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A comparative study of the multicomponent Ugi reactions of an oxabicycloheptene-based β-amino acid in water and in methanol

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Dedicated to Professor György Hajós on the occasion of his 60th birthday

Abstract—Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1**, five aldehydes and two isocyanides were reacted both in methanol and in water to prepare a 10-membered β-lactam library via a Ugi-4-centre-3-component reaction. The yields were found to be similar in water and methanol. The diastereoselectivities of the aqueous reactions were similar, though in a few cases higher than those in methanol. The benefits of water are the facile isolation of the precipitated product and the shorter reaction time.

Combinatorial syntheses provide possibilities for the generation of diverse chemical libraries of potentially pharmacologically active compounds. Multicomponent condensation (MCC), in which several components are reacted in a one-pot reaction, is one of the important strategies in combinatorial chemistry. The most commonly used MCC is the four-component Ugi reaction (U-4CC), in which a carboxylic acid, an amine, a carbonyl compound and an isocyanide are reacted to result in amide derivatives and various heterocycles, for example, benzodiazepines, benzothiazepinones, oxazoles or isoxazoles, α-aminobutyrolactones or naturally occurring alkaloids in high yields and with high diastereoselectivities.[1,2] Intramolecular Ugi reactions (U-4C-3CR and U-5C-4CR), in which the α- or β-amino acids used as the starting materials contain two functional groups on the same compound, may furnish α-amino acid derivatives and β-lactams.[3] Some of these products possess pharmacological activity, for example, β-lactams have been proved to be enzyme inhibitors (serine and cysteine protease) and antibiotics.[4]

In recent years, bicyclo[2.2.1]hept-5-ene- and oxabicyclo[2.2.1]hept-5-ene-based β-amino acids have been utilized in Ugi reactions in organic solvents. The resulting Ugi adducts could be successfully applied for the synthesis of chiral α- or β-amino acid derivatives, for example, the corresponding free amino acids and their esters.[3c–e,5]

In the past few years, U-4CC processes have been also investigated in water. The advantages of this method are the reduced reaction time, the good yields, simple isolation of the products and less environmental pollution.[6] Pirrung and Sarma investigated the U-4C-3CR condensation of aliphatic β-amino acids in water (using a glucose solution to accelerate the reaction). The β-lactams generated were obtained in 70–99% purity and in 71–89% yields in 72 h.[7] Strained β-lactams were also synthetized by means of β-keto acids. The reactions failed in organic media. In contrast, a number of reports revealed a considerable decrease in the reaction rate, and in some cases the Ugi reaction was not accelerated by water.[8]

Our aim was to synthetize an oxabicycloheptene-based β-lactam library in water and in methanol in order to compare the yields, reaction times and diastereoselectivities. We also attempted the transformation of the β-lactams to other heterocycles. The starting di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1** was prepared according to a literature method.[9]

Generally, β-amino acid **1** was used in a small excess (1.1 equiv) and was reacted with two aliphatic aldehydes (**A** or **B**), three aromatic aldehydes (**C**, **D** or **E**) and

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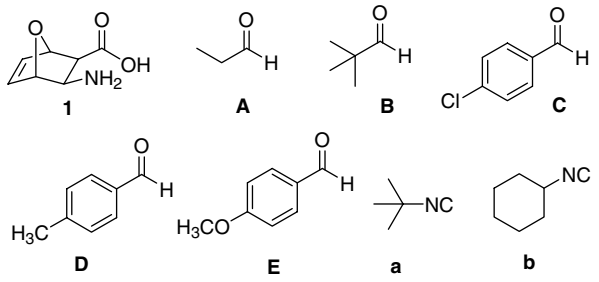
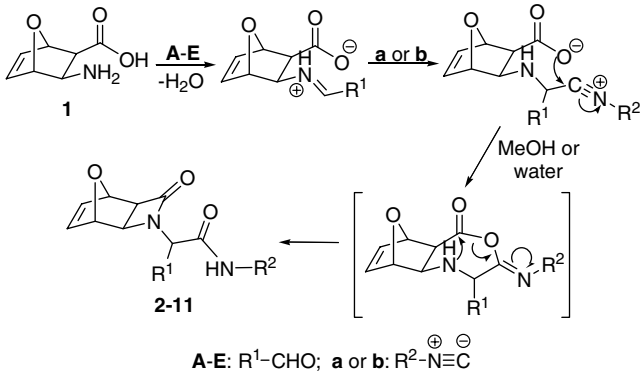


Figure 1. Building blocks of the U-4C-3CR reactions.

t-butyl or cyclohexyl isocyanide (**a** or **b**) in methanol or in distilled water (Fig. 1 and Scheme 1).

When methanol was used as the solvent, the Ugi condensation proceeded in 3 days, resulting in compounds **2**–**11** in moderate to good yields (43–76%) (Table 1).[10] In the crude products, the diastereomeric ratio ranged from 56:44 (**3**) up to 87:13 (**4**). For compounds **8**–**11**, further purification was necessary by means of flash chromatography to remove the remaining aldehyde. Compounds **3**–**7** had an average purity of over 90% without purification (based on ^{1}H NMR measurements).



Scheme 1. Reaction mechanism for the synthesis of the 10-membered β-lactam library.

Table 1. Synthesis of compounds **2**–**11** in methanol via Scheme 1

Compound	R^1	R^2	dr	Yield (%)
2	Et	*t*-Bu	62:38	61
3	Et	Cyclohexyl	56:44	76
4	*t*-Bu	*t*-Bu	87:13	71
5	*t*-Bu	Cyclohexyl	82:18	65
6	4-Chlorophenyl	*t*-Bu	62:38	52
7	4-Chlorophenyl	Cyclohexyl	79:21	76
8	4-Methylphenyl	*t*-Bu	78:22	55
9	4-Methylphenyl	Cyclohexyl	86:14	43
10	4-Methoxyphenyl	*t*-Bu	64:36	48
11	4-Methoxyphenyl	Cyclohexyl	69:31	45

With the aliphatic aldehydes, the intramolecular Ugi cyclization afforded higher yields, and for compound **4** a high diastereomeric ratio (87:13) was found. An increased diastereoselectivity, but decreased yields were obtained when the aromatic aldehydes (**C**, **D** and **E**) were used.

For identification of the major isomers, compounds **4** and **6** were recrystallized from isopropyl ether and submitted to X-ray crystallography (Fig. 2).[11]

The Ugi reactions were also carried out in water, starting from the same materials to allow comparison with the results in methanol (Table 2).[12] It was found that the cyclizations proceeded successfully in distilled water in reaction times ranging from 3 h to 1 day. With the exceptions of compounds **2** and **10**, derivatives **3**–**11** precipitated from the water and were isolated by filtration. It should be mentioned that precipitation depends greatly on the concentrations of the starting materials. When ideal concentrations were achieved, the starting components had just dissolved. After the addition of the isocyanide, the solution became slightly opalescent following precipitation of the target molecules (see experimental example).[12] We tested both concentrated and diluted mixtures to investigate the precipitation process. When the components had only partially dissolved, the yields were lower. In dilute solutions, the products did not precipitate, and organic solvent extraction was

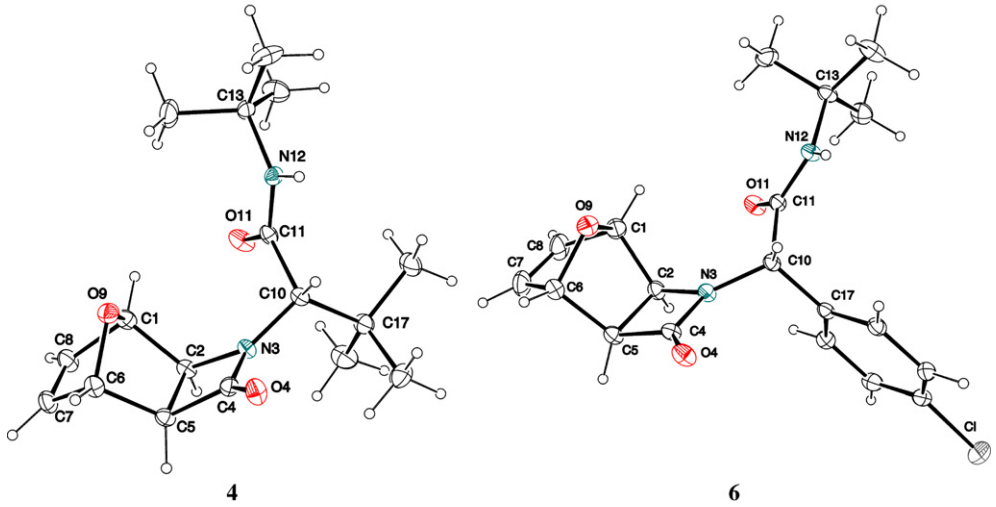


Figure 2. The ORTEP plots of the configurations of the major diastereoisomers of compounds **4** and **6**.

Table 2. Synthesis of compounds **2**–**11** in water via Scheme 1

Compound	R^1	R^2	dr	Yield (%)	2-H (ppm) Major/minor	Mp (°C)	Time (h)
2[a]	Et	*t*-Bu	67:33	71	3.65 (t)/3.72 (m)	97–106	24
3[b]	Et	Cyclohexyl	60:40	61	3.68–3.74 (m)	159–166	15
4[b]	*t*-Bu	*t*-Bu	100:0	59	3.75 (s)	176–178	3
5[b]	*t*-Bu	Cyclohexyl	80:20	64	3.84 (br s)	160–164	6
6[b]	4-Chlorophenyl	*t*-Bu	52:48	69	3.96/3.95 (s)	165–169	15
7[b]	4-Chlorophenyl	Cyclohexyl	55:45	55	3.93/3.92 (s)	155–176	15
8[b]	4-Methylphenyl	*t*-Bu	58:42	54	3.97/3.96 (s)	135–141	15
9[b]	4-Methylphenyl	Cyclohexyl	75:25	54	3.94/3.93 (s)	122–138	15
10[a]	4-Methoxyphenyl	*t*-Bu	57:43	51	3.96/3.95 (s)	120–134	24
11[b]	4-Methoxyphenyl	Cyclohexyl	63:37	47	3.93/3.92 (s)	129–141	24

[a] Isolated by extraction.
[b] Precipitated compound, isolated by filtration.

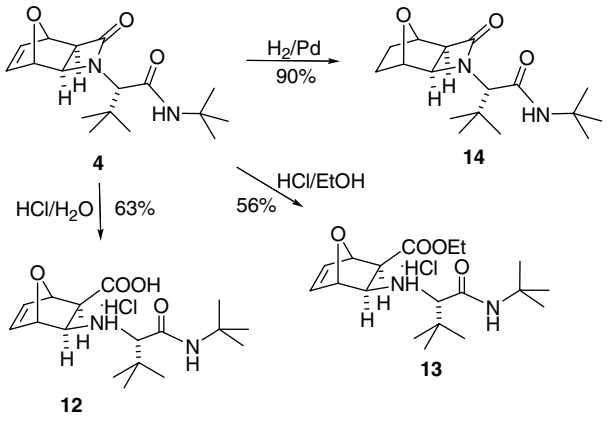
necessary to isolate them. The reaction times were increased to 3 days, while the yields were similar to those when the reaction mixture was saturated with the starting materials. In accordance with these experiments, we assume that a 'personalized' amount of water is necessary to optimize acceleration of the reaction with precipitation in water.

The best result was observed for compound **4** containing bulky *t*-butyl substituents. The reaction time was only 3 h and the diastereomeric ratio was 100:0. Derivatives **2**–**9** and **11** were isolated in average purities of over 90% and further purification was not necessary for the NMR measurements. For product **10**, chromatographic purification was necessary because of the presence of the residual anisaldehyde.

To demonstrate the possibility of further transformations of the resulting azetidinone derivatives, compound **4** was converted into the corresponding carboxylic acid **12** and ethyl ester **13** by means of acid-catalyzed solvolysis in the presence of water or EtOH. Saturation with H_2 at an atmospheric pressure was carried out, catalyzed by palladium on charcoal, to yield derivative **14** (Scheme 2).[13]

Another reaction was performed with $LiAlH_4$ or LDA in an attempt to synthesize 3- or 4-hydroxy-substituted amino acid derivatives,[14] but the target compounds could not be isolated from the complex reaction mixture. To utilize the oxanorbornene moiety of compound **4**, a retro Diels–Alder (RDA) process was attempted by classical methods (heating to the melting point, refluxing in a high boiling point solvent) and microwave-assisted thermolysis (150–250 °C, 100–200 W, for reaction times ranging from 10 min to 1 h, in *o*-DCB or solvent-free, on SiO_2 or $AlCl_3$/toluene), but only the starting material was recovered.

In conclusion, the first syntheses of oxabicyclo β-lactam derivatives **2**–**11** were accomplished, starting from di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1**, during which the solution effects of water and methanol were observed. With water as solvent, the yields were found to be similar to those in methanol; the diastereoselectivity was also similar, but in some cases proved to be better, and even excellent diastereoselectivity could be observed. The advantages of water include a simple isolation of the precipitated products.



Scheme 2. Transformations of compound **4**.

Acknowledgements

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10. General method for the synthesis of compounds **2**–**11** in MeOH: To a suspension of 100 mg (0.65 mmol, 1.1 equiv) of β-amino acid **1** in MeOH (5 mL), the required aldehyde (1 equiv) was added at room temperature. After stirring for 45 min at room temperature, *t*-butyl or cyclohexyl isocyanide (1 equiv) was added dropwise to the solution which was stirred for 3 days at an ambient temperature. Subsequently, the solvent was evaporated in vacuo, and water (5 mL) and chloroform (20 mL) were added. On extraction, drying and evaporation of the organic phase, the crude products **2**–**11** were obtained in yields of 43–76%.
11. For further details see crystallographic data (excluding structure factors) for compounds **4** and **6** which have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers. CCDC 619383 (**4**)–619384 (**6**). Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 122 3336 033; or E-mail: deposit@ccdc.cam.ac.uk].
12. A representative example of the synthesis of compound **4** in water: To β-amino acid **1** (110 mg, 1.1 equiv.) in a minimal amount of water (200 μL), pivalaldehyde (72 μL, 1 equiv) was added dropwise. Next, approximately 1 mL of water was added dropwise until the components had completely dissolved. After vigorous stirring for 30 min at room temperature, *t*-butyl isocyanide (73 μL, 1 equiv) was added to the mixture. The precipitation of the product started immediately. After 3 h, the precipitated product was filtered off and washed with water to yield compound **4** (130 mg, 59%, diastereoisomeric ratio = 100/0).
(*S**)-*N*-(*t*-Butyl)-3,3-dimethyl-2-((2*R**,5*S**)-4-oxo-9-oxa-3-azatricyclo[4.2.1.$0^{2,5}$]non-7-en-3-yl)butyramide (**4**): yield: 59%, white powder, mp: 176–178 °C. ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.07 (9H, s); 1.36 (9H, s); 3.19 (1H, d, $J = 3.5$ Hz); 3.75 (1H, s); 3.94 (1H, d, $J = 4.0$ Hz,); 4.98 (1H, m); 5.09 (1H, m); 5.83 (1H, br s); 6.35 (1H, dd, $J = 1.5$ and 5.5 Hz); 6.43 (1H, dd, $J = 1.5$ and 5.5 Hz). ^{13}C NMR (68 MHz, $CDCl_3$) δ 27.8, 29.1, 37.1, 52.2, 56.5, 59.8, 64.2, 75.9, 78.5, 135.3, 137.4, 168.3 and 169.10. IR (KBr, cm^{-1}): 3340, 2967, 2360, 1734, 1547, 1363; MS (EI, 18 eV, *m*/*z*): 306 (M^+, 7), 238 (40), 182 (18), 171 (29), 138 (100), 99 (24), 83 (27), 57 (4), 41 (7).
13. (a) β-lactam **4** (50 mg) (0.14 mmol) was dissolved in 10% HCl/H_2O (10 mL). The solution was refluxed for 1 h after which the solvent was evaporated and the crude residue was treated with Et_2O to give amino acid hydrochloride salt **12** in a good yield (63%).
(2*S**,3*R**)-3-((*S**)-1-*t*-Butylcarbamoyl-2,2-dimethylpropylamino)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**12**): yield: 63%, white powder, mp: 161–163 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.13 (9H, s); 1.35 (9H, s); 2.97 (1H, d, $J = 7.1$ Hz); 3.39 (1H, d, $J = 7.1$ Hz); 3.81 (1H, s); 5.34 (2H, d, $J = 11.6$ Hz); 6.44 (1H, bd, $J = 5.5$ Hz); 6.71 (1H, bd, $J = 5.5$ Hz). ^{13}C NMR (D_2O, 68 MHz): δ 26.1; 28.0; 33.8, 44.8; 53.2; 58.5; 69.9; 80.1; 82.6; 133.5; 139.6; 166.0 175.8. IR (KBr, cm^{-1}): 3472, 2962, 2364, 2340, 1744, 1674, 1562, 1366; MS (EI, 70 eV, *m*/*z*): 306 (M^+-18, 1), 238 (15), 182 (8), 171 (15), 138 (100), 128 (7), 83 (10), 57 (7), 41 (6).
(b) β-Lactam **4** (50 mg) (0.14 mmol) was dissolved in 10% HCl/EtOH (10 mL). The solution was refluxed for 3 h (checked by TLC) after which the solvent was evaporated and the residue was crystallized and washed with Et_2O to yield 40 mg (56%) of β-amino ester derivative **13**.
(2*S**,3*R**)-3-((*S**)-1-*t*-Butylcarbamoyl-2,2-dimethylpropylamino)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid ethyl ester (**13**): yield: 56%, white powder, mp: 208–210 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.12 (9H, s); 1.34 (3H, t, $J = 5.9$ Hz); 1.36 (9H, s); 3.14 (1H, d, $J = 7.1$ Hz); 3.44 (1H, d, $J = 7.1$ Hz); 3.82 (1H, s); 4.33 (2H, q, $J = 6.6$ and 13.1 Hz); 5.32 (1H, m); 5.45 (1H, m); 6.48 (1H, d, $J = 6.0$ Hz); 6.70 (1H, d, $J = 5.5$ Hz). ^{13}C NMR (D_2O, 68 MHz): δ 13.6; 26.1; 28.0; 33.8, 45.3; 52.4; 58.8; 64.1; 70.4; 80.2; 82.1; 133.8; 139.4; 166.0 173.3. IR (KBr, cm^{-1}): 2967, 2360, 1670, 1558, 1227. MS (EI, 70 eV, *m*/*z*): 352 (M^+, 1), 308 (1), 285 (5), 252 (1), 228 (1), 184 (100), 167 (5), 149 (6), 138 (23), 126 (1), 86 (3), 68 (4).
(c) To a suspension of 5 mg of 10% Pd on activated charcoal in 20 mL of MeOH, 30 mg of β-lactam **4** (0.1 mmol) was added and the mixture was stirred for 2 h under an atmosphere of H_2. Next, the Pd was filtered off and the solvent was evaporated in vacuo. Compound **14** was obtained in a pure form in a yield of 90%.
(*S**)-*N*-(*t*-Butyl)-3,3-dimethyl-2-((2*R**,5*S**)-4-oxo-9-oxa-3-azatricyclo[4.2.1.$0^{2,5}$]non-3-yl)butyramide **(14)**: yield: 90%, white powder, mp: 219–221 °C. ^{1}H NMR (400 MHz, D_2O) δ: 1.06 (9H, s); 1.20–1.44 (2H, m); 1.37 (9H, s); 1.60–1.82 (2H, m); 3.21 (1H, d, $J = 4.0$ Hz); 3.75 (1H, s); 3.89 (1H, d, $J = 3.5$ Hz); 4.61 (1H, bd, $J = 4.5$ Hz); 4.70 (1H, bd, $J = 5.0$ Hz), 5.90 (1H, br s). ^{13}C NMR (D_2O, 68 MHz): δ 26.2; 27.9; 28.8; 29.1; 37.0; 52.4; 58.6; 61.4; 64.4; 73.9; 75.7; 167.9 168.3. IR (KBr, cm^{-1}): 3336, 3084, 2988, 2970, 1742, 1665, 1554, 1452, 1362, 1222; MS (EI, 70 eV, *m*/*z*): 309 ($M+H^+$, 10), 252 (5), 209 (70), 208 (100), 194 (6), 153 (16), 152 (50), 125 (15), 97 (15), 80 (20), 57 (28), 41 (25).
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