

An Efficient Route to Highly Substituted Indoles via Tetrahydroindol-4(5H)-one Intermediates Produced by Ring-Opening Cyclization of Spirocyclopropanes with Amines

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Abstract: An efficient route to highly substituted indoles was developed. It includes regioselective functionalization of tetrahydroindol-4(5H)-ones, prepared by ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes with primary amines, and subsequent oxidation. 6-Substituted indoles were synthesized from a readily available 5-substituted cyclohexane-1,3-dione-2-spirocyclopropane. Synthesis of 5- and 7-substituted indoles was achieved by regioselective electrophilic alkylation of tetrahydroindol-4(5H)-one, followed by oxidation. 4-Substituted indoles were synthesized by nucleophilic alkylation of the corresponding pyrrole derivative, prepared by partial oxidation of tetrahydroindol-4(5H)-one, and a sequential oxidation. Synthesis of 4-substituted indoles was also accomplished by Pd-catalyzed coupling of 4-hydroxyindole-derived triflates. Furthermore, synthesis of 4,5,6,7-tetrasubstituted indoles was achieved by using these regioselective alkylations.

Introduction

Indoles are important structural components of a wide range of biologically-active alkaloids and pharmaceutical agents.^[1] Consequently, the development of efficient synthetic methods for indoles continues to attract considerable attention.^[2] Although a number of effective approaches to indoles substituted on the nitrogen-containing pyrrole ring have been reported, there are only a few examples of regiocontrolled access to indoles bearing multiple substituents on the benzene ring^[3] because of the lower reactivity of the benzene moiety. In general, there are three approaches to indoles possessing substituents on the benzene ring; (A) pyrrole ring formation from substituted aniline derivatives, (B) benzene ring formation from pyrroles possessing side chains, and (C) regioselective functionalization of non-substituted indoles (Scheme 1). Representative examples of approach A include the Larock and Kerr indole syntheses. Larock group reported Pd-catalyzed coupling between highly substituted *o*-iodoanilines and alkynes to afford highly substituted indole derivatives (Scheme 1, eq. 1).^[4] Kerr and co-workers developed a Diels–Alder/Plieninger indolization sequence^[5,6] and demonstrated its application to total syntheses of natural products (Scheme 1, eq. 2).^[7] As representative examples of approach B, two synthetic methods are illustrated. Natsume *et al.* reported the synthesis of indoles that were alkyl-

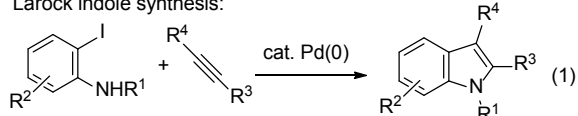
and alkoxy-substituted in the benzene portion employing acid-catalyzed cyclization of pyrroles possessing side chains,^[8] and demonstrated the utility of this approach through the syntheses of various natural products (Scheme 1, eq. 3).^[9] Yanagisawa and Yoshida developed the synthetic method for highly substituted indoles employing the ring-closing olefin metathesis (RCM)/dehydration sequence of highly functionalized pyrrole precursors (Scheme 1, eq. 4).^[10] Recently, approach C, i.e., the direct introduction of substituents onto the indole benzene ring by transition-metal-catalyzed C–H functionalization was reported (Scheme 1, eq. 5).^[11–15] Regioselective functionalization at the C4 (R⁴)^[12,13] and C7 (R³)^[14] positions was achieved by employing directing groups at C3 (R²) and N1 (R¹), respectively. Although these synthetic approaches to highly substituted indoles are useful for the synthesis of specific indoles, they still involve some drawbacks, such as difficulties in the preparation of the cyclization precursors and the limitation of introducible positions. Therefore, the development of efficient and flexible methods for the synthesis of highly substituted indoles remains challenging and highly desirable.

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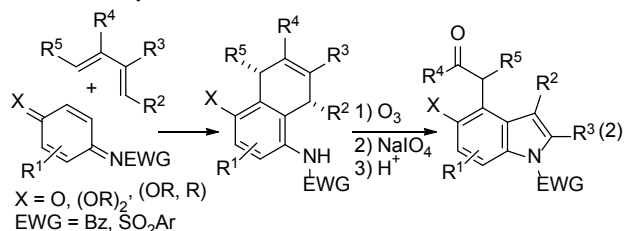
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A. Approach from highly substituted aniline derivatives

Larock indole synthesis:

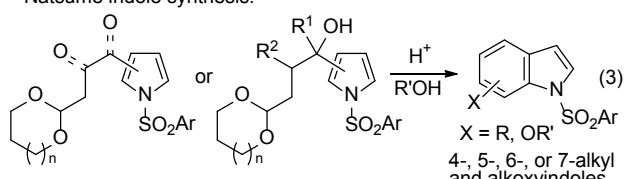


Kerr indole synthesis:

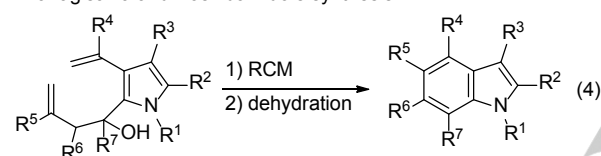


B. Approach from pyrroles possessing side chains

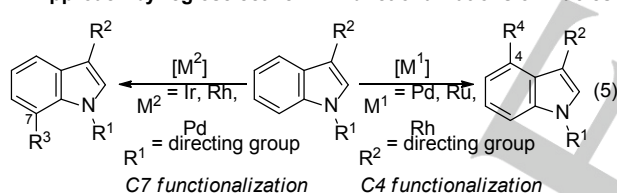
Natsume indole synthesis:



Yanagisawa and Yoshida indole synthesis:

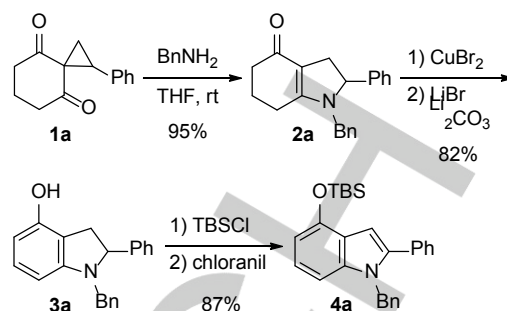


C. Approach by regioselective C–H functionalizations of indoles



Scheme 1. Synthetic approaches to highly substituted indoles.

As a part of our efforts toward the synthesis of functionalized indoles based on cyclopropane chemistry,^[16] we recently reported a novel synthesis of 4-hydroxyindole **4a** through 2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-one **2a**. The ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropane **1a** with benzylamine and the subsequent stepwise oxidation of the resulting product **2a** gave 4-hydroxyindole **4a** via 4-hydroxyindoline **3a** in high overall yield (Scheme 2).^[17] Herein, we report an efficient route to highly substituted indoles employing regioselective alkylations of **2** as a key synthetic intermediate.

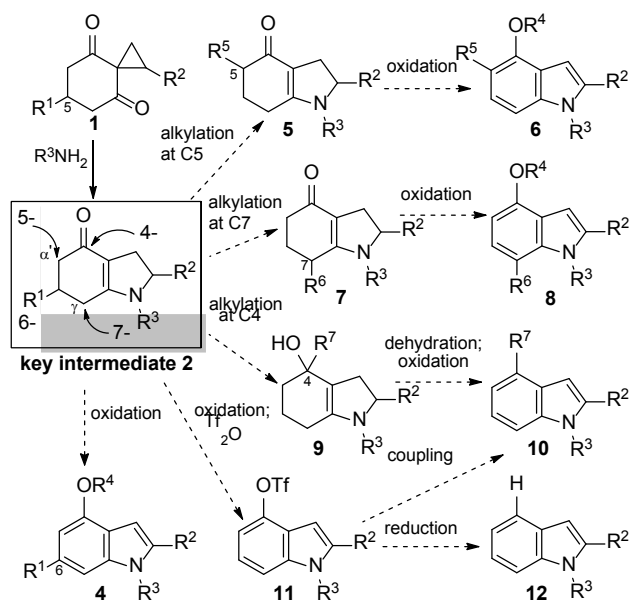


Scheme 2. Synthesis of 4-hydroxyindole **4a** via the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropane **1a** with benzylamine.

Results and Discussion

Synthetic strategy for highly substituted indoles

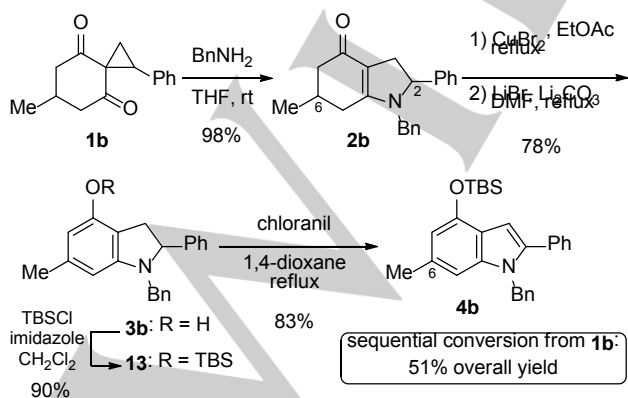
Our synthetic strategy for indoles bearing multiple substituents on the benzene ring is outlined in Scheme 3. Because **2a** is easily oxidized to 4-hydroxyindole **4a**, we planned to use functionalized tetrahydroindol-4(5*H*)-ones as potential key synthetic intermediates for substituted indoles. 6-Substituted tetrahydroindol-4(5*H*)-one **2** (R¹ ≠ H) can be prepared from 5-substituted cyclohexane-1,3-dione-2-spirocyclopropane **1** (R¹ ≠ H) according to our ring-opening cyclization procedure.^[17] Tetrahydroindol-4(5*H*)-one **2** substituted at the other positions could be regioselectively converted from non-substituted **2** using its several reactive sites based on its β-enaminone structure: **2** can react with an electrophile as the corresponding enolate at the α¹- and γ-positions of the enaminone (i.e., the 5- and 7-positions of the indole), and can also react with a nucleophile at the carbonyl carbon (4-position). After regioselective functionalization of **2**, the resulting products **5**, **7**, and **9** would be readily oxidized to the 5-, 7-, and 4-substituted indoles **6**, **8**, and **10**, respectively. Alternatively, transition-metal-catalyzed coupling of indole-4-*O*-triflate **11** would produce the 4-substituted indole **10** and also the non-substituted **12**.



Scheme 3. Strategy for syntheses of highly substituted indoles.

Synthesis of 6-substituted indole derivatives

We initially synthesized 6-substituted indoles according to our published method, as shown in Scheme 2. When 5-methylcyclohexane-1,3-dione-2-spirocyclopropane **1b**^[18] was reacted with benzylamine in tetrahydrofuran (THF) at room temperature, the ring-opening cyclization reaction proceeded smoothly to provide 6-methyltetrahydroindol-4(5*H*)-one **2b** in 98% yield (Scheme 4). Oxidation of **2b** to indoline **3b** was achieved by bromination with $CuBr_2$ followed by aromatization using a combination of $LiBr$ and Li_2CO_3 . After protection of the phenolic hydroxy group in **3b** as a *tert*-butyldimethylsilyl (TBS) ether, oxidation of **13** with chloranil furnished 6-methylindole **4b** in 75% yield from **3b**. Furthermore, we explored a sequential conversion of these processes. Ring-opening cyclization of **1b** followed by oxidation to indole proceeded without purification of any intermediate by column chromatography on silica gel, providing **4b** in 51% overall yield.

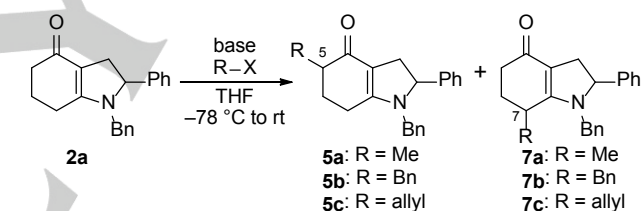


Scheme 4. Synthesis of 6-methylindole **4b**.

Synthesis of 5- and 7-substituted indole derivatives

Next, the synthesis of 5- and 7-substituted indole derivatives was investigated. Mariano and co-workers reported regioselective enolization and alkylation of β -enaminones.^[19] The α -alkylated product was obtained through kinetic enolate formation when using lithium diisopropylamide (LDA) as a base, whereas the γ -alkylated product was formed through thermodynamic enolate formation when using lithium hexamethyldisilazide (LiHMDS). Therefore, we applied this protocol to regioselective alkylation of **2** with alkyl halides (Table 1). **2a** was reacted with LDA in THF at $-78^\circ C$, and then the reaction was quenched with methyl iodide at $-78^\circ C$ to rt to afford 5-methylated product **5a** in 89% yield (entry 1). Similar reactions of **2a** with benzyl and allyl bromides as the alkyl halide gave 5-benzylated and 5-allylated products **5b** and **5c** in 76% and 59% yields, respectively (entries 2 and 3). Conversely, the reaction of **2a** with methyl iodide using LiHMDS as a base produced 7-methylated product **7a** in 84% yield (entry 4). Regioselective benzoylation and allylation at C7 were also achieved by using LiHMDS and 7-benzoylated and allylated products **7b** and **7c** were obtained in 89% and 71% yields, respectively (entries 5 and 6).

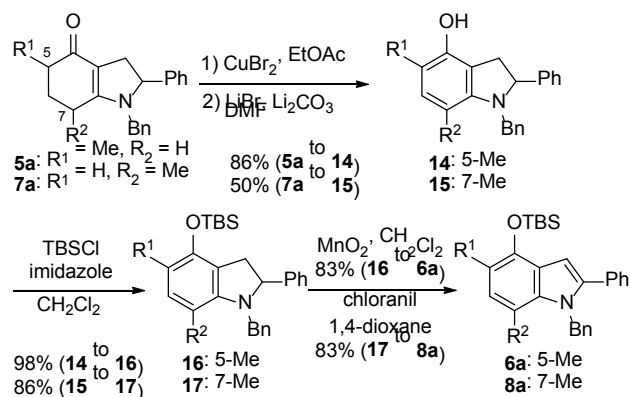
Table 1. Regioselective alkylation of **2a** using LDA or LiHMDS.^[a]



Entry	Base	R-X	Product	Yield [%] ^[b]
1	LDA	methyl iodide	5a	89
2	LDA	benzyl bromide	5b	76
3	LDA	allyl bromide	5c	59
4	LiHMDS	methyl iodide	7a	84
5	LiHMDS	benzyl bromide	7b	89
6	LiHMDS	allyl bromide	7c	71

[a] All reaction were performed on a 0.2 mmol scale with 1.5 equiv of alkyl halides and 1.5 equiv (for LDA) or 1.3 equiv (for LiHMDS) of bases. [b] All products were isolated as a diastereomeric mixture.

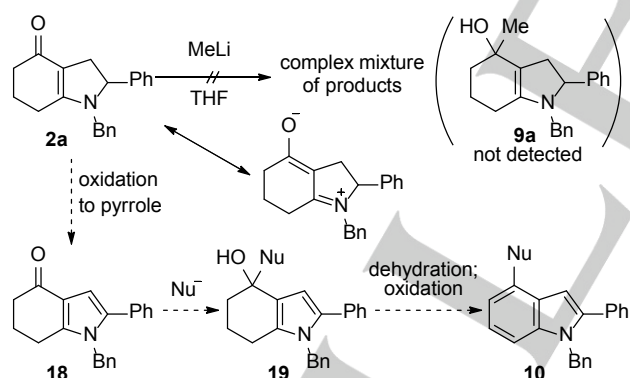
Next, we performed the conversion of the 5- and 7-alkylated products into indoles (Scheme 5). According to Schemes 2 and 4, the bromination of 5- and 7-methyl compounds **5a** and **7a** with $CuBr_2$ followed by aromatization using $LiBr$ and Li_2CO_3 provided the corresponding indoline products **14** and **15** in 86% and 50% yields, respectively. After protection of the phenolic hydroxy groups in **14** and **15** with TBSCl to give the corresponding silyl ethers **16** and **17** in 98% and 86% yields, treatment of **16** and **17** with chloranil afforded 5-methylindole **6a** and 7-methylindole **8a** in 58% and 83% yields, respectively. Oxidation of **16** with MnO_2 furnished **6a** in 83% yield. Thus, regioselective synthesis of 5- and 7-methylindoles was achieved.



Scheme 5. Synthesis of 5-methyl and 7-methylindole derivatives **6a** and **8a**.

Synthesis of 4-substituted indole derivatives

4-Substituted indole **10** was obtained by nucleophilic addition to the carbonyl group at C4 of the tetrahydroindol-4(5*H*)-one. We initially investigated the reaction of **2a** with nucleophiles (Scheme 6). However, the reaction of **2a** with methyl lithium gave a complex mixture of products and tertiary alcohol **9a** was not detected. We assumed that the electrophilicity of the carbonyl group in **2a** was reduced by the donating effect of the nitrogen atom. Therefore, we planned to oxidize **2a** to pyrrole **18** prior to addition of the nucleophile to the carbonyl carbon. The tertiary alcohol **19** obtained by the addition of a nucleophile to ketone could be converted into 4-substituted indole derivative **10** by dehydration and subsequent oxidation.



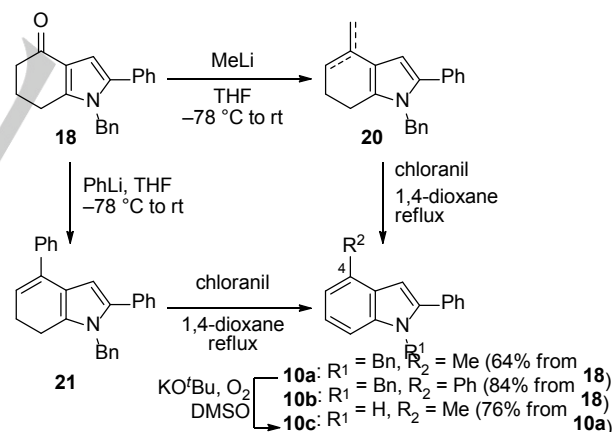
Scheme 6. Attempts to introduce the methyl group at C4 and a synthetic strategy for 4-substituted indole **10**.

Conversion of tetrahydroindol-4(5*H*)-one **2a** to pyrrole **18** was somewhat troublesome (Table 2). The usual oxidation with DDQ and dehydrogenation with Pd/C gave only trace amounts of **18** (entries 1 and 2), and the reaction with chloranil in 1,4-dioxane afforded **18** in moderate yield (entry 3). Gratifyingly, we found that MnO₂ was the most effective oxidant for **2a** and gave **18** in 90% yield (entry 4).

Table 2. Oxidation of **2a** to pyrrole **18**.

Entry	Oxidant	Solvent	t [h]	Yield (%)
1	DDQ	1,4-dioxane	3	trace
2	Pd/C	EtOAc	24	trace
3	chloranil	1,4-dioxane	1	60
4	MnO ₂	CH ₂ Cl ₂	1	90

We then examined nucleophilic addition to pyrrole **18** (Scheme 7). The reaction of **18** with methyl lithium in THF proceeded smoothly to produce a mixture of *exo*- and *endo*-olefin **20** through methylation of the ketone and subsequent dehydration of the resulting tertiary alcohol. The conjugated olefin **20** was easily oxidized with chloranil, and 4-methylindole derivative **10a** was obtained in 64% yield from **18**. The reaction of **18** with phenyllithium also occurred very well to afford conjugated olefin **21** and a sequential oxidation with chloranil gave 4-phenylindole derivative **10b** in 84% yield from **18**. To demonstrate the utility of this synthetic method, we investigated the removal of the benzyl protecting group. According to the procedure of Deaton-Rewolinski,^[20] treatment of *N*-benzylindole **10a** with potassium *tert*-butoxide/dimethyl sulfoxide (DMSO) and oxygen at room temperature afforded *N*-debenzylated product **10c** in 76% yield.

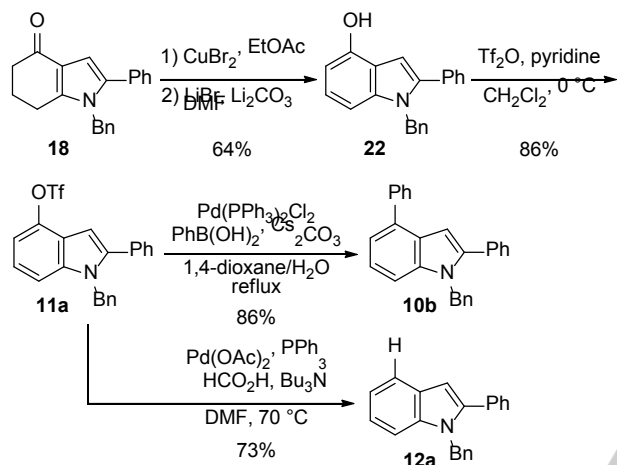


Scheme 7. Synthesis of 4-methyl and 4-phenylindoles **10a-c**.

Introduction of C4 substitutions by Pd-catalyzed coupling of triflates

Here, we demonstrate the transition-metal-coupling method for the synthesis of 4-phenylindole **10b** from 4-hydroxyindole as an alternative (Scheme 8), because it has been disclosed that the 4-hydroxy group of the indole could be converted into other substituents, such as alkynyl, aryl, or hydro groups, by transition-metal-catalyzed coupling of the corresponding *O*-triflate.^[3g, 21] Bromination of pyrrole **18** with CuBr₂ followed by

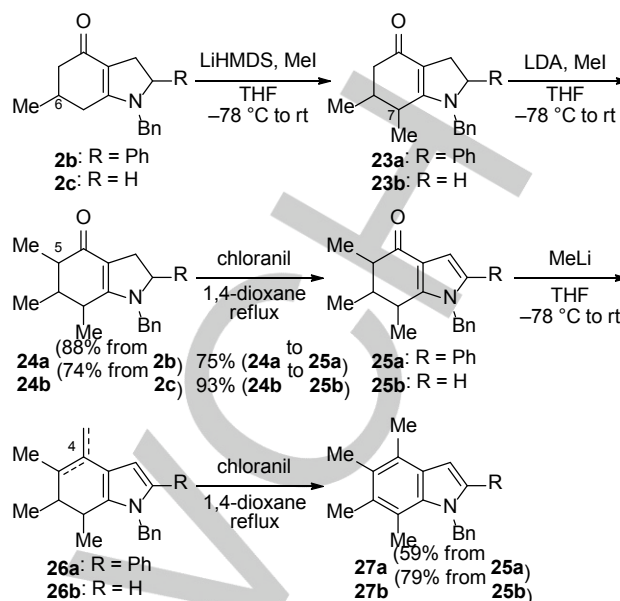
aromatization using LiBr and Li₂CO₃ provided the corresponding 4-hydroxyindole **22**^[22] in 64% yield. Reaction of **22** with triflic anhydride and pyridine afforded indole triflate **11a** in 86% yield. Pd-catalyzed coupling of **11a** with phenylboronic acid and Cs₂CO₃ proceeded smoothly to provide 4-phenylindole **10b** in 86% yield. Furthermore, reductive coupling of **11a** and formic acid in the presence of Pd(OAc)₂ afforded 4-hydroindole **12a** in 73% yield. These results indicate that a variety of 4-substituted indole derivatives can be synthesized via the Pd-catalyzed coupling of indole triflates.



Scheme 8. Synthesis of 4-phenylindoles **10b** and 4-hydroindole **12a** via indole triflate **11a**.

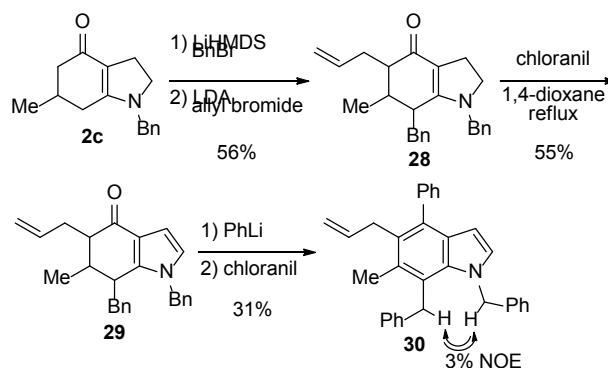
Synthesis of 4,5,6,7-tetrasubstituted indole derivatives

Having achieved the regioselective alkylation of tetrahydroindol-4(5*H*)-one **2**, we then investigated the synthesis of indoles possessing fully substituted benzene rings, such as 4,5,6,7-tetramethylindoles **27a** and **27b** (Scheme 9). C7-Selective methylation of 6-methyltetrahydroindol-4(5*H*)-ones **2b** (R = Ph) and **2c** (R = H)^[23] using LiHMDS and methyl iodide followed by C5-selective methylation with LDA and methyl iodide afforded 5,6,7-trimethyl derivatives **24a** and **24b** in 88% and 74% yields, respectively. After oxidation of **24a** and **24b** with chloranil, C4-selective methylation of pyrroles **25a** and **25b** with methyl lithium followed by oxidation of conjugated olefins **26a** and **26b** with chloranil furnished 4,5,6,7-tetramethylindoles **27a** and **27b** in 59% and 79% yields, respectively.



Scheme 9. Synthesis of 4,5,6,7-tetramethyl-substituted indoles **27a** and **27b**.

Finally, the synthesis of indole bearing various substitutions on the benzene ring was examined (Scheme 10). C7-Selective benzylation of 6-methyltetrahydroindol-4(5*H*)-one **2c** with benzyl bromide using LiHMDS and sequential C5-selective allylation with allyl bromide using LDA provided 5-allyl-7-benzyl-6-methyl-substituted product **28** in 56% yield. After oxidation to pyrrole **29** with chloranil (55% yield), C4-selective phenylation of **29** with phenyllithium followed by oxidation with chloranil furnished 5-allyl-1,7-dibenzyl-6-methyl-4-phenylindole (**30**) in 31% yield. The regioselectivity of **30** was confirmed by an observed ¹H NOE correlation between N1- and C7-benzylic protons.



Scheme 10. Synthesis of 4,5,6,7-tetrasubstituted indole **30**.

Conclusions

We demonstrated the syntheses of highly substituted indoles via the common synthetic intermediates tetrahydroindol-4(5*H*)-ones. 6-Methyl-substituted indoles were synthesized from a readily available 5-methylcyclohexane-1,3-dione-2-spirocyclopropane.

Synthesis of 5- and 7-methyl-substituted indoles was achieved by regioselective methylation of tetrahydroindol-4(5H)-one followed by oxidation to indoles. 4-Methyl-substituted indoles were synthesized by oxidation to the pyrrole derivative, methylation with methylolithium, and oxidation to the indole. In addition, synthesis of 4,5,6,7-tetrasubstituted indoles was achieved from 6-methyl-substituted tetrahydroindol-4(5H)-ones using these regioselective alkylations. Further application of the present synthetic method to the synthesis of biologically active indole alkaloids is currently in progress.

Experimental Section

Typical procedure for the regioselective alkylation of tetrahydroindol-4(5H)-ones **2** and **23** with LDA (Table 1, Schemes 9 and 10)

A solution of LDA (1.0 M in THF, 0.30 mL, 0.30 mmol) was added to a solution of tetrahydroindol-4(5H)-one **2a** (61 mg, 0.20 mmol) in THF (2 mL) at -78°C . After stirring at -78°C for 1 h, methyl iodide (0.019 mL, 0.30 mmol) was added to the mixture and the whole was allowed to warm to room temperature over 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL), and the whole mixture was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 4% Et_3N in EtOAc) to provide 5-methylated product **5a** (57 mg, 89%).

Typical procedure for the regioselective alkylation of tetrahydroindol-4(5H)-ones **2** with LiHMDS (Table 1, Schemes 9 and 10)

A solution of LiHMDS (0.83 M in THF/hexane, 0.66 mL, 0.55 mmol) was added to a solution of **2a** (61 mg, 0.20 mmol) in THF (5 mL) at -78°C . After stirring at -78°C for 1 h, methyl iodide (0.047 mL, 0.75 mmol) was added to the mixture and the whole was allowed to warm to room temperature over 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and the whole mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 4% Et_3N in EtOAc) to provide 7-methylated product **7a** (133 mg, 84%).

Typical procedure for the conversion of pyrrole derivatives **18**, **25**, and **29** to 4-substituted indole derivatives **10**, **27**, and **30** via conjugated olefins (Schemes 7, 9, and 10)

A solution of methylolithium (2.0 M in Et_2O , 0.20 mL, 0.40 mmol) was added to a solution of pyrrole **18** (30 mg, 0.10 mmol) in THF (5 mL) at -78°C . The mixture was allowed to warm to room temperature over 1 h. The reaction mixture was quenched with EtOH (10 mL), and the whole mixture was evaporated in vacuo. The residue was diluted with CH_2Cl_2 (20 mL), and the whole mixture was washed with water (5 mL) and brine (5 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product **20** (27 mg), which was used in the next step without further purification.

Chloranil (37 mg, 0.15 mmol) was added to a solution of the crude product **20** in 1,4-dioxane (1 mL). The mixture was stirred at reflux for 1 h. After cooling, the mixture was evaporated in vacuo. The residue was diluted with Et_2O (10 mL), and the whole mixture was washed with

saturated aqueous NaHCO_3 (3 x 5 mL), water (5 mL) and brine (5 mL), and dried over anhydrous MgSO_4 . Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 5% EtOAc in hexane) to provide **10a** (19 mg, 64%).

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Keywords: indole • regioselective alkylation • enaminone • dehydrogenation • spirocyclopropane

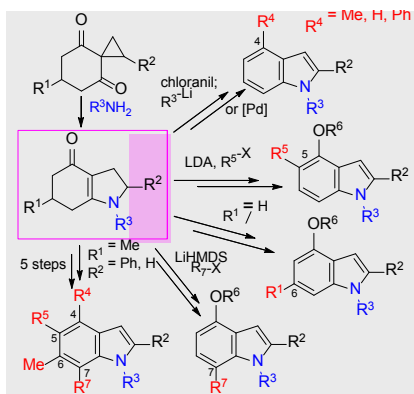
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FULL PAPER

The synthesis of highly substituted indoles via tetrahydroindol-4(5*H*)-one intermediates was developed. The synthesis of 5- and 7-substituted indoles was achieved by regioselective alkylation followed by oxidation to indoles. 4-Substituted indoles were synthesized by oxidation to the pyrrole derivative, alkylation with alkyllithium, and oxidation to the indole. Furthermore, the synthesis of **4,5,6,7-tetrasubstituted indoles** was achieved by using these regioselective alkylations.



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An Efficient Route to Highly Substituted Indoles via Tetrahydroindol-4(5*H*)-one Intermediates Produced by Ring-Opening Cyclization of Spirocyclopropanes with Amines