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NO as temporary guanidino-protecting group provides efficient access to Pbf-protected argininic acid

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Abstract—Pbf-protected argininic acid [H–OArg(Pbf)–OH], a building block for Fmoc-solid phase peptide synthesis, is obtained in high yield when a large excess of nitrosating agent is used in conjunction with intermediate N^{δ}-nitrosyl protection and N^{δ}-denitrosation in aqueous acidic medium.

1. Introduction

Argininic acid, the α-hydroxy analog of arginine, is a building block for natural product synthesis,[1] as well as a constituent of biologically active depsipeptides such as monamidocin[2] and spergualin.[3] Generally, α-hydroxy acids are readily accessible from the corresponding α-amino acids via diazotation.[4] However, diazotation of ornithine, citrulline, and arginine yields proline-analogs due to intramolecular nucleophilic attack of the δ-NH group.[5] This competing reaction reduces the yield and complicates the isolation of the desired α-hydroxy acid. A method comprising diazotation of the substrate in glacial acetic acid, isolation of the resulting *O*-acetyl argininic acid and the subsequent cleavage of the acetyl group was recently described. However, the yield of H–OArg(Tos)–OH was moderate (28% overall yield)[4] and, in our hands, this protocol failed when applied to H–Arg(Pbf)–OH. The conversion of arginine with HNO_3/HCl at elevated temperature followed by saponification of the 2-chloro acid gave rise to argininic acid in good yields (75%).[6] However, this protocol would be less suitable for most acid labile guanidino-protected arginines.

Alternatively, the guanidino moiety can be constructed by reaction of 5-amino-2-hydroxypentanoic acid (hydroxy analog of ornithin) with *C*-activated ureas such as *N*,*N*′-bis-Boc-1-guanidylpyrazole, as demonstrated for the synthesis of (±)-anchinopeptolide D and (±)-cycloanchinopeptolide D.[7] A remarkable feature of this modular approach is the possibility of introducing the guanidino moiety into a complex molecule at a late synthetic stage.[8] This was achieved with amino-iminomethanesulfonic acid for the synthesis of a depsipeptide analog of tendamistat,[9] and with 2-methyl-2-thiopseudourea for the synthesis of ACE inhibitors.[10]

For our current research on depsipeptides, we required ready access to Pbf-protected argininic acid, which is compatible with the Fmoc-strategy of SPPS. Temporary nitrosyl protection of arginine is thus shown herein to solve synthetic problems associated with unprotected N^{δ}-positions.

2. Results and discussion

Reaction of H–Arg(Pbf)–OH **1** with 2 equiv of $NaNO_2$ at 0 °C in aq sulfuric acid (2 equiv) gave the 5-membered ring **2** as the main product, while the unreacted starting material and the product H–OArg(Pbf)–OH **3** were detected in minor amounts by HPLC–MS analysis of the reaction mixture (Scheme 1). Upon use of a more acidic medium (10 equiv H_2SO_4 and 2 equiv $NaNO_2$), a new main component, with the mass of [H–Arg(Pbf)–OH+30], was detected. We assumed that this corresponded

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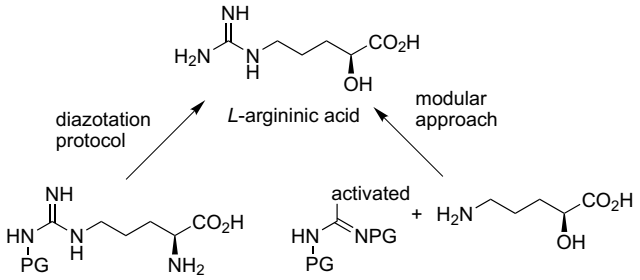
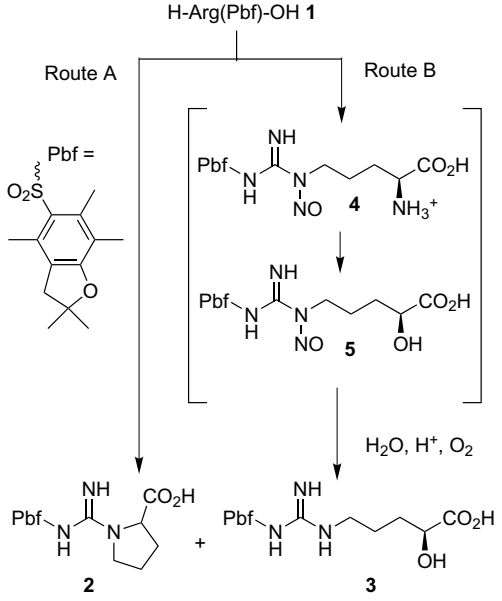


Scheme 1. Approaches to argininic acid.

to the δ-nitrosated product **4**, because protonation competes with electrophilic attack of the nitrosyl-cation more on the α-amino group than on the *δ*-NH due to the weakly basic character of the latter. Related compounds such as *N*-alkyl-*N*′-nitro-*N*-nitrosoguanidines are known precursors of diazoalkanes.[11] Interestingly, nitrosamides can undergo two distinct decomposition pathways. Thermal decomposition was recently reported to be an efficient method for the deamidation of amides of α-amino acids.[12] Noteworthy, nitrosation of amides in strong aqueous acidic media is reversible.[13]

We thus intended to use the nitroso group as temporary protecting group for the *δ*-nitrogen. Compound **1** was reacted with 20 equiv aq H_2SO_4 and 20 equiv of $NaNO_2$ and the reaction was followed by HPLC–MS. After 4 h reaction, the *δ*-nitrosated product **4** and only minor amounts of the 5-membered ring **2** were observed. After 12 h, the α-amino group was completely converted in the hydroxy group and the N^{δ} remained partially nitrosated (intermediate product **5**, see Scheme 2). The reaction mixture was then exposed to air with the aim of oxidizing excess NO. As expected, the acid-catalyzed denitrosation proceeded slowly at room temperature (see Ref. 13). After 48 h, conversion of **5** to **3** was complete. H–OArg(Pbf)–OH **3** was isolated by column chromatography in 79% yield.[14]



Scheme 2. Reagents and conditions: (route A) 2 equiv $NaNO_2$, 2 equiv aq H_2SO_4, rt, **2** main product; (route B) 20 equiv $NaNO_2$, 20 equiv aq H_2SO_4, rt, **3** main product.

3. Conclusion

To the best of our knowledge, the conversion of arginine into argininic acid reported here constitutes the first example of temporary N^{δ}-nitrosyl protection of the guanidino moiety to solve synthetic problems associated with unprotected N^{δ}-position. Extension of this concept to solve other problems related with unprotected N^{δ} of arginine derivatives is currently being studied.

Acknowledgements

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14. Compounds **1**–**5** have distinct HPLC-retention times. Synthesis of H–OArg(Pbf)–OH **3**: H–Arg(Pbf)–OH **1** (4.26 g, 10 mmol) was dissolved in H_2O–DMF–THF (10:1:1; 500 mL) containing sulfuric acid (10.7 mL, 20 equiv) at 0 °C. A solution of sodium nitrite (13.8 g, 20 equiv, in 50 mL H_2O) was added dropwise over 5 min under N_2. The reaction mixture was allowed to come

to rt and stirred for 12 h, at which point the flask was opened to air and stirred for an additional 48 h. The reaction mixture was extracted with ethyl acetate (3×250 mL), and the organic phase was dried over $MgSO_4$ and evaporated to dryness. Flash chromatography (silica gel, 9:1 $CHCl_3$–MeOH) afforded the product as a light yellow solid (3.37 g, 79%). ^{1}H NMR (400 MHz, CD_3OD), δ (ppm) = 1.45 (6H, s), 1.56–1.63 (3H, m), 1.70–1.76 (m, 1H), 2.09 (s, 3H), 2.51 (3H, s), 2.57 (3H, s), 3.01 (2H, s), 3.21 (2H, m), 4.08 (1H, m). HRMS: calcd for $C_{19}H_{30}N_3O_6S$ $[M+H]^+$: 428.1855. Found: 428.1862.