Synthesis of N-Substituted Indoles via Aqueous Ring-Closing Metathesis

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Abstract
We report herein the synthesis of N-substituted indoles resulting from the ring-closing metathesis of indole precursors bearing N-terminal alkenes. The aqueous metathesis of the indole precursors gave good yields of N-substituted indoles (up to 72%) with commercial metathesis catalysts and with artificial metalloenzymes based on the biotin-streptavidin technology. Strikingly, the yield of the N-acetylindole increases in presence of a second metathesis substrate.

Graphic Abstract

Keywords Aqueous catalysis · Ring-closing metathesis · Homogeneous catalysis · Artificial metalloenzymes

1 Introduction

Indoles are important synthetic scaffolds [1, 2]. The indole core is present in many compounds which possess biological activity, such as naturally-occurring alkaloids and chemotherapeutic drugs [3–6]. Additionally, indole is a metabolite in the biosynthetic pathway of tryptophan, an essential amino acid playing a critical role in the metabolism of eukaryotic and prokaryotic cells [7].

Synthetic strategies relying on ring-closing metathesis (RCM) for the synthesis of indole derivatives include (i) the
formation of a pyrrole ring from a functionalized benzene precursor and (ii) the formation of a benzene ring from a functionalized pyrrole precursor.

We sought to design suitable substrates for the synthesis of \( N \)-substituted indoles via aqueous RCM. Two protocols for the RCM of indoles derivatives in organic solvents are displayed in Scheme 1 [8, 9]. Yoshida and coworkers generated indoles via a tandem RCM/1,2-elimination [10, 11] sequence (Scheme 1a) and Nishida and coworkers reported on a mechanism of selective isomerization of terminal olefins promoted by a ruthenium hydride, followed by RCM to yield indoles (Scheme 1b).

Herein, we report on our effort to synthesize \( N \)-protected indoles starting from \( N \)-substituted anilides via RCM in aqueous solution. Both homogeneous and an artificial metathase based on the biotin-streptavidin technology were evaluated, Fig. 1 [12–20].

**2 Results and Discussion**

We initially synthesized the precursors 6a–b via the synthetic route in Scheme 2. Based on the work of Nishida and coworkers [8], starting from \( o \)-nitrobenzaldehyde 1, we reproduced the synthesis of the two substituted indoles 7a–b by generating the indole precursors 6a–b containing an internal alkene via a Ru–H promoted isomerization (Scheme 2) [21–24].

Next, we tested the RCM in aqueous buffer under mild conditions with different commercially-available metathesis catalysts (G-II, HG-I, HG-II and Aquamet) and with the biotinylated catalyst Biot-Ru, Fig. 1.

Substrate 6a is insoluble in water even in the presence of up to 20% of organic solvent. It forms either a milky suspension or a precipitate. The solubility in water improves with the \( N \)-acetylindole precursor 6b, but activity screening in the presence of different buffers barely achieved a single turnover as summarized in Table 1.

Speculating that RCM with an internal olefin is more challenging in aqueous solution [25], we designed the \( N \)-vinylanilide derivatives 9a and 9b, Scheme 3. These substrates are conveniently synthesized in three steps starting from the neat distillation of the commercially available 2-(2-aminophenyl)ethan-1-ol 8 [26], to afford 2-vinylaniline 3. The amino group is functionalized with the acetyl or succinyl appendages to yield respectively 4b and 4c.
The last step is a Cu-catalyzed $N$-vinylation of the secondary amine to afford substrates $9a$ and $9b$, Scheme 3.

Table 3 summarizes the results of the aqueous RCM with the substrate $9a$. The RCM activity assay reveals modest to good yields of indole $7b$ with four metathesis catalysts, among which $G$-II (10 mol % catalyst loading) gave the highest yield of $N$-acetylindole (72%, Table 2, entry 6). The water-soluble catalyst Aquamet (5 mol % catalyst loading) afforded 66% of indole $7b$ (Table 2, entry 7).
Although the \(N\)-acylindole precursor \(9a\) afforded modest conversion with the biotinylated catalyst \textbf{Biot-Ru} (Table 2, entries 1, 2), we screened the RCM activity with artificial metalloenzymes (ArMs) based on the biotin-streptavidin technology. The presence of a biotin anchor on an Hoveyda Grubbs-derived catalyst ensures that, in the presence of equimolar amounts streptavidin (Sav) isoforms, the metathesis catalyst is quantitatively embedded within the Sav host. Site-directed mutagenesis at close-lying residues (e.g. S112 and K121, ref. 13) allows to genetically improve the RCM activity \cite{27-30}. A screening of > 50 Sav mutants at pH 4, 5 and 6 was carried out (see Supporting info, Figure S7-9). Selected results of the RCM activity of substrate \(9a\) are collected in Table 4. This screening reveals the following trends: i) The free catalyst \textbf{Biot-Ru} performs best at pH = 6 (Table 3, entry

\textbf{Table 2} Summary of the screening results for the aqueous RCM of substrate \(9a\)

| Entry | Catalyst (mol %) | Yield (\%)\textsuperscript{b} | TON  |
|-------|------------------|-------------------------------|------|
| 1     | Biot-Ru (5)      | 35 ± 10                       | 7 ± 2 |
| 2     | Biot-Ru (10)     | 41 ± 15                       | 4 ± 1.5 |
| 3     | HG-I (5)         | 56 ± 5                        | 11 ± 1 |
| 4     | Hg-I (10)        | 63 ± 0                        | 6 ± 0 |
| 5     | G-II (5)         | 67 ± 15                       | 13 ± 3 |
| 6     | G-II (10)        | 72 ± 1                        | 7 ± 0 |
| 7     | Aquamet (5)      | 66 ± 6                        | 13 ± 1 |
| 8     | Aquamet (10)     | 66 ± 5                        | 6 ± 1 |

\textsuperscript{a} Substrate concentration: 0.5 mM; \textsuperscript{b} results from two independent catalytic runs
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6–8). Up to 47% yield is achieved with 2.5 mol % Biot-Ru (e.g. 19 TON). ii) In contrast, the ArMs perform best at pH 4, affording up to 16% yield of N-acetylindole (Table 3, entry 2–4, 6 TON). iii) Mutations at position K121 have a positive effect on the RCM activity. We hypothesize that removal of the basic lysine residue contributes to lower the local pH around the Ru-center [31]. Accordingly, the ArM Biot-Ru·SavK121L outperforms Biot-Ru·SavWT at pH 6, yielding 18% (7 TON) of the ring-closed product 7b.

The catalytic activity of ArMs with the substrate 9b is collected in Table 4. Again, removal of the lysine in position 121 had a positive effect on RCM, giving a three-fold increase in activity: from 7% yield of indole 7c with Biot-Ru·SavWT (2 TON) to 18% with Biot-Ru·SavK121A and 20% with both Biot-Ru·SavK121F (6 TON) and

### Table 3 Summary of RCM activity of ArMs Biot-Ru·SavK121L using diolefin 9a

| Entry | Sav | pH | Product (µM) | Yield (%) | TON |
|-------|-----|----|--------------|-----------|-----|
| 1     | –   | 4.0| 155 ± 7      | 8 ± 0     | 3 ± 0|
| 2     | WT  | 4.0| 220 ± 2      | 11 ± 0    | 4 ± 0|
| 3     | K121L | 4.0| 323 ± 24    | 16 ± 1    | 6 ± 1|
| 4     | S112N | 4.0| 282 ± 7     | 14 ± 0    | 6 ± 0|
| 5     | –   | 6.0| 940 ± 4     | 47 ± 0    | 19 ± 0|
| 6     | WT  | 6.0| 167 ± 1     | 8 ± 0     | 3 ± 0|
| 7     | K121L | 6.0| 359 ± 26    | 18 ± 3    | 7 ± 1|
| 8     | S112N | 6.0| 118 ± 10    | 6 ± 0     | 2 ± 0|

*a [9a] = 2.0 mM in PBS buffer and acetone (5% V/V); b results from two independent catalytic runs

### Table 4 Summary of RCM activity of ArMs Biot-Ru·SavK121L using diolefin 9b

| Entry | Sav | mol % Biot-Ru | Yield (%) | TON |
|-------|-----|---------------|-----------|-----|
| 1     | –   | 3.33          | 26.0       | 8   |
| 2     | WT  | 3.33          | 7.0        | 2   |
| 3     | K121A | 3.33      | 18.0       | 5   |
| 4     | K121F | 3.33       | 20.0       | 6   |
| 5     | K121L | 3.33        | 20.0       | 6   |
Next, we tested the influence of the presence of an additional diolefinic substrate \(10\) on the RCM activity. For this purpose, the RCM of the \(N\)-acetylindole precursor \(9a\) was carried out in the presence or absence of diolein \(10\), while keeping the overall catalyst concentration at 5 mol%. Catalysis was performed either with the free catalyst Biot-Ru or with the ArMs Biot-Ru·SavWT and Biot-Ru·SavK121L. Unexpectedly, the yield of \(N\)-acetylindole \(7b\) increased when the catalysis was performed in the presence of both substrates \(9a\) and \(10\). The free cofactor gave 71% yield of \(N\)-acetylindole \(7b\) compared to 38% yield when using substrate \(9a\) alone (Table 5, entry 1–3). This difference in yield was not noticed in previous RCM experiments with substrate \(9a\) alone, even when the catalyst concentration was increased from 5 to 10% (Table 2, entry 1–2). We hypothesize that the presence of a second and more reactive substrate delays the catalyst decomposition, probably due to the suppression of the Ru methylidene species which is known to be highly unstable [32–35]. This effect occurs also with the ArMs, producing over sixfold increase in yield with Biot-Ru·SavWT (Table 5, entry 4–6). The ArM Biot-Ru·SavK121L produced an increase in yield from 11 to 42% (Table 5, entry 7–9). The influence of the pH on this competition assay was evaluated with selected Sav mutants at pH 4,5 and 6 (see supporting info, Figure S10). We finally evaluated the aqueous RCM of the substrate \(10\) alone using the same conditions. Strikingly, in the presence of \(9a\), the yield of \(11\) drops from 20 to 11% (Table 5, entry 5–6) with Biot-Ru·SavWT and from 65 to 39% with Biot-Ru·SavK121L. In contrast, the free catalyst Biot-Ru improves the yield of \(11\) from 35 to 57%, suggesting that the ArMs preferentially lead to higher yields of \(N\)-acetylindole \(7b\) from an equimolar mixture of substrates \(9a\) and \(10\).

### 3 Conclusion

In conclusion, we report herein the synthesis of \(N\)-substituted indoles via aqueous RCM of \(N\)-vinylanilide derivatives. RCM with commercially available catalysts yielded up to 72% of \(N\)-acetylindole in PBS buffer at pH 6 and 2–5% (V/V) organic cosolvents. In the presence of ArMs based on the biotin-streptavidin technology, up to 42% of \(N\)-acetylindole was achieved. Interestingly, the yield of \(N\)-acetylindole could be improved by addition of a metathesis substrate in the reaction medium, revealing that the addition of a second metathesis substrate has a beneficial effect on the RCM of the indole precursor.

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Compliance with Ethical Standards

Conflict of interest: The authors declare that they have no conflict of interest.

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