Origins of Regioselectivity in the Reactions of α-Lactams with Nucleophiles

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Regioselectivity in the reaction of α-lactams with nucleophiles results from two competing steps. Nucleophilic addition to the carbonyl group of the α-lactam, which yields rearranged, acyl-substituted products, is dependent on the nucleophilicity and the concentration of the nucleophile. Ring opening of the α-lactam to an ion pair intermediate, which gives nucleophile incorporation at C-2, is dependent on electronic effects of substituents at C-2. Groups which can stabilize positive charge at C-2 speed up ion pair formation, whereas electron-withdrawing groups slow the ring opening and give more carbonyl addition product. These factors are used to control the regioselectivity and produce a series of unsymmetric urea peptide mimetics in high yields and with complete regiochemical control.

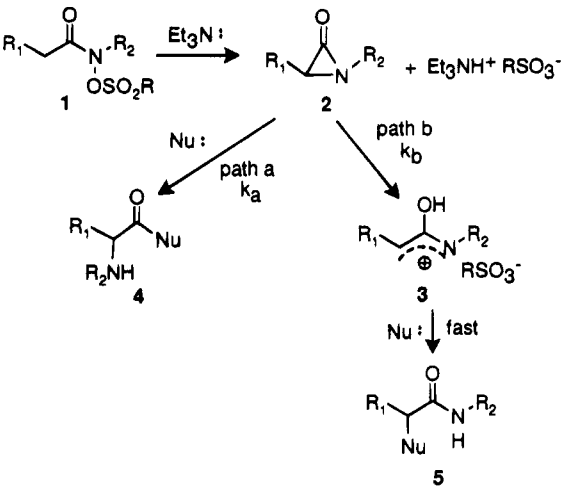
Introduction

It has been shown earlier that *N*-(sulfonyloxy)amides **1** are readily converted to α-lactams **2** in the presence of amine bases.[1] These intermediates give products by one of two pathways, depending on the reaction environment (Scheme 1). If good nucleophiles such as primary or unhindered secondary amines are present in solution, they intercept the α-lactam by addition to the carbonyl group and give rearranged α-amino amides **4** (path a).[2] When only poorer nucleophiles such as Cl^-, Br^-, N_3^-, H_2O, or hindered secondary amines are present in the protic reaction environment, the α-lactam undergoes ring opening to an ion pair intermediate (an azaoxallyl cation) **3**. This cation reacts with nucleophiles at C-2 to produce 2-substituted amides as products **5** (path b).[3]

In the reaction mechanism depicted in Scheme 1, two different reactive intermediates are responsible for the formation of the two regioisomeric products. This scenario is different from the more traditional mechanism which involves the α-lactam as the sole intermediate.[4] In this mechanism, the production of the regioisomeric products from the α-lactam occurs by competitive attack of nucleophiles at either the acyl carbon C-2 or the tetrahedral carbon C-3 to give **4** and **5**, respectively (Scheme 2).

Nearly all of the data on the regiochemistry and stereochemistry of the reactions of α-lactams with nucleophiles has been interpreted in terms of the traditional mechanism of Scheme 2, and a great deal of work has been done to try to understand the factors which dictate whether a nucleophile will attack the acyl carbon C-2 or the saturated carbon C-3.[5] No theory has emerged to explain the results consistently, and these processes remain enigmatic. As a consequence, α-lactams have not seen significant development as synthetic intermediates because, without reliable mechanistic guidance, it has been difficult to control the product mixture. Thus, from both mechanistic and synthetic points of view, it is important to confirm which pathway is followed.

Scheme 1



The mechanisms in Schemes 1 and 2 are distinguished kinetically by the dependence of the product ratio on the concentration of the capturing nucleophile. In the mechanism shown in Scheme 1, the ratio of **4**/**5** is given by the rate at which the nucleophile attacks the α-lactam in a second order process versus the rate at which the

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(2) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355.

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(4) Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25. This is a seminal review of the chemistry of α-lactams which served to define the directions of subsequent studies.

(5) Work on α-lactams since the Sheehan review, ref 4, include: (a) Guziec, F. S., Jr.; Torres, F. F. *J. Org. Chem.* **1993**, *58*, 3493. (b) Maran, F. *J. Am. Chem. Soc.* **1993**, *115*, 6557. (c) D'Angeli, F.; Marchetti, P.; Cavicchioni, G.; Bertolasi, V.; Maran, F. *Tetrahedron: Assymmetry* **1991**, *2*, 1111. (d) Quast, H.; Leybach, H.; Wurthwein, E.-U. *Chem. Ber.* **1992**, *125*, 1249. (e) Quast, H.; Leybach, H. *Chem. Ber.* **1991**, *124*, 2105. (f) Coutts, I. G. C.; Southcott, M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 767. (g) Scrimin, P.; Cavicchioni, G.; D'Angeli, F.; Goldblum, A.; Maran, F. *J. Chem. Soc., Perkins Trans. 1* **1988**, 43. (h) Baumgarten, H. E.; Chaing, N.-C. R.; Elia, V. J.; Beum, P. V. *J. Org. Chem.* **1985**, *50*, 5507. (i) Bladon, C. M.; Kirby, G. M. *J. Chem. Soc., Chem. Commun.* **1982**, 1402. (j) Cavicchioni, G.; Scrimin, P.; Veronese, A. C.; Balboni, G.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2969. (k) Zanotti, G.; Filira, F.; Del Pra, A.; Cavicchioni, G.; Veronese, A. C.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2249. (l) Baumgarten, H. E.; McMahan, D. G.; Elia, V. J.; Gold, B. I.; Day, V. W.; Day, R. O. *J. Org. Chem.* **1976**, *41*, 3798. (m) Talaty, E. R.; Dypuy, A. E., Jr.; Utermoehlen, C. M.; Stekoll, L. H. *J. Chem. Soc., Chem. Commun.* **1973**, 48.

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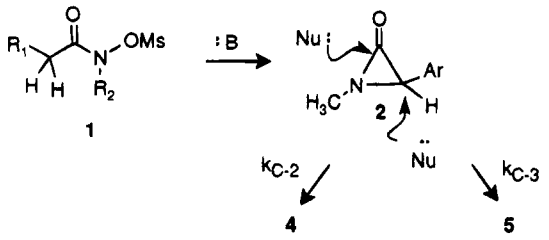
Scheme 2



α-lactam undergoes unimolecular (or acid-catalyzed) ring opening to the ion pair. This ratio is expressed as

$$\frac{4}{5} = \frac{k_a[2][Nu]}{k_b[2]} = \frac{k_a[Nu]}{k_b} \quad (1)$$

The product ratio from the scenario in Scheme 2 is given by the ratio of two competing second order reactions between the nucleophile and the α-lactam

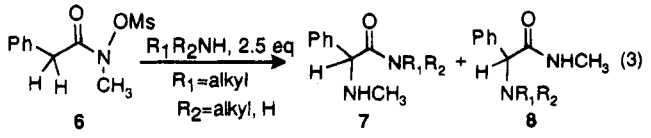
$$\frac{4}{5} = \frac{k_{C\text{-}2}[2][Nu]}{k_{C\text{-}3}[2][Nu]} = \frac{k_{C\text{-}2}}{k_{C\text{-}3}} \quad (2)$$

If Scheme 1 is operative, then two opportunities exist to exert regiochemical control on the reaction. First, the rate of formation of **4** is dependent on the nucleophile's reactivity (k_a) and its concentration according to Scheme 1. Second, structural factors which stabilize or destabilize ion pair **3** could be used to influence the rate of conversion (k_b) of the α-lactam **2** to the ion pair **3** and hence the rate for formation of **5**. On the other hand, if Scheme 2 is followed, the product ratio does not depend on the nucleophile concentration but only on the rate constants for acyl versus C-3 attack for each nucleophile.[6] In this case, there is little opportunity to control the product mixture.

We report here the results of experiments identifying regiochemical control elements in the reactions of α-lactams with nucleophiles which single out Scheme 1 as the operative mechanism in our systems and which provide the basis for the exploitation of α-lactams as synthetic intermediates.

Results and Discussion

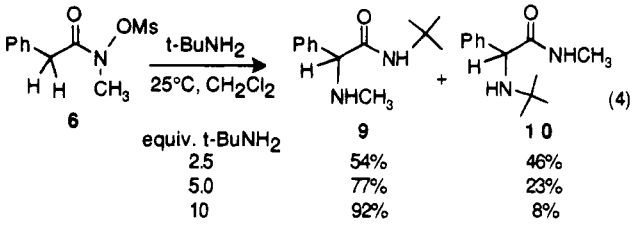
We reported previously (eq 3) that *O*-methanesulfonyl-*N*-methylphenylacetohydroxamate **6** reacts with primary and unhindered secondary amines to give rearranged products **7** by acyl attack (path a, Scheme 1).[1] In



contrast, reaction of **6** with hindered secondary amines gave only the unrearranged 2-amino-*N*-methylamides **8** (path b, Scheme 1). This data provided the first indication that the regioselectivity is nucleophile dependent as seen in eq 1. Since these reactions were run at similar amine concentrations, the change in the observed product must be due to a change in the rate constant k_a for acyl attack by the amine. Unhindered amines are reactive nucleophiles and have k_a's sufficiently large that formation of **7** by acyl attack is the only process observed. Sterically hindered amines have much lower k_a's; thus, the rate of acyl attack k_a[Nu] is much less than the rate constant for ring opening k_b, and only the latter is observed.

These results illustrate that the reactivity of the nucleophile on which k_a is dependent (eq 1) is a significant regiochemical control element. Only very good nucleophiles such as unhindered amines which have nucleophilic constants of $n > 7$ are capable of intercepting the α-lactam to give the rearranged regioisomer **7**.[7] Hindered amines including triethylamine have n values < 7 and fail to trap the α-lactam and thus give **8** via the ion pair intermediate. All of the other nucleophiles we have utilized such as azide, bromide, chloride, alcohols, and water have n values < 6.6, and all fail to trap the α-lactam as well. Instead, ring opening to the ion pair occurs, and the nucleophile is added at C-2. The ion pair is a much stronger electrophile than the α-lactam, and once ring opening has occurred, even very poor nucleophiles such as chloride and even mesylate can be trapped efficiently by the ion pair at the α-position to give regioisomer **5** (Scheme 1). The correlation of regiochemistry with the n value of the nucleophile is probably fortuitous since the S_N2 model from which n values were derived is quite different than addition to the acyl group of the α-lactam.[7] Nevertheless, the use of n values provides an operational way to anticipate the regiochemistry for a given nucleophile.

In that same study,[1] it was found that the reaction of **6** with *tert*-butylamine gave a mixture of the regioisomers **9** and **10** (eq 4). Apparently the steric bulk of *tert*-



equiv. t-BuNH$_2$	9	10
2.5	54%	46%
5.0	77%	23%
10	92%	8%

butylamine decreases its nucleophilic reactivity to the point that the two processes are competitive. The reaction of **6** with *tert*-butylamine thus provides an opportunity to test whether the product ratio is dependent on the nucleophile concentration. When the concentration of *tert*-butylamine was varied, the ratio of **9** to **10** was found to be linearly dependent (eq 4).

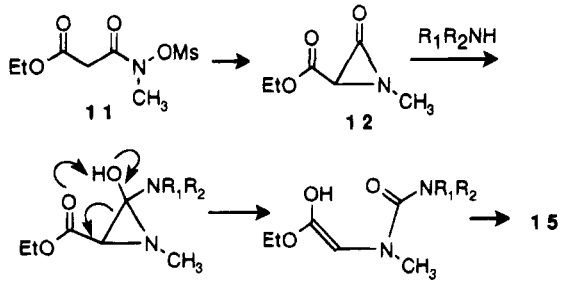
The dependence of the regioselectivity on the reactivity of the nucleophile and its concentration is precisely the behavior predicted by eq 1 and lends strong support to Scheme 1 as the proper mechanistic designation for the reaction. These results also demonstrate that the nucleophile concentration can be used as a regiochemical control element in cases where α-lactam trapping and ring opening are competitive and product mixtures result.

A second approach to controlling the regiochemistry is to change the rate constant k_b of α-lactam ring opening. It was reported earlier[3b] that 1,3-elimination in *N*-(sulfonyloxy)amides **1** to α-lactams requires a conjugating group such as aryl or vinyl at the α-carbon, presumably

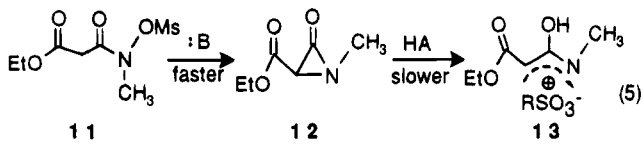
(6) The same product ratio dependence would be seen if the α-lactam and the ion pair are in rapid equilibrium.

(7) (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; 3rd ed.; Harper and Row: New York, 1987; pp 367–373. This is an excellent discussion. (b) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

Scheme 3



to increase the acidity of the α-proton and speed its removal by the base. A carbonyl group attached to the α-carbon, as in malonyl hydroxamate **11**, would also acidify the α-proton significantly and facilitate ring closure to the α-lactam **12**. On the other hand, an electron-withdrawing carbonyl group at C-3 of the α-lactam **12** should significantly slow down the rate of ring opening to the ion pair **13** (eq 5). Therefore, electronic

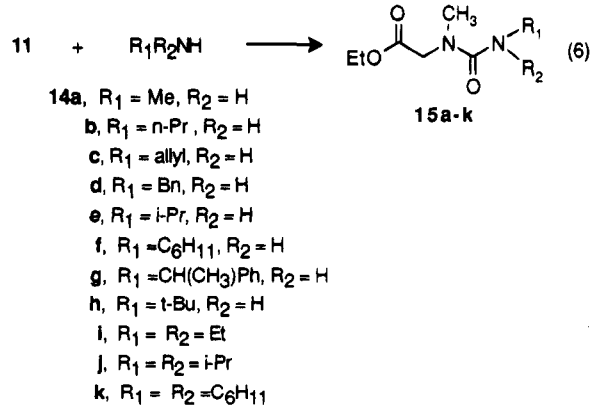


(5)

effects could have a profound influence on the regiochemistry since they would directly influence the partitioning between **12** and **13**.

Sheehan also suggested that the stability of α-lactams is influenced by electronic effects of substituents attached to nitrogen and carbon.[4] Substituents which could stabilize an "acyclic" intermediate [or transition state] by charge delocalization were thought to make the α-lactam ground state more reactive and therefore more difficult to prepare (isolate). However, this electronic effect was not implicated in the regiochemistry of nucleophilic addition to the α-lactam.

To examine electronic effects on the regiochemistry, malonate derivative **11** was reacted with a series of amines **14a–k**. The only product in every case was the rearranged urea derivatives **15a–k** (eq 6), which are produced by acyl attack on the α-lactam **12** followed by ring opening to the enol and tautomerization to **15** (Scheme 3). The ring opening step may be intramolecularly acid-catalyzed, but this has not been established. More important is the fact that product formation takes place subsequent to nucleophilic addition to the carbonyl group.

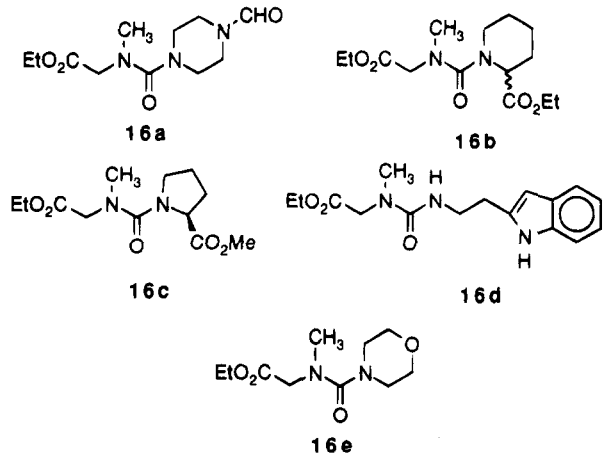


(6)

The electron-withdrawing effect of the carbethoxy group is seen to influence the regiochemistry markedly, since only acyl addition is observed, even for very sterically hindered amines such as dicyclohexylamine. Considering path b of Scheme 1, when the R_1 substituent at C-3 of the α-lactam is phenyl or vinyl, the ion pair intermediate is stabilized by resonance delocalization of the positive charge, and thus, its formation is likely to be rapid. Thus, in eq 1, k_b is large and can compete with k_a[Nu] when bulky nucleophiles which have low k_a values are used. Conversely, a carbonyl group at C-3 would destabilize positive charge at C-3 and would slow the rate of conversion of the α-lactam to the ion pair. In terms of eq 1, k_b would be small and would not compete with k_a[Nu], even when relatively unreactive nucleophiles are employed. These results are nicely rationalized by the mechanism in Scheme 1. In contrast, it is difficult to explain the effect of a carbonyl group at C-3 on the regioselectivity in terms of the traditional mechanism of Scheme 2.

Besides providing convincing mechanistic insight into the chemistry of α-lactams, the reaction of *N*-(mesyloxy)-amide **11** with amines provides a high-yield method for the preparation of unsymmetric ureas **15** in three simple steps from ethyl malonyl chloride. These compounds have been found useful as cholinesterase inhibitors[8] and more recently as peptidase inhibitors.[9]

The usual preparations of unsymmetrical ureas involve either the sequential reaction of two different amines with phosgene equivalents[10] or the reaction of amines with isocyanates.[11] The present method allows for the preparation of unsymmetric ureas under very mild conditions and in yields comparable to the best current method employing triphosgene but with greater structural latitude with respect to the nitrogen substituents.[10] To underscore the versatility of the method, several heterocyclic amines were reacted with **11** to give ureas **16a–e** in excellent overall yields (eq 6). Extension of the



method to the preparation of longer chain peptide mimetics is currently under development. The use of other

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(9) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H. S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288.

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(11) Imrich, J.; Kristian, P.; Podhradsky, D.; Dzurilla, M. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2334.

amine derivatives such as hydrazines as nucleophiles is also under investigation as a route to azapeptide isosteres.[12]

In summary, the results presented here demonstrate that regioselectivity in the reaction of α-lactams with nucleophiles results from two competing steps in the compounds we have studied. Addition to the carbonyl group of the α-lactam is dependent on the nucleophilicity and the concentration of the nucleophile. Competing with nucleophilic acyl addition is ring opening to an ion pair intermediate which is most likely acid-catalyzed and clearly dependent on electronic effects of substituents at C-3. Groups which can stabilize positive charge at C-3 speed up ion pair formation and give more nucleophilic addition at C-3, whereas electron-withdrawing groups slow the ring opening and give more acyl addition product. These factors can be used to control the regioselectivity productively. While we believe that this mechanism will prove to be general for the reactions of α-lactams with nucleophiles, it remains to be demonstrated for systems with other substituents on the α-lactam ring.

Experimental Section

Melting points are uncorrected. Chemical shifts are reported for chloroform-*d* solution in ppm relative to Me_4Si. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on silica gel 60 F254 plates from EM reagents and visualized by UV irradiation or iodine. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Ethyl malonyl chloride, (*S*)-(−)-α-methylbenzylamine, L-proline methyl ester hydrochloride, and benzyl isocyanate were purchased from Aldrich, and sarcosine ethyl ester hydrochloride was purchased from Fluka and used as received. *N*-(Mesyloxy)-*N*-methylphenylacetanilide[2] and *N*-hydroxy-2-carbethoxy-*N*-alkylacetamides[13] were prepared as reported earlier.

Reaction of *N*-(Mesyloxy)-*N*-methylphenylacetanilide 6 with *tert*-Butylamine. To a solution of the *N*-(mesyloxy)-amide **6** (2 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added *tert*-butylamine (5.0, 10, or 20 mmol separately in three different runs) in CH_2Cl_2 (15 mL) over a period of 30 min. The resulting solution was then stirred at 0 °C for 1 h and then stirred at room temperature until the starting material was absent as determined by TLC analysis (hexane/ethyl acetate, 6:4). The solvent was removed, and the residue was treated with 1 N NaOH, extracted with EtOAc (50 mL), washed with water (2 × 10 mL), and dried over $MgSO_4$. After rotary evaporation, the crude product was analyzed for the ratio of regioisomers **9** (*N*-*tert*-butyl-2-(methylamino)-2-phenylethanamide) and **10** (*N*-methyl-2-(*tert*-butylamino)-2-phenylethanamide) from the intensity of the corresponding NMR signals (see eq 4).

Preparation of *N*-(Mesyloxy)-2-carbethoxy-*N*-alkylacetamide (11). To a solution of the *N*-hydroxy-2-carbethoxy-*N*-alkylacetamide[12] (12.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added triethylamine (12.0 mmol). The mixture was stirred for 10–12 min, and methanesulfonyl chloride (13.2 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h, allowed to warm to room temperature, and stirred for another 2 h. The organic layer was washed with water (2 × 20 mL), 1 N HCl (15 mL), and brine (20 mL) and dried over $MgSO_4$. After rotary evaporation, the product was prepared in 75% yield after flash chromatography (hexane/ethyl acetate, 6:4): ^1H NMR δ 1.30 (t, J = 7.1 Hz, 3H), 3.23 (s, 3H), 3.48 (s, 3H), 3.60 (s, 2H), 4.23 (q, J = 7.0 Hz, 2H); ^{13}C NMR δ 14.1, 37.4, 39.4, 41.1, 61.8, 166.2; IR ($CHCl_3$) 3021, 2940, 1742, 1704, 1372, 1328, 1191, 1115 cm^{-1}. Anal. Calcd for $C_7H_{13}NO_6S$: C, 35.14; H, 5.47. Found: C, 35.19; H, 5.52.

General Synthesis of *N*-(1-Carbethoxymethyl)-*N'*-alkylureas (15 and 16). To a solution of the ethyl *N*-(mesyloxy)malonamide monoester **11** (2 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added amine (2.2 mmol) in CH_2Cl_2 (15 mL) over a period of 30 min. The resulting solution was stirred at 0 °C for 1 h and then stirred at room temperature (ca. 6–8 h). The solvent was removed, and the residue was treated with 1 N NaOH, extracted with EtOAc (50 mL), washed with water (2 × 10 mL), and dried over $MgSO_4$. After rotary evaporation, the product was purified by flash chromatography or recrystallization (hexane/dichloromethane, 7:3) or Kugelrohr distillation.

***N*-(1-Carbethoxymethyl)-*N'*-methylurea (15a)** was prepared from **11** (478 mg, 2.0 mmol) as a crude solid (330 mg, 94%) which on recrystallization (hexanes/dichloromethane, 8:2) gave a white solid (280 mg, 1.6 mmol, 80%): mp 45–46 °C; ^1H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 2.82 (d, J = 4.6 Hz, 3H), 2.94 (s, 3H), 4.08 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.55 (bs, 1H); ^{13}C NMR δ 13.6, 27.2, 34.9, 50.1, 60.5, 158.4, 170.0; IR ($CHCl_3$) 3485, 3019, 2400, 1743, 1714, 1649, 1537, 1037 cm^{-1}. Anal. Calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10. Found: C, 48.30; H, 7.96.

***N*-(1-Carbethoxymethyl)-*N'*-propylurea (15b)** was prepared from **11** (478 mg, 2 mmol) as a crude solid (260 mg, 64%) which on recrystallization (hexane/dichloromethane, 7:3) gave a white solid (203 mg, 1.0 mmol, 50%): mp 90–91 °C; ^1H NMR δ 0.92 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.53 (m, 2H), 2.94 (s, 3H), 3.21 (m, 2H), 4.08 (s, 2H), 4.18 (q, J = 7.1, 2H), 4.53 (bs, 1H); ^{13}C NMR δ 11.3, 14.2, 23.5, 35.4, 42.7, 50.6, 60.9, 158.4, 170.5; IR ($CHCl_3$) 3472, 3019, 2438, 1744, 1646, 1529, 1376, 1028 cm^{-1}. Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97. Found: C, 53.32; H, 8.77.

***N*-(1-Carbethoxymethyl)-*N'*-(2-propenyl)urea (15c)** was prepared from **11** (3.15 mg, 13.14 mmol) as a crude solid (2.27 mg, 86%) which on recrystallization (hexanes/dichloromethane, 9:1) gave a colorless solid (2.05 mg, 10.25 mmol, 78%): mp 88–90 °C; ^1H NMR δ 1.27 (d, J = 7.2 Hz, 3H), 2.96 (s, 3H), 3.87 (dd, J = 5.6 and 5.8 Hz, 2H), 4.08 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.7 (bs, 1H), 5.07–5.24 (m, 2H), 5.79–5.98 (m, 1H); ^{13}C NMR δ 14.1, 35.4, 43.3, 50.6, 60.9, 115.3, 135.6, 158.1, 170.4; IR ($CHCl_3$) 3354, 2985, 1742, 1642, 1527 cm^{-1}. Anal. Calcd for $C_9H_{16}N_2O_3$: C, 53.98; H, 8.05. Found: C, 54.09; H, 7.92.

***N*-(1-Carbethoxymethyl)-*N'*-benzylurea (15d)** was prepared from **11** (2.4 mg, 10.01 mmol) as a crude oil (2.2 mg, 88%) which on flash chromatography (hexanes/ethyl acetate, 1:1) gave a colorless solid (2.1 mg, 8.39 mmol, 84%): mp 80–82 °C; ^1H NMR δ 1.27 (t, J = 6.9 Hz, 3H), 2.95 (s, 3H), 4.09 (s, 2H), 4.18 (q, J = 7.3 Hz, 2H), 4.43 (d, J = 5.8 Hz, 2H), 4.92 (bs, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR δ 14.1, 35.3, 44.7, 50.6, 60.9, 127.0, 127.4, 128.4, 139.7, 158.3, 170.4; IR ($CHCl_3$) 3464, 3019, 1743, 1652, 1524 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.24. Found: C, 62.31; H, 7.34. The above compound was identical in all respects to the urea derivative prepared by the addition of a mixture of triethylamine (1.89 mg, 18.77 mmol) and sarcosine ethyl ester hydrochloride (2.88 mg, 18.77 mmol) in 50 mL of CH_2Cl_2 to a solution of benzyl isocyanate (1.0 mg, 7.51 mmol) in 5.0 mL of CH_2Cl_2 over a period of 2 h, followed by an aqueous workup (water, 1 N HCl, water, and then brine).

***N*-(1-Carbethoxymethyl)-*N'*-isopropylurea (15e)** was prepared from **11** (750 mg, 3.12 mmol) as a crude solid (485 mg, 83%) which on recrystallization (hexanes/dichloromethane, 7:3) gave a colorless solid (445 mg, 2.2 mmol, 76%): mp 69–71 °C; ^1H NMR δ 1.16 (d, J = 6.4 Hz, 6H), 1.27 (t, J = 7.0 Hz, 3H), 2.92 (s, 3H), 3.96 (m, 1H), 4.06 (s, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.37 (bs, 1H); ^{13}C NMR δ 14.1, 23.3, 35.3, 42.6, 50.5, 60.8, 157.6, 170.5; IR ($CHCl_3$) 3461, 2981, 1743, 1642, 1522 cm^{-1}. Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97. Found: C, 53.71; H, 8.93.

***N*-(1-Carbethoxymethyl)-*N'*-cyclohexylurea (15f)** was prepared from **11** (478 mg, 2.0 mmol) as a crude oil (450 mg, 93%) which on flash chromatography (hexanes/ethyl acetate, 6:4) gave a colorless white solid (350 mg, 1.4 mmol, 72%): mp 54–55 °C; ^1H NMR δ 1.10–1.68 (m, 10H), 1.27 (t, J = 6.9 Hz,

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3H), 1.94 (d, J = 3.1 Hz, 1H), 2.92 (s, 3H), 4.06 (s, 2H), 4.18 (q, J = 6.9 Hz, 2H), 4.38 (bs, 1H); ^{13}C NMR δ 14.2, 25.1, 25.7, 33.9, 35.4, 49.6, 50.6, 60.9, 157.6, 170.5; IR ($CHCl_3$) 3462, 3019, 2934, 2400, 1744, 1644, 1520, 1029 cm^{-1}. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.49; H, 9.15. Found: C, 55.60; H, 8.99.

***N*-(1-Carbethoxymethyl)-*N'*-((*S*)-α-methylbenzyl)-urea (15g)** was prepared from **11** (590 mg, 2.46 mmol) as a crude oil (530 mg, 81%) which on flash chromatography (hexanes/ethyl acetate, 1:1) gave a colorless solid (460 mg, 1.73 mmol, 88%): mp 66–68 °C; $[\alpha]^{25}_D$ −23.13 (*c* 2.5, MeOH); ^{1}H NMR δ 1.25 (t, J = 7.0 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H), 2.94 (s, 3H), 3.98 and 4.12 (AB q, J = 17.6 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 4.81 (d, J = 6.6 Hz, 1H), 5.0 (quintet, J = 6.9 Hz, 1H), 7.32–7.34 (m, 5H); ^{13}C NMR δ 14.1, 22.5, 35.3, 56.0, 56.5, 60.8, 126.0, 126.8, 128.3, 144.6, 157.5, 170.3; IR (neat) 3346, 2977, 1748, 1635, 1535 cm^{-1}.

***N*-(1-Carbethoxymethyl)-*N'*-*tert*-butylurea (15h)** was prepared from **11** (478 mg, 2.0 mmol) as a crude solid (340 mg, 78%) which on recrystallization (hexanes/dichloromethane, 8:2) gave a white solid (260 mg, 1.2 mmol, 60%): mp 90–91 °C; ^{1}H NMR δ 1.27 (t, J = 6.8 Hz, 3H), 1.34 (s, 9H), 2.91 (s, 3H), 4.04 (s, 2H), 4.18 (q, J = 6.8 Hz, 2H), 4.42 (bs, 1H); ^{13}C NMR δ 14.2, 23.5, 29.5, 35.7, 50.5, 60.9, 157.4, 170.6; IR (neat) 3445, 3019, 2409, 1743, 1704, 1658, 1519, 1028 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.54; H, 9.31. Found: C, 55.76; H, 9.27.

***N*-(1-Carbethoxymethyl)-*N'*-diethylurea (15i)** was prepared from **11** (478 mg, 2.0 mmol) as a crude oil (380 mg, 88%) which on flash chromatography (hexanes/ethyl acetate, 7:3) gave an oil (300 mg, 1.4 mmol, 69%): ^{1}H NMR δ 1.13 (t, J = 7.1 Hz, 6H), 1.27 (t, J = 7.1 Hz, 3H), 2.92 (s, 3H), 3.19 (q, J = 7.1 Hz, 4H), 3.89 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 13.2, 14.2, 38.3, 42.1, 51.9, 60.8, 164.5, 170.4; IR (neat) 3483, 3246, 2977, 2875, 1748, 1646, 1486, 1354, 1200, 1030 cm^{-1}. Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32. Found: C, 55.45; H, 9.15.

***N*-(1-Carbethoxymethyl)-*N'*-diisopropylurea (15j)** was prepared from **11** (478 mg, 2.0 mmol) as a crude oil (450 mg, 92%) which on flash chromatography (hexanes/ethyl acetate, 6:4) gave an oil (290 mg, 1.2 mmol, 59%): ^{1}H NMR δ 1.28 (m, 15H), 2.85 (s, 3H), 3.65 (m, 2H), 3.82 (s, 2H), 4.22 (q, J = 7.0 Hz, 2H); ^{13}C NMR δ 14.2, 21.7, 38.6, 47.5, 52.2, 60.7, 163.7, 170.6; IR (neat) 3475, 2973, 1751, 1645, 1449, 1367, 1198, 1125, 1048 cm^{-1}. Anal. Calcd for $C_{12}H_{24}N_2O_3$: C, 58.98; H, 9.90. Found: C, 58.77; H, 9.72.

***N*-(1-Carbethoxymethyl)-*N'*-dicyclohexylurea (15k)** was prepared from **11** (478 mg, 2.0 mmol) as an oil (500 mg, 1.2 mmol, 61%) after flash chromatography (hexanes/ethyl acetate, 4:6): ^{1}H NMR δ 1.09–1.88 (m, 23H), 2.81 (s, 3H), 3.09 (q, J = 3.3 Hz, 2H), 3.77 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ 14.2, 25.6, 26.6, 32.1, 38.4, 52.5, 57.4, 60.7, 163.9, 170.6; IR (neat) 3495, 3276, 2930, 2853, 1751, 1645, 1451, 1369, 1197, 1035 cm^{-1}. Anal. Calcd for $C_{18}H_{32}N_2O_3$: C, 66.63; H, 9.94. Found: C, 66.69; H, 9.74.

***N*-(1-Carbethoxymethyl)-*N'*-[4-(*N*-formylcyclohexyl)]-urea (16a)** was prepared from **11** (1.8 mg, 7.51 mmol) as a crude oil (1.7 mg, 89%) which on Kugelrohr distillation (190–200 °C/0.5 mm) gave a colorless oil (1.6 mg, 6.2 mmol, 84%): ^{1}H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 2.99 (s, 3H), 3.22–3.93 (m, 8H), 3.93 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 8.08 (s, 1H); ^{13}C NMR δ 14.1, 38.0, 39.6, 45.1, 46.4, 47.2, 51.1, 60.9, 160.9, 163.7, 169.8; IR (neat) 2982, 1746, 1676 cm^{-1}.

***N*-(1-Carbethoxymethyl)-*N'*-(2-carbethoxycyclohexyl)-urea (16b)** was prepared from **11** (1.67 mg, 6.97 mmol) as a crude oil (2.0 mg, 96%) which on flash chromatography (hexane/ethyl acetate, 7:3) gave a colorless oil (1.76 mg, 5.87 mmol, 84%): ^{1}H NMR δ 1.27 (t, J = 7.0 Hz, 6H), 1.43–2.14 (m, 6H), 2.95 (s, 3H), 3.22–3.52 (m, 2H), 3.92 (AB q, J = 17.6 Hz, 2H), 4.15 and 4.18 (two q, J = 7.1 Hz, 4H), 4.49 (dd, J = 3.7 and 5.1 Hz, 1H); ^{13}C NMR δ 14.20, 14.23, 21.5, 25.1, 27.3, 37.9, 45.3, 51.5, 56.2, 60.7, 60.8, 164.3, 170.1, 172.2; IR (neat) 2939, 1743, 1649, 1399 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05. Found: C, 56.12; H, 7.84.

***N*-(1-Carbethoxymethyl)-*N'*-((*S*)-2-carbomethoxycyclopentyl)urea (16c)** was prepared from **11** (2.41 mg, 10.05 mmol) as a crude oil (2.28 mg, 84%) which on Kugelrohr distillation (205–215 °C/0.5 mm) gave a colorless oil (2.19 mg, 8.02 mmol, 80%): $[\alpha]^{25}_D$ −19.74 (c 3.5, MeOH); ^{1}H NMR δ 1.27 (t, J = 7.2 Hz, 3H), 1.84–2.27 (m, 4H), 2.99 (s, 3H), 3.52 (dd, J = 5.4 and 7.2 Hz, 2H), 3.71 (s, 3H), 3.82 and 4.11 (AB q, J = 17.8 and 18.3 Hz, 2H), 4.16 (q, J = 7.3 Hz, 2H), 4.54 (dd, J = 6.9 and 7.2 Hz, 1H); ^{13}C NMR δ 14.1, 25.4, 29.4, 37.5, 49.5, 49.5, 51.7, 52.0, 60.3, 60.9, 161.8, 170.2, 173.6; IR (neat) 2982, 1745, 1637, 1400 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40. Found: C, 52.82; H, 7.38.

***N*-(1-Carbethoxymethyl)-*N'*-(3-indolethyl)urea (16d)** was prepared from **11** (500 mg, 2.08 mmol) as a light yellow solid after recrystallisation (hexane/dichloromethane, 4:6; 460 mg, 1.51 mmol, 73%): mp 149–150 °C; ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 2.80 (s, 3H), 2.99 (t, J = 6.5 Hz, 2H), 3.56 (dd, J = 5.9 and 6.5 Hz, 2H), 4.08 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.62 (bs, 1H), 7.0–7.26 (m, 3H), 7.37 (d, J = 7.2 Hz, 1H), 7.63 (dd, J = 1.3 and 8.4 Hz, 1H), 8.17 (m, 1H); ^{13}C NMR δ 14.1, 25.7, 35.3, 41.4, 50.5, 61.0, 111.2, 113.5, 118.7, 119.3, 122.0, 122.2, 127.4, 136.4, 158.2, 170.4; IR ($CHCl_3$) 3477, 3354, 3019, 1742, 1645, 1527 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.34; H, 6.97. Found: C, 63.64; H, 7.14.

***N*-(1-Carbethoxymethyl)-*N'*-(4-oxocyclohexyl)urea (16e)** was prepared from **11** (2.0 mg, 8.34 mmol) as a crude oil (1.66 mg, 85%) after Kugelrohr distillation (125–135 °C/0.5 mm) gave a colorless oil (1.60 mg, 6.93 mmol, 83%): ^{1}H NMR δ 1.28 (dt, J = 6.8 and 7.2 Hz, 3H), 2.95 (s, 3H), 3.27 (dd, J = 4.4 and 4.8 Hz, 4H), 3.69 (dd, J = 4.4 and 4.8 Hz, 4H), 3.91 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H); ^{13}C NMR δ 14.1, 38.0, 47.2, 51.3, 60.9, 66.5, 164.0, 169.9; IR (neat) 2976, 1747, 1649 cm^{-1}.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **15g**, **16a**, and **16e** for which elemental analysis was not obtained (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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