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Selective C-3 lithiation of 2,3-dibromo- and 2,3-diiodo-1-methylindoles

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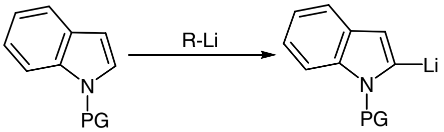
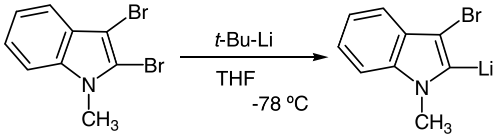
Abstract—Reaction of 2,3-dibromo-1-methylindole with *tert*-butyllithium at −78 °C followed by treatment with tropylium ion gave 2-bromo-3-cycloheptatrienyl-1-methylindole in a moderate yield, indicating that 2-bromo-3-lithio-1-methylindole would be involved as an intermediate instead of 3-bromo-2-lithio-1-methylindole. The structure of 2-bromo-3-cycloheptatrienyl-1-methylindole was unequivocally determined by a single X-ray analysis. 2,3-Diiodo-1-methylindole also gave a 3-lithio derivative exclusively.

1-Protected 2- and 3-lithioindole derivatives which could be obtained by the direct lithiation of 1-protected indoles or halogen–lithium exchange reaction of halogenated 1-protected indoles are most important building bricks for the synthesis of natural products, especially biologically active substances. It has been well known that direct lithiation of 2,3-unsubstituted 1-protected indole derivatives with *n*- or *tert*-butyllithium gave 2-lithiated derivatives exclusively.[1]



PG = CH_3, SO_2Ph, CH_2OMe, Boc etc.

On the other hand, Liu and Gribble, recently, reported that treatment of 2,3-dibromo-1-methylindole (**1**) with *tert*-butyllithium at −78 °C effected the clean monolithiation to 3-bromo-2-lithio-1-methylindole (**2**) which could be trapped with various electrophiles such as CH_3I, DMF, CO_2, and NH_4Cl.[2]



1 **2**

In the course of our studies on the development of a synthesis of aromatic-fused azulenoid enones,[3] however, we found that the reaction of 2,3-dibromo-1-methylindole (**1**) with *tert*-butyllithium at −78 °C followed by treatment with tropylium ion gave 2-bromo-3-cycloheptatrienyl-1-methylindole (**4**), indicating that 2-bromo-3-lithio-1-methylindole (**3**) would be involved as an intermediate instead of 3-bromo-2-lithio-1-methylindole (**2**).

Thus, to a solution of 2,3-dibromo-1-methylindole (**1**) in dry THF, 1.8 M equiv of *tert*-butyllithium (1.44 M *n*-pentane solution) was added dropwise at −78 °C during 3 min. The resulting solution was stirred for 5 min. To the solution, then, 1.8 M equiv of powdered tropylium ion was added at −78 °C in limited amounts. The reaction mixture was stirred for 1 h, allowed to warm to rt, stirred overnight, poured into dilute ammonia solution, and extracted with toluene. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel deactivated with water) and subsequent recrystallization from toluene–hexane to afford colorless prisms in 56% yield. The relatively low

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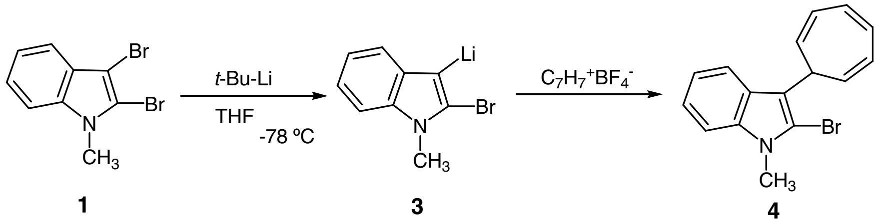


yield is probably due to the poor solubility of the tropylium ion toward THF.[3] The structure of this crystal was unequivocally determined to be 2-bromo-3-cycloheptatrienyl-1-methylindole (**4**) by a single X-ray analysis, as shown in Figure 1.[4]

Neither 3-bromo-2-cycloheptatrienyl-1-methylindole nor 3-bromo-1-methylindole was detected in this reaction.

Moreover, by our synthetic method of aromatic-fused azulenoid enones,[3] as shown in Scheme 1[5] 4-(azuleno[2,1-*b*]*N*-methylindolyl)but-3-enone (**9**) could be obtained starting from 2,3-diiodo-1-methylindole (**5**), strongly suggesting that the reaction of 2,3-diiodo-1-methylindole (**5**) with *tert*-butyllithium also gave a 3-lithio derivative predominantly.

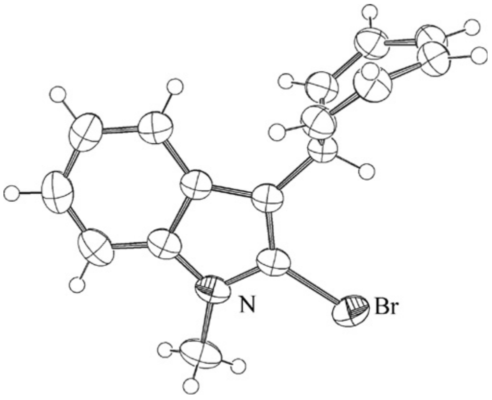
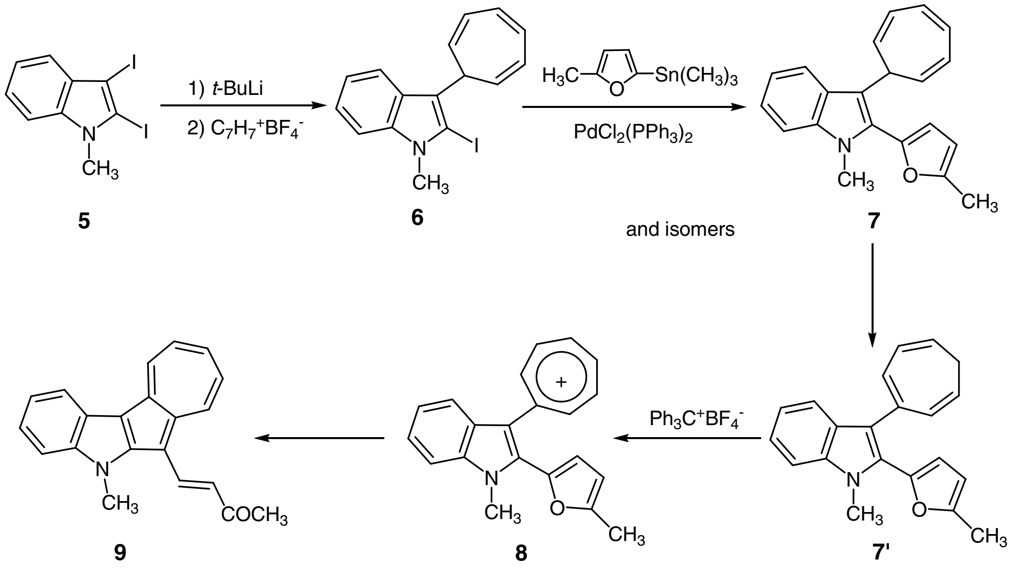


Figure 1. X-ray structure of compound **4**.

Thus, lithiation of 2,3-diiodo-1-methylindole (**5**) with *tert*-butyllithium, followed by addition of the tropylium ion gave 3-cycloheptatrienyl-2-iodo-1-methylindole (**6**) in 54% yield as the only isolable product. The Stille coupling of **6** with 5-methyl-2-trimetyltinfuran gave 3-cycloheptatrienyl-2-(5-methyl-2-furyl)-1-methylindole (**7**) as colorless crystals. After the sigmatropic rearrangement of **7** to **7′**, treatment of **7′** with triphenylmethyl tetrafluoroborate gave the tropylium ion derivative, 2-(5-methyl-2-furyl)-3-tropylio-1-methylindole (**8**). When an acetonitrile solution of **8** was refluxed for 8 h in the presence of 2,6-di-*tert*-butylpyridine as acid scavenger, 4-(azuleno[2,1-*b*]*N*-methylindolyl)but-3-enone (**9**) was obtained in 37% yield. The structure of the azulene derivative **9** was unequivocally established by a single X-ray analysis (see Fig. 2).[6]

These facts show that the reaction of 2,3-diiodo-1-methylindole (**5**) with *tert*-butyllithium at −78 °C gave not 2-lithio-3-iodo-1-methylindole but 3-lithio- 2-iodo-1-methylindole.

The present study leads us to the conclusion that the lithiation of 2,3-dihalo-1-methylindole with *tert*-butyllithium occurs at the 3-position predominantly, although



Scheme 1.

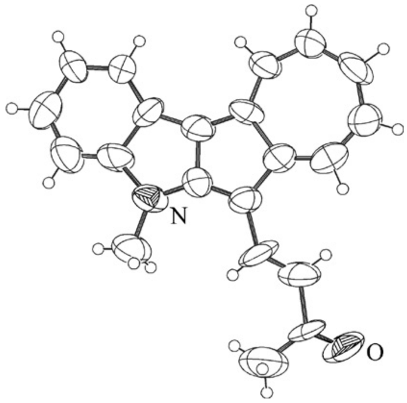


Figure 2. X-ray structure of compound **9**.

Gribble et al., reported that the lithiation of 2,3-dibromo-1-methylindole with *tert*-butyllithium occurred exclusively at the 2-position.[7]

References and notes

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4. *Crystal data for* **4**: $C_{16}H_{14}BrN$, $M = 300.19$, monoclinic, space group $P2_1/m$, $a = 8.5625(12)$, $b = 7.3363(10)$, $c = 11.0611(16)$ Å, $\beta = 107.922(2)°$, $V = 661.11(16)$ Å^3, $Z = 2$, $T = 297(2)$ K, $D_c = 1.508$ cm^{-3}. Unique 1432 reflections were measured by a SMART 1000/CCD diffractometer using graphite monochromated Mo-Kα radiations ($\lambda = 0.71073$ Å, $2\theta < 55°$). The structure was solved by a direct method and refined by full-matrix least-squares calculations against F_o^2 with absorption corrections (SADABS) using a program package SHELXL-97 [SHELXL-97]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms with C–H distance in the range 0.93–0.98 Å and $U_{iso}(H) = 1.2–1.5U_{eq}(C)$. The final $R_1(F) = 0.0310$ and $wR(F^2) = 0.0845$, for 1276 ($I > 2\sigma(I)$) and independent 1432 reflections, respectively. Parameters were 101 and $S = 1.070$. Max shift/esd = 0.000.
5. Unpublished results from our laboratory.
6. *Crystal data for* **9**: $C_{21}H_{16}NO$, $M = 299.36$, triclinic, space group P-1, $a = 7.680(15)$, $b = 11.44(2)$, $c = 19.29(4)$ Å, $\alpha = 82.24(4)$, $\beta = 81.13(4)$, $\gamma = 77.92(5)°$, $V = 1628(6)$ Å^3, $Z = 4$, $T = 298(2)$, $D_c = 1.221$ cm^{-3}. Unique 6116 reflections. The methods of X-ray measurements and structure analysis were the same as for compound **4**. The final $R_1(F) = 0.2209$ and $wR(F^2) = 0.5519$, for 1136 ($I > 2\sigma(I)$) and independent 6116 reflections, respectively. Parameters were 419 and $S = 1.005$. Max shift/esd = 0.001. We could obtain only twinned crystals for this compound. The relatively large R values are due to the twinning.
7. There is a possibility that 3-halo-2-lithio-1-methylindoles, which were formed initially, changed to the corresponding 2-halo-3-lithio-1-methylindoles.