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A NOVEL Δ-THIOLACTONE SCAFFOLD BY A VERSATILE INTRAMOLCULAR MULTICOMPONENT REACTION

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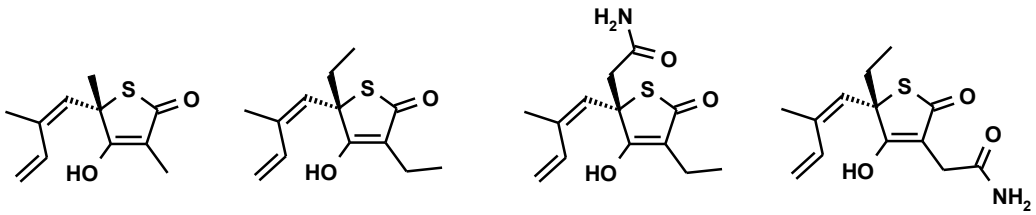
Abstract – The three component reaction of α-aminoacids, mercaptoacetaldehyde and an isocyanide smoothly and stereoselectively yields the novel scaffold 1,2-disubstituted *N*-alkyl(aryl)-6-oxo thiomorpholine-3-carboxamide. In this communication we present our preliminary results on six compounds derived from this unprecedented reaction.

INTRODUCTION

6-Oxothiomorpholine derivatives comprise a class of synthetic and biologically active compounds. Recently reported activities include antibiotic, anticancer and plant protection activities.[1-3] In addition thiolactones are part of the natural product class of thiolactomycins, including U-68204, TUE-3010 and thiotetromycin with antibiotic activity (Scheme 1).[4,5] Analysis of the recent high resolution X-ray structure analysis of thiolactomycin in its biological target β-ketoacyl acyl carrier protein synthase II (FAS-II) prompted us to design novel inhibitors of this important and essential antibacterial target (Figure 1).[6]



thiolactomycin thiotetromycin TUE-3010 U-68204

Scheme 1. Biologically active compounds with a thiolactone moiety.

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

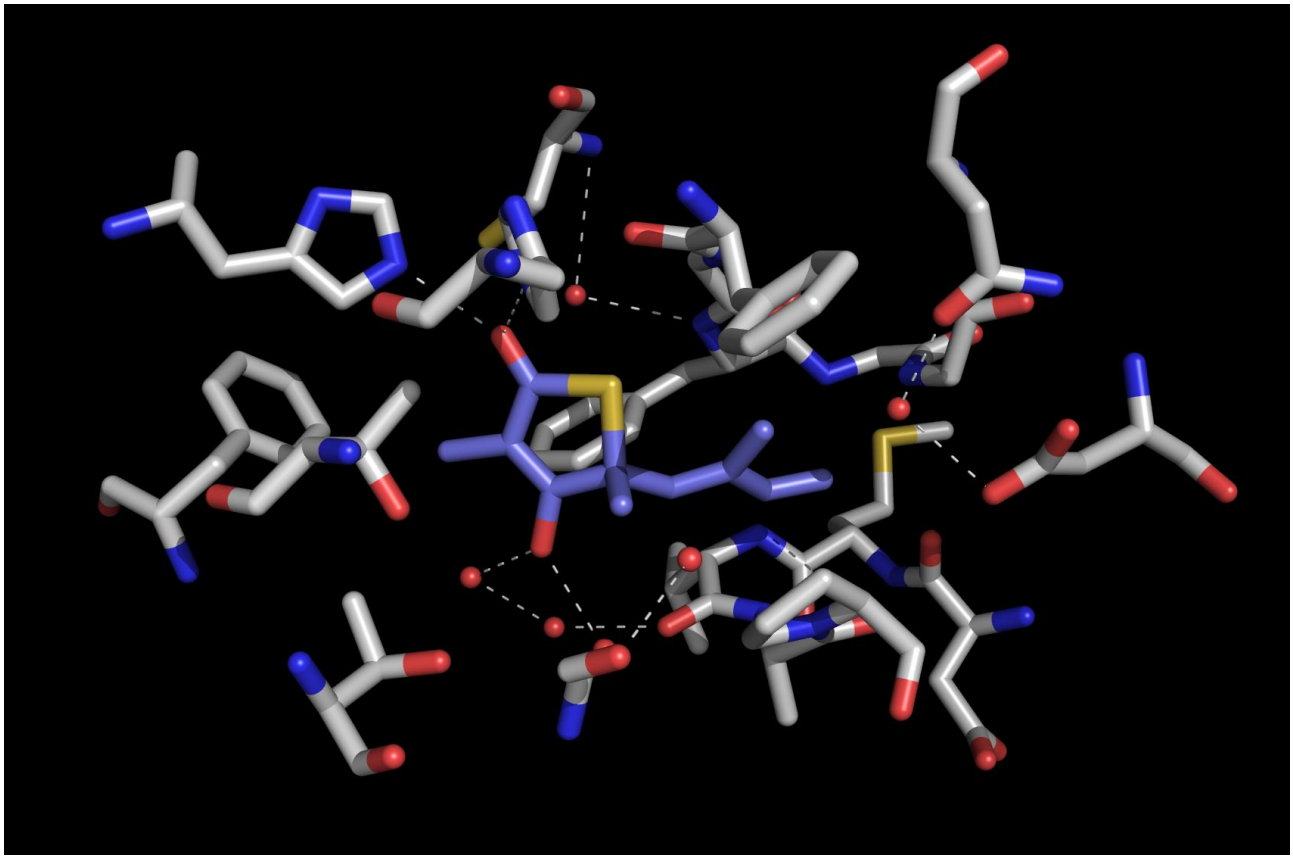
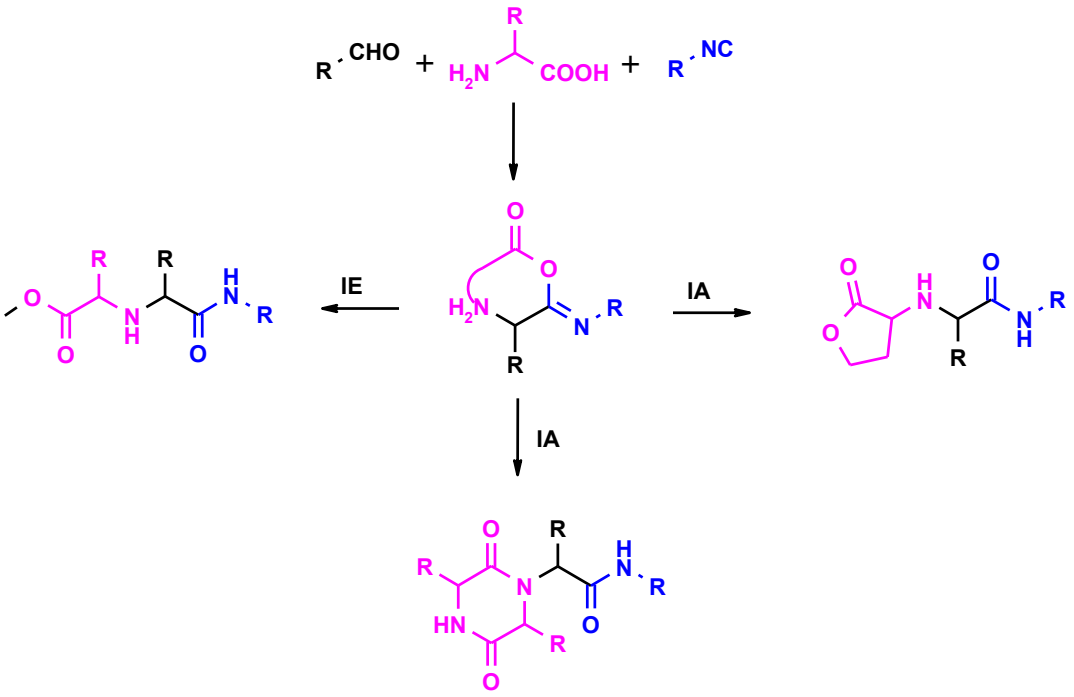


Figure 1. The analysis of the binding site of thiolactomycin serves as a template to design novel bioactive MCR scaffolds, the herein reported thiomorpholine. The binding site of thiolactomycin (PDB ID: 1FJ4) reveals the important hydrogen bond contact between the thiolactone carbonyl and two adjacent histidine protons as well as the hydrogen bond network around the enol moiety including several water molecules and a valine backbone carbonyl. Crucial for the activity of thiolactomycins and derivatives is the soft and hydrophobic sulfur as well as the hydrophobic side chain undergoing strong van der Waals interactions with several surrounding hydrophobic aminoacids phenylalanine, methionine, alanine and proline. The picture was generated using PyMol.

Multicomponent reactions (MCRs) are a very economic way to produce biological active lead structures, since quite elaborated structures are accessible in only one key step, eventually followed by a subsequent chemical transformation.[7] In addition several hundred scaffolds have been described in the past thus potentially offering considerable chemical diversity.[8] Several bioactive MCR products are currently undergoing clinical evaluation or are already marketed.[9-11] As part of our ongoing studies directed to the discovery of novel antibacterial agents against neglected diseases including Tuberculosis, we herein communicate our preliminary results of a recently discovered multicomponent reaction leading to the novel scaffold of 1,2-disubstituted *N*-alkyl(aryl)-6-oxo thiomorpholine-3-carboxamides.[12-14]

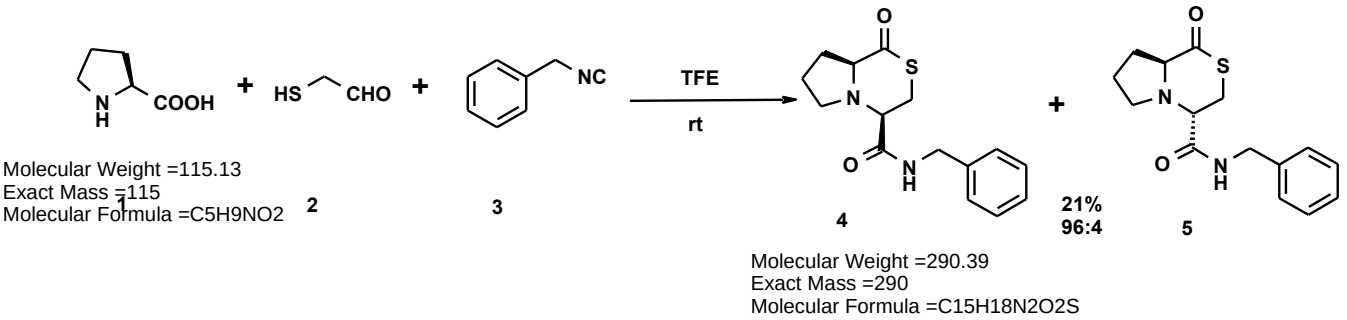
RESULTS AND DISCUSSION

The classical Ugi MCR of an isocyanide, an oxo component, an amine and an acid component yields structurally diverse scaffolds depending on the nature of the acid component, which governs the rearrangement step of the key intermediate α-adduct. The α-adduct is formed as an intermediate, comprising the highly unusual addition of the nucleophilic acid anion and the electrophilic immonium ion onto the isocyano carbon.[15] Another source of scaffold diversity in isocyanide-based MCR arises from intermolecular or intermolecular reactions with nucleophiles and the α-adduct. A very fruitful and stereoselective way to perform Ugi MCRs is using unprotected α-aminoacids, yielding several interesting scaffolds, including iminodicarboxylicacid methylester monoamide, γ-lactones, lactames, ketomorpholine and diketopiperazine.[16-23] All these reactions depend on the intermediate formation of a cyclic α-adduct and a subsequent reaction with an intra- or intermolecular nucleophile. The intermediately formed hetero carbonic acid anhydride represents a strong acylating intermediate and can react in an intermolecular (e.g. with methanol as the solvent) or intramolecular fashion (with nucleophilic side chains in one of the starting materials) and thus determines the structural fate of the formed scaffold (Scheme 2). The ratio inter- vs. intramolecular acylation can be governed by the choice of solvent. E.g. if trifluoroethanol as a non nucleophilic solvent is used the intramolecular reaction pathway is dominant.



Scheme 2. Intra- (IA) and intermolecular (IE) nucleophilic acylation reactions in order to generate scaffold diversity through isocyanide based MCRs of α-aminoacids.

Recently, we discovered the reaction of homocysteine with oxo components and isocyanides in trifluorethanol forming end-on γ-thiolactones.[24] Here we describe a related MCR transformation, in which the intramolecular nucleophile comes with the oxo component, e.g. mercaptoacetaldehyde **2**. To test this reaction hypothesis, we reacted 1 equivalent of each, mercaproacetaldehyde **2**, proline **1** and benzylisocyanide **3** in a 0.1 M solution of trifluoroethanol at rt (Scheme 3). After warming to 20 ^{o}C the initial amino acid suspension became clear and by TLC and HPLC-MS control new products were formed. Isolation of the new material by preparative silicagel chromatography and analysis by NMR revealed the formation of a new compound **4** which was in accordance with the designed thiomorpholine scaffold, e.g. the formation of a downfield signal for the thioester carbonyl carbon at ~200 ppm in the ^{13}C NMR is very indicative.[25] Luckily, a diffraction quality crystal could be grown and the corresponding X-ray structure analysis confirmed the predicted structure (Figure 2).[26]



Scheme 3 The reaction of proline **1**, mercaptoacetaldehyde **2**, and benzylisocyanide **3** in TFE yields highly specifically the syn-isomer **4**.

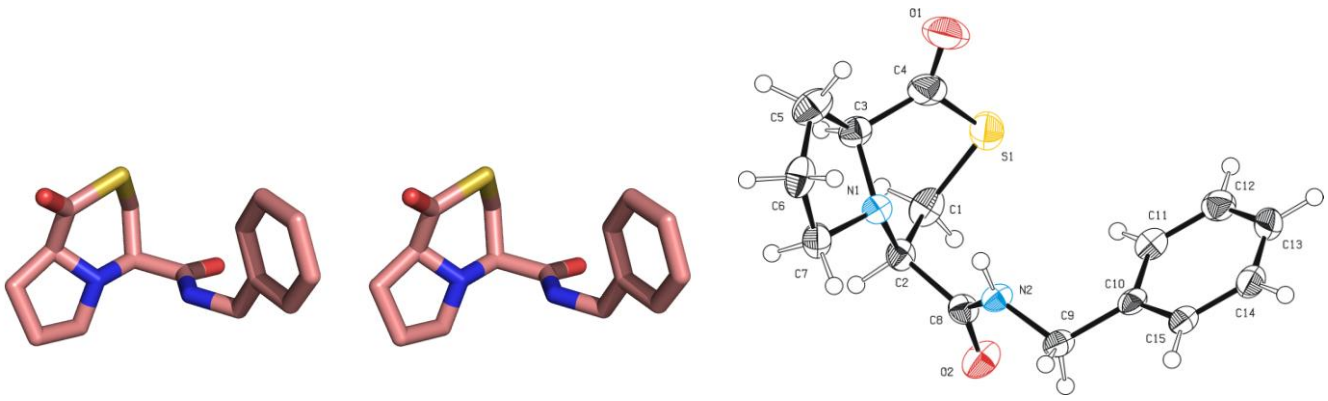
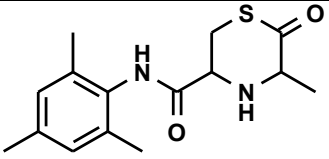
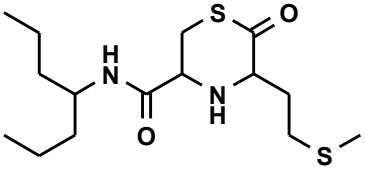
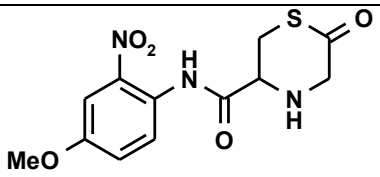
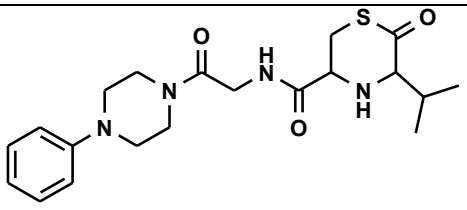
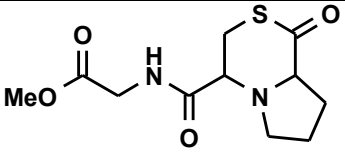


Figure 2. Left: Stereopicture of the X-ray structure of thiomorpholine **4**. The picture was generated using PyMol (www.pymol.com). Right: ORTEP plot of compound **4** with atom numbering.

Next, we performed some variations in the α-aminoacid, including methionine **9**, glycine **7**, alanine **6**, valine **10** and isocyanide component, including aromatic **6**, **7**, sterically hindered aliphatic **9**, complex ones **10**. All performed reactions yielded the expected thiomorpholines. The compounds were generally formed as a mixture of diastereomers. Cyclic amino acids, however, afforded mostly one diastereomer. The diastereomers can be easily separated by silicagel chromatography. We noted that the conversion of the reaction in no case better than 50%. Although the reaction products are formed in medium to pure isolated yields only (much higher based on conversion), the complexity of the products formed, we feel, deserves reporting (Table 1). The two thiolactone scaffolds we reported are complementary in their sterical access of the thioester moiety. Whereas, the earlier described γ-thiolactones is very accessible, the herein described δ-thiolactone is sterically hindered due to the nature of the amino acid motif and the isocyanide. Therefore one can expect differential reaction of the two scaffolds towards biological nucleophiles, which can be leveraged for the design of their biological activity.

Table 1. Structures and isolated yields of thiomorpholines prepared.

no	structure	Yield* [%] (de)	no	structure	yield [%]
6		24 (78:22)	**9**		34 (96:4)
7		16	**10**		22 (73:27)
8		68 (76:24)			

*Yields are calculated on 50% conversion

In summary, we have described a novel 3-component isocyanide-based multicomponent reaction of isocyanides, mercaptoacetaldehyde and α-amino acids yielding substituted *N*-alkyl(aryl)-6-oxo thiomorpholine-3-carboxamide. Noteworthy, the described scaffold is

unprecedented in chemical literature and is of interest with potential inherent biological activities. Current investigations in our laboratory are targeted towards the synthesis of libraries of δ-thiolactone and their biological investigation.

ACKNOWLEDGEMENT

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25. Representative procedure for 1-oxo-hexahydro-pyrrolo[2,1-*c*][1,4]thiazine-4-carboxylic acid benzylamide (**4**): Amino acid (1 mmol) was dissolved in trifluoroethanol (TFE) (10 mL) at rt. Isocyanide (1 mmol) and 2,5-dihydroxy-1,4-dithiane (0.5 mmol) were added simultaneously to it. The reaction mixture was stirred over night at rt. The solvent was evaporated and the residue was dissolved in EtOAc (10mL) and extracted with 2 x 5mL of water, and 1x 5mL of brine. The organic layer was dried over magnesium sulfate and concentrated. The crude product was purified by column chromatography on silica gel with petroleum ether/EtOAc elution gradient from 2/1 to 1/2. **4** Yield: 60 mg (41%), 57 mg of not converted amino acid could be recovered (~50% conversion) [diasteriomeric ratio by ^{1}H NMR of the crude mixture 96:4] Molecular Formula = $C_{15}H_{18}N_2O_2S$ (290.4 g/mol); Calc. Mass = 290.109; HRMS found: m/z: 291.1271 [M+H]+, 313.1153 [M+Na]$^{+}$; ^{1}H-NMR for the major diastereomer ($CDCl_3$, 600 MHz): δ 1.80-1.87 (2H, m), 1.94-2.00 (1H, m), 2.15-2.22 (1H, m), 2.59 (1H, q, J= 8.5 Hz), 3.16-3.19 (1H, m), 3.46 (1H, brd, J= 14.28 Hz), 3.56 (1H, t, J= 7.92 Hz), 3.65 (1H, dd, J= 4.52 Hz & 14.28 Hz), 3.72 (1H, d, J= 6.48 Hz), 4.50 (2H, d, J= 6.06 Hz), 7.23-7.28 (3H, m), 7.32-7.34 (2H, m), 7.54 (1H, brs); ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 22.01, 24.19, 31.64, 43.47,

53.14, 61.90, 65.45, 127.53, 128.70, 138.15, 171.47, 201.35.

26. Crystal structure analysis of compound **4**: $C_{15}H_{18}N_2O_2S$, Mr = 290.38, colorless needle (0.18 × 0.18 × 0.71 mm3), triclinic, P (No.: 2), a = 10.2106(8), b = 11.757(2), c = 13.056(2) Å, α = 102.868(13)°, β = 101.942(11)°, γ = 102.836(12)°, V = 1434.6(4) Å3, Z = 4, d_{calc} = 1.344 gcm-3, F000 = 616, μ = 0.229 mm-1, T = 153. K, Θ range of 3.03° < Θ < 25.33°. A total of 17362 reflections were integrated. After merging (R_{int} = 0.031), 5233 [3150: Io>2σ(Io)] independent reflections remained and all were used to refine 361 parameters. Full-matrix least-squares refinements converged with R1 = 0.0384 [Io>2σ(Io)], wR2 = 0.0984 [all data], GOF = 0.921, and shift/error < 0.001. For more details see Supporting Information. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-683992. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).