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Proline-like β-turn mimics accessed via Ugi reaction involving monoprotected hydrazines

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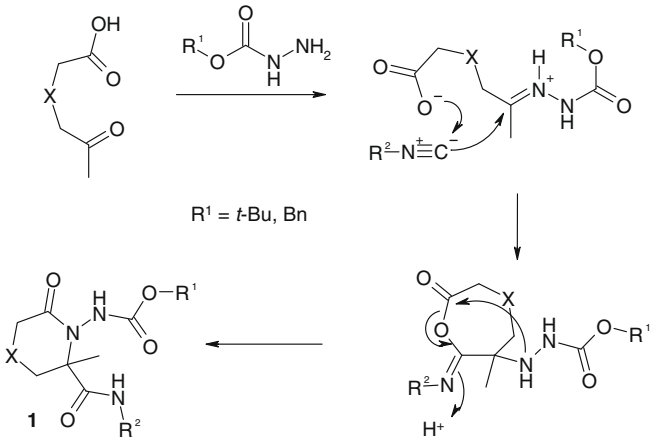
ABSTRACT

A four-center, three-component Ugi-type reaction of a variety of keto acids, Boc- or Cbz-protected hydrazine, and isocyanides offers a simple and high yielding access to cyclic products containing an *N*-aminolactam unit. The latter are shown to form consistently an intramolecular hydrogen bond leading to a β-turn-like secondary structure. The possibility of integrating such *N*-aminolactam units (without disruption of the folded structure) into pseudotripeptide fragments is demonstrated.

The successful use of keto (as well as aldehydo) carboxylic acids as bifunctional inputs for isocyanide-based multicomponent reactions (IMCR) was demonstrated by Harriman[1] and Ugi.[2] This four-center, three-component process was found to provide a simple and efficient (as well as atom-economical) entry into novel dipeptoid lactam structures. The strategy has been widely exploited to give rise to a large variety of novel small- and medium-size lactam-type heterocyclic scaffolds[3] and validated, in general, the use of bifunctional reagents in IMCR as a source of significant product diversity.[4]

Replacement of the amine component in the Ugi reaction with various surrogates has had a number of successful outcomes, as documented in the literature. For example, the use of hydrazine (as *N*-acylhydrazine, *N,N*-dialkylhydrazine, or even a symmetrical hydrazone) in IMCR was described in the earlier work of Ugi[5] and others.[6] *O*-Protected and unprotected hydroxylamines[7] were also found to be good partners for Ugi-type IMCR while *N*-benzylhydroxylamine additionally provided a reactive *N*-hydroxy group as the site for acyl migration.[8] We recently developed a modified protocol to prepare a variety of hydrazinopeptide-like units via the Ugi reaction involving *N*-acyl- and alkoxyacyl-hydrazines.[9] Besides their general appeal as hydrolytically more stable pseudopeptide 'inserts' for the development of new biologically active peptidomimetics,[10] short hydrazinopeptides are known to adopt a β-turn-like secondary structure known as a 'hydrazino turn' (due to an intramolecular bifurcated hydrogen bond involving the sp^3-hybridized nitrogen atom of the hydrazine motif).[11]

In this work, we have investigated the possibility of a new IMCR design using various aliphatic keto carboxylic acids in combination with a Boc- or Cbz-protected hydrazine as a surrogate for the



Scheme 1. A new IMCR design toward susbstituted *N*-aminolactams **1**.

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amine component, which was expected to yield substituted *N*-aminolactams **1** (Scheme 1). Such a design was primarily inspired by: (i) a successful (but low-yielding) five-center, three-component (hence ring-forming) reaction of 4-acetylbutyric acid, *N*-benzylhydroxylamine, and ethyl isocyanoacetate,[8] and (ii) a surprisingly efficient four-center, three-component reaction of substituted α-hydrazino acids with aldehydes and isocyanides reported to yield strained aza-β-lactams.[12]

In a trial experiment, equimolar amounts of levulinic acid, Boc-hydrazine, and 4-methoxybenzylisocyanide in methanol were stirred at room temperature. Although the reaction was markedly slow and proceeded to only a limited conversion over 72 h at room temperature, the expected product **1a** was isolated by chromatography in low yield (<25%). A single crystal of this compound was obtained and the X-ray crystallographic analysis not only confirmed the identity of this new type of *N*-aminolactam, but also revealed the presence of a pronounced hydrogen bond between the carbonyl oxygen atom of the Boc group and the exocyclic secondary amide side-chain (Fig. 1).[13] This feature, in our view, makes **1a** (as well as its subsequently prepared analogs) similar to proline, not only from the viewpoint of shape and chemical structure, but also in terms of its potential ability to mimic β-turns when introduced into a polypeptide chain—a secondary structure bias typically associated with proline in natural polypeptides. Prompted by this exciting finding we proceeded to optimize the reaction toward **1a**. As is evident from the results presented in Table 1, the reaction outcome was more favorable in aqueous methanol when equimolar ammonium chloride was employed as a mildly acidic promoter.[14] The reaction also required excess amounts of both the keto acid and the hydrazine in order to go to completion (with respect to isocyanide) for reasons that so far remain unclear.

Using the optimized reaction protocol we prepared analogous *N*-aminolactams **1b–v** using Boc- and Cbz-hydrazine, various isocyanides and the known or commercially available keto acids **2a**, **2b**, **2c**,[15] **2e**,[3c] and the newly synthesized **2d** (Scheme 2). The products **1** were isolated by column chromatography in good to excellent yields (Table 2) and their identity and purity was established by NMR spectroscopy, mass spectrometry, and elemental analyses (see Supplementary data).

We have also demonstrated that the synthesized *N*-aminolactams could be elaborated into useful proline-like building blocks as well as incorporated into short peptide structures. As shown in Scheme 3, compounds **1e** and **1f** were hydrolyzed by aqueous KOH in methanol into the respective 'glycine-Ψ*Pro*' carboxylic acids **3a** and **3b**, without disruption of the lactam ring or the exocyclic amide bond; likewise, the *N*-Boc group was easily removed from the *N*-terminus of the *N*-aminolactam which was then acylated with Boc-protected glycine, as illustrated by the conversion of **1g** into the 'BnNHGly-Ψ*Pro*-GlyBoc' tripeptoid **4**.

Finally, we were curious to see if the intramolecular hydrogen bonding pattern (leading to a β-turn-like secondary structure) that we initially observed by X-ray analysis for **1a** (vide supra) continued to persist in the newly synthesized compounds and, especially, in the more complex 'tripeptide' **4**. While obtaining X-ray structures for the crystalline compounds **1** could, in principle, provide an insight on how consistent is this H-bonding pattern for these compounds in the solid state, it would not determine if the same was true in solution. Fortunately, by recording ^{1}H NMR spectra of

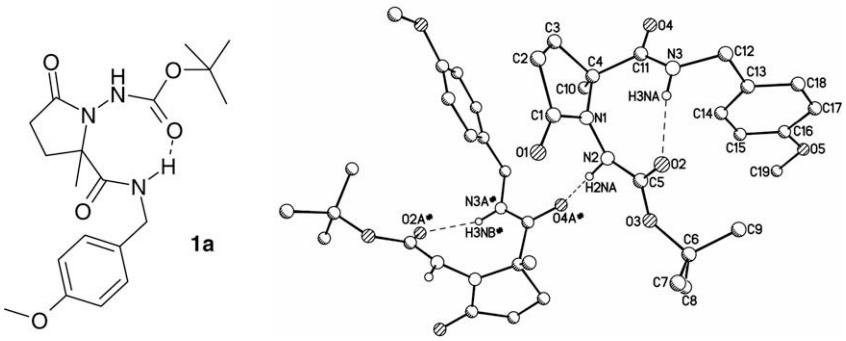
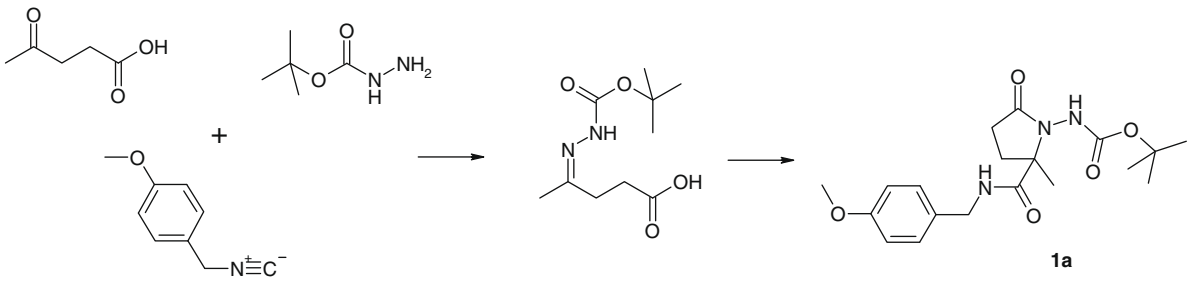
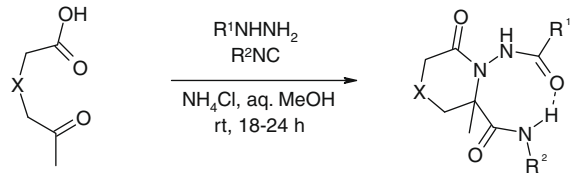


Figure 1. β-Turn-like hydrogen bonding pattern in **1a** as evidenced by X-ray analysis.

Table 1
Optimization results for model compound **1a**

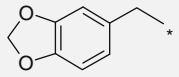
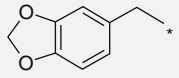
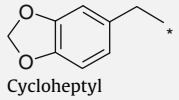


Entry	Keto acid (equiv)	$BocNHNH_2$ (equiv)	Isocyanide (equiv)	Solvent	Acid catalyst	Time (h)	Isolated yield (%)
1	1	1	1	MeOH	–	72	18
2	1	1	1	MeOH/H_2O (3:1)	NH_4Cl (1 equiv)	72	34
3	2	1	1	MeOH/H_2O (3:1)	NH_4Cl (1 equiv)	36	71
4	1	2	1	MeOH/H_2O (3:1)	NH_4Cl (1 equiv)	36	54
5	2	2	1	MeOH/H_2O (3:1)	NH_4Cl (1 equiv)	24	84



Scheme 2. Preparation of *N*-aminolactams **1a**–**v**.

Table 2
N-Aminolactams **1a**–**v** prepared in this work

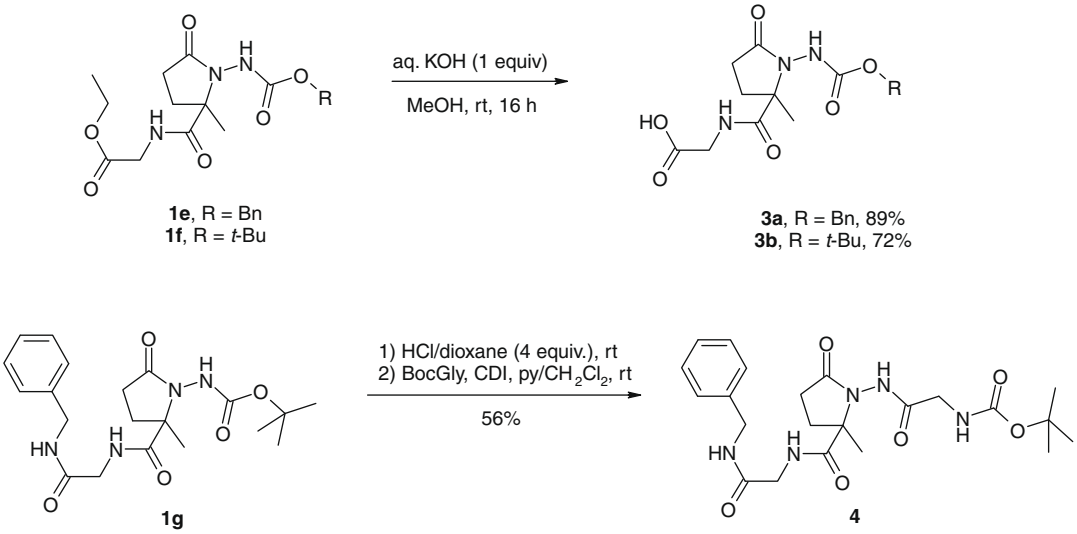
Product	X	R^1	R^2	Isolated yield (%)
1a	Direct bond	*t*-BuO	4-$MeOC_6H_4CH_2$	84
1b	Direct bond	*t*-BuO	4-$FC_6H_4CH_2$	86
1c	Direct bond	*t*-BuO	$MeOCH_2CH_2CH_2$	69
1d	Direct bond	BnO	4-$FC_6H_4CH_2$	75
1e	Direct bond	BnO	$EtOOCCH_2$	69
1f	Direct bond	*t*-BuO	$EtOOCCH_2$	65
1g	Direct bond	*t*-BuO	$PhCH_2NHCOCH_2$	71
1h	Direct bond	*t*-BuO	*t*-Bu	92
1i	Direct bond	*t*-BuO		77
1j	Direct bond	*t*-BuO	Cycloheptyl	67
1k	CH_2	*t*-BuO	4-$FC_6H_4CH_2$	91
1l	CH_2	*t*-BuO		92
1m	CH_2	*t*-BuO	Cycloheptyl	76
1n	CH_2	*t*-BuO	*t*-Bu	89
1o	S	*t*-BuO	4-$FC_6H_4CH_2$	73
1p	S	*t*-BuO		79
1q	S	*t*-BuO	Cycloheptyl	67
1r	S	*t*-BuO	*t*-Bu	94
1s	O	*t*-BuO	4-$FC_6H_4CH_2$	84
1t	O	*t*-BuO	Cycloheptyl	68
1u	$MeSO_2N$	*t*-BuO	Cycloheptyl	72
1v	$MeSO_2N$	*t*-BuO	4-$FC_6H_4CH_2$	78

the compounds in chloroform-*d* and in DMSO-d_6 and observing the resulting changes in the chemical shift of the protons 'suspected' of participation in intramolecular hydrogen bonding versus those protons that do not, it was possible to ascertain the existence of intramolecular hydrogen bonds in solution.[16] Indeed, DMSO-d_6 as a solvent capable of hydrogen bonding with the solute, led to a downfield shift (compared to $CDCl_3$) of both heteroatom-bound protons in model compound **5** where no intramolecular H-bond is possible. However, in the 'tripeptide' **4**, a similar downfield shift was not observed for the amide proton proximal to the lactam ring, which is consistent with the expected intramolecular hydrogen bonding. Likewise, for selected *N*-aminolactams **1a**, **1b**, **1k**, **1l**, **1s,** and **1v**, the same amide proton appears almost insensitive to the solvent change, which also confirms its intramolecular H-bonded character (Table 3).

In conclusion, we have developed an efficient method to prepare a novel racemic proline-like *N*-aminolactams **1** which exist in a folded, β-turn-like conformation, both in solid state and in solution, as demonstrated by X-ray and ^{1}H NMR analyses. These structures can be elaborated into 'dipeptide' acid building blocks and incorporated into a 'tripeptide' structure and thus holds potential as key elements for the design of mimetic analogs of bioactive peptides. Efforts are currently underway in our laboratories to prepare non-racemic versions of these useful structural motifs. The results of these studies will be reported in due course.

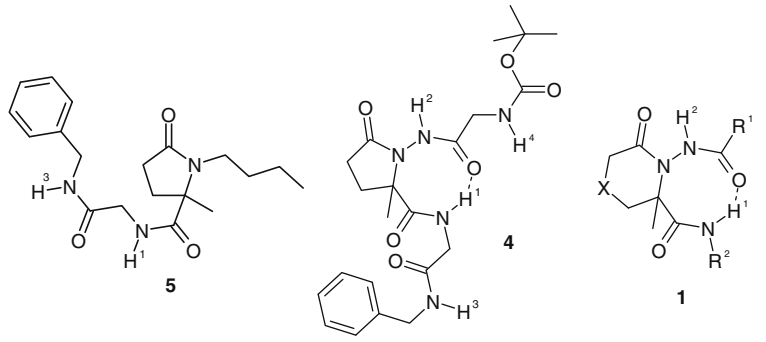
Typical procedure: Synthesis of N-aminolactams **1**: The syntheses reported herein have been performed on 1–3 mmol scale. Equimolar amounts of keto acid **2** and monoprotected hydrazine were dissolved in MeOH (6 mL). Solid NH_4Cl (0.5 equiv) was added followed by water (2 mL). Once a clear solution had formed, the isocyanide (0.5 equiv) was added and the reaction mixture was stirred under an argon atmosphere at rt for 18–24 h. It was then partitioned between EtOAc (25 mL) and H_2O (25 mL). The organic layer was separated and the aqueous layer was back-extracted with an equal volume of EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The *N*-aminolactams **1** were isolated by chromatography (SiO_2) using EtOAc–hexane mixtures as eluents.

Compound ***1a***: White solid, mp = 189–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.07 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 4.36 (dd, J = 14.4, 6.1 Hz, 1H), 4.21 (dd, J = 14.0, 4.5 Hz, 1H), 3.73 (s, 3H), 2.22–2.43 (m, 3H), 1.93–2.04 (m, 1H), 1.48 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$)



Scheme 3. Preparation of the N-protected 'dipeptides' **3a**,**b,** and the protected 'tripeptide' **4**.

Table 3
Downfield shift (Δ, ppm) of various N–H signals in ^{1}H NMR spectra on changing the solvent from chloroform-*d* to DMSO-d_6



Compound	Δ (H^1)	Δ (H^2)	Δ (H^3)	Δ (H^4)
1a	0.2	1.7	—	—
1b	0.1	2.2	—	—
1k	0.0	1.9	—	—
1l	0.1	2.0	—	—
1s	0.2	2.0	—	—
1v	0.0	2.0	—	—
4	0.0	0.9	(Broad)	1.1
5	1.1	—	1.1	—

δ 174.0, 172.8, 158.6, 156.7, 130.3, 128.9, 113.7, 82.6, 67.1, 55.1, 42.8, 31.6, 27.8, 26.8, 21.6. LC–MS (M+H) *m/z* = 378. Anal. Calcd for $C_{19}H_{27}N_3O_5$: C, 60.46; H, 7.21; N, 11.13. Found: C, 60.53; H, 7.28; N, 11.15.

Acknowledgments

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Supplementary data

Characterization data and preparative procedures for the newly synthesized compounds (**1a**–**v**, **2d**, **3a**–**b**, **4** and **5**) and X-ray crystallographic file (CIF) for compound **1a** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.141.

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