Novel Three-component Coupling Reaction of Carbodiimide, Methyl Hydrogen Maleate, and an Alcohol or Amine: Synthesis of *N*-Carbamoylaspartic Acid Derivatives

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A novel three-component coupling reaction of methyl hydrogen maleate **1**, a carbodiimide **2**, and an alcohol or amine gave derivatives of *N*-carbamoylaspartic acid (**3**) in moderate to excellent yields. In the coupling, an intramolecular Michael addition of the acylisourea **6** subsequently occurs to give a new intermediate, 2-iminooxazolidin-5-one **7**. The addition of alcohol or amine to the second intermediate **7** completes the three-component coupling.

Carbodiimides **2** are known as versatile synthetic reagents,[1-7] which are particularly useful for synthesis of carboxylic acid derivatives. Their high reactivity is due to the electrophilic acyl-carbonyl carbon of an acylisourea intermediate,[8] which is easily attacked by various nucleophiles (either amines, alcohols or acids) to give the corresponding derivatives (amides, esters or acid anhydrides). However, the nucleophilic behaviour of acylisoureas has not been reported. In this paper we describe the novel three-component coupling reaction of a carbodiimide **2**, methyl hydrogen maleate **1**, and an alcohol or amine, which proceeds *via* the new intermediate, the 2-iminooxazolidin-5-one **7** generated from the acylisourea **6**. To the best of our knowledge, generation of intermediate **7** is the first example of Michael addition to an acylisourea intermediate. The coupling reaction gave derivatives of *N*-carbamoylaspartic acid. Although unsubstituted *N*-carbamoylaspartic acid was prepared by the reaction of aspartic acid and potassium cyanate,[9] synthesis of *N*, *N'*-disubstituted *N*-carbamoylaspartic acid has yet not been reported.

The reaction of monoester **1** with alcohols gave the urea **3** as a major product (Table 1). Maleate **1** in acetonitrile was added to a solution of the carbodiimide **2** and an excess of an alcohol in acetonitrile at 0 °C. After the addition, the resulting solution was warmed to room temperature and stirred for 5 h. Best yield (95%) was observed in the case of compound **3a** (R^1 = Bn, R^2XH = MeOH, entry 1). Less bulky R^1 groups and smaller alcohols gave better yields of the products **3**. The ratio of ureas **3** to imidazolidinediones **4**[10] is almost unchanged in the reaction of *N,N'*-diisopropylcarbodiimide **2b** and *N,N'*-dicyclohexylcarbodiimide **2c** (entries 3–6).

One mole equivalent of amine was enough for the reaction, because amines are more nucleophilic than alcohols. The reaction of a primary amine (benzylamine) did not give diamide **3g** in the reaction (entry 7 in Table 1). The reaction of compounds **2b** (entry 9) and **2c** (entry 11) afforded diamides **3i** and **3k** as major products, respectively. A competitive intermolecular condensation reaction resulting in formation of the acid anhydride of monoester **1** might occur in the reaction of compound **2a** (R^1 = Bn) to decrease the yield of diamide **3g**. The larger R^1 group gave the better yield because of suppression of the condensation of monoester **1** by steric repulsion. In the reaction of compound **1** with a secondary amine (diethylamine), compounds **3h**, **3j** and **3l** were obtained, each as a single product (entries 8, 10 and 12, respectively), which was due to the increased nucleophilicity of diethylamine compared with that of benzylamine.

The effects of temperature and the solvent on the yield and the product ratio were investigated (Table 2). The best yield of the three-component coupling of substrates **1**, **2d** [R^1 = (*S*)-1-phenylethyl] and methanol was attained at 40 °C to afford product **3m** (84%) together with a minor amount of compound

Table 1 Reaction of maleate **1**, carbodiimide **2**, and alcohol or amine in acetonitrile

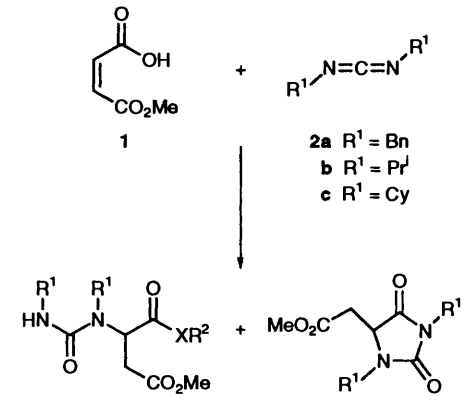
Entry	Carbodiimide	R^2XH	Yield (%)[a] 3	4
1[b]	**2a** (R^1 = Bn)	MeOH	95 **3a**	0 **4a**
2[b]		Pr^iOH	35 **3b**	62 **4a**
3[b]	**2b** (R^1 = Pr^i)	MeOH	60 **3c**	17 **4b**
4[b]		Pr^iOH	65 **3d**	10 **4b**
5[b]	**2c** (R^1 = Cy)	MeOH	73 **3e**	24 **4c**
6[b]		Pr^iOH	68 **3f**	21 **4c**
7[c]	**2a** (R^1 = Bn)	$BnNH_2$	0 **3g**	5 **4a**
8[c]		Et_2NH	44 **3h**	0 **4a**
9[c]	**2b** (R^1 = Pr^i)	$BnNH_2$	71 **3i**	8 **4b**
10[c]		Et_2NH	55 **3j**	0 **4b**
11[c]	**2c** (R^1 = Cy)	$BnNH_2$	92 **3k**	4 **4c**
12[c]		Et_2NH	66 **3l**	0 **4c**

[a] Isolated yield. [b] To a solution of a carbodiimide **2** in an alcohol (1.2 cm^3) and acetonitrile (1.8 cm^3) was added a solution of methyl hydrogen maleate **1** (1 mol equiv.) in acetonitrile (8.3 cm^3) at 0 °C and then the reaction temperature was raised to room temperature. The solution was stirred for 5 h. [c] To a solution of a carbodiimide **2** in an amine (1 mol equiv.) in acetonitrile (1.8 cm^3) was added a solution of methyl hydrogen maleate **1** (1 mol equiv.) in acetonitrile (8.3 cm^3) at 0 °C and then the reaction temperature was raised to ambient. The solution was stirred for 5 h.

Table 2 Temperature and solvent effect in the three-component coupling reaction of monoester **1**, the carbodiimide **2d** and an alcohol[a]

Entry	Solvent	Temp. (T/°C)	Yield (%)[b] 3	4d	5
1	MeOH	23	61 **3m**	7	0
2	MeOH	40	84 **3m**	11	0
3	MeOH	65	54 **3m**	17	0
4	EtOH	40	50 **3n**	9	3
5	Pr^iOH	40	10 **3o**	21	51

[a] To a solution of the carbodiimide **2d** in an alcohol was added dropwise a solution of methyl hydrogen maleate **1** (1 mol equiv.) in the alcohol. The solution was stirred for 1 h. [b] Isolated yield.



1

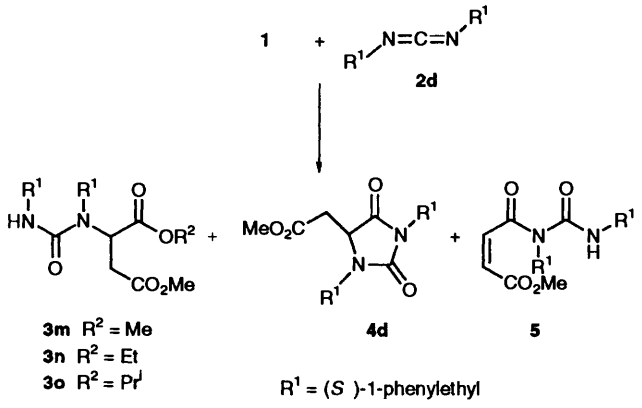
2a R^1 = Bn
b R^1 = Pr^i
c R^1 = Cy

3a R^1 = Bn, XR^2 = OMe
b R^1 = Bn, XR^2 = OPr^i
c R^1 = Pr^i, XR^2 = OMe
d R^1 = Pr^i, XR^2 = OPr^i
e R^1 = Cy, XR^2 = OMe
f R^1 = Cy, XR^2 = OPr^i
g R^1 = Bn, XR^2 = NHBn
h R^1 = Bn, XR^2 = NEt_2
i R^1 = Pr^i, XR^2 = NHBn
j R1 = Pr^i, XR^2 = NEt_2
k R^1 = Cy, XR^2 = NHBn
l R^1 = Cy, XR^2 = NEt_2

4a R^1 = Bn
b R^1 = Pr^i
c R^1 = Cy

(Bn = benzyl, Cy = cyclohexyl)

Reagents and conditions: R^2XH, MeCN, 0 °C to room temp., 5 h



3m R^2 = Me
3n R^2 = Et
3o R^2 = Pr^i

4d

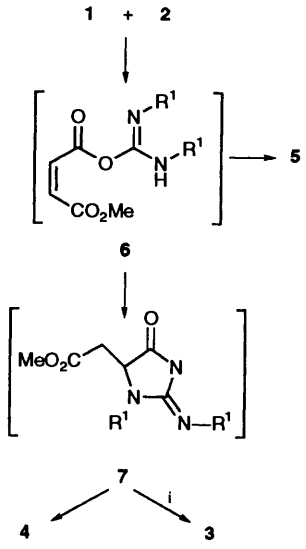
5

R^1 = (*S*)-1-phenylethyl

Reagents and conditions: R^2OH, 1 h

4d (11%) (entries 1–3). The reaction in ethanol (entry 4) gave compound **3n** but in only moderate yield. However, the reaction in propan-2-ol (entry 5) gave compound **5** as the major product. The less polar alcohol propan-2-ol might have some effect in suppressing the generation of intermediate **7** since the Michael addition is known to be suppressed in non-polar solvents.[11]

As for the mechanism of the three-component coupling, first we postulated the mechanism involving esterification of monoester **1** with methanol in the presence of a carbodiimide **2** followed by Michael addition of the urea to the dimethyl maleate to afford the corresponding compound **3**. However, this mechanism was unequivocally disproved since the urea was unreactive to dimethyl maleate under the reaction conditions used. The alternative mechanism is postulated in Scheme 1, where species **7** is a key intermediate to explain the formation of product **3**. The reaction of substrates **1** and **2** gives the first intermediate acylisourea **6**, followed by an intramolecular Michael addition to generate the second intermediate **7**. Subsequently, the alcohol attacks the carbonyl of intermediate **7** to give product **3**. However, in the case of less reactive nucleophiles, cleavage of the CO–O single bond of intermediate



Scheme 1 Plausible mechanism for the reaction. *Reagent:* i, R^2XH.

7 followed by migration of the acyl group to the imino nitrogen, preferentially proceeds to afford an imidazolidinedione **4**. On the other hand, in less polar solvents, acylisourea **6** rearranges to acylurea **5** because of the suppression of the intramolecular Michael addition. AM1 calculation indicated that compound **7** (R^1 = Me) is 10.5 kcal mol^{-1} * more stable than compound **6** (R^1 = Me).[12]

In order to examine the absence of equilibrium between isomers **6** and **7**, coupling with deuteriated alcohols was carried out. The reaction of compound **1** with the carbodiimide **2d** in Pr^{i}OD afforded the maleylurea **5** with no deuterium incorporation at either the α- or the β-position. This observation confirms the lack of equilibrium between the intermediates **6** and **7**. Accordingly, the generation of the products (**3**, **4** and **5**) from intermediate **6** is kinetically controlled.

In summary the novel three-component coupling reaction has been established. A mechanistic investigation showed the involvement of the new intermediate, 2-iminooxazolidin-5-one **7** which was generated by intramolecular Michael addition to acylisoureau **6**. A new synthetic route for derivatives of *N*-carbamoylaspartic acid has been developed.

Experimental

General Details.—M.p.s were determined on a Yanako MP-S3 melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO A-202 spectrometer. NMR spectra were recorded on a JEOL EX90 or a JNM FX270 instrument. All NMR spectra were recorded in deuteriochloroform as solvent and the chemical shifts were recorded relative to internal tetramethylsilane as standard. Coupling constants (*J*) are given in Hz. Exact mass spectra were obtained on an Hitachi RNR-7M mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 analyser.

Preparation of Materials.—Methyl hydrogen maleate **1** was prepared by the reaction of maleic anhydride with stirred MeOH for 1 h at room temperature. Carbodiimides **2** were prepared by the literature method.[7]

General Procedure for the Three-component Coupling Reaction in a Solution of Acetonitrile and Alcohol.—To a solution of a carbodiimide **2** (1.49 mmol) in MeCN (1.2 cm^3)–alcohol (1.8

* 1 cal = 4.184 J.

cm^3) was added dropwise a solution of compound **1** (1.49 mmol) in MeCN (8.3 cm^3) at 0 °C. After being stirred at room temperature for 5 h, the solution was concentrated under reduced pressure. To the residue was added ethyl acetate and the solution was washed successively with 1 mol dm^{-3} HCl and aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The oily products were separated by column chromatography on silica gel and elution with hexane–ethyl acetate (12:1) to give the three-component coupling product **3** and the hydantoin derivative **4**.

Dimethyl 2-(1,3-*dibenzylureido*)*succinate* **3a**. ν_{max}(neat)/cm^{-1} 3368, 3028, 2948, 1738, 1650 and 1586; δ_H(90 MHz; $CDCl_3$) 2.83 (1 H, dd, *J* 16.9 and 7.3), 3.23 (1 H, dd, *J* 16.9 and 6.6), 3.63 (3 H, s), 3.70 (3 H, s,), 4.32 (2 H, d, *J* 5.7), 4.50 (2 H, s), 4.87 (1 H, dd, *J* 7.3 and 6.6), 4.79–4.95 (1 H, m) and 7.00–7.40 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 35.35, 44.57, 51.70, 52.24, 58.03, 126.50, 126.91, 127.00, 127.60, 128.29, 128.79, 136.85, 138.91, 157.79, 171.07 and 171.61 [Found: $(M + H)^+$, 385.1762. Calc. for $C_{21}H_{25}N_2O_5$: *m*/*z*, 385.1764].

Methyl (N,N'-*dibenzyl*-2,5-*dioxoimidazolidin*-4-*yl*)*acetate* **4a**. ν_{max}(neat)/cm^{-1} 3032, 2948, 1770, 1720 and 1500; δ_H(90 MHz; $CDCl_3$) 2.71 (2 H, d, *J* 4.7), 3.36 (3 H, s), 4.02 (1 H, t, *J* 4.7), 4.29 (1 H, d, *J* 15.4), 4.67 (2 H, s), 4.71 (1 H, d, *J* 15.4) and 7.20–7.40 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 33.53, 42.57, 45.08, 51.64, 55.76, 127.60, 127.78, 128.38, 128.47, 128.61, 135.66, 135.81, 156.45, 169.01 and 171.40 [Found: $(M + H)^+$, 353.1499. Calc. for $C_{20}H_{21}N_2O_4$: *m*/*z*, 353.1496].

1-*Isopropyl* 4-*methyl* 2-(1,3-*dibenzylureido*)*succinate* **3b**. M.p. 109–110 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 3420, 2900, 2870, 1725, 1660 and 1535; δ_H(90 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 6.2), 1.27 (3 H, d, *J* 6.6), 2.88 (1 H, dd, *J* 16.3 and 7.2), 3.22 (1 H, dd, *J* 16.3 and 6.5), 3.64 (3 H, s), 4.28 (1 H, dd, *J* 15.2 and 5.6), 4.40 (1 H, dd, *J* 15.2 and 5.6), 4.47 (1 H, d, *J* 16.9), 4.56 (1 H, d, *J* 16.9), 4.68–4.89–(2 H, m), 5.02 (1 H, qq, *J* 6.6 and 6.2) and 7.00–7.50 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 21.57, 21.75, 35.44, 44.66, 51.76, 52.00, 58.68, 69.18, 126.74, 127.00, 127.15, 127.69, 128.38, 128.85, 137.15, 139.09, 157.76, 170.03 and 171.88 (Found: C, 66.9; H, 6.8; N, 7.0. Calc. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79%).

Dimethyl 2-(1,3-*diisopropylureido*)*succinate* **3c**. M.p. 91–93 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 3300, 2960, 1750, 1610 and 1540; δ_H(90 MHz; $CDCl_3$) 1.14 (6 H, d, *J* 6.6), 1.28 (6 H, d, *J* 6.6), 2.47 (1 H, dd, *J* 16.9 and 3.9), 3.54 (1 H, dd, *J* 16.9 and 9.0), 3.70 (3 H, s), 3.71 (3 H, s), 3.65–4.10 (2 H, m), 4.30 (1 H, dd, *J* 9.0 and 3.9) and 4.20–4.50 (1 H, m); δ_C(22.4 MHz; $CDCl_3$) 20.31, 21.18, 22.82, 23.03, 37.05, 42.27, 47.49, 51.40, 51.73, 51.94, 155.97, 171.82 and 172.08 (Found: C, 54.4; H, 8.4; N, 10.2. Calc. for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72%).

Methyl (N,N'-*diisopropyl*-2,5-*dioxoimidazolidin*-4-*yl*)*acetate* **4b**. ν_{max}(neat)/cm^{-1} 2976, 1744, 1712, 1438 and 1370; δ_H(90 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 7.1), 1.28 (3 H, d, *J* 7.0), 1.42 (3 H, d, *J* 7.0), 1.43 (3 H, d, *J* 7.1), 2.83 (1 H, dd, *J* 17.1 and 4.8), 3.07 (1 H, dd, *J* 17.1 and 3.9), 3.68 (3 H, s), 4.05 (1 H, dd, *J* 4.8 and 3.9) and 4.00–4.80 (2 H, m); δ_C(22.4 MHz; $CDCl_3$) 19.09, 19.30, 19.45, 21.15, 34.96, 43.67, 44.66, 51.73, 54.03, 155.97, 169.10 and 171.94 [Found: $(M + H)^+$, 247.1504. Calc. for $C_{12}H_{21}N_2O_4$: *m*/*z*, 257.1501].

1-*Isopropyl* 4-*methyl* 2-(1,3-*diisopropylureido*)*succinate* **3d**. M.p. 83–84 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 2970, 1740, 1615 and 1540; δ_H(90 MHz; $CDCl_3$) 0.99–1.36 (18 H, m), 2.44 (1 H, dd, *J* 16.7 and 3.9), 3.53 (1 H, dd, *J* 16.7 and 8.8), 3.71 (3 H, s), 3.89 (1 H, septet, *J* 6.8), 4.23 (1 H, dd, *J* 8.8 and 3.9), 3.70–4.70 (2 H, m) and 5.00 (1 H, septet, *J* 6.3); δ_C(22.4 MHz; $CDCl_3$) 20.34, 21.06, 21.24, 21.45, 22.85, 23.18, 36.87, 42.15, 47.37, 51.34, 52.03, 68.41, 155.82, 170.71 and 172.14 (Found: C, 56.9; H, 8.9; N, 8.85. Calc. for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85%).

Dimethyl 2-(1,3-*dicyclohexylureido*)*succinate* **3e**. M.p. 128–129 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 3350, 2930, 1720, 1645 and 1545; δ_H(90 MHz; $CDCl_3$) 0.85–2.09 (20 H, m), 2.44 (1 H, dd, *J* 16.8 and 3.9), 3.54 (1 H, dd, *J* 16.8 and 8.7), 3.69 (3 H, s), 3.71 (3 H, s), 3.12–3.95 (2 H, m), 4.32 (1 H, dd, *J* 8.7 and 3.9) and 4.22–4.48 (1 H, m); δ_C(22.4 MHz; $CDCl_3$) 24.76, 25.00, 25.36, 25.59, 25.74, 30.91, 31.77, 33.35, 33.50, 37.14, 49.19, 51.43, 51.94, 52.39, 56.41, 155.94, 171.85 and 172.11 (Found: C, 62.1; H, 8.8; N, 7.7. Calc. for $C_{19}H_{32}N_2O_5$: C, 61.93; H, 8.75; N, 7.60%).

Methyl (N,N'-*dicyclohexyl*-2,5-*dioxoimidazolidin*-4-*yl*)*acetate* **4c**. ν_{max}(neat)/cm^{-1} 2936, 2856, 1744, 1714 and 1694; δ_H(90 MHz; $CDCl_3$) 0.85–2.41 (20 H, m), 2.82 (1 H, dd, *J* 12.0 and 5.0), 3.06 (1 H, dd, *J* 12.0 and 3.7), 3.67 (3 H, s), 3.60–4.00 (2 H, m) and 4.05 (1 H, dd, *J* 5.0 and 3.7); δ_C(22.4 MHz; $CDCl_3$) 24.94, 25.12, 25.65, 28.88, 29.06, 30.10, 31.68, 35.23, 51.52, 51.79, 52.92, 54.24, 155.21, 169.07 and 172.11 [Found: $(M + H)^+$, 337.2129. Calc. for $C_{18}H_{29}N_2O_4$: *m*/*z*, 337.2127].

1-*Isopropyl* 4-*methyl* 2-(1,3-*dicyclohexylureido*)*succinate* **3f**. M.p. 134–136 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 2930, 2860, 1730, 1615 and 1525; δ_H(90 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.2), 1.25 (3 H, d, *J* 6.2), 1.00–2.21 (20 H, m), 2.43 (1 H, dd, *J* 16.6 and 3.7), 3.55 (1 H, dd, *J* 16.6 and 9.2), 3.72 (3 H, s), 3.62–3.94 (2 H, m), 4.28 (1 H, dd, *J* 9.2 and 3.7), 4.49 (1 H, d, *J* 7.7) and 5.00 (1 H, septet, *J* 6.2); δ_C(22.4 MHz; $CDCl_3$) 21.42, 21.63, 24.76, 24.85, 25.15, 25.51, 25.83, 25.92, 31.05, 31.77, 33.50, 33.77, 37.11, 49.19, 51.52, 52.83, 56.47, 68.62, 155.94, 170.89 and 172.32 (Found: C, 63.65; H, 9.2; N, 7.1. Calc. for $C_{21}H_{36}N_2O_5$: C, 63.61; H, 9.15; N, 7.07%).

Methyl N-*benzyl*-3-(1,3-*dibenzylureido*)*succinamate* **3g**. M.p. 123–125 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3330, 1745, 1665 and 1555; δ_H(90 MHz; $CDCl_3$) 2.64 (1 H, dd, *J* 16.8 and 6.7), 3.10 (1 H, dd, *J* 16.8 and 8.7), 3.64 (3 H, s), 4.20–4.48 (5 H, m), 4.56 (1 H, d, *J* 16.3), 5.07 (1 H, t, *J* 5.0), 5.29 (1 H, dd, *J* 8.8 and 6.7), 6.88 (1 H, t, *J* 5.2) and 7.04–7.45 (15 H, m); δ_C(22.4 MHz; $CDCl_3$) 33.65, 43.26, 44.69, 48.69, 51.67, 55.19, 126.35, 126.91, 127.12, 127.33, 127.57, 128.35, 128.41, 128.88, 137.06, 137.95, 138.76, 158.66, 170.29 and 171.22 (Found: C, 70.4; H, 6.15; N, 9.4. Calc. for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14%).

Methyl 3-(1,3-*dibenzylureido*)-N,N-*diethylsuccinamate* **3h**. ν_{max}(neat)/cm^{-1} 3390, 2990, 1740, 1640 and 1530; δ_H(90 MHz; $CDCl_3$) 0.97 (3 H, t, *J* 7.1), 1.24 (3 H, t, *J* 7.1), 2.57 (1 H, dd, *J* 16.0 and 5.5), 3.11 (1 H, dd, *J* 16.0 and 9.1), 3.16 (2 H, q, *J* 7.1), 3.37 (2 H, q, *J* 7.1), 3.62 (3 H, s), 4.31 (1 H, d, *J* 8.6), 4.34 (2 H, d, *J* 5.3), 4.49 (1 H, d, *J* 8.6), 5.10 (1 H, t, *J* 5.3), 5.69 (1 H, m) and 6.97–7.50 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 12.32, 13.87, 34.63, 40.24, 41.53, 44.72, 46.90, 50.98, 51.46, 126.29, 127.39, 128.23, 128.64, 137.24, 138.82, 157.38, 168.77 and 171.34 [Found: $(M + H)^+$, 426.2380. Calc. for $C_{24}H_{32}N_3O_4$: *m*/*z*, 426.2367].

Methyl N-*benzyl*-3-(1,3-*diisopropylureido*)*succinamate* **3i**. M.p. 129–130 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3370, 1740, 1635 and 1535; δ_H(90 MHz; $CDCl_3$) 0.93–1.32 (12 H, m), 2.66 (1 H, dd, *J* 16.5 and 5.7), 3.32 (1 H, dd, *J* 16.5 and 8.1), 3.69 (3 H, s), 3.96 (1 H, septet, *J* 6.8), 3.69–4.16 (2 H, m), 4.38–4.82 (3 H, m), 4.78 (1 H, d, *J* 7.5) and 7.11–7.50 (5 H, m); δ_C(22.4 MHz; $CDCl_3$) 20.94, 21.06, 22.97, 23.24, 35.35, 42.48, 43.35, 47.23, 51.67, 53.70, 127.12, 127.27, 128.38, 137.86, 156.99 and 171.64 (Found: C, 62.5; H, 8.1; N, 12.1. Calc. for $C_{19}H_{29}N_3O_4$: C, 62.78; H, 8.04; N, 11.56%).

Methyl 3-(1,3-*diisopropylureido*)-N,N-*diethylsuccinamate* **3j**. ν_{max}(neat)/cm^{-1} 2968, 1738, 1640 and 1516; δ_H(90 MHz; $CDCl_3$) 0.85–1.45 (18 H, m), 2.61 (1 H, dd, *J* 16.4 and 6.3), 3.06 (1 H, dd, *J* 16.4 and 8.1), 2.90–4.00 (5 H, m), 3.67 (3 H, s), 3.94 (1 H, septet, *J* 6.5), 4.92 (1 H, d, *J* 7.1) and 5.30 (1 H, dd, *J* 8.1 and 6.3); δ_C(22.4 MHz; $CDCl_3$) 12.32, 13.78, 21.24, 22.94, 23.09, 34.78, 40.15, 42.21, 45.55, 51.49, 51.94, 156.06, 169.01 and 171.97

[Found: $(M + H)^+$, 330.2397. Calc. for $C_{16}H_{32}N_3O_4$: *m/z*, 330.2401].

Methyl N-*benzyl*-3-(1,3-*dicyclohexylureido*)*succinamate* **3k**. M.p. 133–135 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3470, 3410, 2930, 2850, 1740, 1630 and 1525; δ_H(90 MHz; $CDCl_3$) 0.70–2.05 (20 H, m), 2.61 (1 H, dd, *J* 16.3 and 5.2), 3.35 (1 H, dd, *J* 16.3, 8.3), 3.39–3.91 (2 H, m), 3.70 (3 H, s), 4.37–4.65 (4 H, m), 4.79 (1 H, d, *J* 7.5) and 7.27–7.49 (5 H, m); δ_C(22.4 MHz; $CDCl_3$) 24.61, 24.97, 25.33, 25.65, 25.83, 31.35, 31.65, 33.17, 33.26, 35.47, 43.32, 49.28, 51.58, 54.15, 56.06, 127.06, 127.21, 128.29, 137.77, 156.75 and 171.64 (Found: C, 67.6; H, 8.3; N, 9.9. Calc. for $C_{25}H_{37}N_3O_4$: C, 67.69; H, 8.41; N, 9.47%).

Methyl 3-(1,3-*dicyclohexylureido*)-N,N-*diethylsuccinamate* **31**. M.p. 104–105 °C (from hexane–EtOAc); ν_{max}(neat)/cm^{-1} 3360, 2920, 1725, 1640 and 1450; δ_H(90 MHz; $CDCl_3$) 1.11 (3 H, t, *J* 7.1), 1.22 (3 H, t, *J* 7.1), 1.20–2.20 (20 H, m), 2.62 (1 H, dd, *J* 16.5 and 6.4), 3.06 (1 H, dd, *J* 16.5 and 7.8), 3.67 (3 H, s), 3.01–3.89 (7 H, m) and 5.24 (1 H, dd, *J* 7.8 and 6.4); δ_C(22.4 MHz; $CDCl_3$) 12.11, 13.72, 24.55, 25.18, 25.33, 26.13, 31.29, 31.59, 33.14, 33.44, 34.90, 40.21, 41.11, 48.99, 51.43, 52.21, 55.19, 156.15, 168.89 and 172.02 (Found: C, 64.4; H, 9.5; N, 10.4. Calc. for $C_{22}H_{39}N_3O_4$: C, 64.51; H, 9.60; N, 10.26%).

General Procedure of Three-component Coupling Reaction in Alcohol.—To a solution of compound **2d** (499 mg, 2.00 mmol) and hydroquinone (0.1 mol equiv.) as a polymerisation inhibitor in an alcohol (130 cm^3) was added dropwise a solution of compound **1** (311 mg, 2.40 mmol) in the alcohol (20 cm^3) within 1 h at 40 °C. After the reaction mixture had been stirred for 3 h, the alcohol was evaporated off under reduced pressure. To the residue was added diethyl ether and the solution was washed successively with 1 mol dm^{-3} HCl and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The crude oily products were purified by column chromatography to give a mixture of products **3**, **4** and **5**. Those products were separated by HPLC [Merck Si 60, 7 mμ; hexane–AcOEt (1.5:1)] and further separation of diastereoisomers **3** and **4** were carried out to afford single diastereoisomers.

Dimethyl 2-{1,3-*bis*-[(S)-1-*phenylethyl*]*ureido*}*succinate* **3m**. (First eluent): m.p. 118–119 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3300, 1740, 1620 and 1510; δ_H(270 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 6.8), 1.69 (3 H, d, *J* 6.8), 2.85 (1 H, dd, *J* 16.4 and 5.9), 3.47 (1 H, dd, *J* 16.4 and 5.9), 3.55 (3 H, s), 3.71 (3 H, s), 4.49 (1 H, dd, *J* 7.7 and 5.9), 4.61 (1 H, d, *J* 7.1), 4.78 (1 H, dq, *J* 7.1 and 6.8), 4.91 (1 H, q, *J* 6.8), 7.00–7.08 (2 H, m) and 7.15–7.46 (8 H, m); δ_C(22.4 MHz; $CDCl_3$) 17.81, 22.37, 36.72, 49.94, 51.85, 52.12, 57.19, 125.66, 126.77, 127.90, 128.26, 128.85, 141.12, 144.19, 156.15, 171.58 and 172.32 (Found: C, 66.6; H, 6.7; N, 6.9. Calc. for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79%).

(Second eluent): ν_{max}(neat)/cm^{-1} 3440, 3360, 2960, 1745, 1640, 1525 and 1455; δ_H(270 MHz; $CDCl_3$) 1.31 (3 H, d, *J* 7.0), 1.65 (3 H, d, *J* 7.2), 2.27 (1 H, dd, *J* 17.2 and 4.8), 3.37 (1 H, dd, *J* 17.2 and 9.2), 3.60 (3 H, s), 3.72 (3 H, s), 4.43 (1 H, dd, *J* 9.2 and 4.8), 4.78–4.97 (2 H, m), 5.06 (1 H, q, *J* 7.2) and 7.09–7.40 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 18.29, 22.76, 36.22, 50.09, 51.64, 52.45, 54.71, 55.94, 125.66, 126.85, 127.87, 128.38, 128.88, 130.82, 141.09, 144.13, 156.30 and 172.02 [Found: $(M + H)^+$, 413.2069. Calc. for $C_{23}H_{29}N_2O_5$: *m/z*, 413.2076].

Methyl {2,5-*dioxo*-N,N′-*bis*-[(S)-1-*phenylethyl*]*imidazolidin*-4-*yl*}*acetate* **4d**. (First eluent): ν_{max}(neat)/cm^{-1} 2970, 1740, 1420, 1380, 1200 and 1160; δ_H(270 MHz; $CDCl_3$) 1.59 (3 H, d, *J* 8.3), 1.88 (3 H, d, *J* 7.7), 2.64 (1 H, dd, *J* 16.5 and 5.3), 2.88 (1 H, dd, *J* 16.6 and 2.9), 3.40 (3 H, s), 3.66 (1 H, dd, *J* 5.3 and 2.9), 5.33–5.48 (2 H, m), 7.18–7.41 (8 H, m) and 7.48–7.56 (2 H, m); δ_C(22.4 MHz; $CDCl_3$) 17.21, 18.20, 34.90, 50.81, 51.28, 51.70, 54.42, 127.12, 127.45, 128.11, 128.29, 128.85, 138.43, 140.10, 156.57, 168.98 and 171.82 [Found: $(M + H)^+$, 381.1809. Calc. for $C_{22}H_{25}N_2O_4$: *m/z*, 381.1814].

(Second eluent): m.p. 110–111 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 1740, 1710 and 1430; δ_H(270 MHz; $CDCl_3$) 1.64 (3 H, d, *J* 6.2), 1.89 (3 H, d, *J* 6.2), 2.28 (1 H, dd, *J* 20.0 and 6.9), 2.61 (1 H, dd, *J* 20.0 and 4.6), 3.33 (3 H, s), 4.05 (1 H, dd, *J* 6.9 and 4.6), 5.35–5.48 (2 H, m) and 7.18–7.53 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 15.87, 16.79, 33.92, 49.85, 51.04, 51.61, 53.61, 127.12, 127.54, 127.63, 127.78, 128.41, 128.53, 140.28, 156.78, 168.89 and 171.97 (Found: C, 66.2; H, 6.3; N, 7.4. Calc. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36%).

1-*Ethyl* 4-*methyl* 2-{1,3-*bis*-[(S)-1-*phenylethyl*]*ureido*}*succinate* **3n**. (First eluent): ν_{max}(neat)/cm^{-1} 3430, 2980, 1725, 1630 and 1460; δ_H(270 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.0), 1.32 (3 H, d, *J* 7.0), 1.65 (3 H, d, *J* 7.0), 2.25 (1 H, dd, *J* 17.3 and 4.3), 3.37 (1 H, dd, *J* 17.3 and 8.6), 3.59 (3 H, s), 4.18 (1 H, q, *J* 7.3, 4.19 (1 H, q, *J* 7.3), 4.39 (1 H, dd, *J* 8.6 and 4.3), 4.85 (1 H, d, *J* 7.6), 4.82–4.95 (1 H, m), 5.11 (1 H, q, *J* 7.0) and 7.10–7.45 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 13.84, 18.02, 22.64, 36.00, 49.97, 51.49, 54.92, 55.76, 61.34, 125.60, 126.74, 126.88, 127.75, 128.29, 128.70, 140.94, 144.01, 156.18, 171.40 and 171.91 [Found: $(M + H)^+$, 427.2238. Calc. for $C_{24}H_{31}N_2O_5$: *m/z*, 427.2233].

(Second eluent): m.p. 91–92 °C (from hexane–AcOEt); ν_{max}(KBr)/cm^{-1} 3300, 2990, 1740, 1615 and 1540; δ_H(270 MHz; $CDCl_3$) 1.05 (3 H, t, *J* 7.1), 1.15 (3 H, d, *J* 7.0), 1.69 (3 H, d, *J* 7.0), 2.81 (1 H, dd, *J* 16.8 and 5.5), 3.48 (1 H, dd, *J* 16.8 and 7.5), 3.71 (3 H, s), 3.97 (1 H, dq, *J* 11.1 and 7.1), 4.03 (1 H, dq, *J* 11.1 and 7.1), 4.46 (1 H, dd, *J* 7.5 and 5.5), 4.65 (1 H, d, *J* 7.0), 4.80 (1 H, quintet, *J* 7.0), 4.94 (1 H, q, *J* 7.0) and 7.00–7.50 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 13.36, 17.66, 22.10, 36.45, 49.61, 51.43, 56.56, 60.80, 125.36, 126.35, 126.62, 127.51, 127.90, 128.47, 140.94, 144.13, 155.79, 170.74 and 171.99 (Found: C, 67.4; H, 7.1; N, 6.75. Calc. for $C_{24}H_{30}N_2O_5$: C, 67.58; H, 7.09; N, 6.57%).

Methyl 3-{2,4-*bis*-[(S)-1-*phenylethyl*]*allophanoyl*}*propenoate* **5**. ν_{max}(neat)/cm^{-1} 3320, 3050, 2960, 1715, 1645 and 1220; δ_H(270 MHz; $CDCl_3$) 1.39 (3 H, d, *J* 7.7), 1.74 (3 H, d, *J* 7.7), 3.72 (3 H, s, 4.90 (1 H, m), 5.75 (1 H, m), 5.90 (1 H, d, *J* 12.3), 6.48 (1 H, d, *J* 12.3) and 7.11–7.39 (11 H, m); δ_C(22.4 MHz; $CDCl_3$) 17.48, 22.01, 50.36, 52.06, 53.34, 122.35, 125.87, 126.74, 127.21, 127.36, 128.56, 138.45, 140.19, 142.73, 153.02, 165.46 and 169.07 [Found: $(M + H)^+$, 381.1823. Calc. for $C_{22}H_{25}N_2O_4$: *m/z*, 381.1815].

1-*Isopropyl* 2-{1,3-*bis*-[(S)-1-*phenylethyl*]*ureido*}*succinate* **3o**. (First eluent): ν_{max}(neat)/cm^{-1} 3430, 2980, 1745, 1645 and 1520; δ_H(270 MHz; $CDCl_3$) 1.21 (3 H, d, *J* 6.2), 1.28 (3 H, d, *J* 6.4), 1.32 (3 H, d, *J* 6.4), 1.63 (3 H, d, *J* 7.0), 2.22 (1 H, dd, *J* 16.9 and 4.4), 3.38 (1 H, dd, *J* 16.9 and 8.5), 3.59 (3 H, s), 4.33 (1 H, dd, *J* 8.5, 4.4), 5.11 (1 H, qq, *J* 6.4 and 6.2), 4.80–5.26 (3 H, m) and 7.00–7.60 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 18.20, 21.60, 21.84, 22.91, 36.01, 50.18, 51.70, 55.34, 55.82, 69.27, 125.84, 126.94, 127.12, 127.90, 128.50, 128.85, 141.18, 141.19, 156.27, 171.10 and 172.14 [Found: $(M + H)^+$, 441.2391. Calc. for $C_{25}H_{33}N_2O_5$: *m/z*, 441.2389].

(Second eluent): m.p. 81–83 °C (from hexane–AcOEt); ν_{max}(neat)/cm^{-1} 3320, 2980, 1740, 1620 and 1545; δ_H(90 MHz; $CDCl_3$) 0.80 (3 H, d, *J* 6.4), 1.04 (3 H, d, *J* 6.2), 1.09 (3 H, d, *J* 6.5), 1.61 (3 H, d, *J* 7.3), 2.70 (1 H, dd, *J* 16.7 and 5.5), 3.42 (1 H, dd, *J* 16.7 and 7.4), 3.63 (3 H, s), 4.34 (1 H, dd, *J* 7.4 and 5.5), 4.65–4.93 (4 H, m) and 6.90–7.40 (10 H, m); δ_C(22.4 MHz; $CDCl_3$) 18.05, 21.09, 21.66, 22.77, 36.78, 50.03, 51.85, 57.04, 57.16, 69.06, 125.78, 126.74, 126.97, 127.87, 128.32, 128.85, 141.44, 144.58, 156.04, 170.59 and 172.50 [Found: $(M + H)^+$, 441.2393].

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