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Rapid and Efficient Microwave-Assisted Synthesis of *N*-Carbamoyl-L-amino Acids

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Abstract: A rapid and efficient method for the synthesis of *N*-carbamoyl-L-amino acids is reported. The procedure, involving the reaction between urea and α-amino acids sodium salts, was performed under microwave conditions using an unmodified domestic microwave oven. A careful study of the operative conditions indicated proline (**1d**) as the less reactive substrate and phenylglycine (**1e**) as the more reactive one among all the α-amino acids tested. Substitution of urea with potassium cyanate produced a low conversion into the corresponding *N*-carbamoyl derivative, and a possible explanation of this result is reported.

Keywords: amino acids, *N*-carbamoyl derivatives, microwave, potassium cyanate, urea

N-Carbamoyl-L-amino acids are important derivatives involved in antimicrobial therapy, used as such[1] or in the role of side chains for different synthetic antibacterial agents,[2] as well as in the prevention of hyperammonemia;[3] moreover, they are useful intermediates in heterocyclic[4] and peptide chemistry.[5]

Among all the reported procedures thus far, the most common source of these derivatives appears to be the enzymatic hydrolysis of 5-substituted hydantoins.[6] Because of the specificity of the enzyme, in connection with the spontaneous racemization of the hydantoins observed under the reaction conditions (pH $>$ 8), this method allows for conversion of the racemic starting materials into the enantiomerically pure *N*-carbamoyl D- or L-amino

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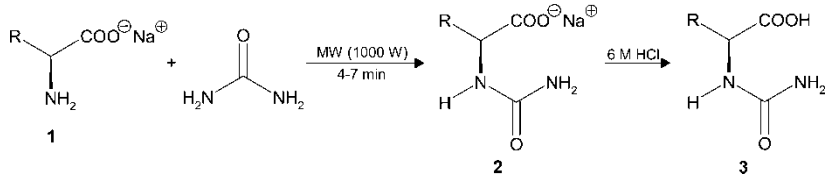
acids. However, the process requires long reaction times (from 10 to 40 h) and the availability of a suitable enzyme. In this context, of particular synthetic value is the reaction of α-amino acids with sodium or potassium cyanate.[2e,2g,2h,4c,7] The protocol is very simple, but the reaction efficiency is significantly dependent either on pH or temperature (10 h at 40–50°C and a pH range of 7–8; 70 h at 50°C and pH 9.4).[7b] On the other hand, little attention has been paid so far to the strightforward reaction of α-amino acids with urea,[8] most likely because of the lower yields obtained when compared with the two previously cited methods, the high reaction temperatures (100–170°C), and the long reaction times (from 4 to 10 h) required.

Recently, microwave (MW) irradiation to effect organic reactions has been widely used by organic chemists, and remarkable reduction in reaction times, clean conditions, and better yields have been reported in MW-induced reactions.[9]

Taking into account these reports, as well as our interest in amino acid derivatives,[10] we describe herein the MW-enhanced reaction between α-amino acids and urea to give the corresponding *N*-carbamoyl derivatives (**3**). The simple and convenient synthesis of **3** here reported involves the reaction of the sodium salt of the appropriate α-amino acid **1** with urea (1.7 equivalents) in water (Scheme 1, Table 1), carried out in an unmodified domestic microwave oven at 1000 W in a beaker of fairly large size (50 mL using 0.5–1.0 g of **1**). An additional beaker (500 mL) filled with water was placed close to the first one to serve as a heat sink, providing a finer control on the amount of MW energy input transmitted to the system. After few minutes, the reaction mixture was cooled to 0°C, and 1.0 equivalent of 6 M HCl was added to precipitate **3**, which was finally washed with water to eliminate excess urea and NaCl.

The amount of water employed as the solvent in the reaction has to be as small as possible (0.3 mL · mmol^{-1} **1**), because its only role is to dissolve and homogenize the salt **1**, obtained from the neutralization of the α-amino acid with 1 equivalent of sodium hydroxide, and urea. Indeed, after 1 min of irradiation at 1000 W, the water was completely distilled off, and the reaction proceeded in the melt state. Moreover, when the reaction of **1b** with urea was carried out (MW, 1000 W) in a more diluted system (1.0 mL · mmol^{-1} **1**), after 10 min, the observed conversion proved to be incomplete, and the ^{13}C NMR spectrum of the intact reaction mixture after



Scheme 1.

Table 1. Identity of compounds **1**–**3**

Compounds **1**–**3**	R
a	CH_3
b	$(CH_3)_2CH$
c	$(CH_3)_2CHCH_2$
d	Proline
e	C_6H_5
f	$C_6H_5CH_2$
g	$CH_3SCH_2CH_2$
h	1*H*-indole-3-CH_2
i	4-HO-$C_6H_4CH_2$
j	$HOOCCH_2CH_2$

dilution with D_2O showed the presence of a mixture of **2b** and starting **1b** in a ratio 3:1. Therefore, to solubilize tyrosine (**1i**) and keep the amount of water as low as possible, 2 equivalents of sodium hydroxide were used; as a consequence, at the end of the reaction, 2 equivalents of 6 M HCl were necessary to precipitate **3i**.

To optimize the reaction time required to achieve a complete conversion of **1** into **2**, the intact reaction mixture was monitored at regular times (2 min) by ^{13}C NMR spectroscopy after dilution with D_2O. This study evidenced that the reaction was complete within 4 min, with the exception of proline (**1d**), which required 7 min. Phenylglycine (**1e**) proved to be the more reactive substrate, giving a complete conversion into **2e** after 2 min.

Because *N*-carbamoyl-L-glutamic acid (**3j**) proved to be very soluble in water, excess urea was eliminated by washing the *N*-carbamoyl-L-glutamic acid disodium salt (**2j**) obtained after the MW irradiation with MeOH, followed by treatment with concentrated HCl, giving the corresponding acid **3j**, which was finally filtered and washed with little water to eliminate NaCl. When the procedure was repeated with L-aspartic acid (**1k**), L-glutamine (**1l**), and L-lysine (**1m**), the ^{13}C NMR analysis of the intact reaction mixture after dilution with D_2O showed the complete conversion into the corresponding *N*-carbamoyl derivatives **2k**–**l**, but unfortunately in these three instances we were unable to obtain pure **3k**–**m** because of the unexpected high solubility in water and also MeOH of the corresponding sodium salts (**2k**–**m**).

Finally, we have attempted to extend the method of MW irradiation to the preparation of **3** using potassium cyanate instead of urea, but with poor results. In fact, all of the tested amino acids **1** showed a low conversion into **2** (20–30%, using the conditions described previously, 1000 W, 4 min), as evidenced by ^{13}C NMR analysis of the intact reaction mixture after dilution with D_2O. On the other hand, better results (50% conversion into **2** after

15 min) have been obtained using 750 W and more water (5 mL · mmol^{-1} **1**), pointing out that the reaction with potassium cyanate occurred in solution and indicating that when water was completely distilled off (5–7 min), the process did not proceed to completion in the solid residue. In this context, we observed that it is difficult to standardize the correct amount of water to be used, being correlated to the type and amount of the substrate **1** as well as to the size of the reaction vessel employed.

The results obtained accompanied by some relevant properties of **3** are reported in Table 2. Data pertinent to the synthesized *N*-carbamoyl-L-amino acids **3** are collected in Table 3.

In conclusion, we describe here a fast, simple, and cheap MW-induced protocol for the preparation of *N*-carbamoyl-L-amino acids, which is useful as an alternative to the currently available procedures.

EXPERIMENTAL

Materials

All the reactions were carried out in an unmodified domestic Bauknecht MCID 1125 microwave oven at 1000 W placed in a hood. All chemicals were commercial grade (Aldrich, Fluka) and were used without further purification. Direct inlet mass spectra (DI-MS) have been obtained with a Fisons TRIO 2000 gas chromatograph–mass spectrometer, working in the positive ion electron impact mode (70 eV; 120–200°C), and were recorded in the range 35–450 u. IR spectra were obtained with a Bruker Vector 22

Table 2. Yields and some properties of *N*-carbamoyl-L-amino acids **3**

Product[a]	Yield (%)[b]	Mp (°C) [Lit.]	$[\alpha]_D^{[20]}$ (*c*, MeOH)
3a	75	177 [178–179][4c]	+4.0 (1.0)
3b	90	200 [200–201][4c]	+18.0 (1.0)
3c	92	217 [216–218][7b]	−6.0 (0.5)
3d	78	203	−53.8 (0.7)
3e	92	194 [195–196][4c]	+140.0 (1.0)
3f	94	193 [192–193][4c]	+33.3 (1.0)
3g	80	186	+2.3 (1.0)
3h	90	198	+18.3 (1.0)
3i	82	218 dec [218][8f]	−5.4 (1.3)[c]
3j	65	151 [150][8f]	+4.2 (2.0)

[a]Satisfactory microanalyses obtained: C ± 0.12, H ± 0.12, N ± 0.14.
[b]Yields refer to pure isolated products.
[c]Solvent: 0.25 M NaOH.

Table 3. Spectroscopic data of *N*-carbamoyl-L-amino acids **3**

Product	IR (KBr) (cm^{-1})	^{1}H NMR δ, J (Hz)	^{13}C NMR δ	MS m/z (%)
3a	3650–3000, 1680, 1635, 1572, 1453, 1408, 1305, 1190, 1065, 1010, 598, 563	1.19 (d, 3H, $J = 7.1$, CH_3), 3.90–4.20 (m, 1H, *CH), 5.63 (br s, 2H, NH_2), 6.34 (br d, 1H, $J = 6.8$, NH), 12.40 (br s, 1H, COOH)[a]	18.5, 48.3, 158.6, 176.5[a]	132 (M^+, 1), 79 (8), 87 (55), 44 (100), 43 (17), 42 (17)
3b	3454, 3300, 1685, 1635, 1560, 1309, 1286, 1176, 1164, 1012, 721	0.85 [app t, 6 H, $J = 6.7$, $CH(CH_3)_2$], 1.85–2.10 [m, 1 H, $CH(CH_3)_2$], 3.99 (dd, 1 H, $J = 8.1$, 5.1, *CH), 5.49 (br s, 2 H, NH_2), 6.23 (br d, 1 H, $J = 8.1$, NH), 12.40 (br s, 1 H, COOH)[a]	17.6, 19.1, 30.2, 57.4, 158.7, 174.0[a]	160 (M^+, 1), 143 (1), 142 (1), 118 (13), 115 (100), 101 (21), 100 (81), 74 (28), 72 (56), 57 (29), 56 (23), 55 (33), 44 (33), 43 (20), 41 (16)
3c	3460, 3355, 3305, 2958, 2925, 1685, 1635, 1574, 1320, 1262, 1173, 716	0.85 and 0.88 [2 d, 6 H, $J = 5.4$, $CH(CH_3)_2$], 1.30–1.50 (m, 2 H, CH_2), 1.50–1.80 (m, 1 H, $CH(CH_3)_2$], 3.90–4.18 (m, 1 H, *CH), 5.58 (br s, 2 h, NH_2), 6.25 (br d, 1 H, $J = 8.3$, NH), 12.30 (br s, 1 H, COOH)[a]	21.6, 22.8, 24.3, 41.1, 50.9, 158.6, 175.2[a]	174 (M^+, 1), 121 (2), 129 (100), 118 (30), 100 (46), 86 (86), 74 (37), 57 (20), 44 (84), 43 (57), 42 (17), 41 (25)

(*continued*)

Table 3. Continued

Product	IR (KBr) (cm^{-1})	^{1}H NMR δ, J (Hz)	^{13}C NMR δ	MS m/z (%)
3d	3420, 3341, 3230, 1688, 1658, 1545, 1458, 1313, 1300, 1077	1.65–2.30 [m, 4 H, *CH(CH_2)$_2$], 3.10–3.50 (m, 2 H, NCH_2), 4.16 (dd, 1 H, J = 8.2, 2.9, *CH), 5.85 (br s, 2 H, NH_2), 10.57 (br s, 1 H, COOH)[a]	24.1, 29.3, 46.0, 58.5, 157.5, 174.4[a]	158 (M^+, 2), 140 (1), 129 (1), 114 (47), 113 (36), 86 (34), 70 (100), 63 (19), 44 (21), 43 (46), 42 (15), 41 (24)
3e	3461, 3356, 3316, 1687, 1630, 1550, 1308, 1270, 1147, 725, 695	4.74 (s, 1 H, *CH), 6.95–7.25 (m, 5 H, H_{arom})[b]	62.6, 129.5, 130.4, 131.5, 142.0, 162.9, 180.1[b]	194 (M^+, 1), 176 (25), 151 (13), 150 (9), 149 (23), 133 (8), 106 (100), 105 (39), 104 (67), 79 (32), 78 (12), 77 (32), 51 (12), 44 (9)
3f	3600–3000, 1695, 1635, 1560, 1302, 1258, 1160, 713, 693	2.87 and 3.03 (AB of ABX, 2 H, J = 13.8, 7.9, 5.3, CH_2), 4.25–4.45 (m, 1 H, *CH), 5.66 (br s, 2 H, NH_2), 6.27 (br d, 1 H, J = 8.2, NH), 7.10–7.35 (m, 5 H, H_{arom}), 11.45 (br s, 1 H, COOH)[a]	37.8, 54.0, 126.3, 128.1, 129.3, 137.7, 158.4, 174.1[a]	208 (M^+, 1), 191 (2), 190 (3), 148 (27), 147 (12), 120 (18), 91 (100), 74 (23), 65 (12), 44 (21), 43 (13)
3g	3600–3000, 1687, 1630, 1560, 1307, 1293, 1195, 1000, 728, 603, 478	1.65–2.10 (m, 2 H, *CHCH_2), 2.03 (s, 3 H, CH_3), 2.46 (t, 2 H, J = 7.6, SCH_2), 4.00–4.25 (m, 1 H, *CH), 5.61 (br s, 2 H, NH_2), 6.39 (br d, 1 H, J = 8.2), 11.32 (br s, 1 H, COOH)[a]	14.6, 29.6, 31.8, 51.6, 158.5, 174.2[a]	192 (M^+, 8), 175 (11), 174 (13), 129 (15), 118 (63), 113 (24), 100 (100), 88 (20), 75 (36), 61 (67), 56 (49), 44 (32), 43 (14)

3h	3600–2700, 1700, 1647, 1573, 1540, 1455, 1340, 1250, 1217, 1060, 748, 545, 510	3.03 and 3.15 (AB of ABX, 2 H, $J = 14.6, 6.7, 5.1$, CH_2), 4.30–4.50 (m, 1 H, *CH), 5.64 (br s, 2 H, NH_2), 6.21 (br d, 1 H, $J = 7.9$, NH), 6.90–7.22 (m, 3 H, H_{arom}), 7.35 (app d, 1 H, $J = 7.6$, H_{arom}), 7.54 (app d, 1 H, $J = 7.3$, H_{arom}), 10.88 (br s, 1 H, NH_{arom}), 12.5 (br s, 1 H, COOH[a]	28.1, 53.6, 109.9, 111.6, 118.6, 118.7, 121.2, 123.9, 127.7, 136.4, 158.9, 174.7[a]	247 (M^+, 1), 130 (100), 103 (6), 102 (4), 77 (9), 44 (5), 43 (3)
3i	3650–2200, 1607, 1590, 1515, 1452, 1364, 1331, 1243, 838, 795, 650, 572	2.54 and 2.72 (AB of ABX, 2 H, $J = 13.7, 7.3, 5.4$, CH_2), 3.28 (dd, 1 H, $J = 7.3, 5.4$, *CH), 6.45 (app d, 2 H, $J = 8.3$, H_{arom}), 6.86 (app d, 2 H, $J = 8.3$, H_{arom})[b]	42.9, 60.6, 121.7, 126.8, 133.7, 167.6, 186.0[b]	224 (M^+, 1), 206 (1), 181 (4), 136 (3), 135 (2), 120 (2), 107 (100), 91 (6), 77 (12), 44 (10), 43 (10)
3j	3650–2500, 1711, 1667, 1635, 1560, 1407, 1341, 1230, 1170, 524	1.77–2.24 (m, 2 H, *CHCH_2), 2.36 (app t, 2 H, J = 7.8, CH_2COOH), 3.97–4.11 (m, 1 H, *CH)[c]	31.6, 36.9, 58.4, 163.8, 183.3, 185.3[c]	190 (M^+, 1), 154 (78), 129 (5), 127 (11), 126 (26), 112 (48), 99 (23), 84 (100), 73 (17), 56 (29), 44 (59), 43 (15), 42 (19), 41 (26)

[a]Solvent: DMSO-d_6.
[b]Solvent: D_2O-NaOH.
[c]Solvent: D_2O.

spectrophotometer, using the KBr technique, and recorded in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using D_2O or D_2O-NaOH at room temperature or DMSO-d_6 at 40°C as solvents. NMR peak locations are reported as δ values from TMS. Some ^1H multiplets are characterized by the term *app* (apparent): this refers only to their appearance and may be an oversimplification. Optical rotations were determined at 20°C (concentration in g/100 mL) using a Atago (Japan) Polax-D polarimeter. Elemental analyses were performed with a Carlo Erba Mod. 1106 elemental analyser. Melting points were determined with an automatic Mettler (Mod. FP61) melting-point apparatus and are uncorrected.

General Procedure

N-Carbamoyl-L-amino Acids **3**

The selected α-amino acid (6.0 mmol) was added into a 50-mL beaker containing a stirred solution of NaOH (0.24 g, 6.0 mmol) in water (1.8 mL). When a clear solution was obtained, urea (0.62 g, 10.30 mmol) was added, and the reaction mixture was made homogeneous by well admixing with the help of a glass rod. The reaction vessel was covered with a watch glass and placed into an unmodified domestic microwave oven, together with a 500-mL beaker containing water (300–400 mL), and irradiated for 4 min [7 min with proline (**1d**)] at 1000 W. The reaction mixture was then cooled at 0°C, and 6 M HCl (1.0 mL, 6.0 mmol) was added while stirring. The obtained solid was filtered and washed with water (3 × 2.0 mL) to eliminate excess urea and NaCl, yielding the *N*-carbamoyl amino acids **3a**–**h** in a spectroscopically pure form.

To solubilize L-tyrosine (**1i**), 2 equivalents of NaOH was used, and therefore at the end of the reaction, 2 equivalents of 6 M HCl was added to give the corresponding *N*-carbamoyl derivative **3i**, after washing with water.

N-Carbamoyl-L-glutamic Acid (**3j**)

L-Glutamic acid (**1j**, 0.88 g, 6.0 mmol) was added into a 50-mL beaker containing a stirred solution of NaOH (0.48 g, 12.0 mmol) in water (1.8 mL). When a clear solution was obtained, urea (0.62 g, 10.30 mmol) was added, and the reaction mixture was made homogeneous by well admixing with the help of a glass rod. The reaction vessel was covered with a watch glass and placed into an unmodified domestic microwave oven, together with a 500-mL beaker containing water (300–400 mL), and irradiated for 4 min at 1000 W. The reaction mixture was then cooled at 0°C, and the residue was triturated in MeOH and thoroughly washed with the same solvent (3 × 1.5 mL) to eliminate excess urea. *N*-Carbamoyl-L-glutamic acid disodium salt (**2j**) was

treated with concd. HCl (1.0 mL, 12.0 mmol), and the solid was finally washed with water (2 × 1.0 mL) to eliminate formed NaCl, yielding **3j** in a spectroscopically pure form.

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REFERENCES

1. Rastogi, N.; Goh, K. S.; Wright, E. L.; Barrow, W. W. Potential drug targets for *Mycobacterium avium* defined by radiometric drug-inhibitor combination techniques. *Antimicrob. Agents Chemother.* **1994**, *38*, 2287–2295.
2. (a) Sykes, R. B.; Parker, W. L.; Cimarusti, C. M.; Koster, W. H.; Slusarchyk, W. A. Preparation of 3-(acylamino)-1-sulfoazetidinones and their salts as antibacterial agents. U. S. Patent 4775670, 1988; *Chem. Abstr.* **1989**, *111*, 194450; (b) Matsumura, H.; Yano, T.; Narisada, M. Oxacephalosporin derivatives and their use. Eur. Patent Appl. 111421, 1984; *Chem. Abstr.* **1985**, *102*, 148983; (c) Narisada, M.; Watanabe, F.; Okada, T.; Matsumura, H. Oxacephalosporins. Ger. Patent 3346775, 1984; *Chem. Abstr.* **1984**, *101*, 191531; (d) Squibb, E. R., and Sons, Inc. Antibiotic β-lactams. Neth. Patent Appl. 81 00571, 1981; *Chem. Abstr.* **1982**, *96*, 181062; (e) Squibb, E. R., and Sons, Inc. 7-Methoxypyridyl- and phenylureidocephalosporins. Neth. Patent Appl. 76 09079; 1978; *Chem. Abstr.* **1978**, *89*, 43453; (f) Ferres, H.; Basker, M. J.; Best, D. J.; Harrington, F. P.; O'Hanlon, P. J. β-Lactam antibiotics, II: Structure–activity relationships of 6-[α-(α'-ureidoacylamino)acylamino]penicillanic acids. *J. Atibiot.* **1978**, *31*, 1013–1022; (g) Dolfini, J. E. 7-Methoxyphenylureidocephalosporins. U. S. Patent 4029654, 1977; *Chem. Abstr.* **1977**, *87*, 102363; (h) Dolfini, J. E. 7-Methoxyphenylureidocephalosporins. U. S. Patent 3989697, 1976; *Chem. Abstr.* **1977**, *86*, 121351; (i) Ferres, H.; Kemmenoe, A. V.; Best, D. J. Penicillin derivatives. Ger. Patent 2421030, 1974; *Chem. Abstr.* **1975**, *82*, 86286; (j) Hardy, K. D.; Roy, P. D. Penicillins. Brit. Patent 1324752, 1973; *Chem. Abstr.* **1973**, *79*, 115569; (k) DuMerritt Welch, A.; Dolfini, J. E.; Giarrusso, F. F. Pivaloyloxymethyl 6-(D-α-ureidophenylacetamido)penicillanate. Ger. Patent 2152769, 1972; *Chem. Abstr.* **1972**, *77*, 34501; (l) Cheney, L. C.; Godfrey, J. C.; Crast, L. B.; Luttinger, J. R. New active esters of 6-aminopenicillanic acid. Fr. Patent 1491583, 1967; *Chem. Abstr.* **1968**, *69*, 52131.
3. (a) Gebhardt, B.; Vlaho, S.; Fischer, D.; Sewell, A.; Bohles, H. *N*-Carbamylglutamate enhances ammonia detoxification in a patient with decompensated methylmalonic aciduria. *Mol. Genet. Metab.* **2003**, *79*, 303–304; (b) Kim, W. H.; Park, H.; Yun, C.; Cho, H.; Kim, S.; Paik, W. K.; Jeon, S. H.; Lee, J. H. Mixture of *N*-carbamoyl-L-glutamate plus L-arginine can protect rats with liver cirrhosis from acute ammonia intoxication. *J. Hepatol.* **2001**, *35*, 719–725;

(c) Park, H. S.; Kim, I. H.; Kim, I. Y.; Kim, K. H.; Kim, H. J. Expression of carbamoyl phosphate synthetase I and ornithine transcarbamoylase genes in Chinese hamster ovary *dhfr*-cells decreases accumulation of ammonium ion in culture media. *J. Biotechnol.* **2000**, *81*, 129–140; (d) Lee, J. H.; Kim, W. H.; Cho, H.; Kwak, Y. S.; Kim, S.; Paik, W. K. *N*-Carbamoyl-L-glutamate plus L-arginine can protect ammonia intoxication in rats with reduced functional liver mass. *Biochem. Biophys. Res. Commun.* **1998**, *248*, 391–394.

4. (a) Suzuki, M.; Yamazaki, T.; Ohta, H.; Shima, K.; Ohi, K.; Nishiyama, S.; Sugai, T. *N*-Carbamoylamino alcohols as the precursors of oxazolidinones via nitrosation-deamination reaction. *Synlett* **2000**, 189–192; (b) Jha, B. K.; Chhatre, A. S.; Kulkarni, B. D. Cyclization and molecular rearrangement under micellar and microemulsion conditions. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1383–1385; (c) Stella, V.; Higuchi, T. Kinetics of the acid-catalyzed closure of hydantoic acids: Effect of 2-aryl and 2-alkyl substituents. *J. Org. Chem.* **1973**, *38*, 1527–1534.
5. Lagrille, O.; Taillades, J.; Boiteau, L.; Commeyras, A. *N*-Carbamoyl derivatives and their nitrosation by gaseous NO_x—A new, promising tool in stepwise peptide synthesis. *Eur. J. Org. Chem.* **2002**, 1026–1032.
6. (a) Li, J.; Wie, P.; Yao, Z.; Zhou, H.; Ouyang, P. Kinetics for production of D-*N*-carbamoyl phenylalanine and influence of temperature on conversion process. *Huagong Xuebao* **2004**, *55*, 629–634; *Chem. Abstr.* **2004**, *141*, 70303; (b) Arcuri, M. B.; Antunes, O. A. C.; Machado, S. P.; Almeida, C. H. F.; Oestreicher, E. G. Stability of immobilized D-hydantoinase from Vigna angularis and repeated cycles of highly enantioenriched production of *N*-carbamoyl-D-phenylglycines. *Amino Acids* **2004**, *27*, 69–74; (c) Arcuri, M. B.; Sabino, S. J.; Antunes, O. A. C.; Oestreicher, E. G. Kinetic study and production of *N*-carbamoyl-D-phenylglycine by immobilized D-hydantoinase from Vigna angularis. *Catal. Lett.* **2002**, *79*, 17–19; (d) Yang, L.; Wang, J.; Xiang, S.; Sun, W. Screening of strains producing hydantoinase and enzyme production conditions. *Gongye Weishengwu* **2002**, *32*, 15–19, *Chem. Abstr.* **2002**, *138*, 350933; (e) Fan, C. H.; Lee, C. K. Purification of D-hydantoinase from adzuki bean and its immobilization for *N*-carbamoyl-D-phenylglycine production. *Biochem. Eng. J.* **2001**, *8*, 157–164; (f) Arcuri, M. B.; Antunes, O. A. C.; Sabino, S. J.; Pinto, G. F.; Oestreicher, E. G. Resolution of DL-hydantoins by D-hydantoinase from Vigna angularis: Production of highly enantioenriched *N*-carbamoyl-D-phenylglycine at 100% conversion. *Amino Acids* **2000**, *19*, 477–482; (g) Sudge, S. S.; Suresh, B.; Kulbhushan, B.; Gokhale, D.; Vitthal, J.; Rohini, R.; Kolkote, U. R.; Ravindranathan, T. Halophilic *Pseudomonas* strain having accession no. NCIM 5109 (ATCC 55940) and a process for preparing D(−)*N*-carbamoylphenylglycine using said strain. U. S. Patent 6121024, 2000; *Chem. Abstr.* **2000**, *133*, 236935; (h) Sudge, S. S.; Bastawde, K. B.; Gokhale, D. V.; Kalkote, U. R.; Ravindranathan, T. Production of D-hydantoinase by halophilic Pseudomonas sp. NCIM 5109. *Appl. Microbiol. Biotechnol.* **1998**, *49*, 594–599; (i) Morin, A.; Poitras, E.; Moresoli, C.; Brion, F. Extraction of cyclic amide amidohydrolase from green hulls of *Pisum sativum* and its use as biocatalyst for *N*-carbamoyl amino acids. *Bioresource Technol.* **1995**, *53*, 31–37; (j) Runser, S.; Ohleyer, E. Properties of the hydantoinase from *Agrobacterium sp.* IP I-671. *Biotechnol. Lett.* **1990**, *12*, 259–264; (k) Takeichi, M.; Tawaki, S.; Tarukawa, H.; Aikawa, T. Manufacture of D-*N*-carbamoyl-α-amino acids with *bacillus cereus*. Japan Patent 02145192, 1990; *Chem. Abstr.* **1990**, *113*, 189784; (l) Abe, T.; Ogishi, H. Manufacture of D-*N*-

carbamoyl-α-amino acids with *Agromyces, Chromobacterium*, or *Cellulomonas* species. Japan Patent 01228489, 1989; *Chem. Abstr.* **1990**, *112*, 156718; (m) Aikawa, T.; Takeichi, M.; Tawaki, S.; Tarukawa, H. Manufacture of *N*-carbamoyl-D-phenylglycine with *Pseudomonas striata* from phanylhydantoin. Japan Patent 01168293, 1989; *Chem. Abstr.* **1990**, *1125*, 75316; (n) Yokozeki, K.; Kubota, K. Enzymic production of D-amino acids from 5-substituted hydantoins, part III: Mechanism of asymmetric production of D-amino acids from the corresponding hydantoins by *pseudomonas* sp. *Agr. Biol. Chem.* **1987**, *51*, 721–728; (o) Kanegafuchi Chemical Industry. Production of *N*-carbamoyl-D-α-amino acids. Japan Patent 81 58493, 1981; *Chem. Abstr.* **1981**, *95*, 185549; (p) Takahashi, S.; Ohashi, T.; Kii, Y.; Kumagai, H.; Yamada, H. Microbial transformation of hydantoins to amino acids, III: Microbial transformation of hydantoins to *N*-carbamoyl-D-amino acids. *J. Ferment. Technol.* **1979**, *57*, 328–332; (q) Yoneta, K.; Nagata, T.; Fukumitsu, H.; Yano, Y. D-*N*-Carbamoylphenylglycine. Japan Patent 79 55788, 1979; *Chem. Abstr.* **1979**, *91*, 106622; (r) Yamada, H.; Takahashi, S.; Yoneda, K. D-*N*-Carbamoyl-α-amino acids. Japan Patent 2757980, 1978; *Chem. Abstr.* **1979**, *90*, 4442; (s) Dudley, K. H.; Roberts, S. B. Dihydropyrimidinase: Stereochemistry of the metabolism of some 5-alkylhydantoins. *Drug Metab. Dispos.* **1978**, *6*, 133–139; (t) Viglia, A.; Fascetti, E.; Perricone, E.; Degen, L. Enzymic complexes suitable for the conversion of racemic hydantoins into optically active amino acids. Ger. Patent 2811303, 1978; *Chem. Abstr.* **1979**, *90*, 2094; (u) Yamada, H.; Takahashi, S.; Yoneta, K. D-*N*-Carbamoylphenylglycines. Japan Patent 78 44690, 1978; *Chem. Abstr.* **1978**, *89*, 74216.

7. (a) Nazaki, H.; Takenaka, Y.; Kira, I.; Watanabe, K.; Yokozeki, K. D-Amino acid production by *E. coli* co-expressed three genes encoding hydantoin racemase, D-hydantoinase and *N*-carbamoyl-D-amino acid amidohydrolase. *J. Mol. Cat. B—Enzym.* **2005**, *32*, 213–218; (b) Taillades, J.; Boiteau, L.; Beuzelin, I.; Lagrille, O.; Biron, J. P.; Vayaboury, W.; Vandenabeele-Trambouze, O.; Giani, O.; Commeyras, A. A pH-dependent cyanate reactivity model: Application to preparative *N*-carbamoylation of amino acids. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1247–1254; (c) Smyth, D. G. Carbamoylation of amino and tyrosine hydroxyl groups: Preparation of an inhibitor of oxytocin with no intrinsic activity on the isolated uterus. *J. Biol. Chem.* **1978**, *242*, 1579–1591; (d) Gopko, V. F.; Shustova, N. D.; Anoshina, G. M.; Zubova, T. E.; Radina, L. B. Synthesis and study of α-(nitrosoureido)carboxylic acids with potential antineoplastic activity. *Khim.-Farm. Zh.* **1978**, *12*, 53; Chem. Abstr. **1978**, *89*, 146399; (e) Williams, A.; Jencks, W. P. Urea synthesis from amines and cyanic acid: Kinetic evidence for a zwitterionic intermediate. *J. Chem. Soc., Perkin Trans.* **1974**, *2*, 1753–1759; (f) Gustafsson, H.; Ragnarsson, U. New route of α-hydrazinopropionic acid of high optical purity. *Acta Pharm. Suec.* **1974**, *11*, 493–494; (g) Bayerlein, F.; Kolbeck, W.; Stark, A. Cysteine *N*-carbamide. Ger. Patent 1518734, 1973; *Chem. Abstr.* **1973**, *89*, 137500; (h) Suzuki, T.; Igarashi, K.; Hase, K.; Tuzimura, K. Optical rotatory dispersion and circular dichroism of amino acid hydantoins. *Agric. Biol. Chem.* **1973**, *37*, 411–416; (i) Diamalt, A.-G. *N*-Carbamides of amino acids containing thiol groups, for treating hyperviscous pituita. Fr. Pat. M. 6492, 1969; *Chem. Abstr.* **1971**, *75*, 36679; (j) Stark, A.; Kolbeck, W.; Bayerlein, F. *N*-Carbamoylcysteine. Brit. Patent 1161029, 1969; *Chem. Abstr*. **1969**, *71*, 128766; (k) Beecham Group Ltd. Substituted 6-aminopenicillanic acids. Neth. Patent Appl. 6509544, 1966; *Chem. Abstr.*; **1966**, *65*, 3883c,; (l) Dakin, H. D. Constitution of allantoin and

allied substances. *J. Chem. Soc.* **1915**, *107*, 434–439; (m) Dakin, H. D.; Dudley, H. W. Resolution of inactive uramido acids and hydantoins into active components, and their conversion into amino acids, I: β-Phenyl-α-uramidopropionic acid, benzylhydantoin and phenylalanine. *J. Biol. Chem.* **1914**, *17*, 29–36.

8. (a) Miyoda, Y.; Saito, M. Preparation of hydantoic acids from α-amino acids and ureas and hydantoins by cyclization of them. Japan Patent 2003321458, 2003, *Chem. Abstr.* **2003**, *139*, 364933; (b) Tokyo Fine Chemicals Co. ω-Ureido amino acids. Japan Patent 58105954, 1983, *Chem. Abstr.* **1983**, *99*, 195405; (c) Pechenkin, A.; Evseeva, A. V.; Gilev, A. P.; Mikhailova, T. V. Ureido acids and their derivatives. *Izv. Tomsk. Politekh. Inst.* **1974**, *233*, 73–75; *Chem. Abstr.* **1975**, *82*, 169967; (d) Mauvernay, R. Y. Ureido acids by reaction of urea with amino acids. Fr. Patent 1226531, 1960; *Chem. Abstr.* **1961**, *55*, 22137a; (e) Shigeyuki, T.; Teruhisa, N.; Yoshiaki, M.; Morizo, I. Synthesis of ureido-C^{14} succinic acid and orotic-2-C^{14} acid from urea-C^{14}. *Pharm. Bull.* **1956**, *4*, 492–494; (f) Lippich, F. Ureido acids, II. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2953–2974.
9. For reviews, see (a) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gun, A. Microwave-assisted synthesis—A critical technology overview. *Green Chem.* **2004**, *6*, 128–141; (b) Larhed, M.; Moberg, C.; Hallberg, A. Microwave-accelerated homogeneous catalysis in organic chemistry. *Acc. Chem. Res.* **2002**, *35*, 717–727; (c) Kidwai, M. Dry media reactions. *Pure Appl. Chem.* **2001**, *73*, 147–151; (d) Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron* **2001**, *57*, 9199–9283; (e) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave-assisted organic synthesis—A review. *Tetrahedron* **2001**, *57*, 9225–9283; (f) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. New solvent free organic synthesis using focused microwaves. *Synthesis* **1998**, 1213–1234; (g) Caddick, S. Microwave-assisted organic-reactions. *Tetrahedron* **1995**, *51*, 10403–10432; (h) Abramovitch, R. A. Applications of microwave energy in organic chemistry—A review. *Org. Prep. Proc. Int.* **1991**, *23*, 683–711.
10. (a) Verardo, G.; Geatti, P.; Lesa, B. Fast and convenient synthesis of alpha-*N*-protected amino acid hydrazides. *Synthesis* **2005**, 559–564; (b) Verardo, G.; Geatti, P.; Pol, E.; Giumanini, A. G. Sodium borohydride: A versatile reagent in the reductive N-monoalkylation of alpha-amino acids and alpha-amino methyl esters. *Can. J. Chem.* **2002**, *80*, 779–788.