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Amino acids as building blocks for the synthesis of substituted 1,2,4-triazoles

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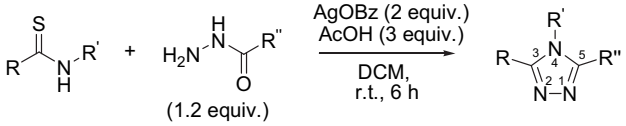
ABSTRACT

We report on the synthesis of 1,2,4-triazoles substituted with 2 or 3 amino acid side chains, using silver benzoate as a key reagent for the cyclization step. A complete study of the optical purity retention during the synthetic process leading to these compounds is described. In addition an improved work-up after the addition-cyclization step was also established leading to better yields and metal-free products.

1. Introduction

We recently reported on the synthesis of 3,4,5-trisubstituted-1,2,4-triazoles using silver benzoate as a key reagent (Scheme 1).[1] This methodology was useful for the synthesis of optically pure compounds, bearing a chiral moiety in position 3 (Scheme 1), as intermediates for the synthesis of GHS–R1a ligands.[2] In our ongoing efforts to develop original compounds with potential biological activities, we decided to work on the synthesis of more complex structures, based on the 1,2,4-triazole scaffold substituted with **1**, **2** or even **3** amino acid side chains. We thus attempted to apply the silver benzoate methodology to the synthesis of these derivatives. Because α-amino acids possess an asymmetric carbon atom, the synthesis of such compounds required a complete study of the optical purity retention during the synthetic process.



Scheme 1. Synthesis of 3,4,5-trisubstituted 1,2,4-triazole using silver benzoate.

2. Results and discussion

Using chiral HPLC, we previously demonstrated that the use of silver benzoate allowed us to introduce a chiral moiety on position 3 of the ring, maintaining the optical purity of this center unchanged.[1] The same strategy was used to study the introduction of chiral centers in positions 4 and 5. We synthesized two analogs of 3,4,5-trisubstituted 1,2,4-triazole enantiomers that were then analyzed by chiral HPLC analysis.

We first studied epimerization when introducing a chiral substituent in position 5 of the triazole (Scheme 2). For this purpose we produced the corresponding hydrazides starting from optically pure Boc-L-Trp-OH and Boc-D-Trp-OH. We used a recently described pathway for the synthesis of these chiral hydrazides.[3] This approach for the synthesis of hydrazides bearing a large variety of chemical groups without epimerization, degradation or deprotection problems, which can occur with classical methods. Hydrazides **4** and **7** were reacted with an achiral thioamide **6** (obtained as previously described via Lawesson's reagent).[4] Silver benzoate-mediated coupling–cyclization afforded triazoles **5** and **8**.

Using chiral HPLC analysis we observed that the synthetic scheme did not induce epimerization when a chiral group was placed in position 5 (ee ≥98%).

Secondly, we studied epimerization when a chiral group is introduced at position 4 of the triazole ring (Scheme 3). For this purpose we synthesized amides **9** and **12** by coupling picolinic acid with HCl·H-L-Phe-OMe and HCl·H-D-Phe-OMe, respectively. Without further purification these amides were reacted with the Lawesson's reagent to obtain thioamides **10** and **13**. The

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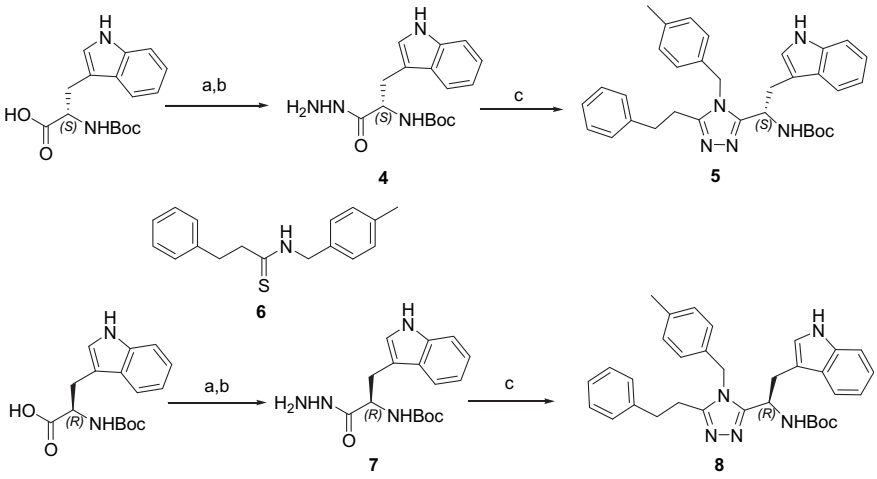
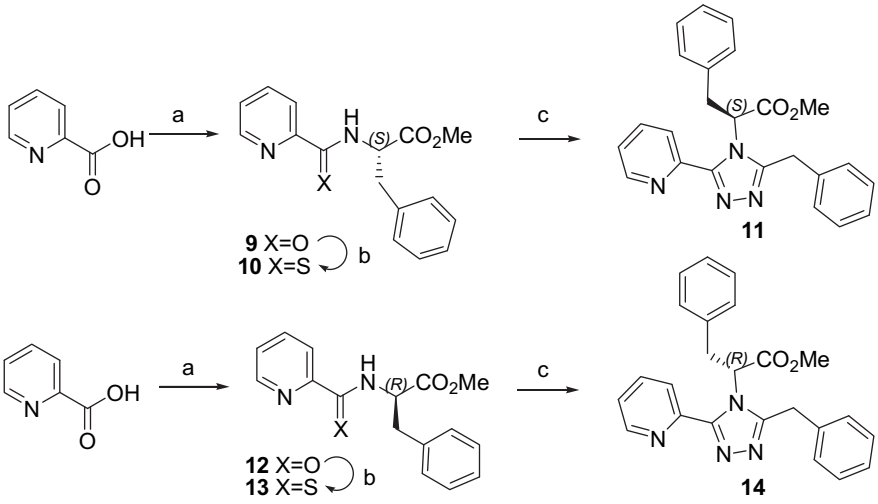


Scheme 2. Synthesis of triazoles **5** and **8**. Experimental conditions: (a) EDC·HCl (1.4 equiv), DCM, 2 h, 0 °C then *N*-aminophthalimide 1 h, 0 °C and overnight rt (b) Aminomethyl polystyrene resin, 1.1 mmol/g, DCM, 24 h, rt (c) **6** (1 equiv), **4** (1.2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 6 h, rt.



Scheme 3. Synthesis of triazoles **11** and **14**. Experimental conditions: (a) BOP (1 equiv), benzylamine (1.1 equiv), DIEA (2 equiv), 30 min, rt (b) Lawesson reagent (0.55 equiv), DME, 2 h, 80 °C (c) phenylacetic hydrazide (2 equiv), AgOBz (2 equiv), AcOH (3 equiv), DCM, 6 h, rt.

coupling–cyclization step with phenylacetic hydrazide in the presence of silver benzoate proceeded very slowly to yield triazoles **11** and **14** in low yields (about 20% after 14 days).

Following isolation by silica gelcompounds **11** and **14** were analyzed by chiral HPLC. No epimerization was detected during the procedure (ee $\geq$98%).

From these experiments, we could conclude that the silver benzoate-mediated coupling–cyclization reaction did not induce epimerization in any asymmetric carbon atom present in α position of the triazole ring.

We then attempted to apply our methodology to the synthesis of the 1,2,4-triazole scaffold, substituted with 2 or 3 amino acid side chains. Three types of diastereoisomers could be synthesized: trisubstituted triazoles bearing chiral groups in positions 3 and 5 of the triazole ring, trisubstituted triazoles bearing chiral groups in positions 3 and 4 of the triazole ring, trisubstituted triazoles bearing chiral groups in positions 3, 4 and 5 of the triazole ring.

In the following section, we describe the synthesis of optically pure diastereoisomers bearing chiral groups in positions 3 and 5. Fmoc, Z or Boc *N*-protected amino acids were coupled to various amines to yield amides that were converted into thioamides **15a**–**q**. The resulting thioamides were allowed to react with different *N*-protected amino acid hydrazides **16a**–**q** to produce the 1,2,4-triazoles **17a**–**q**. Hydrazides **16a**–**o** were prepared according to Ref. 3. Hydrazide **16p** was synthesized by overnight hydrazinolysis of the corresponding methyl ester with hydrazine monohydrate (6 equiv) in MeOH at room temperature, to avoid the epimerization of acylated amino acids that occurs during activation with EDC. Results are summarized in Table 1.

These results indicate that this method in scope is robust, being compatible with usual peptide synthesis protecting groups (Boc, Cbz, and Fmoc) and amino acids functionalized on their side chain can be introduced. Yields ranged from poor to good and were irrespective both of the electron withdrawing or donating effects and of the nature of side chains. In addition, the protecting groups used in these examples were stable under these reaction conditions.

All compounds described in Table 1 were obtained by silica gel purification of the crudes. Usually a very polar eluent was required for elution of triazole derivatives (5% MeOH/95% Ethyl acetate) and low yields were obtained in some cases (**17f** and **17h**, for example).

For the synthesis of 1,2,4-triazoles trisubstituted by amino acid side chains in positions 3, 4, and 5, the same protocol was followed (Scheme 4).

This reaction yielded, after purification, triazole **20** trisubstituted in position 3, 4, and 5 by amino acid side chains in an