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.

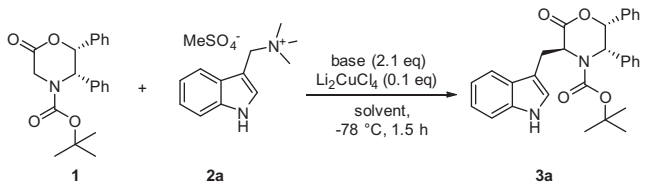
Enantiopure, non-natural tryptophan derivatives are interesting not only as replacements for their proteogenic counterparts,[1,2] but also as useful intermediates in the synthesis of various natural substances such as sarpagine–macrolide group alkaloids,[3] indolactam V,[4] lysergic acid,[5] and other 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
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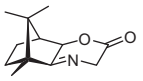
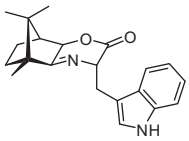
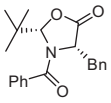
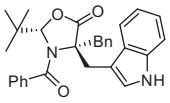
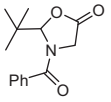
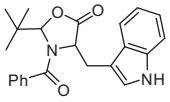
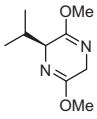
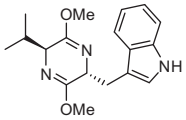
Table 2
Alkylation of chiral glycine equivalents by **2a**[a]

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.

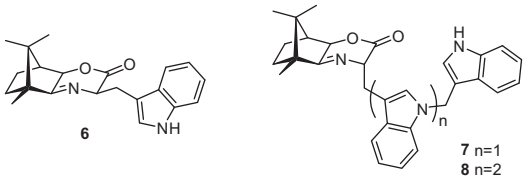
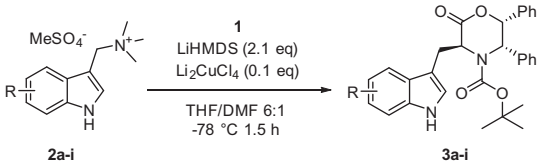


Figure 1. Side products from the alkylation of Xu lactone.

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.

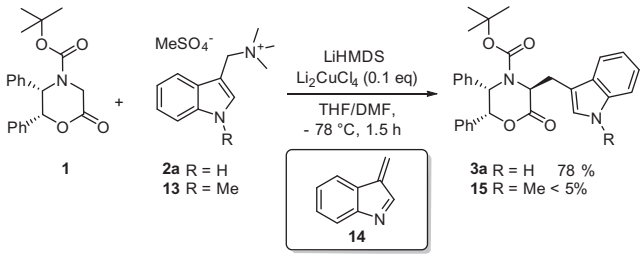


Figure 2. Reaction mechanism investigation.

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