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Immediate deamination from the aminomethyl group attached to 1,2-dihydropyrazin-2-one derivative during catalytic hydrogenation

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Abstract—The catalytic hydrogenation of 3,6-bis(benzyloxycarbonylaminomethyl)-5-methyl-1,2-dihydropyrazin-2-one to remove benzyloxycarbonyl (Z) groups resulted in a side reaction. Purification by reverse-phase HPLC and analysis by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy identified the product as 3-aminomethyl-5,6-dimethyl-1,2-dihydropyrazin-2-one. It was determined through the synthesis of two 1,2-dihydropyrazin-2-one derivatives, composed of alanine and 2,3-diaminopropionic acid that deamination occurred specifically and easily (under atmospheric pressure and at the room temperature) only in the case of 6-benzyloxycarbonylaminomethyl-3,5-dimethyl-1,2-dihydropyrazin-2-one. The catalytic hydrogenation of 3,6-bis(benzyloxycarbonylaminomethyl)-5-methyl-1,2-dihydropyrazin-2-one specifically yields the deaminated product, 3-aminomethyl-5,6-dimethyl-1,2-dihydropyrazin-2-one. © 2002 Elsevier Science Ltd. All rights reserved.

The opioid mimetic, 3,6-bis(4′-tyrosylaminobutyl)-5-methyl-1,2-dihydropyrazin-2-one exhibited moderate binding activity to μ-opioid receptors.[1] In order to synthesize more potent and selective μ-opioid agonists and to study structure–activity relationships, additional Z-protected 1,2-dihydropyrazin-2-one derivatives (Scheme 1; **I**–**IV**) were prepared to be used as synthetic intermediates.

Four 1,2-dihydropyrazin-2-one derivatives (**I**–**IV**) containing one to four methylene linkers were prepared (Scheme 1).[1–3] The Boc group of the protected dipeptidyl chloromethyl ketone was removed with HCl-dioxane, and the resulting peptidyl chloromethyl ketone hydrochloride salt was refluxed in either acetonitrile or methanol to form the 1,2-dihydropyrazin-2-one ring. The Z-protected derivative was hydrogenated over a Pd catalyst in 50% acetic acid to remove the Z groups. Although hydrogenation of three derivatives (**I**–**III**) gave the corresponding desired products (**Ia**–**IIIa**), hydrogenation of compound **IV** produced an unexpected product (**V**) instead of **IVa** during the final step. MALDI-TOF mass spectrometry (MS) was utilized to investigate the side reaction that occurred during the hydrogenation step in the removal of the Z groups. Compounds (**I**–**IV**) were hydrogenated and the products were analyzed by MS as a function of time (10, 20, 30, 60 min). Hydrogenation of compounds **I**–**III** yielded the desired synthetic product (**Ia**–**IIIa**) within 10 minutes and deprotection was completed within 60 minutes. In contrast, the reaction for compound **IV** yielded both the desired (**IVa**) and unexpected products (**V**) within the first 10 minutes and after 60 minutes all of compound **IV** was transformed into the unexpected product (**V**), which had the molecular weight of 153.

This new and unexpected product (**V**) was purified by reverse-phase HPLC and identified by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy in pyridine-d_5. The desired product was anticipated to contain two aminomethyl groups and one methyl group, whereas NMR results indicated that the product had one aminomethyl group and two methyl groups [δ ppm (400MHz): 4.87 (2H, s, methylene of aminomethyl group), 2.23 (3H, s, methyl), 2.15 (3H, s, methyl)]. In addition, the molecular weight of the unexpected product (153) was smaller than that of the desired

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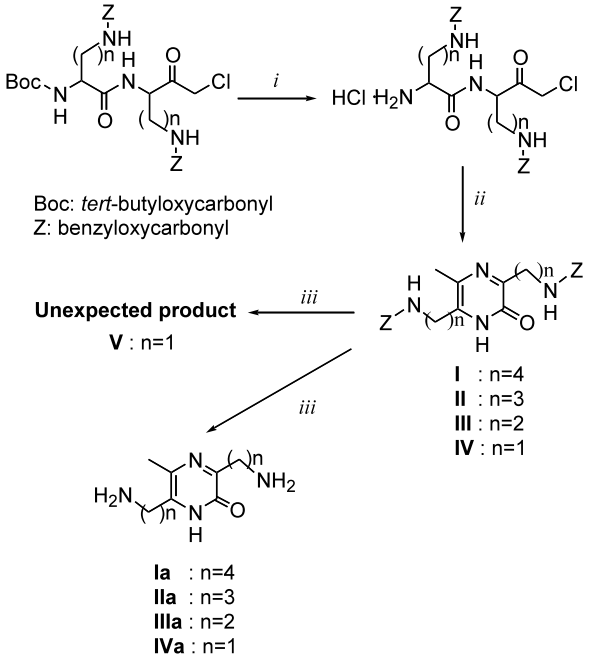
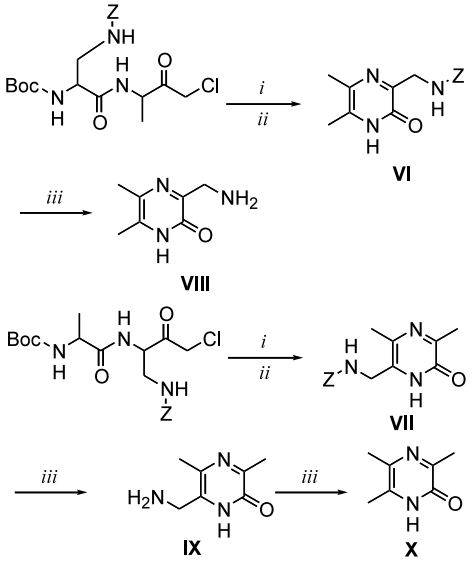
product (**IVa**) (168). The presence of only one aminomethyl group could be explained by deamination of the aminomethyl moiety attached to the 1,2-dihydropyrazin-2-one ring at either position 3 or 6.

To determine from which position the amino group was removed, two 1,2-dihydropyrazin-2-one derivatives, composed of alanine and 2,3-diaminopropionic acid, were prepared (Scheme 2).

Compounds **VI** and **VII** were hydrogenated as stated above, and the reaction mixture was analyzed by MS as a function of time (10, 20, 30 min, and 1, 2, 4 and 6 h). Both deprotected products **VIII** and **IX** obtained during hydrogenation should have the same molecular weight, 153.20; however, the deaminated form (**X**) which had a molecular weight of 138.17, was detected at 20 min and the entire compound **IX** was transformed after 6 h reaction time.



Scheme 1. *Reagents and conditions*: (i) HCl–dioxane; (ii) reflux in either methanol or acetonitrile; (iii) H_2/Pd in 50% acetic acid.



Scheme 2. *Reagents and conditions*: (i) HCl–dioxane; (ii) reflux in methanol; (iii) H_2/Pd, 50% acetic acid.

Purification by reverse-phase HPLC and ^{1}H NMR analysis of compound **VIII** in pyridine-d_5 revealed that the catalytic hydrogenation of compound **VI** produced 3-aminomethyl-5,6-dimethyl-1,2-dihydropyrazin-2-one [δ: ppm 4.87 (2H, s, 3-C$\underline{H}_2$NH$_2$); 2.22 (3H, s, 5- or 6-C$\underline{H}_3$); 2.15 (3H, s, 5- or 6-C$\underline{H}_3$)]. Similar analyses of compound **X** revealed that catalytic hydrogenation of compound **VII** yielded 3,5,6-trimethyl-1,2-dihydropyrazin-2-one; the deaminated product [δ: ppm 2.60, 2.24, 2.15 (3H×3, s, 3- or 5- or 6-C$\underline{H}_3$)].

These data confirm that deamination occurred specifically at position 6 of the 1,2-dihydropyrazin-2-one ring only in the case of compound **VII**. In addition, it demonstrated that catalytic hydrogenation of compound **IV** specifically gave the deaminated product, 3-aminomethyl-5,6-dimethyl-2(1*H*)-1,2-dihydropyrazin-2-one. Furthermore, the time of deamination was shorter for compound **IV** (60 min) relative to compound **VII** (6 h). The dissimilar reaction kinetics may have resulted from the different partial electron densities or differences in the dimensional structure of the starting material (Schemes 1 and 2).

Interestingly, our group reported previously that catalytic hydrogenation of the compounds 6-benzyl-3-benzyloxycarbonylmethyl-5-methy-1,2-dihydropyrazin-2-one (A) and 3-benzyl-6-benzyloxycarbonylmethyl-5-methyl-1,2-dihydropyrazin-2-one (B) specifically produced the decarboxylated 6-benzyl-3,5-dimethyl-1,2-dihydropyrazin-2-one due to low electron density of methylene moiety at position 3 on the 1,2-dihydropyrazin-2-one ring.[4] Decarboxylation was specifically observed at position 3 on the 1,2-dihydropyrazin-2-one ring. These differences allowed us to presume that deamination and decarboxylation were caused by different mechanisms. Deamination would occur owing to the location of an amino group at a similar position to benzyl or allyl,[5–10] rather than owing to low electron density. It can be deduced that the property of C–N bond at position 6 is similar to that of a benzylic or allylic C–N bond, while the property of the C–N bond at position 3 is quite different from that of benzylic or allylic C–N bond.

It is interesting that deamination of an aminomethyl moiety attached to 6 position of 1,2-dihydropyrazin-2-one derivative occurred easily at room temperature under atmospheric pressure, although reactivity of deamination from benzylamine derivatives are very low.[5,6,11] This high reactivity in the present report might be attributable to the low electron density of C–N bond compared with benzyl-amine or relatively high affinity of 1,2-dihydropyrazin-2-one moiety for the palladium

catalyst. We suggested that 1,2-dihydropyrazin-2-one 6-methyl-group can be a candidate for novel benzyl type amino protecting group removable by catalytic hydrogenolysis at ordinary temperature and pressure.

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