF	79	15:1
7	Ts	AgOTf	dioxane	56	18:1
8	Ts	AgOTf	EtOAc	86	>20:1
9	Ms	AgOTf	EtOAc	85	>20:1
10	Bz	AgOTf	EtOAc	0	
11	Ac	AgOTf	EtOAc	0	
12	Ts	$PdCl_2$	EtOAc	69	1.5:1
13	Ts	$Pd(OAc)_2$	EtOAc	55	3:1
14	Ts	$PtCl_2$	EtOAc	75	3:1
15	Ts	$RhCl_3$	EtOAc	0	
16	Ts	$Au(PPh_3)Cl$	EtOAc	0	
17	Ts	$AgNTf_2$	EtOAc	78	8:1
18	Ts	AgOAc	EtOAc	32	2:1
19	Ts	$AgSbF_6$	EtOAc	80	3:1
20	Ts	AgF	EtOAc	0	
21	Ts	$AgBF_4$	EtOAc	89	>30:1

[a]Reactions were carried out on a 0.1 mmol scale using 1.2 equiv of PhIO and 0.10 equiv of catalyst in 2.0 mL of MeOH and 2.0 mL of solvent as noted. [b]Isolated yields. [c]Determined by ^{1}H NMR.

It indicated that the nucleophilic addition by the excess methanol to the dearomatized intermediate **I** might inhibit the intramolecular alkyl migration. After the removal of methanol under vacuum, AgOTf and CH_2Cl_2 were added and the formation of 4-methylindole **2a** was observed, albeit in a mixture with **3a** (Table 1, entry 2). The change of solvent had a significant influence on the reaction selectivity (Table 1, entries 3−8). When the reaction was conducted in ethyl acetate, the ratio of **2a** to **3a** was greater than 20:1 (Table 1, entry 8). The nature of the *N*-protecting group had an effect on the reaction (Table 1, entries 9−11). While the reaction of the *N*-Ms-protected substrate provided compound **2b** in 85% yield, the reaction of the *N*-Bz- or the *N*-Ac-protected substrates failed to give the corresponding 4-methylindoles. Among various metal salts and silver catalysts examined (entries 12−21), silver tetrafluoroborate proved to be the best catalyst, with which the reaction gave rise to 4-methylindole **2a** in 89% yield, and the ratio of **2a** to **3a** is greater than 30:1. The structure of **2a** was confirmed by X-ray crystallography.

With the optimized conditions in hands, the scope of the C4 alkyl groups was investigated (Scheme 3). A range of alkyl

Scheme 3. Investigation on the Scope of the 4-Alkyl Groups[a,b]



[a]Isolated yields. [b]Reactions were carried out using standard conditions of Table 1, entry 21.

groups including linear, branched, or cycloalkyl groups can be introduced into the C4 position of indoles. For example, the linear *n*-butyl or *n*-dodecyl group that normally cannot be introduced into the aromatic rings via Friedel−Crafts alkylation can be installed with high yields. When the reaction of 4-isopropyl-2-(phenylethynyl)aniline provided 4-isopropyl-substituted indole **7** in 66% yield, the dearomatization of 4-*tert*-butyl-substituted substrate failed. The migration of the cyclohexyl or cyclopropyl groups also proceeded smoothly. The reaction was found to tolerate a range of functional groups on the alkyl group such as ester, sulfonate, phthalimido, siloxy group, and halogen atoms. Not only the alkyl group but also a phenyl group can be introduced into the C4 position via this process.

The scope was further investigated by varying the substituents on the 4-alkyl-2-alkynylanilines (Scheme 4). Reaction of substrates bearing an aryl, thienyl, alkyl, or cycloalkyl group at the 2-alkynyl moiety proceeded smoothly. An electronic effect was observed for substrates bearing the 2-arylethynyl groups. With electron-rich substituents such as the methyl or the methoxyl group, reactions gave higher yields than those with electron-deficient groups such as the halogen atoms or the nitro group. The length of the linear alkyl group at the C2 position had no influence on the transformation. For example, the reactions of 2-(hex-1-yn-1-yl)-4-methylaniline and 2-(dodec-1-yn-1-yl)-4-methylaniline gave rise to the corresponding products **34** and **36** in 66% and 59% yield,

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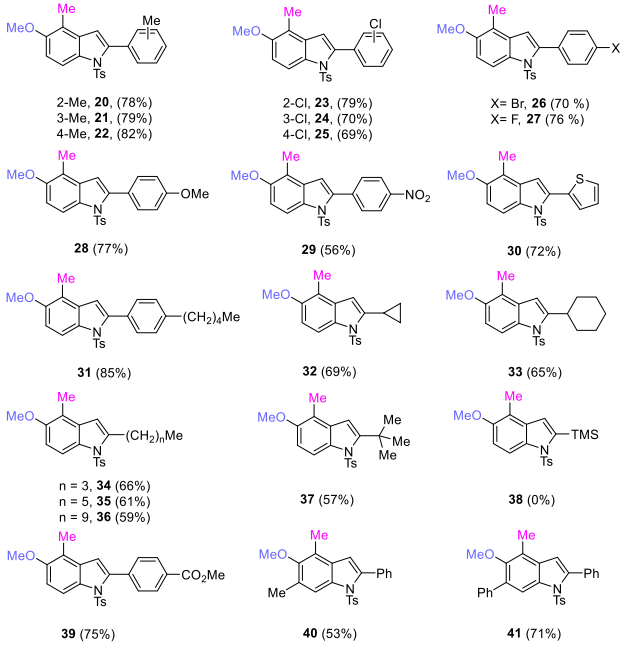
Scheme 4. Investigation on the Scope of the 4-Alkyl-2-alkynylanilines[a,b]

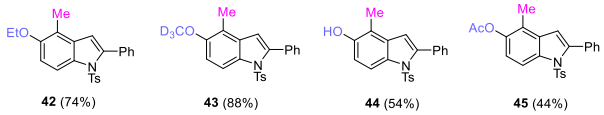


[a]Isolated yields. [b]Reactions were carried out using standard conditions of Table 1, entry 21.

respectively. When 4-methyl-2-((trimethylsilyl)ethynyl)aniline was employed, the dearomatization proceeded well, but the methyl migration did not occur under the standard conditions. The presence of the second methyl group or a phenyl group at the C5 position of 4-alkyl-2-alkynylaniline tended to diminish the yield of compounds **40** and **41** slightly.

Different functional groups could be introduced into the C5 position of indole just by varying the solvent for the oxidative dearomatization step (Scheme 5). For example, besides 5-

Scheme 5. Variable C5 Functionalization by Varying the Solvent for the Dearomatization Step[a,b]

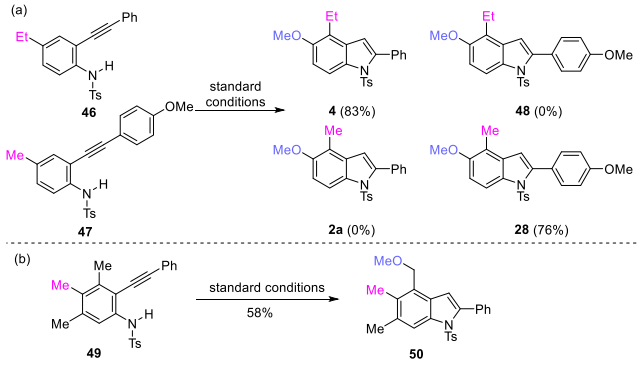


[a]Isolated yields. [b]Reactions were carried out using standard conditions of Table 1, entry 21.

alkoxy-4-methylindoles **42** and **43** obtained using EtOH or CD_3OD, 5-hydroxyl-4-methylindoles **44** and 5-acetoxy-4-methylindoles **45** were formed in moderate yields when the dearomatization reaction was conducted in acetonitrile/water or in acetic acid, respectively.

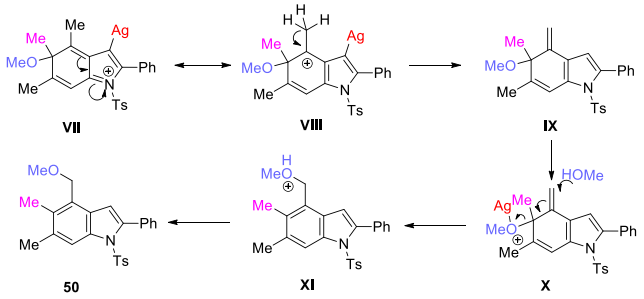
To gain more insight into the reaction, some control experiments were conducted. When 4-alkyl-2-alkynylanilines **46** and **47** were used together as substrates, the reaction gave rise to the corresponding methyl or ethyl migration products **4** and **28**. The formation of the cross products **2a** and **48** were not observed (Scheme 6a). This result indicated that the alkyl migration might proceed via an intramolecular manner. When 3,4,5-trimethyl-2-(phenylethynyl)aniline **49** was employed as substrate, the reaction under the standard conditions provided compound **50** in 58% yield (Scheme 6b). A proposed pathway

Scheme 6. Primary Investigation on the Reaction Mechanism



for the formation of **50** is depicted in Scheme 7. Because both of the C4 and the C6 position in intermediate **VII** are blocked,

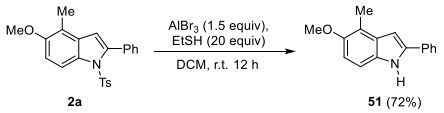
Scheme 7. Proposed Pathway for the Formation of 50



the group migration can not take place. Elimination of a benzyl proton and protonolysis of C−Ag bond leads to the formation of intermediate **IX**. An addition of MeOH on **IX**, eventually assisted by Ag^+ as in **X**, with the driving force by aromatization to promote the leaving of the methoxy group provided compound **50**.

The Ts protecting group at the nitrogen atom could be removed by using $AlBr_3$ and EtSH,[16] and N−H free 4-methylindole **51** was obtained in 72% yield (Scheme 8).

Scheme 8. Deprotection Reaction of 2a



In summary, we have developed a simple process for rapid synthesis of 4-alkylindoles from readily available 4-alkyl-2-alkynylanilines. The protocol involves an oxidative dearomatization and an aromatization-triggered regioselective alkyl migration. A range of alkyl groups including linear, branched, or cycloalkyl groups can be introduced, and a variety of functional groups can be tolerated in this process. The use of this method in the synthesis of natural products is 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.1c00280.

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Org. Lett. 2021, 23, 2130−2134

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

Accession Codes

CCDC 2057887 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 Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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