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Stereoselective synthesis of 2-azetidinylglycine and aminopyrrolidone derivatives from Garner's aldehyde

Latibuddin Thander, Kaushik Sarkar, Shital K. Chattopadhyay *

Department of Chemistry, University of Kalyani, Kalyani 741 235, West Bengal, India

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ABSTRACT

A new route to two hitherto unknown 2-azetidinylglycine derivatives and an aminopyrrolidone derivative has been developed which featured a diastereoselective conjugate addition of benzyl amine to an α,β-unsaturated ester derived from Garner's aldehyde as the key step.

1. Introduction

α,β-Diamino acids belong to an important class of compounds of relevance in chemistry and biology.[1] Therefore, there is continuing interest in their synthesis.[2] Of particular interest have been the derivatives in which one or both of the nitrogen atoms are contained within a heterocyclic ring, for example, compounds **1**–**4** (Fig. 1). Their importance as constrained amino acids/location in natural products and their utility as chiral auxiliaries/building blocks are well documented.[3] Moreover, the synthesis and biological evaluation of heterocycle-substituted non-proteinogenic α-amino acids are a matter of increasing interest.[4] For example, azetidine-2-carboxylic acid and its numerous derivatives have been studied extensively as mimic of proline and pipecolic acid.[5] However, 2-azetidinylglycines of type **5** has not yet received attention as an α,β-diamino acid of similarity to pyrrolidinyl- and piperidinylglycines. Herein, we report a concise asymmetric synthesis of two orthogonally protected 2-azetidinylglycine derivatives in continuation of our interest in the synthesis of heterocyclic α-amino acids[6] and α,β-diamino acids.[7]

2. Results and discussion

Our synthetic strategy relied on the possibility of the conjugate addition of a suitable amine to the known[8] Garner's aldehyde[9]-derived unsaturated ester **7** (Scheme 1), in a diastereoselective manner, as a means for the installation of the required 1,2-diamino functionality en-route to our projected title compounds. Although the aza-Michael reaction is a well-known process, reports on simple diastereoselective conjugate addition of amines to chiral enoates are comparatively less documented.[10] Thus, whilst the conjugate additions of cuprates,[11] hydroxylamine[12] and other carbon-nucleophiles[13] to compound **7** are known, similar additions of aliphatic or aromatic amines to compounds of the general structure **7** have to the best of our knowledge remained unexplored. This led us to consider the exploration of such a possibility. A variety of conditions,[14] including some excellent asymmetric protocols,[15] have been developed over the years for conjugate addition of amines to enoates. Initial experiments revealed that the addition of benzylamine to **7** proceeded better under recently reported conditions[16] using borax as a catalyst, but only when a mixture of ethanol and water (1:1) was used as solvent instead of water as reported. The β-amino esters **8** and **9** were obtained as an inseparable mixture in a 9:1 ratio (HPLC) and in a combined yield of 82%. The addition of allylamine under analogous conditions proceeded smoothly, but the diastereomeric ratio of products **10** and **11** was found to be 67:33. Similarly, the addition of ethylamine solution (70% in water) also proceeded uneventfully to provide products **12** and **13** in a 71:29 ratio. On the other hand, none of the aromatic amines such as aniline, *p*-toluidine or *p*-anisidine underwent conjugate addition to **7** under the developed conditions.

The configuration of the major product in each case of the addition of benzylamine and allylamine was assigned as *syn* based on precedence with further support from the following synthetic work. Thus, the mixture of β-amino esters **8** and **9** on reduction with LAH led to the formation of the corresponding alcohols **14** and **15** (Scheme 2) which were cleanly separated by column chromatography. Hydrogenolytic removal of the *N*-benzyl group of the major product **14** led to the formation of the free amine **16** which was subsequently mono-N-allylated and then *N*-Cbz-protected to secure **17**. The latter was then converted to the *N*-tethered diene **18** following a two-step protocol involving the oxidation of the primary alcohol to the corresponding aldehyde followed by its Wittig methylenation. The *syn*-diamine relationship in **18** was unequivocally established by its conversion to the carbocyclic β-lactam derivative **19** following our earlier report.[7] Similarly, a mixture of β-amino esters **10** and **11** on reduction with LAH provided separable mixture of the alcohols **20** and **21**. The major product **20** was

* Corresponding author. Tel.: +91 33 25828750x306; fax: +91 33 25828282.
E-mail address: skchatto@yahoo.com (S.K. Chattopadhyay).

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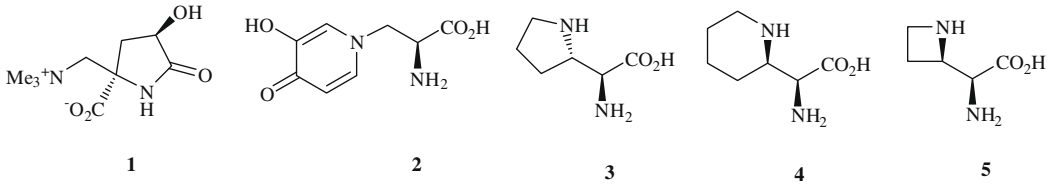
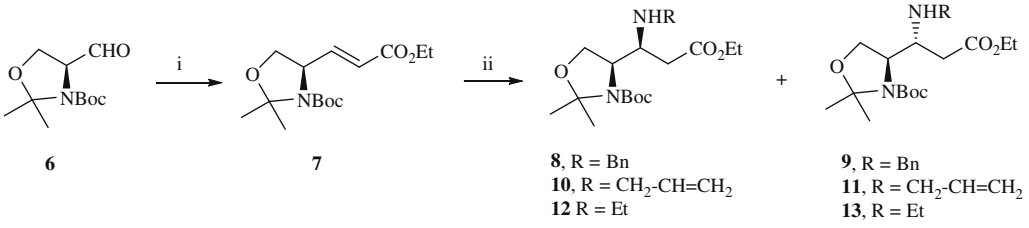


Figure 1.

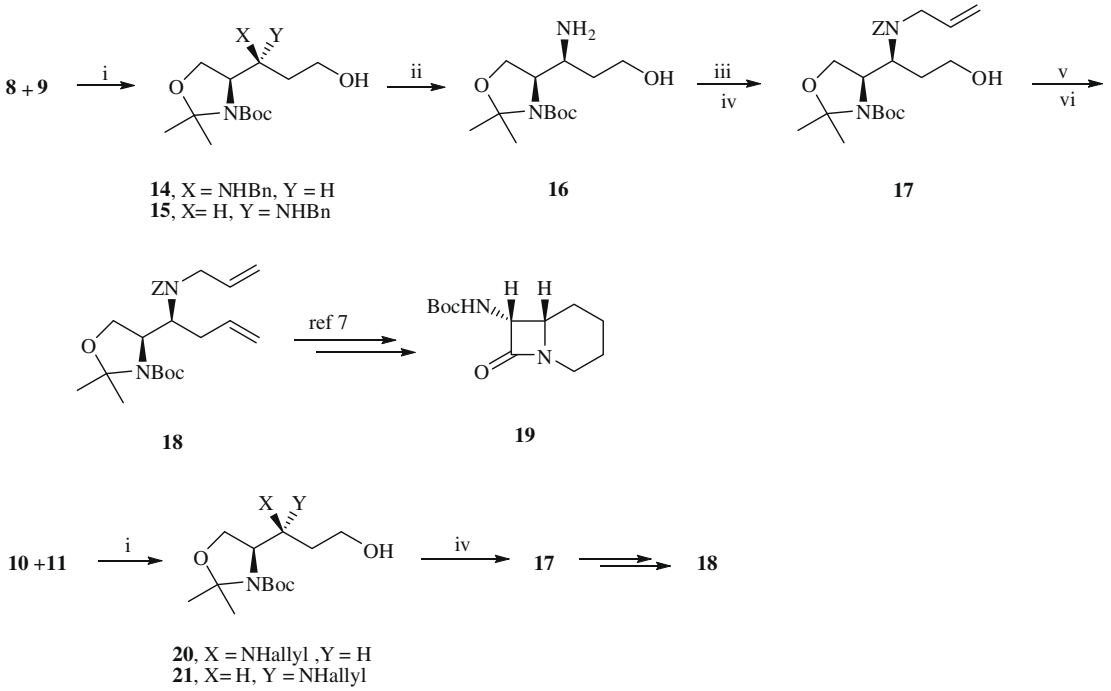


Scheme 1. Reagents and conditions: (i) triethyl phosphonoacetate, aq K_2CO_3, $Bu_4N^+I^-$, rt, 18 h, 86%; (ii) appropriate amine (5 equiv), borax (0.2 equiv), EtOH–H_2O (1:1), rt, 36 h; **8** + **9**, 82%; **10** + **11**, 79%; **12** + **13**, 76%.

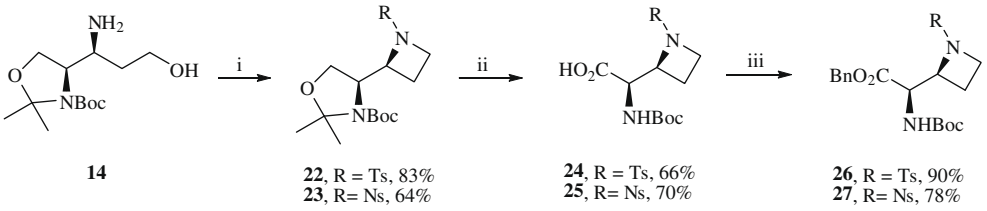
then converted to the Cbz-protected amine **17**, and thence to diene **18** following a similar sequence of reactions detailed for the conversion of **16**→**18**. This synthetic work thus established the *syn*-configuration of each of the major products **8** and **10** formed in the respective conjugate addition reactions. Based on these, the configuration of the major product formed during addition of ethylamine was assigned as **12**.

We then focused on the construction of the azetidine ring involving N-heterocyclisation of the γ-aminoalcohol moiety in compound **14**. N-Heterocyclisation of a β-aminoalcohol or a γ-aminoalcohol through the corresponding N,O-ditosylate leading to the formation of an aziridine or an azetidine ring is well documented.[17] Thus, when a mixture of the β-amino alcohol **16**, *p*-toluenesulfonyl chloride and powdered KOH[17c] was refluxed in tetrahydrofuran, the clean formation of the *N*-tosylazetidine derivative **22** (Scheme 3) took place in very good yield. The latter under Jones' oxidation conditions underwent concomitant opening of the oxazolidine ring and oxidation of the resulting primary alcohol function to provide the carboxylic acid **24**. Esterification of compound **24** with benzyl bromide under conventional conditions then led to the orthogonally protected azetidinylglycine derivative **26** in an overall yield of 49% over three steps. Similarly, the *N*-nosylazetidine derivative **22** was prepared and converted to compound **27** using a similar sequence of reactions.

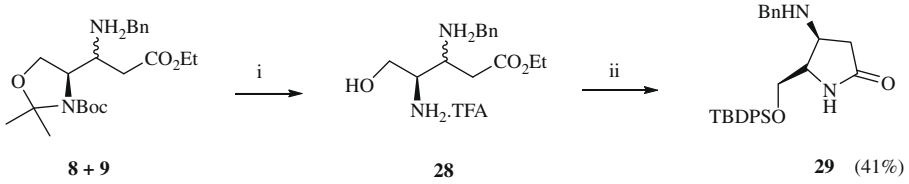
We next considered synthesis of chiral 2-pyrrolidone derivatives from the common intermediate **8** involving an amide bond formation between the ester carbonyl and the masked γ-amino function. Thus, the mixture of compounds **8** and **9** was treated with



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C to rt, 1 h, 80%; (ii) H_2, Pd–C (10%), EtOAc, rt, 12 h, 85%; (iii) allyl bromide, K_2CO_3, acetone, reflux, 6 h, 39%; (iv) CBzCl, $NaHCO_3$, EtOAc, rt, 18 h, 94% (v) PCC, MS 4 Å, DCM, rt, 1.5 h, 81%; (vi) $MePPh_3^+Br^-$, *n*-BuLi, THF, −78 °C to rt, 4 h, 78%.



Scheme 3. Reagents and conditions: (i) TsCl (or NsCl) (2 equiv), KOH, THF, reflux, 5 h; (ii) Jones' oxidation, acetone, 0 °C to rt, 7 h; (iii) BnBr, Cs_2CO_3, *N*,*N*-DMF, rt, 12 h.



Scheme 4. Reagents and conditions: (i) 50% TFA in DCM, 0 °C to rt, 1.5 h; (ii) Et_3N (5 equiv), TBDPSCl (1.4 equiv), DMAP (cat), DCM, rt, 12 h.

trifluoroacetic acid to effect simultaneous oxazoliding ring cleavage and *N*-Boc deprotection. The crude TFA-salt **28** (Scheme 4) when treated with triethylamine in the presence of TBDPS-Cl underwent ring-closure as well as O-silylation to provide the substituted aminopyrrolidone derivative **29** in an overall yield of 41% over three steps. The latter was obtained in diastereomerically pure form after removal of the minor isomer by chromatography. Various substituted aminopyrrolidone derivatives have interesting applications and therefore are important synthetic targets.[18] The stereoselective preparation of compound **29** may therefore prove to be useful.

3. Conclusion

In short, we have developed a methodology for a diastereoselective conjugate addition reaction of a suitable alkyl amine to a Garner's aldehyde-derived α,β-unsaturated ester. Although the stereoselectivity is variable, the sense of stereoselection appears to be consistent. The developed methodology has been utilised for the synthesis of two diastereomerically pure[19] unknown azetidinylglycine derivatives and a stereodefined aminopyrrolidone derivative from readily available starting materials and reagents. The 1,2-diamino compounds prepared may also find other applications. The azetidinylglycine derivatives thus obtained may find new application as a new motif in the design and synthesis of peptides with altered structure and function. Work will be continued in these directions in this laboratory.

Acknowledgement

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19. All new compounds reported here gave satisfactory spectroscopic and/or analytical data. Data for **26**: Mp 60 °C. $[\alpha]_D$ = +9 (*c* 1.51, MeOH). IR (KBr): 3443, 1751, 1724, 1496, 1348, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* = 8.1), 7.45–7.37 (5H, m), 7.29 (2H, d, *J* = 8.1), 5.65 (1H, d, *J* = 9.6), 5.27 (2H, ABq, *J* = 12.5), 4.55 (1H, t, *J* = 7.4), 4.38 (1H, d, *J* = 9.6), 3.68–3.64 (1H, m), 3.43 (1H, q, *J* = 8.4), 2.44 (3H, s), 2.21–2.15 (1H, m), 1.91–1.89 (1H, m), 1.45 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 156.4, 144.3, 135.2, 130.6, 129.7, 128.6, 128.5, 128.3, 126.8, 80.2, 67.7, 63.3, 56.2, 47.8, 28.2, 21.5, 18.1 HRMS (TOF MS ES+): obsd 497.1729 (M+Na); calcd 497.1722.
Compound **27**: Mp 116 °C $[\alpha]_D$ = −13.3 (*c* 1.50, $CHCl_3$). IR (KBr): 3402, 1745,

1697, 1529, 1499, 1348, 1162 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (2H, d, J = 8.7), 7.91 (2H, d, J = 8.7), 7.42 (5H, m), 5.52 (1H, d, J = 9.6), 5.25 (2H, ABq, J = 12.1), 4.64 (1H, t, J = 7.8), 4.44 (1H, d, J = 9.9), 3.74 (1H, m), 3.51 (1H, q, J = 8.3), 2.25 (1H, m), 2.01 (1H, m), 1.46 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 156.3, 150.5, 135.0, 129.7, 128.7, 128.67, 128.65, 128.62, 124.3, 80.6, 68.0, 64.0, 56.0, 48.3, 28.2, 18.3. HRMS (TOF MS ES+): obsd 528.1411 (M+Na); calcd 528.1417. Compound **29**: $[\alpha]_D = -2$ (c 4.25, MeOH). IR ($CHCl_3$): 3360, 1735, 1410, 1059, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64–7.60 (4H, m), 7.45–7.37 (6H, m), 7.30–7.24 (6H, m), 5.71 (1H, s), 3.75–3.65 (3H, m), 3.63–3.57 (2H, m), 3.26–3.25 (1H, m), 2.63 (1H, dd, J = 7.8, 17.1), 2.20 (1H, dd, J = 5.1, 17.1), 1.04 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1 (s), 139.3 (s), 135.5 (d), 135.4 (d), 132.7 (s), 130.0 (d), 129.9 (d), 128.5 (d), 128.0 (d), 127.8 (d), 127.2 (d), 65.9 (t), 62.1 (d), 55.6 (d), 51.5 (t), 37.9 (t), 26.7 (q), 19.1(s). MS (TOF MS ES+): 481 (M+Na).