Note

Revisiting 2-Alkoxy-3-bromoindolines: Control C-2 *vs.* C-3 Elimination for Regioselective Synthesis of Alkoxyindoles

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The regioselective synthesis of both 2- and 3-alkoxyindoles from a common intermediate, 2-alkoxy-3-bromoindolines (ROBIN), is described. The 2-alkoxyindoles are obtained by a base-promoted regioselective elimination of HBr from ROBIN, whereas the synthesis of 3-alkoxyindoles is achieved by a silver-mediated alkoxylation followed by an acid-promoted elimination of alkoxide. This key elimination features the complete regioselectivity and no need for catalysts, that makes it have potential synthetic applications. Furthermore, this protocol is user friendly because ROBIN is able to be prepared from commercially available indoles and is a bench-stable easy-to-handle crystalline substrate, thus allowing the concise synthesis of a variety of both 2- and 3-alkoxyindoles.

Key words 3-alkoxyindole; 2-alkoxyindole; elimination; regioselective synthesis; silver

Alkoxyindoles are privileged structural units that are found in biologically active compounds and natural products[1–7](Chart 1). Therefore, the construction of oxygenated indoles and indolines is a hot topic of interest in the field of indole chemistry.[8–15] One of the conventional methods is indolization of acyclic compounds.[16–19] Dearomative dioxyfuctionalization of indoles is another efficient method,[20–25] and its eco-friendly version using electrochemistry was reported by Xu and colleagues,[26] and Vincent and colleagues,[27] independently. Although the many methodologies to construct alkoxyindoles were developed, there is no reports of a regioselective formation of 2-alkoxyindoles and 3-alkoxyindoles from a same intermediate. An oxidation control was quite challenging because indoles are electron-rich heterocycles. This may be an underlying cause that the selective formation of alkoxyindoles has not been realized until now by an oxidation.

Indoles are easily accessible precursors for assembling the 2-alkoxy-3-haloindolines through haloalkoxylation[28–30] (Chart 2a). These methods have been established to site-selective functionalization at the C2 and C3 position of indoles. However, further application of the 2-alkoxy-3-haloindolines remains challenging mission.

In our continuing efforts in the indole chemistry,[31–43] we recently reported a concise formation of isochromeno[3,4-*b*]-indolines from 2-benzyloxy-3-bromoindolines were achieved using a silver salt.[44] While extending the utility of the silver-mediated functionalization, we preliminary found that the protocol is also applicable for the synthesis of 2,3-dialkoxyinolines by using alcohol as a nucleophile, which could be converting to 3-alkoxyindoles through a selective elimination of the alkoxide at the C-2 position (Chart 2b). Thus, the 2-alkoxy-3-haloindolines would be considered to be a versatile precursor of alkoxyindoles by utilizing two types of the regioselective elimination. Therefore, we next set out to develop a regioselective synthesis of alkoxyindoles from 2-alkoxy (RO)-3-bromoindolines (ROBIN), utilizing different elimination process. Herein, we report the results of this effort.

Investigations started from Ts-protected 2-RO-3-bromoindolines (ROBIN, **2**) according to previous report[28] (Table

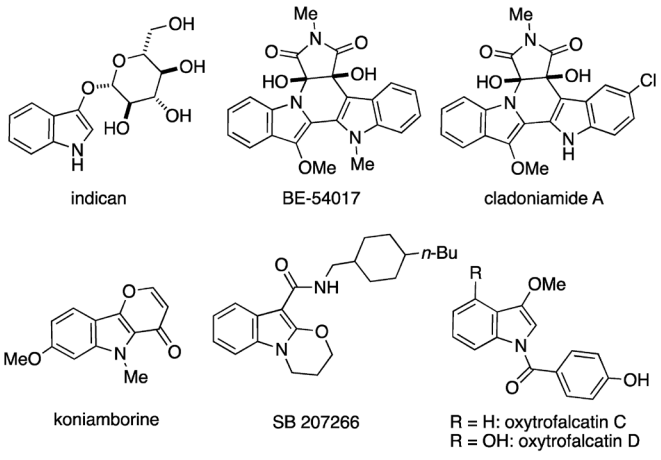

Chart 1. Biologically Active 2- or 3-Alkoxyindoles

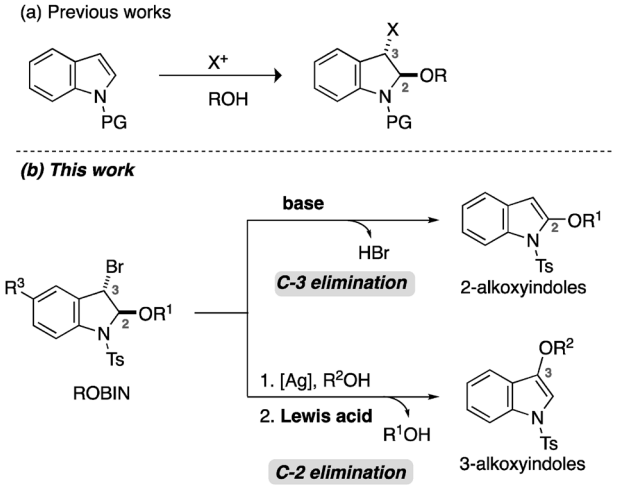

Chart 2. 2-Alkoxy-3-haloindolines

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Table 1. Synthesis of 2-Alkoxy-3-bromoindolines

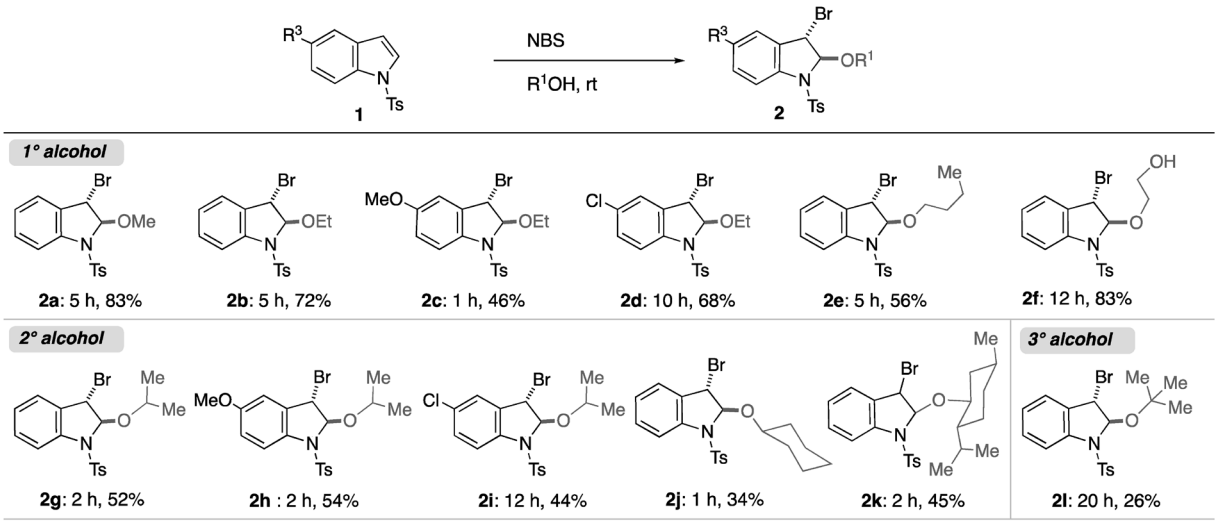


Table 2. Synthesis of 2-Alkoxyindoles

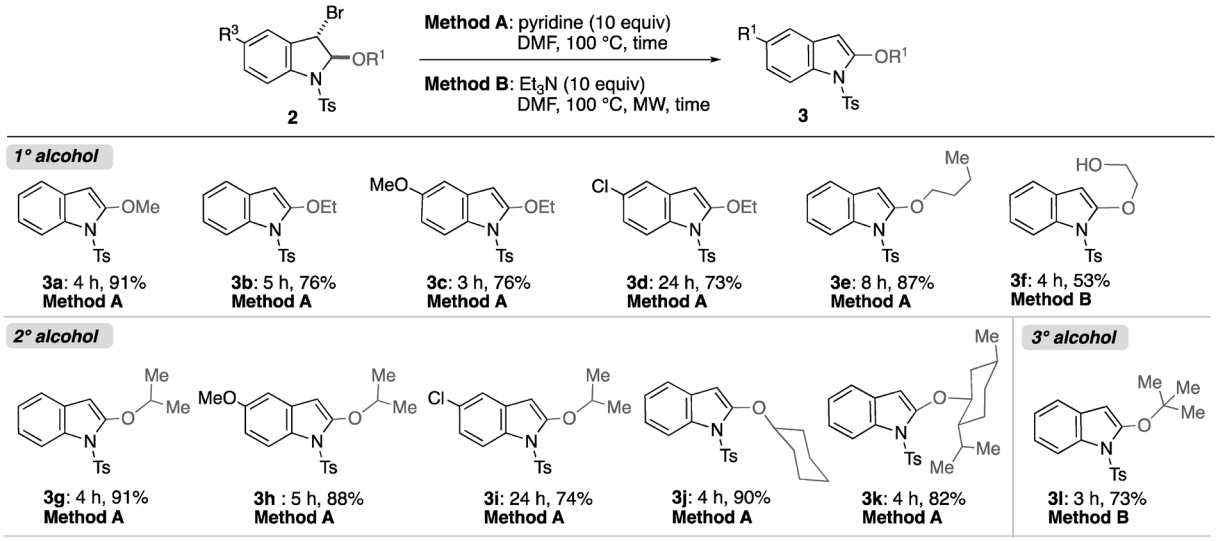
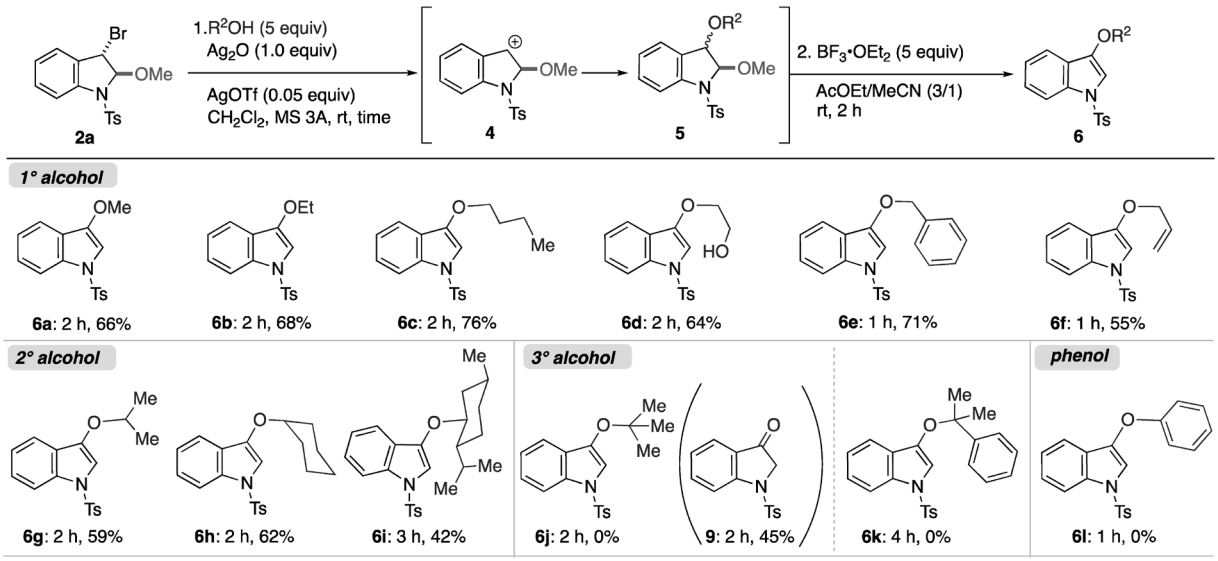


Table 3. Synthesis of 3-Alkoxyindoles



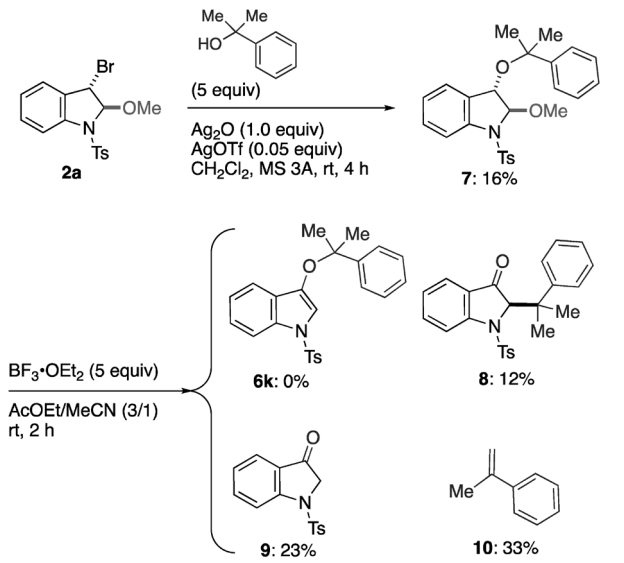


Chart 3. Synthesis of C-2 Alkylated Indolin-3-one **8** under Optimized Conditions

1). The compound **2a** was successfully synthesized in gram quantity without column chromatography. To our delight, all ROBINs (**2**) were a bench-stable easy-to-handle crystalline substrate and could be storable over a year at ambient temperature under air. We confirmed that N-Ts group played a crucial role in stabilization of 2-alkoxy-3-bromoindolines, improving the lifetime from few days to years. In general, transient intermediates as highly reactive species are not easy to handle due to their poor stability. Therefore, stabilization of unstable species for further functionalization is an attractive strategy.

With **2** in hand, we tested an elimination reaction of **2a** to investigate its reactivity (Table 2). As expected, the reaction of **2a** in the presence of pyridine as base (Method A) led to formation of 2-alkoxyindole **3a**. This reaction condition could be applied to ROBINs bearing an electron-donating group and an electron-withdrawing group on the benzene ring and afforded products **3c**, **3d**, **3h**, and **3i** in 88–73% yield. Substrates with either primary or secondary ether were transformed into the corresponding products **3b**, **3e**, **3g**, **3j**, and **3k** in 91–53% yield. The substrate having alcohol or tertiary ether were also effective in this transformation (Method B: Et_3N, *N*,*N*-dimethylformamide (DMF), 100°C, microwave irradiation) affording the desired product **3f** and **3l** in 53 and 73% yield, respectively. As straightforward synthetic protocol to access 2-alkoxyindoles are limited, the present protocol using **2** as a stable key intermediate is synthetically useful.

With synthetic access to **3**, we were next set to answer the question of whether 3-alkoxyindoles **6** could be obtained from the same precursor **2a**. Lei and colleagues reported selective elimination of AcO^- from *trans*-2,3-diacetoxyindoline in the presence of AcOH to afford 3-acetoxyindole.[25] We envisioned that 2,3-dialkoxyindolines **5** would be obtained from **2a** through silver-mediated alkoxylation under the previously reported conditions.[44] Then, the acid-promoted selective elimination of alkoxide from 2,3-dialkoxyindolines would occur to give 3-alkoxyindoles **6**. The reaction of **2a** with methanol in the presence of Ag_2O and AgOTf followed by $BF_3 \cdot OEt_2$ gave the corresponding 3-methoxyindole **6a** in 66% yield (Table 3), while the no use of silver salts gave no desired product. Although the two steps protocol could be applicable to both primary and secondary alcohol (**6a**–**6i**), an attempt to apply the optimized condition to *tert*-butanol and dimethylbenzyl alcohol failed due to the stability of corresponding tertiary cations (**6j**: 0% [**9**: 45%], **6k**: 0%). In addition, phenol as a nucleophile did not give the desired product **6l**, which suggested that the nucleophilicity would be also essential for the C–O bond formation.

We have also shown that 3-alkoxy-2-methoxyindoline **7** are capable undergoing rearrangement to afford 2-alkylindoline-3-one **8** in 12% yield (Chart 3). Although the yield was low, this result opens up for future work aimed at favoring construction of the 2-alkylindoline-3-one.

In conclusion, we have successfully accomplished the regioselective synthesis of both 2- and 3-alkoxyindoles from a common intermediate, 2-RO-3-bromoindolines (ROBIN, **2**). The 2-alkoxyindoles are obtained by a pyridine-promoted regioselective elimination of HBr from ROBIN, whereas the synthesis of 3-alkoxyindoles is achieved by a silver-mediated alkoxylation followed by BF_3-promoted elimination of an alkoxide. We believe that the bench-stable easy-to-handle ROBIN should find an intriguing application to produce diverse indoles.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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