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Formation of Benzyl Oxazole, A Competitive Path with the Classical Bishler-Napieralski Reaction

Zhan Zhu LIU, Ye Feng TANG, Shi Zhi CHEN*

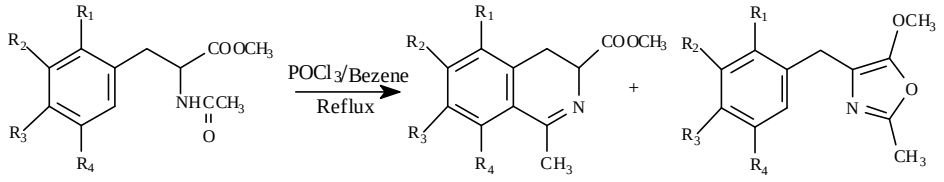
Institute of Materia Medica, Chinese Academy of Material Sciences
& Peking Union Medical College, Beijing 100050

Abstract: Several aromatic ring-substituted N-acetyl-phenylalanine methyl esters were treated with $POCl_3$ in refluxing benzene, which is the typical condition of B-N reaction. It was found that the normal B-N product 3, 4-dihydroisoquinoline-3-carboxylic acid methyl ester and/or 5-benzyl-2-methyl-4-methoxy oxazole could be obtained. The result depended mainly upon the electron-donating property of the substitutes on the benzene ring. Strong electron-donating groups located at para- or ortho- to the cyclization site will facilitate the formation of the normal B-N product **2**. On the other hand, the absence or weak electron-donating groups tended to yield the oxazole product **3**. It was established that the formation of benzyl oxazole is the competitive path with the B-N reaction. In this article, an explanation was given based on the mechanism of Bishler-Napieralski reaction.

Keywords: Bishler-Napieralski reaction, benzyl oxazole, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, N-acetyl-phenylalanine methyl ester.

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (TIC) are of considerable interest due to their biological activity and as an important structural element in several important alkaloids and other medically useful products[1]. Moreover, TIC is a phenylalanine analogue in which the dihedral angle is limited to a very small range because of its bicyclic nature[2]. In connection with the design of topographically constrained peptides, TIC has been utilized in several instance as a replacement of phenylalanine or tyrosine[3]. In our strategy of the synthesis of an anticancer marine alkaloid Ecteinascidin, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was an essential building block. In our previous article[4], we reported that an unexpected oxazole derivative **3a** was obtained when we tried to prepare the desired 3,4-dihydroisoquinoline product using the classical Bishler-Napieralski reaction[5]. This result inspired us to study the behavior of various aromatic ring-substituted N-acetyl-phenylalanine methyl esters and to determine the governing factors. N-acetyl phenylalanine methyl ester **1e** and its analogs **1b**, **1c**, **1d** were chosen to study their behavior under the B-N reaction conditions. The phenylalanine analogs **1b, 1c, 1d** were prepared from the corresponding benzaldehydes sequentially through the following reactions: condensation with monomethyl malonate, Curtius reaction with diphenyl phosphoryl azide, hydrogenation, and acetylation. The result of our investigation was shown as follows **(Scheme 1).**

Scheme 1



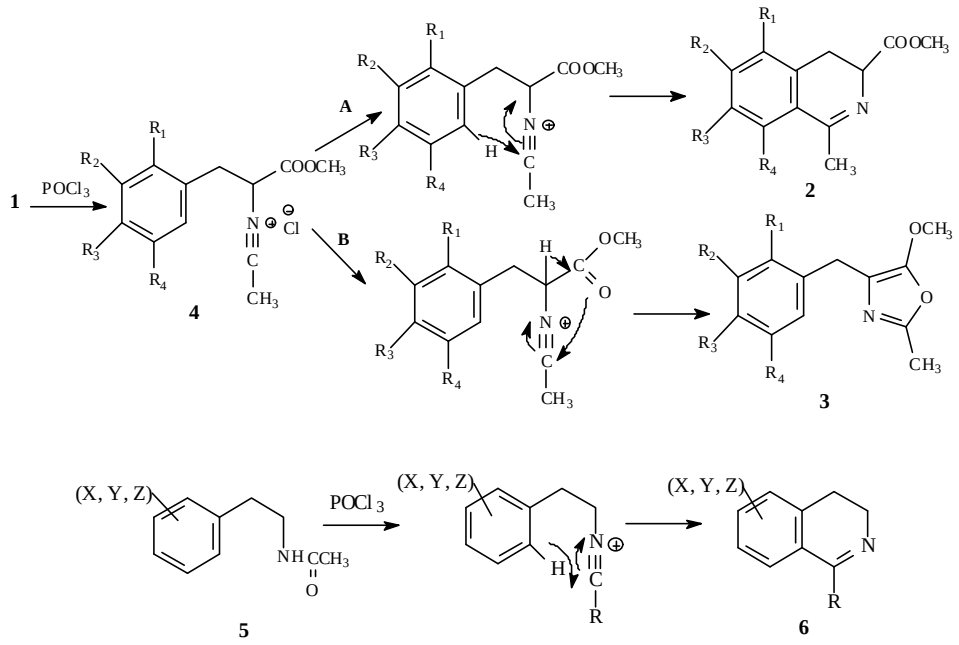
1 **2** **3**

1a. R_1=OMe, R_2=H, R_3+R_4=O-CH_2-O	not found	**3a**, 90%
1b. R_1=H, R_2=R_3=R_4=OMe	**2b**, 85%	not found
1c. R_1=R_4=H, R_2+R_3=O-CH_2-O	**2c**, 60%	**3c**, 28%
1d. R_1=R_4=H, R_2=R_3=OMe	**2d**, 82%	not found
1e. R_1=R_4=R_2+R_3=H	not found	**3e**, 81%

Obviously, whether product **2** or **3** or both of them were obtained was determined by the substitutes on the benzene ring. For compound **1a**, there was only one poor ortho electron-donating methylenedioxo group R_4, which finally prevented the normal B-N reaction from occurring. Instead, the oxazole derivative **3a** was obtained with an excellent yield of 90%. However, in contrast to **1a**, since there were two strong electron-donating methoxy groups R_2 and R_4 in compound **1b**, the dihydroisoquinoline product **2b** was obtained with a good yield of 85%. Even with only one para electron-donating methoxy group R_2, compound **1d** gave the normal B-N product **2d** with a satisfactory yield of 82%. The most interesting case was compound **1c**, which, with only one poor electron-donating methylenedioxo group that was para to the cyclization site, gave both **2c** and **3c** in a ratio of about 2:1. Hence, it was understandable the phenylalanine **1e,** without any activating groups on the benzene ring, yeilded only the benzyl oxazole derivative **3e**.

These results could be satisfactorily explained by the mechanism of Bishler-Napieralski reaction proposed by Sreeramulu Nagubandi and G. Fordor[6] **(Scheme 2)**. As it was shown in **Scheme 2**, the imidoyl chloride **4** was the key intermediate in B-N reaction. For those molecules that did not have the functionality of 3-carboxylic acid methyl ester, in another word, for the amide of 2-phenethylamine derivatives **5**, the only possible reaction would be the intra-molecular electrophilic substitution (the normal B-N reaction), and the dihydroisoquinoline product **6** would be obtained[5]. However, for the N-acetyl phenylalanine methyl ester analogs **1**, there were two possible paths for the imidoyl chloride **4** to go along, namely route **A** and route **B**. Route **A** was the normal B-N reaction. However, in route **B**, enolation of the methoxycarbonyl group and subsequent intra-molecular O-alkylation resulted in the formation of the oxazole compound **3**. Thus we were convinced that, for the N-acetyl-phenylalanine methyl esters, the formation of dihydroisoquinoline **2** and the formation of oxazole **3** were a pair of competitive reactions, and that the determining factor was the substitutes on the benzene ring. Those substituted groups that could enhance the electron cloud density of the cyclization site would facilitate the normal B-N reaction or *vice versa*.

Scheme 2



According to our knowledge, the behavior of N-acetyl phenylalanine methyl esters under the condition of B-N reaction has not been systematically studied so far. Consequently, through our study, it is established for the first time that the formation of oxazole is a competitive reaction with the formation of dihydroisoquinoline-3-carboxylic acid methyl ester.

References and Notes

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7. Data of compound **3a**: ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 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); FAB-MS (*m/z*): 277 (M^+), 262 (M-15), 165 (M-112), 126 (M-151); IR (Film, cm^{-1}): 1672, 1585, 1504, 1487.
8. Data of compound **2b:** ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 6.51 (s, 1H, Ar-H), 4.05 (dd, 1H, J_1=6Hz, J_2=14Hz, CH-$COOCH_3$), 3.88 (s, 3H, OCH_3), 3.87(s, 3H, OCH_3), 3.82(s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.80 (m, 2H, Ar-CH_2), 2.5 (s, 3H, CH_3); MS (*m/z*): 294 (M+1), 264, 234, 204; IR (Film, cm^{-1}): 1736, 1608,1597.
9. Data of compound **2c:** ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 7.00 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.00 (d, 2H, J=2Hz, O-CH_2-O), 4.20 (t, 1H, J=9.6Hz, CH), 3.81 (s, 3H, OCH_3), 2.90 (d, 2H, J=9.6,CH_2), 2.40 (s, 3H, CH_3); MS (*m/z*): 248 (M+1), 189; IR (Film, cm^{-1}): 1739, 1678.
10. Data of compound **3c**: ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 2.31 (s, 3H, CH_3), 3.61

(s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 5.89 (s, 2H, O-CH_2-O), 6.73 (m, 3H, Ar-H); MS (*m/z*): 248 (M+1), 233, 163, 136; IR (Film, cm^{-1}): 1684, 1603, 1504, 1489.

11. Data of compound **2d:** ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 7.00 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 4.20 (t, 1H, J=9.6Hz, CH), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.90 (d, 2H, J=9.6Hz, CH_2), 2.43 (d, 3H, J=1.5Hz, CH_3); MS (*m/z*): 263 (M), 248, 204; IR (Film, cm^{-1}):1724, 1624, 1570.
12. Data of compound **3e**: ^{1}H-NMR (300MHz, d_6-DMSO): δ ppm 2.33 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.26 (m, 5H, Ar-H); MS (*m/z*): 203 (M), 188, 91; IR (Film, cm^{-1}): 1670, 1587, 1495, 1454.

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