STUDIES ON THE PREPARATION OF 1,5-METHANOAZOCINO-INDOLE BASED ON INDOLYLBORATE

Minoru Ishikura,⁎ Norinobu Takahashi, Hidekazu Takahashi, and Kazuo Yanada

⁎Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. e-mail:ishikura@hoku-iryo-u.ac.jp

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagatoge-Cho, Hirakata, Osaka 573-0101, Japan.

Abstract – Conversion of piperidine (8), readily available from the palladium catalyzed tandem cyclization-cross-coupling reaction of indolylborate (6) with bromide (7), to 1H-1,5-methanoazocino[4,3-b]indole (15) through piperidine (14) was investigated.

Uleine (1) and tubotaiwine (dihydrocondylocarpine) (2) are of a class of alkaloids composed of a 1H-1,5-methanoazocino[4,3-b]indole core (3) as its key feature, and several groups have completed the syntheses 1 and 2 as well as more complex molecules of this class of alkaloids. Among the known synthetic approaches, the cyclization of piperidine (4) by way of iminium ions has been developed as a stereoselective method of synthesizing the azocinoindole core (3).

In the course of our investigation to develop the synthetic potential of indolylborate (6), readily available in situ from indole (5), we have previously reported a novel synthesis of ellipticine based on the palladium-catalyzed tandem cyclization-cross-coupling reaction of 6, which involved the construction of pyridocarbazole core by way of the cyclization of piperidine (8; R=Boc, X=Cbz, Y=Me). Thus, facile
availability of 8 from the cross-coupling reaction of 6 with 7 in a one-pot manner prompted us to derive an alternative protocol for the generation of piperidine (4). Herein are the results of our preliminary investigation.

Based on the previous protocol, the palladium-catalyzed cross-coupling reaction of 6 was effected with a mixture of (E/Z)-bromides (7) having sterically hindered group at the acetylenic carbon to give 8 as an inseparable mixture of (E/Z)-isomers, but with somewhat less satisfactory yields, as shown in Table.

### Table  Cross-coupling reaction of 6 with 7

<table>
<thead>
<tr>
<th>R</th>
<th>7</th>
<th>PdLn</th>
<th>Yield(%)(^a) of 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>7a</td>
<td>Pd(OAc)(_2)</td>
<td>33 (8a)</td>
</tr>
<tr>
<td>Me</td>
<td>7b</td>
<td>Pd(_2)(dba)(_3)+4P(_3)(Bu)(_3)</td>
<td>45 (8a)</td>
</tr>
<tr>
<td>Me</td>
<td>7c</td>
<td>Pd(_2)(dba)(_3)+4P(oh)(_3)</td>
<td>50 (8a)</td>
</tr>
<tr>
<td>Me</td>
<td>7d</td>
<td>PdCl(_2)[P(o-tol)](_3)(_2)</td>
<td>55 (8c)</td>
</tr>
<tr>
<td>OMe</td>
<td>7e</td>
<td>Pd(_2)(dba)(_3)+4P(oh)(_3)</td>
<td>40 (8c)</td>
</tr>
<tr>
<td>OMe</td>
<td>7f</td>
<td>PdCl(_2)[P(o-tol)](_3)(_2)</td>
<td>55 (8d)</td>
</tr>
</tbody>
</table>

\(^a\) Yields(\%) based on indole (5)

Next, conversion of piperidine (8) to 12 was investigated (Scheme 1). When 8a,d were subjected to catalytic hydrogenation under medium pressure, followed by treatment with bromoacetal without purification, we obtained only 10 with both isomerization of the double bond and retention of the benzyl group. Piperidines (10) were probably formed from the rapid reduction of the ethylidene group in 8 leading to 9, followed by isomerization of the double bond. Attempts to reduce 10 under various...
conditions resulted only in the recovery of unchanged 10, leaving the benzyl group and the double bond intact.

With these results in mind, we then set about the use of piperidine (11). Treatment of 8c with n-Bu₄NF in THF readily afforded a mixture of 11a and 11b, separable by medium pressure liquid chromatography. Catalytic hydrogenation of 11a and 11b, respectively, using 10%Pd on C in EtOH under 4 atmospheric pressure of hydrogen smoothly proceeded to afford cis-12, trans-12 and 13 as shown in Scheme 2. Then, cis- and trans-12 were respectively subjected to a two-step sequence to cis- and trans-14 involving removal of the N-Boc group and N-alkylation with bromoacetal. The structural assignment of cis-14 and trans-14 was based on a comparison with authentic samples of each isomer, derived from the known piperidines (4;Z=H, R=Bn). The transformation was successful with trans-12 to give trans-14, whereas the reaction of cis-12 with bromoacetal was sluggish, requiring forced conditions to produce cis-14.

Scheme 2
Next, the cyclization of piperidines (cis/trans-14) was investigated (Scheme 3). Cyclization reaction of cis- and trans-piperidines (4; Z=Boc, R=Bn) [1] oxidation with m-CPBA, 2) addition of TFAA, 3) sequential addition of KCN\(^2\) is known to allow the isolation of the corresponding \(\alpha\)-cyanopiperidine derivatives of 4. Using the same reaction conditions, cyclization reaction of trans-14 was carried out to afford 15 without the isolation of \(\alpha\)-cyanopiperidine, but with a somewhat less yield.\(^6\) On the other hand, the same treatment of cis-14 unexpectedly led to dissatisfactory results in which only a small amount of 15 was obtained, accompanied by a considerable formation of unidentified materials. The results encountered in the cyclization stage of 14 seems to be ascribable to the electron-donating nature of the N-methyl group of the indole ring.\(^2\) Structure of 15 was confirmed based on NOE experiments.

In summary, we have described an access to piperidines (14) by way of 8 readily available from the tandem cyclization-cross-coupling reaction of indolylborate (6) with bromide (7), and the subsequent conversion of 14 to 1H-1,5-methanoazocino[4,3-b]indole (15). Further investigation is in progress, including the optimization of the cross-coupling reaction using 6 bearing a versatile N-protecting group.

ACKNOWLEDGEMENTS
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REFERENCES AND NOTES


5. cis-14: $^1$H-NMR (CHCl$_3$): $\delta$ 0.94 (t, 3H, $J=7.5$ Hz), 1.20 (t, 3H, $J=7.5$ Hz), 1.38-1.42 (m, 1H), 1.51-1.67 (m, 5H), 1.91 (br s, 1H), 2.16-2.32 (m, 1H), 2.46 (dd, 1H, $J=5.1, 13.1$ Hz), 2.53 (dd, 1H, $J=5.1, 13.1$ Hz), 2.64-2.76 (m, 3H), 3.51-3.57 (m, 2H), 3.64-3.73 (m, 2H), 3.66 (s, 3H), 4.62 (t, 1H, $J=5.1$ Hz), 6.23 (s, 1H), 7.06 (dt, 1H, $J=1.0, 7.8$ Hz), 7.14 (dt, 1H, $J=1.0, 7.8$ Hz), 7.26 (d, 1H, $J=8.0$ Hz), 7.52 (d, 1H, $J=8.3$ Hz). $^{13}$C-NMR (CHCl$_3$): $\delta$ 12.4, 15.5, 19.8, 28.1, 29.7, 37.8, 40.4, 53.6, 56.4, 61.4, 61.6, 61.8, 100.2, 101.4, 108.9, 119.4, 119.8, 120.6, 128.0, 137.5, 139.8. HR-MS m/z: Calcd for C$_{23}$H$_{36}$N$_2$O$_2$: 372.2776. Found: 372.2779.

trans-14: $^1$H-NMR (CDCl$_3$): $\delta$ 0.95 (t, 3H, $J=7.5$ Hz), 1.19 (t, 3H, $J=7.5$ Hz), 1.21 (t, 3H, $J=7.5$ Hz), 1.20-1.49 (m, 4H), 1.61-1.69 (m, 1H), 1.75-1.85 (m, 2H), 1.93 (dt, 1H, $J=2.3, 11.5$ Hz), 2.37 (dd, 1H, $J=10.1, 14.9$ Hz), 2.49 (dd, 1H, $J=5.1, 13.2$ Hz), 2.53 (dd, 1H, $J=5.1, 13.2$ Hz), 2.86 (dd, 1H, $J=10.9$ Hz), 3.08 (d, 1H, $J=11.5$ Hz), 3.15 (dd, 1H, $J=2.9, 14.9$ Hz), 3.51-3.62 (m, 2H), 3.66 (s, 3H), 3.62-3.74 (m, 2H), 4.63 (t, 1H, $J=5.1$ Hz), 6.23 (s, 1H), 7.06 (t, 1H, $J=7.8$ Hz), 7.14 (dt, 1H, $J=1.0, 7.8$ Hz), 7.25 (d, 1H, $J=8.0$ Hz), 7.51 (d, 1H, $J=8.3$ Hz). $^{13}$C-NMR (CDCl$_3$): $\delta$ 11.3, 15.4, 24.0, 29.7, 30.5, 31.3, 40.0, 42.5, 54.5, 59.3, 61.3, 61.7, 61.9, 100.5, 101.5, 108.8, 119.3, 119.7, 120.5, 127.9, 137.9, 139.6. HR-MS m/z: Calcd for C$_{23}$H$_{36}$N$_2$O$_2$: 372.2776. Found: 372.2776.

6. $^1$H-NMR (benzene-d$_6$): $\delta$ 0.80 (t, 3H, $J=7.4$ Hz), 0.95 (dd, 1H, $J=2.9, 12.6$ Hz), 1.06 (t, 3H, $J=7.5$ Hz), 1.10 (t, 3H, $J=7.5$ Hz), 1.30-1.43 (m, 1H), 1.46-1.55 (m, 2H), 1.60-1.69 (m, 2H), 2.24 (dt, 1H, $J$=11.5 Hz).
\( J = 2.3, 12.1 \) Hz), 2.36 (d, 1H, \( J = 12.1 \) Hz), 2.49 (dd, 1H, \( J = 4.0, 13.8 \) Hz), 2.69 (s, 3H), 2.67-2.72 (m, 1H), 2.81 (dd, 1H, \( J = 6.3, 13.8 \) Hz), 3.08-3.15 (m, 1H), 3.28-3.35 (m, 2H), 3.39-3.45 (m, 1H), 3.53-3.60 (m, 1H), 4.30 (d, 1H, \( J = 4.0 \) Hz), 4.55 (dd, 1H, \( J = 4.0, 6.3 \) Hz), 6.80 (d, 1H, \( J = 8.0 \) Hz), 7.11 (t, 1H, \( J = 7.5 \) Hz), 7.19 (t, 1H, \( J = 7.5 \) Hz), 8.20 (d, 1H, \( J = 8.0 \) Hz). \(^{13}\)C-NMR (benzene-d\(_6\)) \( \delta \): 10.9, 15.3, 22.2, 28.5, 29.1, 29.5, 37.4, 45.1, 50.1, 57.1, 58.2, 61.0, 61.8, 101.7, 108.8, 110.0, 115.4, 120.8, 123.0, 123.3, 124.8, 137.0, 152.0. HR-MS \( m/z \): Calcd for \( \text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2 \): 370.2620. Found: 370.2624. Other products, such as \( 16 \) and \( 17 \), were not isolated in the cyclization reaction of \( 14 \).