Convenient preparation of diastereomerically pure, diversely substituted piperazine-2,5-diones from *N*-protected α -amino acids

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Abstract: Products of the Ugi reaction involving *N*-Boc- α -amino acids and *t*-BuNC, after deprotection, undergo efficient microwave-assisted cyclization in acetic acid to give, unexpectedly, diastereomerically pure, racemic piperazine-2,5-dione. The formation of a single diastereomer has been rationalized by enolization equilibrium in acetic acid at high temperatures that enriches the products mixture in only one, more stable diastereomer. The relative stereochemistry of the latter was confirmed by NOESY experiments and is consistent with Molecular Mechanics calculations.

Key words: isocyanide-based multi-component reactions, post-Ugi modifications, diastereomeric enrichment, microwave-assisted synthesis, combinatorial chemistry

Strategic incorporation of potentially reactive functionalities into the structure of any two components of the Ugi multicomponent reaction (U-MCR) provides dipeptoid templates that can undergo further complexity-generating transformations. Such premeditated post-U-

MCR processes have served¹ as a rich source of diverse heterocyclic compounds that would otherwise be inaccessible or require tedious synthetic elaboration by alternative synthetic strategies.

Recently, we have described post-U-MCR cyclization of the Ugi reaction products containing residues of a pyrazole-3-carboxylic acid² and an indole-2-carboxylic acid,³ under microwave irradiation in glacial acetic acid. In this process, *t*-BuNC manifested itself as a convertible isocyanide in the preceding Ugi reaction as the resulting terminal *tert*-butyl amide was converted, intramolecularly, into *N*-acyl azole moiety (Scheme 1). Clearly, *t*-BuNC appears as an attractive, low-cost alternative to other convertible isocyanides described in the literature.⁴ This consideration prompted us to investigate cyclizations of Ugi reaction-derived *tert*-butyl amides onto other nitrogen nucleophiles under similar conditions.

Scheme 1. Examples of microwave-assisted cyclization in AcOH of Ugi reaction-derived *tert*-butyl amides containing (a) pyrazole² and (b) indole³ moieties.

An opportunity for such a cyclization exists, for example, if *N*-Boc- α -amino acids are used in combination with *t*-BuNC to construct dipeptoid products via U-MCR. Indeed, in the course of our investigation, a report from Hulme's group appeared in the literature⁵ on microwave-assisted cyclization (following deprotection) of U-MCR products derived from *N*-Boc- α -amino acids and *n*-BuNC. The methodology afforded good yields of the respective piperazine-2,5-diones over the U-MCR and the cyclization steps. Notably, the products resulting from chiral *N*-Boc- α -amino acids were obtained as 1:1 mixture of diastereomers (Scheme 2). Herein, we would

like to report on preparation of diastereomerically pure piperazine-2,5-diones via a similar microwave-assisted protocol involving cyclization onto *tert*-butyl amide in glacial acetic acid.

A set of 12 dipeptoids **2a-l** was prepared by Ugi reaction with *t*-BuNC, aldehydes and amines. In all cases the crude products were at least 80% pure by LC MS analysis.⁶ Without further purification, we attempted microwave-assisted cyclization of **2** in glacial acetic acid. Disappointingly, these conditions provided insufficient acidic medium for an efficient Boc group removal and most of the compounds **2**, along with minor unidentified

Scheme 2. *In situ* deprotection and microwave-assisted cyclization of products of Ugi reaction involving natural amino acid components described by Hulme.⁵

Scheme 3. Products of Ugi reaction between *N*-Boc-protected amino acids **1**, *tert*-butyl isocyanide, an aldehyde and an amine: deprotection and microwave-assisted cyclization in AcOH.

impurities, were recovered after heating their solutions in acetic acid at 180 °C for 90 min. Prolonged heating (up to 3 h) or higher temperatures (200–220 °C) only resulted in accumulation of more impurities. Therefore it was decided to perform deprotection of the products **2** prior to submitting them to the microwave-assisted cyclization step. To our delight, the respective free-base deprotected products underwent clean cyclization into the target piperazine-2,5-diones **3** (Scheme 3). Quite surprisingly,

in the crude ¹H NMR spectrum of the product mixtures, only one set of signals corresponding to **3** was identified in all cases, thereby confirming the formation of only one of the two possible diastereomers. Analytically (and, indeed, diastereomerically) pure compounds **3a–l** were obtained either chromatographically or by crystallization in rather uniform yields over 3 chemical operations (Table 1).

Scheme 4. Possible enolization equilibrium in AcOH at 180 °C leading to the formation of a single diastereomer of piperazine-2,5-diones **3**.

The observed formation of a single diastereomer of the compounds **3a–l** can be rationalized by an efficient enolization of the initially formed diastereomeric mixture in glacial acetic acid on prolonged heating and its

equilibration via enol form **4** (an possibly also **5**) into a single, more stable diastereomer (Scheme 4). Indeed, when the

Table 1. U-MCR templates **2** and products of their cyclization **3** investigated in this work.

Entry	1	R ³	R ⁴	LC MS (2), <i>m/z</i> [M+H ⁺]	Isolated yield (3), %
2(3)a				462.5	46 ^a
2(3)b				488.6	42 ^a
2(3)c				538.4	50 ^a
2(3)d				476.7	44 ^a
2(3)e				502.2	50 ^a
2(3)f				544.4	41 ^a
2(3)g				580.3	43 ^a
2(3)h				498.7	45 ^b
2(3)i				560.6	52 ^b
2(3)j				526.3	41 ^b
2(3)k				540.5	45 ^b
2(3)l				540.3	39 ^b

^a Yield after chromatography.^b Yield after crystallization.

microwave-assisted cyclization was stopped in 10 min, signals corresponding to two diastereomers of **3** were observed in the complex ¹H NMR spectrum of the reaction mixture (while the conversion was still <10%). It was noted that the piperazine-2,5-dione products derived from optically pure amino acids (**3a**, **3b**, **3h**, **3j–3l**) are not optically active. We tracked the optical rotation en route to **3h** and established that, indeed, the latter was not optically active (Scheme 5). This appears consistent with the proposed enolization equilibrium.

Trans-stereochemistry of the products **3a–l** was established based on their NOESY spectra (Figure 1). Inter-

estingly, when energies of the MM2-minimized⁷ conformations of *cis*- and *trans*-**3** were compared, no significant difference was noted in the majority of cases (likely, due to the piperazine-2,5-dione cycle being nearly flat). In some cases (**3a**, **3b**, **3g**, **3i**), however, the calculated energy preference toward *cis*-isomer was >20 kcal/mol, which also is consistent with the implicated equilibration of the diastereomeric mixture into a single, *cis*-isomer.

In conclusion, we have developed a convenient protocol toward preparation of diastereomerically pure *cis*-

piperazine-2,5-diones **3** via Ugi reaction with *N*-Boc- α -amino acids and *t*-BuNC, deprotection and microwave-

Scheme 5. Optical rotation loss observed in preparation of **3h**.

assisted cyclization. This methodology extends the utility of *t*-BuNC as a convertible isocyanide useful for the design of Ugi reactions products intended for post-Ugi cyclizations, specifically, under microwave irradiation in acetic acid.

Figure 1. Exemplary relative stereochemistries of **3** assigned based on through-space interactions observed in the NOESY spectrum.

All reactions were run in oven-dried glassware in atmosphere of nitrogen. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Analytical thin-layer chromatography was carried out on EM Separations Technology F₂₅₄ silica gel plates. Compounds were visualized with short-wavelength UV light. ¹H NMR and ¹³C NMR spectra were recorded on Bruker DPX-300 spectrometers in DMSO-*d*₆ using TMS as an internal standard. LCMS analyses were obtained on a PE SCIEX API 150EX mass spectrometer following separation on a Shimadzu LC-10AD liquid chromatography system equipped with Shimadzu SP D-10A UV-Vis detector (254 nm) and Sedex 75 ELSD detector. Elemental analyses were obtained at Research Institute for Chemical Crop Protection (Moscow, Russia) using Carlo Erba Strumentazione 1106 analyzer. All solvents and reagents were obtained from commercial sources and used without purification.

Typical procedure: Synthesis of piperazine-2,5-diones **3**.

The syntheses reported herein have been performed on 10 mmol scale. Equimolar amounts of an aldehyde and an amine were combined in methanol (20 mL) and heated at 60 °C under stirring for 10 min. *N*-Boc- α -amino acid (1 equiv) and *t*-BuNC (1 equiv) were added and the stirring continued at 60 °C for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in 3M HCl in dioxane (20 mL). After stirring at rt for 10 h, the volatiles were removed *in vacuo* and the residues was partitioned between DCM (20 mL) and 10% aq. NaHCO₃ (20 mL). The organic layer was separated, dried over anhydrous sodium sulfate, dried, filtered and concentrated. The residue was dissolved in glacial acetic acid (5 mL), the solution was placed in a microwave reactor tube and heated at 180 °C for 90 min using a Biotage InitiatorTM microwave synthesizer operating at 100W. Upon cooling, the solvent was removed *in vacuo* (using GeneVac[®] equipment) and the residue again subjected to basic aqueous workup (*vide supra*). The crude product was purified by column chromatography on silica (eluent: 10→40% DCM in hexanes) or by crystallization (*i*-PrOH) to afford analytically pure piperazine-2,5-diones **3**.

(±)-(3*R*,8*aS*)-2-(2-methoxyethyl)-3-phenylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**3a**):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 46%.

White solid, mp = 119–121 °C.

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.28–7.46 (m, 5H), 5.18 (s, 1H), 4.16 (t, *J* = 7.9 Hz, 1H), 3.89 (dt, *J*_d = 14.0 Hz, *J*_t = 5.2 Hz, 1H), 3.36–3.63 (m, 3H), 3.22–3.33 (m, 1H), 3.19 (s, 3H), 3.04–3.16 (m, 1H), 2.19 (m, 1H), 1.71–2.04 (m, 3H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 167.4, 163.2, 135.5, 128.9, 128.1, 126.0, 69.4, 66.1, 57.9, 57.6, 45.2, 43.9, 29.0, 21.7.

LC MS (M+H⁺) *m/z* 289.

Anal. calcd for C₁₆H₂₀N₂O₃: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.73; H, 7.07; N, 9.77.

(±)-(3*R*,8*aS*)-3-phenyl-2-(tetrahydrofuran-2-ylmethyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (3b):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 42%.

White solid, mp = 133-135 °C.

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.28-7.46 (m, 5H), 5.30 (d, *J* = 11.5 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 1H), 3.90-4.06 (m, 2H), 3.49-3.81 (m, 3H), 3.22-3.34 (m, 1H), 2.63-2.76 (m, 1H), 2.19-2.34 (m, 1H), 1.69-2.04 (m, 6H), 1.37-1.53 (m, 1H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 167.4, 163.2, 135.3, 128.9, 128.2, 126.0, 77.5, 67.3, 66.3, 57.5, 48.4, 45.2, 29.1, 28.8, 24.7, 21.7.

LC MS (M+H⁺) *m/z* 315.

Anal. calcd for C₁₈H₂₂N₂O₃: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.69; H, 6.98; N, 8.83.

(±)-(3*R*,9*aS*)-2-(4-methoxybenzyl)-3-phenyltetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-(3*H*,6*H*)-dione (3c):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 50%.

White solid, mp = 168 °C (decomp.).

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.20-7.45 (m, 5H), 7.07 and 6.87 (ABq, *J* = 7.3 Hz, 4H), 5.07 (d, *J* = 14.5 Hz, 1H), 4.78 (s, 1H), 4.16-4.38 (m, 2H), 3.75 (s, 3H), 3.49 (d, *J* = 14.4 Hz, 1H), 2.52-2.63 (m, 1H), 2.29-2.45 (m, 1H), 1.81-1.96 (m, 1H), 1.25-1.74 (m, 4H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 165.7, 162.7, 158.7, 137.4, 129.5, 129.2, 128.9, 128.4, 127.7, 127.4, 127.2, 114.0, 62.3, 56.9, 55.0, 45.8, 41.7, 31.5, 23.9, 23.4.

LC MS (M+H⁺) *m/z* 365.

Anal. calcd for C₂₂H₂₄N₂O₃: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.60; H, 6.71; N, 7.75.

(±)-(3*R*,9*aS*)-2-(2-methoxyethyl)-3-phenyltetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-(3*H*,6*H*)-dione (3d):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 44%.

White solid, mp = 139-141 °C.

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.26-7.45 (m, 5H), 5.11 (s, 1H), 4.36 (dt, *J*_d = 13.2 Hz, *J*_t = 2.0 Hz, 1H), 4.13 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.86 (dt, *J*_d = 14.0 Hz, *J*_t = 5.5 Hz, 1H), 3.41-3.52 (m, 1H), 3.30-3.40 (m, 1H), 3.21 (s, 3H), 2.70-2.82 (m, 1H), 2.53-2.63 (m, 1H), 2.28-2.41 (m, 1H), 1.83-1.96 (m, 1H), 1.63-1.74 (m, 1H), 1.26-1.63 (m, 3H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 165.6, 162.9, 138.0, 128.7, 128.3, 127.4, 68.9, 63.8, 58.0, 56.7, 43.1, 41.6, 31.3, 23.9, 23.4.

LC MS (M+H⁺) *m/z* 303.

Anal. calcd for C₁₇H₂₂N₂O₃: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.58; H, 7.43; N, 9.32.

(±)-(3*S*,9*aR*)-3-phenyl-2-(tetrahydrofuran-2-ylmethyl)tetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-(3*H*,6*H*)-dione (3e):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 50%.

White solid, mp = 149-150 °C.

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.23-7.46 (m, 5H), 5.20 (d, *J* = 22.1 Hz, 1H), 4.29-4.41 (m, 1H), 4.08-4.19 (m, 1H), 3.86-4.06 (m, 2H), 3.55-3.81 (m, 2H), 2.53-2.65 (m, 1H), 2.30-2.43 (m, 1H), 1.25-2.02 (m, 10H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 166.4, 165.5, 163.0, 137.9, 128.8, 128.3, 127.4, 77.3, 75.5, 67.3, 67.0, 64.1, 63.6, 56.9, 56.6, 47.4, 45.6, 41.5, 31.7, 31.3, 28.8, 28.0, 25.3, 24.7, 23.9, 23.4.

LC MS (M+H⁺) *m/z* 329.

Anal. calcd for C₁₉H₂₄N₂O₃: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.53; H, 7.42; N, 8.62.

(±)-(3*S*,9*aR*)-3-(4-isopropylphenyl)-2-(tetrahydrofuran-2-ylmethyl)tetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-(3*H*,6*H*)-dione (3f):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 41%.

White solid, mp = 159 °C (decomp.).

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.14-7.31 (m, 4H), 5.16 (d, *J* = 21.5 Hz, 1H), 4.29-4.41 (m, 1H), 3.85-4.16 (m, 3H), 3.54-3.81 (m, 2H), 2.85-2.94 (m, 1H), 2.53-2.66 (m, 1H), 2.29-2.44 (m, 1H), 1.32-2.05 (m, 10H), 1.22 (d, *J* = 6.9 Hz, 6H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 166.4, 165.5, 163.1, 148.5, 135.2, 127.3, 126.7, 77.3, 75.6, 67.3, 67.0, 63.8, 63.3, 56.8, 56.5, 47.4, 45.5, 41.5, 33.0, 31.8, 31.3, 28.7, 27.9, 25.3, 24.7, 23.9, 23.7, 23.4.

LC MS (M+H⁺) *m/z* 371.

Anal. calcd for C₂₂H₃₀N₂O₃: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.44; H, 8.26; N, 7.61.

(±)-(3*S*,9*aR*)-3-(4-isopropylphenyl)-2-(4-methoxybenzyl)tetrahydro-2*H*-pyrido[1,2-*a*]pyrazine-1,4-(3*H*,6*H*)-dione (3g):

Yield after chromatography (silica gel, 10→40% DCM in hexanes) - 43%.

White solid, mp = 173 °C (decomp.).

¹H NMR (*d*₆-DMSO, 300 MHz) δ 7.18 and 7.26 (ABq, *J* = 8.0 Hz, 4H), 6.87 and 7.08 (ABq, *J* = 8.3 Hz, 4H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.71 (s, 1H), 4.24-4.36 (m, 2H), 3.73 (s, 3H), 3.40 (d, *J* = 14.8 Hz, 1H), 2.89 (sept, 1H), 2.52-2.59 (m, 1H), 2.36 (d, *J* = 12.2 Hz, 1H), 1.87 (d, *J* = 12.2 Hz, 1H), 1.25-1.70 (m, 4H), 1.20 (d, *J* = 6.9 Hz, 6H).

¹³C NMR (*d*₆-DMSO, 75 Hz) δ 165.7, 162.8, 158.6, 148.6, 134.8, 129.2, 127.8, 127.3, 126.7, 114.0, 62.0, 56.8, 55.0, 45.8, 41.6, 33.1, 31.5, 23.9, 23.7, 23.4.

LC MS (M+H⁺) *m/z* 407.

Anal. calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.77; H, 7.50; N, 6.78.

(±)-(3*R*,6*S*)-1-(4-methoxybenzyl)-3-methyl-6-phenylpiperazine-2,5-dione (3h):

Yield after crystallization from isopropyl alcohol - 45%.

Beige solid, mp = 127–129 °C.

1H NMR (d_6 -DMSO, 300 MHz) δ 8.38 (s, 1H), 7.25–7.47 (m, 5H), 6.89 and 7.13 (ABq, J = 8.2 Hz, 4H), 5.14 (d, J = 14.3 Hz, 1H), 4.79 (s, 1H), 4.15–4.27 (m, 1H), 3.74 (s, 3H), 3.59 (d, J = 14.4 Hz, 1H), 1.37 (d, J = 6.6 Hz, 3H).

^{13}C NMR (d_6 -DMSO, 75 Hz) δ 167.6, 165.7, 158.7, 135.7, 129.3, 128.9, 128.3, 128.1, 126.6, 114.0, 63.4, 55.0, 48.8, 46.6, 17.9.

LC MS ($M+H^+$) m/z 325.

Anal. calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.40; H, 6.23; N, 8.57.

(±)-(3*R*,6*S*)-1-(4-methoxybenzyl)-3,6-diphenylpiperazine-2,5-dione (3i):

Yield after crystallization from isopropyl alcohol - 52%.

White solid, mp = 164 °C (decomp.).

1H NMR (d_6 -DMSO, 300 MHz) δ 8.45 (d, J = 6.2 Hz, 1H), 7.10–7.50 (m, 10H), 7.04 (t, J = 6.5 Hz, 2H), 6.87 (t, J = 9.0 Hz, 2H), 5.24–5.36 (m, 1H), 5.11 (t, J = 16.0 Hz, 1H), 4.92 (s, 1H), 3.76 (s, 3H), 3.59 (d, J = 14.7 Hz, 1H).

^{13}C NMR (d_6 -DMSO, 75 Hz) δ 165.7, 165.4, 165.0, 164.9, 158.7, 158.6, 139.0, 137.8, 136.6, 135.4, 129.5, 129.1, 128.9, 128.4, 128.3, 128.1, 127.8, 127.6, 127.2, 126.8, 126.3, 114.0, 63.1, 62.4, 58.2, 57.8, 55.0, 46.8, 46.4.

LC MS ($M+H^+$) m/z 387.

Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.68; H, 5.81; N, 7.30.

(±)-(3*R*,6*S*)-3-isopropyl-1-(4-methoxybenzyl)-6-phenylpiperazine-2,5-dione (3j):

Yield after crystallization from isopropyl alcohol - 41%.

White solid, mp = 140–143 °C.

1H NMR (d_6 -DMSO, 300 MHz) δ 7.78 (s, 1H), 7.25–7.46 (m, 5H), 6.88 and 7.10 (ABq, J = 8.5 Hz, 4H), 5.16 (d, J = 14.5 Hz, 1H), 4.77 (s, 1H), 4.07 (s, 1H), 3.76 (s, 3H), 3.52 (d, J = 14.7 Hz, 1H), 2.40–2.48 (m, 1H), 1.03 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H).

^{13}C NMR (d_6 -DMSO, 75 Hz) δ 166.1, 158.7, 136.5, 129.3, 128.9, 128.4, 128.0, 127.0, 114.0, 62.7, 58.4, 55.0, 46.2, 30.9, 18.0, 16.2.

LC MS ($M+H^+$) m/z 353.

Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.64; H, 6.96; N, 7.84.

(±)-(3*R*,6*S*)-3-isobutyl-1-(4-methoxybenzyl)-6-phenylpiperazine-2,5-dione (3k):

Yield after crystallization from isopropyl alcohol - 45%.

White solid, mp = 139–141 °C.

1H NMR (d_6 -DMSO, 300 MHz) δ 7.95 (s, 1H), 7.24–7.45 (m, 5H), 6.87 and 7.10 (ABq, J = 8.4 Hz, 4H), 5.13 (d, J = 14.7 Hz, 1H), 4.79 (s, 1H), 4.11 (t, J = 5.22 Hz, 1H), 3.76 (s, 3H), 3.60 (d, J = 14.7 Hz, 1H), 1.79–1.99 (m, 2H), 1.61–1.74 (m, 1H), 0.89 (d, J = 5.8 Hz, 6H).

^{13}C NMR (d_6 -DMSO, 75 Hz) δ 167.1, 165.6, 158.7, 136.1, 129.4, 128.9, 128.3, 128.0, 126.9, 114.0, 63.0, 55.0, 51.8, 46.4, 23.6, 22.8, 22.2.

LC MS ($M+H^+$) m/z 367.

Anal. calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.10; H, 7.19; N, 7.70.

(±)-(3*R*,6*S*)-3-sec-butyl-1-(4-methoxybenzyl)-6-phenylpiperazine-2,5-dione (3l):

Yield after crystallisation from isopropyl alcohol - 39%.

White solid, mp = 149–152 °C.

1H NMR (d_6 -DMSO, 300 MHz) δ 8.09 (br s) and 8.17 (br s) - 1H total, 7.26–7.47 (m, 5H), 7.10 (dd, J = 8.7, 2.0 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 5.17 (d, J = 14.3 Hz, 1H), 4.72 (d, J = 3.8 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.74 (s, 3H), 3.41 (d, J = 14.8 Hz, 1H), 2.06–2.30 (m, 1H), 1.25–1.50 (m, 2H), 0.76–1.01 (m, 6H).

^{13}C NMR (d_6 -DMSO, 75 Hz) δ 166.3, 166.0, 165.9, 158.7, 136.6, 129.4, 128.9, 128.4, 128.0, 127.0, 114.0, 62.7, 58.0, 56.9, 55.0, 46.2, 46.1, 37.9, 37.7, 24.6, 24.0, 14.8, 13.6, 12.0.

LC MS ($M+H^+$) m/z 367.

Anal. calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.20; H, 7.24; N, 7.59.

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- (6) The ¹H NMR spectra (*d*₆-DMSO, 300 MHz) of all crude products 2 displayed strongly broadened signals when run at ambient temperature, most likely, due to restricted amide bond rotations. Upon running some spectra at elevated temperatures (314K), it was possible to confirm that the products 2 represent an equal mixture of diastereomers, as expected from a non-diastereoselective course of the Ugi reaction.
- (7) Molecular mechanics (MM2) calculations were performed using ChemBio3D (Ultra) v. 11.0.

Diastereomerically Pure piperazine-2,5-diones from *N*-Protected α -Amino Acids