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Synthesis of substituted indoles via a highly selective 7-lithiation of 4,7-dibromoindoles and the effect of indole-nitrogen on regioselectivity

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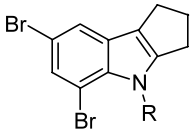
Abstract—We have developed an efficient synthetic pathway to rapidly access 4-bromoindoles, 4-substituted indoles, 4-bromo-7-substituted indoles, and 4,7-disubstituted indoles using a highly selective lithiation at the 7-position of 1-alkyl-4,7-dibromoindoles when treated with *t*-BuLi in ether. Based upon the selectivity obtained with 5,7-dibromoindoles in our previous study and with 4,7-dibromoindoles in the current study, we conclude that the alkylated indole nitrogen plays an important role in controlling selectivity.

The indole nucleus is a common substructure of many biologically active compounds,[1] and indoles with substituent(s) on the benzenoid portion are widely used in medicinal chemistry studies.[2] Although numerous methods are available for indole preparation,[3] we still lack ready access to indoles of certain substituted patterns on the benzenoid portion—especially when substituents are labile. Recently, we reported a general approach to the synthesis of 5,7-disubstituted indoles based upon a selective lithiation at 7-bromine of 5,7-dibromoindoles.[4] This approach is very attractive in terms of efficiency and applicability, and prompted us to extend it to the synthesis of substituted indoles of other substituted patterns on the benzenoid portion.



1a R = Me
1b R = *i*-Pr
1c R = K

Furthermore, we are interested in understanding what causes the highly selective lithium–bromine exchange of 5,7-dibromoindoles. In our previous study, we obtained some useful information about the reaction: steric hindrance of 1-alkyl substituent has no influence on selectivity, both **1a** and **1b** are lithiated at the 7-position; lithiation of 1-potassio-5,7-dibromoindole (**1c**) proceeds with slight selectivity (3:2) for the 7-position. The major selectivity difference between an *N*-alkyl-substituted indole (**1a** or **1b**) and an *N*-potassio-substituted indole (**1c**) could be caused by the dramatic electronic nature change of the indole aromatic system when the substituent R was changed from the *N*-alkyl to the *N*-potassio. The highly selective reaction at the 7-position of *N*-alkylated 5,7-dibromoindoles could involve either a mechanism-based process[5] aided by the alkylated indole-nitrogen or a halogen dance process[6] following an initially non-selective exchange reaction to form the thermodynamic favored 7-lithiated product. Either way, if true, a highly selective exchange reaction could be expected at the 7-position of other types of 7-bromoindoles that have 1–3 bromine substituent(s) on the benzenoid portion. Among all such indoles, 4,7-dibromoindole aroused our interest because of their potential use in the synthesis of 4,7-disubstituted indoles and 4-substituted indoles (Scheme 1)—two types of substituted indoles found in many natural products and bioactive compounds that have proven difficult to synthesize.[7,8] They can also serve as key intermediates for natural product synthesis.[9] We also expected that a study of the lithium–bromine exchange reaction of 4,7-dibromoindoles would provide more insight into the main factor controlling selective lithiation.

The 4,7-dibromoindoles used in this study were prepared by Fisher indole synthesis[10] (for **2a**, Table 1) or by Bartoli indole synthesis[11] (for indole **2b**). Both **2a**

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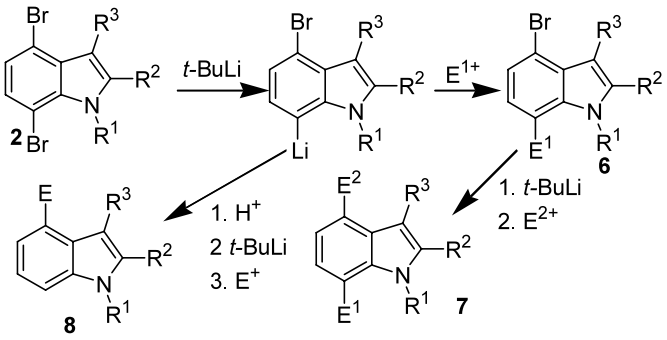
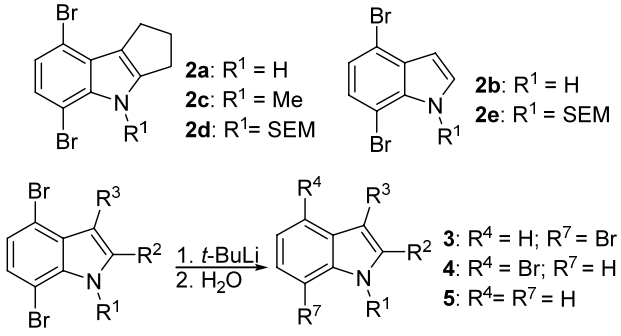


Scheme 1.

Table 1. The determination of regioselectivity of the Li–Br exchange reaction of 4,7-dibromoindoles



Entry	Indole **2**	*t*-BuLi (equiv.)	Products			
			2	**3**	**4**	**5**
1	**2a**[a]	2.1	–	28	72	–
2	**2c**	2.1	10	–	90	–
3	**2d**	1.8	–	–	92	8
4	**2e**	1.8	–	–	89	11

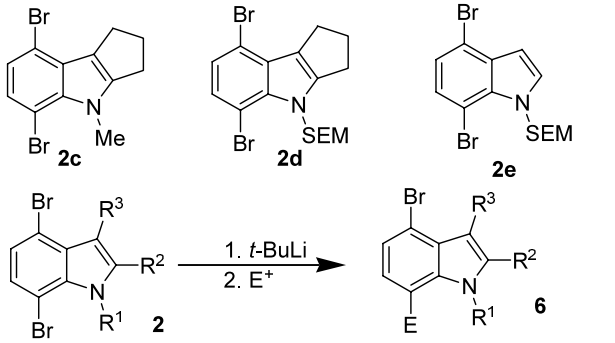
[a] Indole **2a** was treated with 1 equiv. of KH before Li–Br exchange reaction.

and **2b** could be alkylated at the 1-position to afford indoles **2c**, **2d**, and **2e** by using methyl iodide or SEMCl[12] as an alkylating reagent. With the desired 4,7-dibromoindoles in hand, we started to investigate the regioselectivity of their lithium–bromine exchange reaction. This was done by treating a certain indole with a required amount of *t*-BuLi in ether at −78°C for 15 min followed by a water-quench (Table 1). The crude mixture thus obtained was analyzed by using ^{1}H NMR. We found that when 1-potassio indole,[13] formed in situ by the reaction of indole **2a** with KH, was treated with 2.1 equiv. of *t*-BuLi, the corresponding 7-lithiated and 4-lithiated products were afforded in 72 and 28% yields, respectively (Table 1, entry 1). Under the same conditions, *N*-methyl indole **2c** only afforded 7-lithiated product in 90% yield (Table 1, entry 2). When SEM was used as a substituent on nitrogen, 1.8 equiv. of *t*-BuLi was enough to complete the highly selective mono-lithiation at the 7-position for both indoles **2d** and **2e** (Table 1, entries 3 and 4).

Given the results from the first two entries in Table 1, we found that the selectivity of the lithium–bromine exchange reaction of 4,7-dibromoindoles followed the same trend as of 5,7-dibromoindoles. The exchange of *N*-methyl indole proceeded exclusively at the 7-position while the *N*-potassio analog gave much lower selectivity. This provides further support for our previous claim that it is the electronic nature change of the indole aromatic system that caused this dramatic difference in selectivity. Based on these results, we also concluded that the alkylated indole-nitrogen played a key role in controlling regioselectivity, but the complexity associated with the lithium-bromine exchange reaction in nature and the uncertainty of the reaction mechanism still prevent us from proposing a detailed mechanism. However, the possibility of directed metallation by the indole nitrogen can most probably be ruled out, as supported by the following facts: indole-nitrogen uses two electrons to participate in the aromatic system, and loses coordinating ability completely after being blocked by an alkyl substituent; and the experimental results showing that *N*-potassio indoles afford lower selectivity than do *N*-alkyl analogs.

Having determined the regioselectivity of the lithiation, we set out to apply the 7-lithiated intermediates to the preparation of 4-bromo-7-substituted indoles. When the 7-lithiated intermediate from indole **2d** was treated with benzaldehyde, the corresponding alcohol **6a** was obtained in 90% yield (Table 2, entry 1). Using acetaldehyde or acetone to replace benzaldehyde as an electrophile, the reaction gave more modest yields (Table 2, entries 2 and 3). When DMF was used as an electrophile, the corresponding aldehyde **6d** was obtained in 82% yield (Table 2, entry 4). By reacting with CO_2

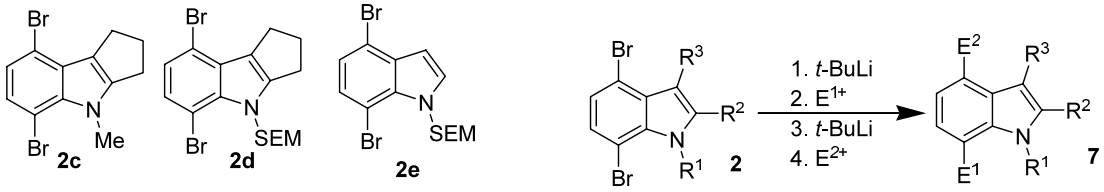
Table 2. The synthesis of 4-bromo-7-substituted indoles



Entry	Indole **2**	E^+	Product **3**, E (isolated yield)
1	**2d**	PhCHO	**6a**, PhCH(OH) (90%)
2	**2d**	MeCHO	**6b**, MeCH(OH) (66%)
3	**2d**	Acetone	**6c**, Me_2C(OH) (68%)
4	**2d**	DMF	**6d**, HC(=O) (82%)
5	**2d**	CO_2	**6e**, MeOC(=O)[a] (79%)
6	**2c**	PhCHO	**6f**, PhCH(OH) (85%)
7	**2c**	CO_2	**6g**, MeOC(=O)[a] (69%)
8	**2e**	PhCHO	**6d**, PhCH(OH) (74%)
9	**2e**	CO_2	**6e**, MeOC(=O)[a] (74%)

[a] Treated with CH_2N_2 after work-up.

Table 3. The synthesis of 4,7-disubstituted indoles



Entry	Indole **2**	E^{1+}	E^{2+}	Product **7**, [E^1,E^2] (isolated yield)
1	**2d**	PhCHO	CO_2	**7a**, [PhCH(OH), MeOC(=O)][a] (59%)
2	**2d**	PhCHO	DMF	**7b**, [PhCH(OH), HC(=O)] (54%)
3	**2d**	PhCHO	PhCONMe(OMe)	**7c**, [PhCH(OH), PhC(=O)] (62%)
4	**2d**	MeCHO	CO_2	**7d**, [MeCH(OH), MeOC(=O)][a] (66%)
5	**2d**	Acetone	CO_2	**7e**, [Me_2C(OH), MeOC(=O)][a] (67%)
6	**2c**	PhCHO	CO_2	**7f**, [PhCH(OH), MeOC(=O)][a] (80%)
7	**2e**	PhCHO	CO_2	**7g**, [PhCH(OH), MeOC(=O)][a] (65%)

[a] Treated with CH_2N_2 after work-up.

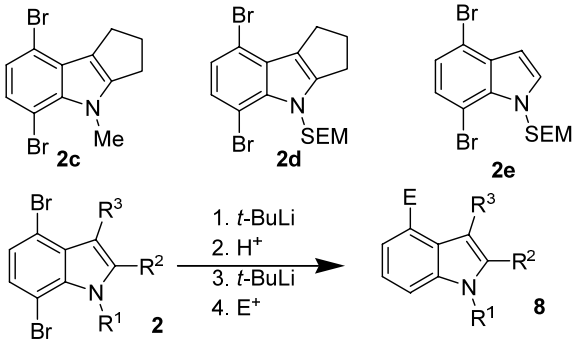
gas followed by treatment with CH_2N_2 after work-up, the methyl ester was obtained in 79% yield (Table 2, entry 5). Indoles **2c** and **2e** were also tested with benzaldehyde and CO_2 as electrophiles; all afforded the desired 7-substituted-4-bromoindoles in good yields (Table 2, entries 6–9).

After our success with the preparation of 4-bromo-7-substituted indoles, we started to look at the possibility of applying the sequential lithium–bromine exchange strategy to the synthesis of 4,7-disubstituted indoles by using 4,7-dibromoindoles as scaffolds. Without the work-up of the reaction mixture, which contained the intermediate leading to 4-bromo-7-substituted indole **6a** (Table 2, entry 1), a second lithium–bromine exchange reaction was performed by treatment with *t*-BuLi. The lithium reagent thus obtained could react with another electrophile like CO_2, DMF, or *N*-methoxy-*N*-methylbenzamide to afford 4,7-disubstituted indoles **7a**, **7b**, and **7c**, respectively, in good yields (Table 3, entries 1–3). Using the same conditions, the intermediates that lead to indoles **6b** (Table 2, entry 2) and **6c** (Table 2, entry 3) were also subjected to a second lithium–bromine exchange. After reacting with CO_2 and treatment with CH_2N_2, the corresponding acid esters **7d** and **7e** were obtained in good yields (Table 3, entries 4 and 5). By using a combination of PhCHO-CO_2 as the first and second electrophiles, both indoles **2c** and **2e** could be efficiently transformed into the corresponding esters **7f** and **7g** (Table 3, entries 6 and 7), respectively, in good yields.

The 4-bromoindoles obtained in Table 1 could serve as valuable intermediates for preparing 4-substituted indoles.[14] In considering the origin of the 4,7-dibromoindoles (**2**), the 7-bromine can be viewed as a protective group of the 7-carbon that helps avoid the regioselectivity problem during the Fisher and Bartoli indole synthesis. In the Bartoli method, the 7-bromine also plays an important role in improving the reaction yield.[15] The sequence of a selective lithiation at 7-position followed by quenching with a proton source serves as a deprotection process. By using a limited amount of proton source, a one-pot process is possible. After the 7-lithiated indole from indole **2d** (Table 1, entry 3) was treated with 1.2 equiv. of MeOH for 5 min at −78°C, the resulting mixture was treated with 2.5 equiv. of *t*-BuLi, followed by the addition of electrophiles. Benzaldehyde, acetaldehyde, acetone, DMF, and CO_2 were chosen as representative electrophiles, all of which gave the corresponding desired products in good yields ranging from 62 to 77% (Table 4, entries 1–5). When PhCHO was used as electrophile, 4-substituted indoles **8f** and **8g** were obtained from indoles **2c** and **2e** (Table 4, entries 6 and 7) in 60 and 70% yields, respectively.

In summary, we have developed an efficient synthetic pathway to rapidly access 4-bromoindoles, 4-substi-

Table 4. The synthesis of 4-substituted indoles



Entry	Indole **2**	E^+	Product **8**, E (isolated yield)
1	**2d**	PhCHO	**8a**, PhCH(OH) (70%)
2	**2d**	MeCHO	**8b**, MeCH(OH) (62%)
3	**2d**	Acetone	**8c**, Me_2C(OH) (72%)
4	**2d**	DMF	**8d**, HC(=O) (77%)
5	**2d**	CO_2	**8e**, MeOC(=O)[a] (74%)
6	**2c**	PhCHO	**8f**, PhCH(OH) (70%)
7	**2d**	PhCHO	**8g**, PhCH(OH) (74%)

[a] Treated with CH_2N_2 after work-up.

tuted indoles, 4-bromo-7-substituted indoles, and 4,7-disubstituted indoles based upon a highly selective lithiation at the 7-position of 1-alkyl-4,7-dibromoindoles when treated with *t*-BuLi in ether. Given the selectivity obtained with 5,7-dibromoindoles in our previous study and with 4,7-dibromoindole in current study, we conclude that the indole nitrogen bearing an alkyl group plays an important role in controlling selectivity. A detailed mechanism study is in progress.

Acknowledgements

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