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A Case of Abnormal Bishler-Napieralski Cyclization Reaction, Leading to Form Benzyl Oxazole Derivatives

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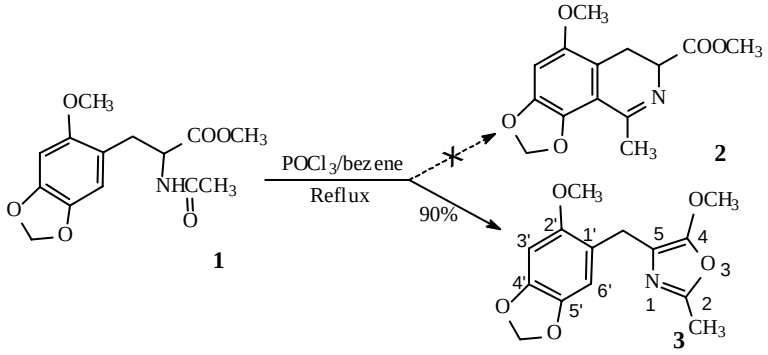
Abstract: A benzyl oxazole compound **3** was obtained with an excellent yield of 90% when N-acetyl-(2'-methoxy-4',5'-methylenedioxy)-phenylalanine methyl ester **1** was refluxed in $POCl_3$ /benzene. However, the anticipated product 3,4-dihydroisoquinoline-3-carboxylic acid methyl ester **2** could not be found. The mechanism was discussed in this article.

Keywords: N-Acetyl amino acid, oxazole, Bishler-Napieralski reaction.

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid is a type of naturally occurring bio-active alkaloid[1]. Moreover, it can be used as building block for the synthesis of other natural products containing the 1,2,3,4-tetrahydroisoquinoline moiety[2]. Compound **2** was an intermediate in our attempt to the total synthesis of Ecteinascidin analogs. We employed the Bishler-Napieralski reaction to prepare this product and refluxed the N-acetyl phenylalanine compound **1** in $POCl_3$/benzene. However, we failed to separate any basic dihydroisoquinoline component. Instead, a neutral compound was obtained with an excellent yield of 90%. Its structure was confirmed unambiguously as compound **3** through its ^{1}H-NMR, ^{13}C-NMR, MS and IR spectra[3]. **3** was an oxazole compound and an isomer of the expected compound **2**. (**Scheme 1**).

Scheme 1

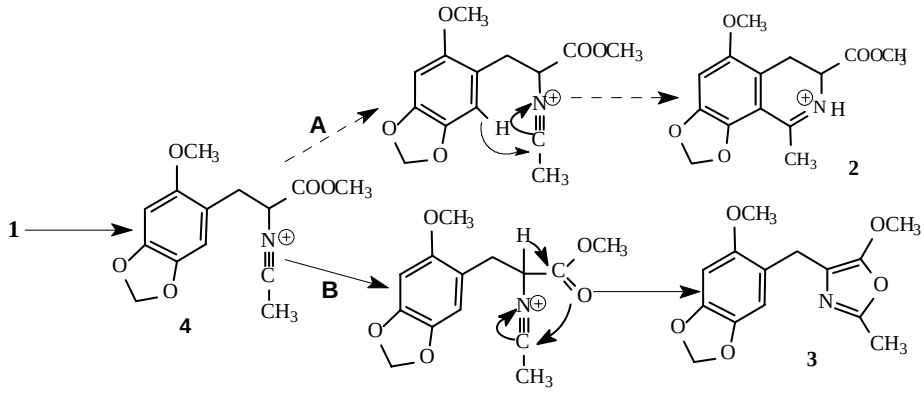


Compound **1** was synthesized from sesamol in seven steps with the total yield of 31.6 %.

The possible mechanism of the formation of the oxazole compound **3** from the N-acetyl phenylalanine compound **1** might be as follows: According to the mechanism of the Bishler-Napieralski reaction, the nitrilium salt **4** was the key intermediate during the reaction[4]. There would be two competitive routes for it to go along, route **A** and **B** (**Scheme2**).

In route **A**, the intra-molecular electrophilic substitution on the benzene ring would lead to the formation of the 3,4-dihydroisoquinoline **2** (the Bishler-Napieralski reaction). In route **B**, enolation of the carbonyl group of the ester and subsequent intra-molecular O-alkylation resulted in the formation of the oxazole compound **3.**

Scheme 2



The reason for the reaction to occur along route **B** instead of route **A** is that, with the 5'-substitution group on the benzene ring, the steric hindrance caused by it is evident. This factor prevented the normal Bishler-Napieralski reaction from occurring, and the reaction chose to go along route **B** to form oxazole compound **3**.

References and Notes

1. M.E. Daxenbichler *et al*, *Tetrahedron Letters*, 1972, *18*, 1801.
2. N. Yoneda, *Chem. Pharm. Bull.*, 1964, *12*, 1478.
3. Data for compound 3: mp 56-57°C; ^{1}H-NMR (300MHz, d_6-DMSO): δ 2.21 (s,3H,CH_3-2), 3.46 (s,2H,CH_2-5), 3.69 (s,3H,OCH_3-4), 3.79 (s,3H,OCH_3-2'), 5.89 (s,2H,O-CH_2-O), 6.63 (s,1H,H-6'), 6.71 (s,1H,H-3'); ^{13}C-NMR (100MHz,d_6-DMSO): δ 13.82 (CH_3-2), 24.04 (CH_2-5), 56.34 (OCH_3-4), 61.40 (OCH_3-2'), 95.01 (O-CH_2-O), 100.74 (C-5), 109.49 (C-4), 113.68 (C-2), 119.04 (C-3'), 140.20 (C-1'), 146.07 (C-6'), 151.55 (C-5'), 151.68 (C-4'), 154.33 (C-2'); FAB-MS (*m/z*): 277 (M^+), 262 (M-15), 165 (M-112), 126 (M-151); IR (film, cm^{-1}): 1672,1585 (oxazole), 1504,1487 (benzene).
4. S. Nagubandi , G. Fodor, *J. Heterocyclic Chem*, 1980, *17*, 1457.

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