Synthesis of 2-substituted tryptophans via a C3- to C2-alkyl migration

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Abstract

The reaction of 3-substituted indoles with dehydroalanine (Dha) derivatives under Lewis acid-mediated conditions has been investigated. The formation of 2-substituted tryptophans is proposed to occur through a selective alkylative dearomatization–cyclization followed by C3- to C2-alkyl migration and rearomatization.

Introduction

Facile access to tryptophan and unnatural tryptophan derivatives is of general interest because tryptophans are found in many naturally occurring compounds and are an important component of biologically active compounds [1-7]. Tryptophan and tryptophan analogs also have applications in chemical biology thanks to the highly environment-sensitive fluorescence properties of the indole ring [8-17] and when incorporated into peptides, they lead to compounds with increased resistance to enzymatic degradation and modification [18-25].

As part of our ongoing research on the use of the unsaturated amino acid dehydroalanine (Dha) in organic synthesis [26-37], we have focused our attention on the syntheses of tryptophans, cyclo-tryptophans (also known as pyrroloindolines), and tryptophan-containing natural products from simple indole starting materials [38-44].

In 2010, we reported a novel one-pot approach for the preparation of pyrroloindolines 4 by a cascade addition/cyclization strategy between simple alkyl C3-substituted indoles 1 and 2-amidoacrylates 2 in the presence of stoichiometric amounts of a hard Lewis acid (Scheme 1, path a) [39]. Good yields and high exo:endo diastereoselectivities were obtained for a variety of indoles.

If the reaction is performed with indoles containing groups with good migratory aptitude at the C3 position, a mixture of the expected pyrroloindoline 4 and 2-substituted tryptophans 3 was...
observed. A plausible mechanism for the formation of this unexpected side product involves rearrangement of pyrroloindoline 4 to the corresponding 2-substituted tryptophan 3 by a C3-to C2-alkyl indole migration and rearomatization (Scheme 1, path b). Therefore, the aim of this study was to exploit the C3 Friedel–Crafts (FC) alkylation/C3- to C2 alkyl migration sequence for the synthesis of 2-substituted tryptophans [45-50].

The known methods for the synthesis of 2-substituted tryptophans are limited and include both the catalytic and non-catalytic union of 2-alkylindole with a protected aziridine-2-carboxylate or an α-aminoenoate [38,51-54] or directly from 2-unsubstituted protected tryptophan and the appropriate nucleophiles via a 3-chloroindolenine intermediate [55-57]. More recently, direct C2-arylation and alkylation of N-protected tryptophan methyl ester have been reported in the context of a more extensive study on C−H activation reactions [58-61].

Results and Discussion
Initially, the optimal conditions for the critical alkylative dearomatization–cyclization followed by the migration/rearomatization reaction process were explored. Our initial attempt involved reacting readily available 3-benzylindole (1a) with commercially available N-acetyl-dehydroalanine methyl ester (2a) under the reaction conditions previously optimized for the synthesis of pyrroloindolines. However, in the presence of ZrCl4 (2 equiv), the reaction gave a low conversion (Table 1, entry 1).

It was found that the non-coordinating solvent CH2Cl2 gave the best results whereas moving to more polar solvents such as ethanol, DMF, and THF proved to be detrimental, presumably due to coordination to the Lewis acid (Table 1, entries 2–4). The use of a strong H-bond donor such as trifluoroethanol (TFE) did not accelerate the reaction and still gave low yields after 24 h (Table 1, entry 5). Next, we tested the effect of different acids on the reaction. Although some Lewis acids such as TiCl4, SnCl4, and Sc(OTf)3 did not show beneficial effects (Table 1, entries 6–8), a good yield of 2-benzyltryptophan was achieved when 2 equiv of EtAlCl2 was used (Table 1, entry 9).

Notably, resubmission of isolated pyrroloindoline 4a, obtained by reducing the reaction time to five hours (Table 1, entry 12), to the exact reaction conditions above, provided another batch of 2-benzyltryptophan (3a), showing that pyrroloindoline is the intermediate of the reaction. However, increasing the amount of acid did not afford a higher yield (Table 1, entry 11); but on the contrary, a smaller amount prevented the reaction from going to completion (Table 1, entry 10). Despite research by Jackson et al. [45-50] showing an intramolecular rearrangement to yield 2,3-disubstituted indoles using TFA or diluted HCl, our synthetic procedure did not work with the addition of these acids, and only some indole oligomers were obtained. The best yield and reactivity were obtained by conducting the reaction with 2 equiv of EtAlCl2 in CH2Cl2 at room temperature for 24 hours (Table 1, entry 9).

Under the optimized reaction conditions (Table 1, entry 9), the substrate scope was then examined, focusing on the relative migratory aptitudes of various C3-indole substituents; the results are summarized in Table 2. The reaction worked well, affording good to excellent yields using 3-(p-methoxy-benzyl)indole (1b) and 3-(p-chlorobenzyl)indole (1c), whereas it did not afford the desired 2-substituted tryptophan when 3-(p-nitrobenzyl)indole (1d) was used as the starting material. These results can be attributed to the greater migratory aptitude of both the p-methoxy- and p-chlorobenzyl groups, compared to the p-nitrobenzyl substituent (even though in this case a detrimental coordination between nitro group and Lewis acid can...
Table 1: Optimization of the reaction conditions.\textsuperscript{a}

![Chemical Structure]

| Entry | Lewis acid | Solvent   | Yield (%)\textsuperscript{b} |
|-------|------------|-----------|------------------------------|
| 1     | ZrCl\textsubscript{4} | CH\textsubscript{2}Cl\textsubscript{2} | 25                           |
| 2     | ZrCl\textsubscript{4} | EtOH      | NR                           |
| 3     | ZrCl\textsubscript{4} | DMF       | NR                           |
| 4     | ZrCl\textsubscript{4} | THF       | NR                           |
| 5     | ZrCl\textsubscript{4} | TFE       | 13                           |
| 6     | TiCl\textsubscript{4} | CH\textsubscript{2}Cl\textsubscript{2} | 15                           |
| 7     | SnCl\textsubscript{4} | CH\textsubscript{2}Cl\textsubscript{2} | 28                           |
| 8     | Sc(OTf)\textsubscript{3} | CH\textsubscript{2}Cl\textsubscript{2} | 12                           |
| 9     | EtAlCl\textsubscript{2} | CH\textsubscript{2}Cl\textsubscript{2} | 70                           |
| 10\textsuperscript{c} | EtAlCl\textsubscript{2} | CH\textsubscript{2}Cl\textsubscript{2} | 29                           |
| 11\textsuperscript{d} | EtAlCl\textsubscript{2} | CH\textsubscript{2}Cl\textsubscript{2} | 68                           |
| 12\textsuperscript{e} | EtAlCl\textsubscript{2} | CH\textsubscript{2}Cl\textsubscript{2} | 25                           |

\textsuperscript{a}Reaction conditions: 1a (0.25 mmol), 2a (0.3 mmol), Lewis acid (0.5 mmol), solvent (2.5 mL), rt, 24 h. \textsuperscript{b}Yields of the isolated products after column chromatography. \textsuperscript{c}Lewis acid (0.25 mmol). \textsuperscript{d}Lewis acid (1 mmol). \textsuperscript{e}The reaction was quenched after 5 hours to isolate the pyrroloindolines 4a, see Supporting Information File 1. NR, no reaction.

Table 2: Synthesis of 2-benzyltryptophans 3a–j.\textsuperscript{a}

![Chemical Structure]

| Entry | Indole | Tryptophan | Time (h) | Yield (%)\textsuperscript{b} |
|-------|--------|------------|----------|------------------------------|
| 1     | ![Chemical Structure](1a) | ![Chemical Structure](3a) | 24 | 70 |
| 2     | ![Chemical Structure](1b) | ![Chemical Structure](3b) | 16 | 74 |
Table 2: Synthesis of 2-benzyltryptophans 3a–j. (continued)

|   | Formula | Yield (%) | Ref. |
|---|---------|-----------|------|
| 3 | ![Chemical structure](3c.png) | 48 | 53 |
| 4 | ![Chemical structure](3d.png) | 72 | NR |
| 5 | ![Chemical structure](3e.png) | 72 | NR |
| 6 | ![Chemical structure](3f.png) | 72 | 11 |
| 7 | ![Chemical structure](3g.png) | 72 | NR |
| 8 | ![Chemical structure](3h.png) | 24 | 67 |
| 9 | ![Chemical structure](3i.png) | 48 | 51 |
occurs), thus agreeing with earlier studies on the benzylation of indoles [46].

Whereas indoles bearing a simple C3-benzyl substituent furnish products in good yields, the reaction is very sensitive to the steric bulk around the electrophilic alkyl carbon atom; this observation is in agreement with the fact that the C3-alkyl group is very likely to attack the electrophilic iminium species generated in situ after the Dha/Friedel–Crafts-type reaction with indoles. Attempts to carry out the alkylation/migration reaction with 3-benzhydrylindole (1e) were unfruitful (Table 2, entry 5). When 3-(tetrahydro naphtalen-1-yl)indole (1f) was used, a very low conversion to the corresponding 2-substituted tryptophan was observed (Table 2, entry 6). For indoles containing 3-heterobenzyl substituents, the results were conflicting. Whereas 3-(furan-2-ylmethyl)indole (1g) did not react under the usual reaction conditions (Table 2, entry 7), bis(indol-3-yl)methane (1h) provided the desired product in an excellent yield and decent time (Table 2, entry 8). The latter is an interesting compound, and to the best of our knowledge, it has never been synthesized previously but only reported as a contaminant in biotechnologically manufactured tryptophan [62,63]. Also 3-benzyl-N-methylindole (1i) performed well in the reaction although a longer reaction time is needed to obtain a reasonable yield of the desired 3i (Table 2, entry 9). Regarding on the influence of the amine protecting group of Dha, the N-acetyl protecting group might promote the C3–C2 rearrangement, rendering the intermediate 3,3-disubstituted indolenium salt more likely to accept the migrating alkyl group at the C2-position that is in equilibrium with the corresponding tricyclic pyrroloindolines. Indeed, the reaction between 3-benzylindole (1a) and methyl 2-phthalimidoacrylate (2b) gave only 48% yield of the desired rearranged product (3j) (Table 2, entry 10) whereas the N-Cbz and N-Boc protecting groups were unstable under the reaction conditions.

As shown in Table 3, this novel reaction with Dha 2a is not restricted to 3-benzylindole derivatives but can also be

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**Table 2: Synthesis of 2-benzyltryptophans 3a–j.**

| Entry | Indole | Tryptophan | Time (h) | Yield (%) |
|-------|--------|------------|----------|-----------|
| 1     | ![](image1) | ![](image2) | 48       | 61        |

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[3a–j]: Reaction Conditions: 1a–i (0.25 mmol), 2a (0.3 mmol), EtAlCl₂ (0.5 mmol), CH₂Cl₂ (2.5 mL), rt.

[b]: Yields of the isolated products after column chromatography.

[c]: Methyl 2-phthalimidoacrylate (2b) was used.

[d]: NR, no reaction.
Table 3: Synthesis of 2-allyltryptophans 3k–o.\(^a\) (continued)

| Entry | Product Structure | Yield | RT |
|-------|------------------|-------|----|
| 2     | ![Image](image2)  | 16    | 86 |
| 3     | ![Image](image3)  | 16    | 70 |
| 4     | ![Image](image4)  | 72    | NR|
| 5     | ![Image](image5)  | 48    | 68 |

\(^a\)Reaction conditions: 1k–o (0.25 mmol), 2a (0.3 mmol), EtAlCl
\(^2\) (0.5 mmol), CH\(_2\)Cl\(_2\) (2.5 mL), rt. \(^\text{Yields of the isolated products after column chromatography. NR, no reaction.}\}

employed for other types of SN\(_1\)-active substrates such as
3-allylindoles [64]. Under the optimized conditions, the use of
3-allyl, 3,3-dimethylallyl (“normal” prenyl), and 3-geranylin-
doles as nucleophiles provided the corresponding 2-allyltrypto-
phans [65] in good yields, after the expected C3- to C2-indole
allyl migration (Table 3, entries 1–3). The high yielding syn-
thesis of these compounds is of particular interest as 2-prenyl-
tryptophan derivatives have been obtained or isolated from a
diverse array of natural sources [66,67] and, in general, prenyla-
tion at the indole ring leads to a significant increase in the anti-
oxidant and/or cytotoxic activity of tryptophan-containing
molecules [68-70]. However, the reaction did not occur with
the indole bearing the more bulky 1,1-dimethylallyl (“reverse"

The electronic properties of the migratory group have a
pronounced effect on the reaction profile. As known from other
Wagner–Meerwein-type rearrangements [71], the migration
tendency is principally controlled by the stability of the migratory
cation. However, we reasoned that indoles with an electron-rich
and polarizable atom/functional group at the C3-position (i.e.,
3-sulfenylindoles) could be good substrates for the reaction.
Notably, 3-(methylthio)indole (1o) underwent the alkylation/
C3–C2 migration sequence to give 2-(methylthio)tryptophan 3o
in good yields (Table 3, entry 5). Remarkably, the presence of a
thioether in the indole ring offers unique, site-specific handles
that can be utilized for further functionalization of the trypto-
phan moiety.

Conclusion
In summary, we have developed the synthesis of 2-functional-
ized/substituted tryptophans through a novel alkylative dea-
romatization–cyclization/migration/rearomatization sequence
between easily accessible 3-substituted indoles and commer-
cially available Dha 2a for the construction of 2-substituted tryptophans. The final rearrangement proceeded in moderate to very good yields, depending on the migration tendencies of the C3-indole substituent. Although the substituent migration from the C3- to C2-indole position is principally limited to benzyl, allyl/prenyl, and sulfenyl groups, the operational simplicity, synthetic brevity, and relatively facile access to 3-substituted indoles should make it very useful for the preparation of C2-functionalized tryptophan derivatives.

**Experimental**

**General procedure for the synthesis of N-acetyl-2-substituted tryptophan methyl ester**

A 1 M solution of EtAlCl₂ in hexane (2 mmol, 2 mL) was added dropwise to a stirred and cooled (0 °C) mixture of methyl 2-acetamidoacrylate (172 mg, 1.2 mmol) and the suitable 3-substituted indole (1 mmol) in dry CH₂Cl₂ (10 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 17–72 hours, then carefully poured into an ice-cold saturated aqueous sodium hydrogen carbonate solution (10 mL). The resulting suspension was filtered through Celite and the filtrate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8:2, or CH₂Cl₂) as eluent) and/or crystallization.

**Supporting Information**

**Supporting Information File 1**

Experimental procedures, characterization data, ¹H and ¹³C NMR spectra of new compounds.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-207-S1.pdf]

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