Scandium Perchlorate as a Superior Lewis Acid for Regioselective Ring Opening of Aziridine Carboxylate with Indoles

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Abstract: In the synthesis of optically active tryptophan derivatives, Lewis acid-promoted coupling between indole and optically active serine-derived aziridine carboxylate is attractive because of the flexibility and convergence. Scandium perchlorate has been found to be a superior Lewis acid to the previously reported scandium triflate with respect to the yields as well as the regioselectivity of aziridine ring opening. The scope and limitation of this Lewis acid are also described.

Key words: tryptophan, indole, aziridine, scandium triflate, scandium perchlorate

In 1989, Kozikowski and Sato reported a novel tryptophan synthesis via a Zn(OTf)₂-mediated coupling of indole with optically active aziridine carboxylate ester. Although the reaction scheme seems to be attractive with respect to high convergence and flexibility, little application has been reported so far, probably because of the low yields in most of the cases. In 1998, Bennani and co-workers reported that scandium triflate [Sc(OTf)₃] was an alternative Lewis acid for this reaction to give the tryptophan derivatives in better yields. 3,4

In the course of our synthetic studies on α-C-mannosyltryptophan, we planned to employ the above coupling between C-mannosylindole and the aziridine. However, our preliminary experiments revealed that 2-methylindole (1) as a model substrate coupled with the aziridine 2 in the presence of Sc(OTf)₃ as a Lewis acid to give a 3:2 mixture of tryptophan 3a and the regioisomer 3b (Scheme 1). 9,10 While a similar reaction between 2-methylindole (1) and the benzyl ester of 2 under the same conditions was reported to give exclusively the benzyl ester of 3a in 66% yield. 3 This unexpected result prompted us to re-examine the conditions including the Lewis acid for this coupling reaction. 11 The extensive examination finally led us to find that Sc(ClO₄)₃ as an alternative superior Lewis acid, which was applicable to the synthesis of mannosyltryptophan. 7 This paper discloses the full details of our study. Initially, we surveyed the effect of Lewis acids in the coupling between 2-methylindole (1) and the aziridine methyl ester 2. 12 The typical results are summarized in Table 1. BF₃·OEt₂, as a conventional Lewis acid for the opening of 3-substituted aziridine-carboxylates with indole, 13 effect a low yield with poor regioselectivity (entry 1). Zn(OTf)₂ exhibited high reactivity in this specific substrate 14 to give 3a in good yield with high regioselectivity (entry 2), while the reactions with other indoles under the same reaction conditions were reported to afford the corresponding products in lower yields. 1 As mentioned above, Sc(OTf)₃ introduced by Bennani et al. 3 showed higher reactivity but with low selectivity (entry 3). In spite of the many attempts to reproduce the reported high regioselectivity in different experimental conditions, we could not significantly improve regioselectivity by means of Sc(OTf)₃. We were concerned about the quality and dryness of the reagent we used in accordance with Murai and co-workers’ report, that endo/exo selectivity in La(OTf)₃-mediated cyclization of hydroxy epoxides strongly dependent on the trace amount of water. 15 The reagent Sc(OTf)₃ purchased from different suppliers 16 and self-made Sc(OTf)₃ reagent according to the original procedure, 17 showed similar selectivity. Interestingly, when Sc(OTf)₃ azeotropically dried with benzene 18 was employed, the reaction was very sluggish, indicating the importance of trace amounts of water. Fortunately, further extensive efforts led us to find that Sc(ClO₄)₃ 19 was a superior Lewis acid to give 3a with high regioselectivity (entry 4) with reproducibility, although the difference between Sc(OTf)₃ and Sc(ClO₄)₃ has not been well docu-

Scheme 1

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mented,\textsuperscript{20} Indium triflate In(OTf)\textsubscript{3},\textsuperscript{21} and ytterbium triflate Yb(OTf)\textsubscript{3},\textsuperscript{22} which have been employed as Lewis acids for opening simple aziridines with a variety of nucleophiles, were examined (entries 5 and 6). Although Yb(OTf)\textsubscript{3} showed the best regioselectivity in the reaction of this specific substrate, this reagent was not applicable to the synthesis of N-benzylindole (6), indicating that N-benzylindole (6)\textsuperscript{23} might be an alternative substrate for indole because the benzyl group of the indole nitrogen was removable. 4-Chlorotryptophan, a plausible biosynthetic precursor of 4-chloroindole-3-acetic acid as a potent naturally occurring auxin type of plant hormone,\textsuperscript{24} was synthesized in moderate yield from 4-chloroindole (entries 7 and 8). In this substrate, the selectivity was significantly improved although the yield was not improved. The reaction of indoles substituted with strong electron-withdrawing or -donating groups such as nitro (8) and methoxy (9) were investigated. In the former case, extremely low yields of the products were obtained under both conditions utilizing of Sc(OTf)\textsubscript{3} and Sc(ClO\textsubscript{4})\textsubscript{3} (entries 9 and 10). In the latter case, coupled products were not obtained under both conditions, while 5-methoxyindole (9) decomposed under the reaction conditions (entries 11 and 12).

### Table 1 The Coupling Between 2-Methylindole (1) and the Aziridine 2 in the Presence of a Variety of Lewis Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lewis acid</td>
<td>Solvent</td>
</tr>
<tr>
<td>1</td>
<td>BF\textsubscript{3}-Et\textsubscript{2}O</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)\textsubscript{3}</td>
<td>CHCl\textsubscript{3}</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
<tr>
<td>4</td>
<td>Sc(ClO\textsubscript{4})\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
<tr>
<td>6</td>
<td>In(OTf)\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
<tr>
<td>7</td>
<td>InCl\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were carried out using 0.4–0.5 mmol of 2-methylindole (1) and the 0.5 equiv of the aziridine 2 and Lewis acid, see experimental.

<sup>b</sup> Yield based on the aziridine 2.

<sup>c</sup> The ratios were determined by integration values of the \textsuperscript{1}H NMR spectrum.

Next, solvent effects in the reaction with Sc(ClO\textsubscript{4})\textsubscript{3} were examined. The reaction in acetonitrile showed no regioselectivity (3a:3b = 1:1). When THF was used as a solvent, coupling products were not obtained while the aziridine 2 decomposed under the reaction conditions. Toluene was not a suitable solvent because of the low solubility of the Lewis acid. These experiments indicated that Sc(ClO\textsubscript{4})\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} was the best combination with respect to the yield and regioselectivity.

In order to ascertain the general usefulness of Sc(ClO\textsubscript{4})\textsubscript{3}, the coupling of a variety of substituted indoles with aziridine 2 was examined in comparison with Sc(OTf)\textsubscript{3} (Scheme 2, Table 2). The reaction of indole (4) in the presence of Sc(OTf)\textsubscript{3} gave a mixture of 10a and 10b in low yield with no selectivity (entry 1). In sharp contrast, the same reaction with Sc(ClO\textsubscript{4})\textsubscript{3} as a Lewis acid gave the products in a moderate yield with higher regioselectivity (entry 2). Furthermore, the reactions of N-alkylinidoles 5 and 6 gave much better yields (entries 3–6), indicating that 5-methoxy (6)\textsuperscript{23} was an alternative substrate for indole because the benzyl group of the indole nitrogen was removable. 4-Chlorotryptophan, a plausible biosynthetic precursor of 4-chloroindole-3-acetic acid as a potent naturally occurring auxin type of plant hormone,\textsuperscript{25} was synthesized in moderate yield from 4-chloroindole (entries 7 and 8).

### Table 2 The Coupling Between a Variety of Indoles and the Aziridine 2 in the Presence of Sc(OTf)\textsubscript{3} and Sc(ClO\textsubscript{4})\textsubscript{3}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. R\textsubscript{1}</td>
<td>R\textsubscript{2}</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Me</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Cl</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>OMe</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>OMe</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were carried out using 0.4–0.5 mmol of indole 4–9 and 0.5 equiv of aziridine 2 and Lewis acid, see experimental.

<sup>b</sup> Yield based on the aziridine 2.

<sup>c</sup> The ratio was determined by separation of the two regioisomers.

<sup>d</sup> The aziridine 2 was not consumed at the indicated time.

In summary, we have shown that Sc(ClO\textsubscript{4})\textsubscript{3} was a superior Lewis acid to Sc(OTf)\textsubscript{3} with respect to regioselectivity and reproducibility. Since this coupling strategy is straightforward,\textsuperscript{26} this improved method by means of
Sc(ClO$_4$)$_3$ has potential applicability to the syntheses of optically active tryptophan derivatives for components of peptideimmunochromatrics, chiral building block for the synthesis of indole-containing biologically active compounds.$^{25}$

Scandium Perchlorate [Sc(ClO$_4$)$_3$]$^{29}$

To a stirred solution of HClO$_4$ (70%, 1.57 mL) in H$_2$O (1.57 mL) was added Sc$_2$O$_3$ as a powder (496 mg). The mixture was heated at 100°C for 4 h, and then cooled to r.t. The resulting mixture was filtered through a pad of Super-Cel, and the precipitate was washed with H$_2$O. The combined filtrate was evaporated in vacuo. The residue (white solid) was treated with Kugelrohr distillation apparatus under vacuum (0.8 mmHg) at 50–130°C over ca. 5 h and dried at 130°C for an additional 33 h. The white solid was crushed and purified and further dried for 64 h at 130°C to afford Sc(ClO$_4$)$_3$ (1.87 g, 89%).

**CAUTION!** We have never encountered any problem of explosion of Sc(ClO$_4$)$_3$, however, we suggest that Sc(ClO$_4$)$_3$ should be handled with special care, because metal per chlorates have potentially exploitive property.$^{25}$ In particular, drying of the reagent with heating under vacuum should be conducted in a hood with a safety shield.

$\text{N}^\circ$-[Benzylxycarbonyl]-2-methyl-$\text{L}$-tryptophan Methyl Ester (3a) and $\alpha$-[Benzylxycarboxynlamino][methyl]-2-$\text{m}$-$\text{h}$-$\text{y}$-$\text{l}$-$\text{i}$-$\text{n}$-$\text{d}$-$\text{o}$-$\text{l}$-$\text{d}$-$\text{e}$-$\text{a}$-$\text{c}$-$\text{i}$-$\text{n}$-$\text{e}$-$\text{t}$ Acid Methyl Esters (3b); Typical Procedure (Tables 1 and 2)

2-Methylindole (1; 52.4 mg, 0.400 mmol) and aziridine carboxylate 2 (47.0 mg, 0.200 mmol), dried azeotropically with benzene before use were dissolved in anhyd CH$_2$Cl$_2$ (1.6 mL) and the solution was cooled to 0°C. To this solution was added Sc(ClO$_4$)$_3$ (68.6 mg, 0.200 mmol). After stirring at the same temperature for 13 h, the reaction was quenched with aq sat. NaHCO$_3$ solution (1.5 mL). The mixture was diluted with CH$_2$Cl$_2$ (1.5 mL) and extracted with CH$_2$Cl$_2$ (3 × 1.5 mL). The combined organic extracts were passed through a column packed with anhyd Na$_2$SO$_4$ and a thin layer of Na$_2$CO$_3$ and concentrated. The residue was purified by column chromatography (silica gel, 10 g, EtOAc-hexane, 1:1 to 1:2) to give a mixture of 3a and 3b (51.2 mg, 70%), 3a:3b = 10:1 by $^1$H NMR. A part of these two products were separated by repeated TLC (CH$_2$Cl$_2$, 5 times).

**3a**

$[\alpha]_D^{20} +57.2$ (c = 1.14, CHCl$_3$) $\text{[Lit.}^2 \text{ d-tryptophan analog } [\alpha]_D^{20} -59.2 \text{ (c = 2.0, CHCl}_3\text{)].}$

IR (KBr): 3393, 2952, 1717, 1507, 1264 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.20$ (3 H, s, CH$_3$CO$_2$H), 3.25 (2 H, d, J = 5.5 Hz, ArCH$_2$CH), 3.65 (3 H, s, CO$_2$CH$_3$), 4.63–4.72 (1 H, m, CHCO$_2$Me), 5.07 (1 H, d, J = 12 Hz, CH$_2$Ph$_3$), 5.13 (1 H, d, J = 12 Hz, CH$_2$Ph$_3$), 5.31 (1 H, br d, J = 8 Hz, NF$_2$C$_6$H$_4$), 7.04 (1 H$_{arom}$, t, J = 8 Hz), 7.10 (1 H$_{arom}$, t, J = 8 Hz), 7.24 (1 H$_{arom}$, d, J = 8.8 Hz), 7.41 (1 H$_{arom}$, d, J = 8 Hz), 7.86 (1 H, br s, NH of indole).

$^1$C NMR (75 MHz, CDCl$_3$): $\delta = 118.6, 119.7, 122.2, 122.9, 127.5, 128.1, 128.2, 128.5, 136.2, 136.4, 155.9, 172.5.

MS (EI): m/z = 366 ($^{13}$M$^+$).

HRMS (FAB): m/z calc for C$_9$H$_6$N$_2$O$_4$ (M + H) 367.1685, found 367.1689.

**3b**

$[\alpha]_D^{20} +84.0$ (c = 0.91, CHCl$_3$).

IR (KBr): 3398, 2951, 1716, 1508, 1458, 1248 cm$^{-1}$.

1H NMR (300 MHz, CDCl$_3$): $\delta = 3.27$(3 H br s, ArCH$_2$), 3.59 (1 H, d, J = 14, 6.5 Hz, CH$_2$NH$_2$), 3.66 (3 H, s, OCH$_3$), 3.88 (1 H, ddd, J = 14, 6.5, 6.5 Hz, CH$_2$NH$_2$), 4.13 (1 H, dd, J = 8.5, 7 Hz, CHCO$_2$Me), 5.05 (1 H, d, J = 12 Hz, OCH$_2$Ph$_3$), 5.13 (1 H, d, J = 12 Hz, OCH$_2$Ph$_3$), 5.18 (1 H, br t, J = 6.5 Hz, NF$_2$C$_6$H$_4$), 7.06 (1 H$_{arom}$, br t, J = 7 Hz), 7.12 (1 H$_{arom}$, t, J = 7, 1 Hz), 7.26 (1 H$_{arom}$, br d, J = 8 Hz), 7.30–7.40 (5 H$_{arom}$, m), 7.52 (1 H$_{arom}$, d, J = 7.5 Hz), 8.07 (1 H, br s, NH of indole).

$^1$C NMR (75 MHz, CDCl$_3$): $\delta = 116.1, 42.0, 42.4, 52.0, 66.6, 106.3, 110.5, 118.4, 119.8, 121.4, 127.0, 128.1, 128.6, 131.3, 133.2, 156.5, 174.0.

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Anal. Calcd for C_{23}H_{27}N_{2}O_{4}: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.93; H, 6.32; N, 7.50.

α-(Benzoylcarbonylamino)methyl-1-methylindole-3-acetic Acid Methyl Ester (11b)

[α]_D^{25} +78.0° (c = 0.90, CHCl_3).

IR (KBrs): 3340, 2953, 1706, 1522, 1436, 1341, 1219, 1047, 936 cm\(^{-1}\).

1\textsuperscript{H} NMR (300 MHz, CDCl_3): δ = 3.68 (3 H, s, CH_3), 3.74 (3 H, s, CH_3), 3.64–3.83 (2 H, m, CH_2NH), 4.18 (1 H, t, J = 7 Hz, CHCH_2), 5.07 (1 H, d, J = 12 Hz, CH_2=CHPh), 5.12 (1 H, d, J = 12 Hz, CH_2=CHPh), 5.15 (1 H, m, CHN=), 6.99 (1 H, s, H-2 of indole), 7.12 (1 H arom, t, J = 7 Hz), 7.20–7.40 (7 H arom, s), 7.67 (1 H arom, br d, J = 8 Hz).

13\textsuperscript{C} NMR (75 MHz, CDCl_3): 111.3, 121.3, 122.9, 124.0, 125.9, 128.0, 128.1, 128.5, 137.5, 155.9, 172.9.

Anal. Calcd for C_{23}H_{25}ClN_{2}O_{4}: C, 60.10; H, 4.95; N, 7.24. Found: C, 61.96; H, 5.16; N, 7.14.

α-(Benzoylcarbonylamino)methyl-4-chloroindole-3-acetic Acid Methyl Ester (12b)

[α]_D^{25} +41.4° (c = 0.29, CHCl_3).

IR (KBrs): 3335, 2951, 1706, 1436, 1341, 1255, 1046 cm\(^{-1}\).

1\textsuperscript{H} NMR (300 MHz, CDCl_3): δ = 3.70 (3 H, s, CO_2CH_3), 3.78 (2 H, m, CHCH=CHCH_3), 4.80 (1 H, t, J = 7 Hz, ArCH), 5.04 (1 H, d, J = 12 Hz, CH_2=CHPh), 7.10 (1 H, d, J = 12 Hz, CH_2=CHPh), 5.21 (1 H, m, CHN=CHPh), 7.06–7.38 (9 H arom, m), 8.32 (1 H, br, s, NH of indole).

13\textsuperscript{C} NMR (100 MHz, CDCl_3): 111.3, 121.3, 122.9, 124.0, 125.9, 128.0, 128.1, 128.5, 137.5, 156.3, 174.1.

HRMS (FAB): m/z calcd for C_{23}H_{25}ClN_{2}O_{4} (M + H) 386.1033, found 386.1109.

Acknowledgments

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(10) The similar byproducts to the regioisomer (12) Kozikowski 1 and Bennani 3 had estimated the effects of the configuration has not been determined. For discussion of the stereochemistry of the similar products to (3b) in this type of coupling, see: Davoli, P.; Forni, A.; Moretti, I.; Prati, F. Tetrahedron: Asymmetry 1995, 6, 2011.


(12) Kozikowski 1 and Bennani 2 had estimated the effects of the Lewis acids such as Zn(OTf) 2 , Sc(OTf) 3 , AlCl 3 , EtAlCl 2 , Me 2 AlCl, TiCl 4 , SnCl 4 , Mg(OTf) 2 , ZnBr 2 , BF 3 ·OEt 2 , BBr 3 , and lanthanide triflates.


(14) As it turned out later, 2-methylindole(1) is the best suitable substrate for this type of coupling.