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Synthesis and Reactions of 2-Substituted Ethyl *N*-Alkylmalonylhydroxamic Acids

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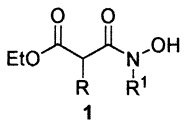
Alkylation of O-silylated *N*-alkylmalonylhydroxamic acids provides a method for the synthesis of 2-substituted *N*-alkylmalonyl hydroxamic acids. The substituent at C-2 does not materially change the chemistry of the α-lactam intermediates produced from them. They can be converted to unsymmetric ureas and hydantoins in high yields. The addition of unsaturated substituents at C-2 is used to produce cyclic ureas containing medium rings via RCM reactions.

We have found that N-alkylated hydroxamic acids are convenient sources of α-lactams when converted to the *N*-mesyloxy derivative and treated with base.[1] Particular interest developed in ethyl *N*-alkylmalonylhydroxamic acids **1**, which proved to be versatile synthetic intermediates for the synthesis of unsymmetric ureas, *N*-aminohydantoins, and 1,2,4-triazolin-3,6-diones via α-lactams.[2−4] In all cases studied thus far, the 2-position has been unsubstituted (**1**, R = H). Substitutents at the 2-position could be useful as elements of diversity as well as for the incorporation of additional functionality that could be manipulated in the products. Moreover, the ability of electron-withdrawing groups to control the regiochemistry of nucleophilic addition to the intermediate α-lactam[1,2] suggests other electron-withdrawing groups such as an acyl group (e.g., **2**) would also lead to potentially new and interesting chemistry.



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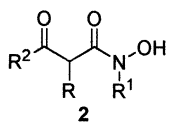

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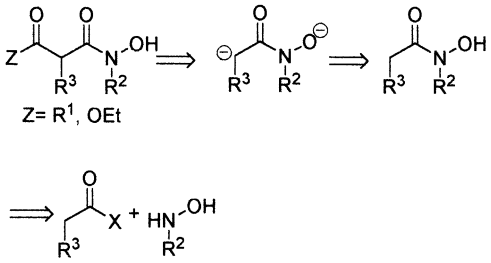
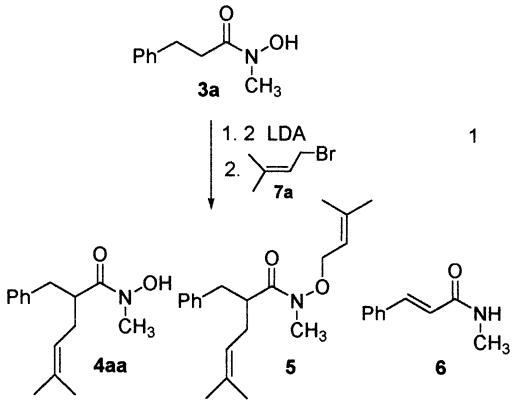
In considering ways to prepare **1** and **2**, it occurred to us that if hydroxamic acids could be converted to their bis-anions (in analogy to carboxylic acid bis-anions[5]), they could be carboxylated or acylated to give **1** and **2** (Scheme 1). This would provide a novel and potentially general way to prepare such materials from readily available starting materials without having to deal with unstable *β*-keto acid or malonic half ester intermediates. To our knowledge, bis-anions of hydroxamic acids have not been reported previously in the literature.

SCHEME 1



Results and Discussion

A. Synthesis. When hydroxamic acid **3a** was treated with 2.2 equiv of LDA at 0 °C for 1 h and then prenyl bromide **7a** was added, prenylated adduct **4aa** could be isolated in yields of 50−55%. In addition to **4aa**, bis-alkylated product **5** (19%) as well as unsaturated amide **6** (10−12%) could be isolated from the reaction mixture (eq 1).



Similar results were obtained if the same sequence was carried out at −20 °C. Lower yields of monoalkylated

(1) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.* **1993**, *115*, 5031.
(2) Hoffman, R. V.; Reddy, M. M.; Cervantes-Lee, F. *J. Org. Chem.* **2000**, *65*, 2591−2595.
(3) Hoffman, R. V.; Reddy, M. M.; Klumas, C. M.; Cervantes-Lee, F. *J. Org. Chem.* **1998**, *63*, 9128−9130.
(4) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, *60*, 5992−5994.
(5) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994.

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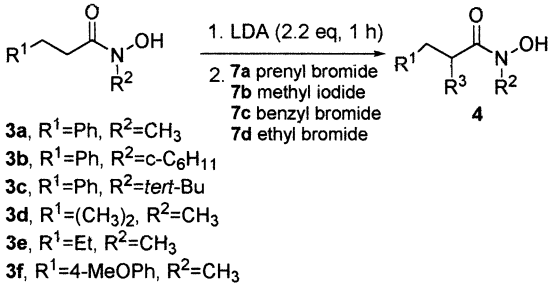
TABLE 1. Alkylation of *N*-Alkylhydroxamic Acid Bis-anions



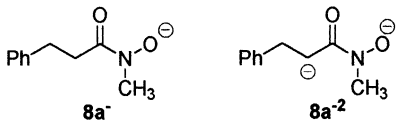
entry	starting material	alkylating agent	product[a]	temp (°C)	yield **4** (%)[b]
1	**3a**	**7a**	**4aa**	0	55
2	**3a**	**7a**	**4aa**	−20	52
3	**3a**	**7b**	**4ab**	0	47
4	**3a**	**7c**	**4ac**	−20	40
5	**3a**	**7d**	**4ad**	0	39
6	**3b**	**7b**	**4bb**	−20	45
7	**3c**	**7a**	**4ca**	−20	26
8	**3e**	**7c**	**4ec**	0	38
9	**3f**	**7a**	**4fa**	0	42

[a] Product structures are indicated by the reaction of starting material **3x** with alkylating agent **7y** to give product **4xy**. [b] Yields are for isolated yields of purified products.

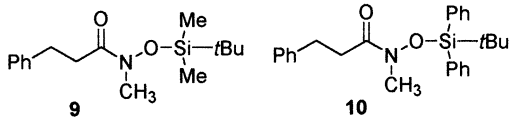
product **4aa** were obtained at −78 °C (35%). A lower yield of **4aa** was observed if the reaction time for bis-anion formation at 0 °C was decreased from 1 h to 30 min (21% **4aa** but 48% of unreacted **3a**) due to incomplete reaction. A lower yield of **4aa** was also observed if the reaction time for bis-anion formation was increased to 2 h (29% **4aa** and 32% **5**). These results define the best conditions for the sequence, namely, bis-anion formation at either 0 or −20 °C for 1 h followed by addition of an alkylating agent **7** at the same temperature. A series of *N*-alkylhydroxamic acids was alkylated using these conditions, and the results are presented in Table 1.

The yields of monoalkylated products were only fair to moderate. It became pertinent to ask (a) if the bis-anion was, in fact, being generated in the reaction mixture and (b) if the bis-anion is stable under the reaction conditions. Treatment of **3a** with 1 equiv of LDA at 0 °C for 1 h followed by aqueous workup led to near quantitative recovery of **3a**; thus, the hydroxamate monoanion **8a**$^{-}$ is stable to the reaction conditions. Treatment of **3a** with 2.2 equiv of LDA for 1 h at 0 °C followed by an aqueous quench led to only 50% recovery of the starting material and 7% of **6**. Finally, treatment of **3a** with 2.2 equiv of LDA for 1 h at 0 °C followed by a D_2O quench gave 51.5% recovered starting material that had a single deuterium at the α-position as well as 10% of **6**.

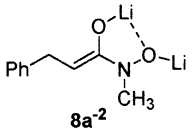
These experiments demonstrate that bis-anion **8a**$^{-2}$ is formed from **3a** under the reaction conditions but that it is unstable and begins to decompose at 0 °C *prior* to the addition of the alkylating agent. This accounts for the modest yields of monoalkylated products. Furthermore, decomposition of the bis-anion would lead to an excess of prenyl bromide, relative to the bis-anion, which accounts for the dialkylated product (eq 1).[6] Thus, decomposition of the bis-anion **8a**$^{-2}$ appears to be a limiting factor in production of monoalkylated product from **3a** and presumably other hydroxamic acids as well.



Several attempts to circumvent the decomposition of **8a**$^{-2}$ were made. O-Silylation with *tert*-butyldimethylsilyl chloride or *tert*-butyldiphenylsilyl chloride gave TBDMS derivative **9** and TBDPS derivative **10**, respectively. Treatment of either **9** or **10** with LDA (1 equiv) and then prenyl bromide gave no alkylated product. In each case, the starting material was recovered in 50% yield along with the corresponding silanol. For comparison purposes, the Weinreb amide was prepared from **3a**. Treatment with LDA and then prenyl bromide led to complete decomposition. This is consistent with observations showing that Weinreb amides are quite unstable to either strong[7] or weak[8] bases. Thus, silylation of the oxygen of a hydroxamic acid does not prevent decomposition of the enolate and appears to retard the alkylation of the α-position.



The importance of lithium ions in the decomposition of **8a**$^{-2}$ was easily shown. When potassium hexamethyldisilylamide was used in place of LDA for enolate formation with **3a**, the yield of alkylation product **4aa** decreased significantly (due to increased decomposition), yet no **6** was formed. This suggests that lithium ions stabilize **8a**$^{-2}$, presumably by stabilization of the oxyanions in **8a**$^{-2}$.



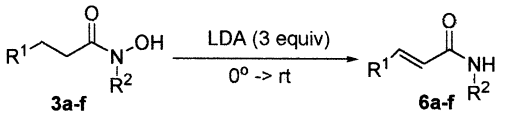
The formation of **6** is quite interesting since nitrogen is reduced and the α- and β-carbons are oxidized relative to the starting material. Moreover, formation of **6** proceeds by cleavage of the N−O bond of **8**$^{-2}$, in which the oxygen bears a negative charge yet functions as a leaving group!

Hydroxamic acids **3a**−**f** were treated with 3 equiv of LDA at 0 °C and then allowed to stir at room temperature until the starting material was consumed (TLC). The unsaturated amides **6a**−**c**,**f** were isolated from the dark red reaction mixtures. The results are presented in Table 2.

The results suggest that the β-proton must be activated by conjugation in order to form **6** (cf. entries 1−4 and 5, 6), and an electron−donating substituent on the aromatic

(6) Treatment of **4a** with 1 equiv of LDA and then 1 equiv of prenyl bromide at 0 °C gives **5** in high yield.
(7) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269.
(8) Keck, G. E.; McHardy, S. F.; Murry, J. A. *Tetrahedron Lett.* **1993**, *34*, 6215.

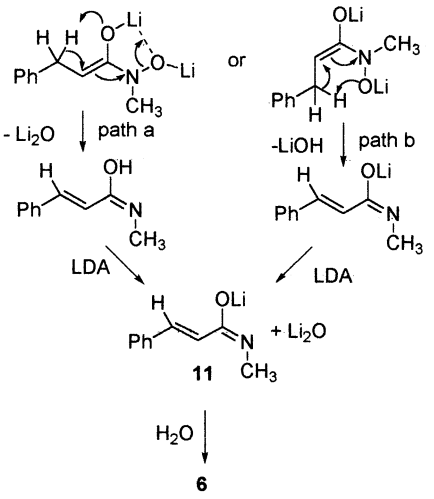
TABLE 2. Conversion of Hydroxamic Acids to α,β-Unsaturated Amides



entry	hydroxamic acid	product	yield (%)[a]
1.	**3a**	**6a**	40
2.	**3b**	**6b**	42
3.	**3c**	**6c**	42
4.	**3f**	**6f**	15
5.	**3d**	**6d**	0
6.	**3e**	**6e**	0

[a] Yield of pure material after column chromatography.

SCHEME 2



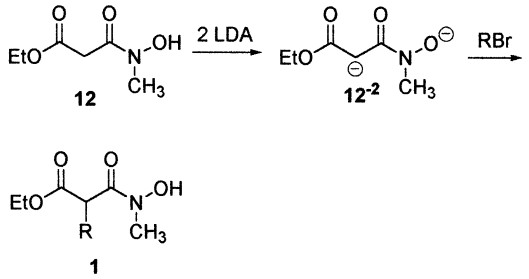
ring suppresses its formation (cf. entries 1−3 and 4). Thus, proton removal from the β-position is required for the formation of **6**. LDA is not involved in its removal, however, since doubling the concentration of LDA in the reaction of **3a** does not change the yield of **6a**.[9] Formation of **6** appears to be a first-order reaction of bis-anion $\mathbf{8}^{-2}$ characterized by an intramolecular proton rearrangement to one of the anionic oxygens to give conjugated ion **11** (Scheme 2). Of the two likely pathways shown in Scheme 2, path b is preferred due to the six-membered ring transition state for proton loss. In either case, a third equivalent of LDA is required to neutralize the ultimate product of proton removal. The formation of **6** occurs upon generation of bis-anion $\mathbf{8}^{-2}$ even at −20 °C, so it is always a part of the product mixture.

Attempts to acylate $\mathbf{8a}^{-2}$ with ethyl chloroformate were uniformly unsuccessful, as complete decomposition was observed on addition of the acylating agent, even at −78 °C. While hydroxamic acid dianions can be alkylated with modest success, they do not provide a viable route to **1**.

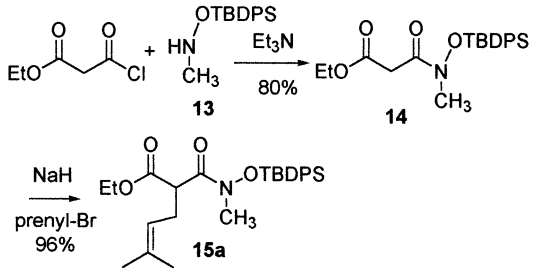
In considering alternate synthetic approaches to **1**, R ≠ H, a straightforward strategy would be to simply alkylate **12** (Scheme 3). We anticipated that the ester group in the malonylhydroxamate bis-anion should stabilize the negative charge of dianion $\mathbf{12}^{-2}$ and hopefully reduce the amount of competing decomposition.

Treatment of *N*-methylhydroxamate **12**[10] with 2 equiv of LDA followed by prenyl bromide, conditions used to

SCHEME 3



SCHEME 4



alkylate simple hydroxamic acids, led to complete destruction of the starting material! Of the two anionic sites in $\mathbf{12}^{-2}$, the resonance-delocalized malonyl anion should be reasonably stable. Thus, blocking the hydroxamic acid group by silylation should result in a more stable malonyl monoanion. Treatment of **12** with 1 equiv of sodium hydride and TBDMSCl or treatment with triethylamine and TBDMSCl also led to decomposition of the starting material. Clearly, the hydroxamate anion of **12** is unstable and does not survive long enough to be silylated.[11]

Since direct O-silylation of **12** could not be accomplished, *N*-methylhydroxylamine was O-silylated with TBDPSCl to give **13**.[12] Slow addition of ethyl malonyl chloride to a mixture of **13** and Et_3N (1 equiv) gave O-silylated hydroxamic acid **14** in good yield. Consistent with prediction, the O-silylated hydroxamate **14** could be alkylated with prenyl bromide to give **15a** in very high yields (Scheme 4).

Desilylation of **15a** with TBAF in THF[13] failed to deliver the hydroxamic acid. Instead, a compound that appeared to be the cyclized product **16** by IR and NMR spectroscopy was isolated in 16% yield. Since **16** presumably results from cyclization of the hydroxamate anion of **15a**, a process suspected earlier in the reaction of hydroxamic acid **12** with bases, the use of fluoride to desilylate **15** is not a good choice. We found, however, that 1% methanesulfonic acid in absolute ethanol desi-

(9) α-Lactams with β-hydrogens can react with bases to produce α,β-unsaturated amides in a second-order reaction. (See for example: Quast, H., Meichsner, G., Seiferling, B. *Chem. Ber.* **1987**, *120*, 217−223.) This scenario predicts that the yield of **6** should increase as the concentration of LDA is increased, contrary to observations. Thus, the involvement of α-lactams in the formation of **6** is discounted.

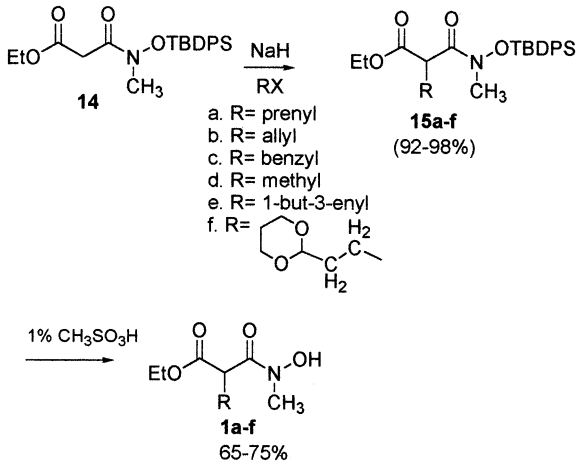
(10) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Org. Chem.* **1995**, *60*, 4121−4125

(11) A product was isolated that lacked the ethoxy group and appeared to be the result of intramolecular cyclization between the hydroxamate oxyanion and the ester group to give an isoxazolidine dione.

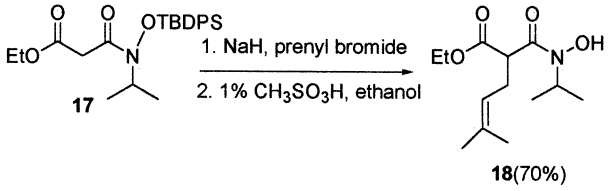
(12) Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33* 5055−5058.

(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

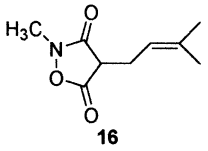
SCHEME 5



SCHEME 6



lylated **15a** smoothly to the hydroxamic acid in 70% yield.[14]



A series of *N*-methyl ethyl malonylhydroxamates **15** was prepared by the alkylation and desilylation of **14** (Scheme 4). Activated alkyl bromides (allyl, prenyl, benzyl) reacted smoothly at room temperature as did methyl iodide. Unactivated primary bromides (4-butenyl bromide and the acetal of 3-bromopropanal) required the addition of 1 equiv of sodium iodide and overnight reflux for efficient reaction. Nevertheless excellent yields of **15** were obtained. Desilylation gave the hydroxamic acids **1a**−**f** in good yields.

N-Isopropyl analogue **17** was alkylated with prenyl bromide and desilylated to give **18** in 70% overall yield (Scheme 6), which suggests that it is possible to prepare other N-substituted analogues as well.

The TBDPS protecting group was chosen so that the intermediate alkylation products **15** could be isolated and purified. In practice, however, the crude alkylation product was quite pure and could be desilylated without purification. Good results could also be obtained using the TBDMS protecting group if the crude alkylation product was carried on without purification.

B. Reactions. With a source of malonyl hydroxamic acids **1** in hand, their chemistry could be investigated. Hydroxamic acids **1a**−**e** and **18** were converted to the *N*-mesyloxy derivatives **19a**−**e** and **20**, respectively, by reaction with methanesulfonyl chloride and triethylamine.[10] Mesylates **19a**−**e** and **20** were reacted with amines to provide unsymmetric ureas in high yields (Scheme 7). The results are shown in Table 3.

SCHEME 7

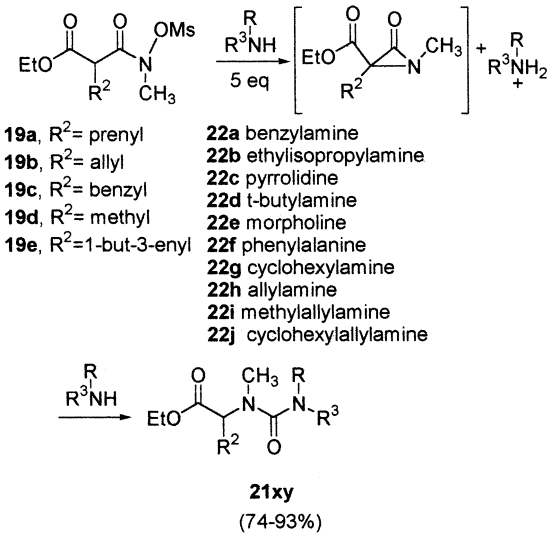


TABLE 3. Preparation of Unsymmetric Ureas from the Reaction of *N*-Mesyloxy Amides with Amine Nucleophiles in Refluxing Dichloromethane

entry	mesylate	amine	product[a]	time[b]	yield (%)[c]
1	**19a**	**22d**	**21ad**	4 h	86
2	**19a**	**22e**	**21ae**	4 h	81
3	**19b**	**22g**	**21bg**	2 h	79
4	**19b**	**22h**	**21bh**	15 h	76
5	**19b**	**22i**	**21bi**	2 h	93
6	**19b**	**22j**	**21bj**	4 h	87
7	**19c**	**22b**	**21cb**	2 h	92
8	**19c**	**22c**	**21cc**	2 h	91
9	**19d**	**22a**	**21da**	7 h	81
10	**19d**	**22f**	**21df**	5 h	77
11	**19e**	**22h**	**21eh**	24 h	74
12	**19e**	**22i**	**21ei**	2 h	90
13	**19e**	**22j**	**21ej**	5 h	88
14	**20**	**22h**	**23**	5 h	82

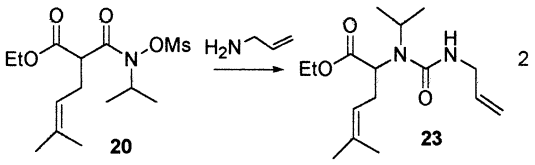
[a] Mesylate **19x** reacting with amine **22y** would give product **21xy**. [b] Time for complete disappearnace of starting material by TLC. [c] Yields of pure product after column chromatography.

The data in Table 3 show that both primary and secondary amines react effectively to give unsymmetric ureas in high yields. Thus, a substituent at the 2-position of the malonyl hydroxamate does not alter the course of the reaction. It does, however, slow the rate of reaction. It was reported that the reactions of amines (2.2 equiv) with ethyl *N*-methyl-*N*-mesyloxymalonamide (**19**, R^2 = H) require 6−8 h at room temperature for completion.[10] Similar reactions of **19a**−**f** were very sluggish, and it was necessary to use 5 equiv of amine and refluxing dichloromethane to achieve complete reaction in comparable times. We attribute this to a steric effect that produces greater strain in the transition state for ring closure to the α-lactam intermediate. Steric retardation of ring closure to an α-lactam was previously observed in the reactions of 2-substituted phenylacetohydroxamates.[15]

Steric retardation is further exacerbated in substrate **20**, which reacts with allylamine to give **23** (eq 2) nearly

(14) We have just recently learned that 0.5% methanesulfonic acid in absolute ethanol gives even higher yields of desilylation (80−85%).

three times more slowly than *N*-methyl analogue **19b** (cf. entries 4 and 19, Table 3). Despite the reduced reactivity, however, the reactions of **19a**−**f** and **20** with amine nucleophiles are quite clean and give generally high yields. Moreover, the sequence **14** to **21** provides a way to prepare complex ureas rapidly and easily.

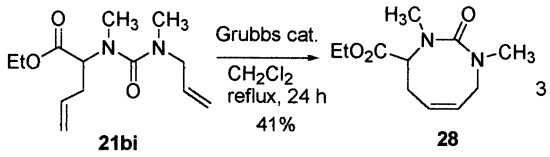


2

The use of sodium hydride as a consumable base permitted a single equivalent of the amine to serve as the capturing nucleophile.[2] Under these conditions, however, the initial urea product underwent base-promoted cyclization to a hydantoin (Scheme 8). Hydantoins **24**−**27** were prepared in good yields. Ultrasonic irradiation gave comparable yields but a shorter reaction time.

It was reported earlier that unsubstituted **19** ($R^2 = H$) reacts with primary amines in the presence of 1 equiv of sodium hydride to give unsymmetric ureas.[2] Addition of a second equivalent of sodium hydride resulted in cyclization to the hydantoin. In the present case, slightly more than 1 equiv of sodium hydride results in both α-lactam formation and cyclization of the urea. This suggests that ureas derived from 2-substituted malonylhydroxamates **19** are more prone to cyclization than unsubstituted analogues. Therefore, open chain ureas must be prepared using primary amines in excess, not using sodium hydride as a consumable base.

The use of unsaturated substituents at C-2 of malonylhydroxamates **19** and an allylamine as the trapping nucleophile provides a potential route to medium-ring ureas. When urea **21bi** was added to a solution of Grubbs catalyst in refluxing dichloromethane and stirred for 24 h, eight-membered cyclic urea **28** was obtained in 41% yield (eq 3). The same reaction in benzene at 55 °C gave a 34% yield.



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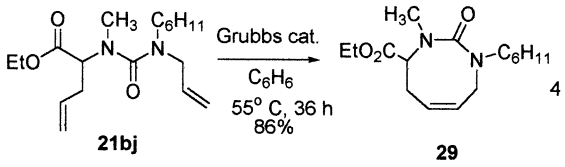
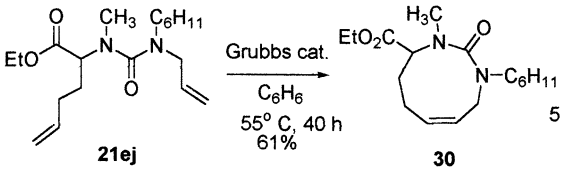
The substituent on the external urea nitrogen exerts a remarkable effect on the reaction. If there is no external nitrogen substituent present as in **21bh**, no RCM is observed. A methyl substituent gives 34%. However, when *N*-cyclohexyl analogue **21bj** was treated with Grubbs catalyst in benzene at 55 °C, cyclic urea **29** was obtained in 86% yield (eq 4).



4

A butenyl substituent at C-2 provides an opportunity to prepare nine-membered ring products. However *N*-methyl urea **21ei** gave no cyclic products but instead yielded dimers from intermolecular metathesis. In contrast, *N*-cyclohexyl analogue **21ej** gave the nine-membered RCM product **30** in 61% yield (eq 5).



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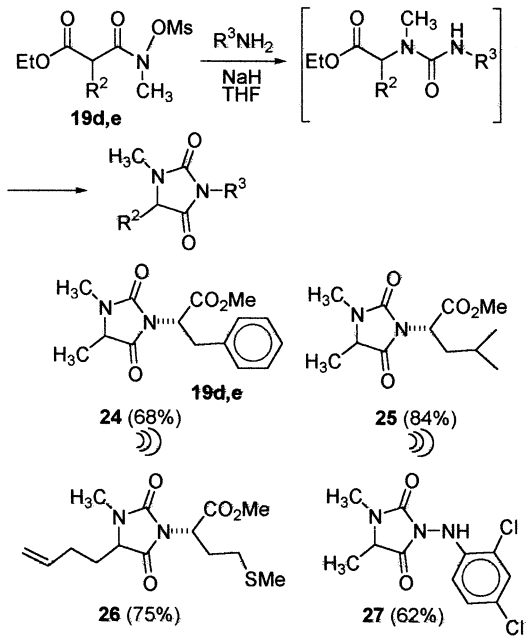
These results suggest that bulkier substituents on the external nitrogen provide a conformational bias around the urea linkage, which causes the olefinic bonds to be in closer proximity to each other, thus providing an entropic advantage for cyclization.[16] Without such conformational control, the formation of medium (8−11-membered) rings by RCM is not usually successful. By imposing conformational bias either by structural constraints[16] or by hydrogen bonding[17] it is possible to successfully construct medium rings by RCM. Moreover, it appears that an amide group, probably due to restricted rotation, is a common feature of successful medium-ring RCM processes.[16,18] In the present study, the urea group is sufficiently rigid that conformational preferences dictated by substituents on the external nitrogen significantly influence the proximity of the olefin groups.

These are the first examples of cyclic ureas to be produced by RCM and the first examples of medium-ring cyclic ureas. Moreover, many structural variations can

SCHEME 8



(15) Hoffman, R. V.; Nayyar, N. K.; Chen, W. *J. Am. Chem. Soc.* **1993**, *115*, 5031.
(16) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.
(17) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606.
(18) Chacun-Lefèvre, L.; Bénéteau, V.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2002**, *58*, 10181.

be incorporated into the basic synthetic scheme so that ring size and substitution pattern can be modified easily. This approach should provide a rich source of cyclic ureas.

In summary, the addition of substituents to the 2-position of malonyl hydroxamates does not materially change the chemistry of the α-lactams produced from them. Such additions do, however, reduce the rate of 1,3-elimination that produces the α-lactam. The addition of unsaturated substituents at C-2 offers the opportunity to further manipulate the unsymmetric urea products via RCM reactions to produce cyclic ureas containing medium rings.

Experimental Section

Hydroxamic acids were prepared by reported procedures.[19] *N*-Mesyloxyamides were prepared as reported earlier.[10] *N*-Methyl-*O*-TBDPS hydroxylamine and *N*-isopropyl-*O*-TBDPS hydroxylamine were prepared from their corresponding hydrochloride salts.[12]

Synthesis of *N*-Alkyl-*N*-hydroxy-2-alkylcarboxamides 4: General Procedure. To a 0 °C solution of LDA prepared from diisopropylamine (0.26 mL, 1.87 mmol) and *n*-BuLi (0.75 mL, 2.5 M solution in hexanes, 1.87 mmol) in dry THF (2.5 mL) was added dropwise a solution of hydroxamic acid **3** (0.85 mmol) in dry THF (2.5 mL), and the mixture was stirred for 1 h at 0 °C. An alkyl halide **7** (0.85 mmol) was added very slowly, and the reaction mixture was stirred for another 1 h. The reaction mixture was diluted with water, acidified (pH = 6) with 1 N HCl, and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and then dried ($MgSO_4$). After rotary evaporation, the crude product was purified by flash chromatography.

***N*-Methyl-*N*-hydroxy-2-prenyl-3-phenylpropionamide (4aa)** was prepared from **3a** and **7a** in 55% yield as a colorless oil after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.65 (d, 6H, J = 16.0 Hz), 2.30−2.38 (m, 2H), 2.91 (s, 3H), 5.08 (t, 1H), 7.16−7.32 (m, 5H); ^{13}C NMR δ 17.6, 25.5, 31.1, 35.2, 38.4, 43.7, 120.5, 126.2, 128.2, 128.7, 134.2, 139.2, 168.7; IR 3171, 1608 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.89; H, 8.49; N, 5.66. Found: C, 72.73; H, 8.39; N, 5.45. When the same reaction was carried out at −20 °C, **3aa** was obtained in 52% yield.

***N*-Methyl-*N*-hydroxy-2-methyl-3-phenylpropionamide (4ab)** was prepared from **3a** and **7b** in 47% yield as an oil after flash chromatography (ethyl acetate/hexane, 4:6): ^{1}H NMR δ 1.12 (d, 3H), 2.68−2.78 (m, 2H), 2.99 (s, 3H), 3.40−3.46 (m, 1H), 7.12−7.22 (m, 5H), 8.22 (br s, 1H); ^{13}C NMR δ 17.5, 35.81, 37.5, 40.3, 126.6, 128.6, 129.1, 139.6, 170.1; IR 3174, 1608 cm^{-1}.

***N*-Methyl-*N*-hydroxy-2-benzyl-3-phenylpropionamide (4ac)** was prepared from **3a** and **7c** in 40% yield as a light yellow solid after flash chromatography (ethyl acetate/hexane, 1:3): mp 79−81 °C; ^{1}H NMR δ 2.56 (s, 3H), 2.82−3.05 (m, 5H), 7.13−7.30 (m, 10H); ^{13}C NMR δ 35.0, 37.8, 39.1, 46.2, 126.3, 126.7, 128.6, 128.9, 139.1, 140.0, 168.1; IR 3172, 1613 cm^{-1}.

***N*-Methyl-*N*-hydroxy-2-ethyl-3-phenylpropionamide (4ad)** was prepared from **3a** and **7d** in 39% yield as a colorless oil after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 0.89 (t, 3H), 1.61−1.67 (m, 2H), 2.63−2.67 (m, 2H), 2.91 (s, 3H), 3.18−3.20 (m, 1H), 7.11−7.29 (m, 5H), 8.45 (br s, 1H); ^{13}C NMR δ 12.0, 26.0, 35.4, 39.2, 45.5, 126.7, 128.6, 128.9, 139.4, 169.1; IR 3196, 1618 cm^{-1}.

***N*-Cyclohexyl-*N*-hydroxy-2-methyl-3-phenylpropionamide (4bb)** was prepared from **3b** and **7b** in 45% yield as a white solid after flash chromatography (ethyl acetate/hexane, 1:5): mp 115−117 °C; ^{1}H NMR δ 1.10−1.16 (m, 4H), 1.24 (d, 3H), 1.62−1.66 (m, 7H), 2.75−2.77 (m, 1H), 2.92−2.94 (m, 1H), 3.47−3.51 (m, 1H), 6.61 (br s, 1H), 7.17−7.26 (m, 5H); ^{13}C NMR δ 18.4, 25.1, 25.7, 29.9, 30.6, 37.7, 40.7, 58.2, 126.6, 128.7, 129.0, 139.6, 168.6; IR 3169, 1603 cm^{-1}.

***N*-(*tert*-Butyl)-*N*-hydroxy-2-prenyl-3-phenylpropionamide (4ca)** was prepared from **3c** and **7a** in 26% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:5): ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.66 (d, 6H, J = 16.0 Hz), 2.27−2.29 (m, 2H), 2.80−2.82 (m, 2H), 3.26−3.28 (m, 1H), 5.15 (t, 1H), 7.19−7.27 (m, 5H); ^{13}C NMR δ 18.0, 25.5, 25.9, 28.2, 29.0, 35.2, 41.4, 117.8, 126.3, 129.1, 129.7, 133.8, 140.2, 175.0; IR 3411, 1670, 1605 cm^{-1}.

***N*-(Methyl)-*N*-hydroxy-2-prenyl-3-(*p*-methoxyphenyl)-propionamide (4fa)** was prepared from **3f** and **7a** in 42% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:4): ^{1}H NMR δ 1.65 (d, 6H, J = 16.0 Hz), 2.30−2.34 (m, 2H), 2.77−2.79 (m, 3H), 2.93 (s, 3H), 3.77 (s, 3H), 5.07 (t, 1H), 6.80 (d, 2H), 7.04 (d, 2H), 8.66 (br s, 1H); ^{13}C NMR δ 17.9, 25.9, 31.4, 35.4, 37.9, 44.2, 55.3, 114.0, 120.8, 129.9, 131.5, 134.6, 158.3, 169.0; IR 3186, 1612 cm^{-1}.

***N*-(Methyl)-*N*-hydroxy-2-benzylhexanamide (4ec)** was prepared from **3e** and **7c** in 38% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 0.88 (t, 3H), 1.23−1.27 (m, 4H), 1.72−1.74 (m, 1H), 2.74 (d, 1H), 2.88 (s, 3H), 3.15 (d, 1H), 7.14−7.27 (m, 5H), 8.68 (br s, 1H); ^{13}C NMR δ 14.1, 20.7, 35.2, 39.3, 43.6, 126.3, 128.5, 128.9, 139.5, 169.3; IR 3186, 1615 cm^{-1}.

Preparation of *N*-Alkyl-α,β-unsaturated Carboxamides 6: General Procedure. To a 0 °C solution of LDA (2.5 mmol) in dry THF (2.5 mL) was added dropwise a solution of hydroxamic acid **3** (0.83 mmol) in dry THF (2.5 mL). The reaction was allowed to warm to room temperature and stirred for 4 h. It was diluted with water, acidified (pH = 6) with 1 N HCl, and extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with brine (10 mL) and then dried ($MgSO_4$). After rotary evaporation, the crude product was purified by flash chromatography.

***N*-Methyl-3-phenyl-2-propenamide (6a)** was prepared from **3a** in 40% yield as a light yellow solid after flash chromatography (ethyl acetate/hexane, 1:1): mp 84−88 °C; ^{1}H NMR δ 2.94 (d, 3H, J = 6.0 Hz), 6.31 (br s, 1H), 6.47 (d, 1H, J = 16.0 Hz), 7.31−7.50 (m, 5H), 7.62 (d, 1H, J = 16.0 Hz); ^{13}C NMR δ 26.7 and 31.4 (rotamers), 120.7, 126.5, 128.0, 128.6, 128.76, 129.0, 129.9, 135.1, 141.2, 167.0; IR 3284, 1657 cm^{-1}.

***N*-Cyclohexyl-3-phenyl-2-propenamide (6b)** was prepared from **3b** in 42% yield as a white solid after flash chromatography (ethyl acetate/hexane, 1:3): mp 152−156°C; ^{1}H NMR δ 1.17−1.21 (m, 3H), 1.36−1.38 (m, 2H), 1.65−1.69 (m, 3H), 1.97 (d, 2H), 3.90−3.92 (m, 1H), 5.45 (br s, 1H), 6.34 (d, 1H, J = 16.0 Hz), 7.32−7.51 (m, 5H), 7.59 (d, 1H, J = 16.0 Hz); ^{13}C NMR δ 25.0, 25.7, 33.3, 48.6, 121.4, 127.9, 128.9, 129.6, 135.1, 140.7, 165.2; IR 3272, 1656 cm^{-1}. This compound has been reported in the literature, but no data was given.[20]

***N*-(*tert*-Butyl)-3-phenyl-2-propenamide (6c)** was prepared from **3c** in 42% yield (after stirring overnight) as a white solid after flash chromatography (ethyl acetate/hexane, 1:4): mp 130−134 °C; ^{1}H NMR δ 1.43 (s, 9H), 5.61 (br s, 1H), 6.35 (d, 1H, J = 16.0 Hz), 7.32−7.46 (m, 5H), 7.57 (d, 1H, J = 16.0 Hz); ^{13}C NMR δ 26.7 & 31.4 (for rotamers), 120.7, 126.5, 128.0, 128.6, 128.7, 129.0, 129.9, 135.1, 141.2, 167.0; IR 3294, 1657 cm^{-1}. This compound has been reported in the literature, but no data were given.[19]

***N*-Methyl-3-(*p*-methoxyphenyl)-2-propenamide (6f)** was prepared from **3f** in 15% yield (after stirring the reaction for 2 days) as a white solid after flash chromatography (ethyl acetate/hexane, 1:1): mp 118−120 °C; ^{1}H NMR δ 2.92 (d, 3H), 3.77 (s, 3H), 5.81 (br s, 1H), 6.31 (d, 1H, J = 16.0 Hz), 6.87 (d, 3H, J = 8.0 Hz), 7.43 (d, 2H, J = 8.0 Hz), 7.57 (d, 1H, J =

(19) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1994**, *59*, 3530.

(20) Sugihara, T.; Okada, Y.; Yamaguchi, M.; Nishigawa, M. *Synlett* **1999**, 768.

16.0 Hz); ^{13}C NMR δ 26.6, 55.3, 14.2, 118.5, 127.6, 129.5, 140.0, 160.8, 167.5; IR 3280, 1658 cm^{-1}.

Reaction of **3d** and **3e** under the same conditions led to the quantitative recovery of starting material.

Preparation of *N*-(Silyloxy)-*N*-alkyl-2-carbethoxy Acetamides, 14 and 17: General Procedure. To a well-stirred solution of *O*-(*tert*-butyldiphenylsilyl)-*N*-alkylhydroxylamine (5.2 mmol) and triethylamine (5.72 mmol) in dry methylene chloride (100 mL) at 0 °C was added dropwise a solution of ethylmalonyl chloride (5.72 mmol) in dry methylene chloride (30 mL). The reaction mixture was warmed to room temperature and allowed to stir for 2 h. It was diluted with water (100 mL), and the organic layer was washed with 1 N HCl (2 × 20 mL) and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was then purified by flash chromatography.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxyacetamide (14)** was prepared in 76% yield as a colorless oil after flash chromatography (EtOAc/hexane, 1:10): ^{1}H NMR δ 1.14 (s, 9H), 1.26 (t, 3H), 3.12 (s, 3H), 3.31 (s, 2H), 4.16 (q, 2H), 7.41−7.71 (m, 10H); IR 1746, 1677 cm^{-1}.

***N*-(OTBDPS)-*N*-Isopropyl-2-carbethoxyacetamide (17)** was prepared in 42% yield as an oil after flash chromatography (EtOAc/hexane, 1:15): ^{1}H NMR δ 1.11 (s, 9H), 1.20−1.22 (m, 9H), 3.27 (s, 2H), 3.81−3.83 (m, 1H), 4.13 (q, 2H), 7.38−7.73 (m, 10H); IR 1742, 1672 cm^{-1}.

Preparation of *N*-(Silyloxy)-*N*-alkyl-2-carbethoxy-2-alkyl Acetamides 15: General Procedure. To a solution of **14** (or **17**) (4.0 mmol) in dry THF (100 mL) was added NaH (4.0 mmol, 60% dispersion in mineral oil) at room temperature. After the reaction was stirred for 15 min, the alkylating agent (4.4 mmol) was added over a period of 5 min. Progress of the reaction was monitored by TLC. The reaction mixture was evaporated under reduced pressure, and the residue was triturated with methylene chloride (3 × 100 mL). The organic extracts were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to give the crude product in almost quantitative yield that was sufficiently pure, in most cases, for the next reaction.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-prenylacetamide (15a)** was prepared from **14** and prenyl bromide. After a reaction time of 5−6 h, **15a** was obtained in 95% yield as a colorless oil: ^{1}H NMR δ 1.14 (s, 9H), 1.26 (t, 3H), 1.59 (d, 6H, J = 12.0 Hz), 2.42 (t, 2H), 3.08 (s, 3H), 4.11−4.15 (m, 3H), 4.79 (t, 1H), 7.39−7.46 (m, 6H), 7.66−7.74 (m, 4H); IR 1739, 1682 cm^{-1}.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-allylacetamide (15b)** was prepared from **14** and allyl bromide. After a reaction time of 6 h, **15b** was obtained in 96% yield as an oil: ^{1}H NMR δ 1.15 (s, 9H), 1.24 (t, 3H), 2.43 (t, 2H), 3.11 (s, 3H), 3.75 (t, 1H), 4.13 (q, 2H), 4.93−4.97 (m, 2H), 5.47−5.49 (m 1H), 7.39−7.47 (m, 6H), 7.67−7.74 (m, 4H); IR 1739, 1678, 1644 cm^{-1}.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-benzylacetamide (15c)** was prepared from **14** and benzyl bromide. After a reaction time of 4 h, **15c** was obtained in 97% yield as an oil: ^{1}H NMR δ 1.14 (s, 9H), 1.26 (t, 3H), 3.14 (s, 3H), 3.23 (d, 2H), 4.13−4.17 (m, 3H), 6.97−7.04 (m, 2H), 7.17−7.20 (m, 3H), 7.28−7.45 (m, 6H), 7.56−7.59 (m, 4H); IR 1738, 1676 cm^{-1}.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-methylacetamide (15d)** was prepared from **1** and methyl iodide. After a reaction time of 6 h, **15d** was obtained in 96% yield as a colorless oil: ^{1}H NMR δ 1.12 (d, 3H, J = 7.0 Hz), 1.15 (s, 9H), 1.24 (t, 3H), 3.13 (s, 3H), 3.70 (q, 1H), 4.15 (q, 2H), 7.40−7.47 (m, 6H), 7.67−7.73 (m, 4H); IR 1741, 1675 cm^{-1}.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-(1-but-3-enyl)-acetamide (15e)** was prepared from **14**, 4-bromo-1-butene, and NaI (4.4 mmol) after refluxing overnight in 75% yield as an oil after flash chromatography (EtOAc/hexane, 1:10): ^{1}H NMR δ 1.15 (s, 9H), 1.25 (t, 3H), 1.77−1.79 (m, 4H), 3.11 (s, 3H), 3.62 (t, 1H), 4.12 (q, 2H), 4.90−4.93 (m, 2H), 5.61−5.65 (m 1H), 7.38−7.46 (m, 6H), 7.65−7.75 (m, 4H); IR 1737, 1677 cm^{-1}.

***N*-(OTBDPS)-*N*-Methyl-2-carbethoxy-2-(2-ethyl-1,3-dioxane)acetamide (15f)** was prepared from **14**, 2-(2-bromoethyl)-1,3-dioxane, and NaI (4.4 mmol) after refluxing overnight in 81% yield as a colorless oil after flash chromatography (EtOAc/hexane, 1:4): ^{1}H NMR δ 1.14 (s, 9H), 1.24 (t, 3H), 1.66−1.68 (m, 2H), 1.80−1.83 (m, 4H), 3.08 (s, 3H), 3.69 (t, 3H), 4.10−4.12 (m, 4H), 4.42 (t, 1H), 7.38−7.47 (m, 6H), 7.66−7.74 (m, 4H); IR 1737, 1676 cm^{-1}.

***N*-(OTBDPS)-*N*-Isopropyl-2-carbethoxy-2-prenylacetamide** was prepared from **17** and prenyl bromide in 98% yield as a colorless oil: ^{1}H NMR δ 1.08−1.25 (m, 18H), 1.50−1.62 (d, 6H), 1.59 (d, 6H, J = 12.0 Hz), 2.43 (t, 2H), 3.20−3.24 (m, 1H), 3.74 (t, 1H), 4.11 (q, 2H), 4.82−4.85 (m, 1H), 7.39−7.41 (m, 6H), 7.68−7.73 (m, 4H); IR 1743, 1667 cm^{-1}.

Preparation of *N*-Hydroxy-*N*-alkyl-2-carbethoxy-2-alkyl Acetamides, 1: General Procedure. To the *N*-(silyloxy)-*N*-alkyl-2-carbethoxy-2-alkyl acetamide **15** or **18** (2 mmol) was added a solution of methanesulfonic acid (1% solution in ethanol, 100 mL), and the reaction mixture was stirred at room temperature for 1 h. The solvent was reduced to one half of its volume under reduced pressure and the reaction mixture extracted with methylene chloride (4 × 100 mL). The organic extracts were washed with water (2 × 50 mL) and brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product that was purified by flash chromatography (EtOAc/hexane, 4:6).

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-prenylacetamide (1a)** was prepared in 65% yield after flash chromatography (ethyl acetate/hexane, 4:6) as a colorless oil: ^{1}H NMR δ 1.26 (t, 3H), 1.66 (d, 6H, J = 8.0 Hz), 2.60 (t, 2H), 3.28 (s, 3H), 3.87 (t, 1H), 4.18 (q, 2H), 5.09 (t, 1H), 7.93 (br s, 1H); IR 3199, 1738, 1626 cm^{-1}; m/z 229 (M$^+$), 230 (M + 1)$^+$.

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-allylacetamide (1b)** was prepared in 67% yield after flash chromatography (ethyl acetate/hexane, 1:1) as an oil: ^{1}H NMR δ 1.28 (t, 3H), 2.66 (t, 2H), 3.29 (s, 3H), 3.99 (t, 1H), 4.19 (q, 2H), 5.06−5.10 (m, 2H), 5.77−5.81 (m 1H), 7.94 (br s, 1H); IR 3195, 1739, 1678, 1627 cm^{-1}; m/z 202 (M + 1) $^+$, 203 (M + 2) $^+$.

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-benzylacetamide (1c)** was prepared in 68% yield after flash chromatography (ethyl acetate/hexane, 1:3) as an oil: ^{1}H NMR δ 1.23 (t, 3H), 3.15 (d, 2H), 3.22 (s, 3H), 3.69 (t, 1H), 4.17 (q, 2H), 7.16−7.25 (m, 5H); IR 3190, 1733, 1626 cm^{-1}; m/z 253 (M + 2)$^+$.

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-methylacetamide (1d)** was prepared in 70% yield after flash chromatography (ethyl acetate/hexane, 1:1) as an oil: ^{1}H NMR δ 1.26 (t, 3H), 1.36 (d, 3H, J = 8.0 Hz), 3.26 (s, 3H), 3.92 (q, 1H), 4.17 (q, 2H), 9.06 (br s, 1H); IR 3187, 1739, 1639 cm^{-1}; m/z 175 (M$^+$), 176 (M + 1)$^+$.

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-(1-but-3-enyl)-acetamide (1e)** was prepared in 78% yield after flash chromatography (ethyl acetate/hexane, 1:1) as an oil: ^{1}H NMR δ 1.28 (t, 3H), 2.08−2.12 (m, 4H), 3.29 (s, 3H), 3.92−3.94 (m, 1H), 4.19 (q, 2H), 5.02−5.06 (m, 2H), 5.78−5.82 (m 1H); IR 3182, 1738, 1626 cm^{-1}; m/z 215 (M$^+$), 216 (M + 1)$^+$.

***N*-Hydroxy-*N*-methyl-2-carbethoxy-2-(2-ethyl-1,3-dioxane)acetamide (1f)** was prepared in 51% yield after flash chromatography (R_f = 0.2; ethyl acetate/hexane, 6:4) as an oil: ^{1}H NMR δ 1.23−1.29 (m, 8H), 1.60−1.64 (m, 3H), 2.01−2.05 (m, 6H), 3.28 (s, 3H), 3.42 (s, 3H), 3.75−3.77 (m, 4H), 3.97 (t, 1H), 4.08−4.10 (m, 4H), 4.18 (q, 4H), 4.54−3.58 (m, 1H), 8.04 (s, 1H); IR 3202, 1738, 1627 cm^{-1}; m/z 229 (M − 46). In addition to **1f**, a product of trans acetalization was isolated in which the cyclic 1,3-propanedioxy acetal was exchanged to the diethyl acetal. *N*-Hydroxy-*N*-methyl-2-carbethoxy-2-(3,3-diethoxy-1-propyl)acetamide was isolated in 22% yield after flash chromatography (R_f = 0.3; ethyl acetate/hexane, 6:4) as an oil: ^{1}H NMR δ 1.21−1.27 (m, 13H), 1.64−1.68 (m, 3H), 1.93−1.97 (m, 3H), 3.27 (s, 3H), 3.48−3.54 (m, 4H), 3.61−3.67 (m,

4H), 3.91 (t, 1H), 4.16 (q, 2H), 4.51 (t, 1H), 8.43 (s, 1H); IR 3204, 1739, 1627 cm^{-1}; *m/z* 246 (M − 45).

***N*-Hydroxy-*N*-isopropyl-2-carbethoxy-2-prenylacetamide (18)** was prepared in 72% yield after flash chromatography (ethyl acetate/hexane, 1:3) as a colorless oil: ^{1}H NMR δ 1.21−1.25 (m, 9H), 1.66 (d, 6H, J = 8.0 Hz), 2.60 (t, 2H), 3.81−3.85 (m, 1H), 4.18 (q, 2H), 4.68−3.70 (m, 1H), 5.06−5.10 (m, 1H), 6.85 (br s, 1H); IR 3201, 1740, 1667, 1620 cm^{-1}; *m/z* 256 $(M - 1)^+$.

Preparation of *N*-(Mesyloxy)-*N*-alkyl-2-carbethoxy-2-alkyl Acetamides, 19 and 20: General Procedure. To a solution of *N*-hydroxy-*N*-alkyl-2-carbethoxy-2-alkylacetamide **1** or **18** (2 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added triethylamine (2 mmol). The mixture was stirred for 10 min, and methanesulfonyl chloride (2.2 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred for another 2 h. The reaction mixture was washed with water (2 × 20 mL), 1 N HCl (2 × 10 mL), and brine (20 mL) and dried over anhydrous $MgSO_4$. After rotary evaporation, the crude product obtained that was purified by flash chromatography (EtOAc/hexane). Mesylates **19** and **20** should be stored in the refrigerator. Due to slow decomposition, accurate elemental analyses could not be obtained.

***N*-(Mesyloxy)-*N*-methyl-2-carbethoxy-2-prenylacetamide (19a)** was prepared from **1a** in 88% yield after flash chromatography (ethyl acetate/hexane, 1:5) as a colorless oil: ^{1}H NMR δ 1.27 (t, 3H), 1.66 (d, 6H, J = 8.0 Hz), 2.64 (t, 2H), 3.18 (s, 3H), 3.49 (s, 3H), 3.68 (t, 1H), 4.19 (q, 2H), 5.08 (t, 1H); IR 1740, 1705 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-2-carbethoxy-2-allylacetamide (19b)** was prepared from **1b** in 95% yield after flash chromatography (ethyl acetate/hexane, 1:4) as an oil: ^{1}H NMR δ 1.27 (t, 3H), 2.67−2.69 (m, 2H), 3.19 (s, 3H), 3.49 (s, 3H), 3.76 (t, 1H), 4.20 (q, 2H), 5.08−5.12 (m, 2H), 5.76−5.78 (m 1H); IR 1737, 1708 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-2-carbethoxy-2-benzylacetamide (19c**) was prepared from **1c** in 83% yield after flash chromatography (ethyl acetate/hexane, 1:5) as an oil: ^{1}H NMR δ 1.23 (t, 3H), 2.95 (s, 3H), 3.26 (d, 2H), 3.38 (s, 3H), 3.96 (t, 1H), 4.18 (q, 2H), 7.19−7.28 (m, 5H); IR 1739, 1703 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-2-carbethoxy-2-methylacetamide (19d**) was prepared from **1d** in 86% yield after flash chromatography (ethyl acetate/hexane, 1:3) as an oil: ^{1}H NMR δ 1.26 (t, 3H), 1.44 (d, 3H, J = 8.0 Hz), 3.20 (s, 3H), 3.49 (s, 3H), 3.77 (q, 1H), 4.21 (q, 2H); IR 1738, 1708 cm^{-1}.

***N*-(Mesyloxy)-*N*-methyl-2-carbethoxy-2-(1-but-3-enyl)-acetamide (19e)** was prepared from **1e** in 93% yield after flash chromatography (ethyl acetate/hexane, 1:4) as an oil: ^{1}H NMR δ 1.28 (t, 3H), 2.08−2.14 (m, 4H), 3.21 (s, 3H), 3.49 (s, 3H), 3.68 (t, 1H), 4.20 (q, 2H), 5.0−5.02 (m, 2H), 5.74−5.78 (m 1H); IR 1739, 1706 cm^{-1}.

***N*-(Mesyloxy)-*N*-isopropyl-2-carbethoxy-2-prenylacetamide (20)** was prepared from **18** in 87% yield after flash chromatography (ethyl acetate/hexane, 1:5) as a colorless oil: ^{1}H NMR δ 1.30−1.32 (m, 9H), 1.66 (d, 6H, J = 10.0 Hz), 2.62 (t, 2H), 3.29 (s, 3H), 3.58 (t, 1H), 4.18 (q, 2H), 4.48−4.52 (m, 1H), 5.08 (t, 1H); IR 1739, 1693 cm^{-1}.

Reaction of *N*-Mesyloxy-2-alkyl Malonamides with Nucleophiles: General Procedure. A solution of *N*-mesyloxy-2-alkyl malonamide **19** or **20** (1 equiv) and the corresponding nucleophile (5 equiv) in methylene chloride (30 mL) was refluxed. After completion of the reaction (TLC), the reaction mixture was diluted with water and extracted with methylene chloride (2 × 20 mL). The organic extracts were washed with 1 N HCl (2 × 10 mL) and brine and then dried ($MgSO_4$). The solvent was removed under vacuum, and the product was purified by flash chromatography.

Urea 21ad was prepared from **19a** (110 mg, 0.35 mmol) and *tert*-butylamine **22d** (0.18 mL, 1.75 mmol). After a reaction time of 4 h, **21ad** was obtained as a white solid in 86% yield after flash chromatography (ethyl acetate/hexane, 1:5): mp 64−66 °C; ^{1}H NMR δ 1.26 (t, 3H), 1.35 (s, 9H), 1.65 (d, 6H, J = 10.0 Hz), 2.50−2.52 (m, 2H), 2.77 (s, 3H), 4.17 (q, 2H), 4.43 (br s, 1H), 4.84 (dd, 1H), 5.05 (t, 1H); ^{13}C NMR δ 14.2, 17.9, 25.8, 28.4, 29.4, 30.9, 50.8, 57.4, 60.9, 119.7, 134.2, 157.6, 172.4; IR 3364, 1738, 1641 cm^{-1}. Anal. Calcd for $C_{15}H_{28}N_2O_3$: C, 63.35; H, 9.92; N, 9.85. Found: C, 63.60; H, 9.75; N, 9.68.

Urea 21ae was prepared from **19a** (110 mg, 0.35 mmol) and morpholine **22e** (0.15 mL, 1.75 mmol). After a reaction time of 4 h, **21ae** was obtained as a colorless oil in 81% yield after flash chromatography (ethyl acetate/hexane, 1:4): ^{1}H NMR δ 1.27 (t, 3H), 1.66 (d, 6H, J = 7.0 Hz), 2.52−2.58 (m, 2H), 2.88 (s, 3H), 3.19−3.23 (m, 4H), 3.65−3.71 (m, 4H), 4.19 (q, 2H), 4.38 (dd, 1H), 5.03 (t, 1H); ^{13}C NMR δ 14.2, 17.9, 25.7, 27.8, 33.6, 47.2, 59.5, 60.8, 66.5, 119.6, 134.2, 164.5, 171.9; IR 1739, 1651 cm^{-1}. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.11; H, 8.69; N, 9.35.

Urea 21bg was prepared from **19b** (70 mg, 0.25 mmol) and cyclohexylamine **22g** (0.14 mL, 1.25 mmol). After a reaction time of 2 h, **21bg** was obtained in 79% yield as a white solid after flash chromatography (ethyl acetate/hexane, 1:4): mp 68−70 °C; ^{1}H NMR δ 1.10−1.17 (m, 3H), 1.26 (t, 3H), 1.37−1.41 (m, 2H), 1.63−1.69 (m, 3H), 1.93−1.97 (m, 2H), 2.46−2.50 (m, 1H), 2.6−2.70 (m, 1H), 2.79 (s, 3H), 3.64−3.68 (m, 1H), 4.16 (q, 2H), 4.35 (d, 1H), 5.05−5.09 (m, 3H), 5.73−5.77 (m, 1H); ^{13}C NMR δ 14.3, 25.2, 25.8, 30.5, 34.1, 49.7, 57.1, 61.1, 117.6, 134.3, 157.8, 172.1; IR 3348, 1739, 1627 cm^{-1}. Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.92. Found: C, 63.76; H, 9.43; N, 9.70.

Urea 21bh was prepared from **19b** (170 mg, 0.61 mmol) and allylamine **22h** (0.14 mL, 1.83 mmol). After the mixture was refluxed overnight, **21bh** was obtained as a colorless oil in 76% yield after flash chromatography (ethyl acetate/hexane, 1:4): ^{1}H NMR δ 1.26 (t, 3H), 2.46−2.50 (m, 1H), 2.70−2.72 (m, 1H), 2.83 (s, 3H), 3.88 (t, 2H), 4.19 (q, 2H), 4.61 (t, 1H), 5.13−5.15 (m, 5H), 5.83−5.87 (m, 2H); ^{13}C NMR δ 14.1, 30.3, 33.7, 43.3, 57.1, 60.9, 115.3, 117.4, 134.0, 135.6, 158.2, 171.7; IR 3348, 1738, 1635 cm^{-1}.

Urea 21bi was prepared from **19b** (200 mg, 0.7 mmol) and *N*-methylallylamine **22i** (0.33 mL, 3.5 mmol). After a reaction time of 2 h, **21bi** was obtained as an oil in 93% yield after flash chromatography (ethyl acetate/hexane, 4:6): ^{1}H NMR δ 1.27 (t, 3H), 2.50−2.54 (m, 1H), 2.73 (s, 3H), 2.74−2.78 (m, 1H), 2.88 (s, 3H), 3.71 (d, 2H), 4.19 (q, 2H), 4.44 (dd, 1H), 5.14−5.20 (m, 4H), 5.80−5.83 (m, 2H); ^{13}C NMR δ 13.9, 33.2, 33.7, 35.5, 53.1, 59.1, 60.6, 116.8, 117.1, 133.8, 134.2, 164.8, 171.72; IR 1739, 1639 cm^{-1}. Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 60.97; H, 8.65; N, 10.82.

Urea 21bj was prepared from **19b** (200 mg, 0.7 mmol) and *N*-allylcyclohexylamine **22j** (0.52 mL, 3.5 mmol). After a reaction time of 4 h, **21bj** was obtained in 87% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:10): ^{1}H NMR δ 1.09−1.12 (m, 3H), 1.26 (t, 3H), 1.53−1.57 (m, 4H), 1.73−1.77 (m, 4H), 2.53−2.57 (m, 1H), 2.65−2.70 (m, 1H), 2.88 (s, 3H), 3.30 (t, 1H), 3.74−3.78 (m, 2H), 4.17 (q, 2H), 4.40−4.43 (m, 1H), 5.03−5.07 (m, 4H), 5.78−5.82 (m, 2H); ^{13}C NMR δ 14.1, 25.6, 26.2, 26.2, 30.9, 30.9, 33.5, 33.7, 46.2, 58.7, 59.6, 60.7, 114.91, 117.1, 134.5, 136.6, 164.8, 171.8; IR 1740, 1651 cm^{-1}.

Urea 21cb was prepared from **19c** (120 mg, 0.36 mmol) and *N*-ethylisopropylamine **22b** (0.22 mL, 1.8 mmol). After a reaction time of 2 h, **21cb** was obtained as a colorless oil in 92% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 0.92 (t, 6H), 1.05 (d, 3H), 1.25 (t, 3H), 3.02−3.06 (m, 2H), 3.30−3.36 (m, 2H), 4.19 (q, 2H), 4.64 (dd, 1H), 7.17−7.31 (m, 5H); ^{13}C NMR δ 14.3, 15.0, 20.4, 34.3, 35.3, 36.2, 49.9, 60.9, 61.2, 126.5, 128.4, 128.8, 138.1, 164.8, 172.1; IR 1739, 1636 cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.60; H, 8.64; N, 8.97.

Urea 21cc was prepared from **19c** (120 mg, 0.36 mmol) and pyrrolidine **22c** (0.15 mL, 1.8 mmol). After a reaction time of 2 h, **21cc** was obtained as an oil in 91% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.25

(t, 3H), 1.65−1.77 (m, 4H), 2.82 (s, 3H), 3.01−3.07 (m, 3H), 3.25−3.31 (m, 3H), 4.17 (q, 2H), 4.67 (dd, 1H), 7.18−7.26 (m, 5H); ^{13}C NMR δ 14.2, 25.5, 34.4, 35.3, 48.1, 60.9, 126.5, 128.3, 128.9, 138.1, 162.9, 172.2; IR 1738, 1636 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.86; H, 7.63; N, 9.22.

Urea 21da was prepared from **19d** (160 mg, 0.6 mmol) and benzylamine **22a** (0.34 mL, 5 mmol). After a reaction time of 7 h, **21da** was obtained as an oil in 81% yield after flash chromatography (ethyl acetate/hexane, 4:6): ^{1}H NMR δ 1.26 (t, 3H), 1.41 (d, 3H), 2.83 (s, 3H), 4.18 (q, 2H), 4.46 (d, 2H), 4.83 (t, 1H), 5.13 (q, 1H), 7.25−7.32 (m, 5H); ^{13}C NMR δ 14.2, 15.2, 30.1, 44.9, 53.1, 61.0, 127.2, 127.5, 128.5, 139.6, 158.2, 172.8; IR 3352, 1734, 1635 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.59. Found: C, 62.89; H, 7.24; N, 11.06.

Urea 21df was prepared from **19d** (110 mg, 0.4 mmol) and methyl phenylalanate **22f** (230 mg, 1.2 mmol). After a reaction time of 5 h, **21df** was obtained as an oil in 77% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.26 (t, 3H), 1.41 (d, 3H), 2.76 (s, 3H), 3.14 (d, 2H), 3.72 (s, 3H), 4.16 (q, 2H), 4.80−4.83 (m, 1H), 4.97−5.03 (m, 2H), 7.08−7.33 (m, 5H); ^{13}C NMR δ 14.3, 15.2, 30.0, 38.3, 52.3, 53.0, 54.6, 61.2, 127.2, 128.6, 129.5, 136.3, 157.3, 172.7, 173.0; IR 3354, 1739, 1644 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.09; N, 8.33; Found C, 60.81; H, 6.95; N, 8.24.

Urea 21eh was prepared from **19e** (140 mg, 0.47 mmol) and allylamine **22h** (0.11 mL, 1.41 mmol). After a reaction time of 24 h, **21eh** was obtained in 74% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.26 (t, 3H), 1.76−1.82 (m, 1H), 2.03−2.09 (m, 3H), 2.84 (s, 3H), 3.88 (t, 2H), 4.15 (q, 2H), 4.82 (t, 1H), 5.03−5.10(m, 5H), 5.83−5.89 (m, 2H); ^{13}C NMR δ 14.25, 28.58, 30.24, 30.39, 43.48, 57.03, 61.01, 115.51, 115.55, 135.66, 137.29, 158.36, 172.34; IR 3352, 1738, 1634 cm^{-1}.

Urea 21ei was prepared from **19e** (200 mg, 0.68 mmol) and *N*-allylmethylamine **22i** (0.32 mL, 3.4 mmol). After a reaction time of 2 h, **21ei** was obtained in 90% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:5): ^{1}H NMR δ 1.27 (t, 3H), 2.0−2.02 (m, 4H), 2.76 (s, 3H), 2.88 (s, 3H), 3.73 (d, 2H), 4.17 (q, 2H), 4.28−4.32 (m, 1H), 5.14−5.20 (m, 4H), 5.80−5.86 (m, 2H); ^{13}C NMR δ 13.9, 28.0, 30.3, 33.3, 35.6, 53.1, 58.8, 60.4, 115.3, 116.8, 133.7, 136.9, 164.9, 172.2; IR 1739, 1651 cm^{-1}.

Urea 21ej was prepared from **19e** (200 mg, 0.68 mmol) and *N*-allylcyclohexylamine **22j** (0.5 mL, 3.4 mmol). After a reaction time of 5 h, **21ej** was obtained in 88% yield as an oil after flash chromatography (ethyl acetate/hexane, 1:8): ^{1}H NMR δ 1.08−1.12 (m, 3H), 1.26 (t, 3H), 1.52−1.58 (m, 4H), 1.80−1.84 (m, 4H), 2.05−2.07 (m, 3H), 2.88 (s, 3H), 3.35 (t, 1H), 3.70−3.76 (m, 2H), 4.17 (q, 2H), 4.27−4.31 (m, 1H), 5.00−5.04 (m, 4H), 5.80−5.84 (m, 2H); ^{13}C NMR δ 14.0, 25.4, 26.0, 28.2, 30.4, 30.6, 30.8, 33.4, 46.0, 58.5, 59.1, 60.4, 114.8, 115.3, 136.5, 137.0, 164.7, 172.3; IR 1739, 1646 cm^{-1}.

Urea 23 was prepared from **20** (160 mg, 0.48 mmol) and **22h** (0.18 mL, 2.4 mmol). After a reaction time of 6 h, **23** was obtained as an oil in 82% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.17 (dd, 6H), 1.25 (t, 3H), 1.66 (d, 6H, J = 8.0 Hz), 2.50−2.53 (m, 1H), 2.84−2.90 (m, 1H), 3.79−3.83 (m, 3H), 4.16−4.22 (m, 3H), 5.11−5.15 (m, 3H), 5.47 (t, 1H), 5.86−5.92 (m, 1H); ^{13}C NMR δ 14.2, 20.2, 21.3, 25.9, 29.7, 43.4, 47.6, 56.3, 61.4, 115.4, 120.4, 134.8, 136.9, 157.6, 173.4; IR 3359, 1738, 1627 cm^{-1}. Anal. Calcd for $C_{16}H_{28}N_2O_3$: C, 64.33; H, 9.72; N, 9.45. Found: C, 63.82; H, 9.87; N, 9.42.

Imidazolidinedione 24 was prepared from **19d** (110 mg, 0.4 mmol), NaH (35 mg, 0.8 mmol), and L-Phe-Me ester HCl salt (94 mg, 0.4 mmol) in dry THF (30 mL). The reaction mixture was irradiated with ultrasound for 2 h. After the completion of reaction (TLC), **24** was obtained as a colorless oil in 68% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR for one diastereomer δ 1.11 (d, 3H), 2.83 (s, 3H), 3.48 (d, 2H), 3.72 (q, 1H), 3.78 (s, 3H), 4.94 (t, 1H), 7.15−7.29 (m, 5H); ^{1}H NMR for the second diastereomer δ 1.24 (d, 3H), 2.85 (s, 3H), 3.50 (d, 2H), 3.72 (q, 1H), 3.78 (s, 3H), 4.95 (t, 1H), 7.15−7.29 (m, 5H); ^{13}C NMR δ 14.9, 27.5, 34.3, 53.0, 56.8, 27.1, 128.6, 129.2, 136.7, 155.1, 169.3, 173.7; IR 1775, 1747, 1714 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.20; H, 6.28; N, 9.90.

Imidazolidinedione 25 was prepared from **19d** (110 mg, 0.4 mmol), NaH (35 mg, 0.8 mmol), and L-leucine methyl ester (45 mg, 0.4 mmol) in dry THF (30 mL). The reaction mixture was irradiated with ultrasound for 6 h. After the completion of reaction (TLC), **25** was obtained as a colorless oil in 84% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 0.93 (d, 6H, J = 6.6 Hz), 1.45 (d, 3H, J = 6.6 Hz), 1.84−1.88 (m, 1H), 2.25−2.29 (m, 1H), 2.97 (s, 3H), 3.73 (s, 3H), 3.91 (q, 1H), 4.72 (dd, 1H); ^{13}C NMR δ 15.3, 21.2, 23.3, 25.3, 27.6, 36.9, 51.5, 52.9, 57.1, 155.5, 170.3, 173.4; IR 1777, 1747, 1713 cm^{-1}.

Imidazolidinedione 26 was prepared from **19e** (60 mg, 0.2 mmol), NaH (8 mg, 0.2 mmol), and l-methionine methyl ester (50 mg, 0.3 mmol) in dry THF (20 mL) after stirring overnight. After the completion of reaction (TLC), **26** was obtained as a colorless oil in 75% yield after flash chromatography (ethyl acetate/hexane, 1:4): ^{1}H NMR δ 2.06−2.12 (m, 7H), 2.44−2.50 (m, 4H), 2.97 (s, 3H), 3.74 (s, 3H), 3.95−4.00 (m, 1H), 4.87 (t, 1H), 5.04−5.08 (m, 2H), 5.76−5.80 (m, 1H); ^{13}C NMR δ 15.5, 27.5, 27.8, 28.0, 29.9, 31.0, 51.8, 52.9, 60.7, 116.2, 136.7, 155.8, 169.5, 172.5; IR 1773, 1744, 1718 cm^{-1}.

1,5-Dimethyl-3-(2,5-dichloroanilino)-2,4-imidazolidinedione 27 was prepared from **19d** (85 mg, 0.33 mmol), NaH (12 mg, 0.3 mmol), and 2,5-dichlorophenyl hydrazine (60 mg, 0.33 mmol). After a reaction time of 22 h at room temperature, **27** was obtained as pale yellow oil in 62% yield after flash chromatography (ethyl acetate/hexane, 1:3): ^{1}H NMR δ 1.53 (d, 3H, J = 6.0 Hz), 3.01 (s, 3H), 4.06 (q, 1H), 6.55−6.60 (m, 2H), 6.83−6.89 (m, 1H), 7.24−7.26 (m, 1H); ^{13}C NMR δ 15.2, 28.0, 56.2, 113.6, 118.2, 122.4, 130.7, 133.8, 142.7, 153.8, 171.2; IR 1789, 1733 cm^{-1}.

1,3-Dimethyl-4-ethoxycarbonyl-(6*H*)1,3-diazocine (28). To a refluxing solution of Grubb's catalyst $(PCy_3)_2Cl_2Ru$ benzylidene (41 mg, 0.05 mmol, 10 mol %) in dry CH_2Cl_2 (300 mL, 0.001 M) was added a solution of **21bi** (130 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was refluxed for 24 h. The reaction mixture was then exposed to air, and the solvent was removed under reduced pressure to afford a black residue. Flash chromatography (EtOAc/hexane, 4:6) afforded **28** (48 mg, 41%) as an oil: ^{1}H NMR δ 1.27 (t, 3H), 2.73 (s, 3H), 2.77−2.81 (m, 2H), 2.87 (s, 3H), 3.46−3.52 (m, 1H), 4.16−4.22 (m, 3H), 4.32−4.38 (m, 1H), 5.70−5.75 (m, 2H); ^{13}C NMR δ 14.4, 28.4, 36.2, 37.3, 49.5, 61.3, 65.5, 128.1, 129.7, 163.2, 171.3; IR 1741, 1646 cm^{-1}. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.93; H, 7.87; N, 12.47.

When the same reaction was carried out in dry benzene (0.005 M) at 55 °C for 3 days using 10 mol % Grubb's catalyst and **21bi**, cyclized product **28** was obtained in 34% yield after flash chromatography.

1-Cyclohexyl-3-methyl-4-ethoxycarbonyl-(6*H*)1,3-diazocine, 29. To a well-stirred solution of Grubb's catalyst $(PCy_3)_2Cl_2Ru$ benzylidene (25 mg, 0.03 mmol, 10 mol %) in dry benzene (50 mL, 0.005 M) at 55 °C was added dropwise a solution of **21bj** (97 mg, 0.3 mmol) in dry benzene (10 mL). The reaction mixture was stirred at 55 °C for 36 h. The reaction mixture was then exposed to air, and the solvent was removed under reduced pressure to afford a black residue. Flash chromatography (EtOAc/hexane, 1:5) afforded **29** (74 mg, 86%) as an oil: ^{1}H NMR δ 1.26 (t, 3H), 1.30−1.34 (m, 6H), 1.73−1.79 (m, 6H), 2.71 (s, 3H), 2.76−2.81 (m, 2H), 3.54−3.57 (m, 1H), 3.85 (t, 1H), 4.17−4.22 (m, 4H), 5.67−5.73 (m, 2H); ^{13}C NMR δ 14.1, 25.5, 25.6, 26.0, 27.9, 29.3, 31.7, 37.0, 42.5, 56.4, 60.9, 65.4, 128.9, 130.0, 162.6, 171.1; IR 1746, 1635 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.75; N, 9.51. Found: C, 65.45; H, 8.75; N, 9.50.

1-Cyclohexyl-3-methyl-4-ethoxycarbonyl-(6*H*)1,3-diazonine, 30. To a well-stirred solution of Grubb's catalyst $(PCy_3)_2Cl_2Ru$ benzylidene (25 mg, 0.03 mmol, 10 mol %) in dry benzene (50 mL, 0.005M) at 55 °C was added dropwise a solution of **21ej** (100 mg, 0.3 mmol) in dry benzene (10 mL). The reaction mixture was stirred at 55 °C for 40 h. The reaction mixture was then exposed to air, and the solvent was removed under reduced pressure to afford a black residue. Flash chromatography (EtOAc/hexane, 1:5) afforded **30** (55 mg, 61%) as an oil: ^{1}H NMR δ 1.10−1.17 (m, 1H), 1.25 (t, 3H), 1.40−1.44 (m, 3H), 1.75−1.83 (m, 3H), 1.96−2.03 (m, 2H), 2.05−2.10 (m, 1H), 2.49 (s, 3H), 2.55−2.60 (m, 1H), 3.35−3.39 (m, 2H), 3.90−3.94 (m, 1H), 4.14−4.20 (m, 2H), 4.48 (d, 1H), 5.75−5.80 (m, 2H); ^{13}C NMR δ 14.3, 21.7, 25.3, 25.5, 26.0, 26.2, 29.2, 29.9, 32.5, 42.7, 57.1, 60.9, 61.5, 130.0, 131.8, 168.3, 171.8; IR 1736, 1657 cm^{-1}. Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.36; N, 9.03. Found: C, 66.28; H, 9.36; N, 8.97.

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Supporting Information Available: ^{1}H or ^{13}C NMR spectra are provided for **4ab**, **4ac**, **4ad**, **4bb**, **4ca**, **4ec**, **4fa**, **6a**−**c**,**f**, **14**, **17**, **19a**−**e**, **20**, **21bh**, **21bj**, **21eh**, **21ei**, **21ej**, and **25**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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