A SYNTHESIS OF 6-METHYLINDOLE DERIVATIVES BY METHYLTHIOMETHYLATION AT 6-POSITION IN INDOLE NUCLEUS

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Abstract- 6-Methylindole derivatives were synthesized by introduction of methylthiomethyl group onto the 6-position of indole nucleus and subsequent desulfurization.

Introduction of substituents on the benzene part (4~7 position) of indole ring is one of the most difficult problems in the organic syntheses.\textsuperscript{1} We have developed several useful methods to resolve the problem and applied those to the syntheses of some natural products.\textsuperscript{2~4} Mitomycin\textsuperscript{5} is one of the most complicated natural products containing modified indole nucleus. All attempts toward total syntheses\textsuperscript{6} of mitomycins or its common structure: mitosenes\textsuperscript{4d, e, 7} started from substituted aniline and no synthetic route toward mitomycins from simple indole have been appeared.

\begin{align*}
\text{Mitomycin A}\quad \text{X=OCH}_3 \quad (1) \\
\text{C}\quad \text{X=NH}_2 \quad (2)
\end{align*}

\begin{align*}
\text{3} & \rightarrow \\
\text{4}
\end{align*}
We have been reported efficient methods for the synthesis of indoloquinone and applied them for the synthesis of 7-methoxymitosene (4) starting from 6-methylindole (3). In this paper, we report a novel method for the synthesis of 6-methylindole derivative by methylation at 6-position of indole nucleus.

Although Friedel-Crafts acylation of methyl indole-3-carboxylate (5) afforded corresponding 5- and 6-monoacyl derivatives in reasonable yields, Friedel-Crafts alkylation of 5 gave only small amount of 5- and Galkylated products. For the synthesis of mitomycin, we tried methylation of methyl 1-methylindole-3-carboxylate (6) by CH₃Br/AlCl₃, (CH₃)₂SO₄/AlCl₃ etc., but no desired methylated product was obtained. On the other hands, Friedel-Crafts alkylation of 6 using stabilized alkylating agent: chloromethyl methyl sulfide (5 eq. CICh₂SCH₃)/5 eq. AlCl₃ at 25°C for 1 h gave desired monoalkylated products (8 and 9) as unseparable mixture in 28% yield(1:1). 8; ¹H-nmr (CDCl₃) δ(ppm) 2.02 (3H, br s), 3.82 (3H, s), 3.83 (2H, s), 3.90 (3H, s), 7.23 (1H, br d, J=8.2 Hz), 7.26 (1H, s), 7.78 (1H, s), 8.09 (1H, d, J=8.2 Hz). 9; ¹H-nmr (CDCl₃) δ(ppm) 2.00 (3H, s), 3.82 (3H, s), 3.84 (2H, s), 3.91 (3H, s), 7.29~7.34 (2H, m), 7.76 (1H, s), 8.04 (1H, s). Desulfurization of 8 and 9 was achieved with Raney Ni to give 5- and 6-methyl derivatives (10 and 11) in 90% yield but those were also unseparable on silica gel tlc or column chromatography.

N-Benzyl derivative (7) was obtained by benzylation of 5 with BnBr/K₂CO₃ in DMF in 96% yield. Bromination of 7 with 1.5 eq. Br₂ at 0°C for 2 h afforded 5-bromo derivative (13,11 31%) with its 6-bromo isomer (12,10 61%). Those were easily separated on silica gel column chromatography. The brominated positions of 12 and 13 were easily determined by ¹H-nmr spectra [H-4 proton signal. 12; 8.05 ppm (1H, d, J=8.6 Hz), 13; 8.33 ppm (1H, d, J=1.8 Hz)]. Methyliothiomethylation of 13 with 1.2 eq. CICh₂SCH₃/5 eq. AlCl₃ in CH₂Cl₂ at -20°C for 30 min was very clean and 6-methylthiomethyl derivative (14) was obtained in 91% yield after short column chromatography using silica gel. We understand that bromine atom at the 5-position of 13 accelerated the reactivity of the 6-position and alkylating yield was very high.

Not only desulfurization but also debromination of 14 with Raney Ni in methanol at 25°C for 10 min gave desired 6-methylindole derivative (15,13 76%). Removal of N-benzyl group of 15 was achieved with AlCl₃ in CH₂Cl₂ at 25°C to give methyl 6-methylindole-3-carboxylate (16,14 87%). Consequently, methyl group was introduced at the 6-position of indole nucleus by (1) bromination, (2) methylthiomethylation, (3)
5. R = H  6. R = CH₃  7. R = Bn

Unseparable mixture of 8 and 9
8. R₁ = CH₂SCH₃, R₂ = H
9. R₁ = H, R₂ = CH₂SCH₃

Unseparable mixture of 10 and 11
10. R₁ = CH₃, R₂ = H
11. R₁ = H, R₂ = CH₃

Reagents: a) CICH₂SCH₃, AlCl₃ (28%); b) Raney Ni (90%); c) BnBr, K₂CO₃ (96%);
d) Br₂ (12; 61%, 13; 31%); e) CICH₂SCH₃, AlCl₃ (91%); f) Raney Ni (76%);
g) AlCl₃ (87%); h) BrCH₂CH₂CH₂Cl, K₂CO₃ (94%).

reduction with Raney Ni in 21% over all yield (7 → 15).

Then, 6-methylindole derivative (16) was treated with Br(CH₂)₃Cl/K₂CO₃ in DMF to afford N-chloropropyl derivative (17) in 94% yield. Since we reported a synthetic route toward 7-methoxymitosene (4) from 17 as a key intermediate, we could establish an improved route to 4.

By combination of those results and the previous publication, we could introduce all functional groups found in 7-methoxymitosene (4) in a simple indole (5). Further synthetic studies toward mitomycins are now in progress.

REFERENCES AND FOOTNOTES


9. 7; mp 69.5-70°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 3.91 (3H, s), 5.34 (2H, s), 7.14-7.33 (8H, m), 7.84 (1H, s), 8.20 (1H, m).

10. 12; mp 113.5-114°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 3.89 (3H, s), 5.28 (2H, s), 7.12-7.38 (6H, m), 7.46 (1H, d, J=1.5 Hz), 7.78(1H, s), 8.05 (1H, d, J=8.6 Hz).

11. 13; mp 118°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 3.91 (3H, s), 5.30 (2H, s), 7.11-7.17 (3H, m), 7.30-7.33 (4H, m), 7.83 (1H, s), 8.33 (1H, d, J=1.8 Hz).

12. 14; mp 131°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 1.92 (3H, s), 3.88 (2H, s), 3.91 (3H, s), 5.32 (2H, s), 7.12-7.15 (2H, m), 7.27-7.34 (3H, m), 7.83 (1H, s), 8.39 (1H, s).

13. 15; mp 81°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 2.44 (3H, s), 3.89 (3H, s), 5.28 (2H, s), 7.09-7.15 (4H, m), 7.30-7.36 (3H, m), 7.76 (1H, s), 8.38 (1H, d, J=8.6 Hz).

14. 16; mp 155°C, $^1$H-nmr (CDCl$_3$) $\delta$(ppm) 2.46 (3H, s), 3.92 (3H, s), 7.11 (1H, br d, J=8.2 Hz), 7.20 (1H, br s), 7.84 (1H, d, J=3.1 Hz), 8.05 (1H, d, J=8.2 Hz), 8.56 (1H, br s).

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