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Cyclic products of the Ugi reaction of aldehydo and keto carboxylic acids: chemoselective modification

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ABSTRACT

A method for the chemoselective reduction of Ugi-type lactam amides at the lactam carbonyl functionality with borane complexes has been developed. The novel reduction products can be further manipulated synthetically to yield various novel N- and C-terminally active unnatural amino acid building blocks.

1. Introduction

Replacement of two participants in the Ugi four-component reaction with a single bifunctional reagent has proved itself a fruitful strategy towards various drug-like heterocycles.[1] Specifically, various tethered keto (or aldehydo) carboxylic acids, when employed in the Ugi process, provide a facile (and high-yielding) entry into diverse lactam amides (Fig. 1). Since the initial publications describing this methodology by Harriman[2] and Ugi[3] in the late 1990s, a significant number of these peptidomimetic scaffolds have appeared in the literature. This, in turn, resulted in extensive investigations on the associated biological activities which have yielded promising leads for modulation of important biological targets such as androgen receptors[4] and γ-secretase.[5]

We have been involved in identifying opportunities for chemoselective modification of these intriguing drug-like scaffolds, in pursuit of a dual goal: (i) improving the physicochemical properties of lactam amides (specifically, their aqueous solubility) and (ii) preparing functionalized peptidomimetic building blocks based on these scaffolds which are useful in designing yet more novel compound libraries for biological screening. Herein, we report several examples of efficient, chemoselective reduction of such lactam amides and further transformation of the resulting cyclic tertiary amines into N- and C-terminally active unnatural amino acid building blocks.

2. Results and discussion

A set of 22 3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamides **1a**–**x** (Scheme 1) was prepared in good to excellent yields from the known 2-(2-formylphenoxy)acetic acid[6] using various amines and two isocyanides as described earlier.[7] Inspired by the successful application of borane complexes for reduction of linear Ugi reaction derived diamides, as recently disclosed by Tron,[8] we exposed lactam amides **1a**–**x** to an excess of borane–dimethyl sulfide complex in THF at room temperature (Scheme 1). To our delight, in all cases, this led to a clean and complete reduction of the lactam function only, with no trace of secondary amide reduc-

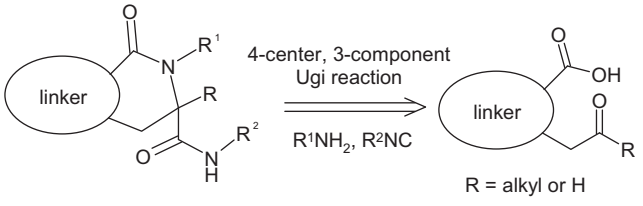

Figure 1. Cyclic lactam amides resulting from the Ugi reaction of bifunctional keto (aldehydo) carboxylic acids.

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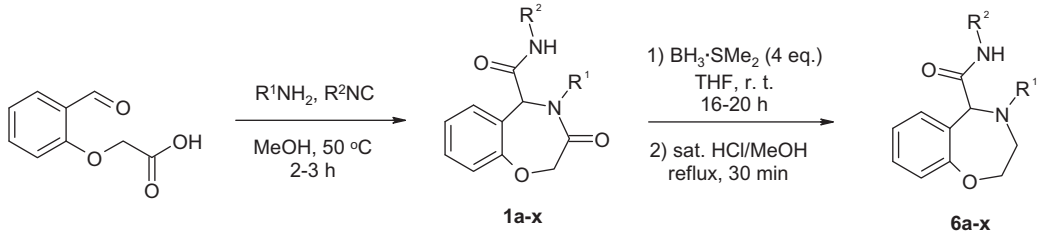
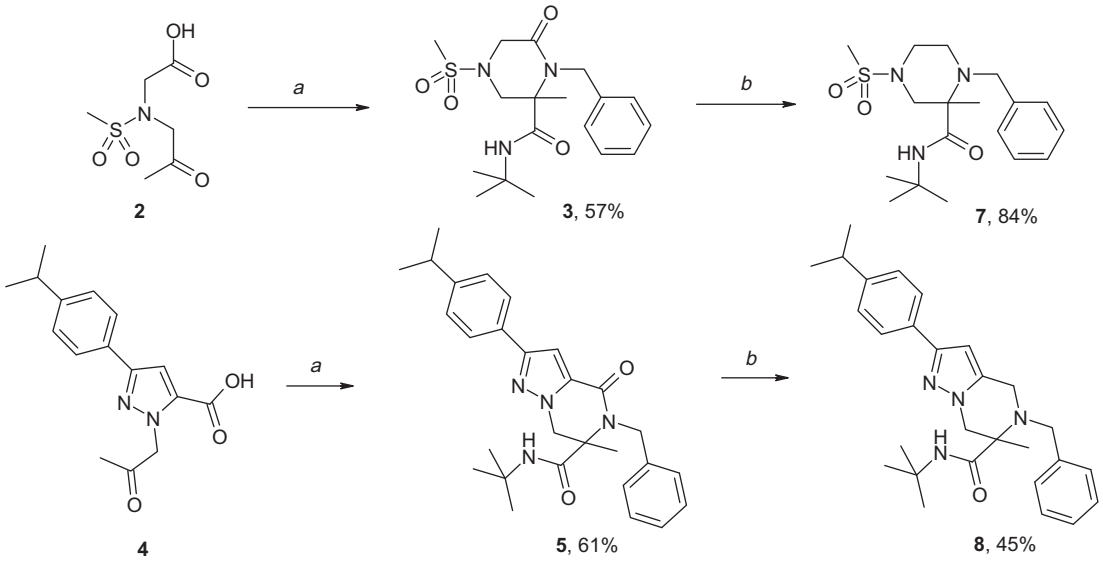
tion, even on prolonged (3 days) treatment at room temperature (heating of selected reaction mixtures to reflux ultimately led to the accumulation of the double-reduction material, however, this was never characterized due to difficulties in its isolation). The stable tertiary amine–borane complex immediately resulting from such reductions was destroyed by briefly refluxing the crude reac-



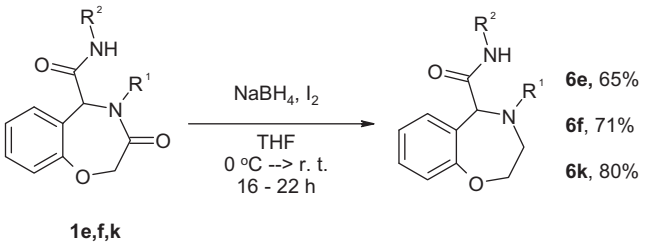
Scheme 1. Ugi reaction of 2-(2-formylphenoxy)acetic acid and chemoselective reduction of the resulting lactam amides **1a–x**.

Table 1
Preparation and chemoselective reduction of the lactam amides **1a–x** (Scheme 1)

Entry	R^1	R^2	Yield of **1** (%)	LC–MS $[M+H^+]$ *m*/*z*	Yield of **6** (%)	LC–MS $[M+H^+]$ *m*/*z*
1(6)a	*n*-Pr	*t*-Bu	60	305.6	78	291.4
1(6)b	*i*-Pr	*t*-Bu	64	305.7	50	291.3
1(6)c	*i*-Bu	*t*-Bu	51	319.7	53	305.7
1(6)d	$EtO(CH_2)_3$	*t*-Bu	68	349.2	56	335.6
1(6)e	Cyclopropyl	*t*-Bu	86	303.5	81	289.5
1(6)f	Cyclopentyl	*t*-Bu	74	331.4	74	317.2
1(6)g	Cycloheptyl	*t*-Bu	66	359.8	63	345.8
1(6)h	$Ph(CH_2)_2$	*t*-Bu	46	367.1	57	353.7
1(6)i	4-$MeC_6H_4(CH_2)_2$	*t*-Bu	54	381.6	63	367.7
1(6)j	3,4-$(MeO)_2C_6H_3(CH_2)_2$	*t*-Bu	56	427.5	70	413.2
1(6)k	Bn	*t*-Bu	72	353.5	82	339.5
1(6)l	4-$ClC_6H_4CH_2$	*t*-Bu	66	387.5	51	373.8
1(6)m	*n*-Pr	4-$CF_3C_6H_4CH_2$	67	407.5	71	393.6
1(6)n	*i*-Pr	4-$CF_3C_6H_4CH_2$	52	407.5	89	393.3
1(6)o	*i*-Bu	4-$CF_3C_6H_4CH_2$	43	420.6	93	407.6
1(6)p	$EtO(CH_2)_3$	4-$CF_3C_6H_4CH_2$	74	451.3	65	437.6
1(6)q	Cyclopropyl	4-$CF_3C_6H_4CH_2$	86	405.6	94	391.5
1(6)r	Cyclopentyl	4-$CF_3C_6H_4CH_2$	58	433.3	67	419.5
1(6)s	Cycloheptyl	4-$CF_3C_6H_4CH_2$	74	461.7	54	447.7
1(6)t	$Ph(CH_2)_2$	4-$CF_3C_6H_4CH_2$	69	469.4	67	455.6
1(6)u	4-$MeC_6H_4(CH_2)_2$	4-$CF_3C_6H_4CH_2$	55	483.5	65	469.6
1(6)v	3,4-$(MeO)_2C_6H_3(CH_2)_2$	4-$CF_3C_6H_4CH_2$	82	529.5	75	515.4
1(6)w	Bn	4-$CF_3C_6H_4CH_2$	79	455.6	56	441.7
1(6)x	4-$ClC_6H_4CH_2$	4-$CF_3C_6H_4CH_2$	47	489.6	71	475.9



Scheme 2. Preparation and chemoselective reduction of lactam amides **3** and **5**. Reagents and conditions: (a) *t*-BuNC (1.2 equiv), $BnNH_2$ (1.0 equiv), MeOH, 50 °C, 3 h; (b) $BH_3{\cdot}SMe_2$ (4.0 equiv), THF, rt, 18 h; satd MeOH–HCl, reflux, 30 min.

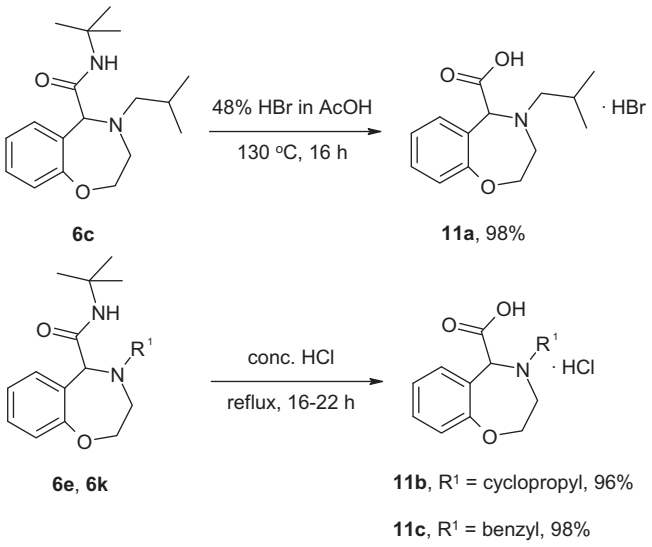


Scheme 3. Chemoselective reduction of selected lactam amides **1** using the $NaBH_4$–I_2 protocol.

tion mixture in saturated methanolic HCl. The product 2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamides **6a**–**x** were isolated chromatographically in good to excellent yields (Table 1). A notable feature of these hitherto unknown compounds **6** is that they are close shape mimics of the peptidomimetic lactam amides **1** containing a basic nitrogen. Hence, they are expected to have better aqueous solubility and the basic centre can be utilized for the preparation of various salts (including diastereomeric salts for enantiomer resolution)—both features having much appeal for the development of drug candidates based on this novel scaffold. Moreover, the utility of this chemoselective lactam reduction procedure can be extended to other lactam amides (**3** and **5**), also prepared via the Ugi reaction of the keto acids **2** and **4**, respectively. The yield from the reduction of aromatic lactam **5** was low (45%) while the aliphatic lactam **3** was reduced in an excellent 84% yield (Scheme 2).

The nature of the borane reducing agent seems unimportant for the outcome of the lactam reduction. For example, the borane–THF complex generated in situ from sodium borohydride and iodine[9] reduced selected lactams **1** in yields similar to those obtained using the $BH_3{\cdot}SMe_2$ procedure (Scheme 3).

Compounds **6** are, essentially, amides of unnatural α-amino acids. We were successful in removing a benzyl group from the compounds **6k** and **6w** (with remarkable chemoselectivity with respect to the second benzyl group in the latter case) and exposing the secondary nitrogen atom in the resulting products **9a**,**b** to further modifications (for example, efficient reductive alkylation with aldehydes or ketones, Scheme 4). Likewise, selected *tert*-butyl amides **6c** and **6e**(**6k**), when treated with strong Brønsted acids at reflux, furnished nearly quantitative yields of the novel cyclic α-amino acids **11a**–**c**, without disruption of the tetrahydro-1,4-benzoxazepine ring (Scheme 5).



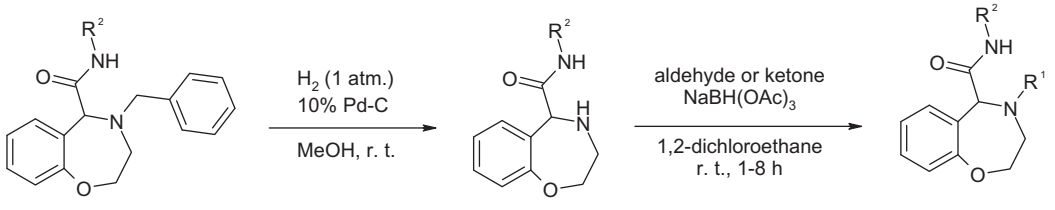
Scheme 5. *tert*-Butyl amide hydrolysis.

In summary, we have described some new evolutionary directions for Ugi reaction derived lactam amides to be developed into novel, drug-like heterocyclic scaffolds and unnatural amino acid building blocks.

3. General procedure 1: synthesis of lactam amides 1 (3 or 5)

The aldehydo or keto carboxylic acid (1.0 equiv) and primary amine (1.0 equiv) were dissolved in MeOH. The solution was stirred at rt for 10 min. The appropriate isocyanide (1.2 equiv) was added and the resulting mixture was stirred at 50 °C for 2–3 h. On completion, the reaction mixture was cooled to rt, and the resulting precipitate was filtered, washed with MeOH, and purified by crystallization from Et_2O by chromatography on silica gel, using an appropriate gradient of MeOH in CH_2Cl_2 as eluent.

Compound **1a**: white solid, mp = 130–132 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.07–7.05 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 5.09 (d, J = 14.4 Hz, 1H), 4.99 (s, 1H), 4.19 (d, J = 14.4 Hz, 1H), 3.57 (m, 1H), 3.15–3.11 (m, 1H), 1.55–1.52 (m, 2H), 1.23 (s, 9H), 0.81 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 168.1, 156.4, 130.3, 129.2, 127.5, 122.8, 119.9,



10a, R^2 = *t*-Bu, R^1 = 4-$FC_6H_4CH_2$, 74%

10b, R^2 = *t*-Bu, R^1 = 1-acetylpiperidin-4-yl, 55%

10c, R^2 = *t*-Bu, R^1 = 1-Boc-piperidin-4-yl, 53%

10d, R^2 = 4-$CF_3C_6H_4CH_2$, R^1 = 4-$FC_6H_4CH_2$, 66%

6b, R^2 = *t*-Bu, R^1 = *i*-Pr, 69%

6n, R^2 = 4-$CF_3C_6H_4CH_2$, R^1 = *i*-Pr, 78%

Scheme 4. N-Debenzylation of compounds **6k** and **6w**, and reductive alkylation of the resulting amines.

72.4, 63.9, 50.6, 49.9, 28.1, 20.5, 11.0. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.14; H, 8.01; N, 9.23.

4. General procedure 2: reduction of lactam amides 1 (3 or 5)

A solution of **1** (**3** or **5**) (1 mmol) in anhydrous THF (3 mL) was treated with $BH_3{\cdot}SMe_2$ in THF (2 M solution, 2 mL, 4 mmol). This mixture was stirred overnight at rt after which the solvent was evaporated and the residue was dissolved in satd MeOH–HCl. The solution was heated at reflux for 30 min and after cooling to rt, was neutralized with 10% aq K_2CO_3, and the resulting neutral solution was extracted with CH_2Cl_2 (3×50 mL). The combined organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, CH_2Cl_2).

Compound **6a**: waxy-beige solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.24–7.17 (m, 2H), 7.03 (t, J = 10.0 Hz, 1H), 6.97 (d, J = 10.8 Hz, 1H), 4.27 (s, 1H), 4.09–3.98 (m, 2H), 3.12–3.04 (m, 1H), 2.90–2.82 (m, 1H), 2.48 (t, J = 8.0 Hz, 2H), 1.52 (m, 2H), 1.37 (s, 9H), 0.92 (t, J = 9.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 155.8, 130.8, 128.7, 123.1, 120.7, 70.0, 67.4, 54.9, 50.1, 49.6, 28.2, 20.4, 11.2. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.28; H, 8.92; N, 9.55.

Acknowledgements

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Supplementary data

Characterization data and preparative procedures for the newly synthesized compounds (**1a–x**, **6a–x**, **3**, **5**, **7**, **8**, **9a–b**, **10a–d**, **11a–c**) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.028.

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