Reaction of Hydrazines with α-Lactams for the Preparation of 1,2,4-Triazine-3,6-diones and Aza-Urea Peptide Mimetics

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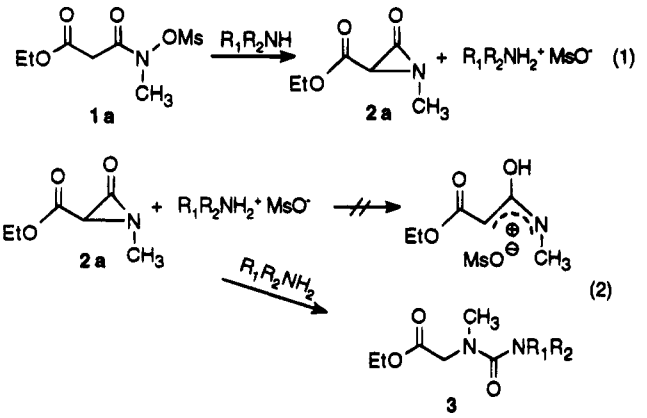
It was recently reported that amine bases convert *N*-(mesyloxy)malonamide **1a** to α-lactam **2a** (eq 1).[1] Electron withdrawal by the carbethoxy group not only makes **2a** a good electrophile but also retards acid-promoted ring opening to an ion pair.[2] As a consequence, α-lactam **2a** reacts with amine nucleophiles, even poor ones such as dicyclohexylamine, exclusively by acyl addition to produce unsymmetric ureas **3** in high yields (eq 2).[1]



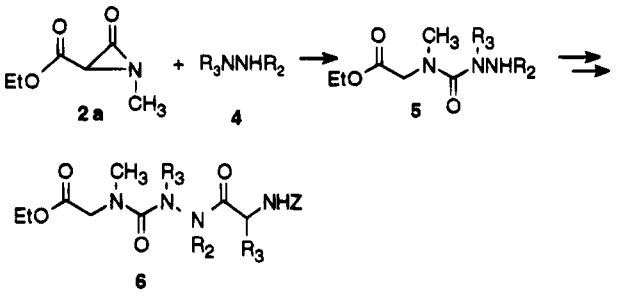
Unsymmetrical ureas **3** have been found useful as cholinesterase inhibitors[3] and recently have been evaluated as peptidase inhibitors.[4] In considering other nucleophilic traps for α-lactams, hydrazines appeared to be interesting candidates. Acyl addition to **2a** by hydrazine **4** would give hydrazido urea **5** which could potentially be elaborated into aza-urea peptide isostere **6**, a new class of peptide mimetics. Isostere **6** incorporates the structural features of *both* urea peptide mimetics[3,4] and aza-peptides,[5] which have been of recent interest (Scheme 1).

We are pleased to report that hydrazines react effectively with α-lactams **2** to give urea hydrazides (e.g. **5**) in high yields whose fate is dependent upon the substitution pattern of the hydrazine.

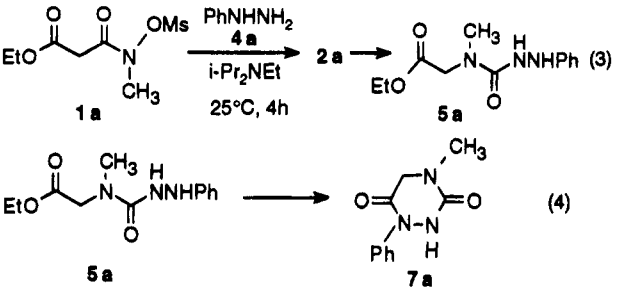
Results and Discussion

Treatment of a mixture of *N*-(mesyloxy)malonamide **1a** (R = CH_3)[1] and phenylhydrazine (**4a**) (1.1 equiv) with

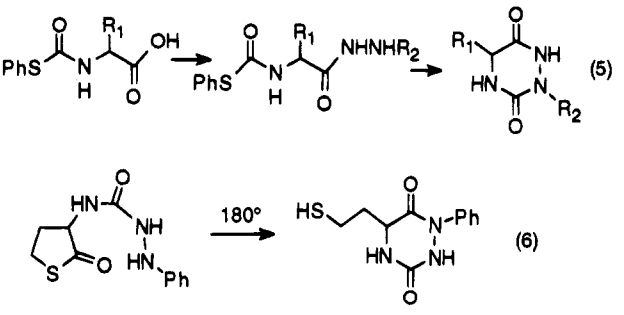
Scheme 1



Hunig's base (1.1 equiv) produced urea hydrazide **5a** in 85% yield (eq 3). The formation of **5a** probably involves initial formation of α-lactam **2a** which acylates **4a** on the terminal amine group of the hydrazine (eq 3). If the reaction mixture was kept at room temperature longer than 6 h, or if **5a** was kept in solution at room temperature for several days, conversion of **5a** to 1,2,4-triazine-3,6-dione **7a** by intramolecular cyclization was observed (eq 4).



Hexahydro-1,2,4-triazine-3,6-diones such as **7a** are a relatively unstudied class of heterocycles.[6] They have usually been prepared by the cyclization of thiocarbamate derivatives of amino acid hydrazides. This approach gives rise to substituent variations at the 2- and 5-positions (eq 5).[7] To our knowledge, only a single example of the cyclization of a urea hydrazide, analogous to the cyclization of **5a**, has been reported (eq 6).[8]



Since the reaction of α-lactams with hydrazines appears to be a simple and facile method for the preparation of hexahydro-1,2,4-triazine-3,6-diones, the process was investigated further (eq 7). Mesylates **1a** and/or **1b** were mixed with hydrazines **4a**–**f**, and ethyldiisopropylamine

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(2) Acid-catalyzed α-lactam ring opening to an ion pair is the most commonly described process of α-lactams. (a) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.* **1993**, *115*, 5031. (b) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1993**, *58*, 2355.

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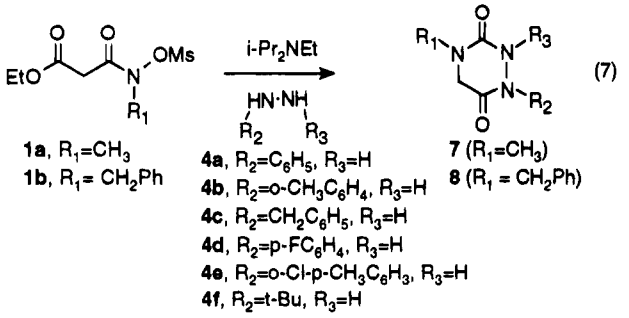
Table 1. Preparation of Hexahydro-1,2,4-triazine-3,6-diones from the Reaction of 1a,b with Hydrazines 4a–f and Ethyldiisopropylamine

entry	reactant	hydrazine	product	yield (%)[a]
1	**1a**	**4a**	**7a**	62
2	**1a**	**4b**	**7b**	70
3	**1a**	**4c**	**7c**	52
4	**1b**	**4a**	**8a**	92
5	**1b**	**4b**	**8b**	64
6	**1b**	**4c**	**8c**	57
7	**1b**	**4d**	**8d**	80
8	**1b**	**4e**	**8e**	74
9	**1b**	**4f**	**8f**	71

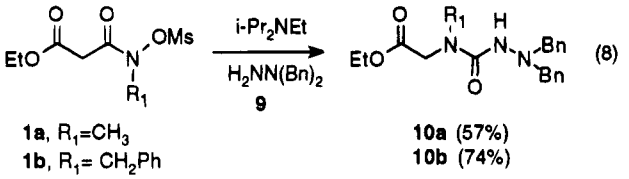
[a] Yields of recrystallized products of analytical purity.

was added slowly over 6–12 h. After stirring overnight, cyclized products **7** and **8** were obtained in the yields indicated in Table 1. The yields in Table 1 are for recrystallized products. The yields of crude product were usually >90%, and the purity of the crude product, as judged by NMR, was very good. The structures were assigned on the basis of the NMR spectra and by the presence of IR absorptions near 1785 and 1735 cm^{-1} which had been reported for hexahydro-1,2,4-triazine-3,6-diones previously.[7b,8]

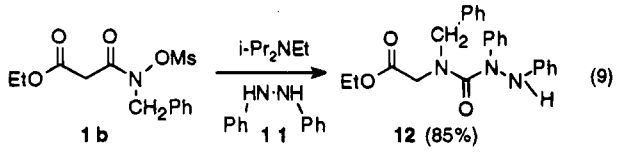


(7)

The cyclization of hydrazido urea intermediates **5** to hexahydro-1,2,4-triazine-3,6-diones **7** and **8** could be blocked by using a 1,1-disubstituted hydrazine as the trapping agent. Thus the reaction of **1a** and **1b** with 1,1-dibenzylhydrazine (**9**) gave hydrazido ureas **10a** and **10b**, respectively (eq 8). The failure of **10a** and **10b** to cyclize is evidenced by the normal ester stretch of 1744 cm^{-1} in the IR. Moreover, the use of 1,2-diphenylhydrazine (**11**) as the nucleophile with **1b** gave hydrazido urea **12** in 85% yield. The failure of **12** to cyclize, as revealed by an ester stretch at 1735 cm^{-1}, might be attributed to reduced nucleophilicity of the hydrazide nitrogen due to the second phenyl substituent (eq 9).



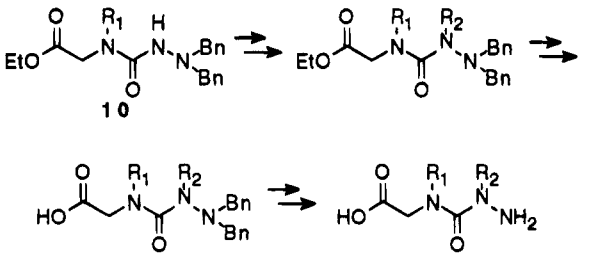
(8)



(9)

These results show that with appropriate control of the cyclization process, the framework for aza-urea peptide mimetics can readily be assembled by this methodology.

Scheme 2



In fact intermediates **10** are prime candidates for further elaboration to aza-urea peptide mimetics by alkylation of nitrogen, hydrolysis of the ester group, and debenzylation of the hydrazide group to produce an aza-urea dipeptide isostere (Scheme 2).

In summary, a simple and direct method for the preparation of urea hydrazides and hexahydro-1,2,4-triazine-3,6-diones results from the reaction of hydrazines with the α-lactam derived from ethyl malonyl hydroxamate **1**. Elaboration of the former into aza-urea peptide isosteres is under investigation. The development of the latter as potential β-turn mimics is also being pursued.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr disks. Chemical shifts are reported for $CDCl_3$ solution in ppm relative to TMS. 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). *N*-Hydroxy-*N*-(ethoxymalonyl)-*N*-methylamine[9] and *N*-(mesyloxy)-N-(ethoxymalonyl)-*N*-methylamine[10] were prepared by the literature methods, and the products were purified by flash column chromatography (hexanes–ethyl acetate) or recrystallization (hexanes–CH_2Cl_2). Ethyl malonyl chloride, phenylhydrazine, *N,N'*-diphenylhydrazine, *o*-tolylhydrazine hydrochloride, benzylhydrazine dihydrochloride, (4-fluorophenyl)-hydrazine, (2-chloro-4-methylphenyl)hydrazine, and *tert*-butylhydrazine hydrochloride were purchased from Aldrich and used as received. *N*-Benzylhydroxylamine[11] and *N,N*-dibenzylhydrazine[12] were prepared according to known procedures.

Preparation of *N*-Hydroxy-*N*-(ethoxymalonyl)-*N*-benzylamine. Ethyl malonyl chloride (2.44 g, 16.24 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a solution of *N*-benzylhydroxylamine (4.2 g, 34.10 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then at rt for 2 h. The solvent was then removed under reduced pressure, and the residue was treated with saturated NaCl (20 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extract was dried over $MgSO_4$. After rotary evaporation, the crude product (4.0 g, 100%) was purified by recrystallization (hexane–dichloromethane, 7:3) to give a colorless solid (3.2 g, 13.50 mmol): mp 67–69 °C; ^1H NMR δ 1.21 (t, J = 6.7 Hz, 3H), 3.56 (s, 2H), 4.14 (d, J = 7.0 Hz, 2H), 4.81 (s, 2H), 7.26–7.32 (m, 5H), 7.83 (bs, 1H); IR ($CHCl_3$) 3028, 2946, 1740, 1700, 1370, 1325, 1198, 1119 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37. Found: C, 60.90; H, 6.45.

Preparation of *N*-(Mesyloxy)-*N*-(ethoxymalonyl)-*N*-benzylamine (1b). To a solution of the *N*-hydroxy-*N*-(ethoxymalonyl)-*N*-benzylamine (2.84 g, 12.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added triethylamine (1.21 g, 12.0 mmol). The mixture was stirred for 10–12 min, and methanesulfonyl chloride (1.55 g, 13.2 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h, allowed to warm to rt, 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

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evaporation, **1b** was isolated (2.83 g, 75%) after flash chromatography (hexane–ethyl acetate (6:4)): ^{1}H NMR δ 1.16 (t, J = 7.1 Hz, 3H), 3.04 (s, 3H), 4.11 (q, J = 7.0 Hz, 2H), 5.04 (s, 2H), 7.35 (s, 5H); ^{13}C NMR δ 13.9, 37.4, 41.5, 54.8, 61.6, 128.4, 128.7, 128.8, 134.1, 166.1; IR (neat) 2983, 1742, 1697, 1370, 1186 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_6S$: C, 49.51; H, 5.43. Found: C, 49.63; H, 5.61.

Synthesis of 1,4-Dialkyl-1,2,4-triazine-3,6-diones. General Procedure. To a solution of the *N*-(mesyloxy)-*N*-(ethoxymalonyl)-*N*-alkylamine (2 mmol) in CH_2Cl_2 and a hydrazine (2.2 mmol) was added triethylamine (202 mg, 2.1 mmol) in 24 mL of CH_2Cl_2 over a period of 6–12 h. The mixture was stirred overnight (ca. 18–24 h). The solvent was removed, and the residue was diluted with ethyl acetate (60 mL), washed with water (4 × 20 mL) and brine (20 mL), and dried over $MgSO_4$. After rotary evaporation, the product was purified by flash column chromatography or recrystallization.

Hexahydro-1-phenyl-4-methyl-1,2,4-triazine-3,6-dione (7a) was prepared from **1a** (1.0 g, 4.17 mmol) and **4a** as a crude oil (840 mg, 98%) which on flash chromatography (hexanes–ethyl acetate, 1:1) gave **7a** as a colorless solid (530 mg, 62%): mp 150–152 °C; ^{1}H NMR δ 3.01 (s, 3H), 3.94 (s, 2H), 6.27 (s, 1H), 6.76–6.81 (m, 2H), 6.95–6.99(m, 1H), 7.18–7.26 (m, 2H); ^{13}C NMR δ 30.1, 50.2, 114.1, 122.1, 129.2, 145.4, 155.1, 168.0; IR ($CHCl_3$) 3289, 3019, 1787, 1731, 1605 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.52; H, 5.40. Found: C, 58.38; H, 5.36.

Hexahydro-1-*o*-tolyl-4-methyl-1,2,4-triazine-3,6-dione (7b) was prepared from **1a** (1.25 g, 5.21 mmol) and **4b** as a crude oil (1.06 g, 93%) which on flash chromatography (hexanes–ethyl acetate, 4:6) gave **7b** as an light yellow solid (800 mg, 70%): mp 138–139 °C; ^{1}H NMR δ 2.31 (s, 3H), 3.04 (s, 3H), 3.99 (s, 2H), 5.97 (s, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H) 7.08 (dd, J = 6.6, 4.4 Hz, 2H); ^{13}C NMR δ 16.8, 30.1, 50.3, 112.3, 122.0, 123.6, 126.9, 130.7, 143.2, 155.0, 167.9; IR ($CHCl_3$) 3318, 3018, 1788, 1733, 1592 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.97. Found: C, 60.20; H, 6.12.

Hexahydro-1-benzyl-4-methyl-1,2,4-triazine-3,6-dione (7c) was prepared from **1a** (1.63 g, 6.80 mmol) and **4c** as a crude oil (1.28 g, 86%) which on flash chromatography (hexanes–ethyl acetate, 6:4) gave **7c** as an off white solid (780 mg, 52%): mp 127–129 °C; ^{1}H NMR δ 2.91 (s, 3H), 3.68 (s, 2H), 4.67 (s, 2H), 7.29 (m, 5H), 9.75 (bs, 1H); ^{13}C NMR δ 34.8, 51.0, 51.2, 128.1, 128.2, 128.4, 128.7, 135.5, 154.5, 163.4; IR ($CHCl_3$) 3017, 1659 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.97. Found: C, 60.30; H, 5.96.

Hexahydro-1-phenyl-4-benzyl-1,2,4-triazine-3,6-dione (8a) was prepared from **1b** (650 mg, 2.06 mmol) and **4a** as a crude solid (780 mg, 100%) which on recrystallization (hexanes–$CHCl_3$, 8:2) gave **8a** as a white solid (530 mg, 92%): mp 148–149 °C; ^{1}H NMR δ 3.84 (s, 2H), 4.59 (s, 2H), 6.13 (s, 1H), 6.81 (dd, J = 7.4, 2.0 Hz, 2H), 6.97 (dd, J = 7.4, 7.3 Hz), 7.21–7.40 (m, 7H); ^{13}C NMR δ 47.1, 47.6, 114.1, 122.2, 128.2, 128.3, 129.0, 129.2, 134.9, 145.4, 155.1, 168.0; IR ($CHCl_3$) 3351, 3020, 1785, 1733, 1605 cm^{-1}. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37. Found: C, 68.12; H, 5.52.

Hexahydro-1-*o*-tolyl-4-benzyl-1,2,4-triazine-3,6-dione (8b) was prepared from **1b** (1.5 g, 4.76 mmol) and **4b** as a crude yellow solid (1.25 g, 89%) which on flash chromatography (hexanes–ethyl acetate, 1:1) gave **8b** as an light yellow solid (900 mg, 64%): mp 142–143 °C; ^{1}H NMR δ 2.33 (s, 3H), 3.85 (s, 2H), 4.60 (s, 2H), 6.00 (bs, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.89 (dd, J = 7.5 and 7.2 Hz, 1H), 7.07–7.12 (m, 2H), 7.26–7.41 (m, 5H); ^{13}C NMR δ 16.9, 47.1, 47.6, 112.3, 122.0, 123.6, 126.9, 128.2, 128.3, 129.1, 130.8, 134.8, 143.2, 155.0, 167.8; IR ($CHCl_3$) 3324, 3018, 1784, 1729, 1592, 1462, 1239 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80. Found: C, 69.29; H, 6.00.

Hexahydro-1,4-dibenzyl-1,2,4-triazine-3,6-dione (8c) was prepared from **1b** (1.5 g, 4.76 mmol) and **4c** as a crude oil (1.0 g, 71%) which on flash chromatography (hexanes–ethyl acetate, 6:4) gave **8c** as an oil (800 mg, 57%): ^{1}H NMR δ 3.55 (s, 2H), 4.51 (s, 2H), 4.69 (s, 2H), 7.28–7.32 (m, 11H); ^{13}C NMR δ 48.3, 50.8, 51.5, 127.9, 128.2, 128.7, 128.8, 135.3, 135.6, 154.3, 163.6; IR ($CHCl_3$) 3030, 1661, 1453, 1249 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3O_2 \cdot {}^1/_2H_2O$: C, 67.14; H, 5.63. Found: C, 67.20; H, 5.69.

Hexahydro-1-(4-fluorophenyl)-4-benzyl-1,2,4-triazine-3,6-dione (8d) was prepared from **1b** (1.0 g, 3.17 mmol) and **4d** as a colorless solid (940 mg, 99%) which on recrystallization (hexanes–CH_2Cl_2, 3:7) gave **8d** as a colorless solid (760 mg, 80%): mp 149–150 °C; ^{1}H NMR δ 3.82 (s, 2H), 4.58 (s, 2H), 6.13 (s, 1H), 6.77–6.99 (m, 4H), 7.24–7.39 (m, 5H); ^{13}C NMR δ 47.2, 47.6, 115.8, 116.0, 116.3, 116.4, 128.2, 128.4, 129.1, 134.7, 141.5, 141.6, 155.0, 157.4, 159.8, 167.8; IR ($CHCl_3$) 3419, 3019, 1787, 1733, 1650, 1509 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_3O_2F$: C, 64.20; H, 4.71. Found: C, 64.16; H, 4.55.

Hexahydro-1-(2-chloro-4-methylphenyl)-4-benzyl-1,2,4-triazine-3,6-dione (8e) was prepared from **1b** (1.0 g, 3.17 mmol) and **4e** as a colorless solid (920 mg, 100%) which on recrystallization (hexanes–CH_2Cl_2, 4:6) gave **8e** as a colorless solid (688 mg, 74%): mp 188–189 °C; ^{1}H NMR δ 2.28 (s, 3H), 3.85 (s, 2H), 4.60 (s, 2H), 6.03 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR δ 19.2, 47.2, 47.6, 113.0, 115.0, 128.2, 128.5, 129.2, 130.0, 131.4, 134.7, 134.9, 144.2, 154.8, 167.6; IR ($CHCl_3$) 3425, 3019, 1733, 1683, 1613, 1498, 1453 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_3O_2Cl$: C, 61.91; H, 4.89. Found: C, 62.11; H, 5.00.

Hexahydro-1-*tert*-butyl-4-benzyl-1,2,4-triazine-3,6-dione (8f) was prepared from **1b** (650 mg, 2.06 mmol) and **4f** as a colorless oil (500 mg, 93%) which on flash chromatography (hexanes–ethyl acetate, 6:4) gave **8f** as a colorless solid (380 mg, 71%): mp 104–105 °C; ^{1}H NMR δ 1.18 (s, 9H), 3.75 (s, 2H), 4.27 (s, 1H), 4.57 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR δ 28.0, 47.1, 47.5, 57.0, 128.2, 128.3, 129.0, 135.1, 156.6, 168.9; IR ($CHCl_3$) 3424, 3019, 1778, 1723, 1511, 1453 cm^{-1}. Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.32. Found: C, 64.45; H, 7.21.

***N*-(Carbethoxymethyl)-*N*-methyl-*N'*-(dibenzylamino)-urea (10a)** was prepared from **1a** (1.0 g, 4.17 mmol) and **9** as a crude solid (1.36 g, 92%) which on flash chromatography (hexanes–ethyl acetate, 1:1) gave **10a** as a colorless solid (840 mg, 57%): mp 128–129 °C; ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 2.68 (s, 3H), 3.95 (s, 2H), 4.11–4.19 (m, 6H), 5.63 (s, 1H), 7.25–7.40 (m, 10H); ^{13}C NMR δ 14.1, 35.4, 50.5, 59.4, 60.9, 127.2, 128.2, 129.4, 137.5, 157.9, 169.9; IR ($CHCl_3$) 3453, 3018, 1744, 1663, 1495, 1455 cm^{-1}. Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.08. Found: C, 67.43; H, 7.19.

***N*-(Carbethoxymethyl)-*N*-benzyl-*N'*-(dibenzylamino)-urea (10b)** was prepared from **1b** (2.18 g, 6.91mmol) and **9** as a crude solid (2.76 g, 93%) which on recrystallization (hexanes–CH_2Cl_2, 8:2) gave **10b** as a light yellow solid (2.2 g, 74%): mp 95–96 °C; ^{1}H NMR δ 1.22 (t, J =7.0 Hz, 3H), 3.85 (s, 2H), 4.10–4.14 (m, 6H), 4.25 (s, 2H), 5.70 (s, 1H), 6.96–7.34 (m, 15H); ^{13}C NMR δ 14.1, 48.9, 51.7, 61.0, 126.8, 127.2, 127.4, 128.2, 128.7, 129.4, 136.4, 137.5, 158.0, 170.0; IR ($CHCl_3$) 3434, 3017, 1744, 1664, 1495, 1454 cm^{-1}. Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.36; H, 6.77. Found: C, 72.47; H, 6.93.

***N*-(Carbethoxymethyl)-*N*-benzyl-*N'*-phenyl-*N'*-(phenylamino)urea (12)** was prepared from **1b** (1.0 g, 3.17 mmol) and **11** as a crude solid (940 mg, 76%) which on recrystallization (hexanes–CH_2Cl_2, 7:3) gave **12** as a yellow solid (560 mg, 45%): mp 122–123 °C; ^{1}H NMR δ 1.19 (t, J =7.1 Hz, 3H), 3.95 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.48 (s, 2H), 6.87–7.47 (m, 15H); ^{13}C NMR δ 14.0, 48.0, 52.7, 61.1, 113.6, 121.1, 121.6, 124.9, 127.8, 128.7, 129.2, 135.9, 145.6, 148.1, 160.7, 169.4; IR ($CHCl_3$) 3317, 2984, 1743, 1663, 1601, 1495, 1200 cm^{-1}. Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.56; H, 6.43. Found: C, 71.27; H, 6.46.

***N*-(Carbethoxymethyl)-*N*-methyl-*N'*-(phenylamino)-urea (5a)** was isolated in low yield from the reaction of **1a** (1.0 g, 4.17 mmol) and **4a** by flash chromatography (hexanes–ethyl acetate, 1:1) as a colorless oil (100 mg, 9.8%): ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 2.98 (s, 4H, exchangeable with D_2O), 4.05 (s, 2H), 4.17 (q, J = 7.0 Hz, 2H), 6.09 (bs, 1H), 6.72–6.88 (m, 3H), 7.19–7.26 (m, 2H); ^{13}C NMR δ 14.1, 35.1, 50.6, 61.2, 113.5, 120.6, 128.9, 149.0, 159.0, 170.0; IR ($CHCl_3$) 3327, 2984, 1735, 1660, 1604, 1496 1209 cm^{-1}. Elemental analysis could not be obtained due to the tendency of **5a** to cyclize to **7a**. Hydrazido urea **5a** can also be prepared in 85% isolated yield if *N,N*-diisopropyl-*N*-ethylamine is added over 4 h to a mixture of **1a** and **4a** and the reaction mixture is worked up after stirring 3–4 h at rt.

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Supporting Information Available: ^{13}C NMR spectra (fully decoupled and off-resonance decoupled) for compound **5a** and the fully decoupled spectrum of **12** (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 page for ordering information.

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