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Reinvestigation of a Modified Hantzsch Thiazole Synthesis

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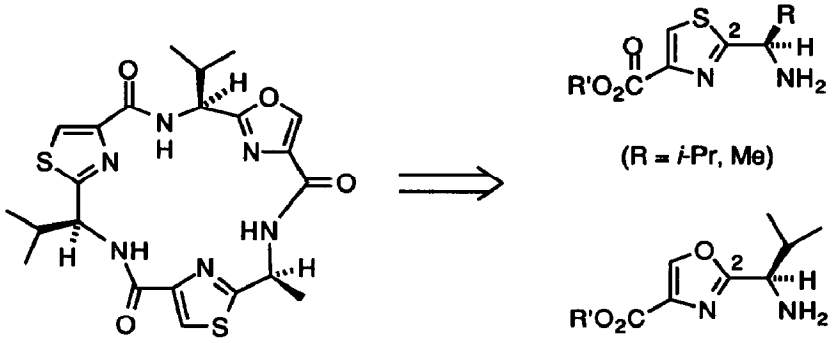
Abstract: *A recently reported modified Hantzsch reaction was reinvestigated and conditions were found to reach enantiomerically pure thiazole amino acid derivatives.*

The presence of the thiazole moiety in the structures of several natural products with important antibiotic properties has been known for several years.[1] In the last two decades, a new group of amino acid derived metabolites containing the thiazole ring have been isolated from marine species, mainly sponges and ascidians[2] and exhibited anti-neoplastic and cytotoxic activity. The possibility of these systems acting as metal ion chelating compounds has also been suggested.[2b] These properties have spurred considerable structural[3] and synthetic[4] efforts.

We have recently focused our attention on the synthesis of Bistatramide C **1**, a macrocyclic hexapeptide isolated from *Lissoclinum bistratum*, which contains one oxazole and two thiazole rings in its structure[5] and is described in the following Letter. However, it was necessary to assess routes to the requisite oxazole and thiazole moieties, particularly with regard to preservation of absolute stereochemistry at the side chain at C-2.



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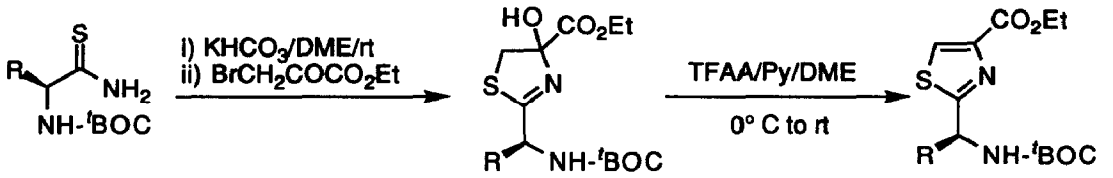
Methods used to prepare the thiazole ring in these natural products include: a) condensation of an aldehyde or imidate with a cysteine ester derivative, followed by oxidation of the resulting thiazolidine[6] or thiazoline;[7] b) $TiCl_4$ mediated closure of amidothiols[8] to thiazolines

and subsequent oxidation or c) modifications of the Hantzsch synthesis.[9] The latter, however, usually occurs with some degree of racemization.

Holzapfel and coworkers[10] recently reported a modified Hantzsch synthesis that allows the preparation of enantiomerically pure thiazole rings. This procedure has been used by Pattenden[11] to reach several marine natural products and we felt it would be useful in our synthesis of Bistatramide C **1**.

Thus, treatment of thioamides **2**[12] with ethyl bromopyruvate under the conditions reported by Holzapfel[10] gave thiazoles **4** with satisfactory yields. However, after coupling the thiazole and the optically pure oxazole moieties, large quantities of other diastereomers were unexpectedly detected by NMR and GC. This prompted a reinvestigation of the general applicability of Holzapfel's method to the synthesis of enantiomerically pure thiazole amino acid derivatives.



2 **3** **4**

Chiral HPLC analysis of the thiazoles **4**, obtained by repeating Holzapfel's exact conditions, indicated (Table 1) that racemization had not occurred in the formation of the glutamic acid or phenylalanine derived thiazoles (entries 1 and 3). This was, therefore, in agreement with the findings of the South African group. However, a small degree of racemization was observed in the formation of the valine derivative (entry 2), and a high degree of racemization occurred in the alanine derived thiazole (entry 4). Surprisingly, a totally racemic mixture was obtained in the phenylglycine thiazole (entry 5).

Table 1. Amino Acid Thiazoles 4 obtained using modified Hantzsch conditions.[10]

Entry	R[a]	Enantiomeric ratio[b]	Yield (%)	$[\alpha]_D$ (conc) Found[c,d]	$[\alpha]_D$ (conc) Reported[d,e]
1	Glu	>99:1[f]	53	–31.7 (0.74)	–31.9 (1.4)
2	*i*Pr	97:3[f]	84	–37.5 (2.60)	–42.0 (2.6)
3	Bn	>99:1	69	–19.3 (1.04)	–20.1 (1.0)
4	Me	74:26	69	–20.4 (5.07)	–41.8 (5.1)
5	Ph	49:51	87		

a) Glu: $CH_2CH_2CO_2Bn$. b) Determined by HPLC using CHIRACEL OD as chiral column. c) This study. d) In $CHCl_3$. e) Ref. 10. f) Determined as their *N*-Acetyl derivatives.

The poor enantiomeric ratio obtained for the alanine derived thiazole (**4**, R = Me) prompted a search for improved conditions (Table 2).

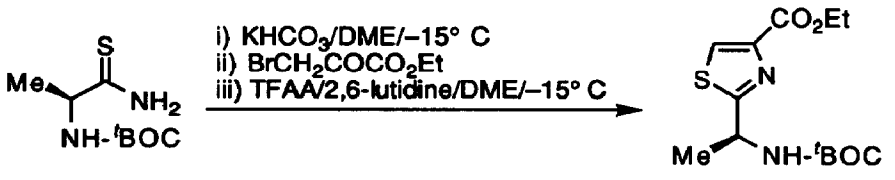
Initially, it was believed that racemization was occurring in the dehydration step (**3** to **4**). The employment of a more bulky base (collidine, entry 1), and lowering the temperature (–20° C, entry 2) to inhibit enolization at the stereocenter, led to a considerable increase in the enantiomeric purity of **4**. However, no further improvements were achieved by adjusting the strength of the base (lutidine *vs* collidine, entries 3, 4), the use of even bulkier bases (2,6-di-*tert*-butyl-4-methylpyridine, entry 5), further decreasing the temperature (–78° C, entries 4, 5) or employing a different dehydrating reagent (entry 6).

Table 2. Effect of Reaction Conditions on Enantiomeric Purity of 4 (R = Me).

Entry	Initial Base/Temperature	Dehydration Conditions[a]	Enantiomeric Ratio[b]	Yield (%)	[α]D (conc) Found[c]
1	$KHCO_3$/r.t.	Col/TFAA/0° C	88:12	87	–30.0 (1.12)
2	$KHCO_3$/r.t.	Col/TFAA/–20° C	92:8	92	–28.0 (1.13)
3	$KHCO_3$/r.t.	Lu/TFAA/0° C	88:12	86	–27.3 (1.10)
4	$KHCO_3$/r.t.	Lu/TFAA/–78° C	91:9	73	n.d.
5	$KHCO_3$/r.t.	Bpy/TFAA/–78° C	91:9	62	n.d.
6	$KHCO_3$/r.t.	$Et_3NSO_2NCO_2Me$/rt[e]	91:9	87	n.d.
7	NaH/–78° C	Lu/TFAA/–78° C	84:16	80	n.d.
8	**$KHCO_3$/–15° C**	**Lu/TFAA/–15° C**	**>99:1**	**96**	**–40.0 (1.15)**

a) Col: 2,4,6-Trimethylpyridine; Lu: 2,6-dimethylpyridine; Bpy: 2,6-di*tert*-butyl-4-methylpyridine. b) Determined by HPLC using CHIRACEL OD as chiral column. c) In $CHCl_3$. d) n.d.= Not determined. e) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

The results indicate that in spite of a large variation in the dehydration step, some racemization was still proceeding in the formation of the hydroxythiazolines **3**. Changing the base in the first step (**2** to **3**) from $KHCO_3$ to Et_3N yielded a variety of other products, while NaOAc gave no reaction at all, and NaH, at –78° C, still produced some epimerization (entry 7, Table 2). When the reaction was simply repeated with $KHCO_3$ at –15° C, the desired thiazole was obtained enantiomerically pure (entry 8, Table 2). Thus, racemization of the thioamide **2** during the Hantzsch synthesis, was the root cause of the stereochemical problem. With confidence in the enantiomeric purity of the thiazoles **4**, the total synthesis of Bistatramide C was undertaken and will be described in the following Letter.



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12. Prepared according to the procedures described in refs. 7a and 10. In all cases, the enantiomeric purity of the starting material was determined by chiral HPLC using CHIRACEL® OD columns (DIACEL).

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