Enantioselective Organocatalysis in Ionic Liquids: Addition of Aliphatic Aldehydes and Ketones to Diethyl Azodicarboxylate

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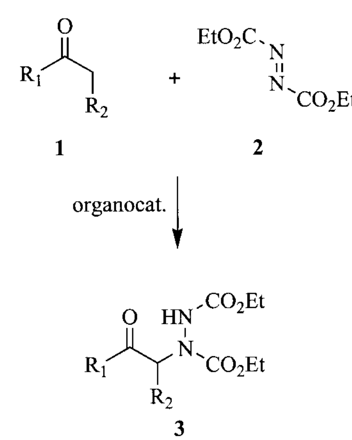
The enantioselective addition of aldehydes to diethyl azodicarboxylate in ionic liquids in the presence of chiral organocatalysts has been investigated. Of seven different organocatalysts tested, L-proline and L-thiazoline-2-carboxylic acid gave the highest enantioselectivities (up to 94 % *ee*). The best results were obtained by using [bmim]PF_6 and [hmim]BF_4 as ionic liquids. The scope of the methodology was probed by using various aldehydes and ketones.

Introduction

The catalysis of asymmetric reactions by small organic molecules, so-called organocatalysts, has received a tremendous amount of interest in recent years.[1–5] Besides asymmetric aldol-type reactions, which represent the earliest and most prominent examples, many other transformations involving enamine intermediates are suitable for organocatalysis, for example, the Michael addition of aldehydes or ketones to β-nitrostyrenes.[6–9]

Recently, it was shown that the enantioselective addition of aldehydes[10,11] or ketones[12,13] to dialkyl azodicarboxylates such as DEAD (**2**) can be performed in the presence of chiral organocatalysts (Scheme 1). Reactions were most frequently carried out at room temperature in acetonitrile in the presence of 10–20 mol-% of L-proline as catalyst. By switching to dichloromethane as the solvent, rather long reaction times (up to several days) could be dramatically shortened. This way, high yields of products (80–96%) were obtained within a few hours by using as little as 2 mol-% of the catalyst. To avoid racemization, enantioselectivities were determined after reduction of the aldehyde/ketone functionality of the primary reaction products and subsequent cyclization to the corresponding oxazolidinones. In many cases, the oxazolidinones were prepared in ≥99% *ee*.



Scheme 1.

As an extension of this methodology, Bräse and co-workers[14] described the amination of α,α-disubstituted aldehydes while Barbas and co-workers[15] achieved an L-proline-catalyzed one-pot transformation with the initially formed α-aminated aldehydes being directly trapped in an aldol reaction with acetone. Instead of an azodicarboxylate, nitrosobenzene was identified as a suitable electrophile in related organocatalytic α-oxyaminations of aldehydes.[12,16–18] Again, L-proline was found to be a very good catalyst and high yields and enantioselectivities were obtained by using acetonitrile, DMSO or chloroform as the solvent.

In recent years, ionic liquids have emerged as frequently used "green" solvents for many organic reactions including transition-metal-catalyzed reactions.[19–25] In organocatalysis, ionic liquids have been used for the quinidinium bromide catalyzed Michael addition of dimethyl malonate to chalcone.[26] Recently, we[27] and (independently) Loh et al.[28] found that ionic liquids are excellent solvents for L-

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proline-catalyzed aldol reactions. In addition, we have demonstrated that the combination of L-proline and an ionic liquid also represents an excellent medium for the enantioselective Michael addition of aldehydes and ketones to β-nitrostyrenes.[29] Following from this, the aim of the work described herein was to further explore and evaluate the applicability of ionic liquids in organocatalysis. As a specific reaction system, the enantioselective addition of aldehydes and ketones to DEAD was studied (Scheme 1).

Results and Discussion

We started our investigation by examining the L-proline-catalyzed addition of different aldehydes and ketones (Figure 1) to DEAD using [bmim]PF_6 as a (common) ionic liquid. All reactions were performed at room temperature on a 1 mmol scale in 1 mL of ionic liquid. Decoloration of the reaction mixture indicated complete consumption of DEAD. The results of this first set of experiments are given in Table 1. Not unexpectedly, reaction rates were found to correlate with the structures of the carbonyl derivatives. In the presence of 5 mol-% of L-proline, the reaction of 3-methylbutanal (**1a**) was complete within 1 hour while significantly longer reaction times (≥18 h) were necessary for the reactions of the sterically hindered aldehyde **1d** and the various ketones.

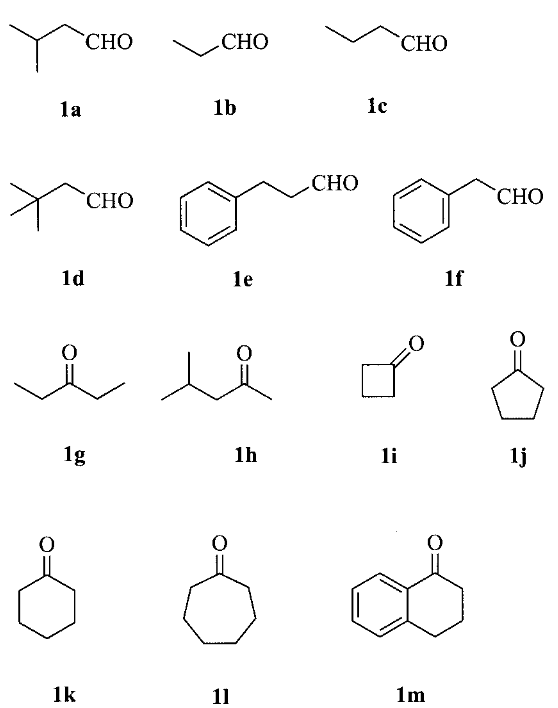


Figure 1. Carbonyl substrates used in this study.

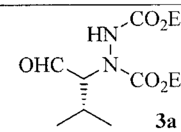
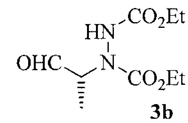
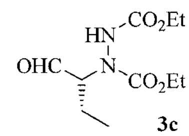
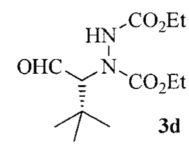
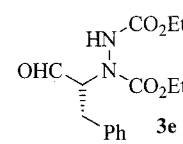
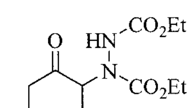
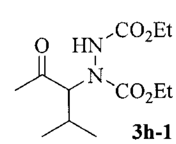
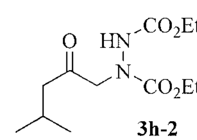
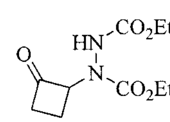
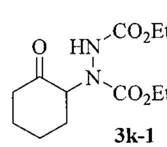
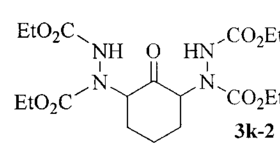
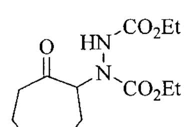
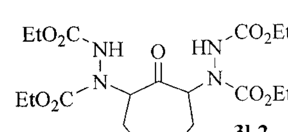
It is remarkable that very high product yields were obtained with the simple aldehydes **1a**, **1b** and **1e** despite the fact that only a slight excess (1.1 equiv.) of these substrates and only 5 mol-% of the catalyst were employed. For comparison purposes, two additional experiments (Table 1, entries 2 and 3) were performed with larger amounts of substrate **1a** (1.5 equiv.) and the catalyst (10%). The almost quantitative yields (≥98%) match those previously reported for the same reaction system in acetonitrile[12] and thus demonstrate the competitiveness of the ionic liquid.

The data in Table 1 also show that reactions involving ketones as substrates gave less satisfactory results. Only in the case of cyclobutanone (**1i**) was the mono-aminated product isolated in 43% yield. On the other hand, cyclohexanone (**1k**) afforded a significant amount of an inseparable mixture of the mono- and bis-aminated products **3k–1** and **3k–2** (38 and 21%, respectively). This result seemingly contrasts the work of Jørgensen and co-workers[12] who reported high yields and enantioselectivities for related reactions in traditional solvents (using 1.5 equiv. of the substrate and up to 20 mol-% of L-proline) without mentioning the formation of any bis-aminated product. We therefore performed an experiment with an increased amount (1.5 equiv.) of cyclohexanone and obtained the mono-aminated product in a respectable yield (58%) along with 11% of the bis-addition product (Table 1, entry 13). In the reaction with cycloheptanone we were able to isolate only 11% of a mixture of the mono- and bis-aminated products even after a prolonged reaction time of 24 h. Note that the mono- and bis-aminated products could not be separated by column chromatography and the ratios of isomers was determined from the ^{1}H NMR spectra of the crude mixtures. To our surprise the reactions with cyclopentanone (**1j**) and 1-tetralone (**1m**) failed in spite of the fact that experiments were performed several times with prolonged reaction times or at a higher temperature (40 °C).

As mentioned above, the complete consumption of DEAD was indicated by the decoloration of the reaction mixtures at the end of the reaction. The rather low product yields observed in several cases (Table 1) can nevertheless be explained by a competitive reduction of the azo group in DEAD. In fact, during the slow reactions the corresponding hydrazo derivative, that is, EtOOC–NH–NH–CO-OEt, was isolated. It is well known that the 2-C–H hydrogen atom of the 1,3-dialkylimidazolium ionic liquid is acidic and we assumed that DEAD could oxidize the imidazolium moiety of the ionic liquid by formation of the respective dimer in a way similar to that described for the oxidation by DEAD of thiols to disulfides.[30] To check this possibility we dissolved DEAD in [bmim]PF_6 and left it standing (in darkness) at room temperature. After 48 hours the color of the solution had changed from red to yellow, which indicates reduction of diethyl azodicarboxylate to diethyl hydrazodicarboxylate.

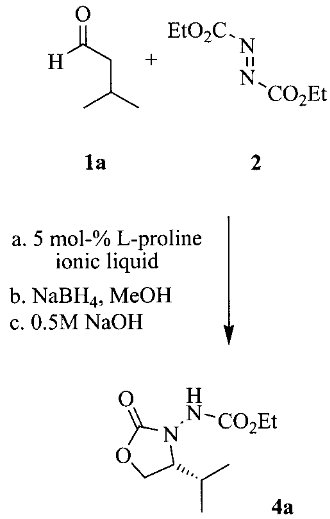
Having so far demonstrated that in general it is possible to perform the proline-catalyzed addition of aldehydes to DEAD in an ionic liquid, our next aim was to study the enantioselectivity of such reactions and particularly the effects of solvent and catalyst. Initial attempts to determine the enantiomeric purity of the product derived from **1a** by means of ^{1}H NMR spectroscopy in the presence of a chiral shift reagent did not lead to reliable results due to relatively rapid racemization.[10,11] We therefore decided to convert the sensitive primary reaction products (aldehydes of type

Table 1. Results of the L-proline-catalyzed addition of aliphatic aldehydes and ketones to DEAD in [bmim]PF_6 (see Scheme 1).[a]

Entry	Substrate	Time (min)	Yield (%) [a]	Product
1	**1a**	60	92	 **3a**
2[b]	**1a**	60	99	
3[c]	**1a**	30	98	
4	**1b**	180	82	 **3b**
5	**1c**	360	52	 **3c**
6	**1d**	1080	28	 **3d**
7	**1e**	120	83	 **3e**
8	**1g**	1500	14	 **3g**
9	**1h**	1320	8[d]	 **3h-1**  **3h-2**
10	**1i**	1320	43	 **3i**
11	**1j**	2680	0	
12[g]	**1k**	1020	38+21[e]	 **3k-1**  **3k-2**
13[f,g]	**1k**	1020	58+11[e]	
14[g]	**1l**	1440	8+3[e]	 **3l-1**  **3l-2**
15	**1m**	2680	0	

[a] Unless otherwise stated, reactions were performed at room temperature using 1.1 equiv. of the carbonyl substrate (see Figure 1), 1.0 equiv. of DEAD and 5 mol-% of L-proline; yield of isolated product **3**. [b] 1.5 Equiv. of **1a** and 5 mol-% of L-proline were used. [c] 1.5 Equiv. of **1a** and 10 mol-% of L-proline were used. [d] An inseparable mixture of regioisomers (85:15) was obtained. [e] Bis-aminated product. [f] 1.5 Equiv. of cyclohexanone was used. [g] An inseparable mixture of mono- and bis-products was obtained.

3) into configurationally stable *N*-(ethoxycarbonylamino)-oxazolidinone derivatives **4**[10,12] by reduction with $NaBH_4$ and subsequent treatment with aqueous NaOH. A series of experiments was performed by using aldehyde **1a** as the substrate (Scheme 2) and by keeping the reaction time constant (65 min). The results are summarized in Table 2.



Scheme 2.

Table 2. L-Proline-catalyzed addition of **1a** to DEAD and subsequent conversion of the product to **4a** using the conditions given in Scheme 2.

Entry	Ionic liquid	Yield [%][a]	*ee* [%][b]
1	[bmim]BF_4	85	84
2	[bmim]BF_4	76[c]	84
3	[bmim]BF_4	51[d]	79
4	[bmim]BF_4	41[e]	72
5	[bmim]PF_6	68	79
6	[hmim]BF_4	88	36
7	[hmim]PF_6	44	81
8	[bbim]PF_6	65	83
9	[C_{10}mim]BF_4	48	70
10	[bmim]$C_8H_{17}SO_4$	46	17
11	AMMOENG 100[f]	44	11
12	CYPHOSIL 101	45[g]	n.d.

[a] Reactions were performed at room temperature using 1.1 equiv. of **1a**, 1.0 equiv. of DEAD and 5 mol-% of L-proline; yield of isolated product (after column chromatography). [b] The enantiomeric excess was determined by GC using a chiral stationary phase [heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin on silica gel]. [c] First re-use of the catalytic system. [d] Second re-use of the catalytic system. [e] Third re-use of the catalytic system. [f] From Solvent Innovation GmbH, Köln, formerly called ECOENG 500. [g] The product was very difficult to isolate in this case.

As Table 2 shows, [bmim]BF_4 proved to be the best ionic liquid investigated with respect to both yield (85%) and enantioselectivity (84% *ee*). Re-use of the catalytic system (ionic liquid and catalyst after extraction with diethyl ether) was possible, however, the yield dropped considerably possibly due to partial loss of the organocatalyst during the extraction. The enantioselectivity remained high in the repeated experiments (Table 2, entries 2–4). Interestingly, the so-called "even greener" ionic liquids, AMMOENG 100 (formerly called ECOENG™ 500), CYPHOSIL 101 and [bmim]$C_8H_{17}SO_4$, gave unsatisfactory results. Whilst the yield and enantioselectivity observed for the reaction in [bmim]BF_4 are quite pleasing, it should be mentioned that the values obtained are lower than those reported for the reaction of compound **1a** in acetonitrile by List,[11] who, however, used a larger excess of substrate and twice the amount (10 mol-%) of L-proline.

As part of this study, we intended to probe the relative efficacy of several different organocatalysts (**C1**–**C7**; see Figure 2) in the synthesis of oxazolidinones of type **4** in an ionic liquid. For reasons of comparison, we used the same reaction system as that used to obtain product **4a** (Scheme 2). The results are summarized in Table 3.

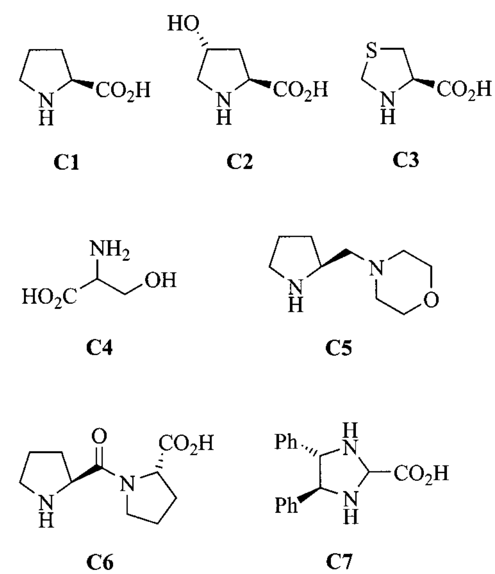
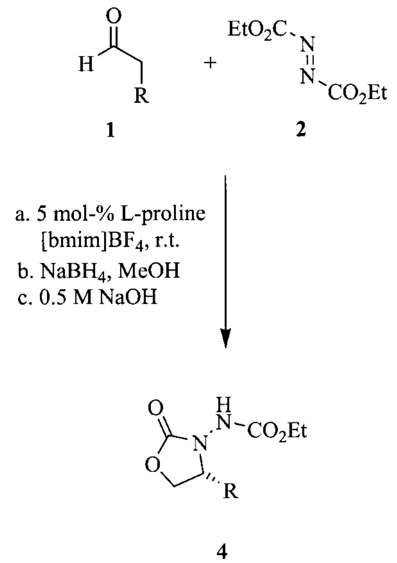


Figure 2. Organocatalysts used in this study.

Table 3. Addition of **1a** to DEAD in [bmim]BF_4 under the conditions given in Scheme 3. Relative performance of different organocatalysts.

Entry	Catalyst	Time, temperature	Yield [%] [a]	*ee* [%][b]
1	**C1**	65 min, room temp.	85	84
2	**C1**	65 min, room temp.	89	85[c]
3	**C2**	360 min, room temp.	8	72
4	**C2**	65 min, room temp.	45	73[c]
5	**C2**	380 min, room temp.	27	94
6	**C3**	480 min, room temp.	17	92
7	**C3**	330 min, 60–70 °C	65	58
8	**C4**	420 min, room temp.	<4	n.d.
9	**C4**	280 min, room temp. + 300 min, 70 °C	36	33[d]
10	**C5**	65 min, room temp.	46	≤2
11	**C6**	50 min, room temp.	62	≤2
12	**C7**	330 min, room temp.	22	36

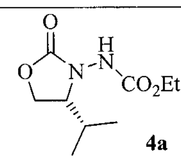
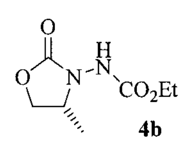
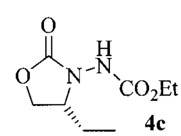
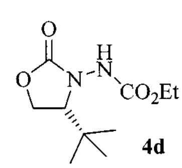
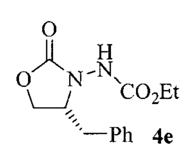
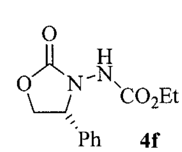
[a] Unless otherwise stated, reactions were performed with 1.1 equiv. of substrate (**1a**), 1 equiv. of DEAD and 5 mol-% of organocatalyst at room temperature; yield of isolated product (**4a**) after column chromatography. [b] The enantiomeric excess was determined by GC using a chiral stationary phase [heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin on silica gel]. [c] Reactions were performed with 30 mol-% of catalyst. [d] After 200 min, an additional 5 mol-% of catalyst was added.



Scheme 3.

As the data in Table 3 show, L-proline (**C1**) is the best of the catalysts tested with respect to turnover rate (85% yield in 65 min) and it also gave a good enantioselectivity (84% *ee*). *trans*-4-Hydroxy-L-proline (**C2**) and L-thiazolidine-2-carboxylic acid (**C3**) afforded products with higher enantioselectivities (94 and 92% *ee*, respectively), however, the reactions with these catalysts were very slow and only low yields were obtained even after prolonged reaction times. Increasing the amount of catalyst from 5 to 30 mol-% had only a minor effect in the case of L-proline (Table 3, entry 2), however, it led to a significant increase in yield (from 8 to 45%) in the case of catalyst **C2** (entries 3 and 4). An attempt to use serine (**C4**) as the catalyst, which may form octamers with an inert chiral cavity,[31] was not successful; only traces of the product were formed with 5 mol-% of catalyst **C4** at room temperature and even heating the mixture to 60–70 °C for several hours in the presence of 10 mol-% of catalyst only gave a 36% yield of product and a rather low enantioselectivity (33% *ee*). The other catalysts (**C5**–**C7**) also gave low yields and enantioselectivities. Note that use

Table 4. L-Proline-catalyzed addition of various aldehydes to DEAD in $[bmim]BF_4$ under the conditions indicated in Scheme 3.

Entry	Aldehyde	R	Time (min)	Product	Yield (%)[a]	*ee* (%)[b]
1	**1a**	*i*Pr	65	 **4a**	85	84
2	**1b**	Me	100	 **4b**	63	89
3	**1c**	Et	70	 **4c**	63	83
4	**1d**	*t*Bu	360	 **4d**	34	70
5	**1e**	Bn	200	 **4e**	43	76
6	**1f**	Ph	120	 **4f**	42	≤1[c]

[a] Reactions were performed at room temperature using 1.1 mmol of aldehyde, 1 mmol of DEAD in 1 mL of $[bmim]BF_4$ in the presence of 5 mol-% of L-proline; yield of isolated product **4** after column chromatography. [b] Determined by GC using a chiral stationary phase [heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin on silica gel]. [c] *ee* determined by HPLC.

of **C7** as the catalyst afforded the opposite enantiomer to that obtained with the other catalysts; the bulky phenyl group probably hinders the approach of the enamine intermediate to DEAD from the same side as the L-proline-derived enamine. The formation of an excess of the opposite enantiomer was proved by HPLC.

Finally, to explore the scope of this methodology, we investigated the reactions of different aldehydes (Scheme 3) under the conditions optimized for the model substrate **1c** (5 mol-% L-proline in [bmim]BF_4). As the results summarized in Table 4 indicate, good yields and enantioselectivities (up to 89% *ee*) were obtained for the small aliphatic aldehydes **1a**, **1b** and **1c**. The sterically crowded substrate **1e** reacted much more slowly, but the enantioselectivity was only slightly lower. With phenylacetaldehyde (**1f**) no conversion was observed under the standard conditions (addition of DEAD to a stirred solution of L-proline and the aldehyde). In contrast, when aldehyde **1f** was added to a solution of L-proline and DEAD in the ionic liquid the addition product **3f** was formed, but due to the lability of this compound it was immediately converted into the corresponding oxazolidinone **4f**. A reasonable yield of compound **4f** was obtained (43%), but the enantioselectivity was rather low.

Conclusions

The aim of this study was to probe the potential of ionic liquids as solvents for organocatalysis. By using the addition of aldehydes (and ketones) to DEAD as an example, the combination of [bmim]BF_4 as an ionic liquid and L-proline (5 mol-%) as an organocatalyst was identified as a suitable reaction system. While the reactions of ketones did not produce useful results, the reactions of various aldehydes afforded products in good chemical yields (up to 85%) and enantioselectivities (up to 89%). As shown in one case, even higher yields and enantioselectivities can be obtained if larger amounts of catalyst (10 mol-%) and aldehyde (1.5 equiv.) are employed. These results are comparable to those obtained under similar conditions in traditional solvents, however, for the transformation investigated, the reaction rates seem to be even faster in ionic liquids. Therefore, it can be concluded that ionic liquids are, in principle, very well suited to such reactions. Owing to the special qualities of ionic liquids as "green" solvents, further exploration of their potential application in other organocatalytic systems seems worthwhile.[32]

Experimental Section

General Experimental Procedure for the Preparation of Compounds 3: The catalyst (5 mol-%) and the chosen substrate **1** (1.1 equiv.) were added to the degassed ionic liquid (1 mL). After stirring the resulting mixture for 15 min at room temp. DEAD (1 mmol, 40% solution in toluene) was added and vigorous stirring was continued for the time and at the temperature specified in the tables. The product was isolated by extraction with several portions of diethyl ether followed by solvent evaporation using a rotary evaporator. The crude product **3** was purified by column chromatography on SiO_2 (Table 1).

General Experimental Procedure for the Preparation of Compounds 4: The catalyst (5 mol-%) and the chosen substrate **1** (1.1 equiv.) were added to the degassed ionic liquid (1 mL). After stirring the resulting mixture for 15 min at room temp. DEAD (1 mmol, 40% solution in toluene) was added and vigorous stirring was continued for the time and at the temperature specified in the tables. The product was isolated by extraction with several portions of diethyl ether followed by solvent evaporation using a rotary evaporator. To achieve the latter, the crude product **3** was dissolved in MeOH (3 mL). The mixture was cooled to 3 °C and $NaBH_4$ (1.1 equiv.) was added. After stirring for 15 min at room temp., a 0.5 M solution of NaOH was added and stirring was continued for 25 min before water (7 mL) was added. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried with Na_2SO_4. After evaporating the solvent in vacuo, the crude product **4** was purified by column chromatography on SiO_2 with hexane/EtOAc (4:1) or hexane/dichloromethane (2:1) as eluent.

***N,N'*-Bis(ethoxycarbonyl)-2-hydrazino-3-methylbutyraldehyde (3a):** Yield: 239 mg (92%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 6.61 (br. s, 1 H), 4.42 (m, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 4.37–4.25 (m, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.15 (d, *J* = 4.5 Hz, 3 H), 1.07 (d, *J* = 4.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 156.7, 72.4, 63.4, 62.4, 27.6, 20.2, 19.7, 14.6, 14.5 ppm. $C_{11}H_{20}N_2O_5$ (260,29): calcd. C 50.76, H 7.74, N 10.76; found C 49.85, H 7.90, N 10.59. Colourless oil, R_F = 0.05 (SiO_2, Hex/EtOAc = 9:1).

***N,N'*-Bis(ethoxycarbonyl)-2-hydrazinopropionaldehyde (3b):**[10] Yield: 232 mg (82%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (br. s, 1 H), 6.57 (br. s, 1 H), 4.76 (br. s, 1 H), 4.21–4.11 (m, 4 H), 1.31 (d, *J* = 7.5 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H) ppm. Colourless oil, R_F = 0.02 (SiO_2, Hex/EtOAc = 9:1).

***N,N'*-Bis(ethoxycarbonyl)-2-hydrazinobutyraldehyde (3c):**[10] Yield: 190 mg (52%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (br. s, 1 H), 6.69 (br. s, 1 H), 4.46 (m, 1 H), 4.21 (q, 2 H), 4.16 (q, 2 H), 1.92 (m, 1 H), 1.69 (m, 1 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H) ppm. Colourless oil, R_F = 0.07 (SiO_2, Hex/EtOAc = 9:1).

***N,N'*-Bis(ethoxycarbonyl)-2-hydrazino-3,3-dimethylbutyraldehyde (3d):** Yield: 77 mg (28%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (s, 1 H), 6.52 (br. s, 1 H), 4.56 (m, 1 H), 4.19–4.08 (m, 4 H), 1.59 (t, 3 H), 1.50 (t, 3 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.87, 156.37, 151.42, 71.80, 62.37, 59.32, 44.18, 29.50, 14.04, 13.93 ppm. $C_{12}H_{22}N_2O_5$ (274.32): calcd. C 52.54, H 8.08, N 10.21; found C 52.60, H 8.12, N 10.27. Colourless oil, R_F = 0.06 (SiO_2, Hex/EtOAc = 9:1).

2-[*N,N'*-Bis(ethoxycarbonyl)hydrazino]-3-phenylpropionaldehyde (3e): Yield: 256 mg (83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (d, 1 H), 8.92 (br. s, 1 H), 7.24–7.14 (m, 3 H), 6.97 (m, 2 H), 5.42 (m, 1 H), 4.14 (m, 4 H), 3.22 (t, 2 H), 1.66 (m, 6 H) ppm. $C_{15}H_{20}N_2O_5$ (308.34): calcd. C 58.43, H 6.54, N 9.09; found C 58.35, H 6.58, N 9.15. Colourless oil, R_F = 0.12 (SiO_2, Hex/EtOAc = 9:1).

2-[*N,N'*-Bis(ethoxycarbonyl)hydrazino]-3-pentanone (3g):[12] Yield: 36 mg (14%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.66 (br. s, 1 H), 4.92 (br. s, 1 H), 4.25–4.14 (m, 4 H), 2.54–2.48 (m, 2 H), 1.42 (d, *J* = 7.5 Hz, 3 H), 1.30–1.23 (m, 6 H), 1.07 (t, *J* = 7.5 Hz, 3 H) ppm. R_F = 0.32 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

3-[*N,N'*-Bis(ethoxycarbonyl)hydrazino]-4-methyl-2-pentanone (3h-1):[12] Yield: 201 mg (8% total for a mixture of **3h-1** and **3h-2**); ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 6.61 (br. s, 1 H), 4.59 (br. s, 1 H), 4.25–4.14 (m, 4 H), 2.38–2.28 (m, 1 H), 2.29 (s, 3 H), 1.29–1.24 (m, 6 H), 1.02–0.93 (m, 6 H) ppm. R_F = 0.41 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

1-[*N*,*N′*-Bis(ethoxycarbonyl)hydrazino]-4-methyl-2-pentanone (3h-2):[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89 (br. s, 1 H), 4.25–4.14 (m, 6 H), 2.61 (m, 2 H), 2.19–2.11 (m, 1 H), 1.29–1.24 (m, 6 H), 1.02–0.93 (m, 6 H) ppm. R_F = 0.41 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

2-[*N*,*N′*-Bis(ethoxycarbonyl)hydrazino]-1-cyclobutanone (3i): Yield: 105 mg (43%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.32 (br. s, 1 H), 6.07 (m, 1 H), 4.12 (m, 4 H), 2.71 (m, 2 H), 2.01 (m, 2 H), 1.59 (t, 3 H), 1.46 (t, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.68, 155.19, 154.20, 62.42, 59.39, 56.82, 41.44, 23.75, 14.49, 14.03 ppm. $C_{10}H_{16}N_2O_5$ (244.25): calcd. C 49.18, H 6.60, N 11.47; found C 49.23, H 6.65, N 11.50. Colourless wax, R_F = 0.56 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

2-[*N*,*N′*-Bis(ethoxycarbonyl)hydrazino]-1-cyclohexanone (3k-1):[12] Yield: 208 mg (as a mixture of 38% of **3k-1** and 21% of **3k-2**); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68 (br. s, 1 H), 4.90 (m, 1 H), 4.23–4.13 (m, 4 H), 2.52–2.48 (m, 1 H), 2.42–2.30 (m, 2 H), 2.13–2.05 (m, 1 H), 2.00–1.97 (m, 1 H), 1.87–1.71 (m, 2 H), 1.65–1.55 (m, 1 H), 1.29–1.24 (m, 6 H) ppm. Colourless wax, R_F = 0.30 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

2,6-Bis[*N*,*N′*-bis(ethoxycarbonyl)hydrazino]-1-cyclohexanone (3k-2):[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (br. s, 2 H), 4.66–4.60 (m, 2 H), 4.17–4.11 (m, 8 H), 2.76 (m, 2 H), 2.14 (m, 4 H), 1.61 (t, 12 H) ppm. Colourless wax, R_F = 0.30 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

Note: An inseparable mixture of mono- and bis-aminated products was isolated but the two products could be distinguished by NMR spectroscopy.

2-[*N*,*N′*-Bis(ethoxycarbonyl)hydrazino]-1-cycloheptanone (3l-1): Yield: 38 mg (8% total for a mixture of **3l-1** and **3l-2**); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (br. s, 1 H), 4.99 (m, 1 H), 4.23–4.12 (m, 4 H), 2.66–2.59 (m, 2 H), 2.43–2.32 (m, 2 H), 2.21 (m, 1 H), 1.98–1.92 (m, 2 H), 1.75–1.65 (m, 3 H), 1.29–1.23 (m, 6 H) ppm. Colourless oil, R_F = 0.39 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

2,7-Bis(*N*,*N′*-bis(ethoxycarbonyl)hydrazino]-1-cycloheptanone (3l-2): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.90 (br. s, 2 H), 5.11 (m, 2 H), 4.14 (m, 8 H), 2.03–1.93 (m, 4 H), 1.68–1.54 (m, 16 H) ppm. Colourless oil, R_F = 0.39 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

Note: An inseparable mixture of mono- and bis-aminated products was isolated but the two products could be distinguished by NMR spectroscopy.

3-(Ethoxycarbonylamino)-4-isopropyl-2-oxazolidinone (4a):[10] Yield: 181 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (br. s, 1 H), 4.39 (t, J = 8.7 Hz, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.08 (t, J = 8.4 Hz, 1 H), 3.97 (m, 1 H), 2.00–2.11 (m, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.94 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.25, 155.48, 64.21, 62.69, 61.02, 61.02, 28.68, 18.01, 16.04, 14.55 ppm. $C_9H_{16}N_2O_4$ (216.24): calcd. C 49.99, H 7.46, N 12.95; found C 49.96, H 7.42, N 12.98. Colourless oil, R_F = 0.48 (SiO_2, CH_2Cl_2/EtOAc = 4:1).

3-(Ethoxycarbonylamino)-4-methyl-2-oxazolidinone (4b):[10] Yield: 118 mg (63%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.57 (br. s, 1 H), 4.51 (t, J = 8.4 Hz, 1 H), 4.23 (q, J = 6.9 Hz, 2 H), 4.13 (m, 1 H), 3.91 (t, J = 8.4 Hz, 1 H), 1.32 (d, J = 6 Hz, 3 H), 1.30 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.32, 155.43, 68.81, 62.52, 52.87, 16.89, 14.36 ppm. $C_7H_{12}N_2O_4$ (188.18): calcd. C 44.68, H 6.43, N 14.89; found C 44.71, H 6.45, N 14.92. Pale yellow oil, R_F = 0.35 (SiO_2, CH_2Cl_2/Et_2O = 4:1).

3-(Ethoxycarbonylamino)-4-ethyl-2-oxazolidinone (4c):[10] Yield: 127 mg (63%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.50 (br. s, 1 H), 4.91 (m, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.00 (m, 2 H), 1.85 (m, 1 H), 1.59 (m, 1 H), 1.30 (t, J = 7.2 Hz, 3 H), 0.94 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.76, 155.60, 67.31, 62.64, 57.82, 24.52, 14.53, 8.62 ppm. $C_8H_{14}N_2O_4$ (202.21): calcd. C 47.52, H 6.98, N 13.85; found C 47.58, H 6.71, N 13.82. Pale yellow oil, R_F = 0.56 (SiO_2, CH_2Cl_2/Et_2O = 4:1).

4-*tert*-Butyl-3-(ethoxycarbonylamino)-2-oxazolidinone (4d):[10] Yield: 78 mg (34%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (br. s, 1 H), 4.41 (t, J = 8.7 Hz, 1 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.12 (t, J = 8.4 Hz, 1 H), 3.84 (m, 1 H,), 1.29 (t, J = 7.2 Hz, 3 H), 0.97 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.14, 155.30, 64.76, 62.68, 33.58, 25.68, 14.58 ppm. $C_{10}H_{18}N_2O_4$ (230.27): calcd. C 52.16, H 7.88, N 12.17; found C 52.20, H 7.90, N 12.21. Pale yellow oil, R_F = 0.50 (SiO_2, CH_2Cl_2/Et_2O = 4:1).

4-Benzyl-3-(ethoxycarbonylamino)-2-oxazolidinone (4e):[10] Yield: 113 mg (43%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 3 H), 7.17–7.15 (m, 2 H), 6.54 (br. s, 1 H), 4.32 (m, 2 H), 4.23 (q, J = 6.9 Hz, 2 H), 4.07 (m, 1 H), 3.18 (dd, J = 13.8, J = 4.2 Hz, 1 H), 2.81 (dd, J = 13.8, J = 8.7 Hz, 1 H), 1.29 (t, J = 6.9 Hz, 3 H) ppm. $C_{13}H_{16}N_2O_4$ (264.28): calcd. C 59.08, H 6.10, N 10.60; found C 59.12, H 6.08, N 10.67. Pale yellow oil, R_F = 0.45 (SiO_2, CH_2Cl_2/Et_2O = 4:1).

3-(Ethoxycarbonylamino)-4-phenyl-2-oxazolidinone (4f): Yield: 105 mg (42%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 6.26 (br. s, 1 H), 4.12 (m, 3 H), 3.81 (dd, J = 11.7, J = 4.2 Hz, 1 H), 3.68 (dd, J = 11.7, J = 8.1 Hz, 1 H), 1.23 (t, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.19, 138.85, 128.80, 128.14, 127.97, 66.25, 64.51, 61.83 ppm. $C_{12}H_{14}N_2O_4$ (250.26): calcd. C 57.59, H 5.64, N 11.19; found C 57.71, H 5.69, N 11.10. Pale yellow oil, R_F = 0.49 (SiO_2, CH_2Cl_2/Et_2O = 4:1).

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