Tetrahedron Letters 56 (2015) 5882–5885

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Synthesis of tryptophans by alkylation of chiral glycine enolate equivalents with quaternary gramines

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ARTICLE INFO

*Article history:*
Received 8 June 2015
Revised 27 August 2015
Accepted 4 September 2015
Available online 5 September 2015

*Keywords:*
Gramine
Williams' morpholinone
Diastereoselective alkylation
Tryptophan

ABSTRACT

Quaternary gramines were found to be a suitable source of the 3-methylindole fragment for diastereoselective alkylation. The best yields and stereoselectivity were obtained for the alkylation of a chiral William's morpholinone enolate. Based on this transformation, a general method for the synthesis of enantiopure, indole ring substituted tryptophan derivatives was developed with good overall yields.



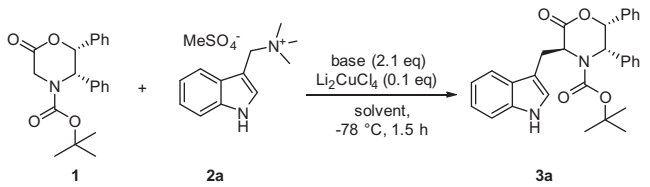
Enantiopure, non-natural tryptophan derivatives are interesting not only as replacements for their proteogenic counterparts,[1,2] but also as useful intermediates in the synthesis of various natural substances such as sarpagine–macrolide group alkaloids,[3] indolactam V,[4] lysergic acid,[5] and other ergot alkaloids.[6] Indole ring-substituted tryptophan derivatives show activity as potent necroptosis inhibitors,[7] epigenetic modulators,[8] and are prospective anticancer agents.[9] Synthesis of non-natural amino acids via the alkylation of a chiral auxiliary which contains a glycine equivalent is a well accepted procedure.[10] For the synthesis of tryptophan derivatives, suitable 3-methylene indole halides are required; however their synthesis tends to be complicated.[11]

On the other hand, quaternary gramines are readily accessible by the Mannich reaction and subsequent quaternization, usually with MeI or $Me_2SO_4$. Although they have long been employed for the synthesis of racemic tryptophans,[1,12] few examples of their application in asymmetric synthesis have been reported.[13]

We considered that quaternary gramines might also be suitable for the synthesis of enantiopure, indole ring substituted tryptophan derivatives and herein we report our study for the development of a general method for the alkylation of glycine equivalents with quaternary gramine salts.

Initially we tested commercially available Williams' morpholinone **1** as a chiral glycine equivalent.[14] Employing literature conditions,[15] tryptophan **3a** was obtained in only 14% yield. Therefore, an optimization of the reaction conditions was performed.

**Table 1**
Optimization of reaction conditions for Williams' morpholinone




1 2a 3a

| Entry | Base | Co-solvent | Yield[a] **3a** (%) |
|---|---|---|---|
| 1 | LDA | THF | 14 |
| 2 | LDA | HMPA[b] | 45 |
| 3 | LDA | DMPU[b] | 64 |
| 4 | LDA | DMF[b] | 72 |
| 5 | LiHMDS | THF | 45 |
| 6 | LiHMDS | DMF[b] | 78 |
| 7[c] | LiHMDS | DMF[b] | 60 |
| 8[d] | LiHMDS | DMF[b] | 69 |

[a] Isolated yield.
[b] Used in a 1:1 mixture with THF.
[c] 1.0 equiv of LiHMDS.
[d] Without $Li_2CuCl_2$.

A variety of co-solvents, capable of dissolving gramine better than THF, were tested, and in comparison to THF (Table 1, entry 1), the yields were significantly improved using HMPA, DMPU, or DMF (Table 1, entries 2–4).

Additionally, LiHMDS was found to be a more effective base than LDA (Table 1, entry 5) and the highest yield (78%) was

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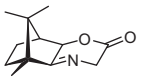
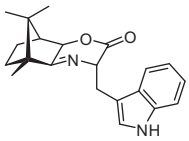
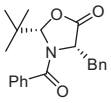
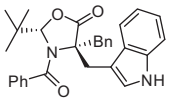
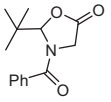
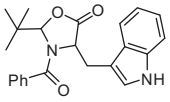
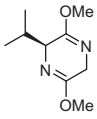
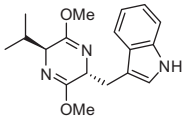
http://dx.doi.org/10.1016/j.tetlet.2015.09.017
0040-4039/

**Table 2**
Alkylation of chiral glycine equivalents by **2a**[a]

| Entry | Substrate | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **4** |  **5** | 40 |
| 2 |  **9a** |  **10a** | 50 |
| 3 |  **9b** |  **10b** | 22 |
| 4 |  **11** |  **12** | 0 |

[a] Reaction conditions: LiHMDS 2.1 equiv, $LiCuCl_4$ 0.1 equiv THF/DMF 6:1, −78 °C, 1.5 h.
[b] Isolated yields.

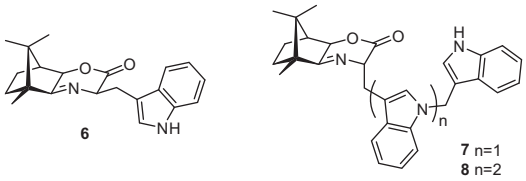
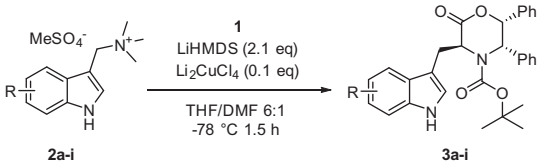



**Figure 1.** Side products from the alkylation of Xu lactone.

achieved when LiHMDS was used in combination with DMF (Table 1, entry 6). In all cases (Table 1, entries 1–5) the conversion of starting material **1** was complete and only one diastereomer **3a** was detected in the crude reaction mixture (confirmed by $^1$H NMR and LC–MS). However, when only one equivalent of LiHMDS was used, unreacted **1** remained and **3a** was isolated in only 60% yield (Table 1, entry 7). In the absence of $Li_2CuCl_4$ the yield of **3a** was slightly reduced (Table 1, entry 8).[16,17]

After the successful results with Williams' morpholinone, our attention turned to the recently developed Xu lactone **4**,[18] which was synthesized according to literature procedures.[19] This was subjected to the conditions optimized for morpholinone **1** to give indole derivative **5** in only 40% yield (Table 2, entry 1). During the course of the reaction, the formation of minor isomer **6** (*endo*) in up to 2% yield, as well as double **7** and triple **8** alkylation products were observed (see Fig. 1). The ratio of mono, di, and tri alkylated products in the crude reaction mixture were 1:0.2:0.1, respectively. It is difficult to explain the observed reactivity. Any speculation regarding the formation of aggregates was avoided since DMF was used as a co-solvent. Changing the solvent from DMF to HMPA did not influence the product distribution. The amounts of bis and tris alkylated products were reduced to nearly undetectable amounts when 1.1 equiv of base was used during the alkylation with gramine **2a**. In this case, however, unreacted starting material **4** was present in the reaction mixture. These results suggested that bis **7** and tris **8** alkylated products originated from overalkylation of the initial alkylation product **5**, not from pre-formation of gramine dimers (or trimers), which then react with lactone **4**.

**Table 3**
Alkylation of Williams' morpholinone by quaternary gramines




| Entry | Gramine | R | Product | Yield[a] (%) |
|---|---|---|---|---|
| 1 | **2a** | H | **3a** | 78 |
| 2 | **2b** | 2-Me | **3b** | 82 |
| 3 | **2c** | 7-Et | **3c** | 75 |
| 4 | **2d** | 5-OMe | **3d** | 75 |
| 5 | **2e** | 4-OBn | **3e** | 76 |
| 6 | **2f** | 5-OBn | **3f** | 80 |
| 7 | **2g** | 5-F | **3g** | 76 |
| 8 | **2h** | 6-Br | **3h** | 65 |
| 9 | **2i** | 5-CN | **3i** | 45 |

[a] Isolated yield.

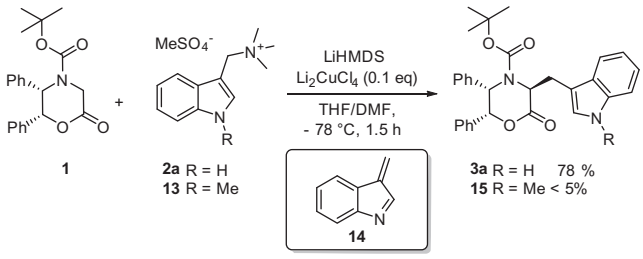



**Figure 2.** Reaction mechanism investigation.

The next glycine equivalent examined, Seebach's oxazolidinone[20] **9a**, was subjected to the optimized reaction conditions to give indole derivative **10a** in 50% yield. To test whether the steric bulk of the α-Bn group reduced the oxazolidinone reactivity, racemic oxazolidinone **9b** was also tested, however to our disappointment alkylation of this sterically less hindered substrate proceeded in only 22% yield.

Finally, we attempted to alkylate Schöllkopf's dihydropyrazine[21] **11** using gramine **2a** under the optimized conditions, however only trace amounts of the desired product **12** were detected (Table 2, entry 4).

Therefore, none of the tested glycine equivalents provided better yields than Williams' morpholinone **1**.

Having evaluated various chiral enolates, we next examinated a number of quaternary gramine derivatives[22] for the alkylation of Williams' morpholinone.[23] Compounds **3a–g** were obtained in good yields (Table 3, entries 1–8). In all cases only one diastereomer was detected in the crude reaction mixture (confirmed by $^1$H NMR and LC–MS). The cyano substituted gramine **2i** formed large aggregates after addition to the reaction mixture and as a result, considerable amounts of unreacted starting material **2i** as well as the dialkylated product were obtained from the reaction mixture with **3i** being obtained in 45% yield.[24]

As reported,[15,25] alkylation of enolates with quaternary gramines proceeds via the 3-methylene-3*H*-indole **14** intermediate (Fig. 2). Indeed, when *N*-methyl quaternary gramine **13** that could react only by the $S_N2$ mechanism, was applied to the alkylation of Williams' morpholinone, only a small amount of product **15** was detected.

The yield of **3a** reached 60% when only one equivalent of base was used (Table 1, entry 7). Conversion of the starting material was incomplete because the initially prepared enolate could be

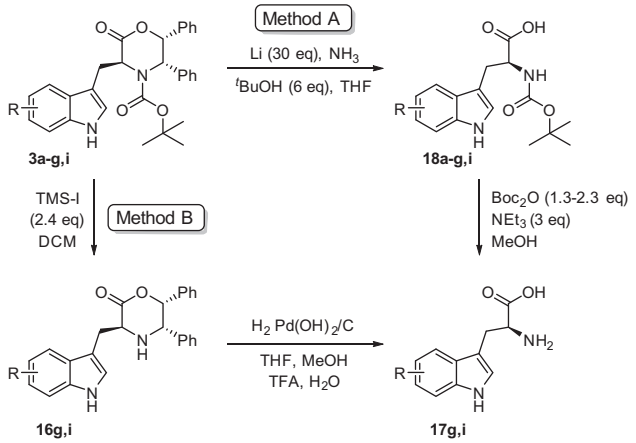



**Figure 3.** Synthesis of tryptophan derivatives.

**Table 4**
Synthesis of tryptophan derivatives

| Entry | Substrate | R | Method | Product | R | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | A | **18a** | H | 68 |
| 2 | **3b** | 2-Me | A | **18b** | 2-Me | 76 |
| 3 | **3c** | 7-Et | A | **18c** | 7-Et | 75 |
| 4 | **3d** | 5-OMe | A | **18d** | 5-OMe | 64 |
| 5 | **3e** | 4-OBn | A | **18e** | 4-OH | 72 |
| 6 | **3f** | 5-OBn | A | **18f** | 5-OH | 72 |
| 7 | **3g** | 5-F | B | **18g** | 5-F | 93 |
| 8 | **3i** | 5-CN | B | **18i** | 5-$CH_2NHBoc$ | 78 |

[a] Isolated yield.

protonated by gramine **2a**. In this case intermediate **14** would still be formed which could then react with any enolate still present in the reaction mixture; the maximum yield would then be close to 50%. However, the obtained yield was higher than this, suggesting that some parallel mechanism must be in action. Probably the quaternary gramine reacts with some weak base present in the reaction mixture ($NMe_3$, $(Me_3Si)_2NH$).

In order to demonstrate the utility of indole substituted morpholinones **3**, several examples were converted into the corresponding Boc protected tryptophan derivatives **18**. The most straightforward method for cleavage of the chiral auxiliary was reduction with lithium in liquid ammonia[15a] in the presence of *tert*-butyl alcohol (Fig. 3, Method A).[26] Using this method compounds **18a–d** were obtained in good yields (Table 4, entries 1–4). As expected, benzyl ethers were also cleaved from the corresponding indole derivatives **3e,f** (Table 4, entries 5 and 6).

For compounds **3g,i** which were not compatible with the conditions for Method A, a three step protocol that included removal of Boc group by TMS-I[15c] (**16**), hydrogenation over Pearlmann's catalyst[27] (**17**) and subsequent Boc-protection of the formed amine group was applied (Fig. 3, Method B). Tryptophan derivatives **18g,i** were isolated in 93% and 78% yields, respectively (Table 4, entries 7 and 8).[28] It should be noted that during the reduction with $H_2$ over $Pd(OH)_2/C$, the cyano group was reduced to an amino group (entry 8).

Finally, we performed the alkylation reaction using the opposite Williams' morpholinone enantiomer with gramine **2b** under the developed conditions (78% yield) which was cleaved by Method A (68% yield) to obtain the (*R*) enantiomer **18b*R***, that had the reverse sign for the specific rotation.[29]

In summary, we have demonstrated the potential of quaternary gramines as alkylating agents for enolates of glycine synthetic equivalents. The best yields and diastereoselectivity were found with William's morpholinone. Presumably the alkylation proceeds via a 3-methylene-3*H*-indole intermediate that acts as a Michael acceptor. Based on these transformations, a general method for the synthesis of enantiopure, indole ring substituted tryptophan derivatives with good overall yields was developed.

## Acknowledgement

This work was supported by the European Regional Development Fund (No. 2DP/2.1.1.1.0/14/APIA/VIAA/062).

## Supplementary data

Supplementary data (experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.017.

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22. Quaternary gramines were synthesized by the Mannich reaction followed by alkylation with dimethylsulphate (see ESI). During the quaternization, gramines can form dimeric compounds. These dimers react similarly to monomers, thus the presence of them should be considered only in stoichiometry calculations.

23. *General procedure for alkylation of Williams' morpholinone by quaternary gramines:* To a cold (−78 °C), magnetically stirred solution of (2*R*,3*S*)-(−)-*N*-Boc-6-oxo-2,3-diphenylmorpholine **1** (1.0 mmol) in THF (10 mL), a solution of lithium bis(trimethylsilyl)-amide (2.1 mL, 2.1 mmol; 1 M solution in THF) was added dropwise. After 30 min a solution of $Li_2CuCl_4$ (1.0 mL, 0.1 mmol; 0.1 M in THF) was added followed by a solution of gramine methosulfate **2** (1.1 mmol) in a 1:1 mixture of DMF and THF (4 mL). The reaction mixture was stirred for 1.5 h at −78 °C, then allowed to reach room temperature, quenched with saturated $NH_4Cl$ aqueous solution (20 mL) and diluted with ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the combined organic layer was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography on silica.
24. The second 3-methylene indole moiety is attached to first indole cycle nitrogen, not to an α-carbon.
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26. *General procedure A for cleavage of the chiral auxiliary:* Lithium wire (176 mg, 25.5 mmol) was dissolved in liquid ammonia (20 mL) at −78 °C. The resulting blue solution was stirred for 30 min and then *t*-BuOH (0.73 mL, 7.65 mmol) was added followed by a solution of **3** (0.85 mmol) in THF (2 mL). After 30 min the reaction mixture was carefully quenched with solid $NH_4Cl$ (2.73 g, 51.0 mmol) and allowed to warm to room temperature. The remaining solid residue was dissolved in water (40 mL), extracted with $Et_2O$ (2 × 30 mL). The aqueous layer was acidified to pH 1 with HCl (1 M) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography on silica.
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28. *General procedure B for cleavage of the chiral auxiliary:* To a solution of **3** (0.96 mmol) in dry DCM (10 mL) was added $Me_3SiI$ (459 mg, 2.30 mmol). After 20 min the mixture was quenched with a 10% solution of $Na_2S_2O_3$ (15 mL) and diluted with DCM (30 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. Flash chromatography purification afforded **16**. Compound **16** was dissolved in MeOH–THF mixture 1:1 (15 mL), TFA (74 μL, 0.96 mmol) and 20% $Pd(OH)_2/C$ (90 mg) were added and the mixture was stirred under a positive pressure of $H_2$ for 3 h. The reaction mixture was filtrated through Celite, the solvents were evaporated to dryness. Solid residue was re-dissolved in MeOH (10 mL), $Boc_2O$ (278 mg; 1.27 mmol) and $Et_3N$ (270 μL; 1.96 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated and the residue was purified by column chromatography on silica.
29. Both enantiomers **18b** and **18b*R*** were obtained with more than 99% ee.