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A REGIOSELECTIVE LITHIATION OF 1-METHOXYMETHOXYINDOLE
AT THE 2-POSITION AND ITS APPLICATION FOR THE SYNTHESIS
OF 2-SUBSTITUTED INDOLES¹

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Abstract— A regioselective lithiation of 1-methoxymethoxyindole at the 2-position was achieved with *n*-BuLi at 0°C. Subsequent treatment with electrophiles afforded 2-substituted 1-methoxymethoxyindoles, which were readily converted to 2-substituted indoles.

Much efforts have been focused on developing a new directing group for the regioselective lithiation at the 2-position² in the indole chemistry. The ideal directing group should realize the formation of 2-lithioindole species by the reaction with milder and safer lithium reagent, and the reaction temperature to be as close to room temperature as possible. Therefore, *n*-butyllithium (*n*-BuLi) is more favorable than *sec*-BuLi and *tert*-BuLi. In addition, the directing group must be removed under mild reaction conditions if necessary. Actually, almost all directing groups thus far known² require low reaction temperature (-76°C) and an extremely pyrophoric *tert*-butyllithium for the formation of 2-lithioindoles due to their instability at higher temperatures. An exception is a dimethylaminomethyl group which enables lithiation with *n*-BuLi under ice-sodium chloride cooling, but its removal was reported to be troublesome.^{2c}

In the previous paper,³ we reported that 1-methoxy group⁴ was a suitable

directing group and regioselective lithiation at the 2-position was performed with *n*-BuLi at about -18°C (ice-sodium chloride). Nevertheless, when the reaction was carried out at 0°C , the yields of products dropped down to 30~50%. Now, we wish to report that 1-methoxymethoxy group is superior to the 1-methoxy group. Thus, 1-methoxymethoxyindole (**3**, Scheme 1) was regioselectively lithiated at the 2-position with *n*-BuLi at 0°C (ice cooling), and subsequent reaction with electrophiles produced the corresponding 2-substituted 1-methoxymethoxyindoles in good to excellent yields. The compound (**3**) was easily prepared as follows, though the optimum reaction conditions were not made. 2,3-Dihydroindole (**1**) was oxidized with sodium tungstate dihydrate⁴ (0.2 mol eq.) and 30% aq. hydrogen peroxide (H_2O_2 , 10 mol eq.) in methanol-water (10:1) for 15 min at room temperature, then the whole was extracted with benzene. After the extract was washed with water and dried over sodium sulfate, the resultant benzene solution containing 1-hydroxyindole (**2**) was treated with methoxymethyl chloride (3 mol eq.) in the presence of potassium carbonate (18 mol eq.) and tetra-*n*-butylammonium bromide (0.1 mol eq.) at room temperature, resulting in the formation of **3** (mp $27.0\text{-}27.5^{\circ}\text{C}$) in 31% yield. In the above procedure, urea hydrogen peroxide addition compound could also be used as an oxidizing reagent instead of 30% H_2O_2 with more effectiveness (yield of **3**, 39%). Similar trapping of **2** with 2-methoxyethoxymethyl chloride afforded 1-(2-methoxyethoxymethoxy)indole (**4**, oil) in 11% yield.

Treatment of **3** in anhydrous tetrahydrofuran with *n*-BuLi (1.1 mol eq.) at 0°C (ice bath) for 15 min under argon atmosphere produced yellowish brown solution (color of 2-lithium salt **5**), and subsequent addition of *N,N*-dimethylformamide at 0°C afforded 1-methoxymethoxyindole-2-carboxaldehyde (**6a**) in 96% yield. The reaction of **5** with other electrophiles also proceeded successfully and the results are summarized in Table I.

Catalytic hydrogenation of **6a-e** over 10% palladium on charcoal in methanol at room temperature and atmospheric pressure afforded the corresponding 2-

substituted indoles (**7a-e**) in good to excellent yields, as shown in Table I. In the case of entry 1, **7a** was produced in 67% yield together with 26% yield of 2-indolemethanol (**8a**) after hydrogenation for 5 min. The yield of **8a** was improved to 96% when the hydrogenation was carried out more than 10 min. In entries 3 and 5, benzylic hydroxy group was partly removed to produce **8c** and **8e** in 10 and 6% yields, respectively.

In summary, we could develop a simple 2-lithiation method of indoles. Utilizing **4** and other 1-hydroxyindole derivatives, attempts to realize 2-metallation at room temperature and biological evaluations are currently in progress.

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