SHORT COMMUNICATION

Efficient entry into hydrazinopeptide-like structures via sequential Ugi reactions

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Received: 7 June 2009 / Accepted: 19 October 2009 / Published online: 10 November 2009 © Springer Science+Business Media B.V. 2009

Abstract Novel types of hydrazinopeptide-like units containing five elements of diversity have been prepared in two steps using sequential Ugi reactions.

Keywords Isocyanide-based multicomponent reactions · Peptidomimetics · Hydrazinopeptides · β-Turn mimics · Sequential Ugi reactions

Introduction

The idea of replacing the primary amine component in the Ugi reaction with monoacylated hydrazine was first reduced to practice over 40 years ago to deliver N,N′-biscyctlated hydrazines 1 [1] or tetrazoles 2 [2], in the latter case azide anion replacing the traditional carboxylate nucleophile (Scheme 1). However, in subsequent decades this reaction received little attention [3–5], perhaps due to limited room for further chemical manipulation of the products resulting from it.

We reasoned that if the carboxylic acid component in the “hydrazino-Ugi” reaction is chosen such as to allow selective removal of the Nα-acyl group, this would provide a facile method to prepare hydrazinopeptide [6] units and also liberate the reactive nitrogen atom for introducing further molecular diversity. Hydrazinopeptides represent a valuable class of mimetic replacements for the natural peptide backbone often leading to analogs of bioactive peptides with preserved biological activity [7] yet enhanced proteolytic stability [8]. Hydrazinopeptide units within short peptide fragments have also been shown [9] to adopt a unique secondary structure termed a “hydrazino turn” (similar to natural peptide β-turn) due to additional hydrogen bonding via the sp3-hydridized nitrogen atom (Fig. 1).

Results and discussion

A series of carboxylic acid hydrazides 3 were reacted with aliphatic aldehydes 4 in methanol to prepare the respective acylhydrazones 5. Reaction with the isocyanides 6 and TFA was carried out in dioxane as the same reaction in methanol had been found to lead to by-product formation.1 The expected Nβ-acyl-Nα-trifluoroacetyl hydrazocarboxamides 7 were indeed observed by LC–MS analysis (and isolated in one case—see “Experimental” section) on completion of the reaction. However, upon basic workup, the trifluoroacetyl group was found to partially come off. Therefore, the hydrazo-Ugi reaction with TFA was repeated and on its completion, the trifluoroacetyl group was cleanly removed with aqueous K2CO3 solution to provide good to excellent yields of Nβ-monoacylated hydrazino carboxamides 8a–c (Scheme 2). The structure of the synthesized compounds was confirmed by 1H- and 13C-NMR spectroscopy. For the compound 8a, a single-crystal X-ray structure was obtained2 to reveal that in the crystalline state,

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1 Detailed investigation of the by-product structure and mechanistic origin is currently underway and will be reported on in a separate publication.
2 Crystallographic data (excluding structure factors) for the structure 8a in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 743067. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Scheme 1 Earlier examples (see footnotes 1 and 2) of using monoacylated hydrazine in Ugi reaction

this compound adopts a hydrazino turn-like conformation (Fig. 2). NMR studies are currently underway in our laboratories to establish if this conformational bias persists in solution as well.

The compounds 8 contain three elements of diversity resulting from the acylhydrazine, the aldehyde, and the isocyanide used. We reasoned that, in principle, these diversely substituted hydrazino carboxamides can be viewed as the starting materials for another Ugi reaction, as the reactive α-nitrogen atom can again serve as a replacement for the amine component in this process. Indeed, when 8b and 8c were reacted with an aliphatic aldehyde and an isocyanide in methanol in the presence of TFA, the expected products of the second “hydrazino-Ugi” reaction 9a–c were obtained in good yields as mixture of diastereomers, with no noticeable diastereomeric control (Scheme 3). In one case (9a), we were able to separate the diastereomers nearly quantitatively by preparative reverse-phase HPLC. Notably, in the NOESY spectrum, only one diastereomer 9a(1) displayed a through-space interaction between the two methine protons at the chiral carbon atoms, which provided a basis for the assignment of the relative stereochemistry (Fig. 3).

Formation of the difficult-to-separate diastereomeric mixtures in the hydrazo-Ugi reaction of the chiral substrates 8 can be avoided if a non-prochiral carbonyl input is used. Indeed, when 8a and 8b were reacted with excess amount of either acetone or paraformaldehyde and an equimolar amount of an isocyanide in methanol in the presence of TFA, the expected products 9d–f were formed in good yields (Scheme 4).

The compounds 9a–f synthesized via two operationally simple sequential hydrazo-Ugi reactions, remarkably, contain five elements of diversity which originate from an acylhydrazine, two carbonyl components, and two isocyanide components and are introduced sequentially, in a regiochemically controlled manner. Trifluoroacetic acid functions as a “silent” carboxylic component in both multi-component reactions. In the first reaction, it is removed upon mildly basic workup to liberate the reactive Nα.

In the second reaction, trifluoroacetyl group in the initial four-component adduct 10 cannot undergo the usual Mumm rearrangement [10] (i.e., acyl migration according to the generally accepted mechanism of Ugi reaction) and is cleaved by the nucleophilic solvent molecule (Scheme 5).

Notably, the hydrazinopeptide units 9 represent a conceptually novel class of peptidomimetic structures capable of introducing a “fork” in the polypeptide chain after which the latter may take two alternative ways to continue toward the C-terminus (Fig. 4).