Preparation of β-nitroalanine using the Easton three-component coupling method

Short Communication

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Summary. A simple one-step preparation of β-nitroalanine has been developed using the Easton three-component coupling method. To date one limitation of this method has been that use of nitromethane as the nitroalkane component does not yield β-nitroalanine. We report that use of the dipotassium salt of nitroacetic acid in the Easton three-component coupling gives β-nitroalanine in high yield, presumably via facile decarboxylation of a β-nitroaspartate intermediate.

Keywords: Amino acid – Nitroalanine – Three-component coupling – Decarboxylation

Introduction

β-Nitro amino acids have found widespread use as enzyme inhibitors (Alston and Bright, 1981), modified enzyme substrates (Foote et al., 1985; Porter and Bright, 1980; Porter et al., 1983; Raushel, 1984), and as precursors to α,β-diamino acids and α,β-dehydro amino acids (Coghlan and Easton, 1999, 2004). The simplest of the β-nitro amino acids, β-nitroalanine, has been used extensively as an analogue of aspartate to study various enzymes of aspartate metabolism (Porter and Bright, 1980; Porter et al., 1983; Raushel, 1984). β-Nitroalanine is particularly useful in this regard as it is not only isosteric with aspartate but also isoelectronic with aspartic acid/aspartate in its neutral and nitronate forms, respectively.

Most studies employing β-nitroalanine as an aspartate analogue have prepared the nitro amino acid according to the method of Porter and Bright (1980), in which acrylic acid is first treated with nitryl chloride to give 2-chloro-3-nitropropionic acid (Shechter et al., 1952), which is then treated with aqueous ammonia to give the desired product. However, nitryl chloride is a noxious gas that is prepared by the mixing of fuming nitric and fuming sulfuric acids with chlorosulfonic acid. Clearly, a less noxious and hazardous procedure would be beneficial.

Easton et al. (1995) have prepared protected β-nitro amino acids through reaction of alkyl nitronates with α-bromoglycine derivatives. The use of N-Boc-glycine t-butyl ester as a starting material allows for simple deprotection of the resultant protected β-nitroamino acid derivatives upon treatment with TFA in chloroform. While eliminating the use of noxious nitryl chloride, a multistep procedure is required to furnish the desired free β-nitro amino acids.

Coghlan and Easton (1999a) subsequently developed a one-pot, three-component coupling method for the preparation of β-nitro amino acids. The three-component coupling of a nitroalkane, glyoxylic acid and ammonia under basic conditions gives the β-nitro amino acids directly in good yield (Scheme 1). This procedure is closely related to the Petasis reaction (Petasis and Zavialov, 1997), in which the three-component coupling of an amine, glyoxylic acid and an organoboronic acid gives aryl- or vinylglycine derivatives, and is one of growing class of efficient multicomponent couplings for the preparation of amino acid derivatives.

A range of β-nitro amino acids have been prepared using the three-component coupling approach, employing
a variety of readily available nitroalkanes. Unfortunately, β-nitroalanine 1a has to date remained unattainable by this three-component coupling reaction as the requisite nitroalkane, nitromethane, is unstable under basic conditions (Coghlan, 2000). We herein report a facile synthesis of β-nitroalanine using the Easton three-component coupling methodology by employing the dipotassium salt of nitroacetic acid as the alkyl nitronate coupling component.

Results and discussion

As part of our studies toward the synthesis of the α,β-dehydroaspartate component of the phomopsins, we were investigating the preparation of β-nitroaspartate as a stable precursor to the corresponding α,β-unsaturated amino acid. While β-nitroaspartate had been prepared by Easton’s multistep procedure, it has not been prepared using the three-component coupling methodology. We therefore investigated the preparation of β-nitroaspartate through the three-component coupling of ammonia, glyoxylic acid and methyl nitroacetate 4. Methyl nitroacetate 4 was prepared according to the method of Zen et al. (1988), in which nitromethane 2 is treated with potassium hydroxide to give the dipotassium salt of nitroacetic acid 3, followed by acid-catalysed esterification to give the ester 4 (Scheme 2). Subsequent treatment of methyl nitroacetate 4 with glyoxylic acid and potassium hydroxide in aqueous ammonia gave a complex mixture of products from which the β-nitroaspartate derivative could not be isolated. Lack of formation of the β-nitroaspartate derivative is presumably due to initial hydrolysis of methyl nitroacetate 4 under the basic reaction conditions to give nitroacetate. Nitroacetate is known to undergo rapid decarboxylation to form the nitromethane anion (Finkbeiner and Stiles, 1963), which is unstable under basic conditions as mentioned above.

Due to the instability of methyl nitroacetate under basic conditions, we decided to employ the dipotassium salt of nitroacetic acid 3 in a three-component coupling reaction. The dianion of nitroacetic acid is stable in aqueous solution (Finkbeiner and Stiles, 1963), in stark contrast to the instability of the mono-anion. Additionally, use of a preformed nitronate anion would obviate the need for potassium hydroxide in the reaction mixture. Accordingly, dipotassium nitroacetate 3 was treated with glyoxylic acid in aqueous ammonia, and a solid product was isolated in good yield. Surprisingly, the product was not the expected β-nitroaspartate, but instead was identified as β-nitroalanine 1a, and was obtained in 81% yield (Scheme 2).

β-Nitroalanine 1a was identified by comparison of its 1H NMR spectrum – which exhibited a one-hydrogen doublet of doublets and a two-hydrogen multiplet, attributed to the α- and β-protons, respectively – with that previously reported (Easton et al., 1995). The ESI mass spectrum displayed a peak at m/z 135 corresponding to the M+H⁺ ion, further confirming the identity of the product.

The mechanism of formation of β-nitroalanine 1a under these conditions is intriguing, with a three-component coupling step and a decarboxylation step required. Both