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Reactivity of 1-aminoazetidine-2-carboxylic acid during peptide forming procedures: observation of an unusual variant of the hydrazino turn

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ABSTRACT

Peptide formation on the N-terminal of 1-aminoazetidine-2-carboxylic acid is rendered problematic due to a ring opening reaction. However C-terminal development is possible and two diastereomeric mixed hydrazino dipeptides were prepared. Solution-state studies of these compounds suggest the presence of intramolecular hydrogen bonding, consistent with a hydrazino turn, and the crystal structure of one of these compounds shows a horse-shoe conformation, centered around what appears to be a hydrazino turn involving three hydrogen bond acceptors.

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There is an increasing general interest in α-hydrazino acids.[1] These compounds are of notable potential in the peptidomimetic field, and the hydrazidic bond is resistant to proteases.[2] Modification of peptides by inclusion of an α-hydrazino acid was considered some time ago,[3] although synthetic difficulties have hampered progress. More recently, a variety of biologically and/or structurally interesting peptides containing one or several α-hydrazino acid residues have become more accessible,[4] although selective N-functionalization remains something of a challenge. Hydrazino peptides can be considered as aza-analogs of β-peptides, and the presence of the extra nitrogen can give rise to a structural feature known as a 'hydrazino turn' implicating a bifurcated intramolecular hydrogen bond (Fig. 1).[5]

The hydrazino turn dictates conformational preferences in mixed α-hydrazino/α-amino acid oligomers[4f] and in homo hydrazino peptides,[6] and controls nitrogen chirality in aza-β^3-peptides.[7] The analogy with β-peptides has attracted further attention from the foldamer community, and pioneering theoretical studies on hydrazino peptides suggest that a variety of low-energy regular helical structures may be accessible.[8] As part of a program which examines oligomers of 2-aminocyclopentane-1-carboxylic acid (ACPC), oligomers composed of alternating sequences of ACPC and aza-ACPC were studied, and it was found that the latter residues easily accommodated the secondary structure type induced by the former.[9] In some sequences, enhanced intramolecular hydrogen bonding was implicated, although no direct evidence for a hydrazino turn emerged. Indeed, the ring nitrogen atoms of the aza-ACPC residues appeared to be solvent accessible and could be protonated without disruption to the secondary structures. Previously, aza-ACPC had displayed hydrazino turn behavior in crystal structures of smaller peptides.[10]

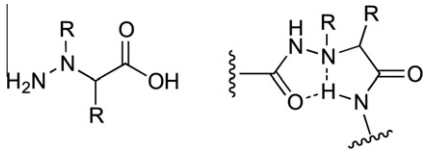

Figure 1. An α-hydrazino acid (left) and the hydrazino turn feature of a hydrazino peptide (right). The R groups may be H, alkyl, aryl, or other.

The lower ring-size homolog of ACPC, 2-aminocyclobutane-1-carboxylic acid (ACBC),[11] also has the ability to promote particular conformations in dipeptides[12] and in longer oligomers.[13] We recently prepared the aza-analog of ACBC, 1-aminoazetidine-2-carboxylic acid (AAzC), (**1**), a novel small-ring α-hydrazino acid.[14] Here, we disclose our findings on the particular reactivity of this compound as regards hydrazino peptide construction.

In initial studies to determine appropriate conditions for peptide coupling, we used racemic material (Scheme 1). (±)-*N*-Boc-AAzC (**2**) was prepared according to the literature.[14] Methyl ester formation was achieved uneventfully via EDCI/DMAP activation, to give compound **3** in 83% yield. All attempts to liberate the *N*-terminal nitrogen, however, were unsuccessful. The numerous efforts using varied acidic conditions either failed to transform **3** or

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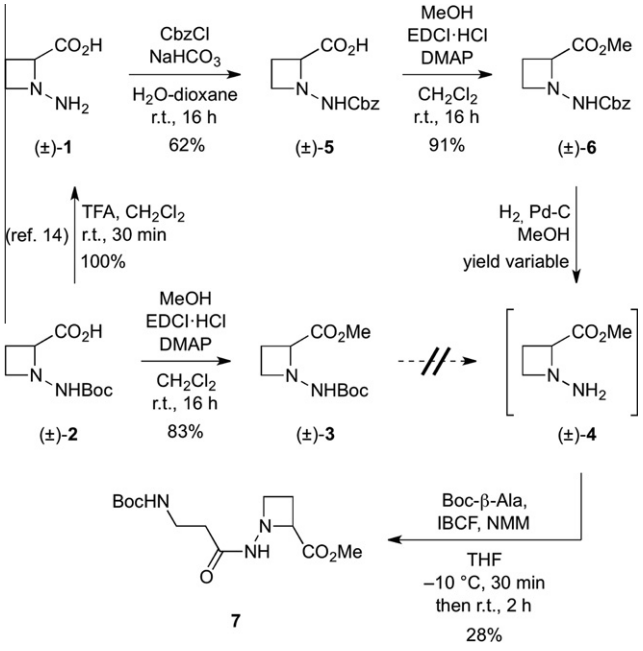
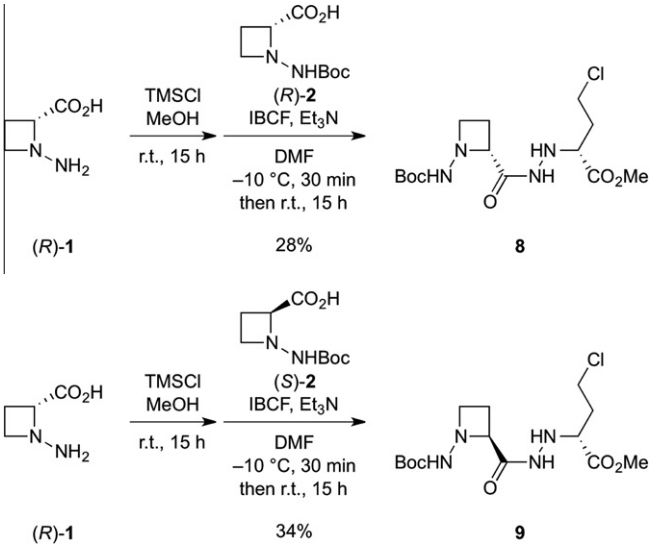


Scheme 1.

induced an extensive degradation thereof. TLC and NMR spectral analysis of the crude reaction product indicated several products were present, and efforts to isolate the desired hydrazine **4** (or its salt) were fruitless. We decided to obviate the use of acidic conditions to liberate the amine, and decided to study the Cbz-group protected AAzC ester as an alternative (Scheme 1). In stark contrast to the behavior of **3**, TFA-mediated Boc-cleavage of **2** proceeded smoothly to furnish (±)-AAzC (**1**) in near quantitative yield![14] Cbz-group introduction followed by esterification as before proceeded without incident to provide **6** via **5**. Here again, however, deprotection was problematic. Hydrogenolysis of **6** over palladium-on-charcoal was investigated under various conditions (catalyst loading, time, solvent). In all cases, complete conversion was achieved, although the reaction product profile was capricious, varying considerably from one run to the next. NMR spectral analysis suggested that the requisite free hydrazine **4** was present (in one non reproducible case, the yield was around 90%) although other components were always in evidence. Chromatographic separation of crude mixtures simply produced further degradation, so we used crude samples of **4** to attempt peptide coupling reaction using *N*-Boc-β-alanine as a model partner (Scheme 1). Numerous activating reagents were investigated (DCC, EDCI, FDPP, HATU, HBTU) without success. Finally, the use of IBCF/NMM in THF provided dipeptide **7** in 28% isolated yield, after repeated chromatographic separation from other components.

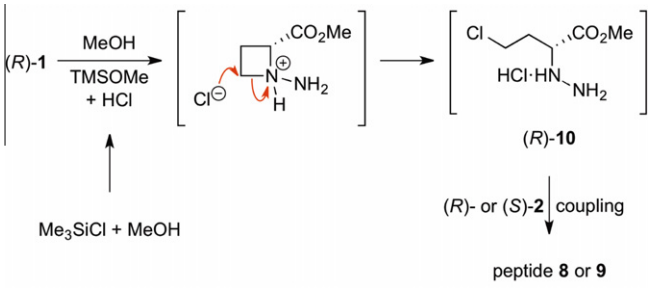
Pursuing our efforts towards dipeptide coupling, we next considered a procedure intended to provide the hydrochloride salt of hydrazino ester **4** directly from **1** (Scheme 2). For these studies, we used enantiomerically pure samples of **1** and **2**, obtained according to the literature.[14] Treatment of (*R*)-**1** with TMSCl (3 equiv) in methanol produced a material which was difficult to characterize and was used directly in a coupling reaction with (*R*)-**2** using IBCF/Et_3N as the activating system. To our surprise, the main component, isolated pure in 28% yield after chromatography, was hydrazino dipeptide **8**, in which the C-terminal residue was the previously unknown 2-hydrazino-4-chlorobutanoic acid (hCBA). A repeat of the above procedure using (*S*)-**2** as the intended N-terminal residue provided the diastereomeric hydrazino dipeptide **9** in 34% yield.



Scheme 2.

The nucleophilic component in each of the above coupling reactions was clearly not the anticipated hydrazino ester **4**. The hydrogen chloride generated by the reaction of TMSCl with methanol not only catalyzes the esterification, but presumably also protonates the more basic ring nitrogen (Scheme 3). By analogy with azetidine chemistry,[15] this quaternarization activates the four-membered cycle for nucleophilic ring opening by chloride ion. It is possible that the quaternarization process may be enhanced by a donating effect from the adjacent nitrogen atom, in analogy with the so-called α-effect which is sometimes invoked in connection with the nucleophilicity of hydrazines.[16] Thus the hydrazino ester component present at the moment when the peptide coupling reactions are initiated is in fact the hCBA derivative **10**, presumably as its monohydrochloride. Retrospectively, the acid-promoted ring opening of the AAzC skeleton is a plausible explanation for the failure to obtain **4** from **3** in Scheme 1.

Hydrazino dipeptide **9** gave crystals amenable to X-ray diffraction analysis.[17] The solid state conformation of the molecule is illustrated in Figure 2. The pyramidal chiral ring nitrogen adopts an *R* configuration, which means the four-membered ring adopts a *trans*-like relative configuration with a backbone torsion angle of −96.3°. The 5-atom chain from the ring N^{α} to the quaternary carbon of the *t*-butyl group is completely extended and occupies a single plane. The carbonyl group of the AAzC residue is a part of a regular planar *trans* amide bond with the N^{β} of the hCBA residue (torsion angle 177.8°). The torsion angles of 174.7° for N^{α}–C^{α}–C=O and −59.9° for H–N^{β}–N^{α}–C^{α} of the AAzC residue allow a network of strong intermolecular hydrogen bonds to link up the



Scheme 3.

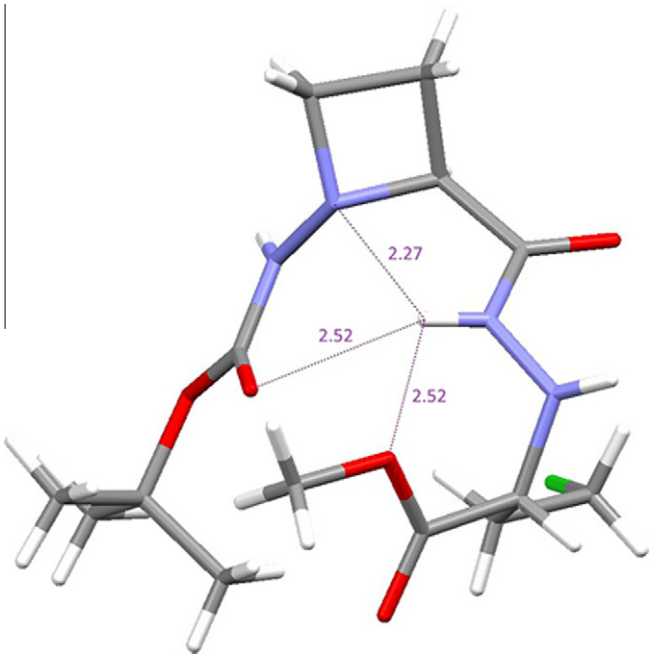


Figure 2. X-ray structure of hydrazino dipeptide **9**.

molecules in the lattice (C═O···H–N distance 2.04 Å), and facilitate an 8-membered turn feature linking the AAzC Boc C═O and the hCBA N^{β}–H (C═O···H–N distance 2.52 Å) within each molecule (Fig. 2). The AAzC ring nitrogen is at a distance of 2.27 Å from the hCBA N^{β}–H and, although the geometrical alignment is not optimal due to ring constraints, a hydrazino turn would appear to be in evidence. What is intriguing is that the hydrazine moiety of the hCBA residue is twisted so that the C-terminal can bend back and present the sp^3 oxygen of the methyl ester towards N^{β}–H. The O···H–N distance (2.52 Å) and the geometry (O···H–N bond angle 111.1°) are at the acceptable upper limit for constituting a hydrogen bond. There are no other significant close contacts (hydrogen bonds or packing effects) in evidence which might induce this horse-shoe conformation for the molecule. The hCBA N^{β}–H thus appears to be involved in a modified hydrazino turn in which three hydrogen bond acceptors are implicated. On one previous occasion, the carbonyl oxygen (as opposed to the alkoxy oxygen) of a methyl ester-capped hydrazino peptide was observed to make an intra-residue H-bond contact with the hydrazidic NH in the solid state.[6b]

We obtained some support for the existence of the hydrazino turn feature for each of the dipeptide **8** and **9** in solution. When a 60 mM $CDCl_3$ solution of either peptide was treated with methanol-d_4 (30 equiv) the change in chemical shifts in the ^{1}H NMR spectra was significant for the AAzC hydrazidic protons ($\Delta\delta$ = 0.84 ppm for **8**; 0.79 ppm for **9**) but not for the hCBA hydrazidic protons ($\Delta\delta$ = 0.08 ppm for **8**; 0.07 ppm for **9**), suggesting that the latter are involved in intramolecular hydrogen bonds.[18] In the N–H stretching frequency range of the solution state IR spectra of peptides **8** and **9** (10 mM solutions in $CHCl_3$), two absorptions were observed in each case, at around 3360 and 3300 cm^{-1}. The appearance of the latter band provides strong evidence for an intramolecularly hydrogen-bonded hydrazidic NH, consistent with the hydrazino turn.

In summary, the synthetic work described here underlines the particular difficulties which may be encountered in the preparation of hydrazino peptides of AAzC by coupling at the N-terminal. This objective looks likely to remain a considerable challenge, although the ring opening during the liberation of the amine to provide the hCBA residue suggests that other side-chain substituted α-hydrazino butanoic acids might be available via **1**. Nonetheless, the preparation of dipeptides **8** and **9** shows that C-terminal coupling of AAzC can be achieved without difficulty, and conformational studies suggest an interesting folding potential for hydrazino peptides bearing AAzC at the C-terminal. Future work will be directed by this premise.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.112.

References and notes

1. Vidal, J. Synthesis and Chemistry of α-Hydrazino Acids In *Amino Acids, Peptides and Proteins in Organic Chemistry*; Hughes, A. E., Ed.; Wiley-VCH: Origins and Synthesis of Amino Acids, 2009; Vol. 1, pp 35–92.
2. Lelais, G.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4152–4168.
3. (a) Niedrich, H.; Köller, G. *J. Prakt. Chem.* **1974**, *316*, 729–740; (b) Niedrich, H.; Oehme, C.; Bergmann, J. *J. Prakt. Chem.* **1974**, *316*, 741–749.
4. (a) Guy, L.; Vidal, J.; Collet, A.; Amour, A.; Reboud-Ravaux, M. *J. Med. Chem.* **1998**, *41*, 4833–4843; (b) Raju, B.; Mortell, K.; Anandan, S.; O'Dowd, H.; Gao, H.; Gomez, M.; Hackbarth, C.; Wu, C.; Wang, W.; Yuan, Z.; White, R.; Trias, J.; Patel, D. V. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2413–2418; (c) Vilaivan, T.; Suparpprom, C.; Duanglaor, P.; Harnyuttanakorn, P.; Lowe, G. *Tetrahedron Lett.* **2003**, *44*, 1663–1666; (d) Busnel, O.; Bi, L.; Dali, H.; Cheguillaume, A.; Chevance, S.; Bondon, A.; Muller, S.; Baudy-Floc'h, M. *J. Org. Chem.* **2005**, *70*, 10701–10708; (e) Acherar, S.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2009**, *50*, 6377–6379; (f) Moussodia, R.-O.; Acherar, S.; Bordessa, A.; Vanderesse, R.; Jamart-Grégoire, B. *Tetrahedron* **2012**, *68*, 4682–4689.
5. Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Sterin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793–801.
6. (a) Cheguillaume, A.; Salaün, A.; Sinbandhit, S.; Potel, M.; Gall, P.; Baudy-Floc'h, M.; Le Grel, P. *J. Org. Chem.* **2001**, *66*, 4923–4929; (b) Salaün, A.; Potel, M.; Roisnel, T.; Gall, P.; Le Grel, P. *J. Org. Chem.* **2005**, *70*, 6499–6502; (c) Salaün, A.; Favre, A.; Le Grel, B.; Potel, M.; Le Grel, P. *J. Org. Chem.* **2006**, *71*, 150–158.
7. (a) Le Grel, P.; Salaün, A.; Potel, M.; Le Grel, B.; Lassagne, F. *J. Org. Chem.* **2001**, *71*, 5638–5645; (b) Moquet, C.; Salaün, A.; Claudon, P.; Le Grel, B.; Potel, M.; Guichard, G.; Jamart-Grégoire, B.; Le Grel, P. *J. Am. Chem. Soc.* **2009**, *131*, 14521–14525.
8. Günther, R.; Hofmann, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 247–255.
9. Hetényi, A.; Tóth, G. K.; Somlai, C.; Vass, E.; Martinek, T. A.; Fülöp, F. *Chem.-Eur. J.* **2009**, *15*, 10736–10741.
10. Aubry, A.; Mangeot, J.-P.; Vidal, J.; Collet, A.; Zerkout, S.; Marraud, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 305–311.
11. (a) Gauzy, C.; Pereira, E.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2004**, *45*, 7095–7097; (b) Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S.; Aitken, D. J. *Synthesis* **2007**, 2222–2232; (c) Fernandes, C.; Pereira, E.; Faure, S.; Aitken, D. J. *J. Org. Chem.* **2009**, *74*, 3217–3220; (d) Declerck, V.; Aitken, D. J. *Amino Acids* **2011**, *41*, 587–595.
12. Torres, E.; Gorrea, E.; Da Silva, E.; Nolis, P.; Branchadell, V.; Ortuño, R. M. *Org. Lett.* **2009**, *11*, 2301–2304.
13. (a) Fernandes, C.; Faure, S.; Pereira, E.; Théry, V.; Declerck, V.; Guillot, R.; Aitken, D. J. *Org. Lett.* **2010**, *12*, 3606–3609; (b) Torres, E.; Gorrea, E.; Burusco, K. K.; DaSilva, E.; Nolis, P.; Rúa, F.; Boussert, S.; Díez-Pérez, I.; Dannenberg, S.; Izquierdo, S.; Giralt, E.; Jaime, C.; Branchadell, V.; Ortuño, R. M. *Org. Biomol. Chem.* **2010**, *8*, 564–575.
14. Declerck, V.; Aitken, D. J. *J. Org. Chem.* **2011**, *76*, 708–711.
15. (a) Banide, E.; Lemau de Talencé, V.; Schmidt, G.; Lubin, H.; Comesse, S.; Dechoux, L.; Hamon, L.; Kadouri-Puchot, C. *Eur. J. Org. Chem.* **2007**, 4517–4524; (b) Kenis, S.; D'hooghe, M.; Verniest, G.; Thi, T. A. D.; The, C. P.; Nguyen, T. V.; De Kimpe, N. *J. Org. Chem.* **2012**, *77*, 5982–5992.
16. For a review and discussion, see: (a) Buncel, E.; Um, I.-H. *Tetrahedron* **2004**, *60*, 7801–7825; For recent leading references and a critical assessment, see: (b) Nigst, T. A.; Antipova, A.; Mayr, H. *J. Org. Chem.* **2012**, *77*, 8142–8155.

17. CCDC 893998 contains the crystallographic data for compound **9**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. Other ^{1}H NMR data obtained for hydrazidic NH atoms were inconclusive. Extensive H/D isotopic exchange in the methanol-d_4 dilution experiment was observed after only 5 min for both the AAzC (22% H signal remaining in **8**, 12% in **9**) and the hCBA (10% H signal remaining in both **8** and **9**) hydrazidic NH atoms. The chemical shift temperature gradients of 60 mM $CDCl_3$ solutions of each of the peptides were also difficult to interpret: in the range 300–325 K, $\Delta\delta/\Delta T$ values were about −6 ppb/K for hCBA residues and −4 ppb/K for AAzC residues. Care in interpreting such data has been advocated before (Ref. 9): relatively quick proton exchange in azapeptides is not necessarily an indication of conformational inhomogeneity (see also Ref. 2), and temperature gradient values cannot be directly compared to values observed for amide hydrogens due to the increased H-bond acidity.