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A facile approach to the synthesis of 5,7-disubstituted indoles via a highly selective lithium–bromine exchange of 5,7-dibromoindoles

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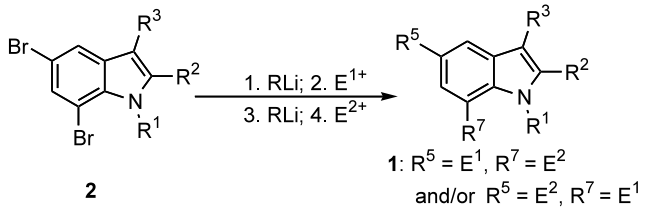
Abstract—A general approach to the synthesis of 5,7-disubstituted indoles has been developed based upon a highly selective lithium–bromine exchange reaction at the 7-position when 1-alkyl-5,7-dibromoindoles were treated with *t*-BuLi in ether. The resulting 5-bromo-7-lithiated indoles could react with various electrophiles to afford 5-bromo-7-substituted indoles (**6**) upon work-up. Without isolation of **6**, the intermediates thus obtained could be exposed to a second lithium–bromine exchange reaction in a one-pot procedure and further reacted with various electrophiles to afford 5,7-disubstituted indoles (**1**). © 2003 Published by Elsevier Science Ltd.

In a recent medicinal chemistry study, we needed a general approach to the synthesis of indoles bearing various functionalized carbon substituents at the 5- and 7-positions with an alkyl substituent on nitrogen (**1**).[1] Although numerous methods are available for indole preparation,[1,2] the synthesis of this type of indole still remains a great challenge. To date, a general but indirect approach to indoles with substituent(s) on its benzenoid portion involves the annulation of a pyrrole portion with a suitably functionalized benzene as starting material.[3] There are obvious disadvantages like lengthy synthesis, low compatibility to labile functional groups, and difficulty in synthesis of complicated starting materials. A better approach to serve our purpose is to directly introduce the desired substituents to indole's 5- and 7-positions. Due to indole's distinct electron density distribution, introduction of substituents on its benzenoid portion by reaction with an activating electrophile, i.e. Friedel–Crafts reaction, usually suffers from problems with regioselectivity.[4–6] Our strategy to solve this problem is illustrated in Scheme 1. We used the easily prepared 5,7-dibromoindoles **2**[7] as scaffold, in which the bromine substituents would act as activating and directing groups if a selective lithium–bromine exchange could be achieved.[8–11]

The 5,7-dibromoindoles (**2**) used in this study are presented in Table 1. To study the selectivity of lithium–bromine exchange, **2b** was used as substrate to screen the alkyllithium and solvent. **2b** was treated either with 1.1 equiv. of *n*-BuLi or with 2.2 equiv. of *t*-BuLi either in THF or in ether at −78°C for 10 min, and was then quenched by water. The composition of the crude product was determined by ^{1}H NMR. We found that the exchange could be achieved selectively at 7-bromine and *t*-BuLi in ether gave the best results (Table 1, entry 1).[12] An attempt with a non-coordinating solvent toluene with *t*-BuLi resulted in no reaction (Table 1, entry 2). Optimized conditions were established by reducing the amount of *t*-BuLi from 2.2 equiv. to 2.1 equiv. This afforded **4b** and **5b** as a mixture of ratio 94:6 (Table 1, entry 3). Satisfied with the conditions, we applied them to indoles **2c**, **2f**, **2h**, and **2k** (entries 3–7). The results showed that the selective lithium–bromine exchange was a common reaction for indoles with various substituents at their 1-, 2-, 3-positions. No influence of



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Scheme 1.

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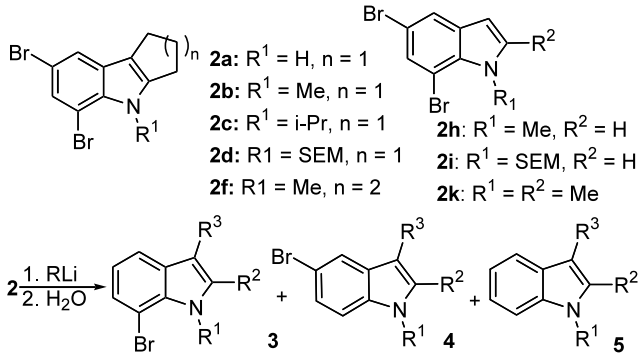
Table 1. The selectivity of lithium–bromine exchange of 5,7-dibromoindoles



Entry	Indole **2**	RLi (equiv.)	Solvent	Products			
				2	**3**	**4**	**5**
1	**2b**	*t*-BuLi (2.2)	Et_2O	–	–	88	12
2	**2b**	*t*-BuLi (2.2)	$PhCH_3$	100	–	–	–
3	**2b**	*t*-BuLi (2.1)	Et_2O	–	–	94	6
4	**2c**	*t*-BuLi (2.1)	Et_2O	–	–	88	12
5	**2f**	*t*-BuLi (2.1)	Et_2O	–	–	94	6
6	**2h**	*t*-BuLi (2.1)	Et_2O	–	–	92	8
7	**2k**	*t*-BuLi (2.1)	Et_2O	–	–	90	10
8	**2a**	*t*-BuLi (2.1)	Et_2O	–	40	60	–
9	**2d**	*t*-BuLi (2.1)	Et_2O	–	–	78	22
10	**2d**	*t*-BuLi (1.8)	Et_2O	–	–	92	8
11	**2i**	*t*-BuLi (1.8)	Et_2O	–	–	89	11

steric hindrance of the 1-substituent on selectivity was observed, as shown by the results from indole **2c** (Table 1, entry 4).

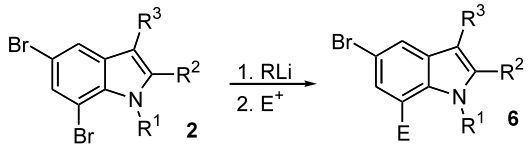
To extend our study to the synthesis of indoles without a substituent at 1-position, we applied the best conditions to indole **2a** after treatment with 1 equiv. of base (EtMgCl, MeLi, or KH). Only the use of KH gave a clean reaction to afford a 2:3 ratio of **3a** and **4a**, while the other cases afforded complicated mixtures of products.[13] Hence, indole **2d** bearing a removable alkyl substituent SEM (2-(trimethylsilyl)ethoxymethyl)[14] was examined, and more bis-exchange product **5d** formed (Table 1, entry 9). But satisfactory results could be obtained with both indoles **2d** and **2i** when 1.8 equiv. of *t*-BuLi was used in ether (Table 1, entries 10–11).

Having the selectivity of the exchange reaction determined and the reaction conditions optimized, we set out to examine the reaction of the resulting 7-lithiated indoles with various electrophiles (see Table 2). We first treated the lithiated intermediates from indoles **2b** and **2d** with various electrophiles like aromatic and aliphatic aldehydes, acetone, DMF, and CO_2. All yielded the corresponding products in good to excellent yield without modifying reaction conditions (Table 2, entries 1–5 and 10–14). The reaction of the lithiated species from indoles **2c**, **2f**, **2h**, **2k**, and **2i** with benzaldehyde as electrophile also gave the corresponding alcohols in good yields (Table 2, entries 6–9 and 15).

Apparently, various reactions[15] could be used to replace the 5-bromo group of indoles **6** with other substituents. Among them, another sequence of lithium–bromine exchange followed by reaction with electrophiles in one-pot seemed convenient and promising.[16] The idea was tested by using indole **2b**. After the first lithium–bromine exchange and reaction with benzaldehyde, the reaction mixture was treated with *t*-BuLi again and further reacted with CO_2 to afford the corresponding 5,7-disubstituted indole **1a** after esterification of the acid in 86% yield (Table 3, entry 1).[17] Then we applied similar reaction conditions to various combinations of electrophiles to afford valuable products **1b–e** in good yields (Table 3, entries 2–5). Using the same method, we also examined indole **2d**, which afforded the corresponding indoles **1f–j** in good yields (Table 3, entries 6–10). Examinations of other indoles **2f**, **2h**, **2k**, and **2i** with an electrophile combination of PhCHO-CO_2 were further performed and afforded products in good yields (Table 3, entries 11–15).

In summary, we have developed a general approach to the synthesis of 5,7-disubstituted indoles based upon a highly selective lithium–bromine exchange reaction at the 7-position when 1-alkyl-5,7-dibromoindoles were treated with *t*-BuLi in ether. The resulting 5-bromo-7-lithiated indoles could react with various electrophiles to afford 5-bromo-7-substituted indoles (**6**) upon work-up. Without isolation of **6**, the intermediates thus obtained could be exposed to a second lithium–bromine

Table 2. The synthesis of 5-bromo-7-substituted indoles

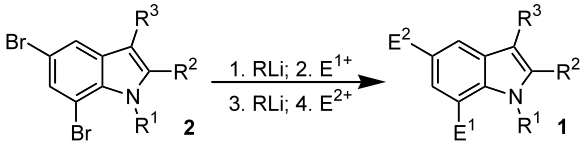


Entry	Indole **2**	E^+	Product[a]	E	Isolated yield
1	**2b**	PhCHO	**6a**	PhCH(OH)	88
2	**2b**	CH_3CHO	**6b**	$CH_3CH(OH)$	65
3	**2b**	MeC(=O)Me	**6c**	$(CH_3)_2C(OH)$	75
4	**2b**	DMF	**6d**	HC(=O)	78
5	**2b**	CO_2	**6e**	MeOC(=O)	79
6	**2c**	PhCHO	**6f**	PhCH(OH)	49
7	**2f**	PhCHO	**6g**	PhCH(OH)	82
8	**2h**	PhCHO	**6h**	PhCH(OH)	67
9	**2k**	PhCHO	**6i**	PhCH(OH)	48
10	**2d**	PhCHO	**6j**	PhCH(OH)	83
11	**2d**	CH_3CHO	**6k**	$CH_3CH(OH)$	71
12	**2d**	MeC(=O)Me	**6l**	$(CH_3)_2C(OH)$	74
13	**2d**	DMF	**6m**	HC(=O)	79
14	**2d**	CO_2	**6n**	MeOC(=O)	76
15	**2i**	PhCHO	**6o**	PhCH(OH)	74

[a] The yielded carboxylic acid was treated with CH_2N_2, and methyl ester was isolated.

exchange reaction in a one-pot procedure and further reacted with various electrophiles to afford 5,7-disubstituted indoles (**1**).

Table 3. The synthesis of 5,7-disubstituted indoles



Entry	Indole **2**		Product[a] E^1, E^2	Yield
1	**2b**	**1a**	PhCH(OH), MeOC(=O)[b]	86
2	**2b**	**1b**	$CH_3CH(OH)$, MeOC(=O)[c]	49
3	**2b**	**1c**	MeOC(=O), PhCH(OH)[d]	58
4	**2b**	**1d**	PhCH(OH), HC(=O)[e]	73
5	**2b**	**1e**	MeOC(=O), PhC(=O)[f]	50
6	**2d**	**1f**	PhCH(OH), MeOC(=O)[b]	52
7	**2d**	**1g**	PhCH(OH), HC(=O)[e]	78
8	**2d**	**1h**	PhCH(OH), PhC(=O)[g]	61
9	**2d**	**1i**	$CH_3CH(OH)$, MeOC(=O)[c]	53
10	**2d**	**1j**	$Me_2C(OH)$, MeOC(=O)[h]	72
11	**2f**	**1k**	PhCH(OH), MeOC(=O)[b]	48
12	**2h**	**1l**	PhCH(OH), MeOC(=O)[b]	57
13	**2k**	**1m**	PhCH(OH), MeOC(=O)[b]	42
14	**2i**	**1n**	PhCH(OH), MeOC(=O)[b]	82
15	**2i**	**1o**	MeOC(=O), PhCH(OH)[d]	52

[a] The yielded carboxylic acid was treated with CH_2N_2, and methyl ester was isolated.
[b] E^{1+}, E^{2+} = PhCHO, CO_2.
[c] E^{1+}, E^{2+} = MeCHO, CO_2.
[d] E^{1+}, E^{2+} = CO_2, PhCHO.
[e] E^{1+}, E^{2+} = PhCHO, DMF.
[f] E^{1+}, E^{2+} = CO_2, PhCONMe(OMe).
[g] E^{1+}, E^{2+} = PhCHO, PhCONMe(OMe).
[h] E^{1+}, E^{2+} = acetone, CO_2.

Acknowledgements

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