Improved Methodology for the Generation and Trapping of α-Lactams by Weak Nucleophiles

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Introduction

Earlier papers from this laboratory have described the generation of α-lactams **2** from *N*-mesyloxyamides **1** derived from malonic esters and their reactions with nucleophiles to produce a wide variety of α-substituted esters and ureas **3**, which themselves can be converted to heterocycles (Scheme 1).[1−3] Reaction of **1** with amines is a very effective way to produce ureas since the amine has the base strength required to produce the α-lactam from **1** as well as the nucleophilicity needed to trap it.[2] For weaker nucleophiles/bases such as hydrazines, hydrazides, and anilines, the reaction rate was quite slow. In these cases successful reaction required slow (syringe pump, 10−15 h) addition of a hindered tertiary amine base such as Hunig's base to a mixture of **1** and the nucleophile. The tertiary amine was sufficiently basic to convert **1** to the α-lactam **2** but, being protonated, did not compete as a nucleophile.

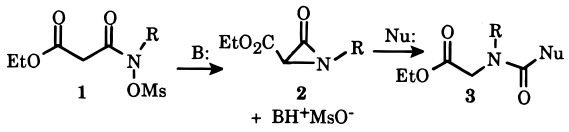
This method was effective but requires fairly long reaction times. Moreover, if the rate of addition was not controlled accurately, reduced yields were observed because the tertiary amine could itself act as a competitive nucleophile.[4]

We felt these difficulties could be minimized by employing a consumable, non-nucleophilic base in place of an amine base. Sodium hydride appeared to be an excellent choice since it is basic enough to form the α-lactam but insufficiently soluble to function effectively as a nucleophile. We are pleased to report that this approach provides a much improved method to effect this transformation. In addition the method can be extended to phosphonoacetohydroxamates which yield phosphonomethyl ureas. Finally, sonication was found to enhance the rate of the heterogeneous reaction by 3−5 times.

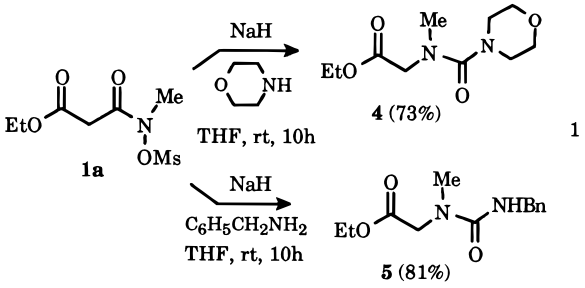
Results and Discussion

Treatment of *N*-mesyloxyamide **1a** with benzylamine or morpholine and suspended NaH produced the corresponding ureas **4** and **5** in good yields (eq 1). Only 1 equiv

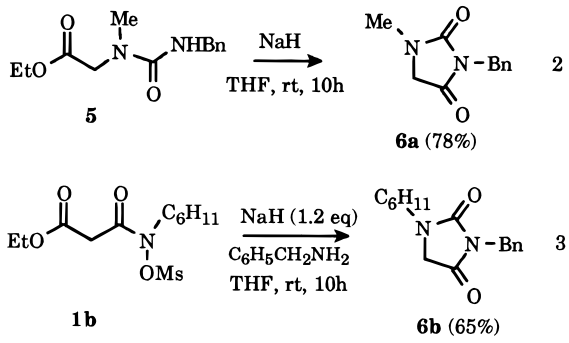
Scheme 1



of amine is needed. Without NaH, 2 equiv of amine are required since one is converted to an ammonium salt upon formation of the α-lactam and the other serves as the nucleophile to trap it.



When primary amines are utilized as nucleophiles, sodium hydride can also be used to effect the base-induced closure of the resulting urea **5** to hydantoin **6a** (eq 2).[3] The overall transformation of **1a** to **6a** could also be accomplished in one pot using an excess of NaH. Likewise mesylate **1b** was converted directly to hydantoin **6b** using an excess of NaH (eq 3). The byproduct of the NaH-induced ring closure is NaOEt which may itself be sufficiently basic to promote hydantoin formation. This explains why ring closure is observed cases such as the above where less than 2 equiv of NaH is present. Ring closure is ensured by using 2 equiv of NaH.



When using less reactive nucleophile/base trapping agents, it was found that NaH is quite advantageous in promoting α-lactam formation. For example, treatment of **1a** with phenylhydrazine **7a** gave no reaction after 30 h because phenylhydrazine is insufficiently basic to promote α-lactam formation. In contrast, **1a** was converted to *N*-aminohydantoin **8a** (78%) in 7 h upon treatment with a mixture of phenylhydrazine **7a** and sodium hydride (eq 4). Acid hydrazides **7b** and **7c** can also be used as the trapping agent to give *N*′-acyl-*N*-aminohydantoins **8b** and **8c** in good yields.

Aromatic amines also gave good yields of products. Reaction of **1a** with indoline and sodium hydride gave urea **9** which, being a tertiary amide, cannot close to a hydantoin (eq 5). However, reaction of **1a** with aniline

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(1) Hoffman, R. V.; Nayyar, N. K.; Chen, W., *J. Org. Chem.* **1995**, *60*, 4121.
(2) Hoffman, R. V.; Nayyar, N. K., *J. Org. Chem.* **1995**, *60*, 5992.
(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.; Klinekole, B. W., *J. Am. Chem. Soc.* **1992**, *114*, 6262.

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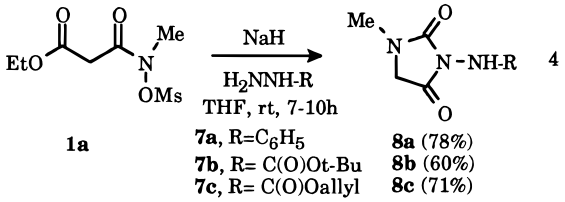

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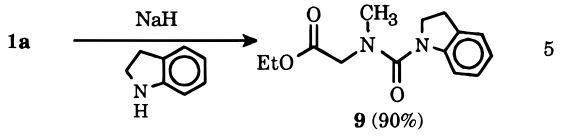
and NaH (1.2 equiv) gave a 1:1 mixture of urea 1**0** and *N*-phenylhydantoin **11** (77%). Use of 2.2 equiv of NaH gave only ring closed **11** (64%).



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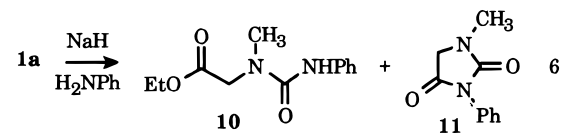
The success of this method suggested that other electron-withdrawing groups which could acidify the α-protons of an *N*-mesyloxy amide could be incorporated into the resulting α-lactam, thus leading to a general synthesis of N-substituted ureas. To this end, diethylphosphonoacetic acid was converted to *N*-mesyloxyamides **12a**,**b**. Treatment of **12a** with a variety of nitrogen nucleophiles **13a**−**h** and sodium hydride in THF led to the formation of diethyl phosphonomethylureas **14a**−**h** in good yields (Chart 1). Treatment of **12b** with benzylamine,**13a**, in the presence of sodium hydride, gave **15a** as well. This methodology can assemble relatively complicated arrays in a straightforward manner and appears to be extendible to other hydroxamic acids with acidified α-hydrogens.

Our working hypothesis is that the nucleophiles are converted at the NaH surface to strong soluble bases (amide anions) which are the base species actually involved in α-lactam formation. This hypothesis derives from the observation that when **1a** is simply stirred at room temperature with sodium hydride in THF, it takes 32 h for complete decomposition of the starting material. However, in the presence of sodium hydride and benzylhydrazine, **1a** is converted to **8a** in 7 h. The hydrazine apparently serves as a proton shuttle between **1a** and the sodium hydride surface. Further data are needed to confirm this mechanistic hypothesis.

Ultrasonication of the reaction mixture was found to give 3−5-fold increases in the rate of conversion to products. For example, reaction of **1a** with benzylamine and NaH proceeded to completion in 3 h at 0 °C (compared to 10 h at room temperature without sonication, cf. eq 1) and produced **5** in the same yield. Phosphonate **12b** reacts readily with benzyl hydrazine **13f** and NaH at 0 °C in 2 h to give **15f** (67%, eq 7). The analogous reaction of **12a** without sonication requires 10h at room temperature for completion.



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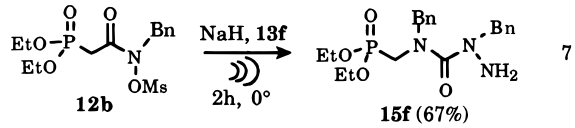

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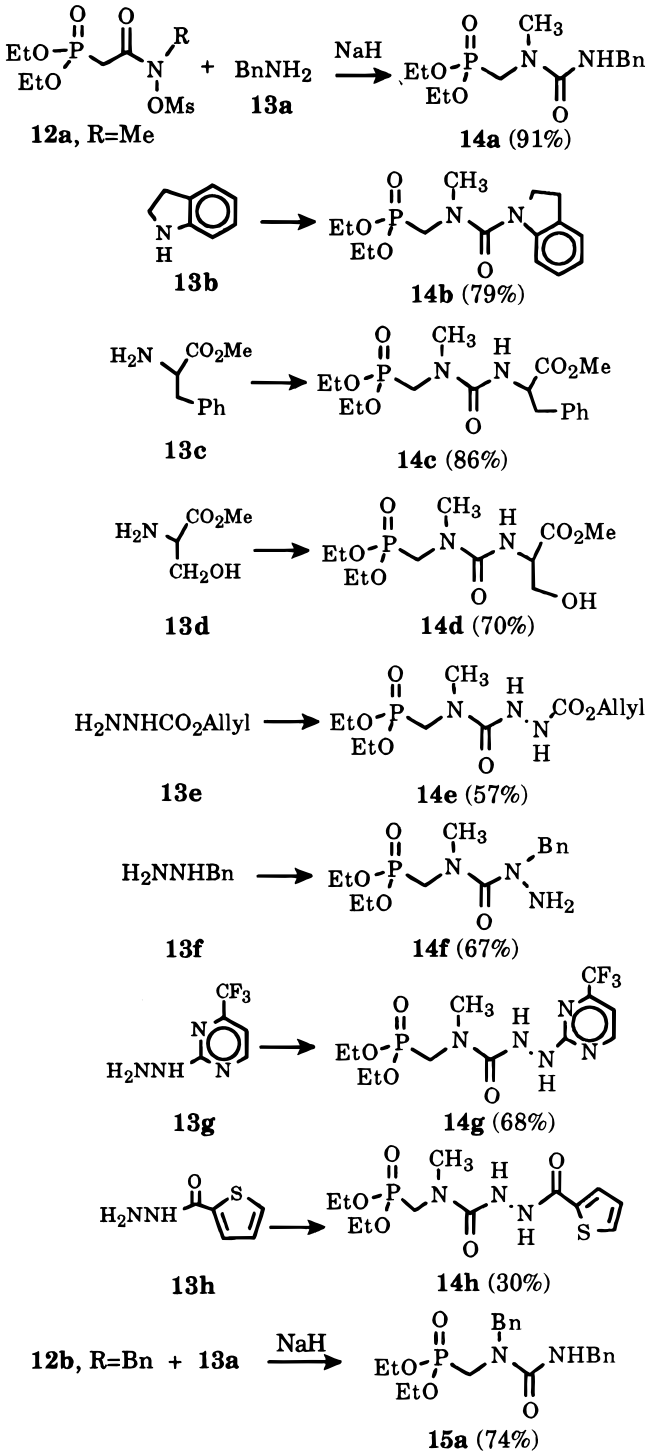
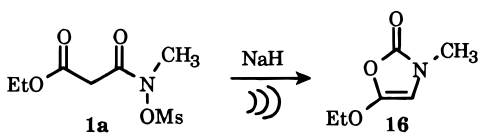
Chart 1



Sonication of a mixture of **1a** and NaH led to the disappearance of **1a** in 5 h (compared to 32 h without sonication) and yielded oxazolone **16** as the only product in 83% yield (eq 8). The structure of **16** was ultimately proven by X-ray crystallography.



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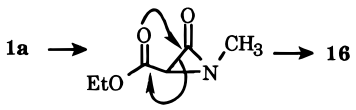
This novel product is most likely formed by a vinylcyclopropane-like rearrangement of the intermediate α-lac-

Scheme 2



tam (Scheme 2). This type of rearrangement was postulated for several α-lactams that were accessed photochemically,[5−7] but has not been observed previously for α-lactams generated chemically. It is likely that these rearrangements have been missed in most solution phase α-lactam studies because unsaturated α-lactams are relatively rare and because nucleophiles are usually present in the reaction mixture. The ability to produce α-lactams in solution in the absence of nucleophiles permits this reaction manifold to now be explored further.

In summary, sodium hydride can be used as an effective consumable base for the generation and trapping of α-lactams by weak nucleophiles. Only a slight excess of the trapping nucleophile is required. Ultrasonication can increase the rate of the reaction significantly. The best general protocol appears to be reaction of an *N*-mesyloxyamide, sodium hydride (1.1−2 equiv), and the nucleophile (1.1 equiv) in THF with ultrasonication at 0 °C.

Experimental Section

Melting points are uncorrected. Chemical shifts are reported in parts per million for chloroform-*d* solutions. Flash chromatography was performed using Silica Gel 60 (230−400 mesh). Ethylmalonyl chloride, *N*-methylhydroxylamine hydrochloride, diethyl phosphonoacetic, and the amines and hydrazines used in this study were all commercially available and were used without further purification. *N*-Mesyloxyamides **1a**[1] and **1b**[3] were prepared as reported earlier.

General Procedure for the Reaction of *N*-Mesyloxy Malonamides 1a and 1b with Nucleophiles. A solution of the *N*-mesyloxy malonamide (3.0 mmol) in THF (20 mL) was added dropwise over 30 min to a suspension of NaH (3.3 mmol) in THF (20 mL) at 0 °C. A solution of the amine or hydrazine (3.3 mmol) in THF (20 mL) was then added dropwise. The reaction was stirred at 0 °C for 1 h and then at room temperature for 10−15 h. The solvent was removed by rotary evaporation, and the residue was taken up in EtOAc (75 mL), washed with 1 M HCl (2 × 10 mL) and water (2 × 20 mL), and dried over $MgSO_4$. The solvent was removed under vacuum and the product was purified by flash chromatography using hexane/EtOAc 3:2 unless otherwise specified.

***N*-Methyl-*N*-(carbethoxymethyl)-N′-(4-oxocyclohexyl)-urea, 4**, was prepared from **1a** (0.71 g, 2.96 mmol), NaH (0.13 g, 3.26 mmol), and morpholine (0.28 g, 3.26 mmol). After a reaction time of 10 h, **4** was obtained as an oil in 73% yield after flash chromatography: ^{1}H NMR: δ 4.20 (q, J = 7.0 Hz, 2H), 3.91 (s, 2H), 3.69 (t, J = 4.9 Hz, 4H), 3.27 (t, J = 4.9 Hz, 4H), 2.95 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR: δ 169.9, 164.0, 66.5, 60.9, 51.3, 47.2, 38.0, 14.1; IR (neat) 2976, 1747, 1649 cm^{-1}. These data are in agreement with data reported earlier for **4**.[1]

***N*-(Carbethoxymethyl)-*N*′-benzylurea, 5**, was prepared from **1a** (1.0 g, 4.17 mmol), NaH (0.20 g, 5.0 mmol), and benzylamine (0.49 g, 4.6 mmol). After a reaction time of 15 h, **5** was obtained as an oil in 81% yield after flash chromatography. ^{1}H NMR: δ 7.45−7.2 (m, 5H), 4.41 (s, 2H), 4.2 (q, J = 7.2 Hz, 2H), 4.08 (s, 2H), 2.94 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); IR (neat) 3386, 3080, 2934, 1713, 1644 cm^{-1}. These data are in agreement with data reported earlier for **5**.[1]

1-Methyl-3-benzyl-2,4-imidazolidinedione, 6a. Urea **5** (0.54 g, 2.15 mmol) in THF (10 mL) was added dropwise to a suspension of NaH (0.095 g, 2.37 mmol) in THF (15 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then at room temperature. for 10 h. Removal of solvent gave a residue which was taken up in EtOAc (50 mL), washed with water (2 × 10 mL), and dried ($MgSO_4$). The solvent was evaporated and the product purified by flash chromatography to afford **6a** (78%) as a solid: mp 148−149 °C. ^{1}H NMR: δ 7.45−7.2 (m, 5H), 4.64 (s, 2H), 3.82 (s, 2H), 2.95 (s, 3H). ^{13}C NMR: δ 169.5, 156.6, 136.1, 128.8, 128.6, 127.9, 51.7, 42.5, 29.6. IR (neat): 1770, 1715 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.55; H, 5.97; N, 13.59. Compound **6a** could also be obtained directly from **1a** with NaH (2 equiv) and benzylamine (1.2 equiv).

1-Cyclohexyl-3-benzyl-2,4-imidazolidinedione, 6b, was prepared from **1b** (0.7 g, 2.27 mmol), NaH (0.1 g, 2.5 mmol), and benzylamine (0.26 g, 2.5 mmol) by the general procedure above. After a reaction time of 10 h, **6b** was obtained as a solid in 65% yield after flash chromatography. mp 71−72 °C. ^{1}H NMR: δ 7.45−7.23 (m, 5H), 4.65 (s, 2H), 4.0−3.82 (m, 1H), 3.76 (s, 2H), 1.9−1.0 (m, 10H); ^{13}C NMR: δ 170.4, 156.1, 136.6, 129.1, 128.2, 51.4, 46.3, 42.7, 31.0, 25.6; IR (KBr): 3080, 1768, 1714 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.55; H, 7.41; N, 10.29. Found: C, 70.70; H, 7.19; N, 10.40.

1-Methyl-3-(*N*-phenylamino)-2,4-imidazolidinedione, 8a, was prepared from **1a** (1.21 g, 5.05 mmol), NaH (0.22 g, 5.55 mmol), and phenylhydrazine **7a** (0.60 g, 5.55 mmol). After a reaction time of 7 h, **8a** was obtained as an oil in 78% yield after flash chromatography. ^{1}H NMR: δ 7.25−7.0 (m, 2H), 6.97−6.7 (m, 3H), 6.46 (s, 1H), 3.90 (s, 2H), 2.96 (s, 3H). ^{13}C NMR: δ 168.5, 155.5, 145.9, 129.6, 122.6, 114.6, 50.7, 30.6. IR (KBr): 3289, 3019,1787,1731,1605 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.14; H, 6.60; N, 18.34. Found: C, 47.00; H, 6.70; N, 18.41. The data are in agreement with data reported earlier for **8a**.[2]

1-Methyl-3-(*N*-*tert*-butoxycarbonylamino)-2,4-imidazolidine-dione, 8b, was prepared from **1a** (1.05 g, 4.38 mmol), NaH (0.193 g, 4.82 mmol), and *tert*-butyl carbazate **7b** (0.608 g, 4.6 mmol). After a reaction time of 10 h, **8b** was obtained as a solid in 60% yield after purification by flash chromatography (1:1 hexane:EtOAc). mp 160−61 °C. ^{1}H NMR: δ 6.89 (s, 1H), 3.96 (s, 2H), 3.0 (s, 3H), 1.48 (s, 9H). ^{13}C NMR: δ 167.4, 154.2, 153.4, 82.9, 50.2, 30.1, 27.9. IR (KBr) 3293, 2983,1790,1736 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.14; H, 6.60; N, 18.34. Found: C, 47.00; H, 6.70; N, 18.41.

1-Methyl-3-(*N*-allyloxycarbonylamino)-2,4-imidazolidinedione, 8c, was prepared from **1a** (1.21 g, 5.06 mmol), NaH (0.222 g, 5.56 mmol), and alloc hydrazide **7c** (0.675 g, 5.8 mmol). After a reaction time of 10 h, **8c** was obtained as an oil in 73% yield after purification by flash chromatography. ^{1}H NMR: δ 7.65 (s, 1H), 6.05−5.8 (m, 1H), 5.42−5.2 (m, 2H), 4.65 (d, J = 5.0 Hz, 2H), 3.98 (s, 2H), 3.0 (s, 3H). ^{13}C NMR: δ 168.1, 155.5, 132.3, 119.1, 67.8, 51.4, 30.2. IR (neat) 3271, 2942,1795,1736, cm^{-1}. M/S (*m*/*e*) 236.1 (M + Na$^+$), 214.1 (M + H$^+$), 170.1. Anal. Calcd for $C_8H_{11}N_3O_4$: C, 45.05; H, 5.20; N, 19.72. Found: C, 44.96; H, 5.03; N, 19.57.

***N*-Methyl-*N*-(carbethoxymethyl)-*N*′-indolinylurea, 9**, was prepared from **1a** (1.05 g, 4.38 mmol), NaH (0.193 g, 4.82 mmol), and indoline (0.54 g, 4.5 mmol). After a reaction time of 15 h, **9** was obtained as an oil in 90% yield after purification by flash chromatography. ^{1}H NMR: δ 7.2−7.1 (m, 3H), 6.95−6.84 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 3.92 (t, J = 8.1 Hz, 2H), 3.03 (t, J = 8.1 Hz, 2H), 3.01 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 170.2, 160.2, 144.5, 131.9, 127.5, 125.2, 122.0, 114.2, 61.4, 51.4, 50.8, 38.3, 28.5, 14.5. IR (neat) 2980, 1746, 1652 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.91; N, 10.67. Found: C, 63.90; H, 6.84; N, 10.62.

***N*-Methyl-*N*-(carbethoxymethyl)-*N*′-phenylurea, 10**, was prepared from **1a** (1.37 g, 5.71 mmol), NaH (0.25 g, 6.29 mmol), and aniline (0.56 g, 6.0 mmol). After a reaction time of 15 h, **10** was obtained in 39% yield after flash chromatography, mp 68−70 °C. ^{1}H NMR: δ 7.4−6.98 (m, 5H), 6.85 (bs, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 3.03 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 170.2, 155.8, 138.9, 128.7, 123.1, 120.1, 61.2, 50.6, 35.8, 14.1. IR (KBr) 3355, 3062, 2986, 1742, 1647 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 60.99; H, 6.83; N, 11.86. Found: C, 61.00; H, 6.89; N, 12.01.

1-Methyl-3-phenyl-2,4-imidazolidinedione, 11, was also isolated from the above reaction mixture by flash chromatography in 38% yield. mp 97−99 °C. ^{1}H NMR: δ 7.5−7.34 (m, 5H),

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(6) Aurich, H. G. *Leibigs Ann. Chem.* **1970**, *732*, 195
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3.96 (s, 2H), 3.00 (s, 3H). ^{13}C NMR: δ 168.6, 155.7, 131.7, 129.0, 128.1, 125.9, 51.5, 29.8. IR (KBr) 3061, 2919, 1780, 1732 . M/S (*m*/*z*): 191.1, 156.1. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H,5.26; N, 14.73. Found: C, 62.96; H,5.53; N,14.73. Compound **11** was obtained as the only product (64%) from the reaction of **1a**, NaH (2.2 equiv), and aniline (1.1 equiv).

***N*-Methyl-*N*-mesyloxy diethylphosphonoacetamide, 12a**. Diethylphosphonoacetic acid was converted to diethylphosphonoacetyl chloride using thionyl chloride by a standard procedure:[8] ^{1}H NMR: δ 4.23 (m, 4H), 3.53 (d, J = 21 Hz, 2H), 1.38 (t, J = 7.2 Hz, 6H).

Triethylamine (4.74 g, 46.86 mmol) in methylene chloride (30 mL) was added to a solution of *N*-methylhydroxylamine hydrochloride (4.30 g, 51.55 mmol) in methylene chloride (120 mL), and the mixture was stirred for 10 min in an ice bath. Diethyl phosphonoacetyl chloride (7.57 g, 35.2 mmol) in methylene chloride (18 mL) was added over a period of 25 min, and the reaction was stirred for 2 h at 0 °C and then for 6 h at room temperature. The reaction was washed with saturated NaCl (2 × 20 mL). The aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered through a one inch silica pad, and evaporated. The crude product was subjected to flash chromatography (8% MeOH in ethyl acetate) to give *N*-methyl diethylphosphonoacetohydroxamic acid as an oil: ^{1}H NMR δ 9.38 (br s, 1H), 4.19 (m, 4H), 3.28 (s, 3H), 3.23 (d, J = 20 Hz, 2H), 1.36 (t, J = 7 Hz, 6H); IR (neat) 3172, 1650 cm^{-1}. This material was carried on in the next step without further purification or analysis.

Methanesulfonyl chloride (7.8 mmol) was added to a solution of *N*-methyl diethylphosphonoacetohydroxamic acid (1.6 g, 7.1 mmol) and pyridine (1.23 g, 15.62 mmol) in methylene chloride (10 mL). The mixture was stirred at 0 °C for 2 h, during which time the color changed to orange. Water (2 mL) was added and the stirring continued for 10 min. Additional methylene chloride (30 mL) was added, and the mixture was washed with 2.5 M HCl (15 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, and the crude product was purified by flash chromatography (hexanes/ EtOAc 2:8) to give mesylate **12a** as an oil in 70% yield, ^{1}H NMR: δ 4.20 (m, 4H), 3.52 (s, 3H), 3.28 (s, 3H), 3.20 (d, J = 21 Hz, 2H), 1.36 (t, J = 7 Hz, 6H); IR 1691 cm^{-1}. Anal. Calcd for $C_8H_{18}NO_7SP\cdot H_2O$: C, 29.90; H, 6.23; N, 4.36. Found: C, 29.32; H, 6.29; N, 3.93. This material is somewhat unstable but can be stored for several months at −20 °C. Attempts to further purify **12a** led to increased decomposition.

***N*-Benzyl-*N*-mesyloxydiethylphosphonoacetamide, 12b**, was prepared by the same route utilized for **12a**. Diethylphosphonoacetyl chloride (11.0 g, 51.3 mmol) was reacted with *N*-benzylhydroxylamine hydrochloride (8.8 g, 55.1 mmol) and triethylamine (15 mL, 107 mmol) to give *N*-benzyl diethylphosphonoacetohydroxamic acid (oil) which was purified by flash chromatography (8% MeOH in ethyl acetate) and used directly in the next step. ^{1}H NMR: δ 9.3 (br s, 1H), 7.31 (m, 5H), 4.82 (s, 2H), 4.12 (m, 4H), 3.21 (d, J = 20 Hz, 2H), 1.29 (t, J = 7.1 Hz, 6H); IR 1635 cm^{-1}.

Methanesulfonyl chloride (3.09 g, 27 mmol) was added to a solution of benzyl diethylphosphonoacetohydroxamic acid (7.4 g, 24.56 mmol) and pyridine (4.37 mL, 54.0 mmol) in dichloromethane (20 mL). The mixture was stirred of 4 h at 0 °C and water (4 mL) was added and stirring was continued for 10 min. The reaction mixture was washed with 2.5 M HCl (3 × 20 mL), dried and evaporated. The crude product was purified by column chromatography (EtOAc) give *N*-benzyl-*N*-mesyloxy diethylphosphonoacetamide **12b** in 52% yield, ^{1}H NMR: δ 7.35 (s, 5H), 5.09 (s, 2H), 4.11 (m, 4 Hz), 3.18 (d, J = 20 Hz, 2H), 3.13 (s, 3H), 1.30 (t, J = 7 Hz, 6H); IR 1691 cm^{-1}; ^{13}C NMR: δ 167.4, 134.3, 128.8, 128.4, 62.9, 62.8, 55.3, 37.7, 34.2, 32.9, 16.3. This material could be stored for several months at −20 °C but was insufficiently stable to obtain satisfactory elemental analysis.

General Procedure for the Synthesis of *N*-(Diethylphosphonomethyl)-*N*-methylureas, 14. Diethylphosphano-(*N*-mesyloxy)acetamide (3 mmol) in THF (20 mL) was added over a period of 30 min to a suspension of NaH (3.6 mmol) in THF (20 mL) at 0 °C. A solution of amine or hydrazine in THF (20 mL) was added dropwise. The reaction was stirred at 0 °C for 1 h and then at room temperature for 15−20 h. The solvent was evaporated, and the residue was taken into EtOAc (75 mL), washed with water (2 mL), and dried over $MgSO_4$. The solvent was removed under vacuum, and the product was purified by flash chromatography (8% MeOH in EtOAc).

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-benzylurea, 14a** was prepared from mesylate **12a** (0.77 g, 2.54 mmol), NaH (0.111 g, 2.79 mmol), and benzylamine **13a** (0.333 g, 3.05 mmol) in THF (60 mL). The usual workup followed by flash chromatography afforded **14a** in 91% yield. ^{1}H NMR: δ 7.3 (s, 5H), 5.63 (t, J = 5.2 Hz, 1H), 4.39 (d, J = 5.7 Hz, 2H), 4.2−4.08 (m, 4H), 3.71 (d, J = 8.9 Hz, 2H), 3.0 (s, 3H), 1.29 (t, J = 7.05 Hz, 6H); ^{13}C NMR: δ158.7, 139.9, 128.8, 127.8, 127.4, 52.9, 45.7, 45.3, 43.5, 36.2, 16.7. IR (neat) 3338, 1638 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_2O_4P$: C, 53.48; H, 7.38; N, 8.92. Found: C, 53.32; H, 7.36; N, 9.00.

***N*-(Diethylphosphanomethyl)-*N*-methyl-*N*′,*N*′-indolinylurea, 14b**, was prepared from mesylate **12a** (0.77 g, 2.54 mmol), NaH (0.112 g, 2.8 mmol), and indoline **13b** (0.32 g, 2.67 mmol) in THF (60 mL). The usual workup followed by flash chromatography gave **14b** in 79% yield. ^{1}H NMR: δ 7.28−6.87 (m, 4H), 4.24−4.09 (m, 4H), 3.95−3.84 (m, 4H), 3.08 (s, 3H), 3.03 (t, J = 8.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 6H). ^{13}C NMR: δ 159.9, 144.3, 131.8, 127.6, 125.2, 122.0, 113.9, 62.6, 50.8, 46.7, 43.5, 39.5, 28.4, 16.8. IR (neat) 2978, 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{23}N_2O_4P\cdot 1/2H_2O$: C, 53.73; H, 7.16; N, 8.36. Found: C, 54.18; H, 7.23; N, 8.35.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-(2-(methyl 3-phenylpropanoyl)urea, 14c**, was prepared from mesylate **12a** (0.89 g, 2.93 mmol), NaH (0.129 g, 3.22 mmol), and racemic phenylalanine methyl ester (free base) **13c** (0.63 g, 3.52 mmol) in THF (60 mL). The usual workup followed by flash chromatography gave **14c** in 85% (0.97 g) yield as a yellow oil. ^{1}H NMR: δ 7.29−7.09 (m, 5H), 5.36 (bd, J = 9.2 Hz, 1H), 4.68 (q, J = 6.2 Hz, 1H), 4.18−4.02 (m, 4H), 3.67 (s, 3H), 3.62 (d, J = 6.3 Hz, 2H), 3.10−3.04 (m, 2H), 2.92 (s, 3H), 1.34−1.19 (m, 6H). ^{13}C NMR: δ 172.9, 157.3, 136.3, 129.1, 128.4, 127.0, 62.5, 54.8, 52.2, 45.3, 43.7, 38.1, 35.6, 16.4. IR (neat): 3328, 1743, 1651 cm^{-1}. Anal. Calcd for $C_{17}H_{27}N_2O_6P$: C, 52.83; H, 7.05; N, 7.25. Found: C, 52.76; H, 7.00; N, 6.55.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-(2-(methyl 3-hydroxypropanoyl)urea, 14d** was prepared from mesylate **12a** 0.77 g, 2.54 mmol), NaH (0.111 g, 2.79 mmol), and racemic serine methyl ester (free base) **13d** (0.474 g, 3.05 mmol) in THF (60 mL). The usual workup followed by flash chromatography gave **14d** as a mixture of rotamers in 70% yield. ^{1}H NMR for isomer 1: δ 8.1 (bd, 1H), 4.75−4.65 (m, 1H), 4.25−4.12 (m, 4H), 3.9 (m, 2H), 3.79 (s, 3H), 3.73 (d, J = 7.7 Hz, 2H), 3.2 (bs, 1H), 3.06 (s, 3H), 1.4−1.30 (m, 6H). ^{1}H NMR for isomer 2: δ 7.55 (bd, 1H), 4.6−4.5 (m, 1H), 4.25−4.12 (m, 4H), 3.9 (m, 2H), 3.77 (s, 3H), 3.57 (d, J = 5.8 Hz, 2H), 3.2 (bs, 1H), 2.51 (s, 3H), 1.40−1.30 (m, 6H). ^{13}C NMR (mixture): δ 172.3, 171.0, 168.2, 167.9, 158.0, 65.3, 64.6, 64.1, 63.6, 62.7, 61.7, 56.8, 55.7, 55.2, 52.8, 46.7, 43.5, 36.9, 36.6, 36.2, 16.7. IR (neat): 3344, 1746, 1666 cm^{-1}. Anal. Calcd for $C_{11}H_{23}N_2O_7P$: C, 40.48; H, 7.11; N, 8.59. Found: C, 40.25; H, 6.94; N, 8.78.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-(allocamino)-urea, 14e,** was prepared from mesylate **12a** (0.606 g, 2.0 mmol), NaH (0.088 g, 2.2 mmol), and alloc hydrazide **13e** (0.28 g, 2.4 mmol) in THF (60 mL). The usual workup followed by flash chromatography gave **14e** in 57% yield as a mixture of rotomers. ^{1}H NMR: δ 7.55 (bs, 1H), 7.1 (bs, 1H), 6.05−5.8 (m, 1H), 5.42−5.2 (m, 2H), 4.65 (m, 2H), 4.3−4.1 (m, 4H), 3.75 (d, J = 9.4 Hz) and 3.62 (d, J = 22.1 Hz, 2H total), 3.05 (s) and 2.5 (s, 3H total), 1.34 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 167.9, 158.8, 157.6, 156.3, 132,6, 118.5, 66.8, 64.0, 63.6, 63.1, 60.7, 46.9, 43.8, 36.8, 36.5, 36.2, 16.7. IR (neat) 3231, 1738,1682 cm^{-1}. Anal. Calcd for $C_{11}H_{22}N_3O_6P$: C, 40.85; H, 6.86; N, 13.00. Found: C, 40.68; H, 6.78; N, 13.06.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-benzyl-*N*′-aminourea, 14f**, was prepared from mesylate **12a** (0.7 g, 2.3 mmol), NaH (0.133 g, 2.77 mmol), and benzyl hydrazine **13f** (0.34 g, 2.77 mmol) in THF (60 mL). The usual workup and purification afforded **14f** in 67% yield. ^{1}H NMR: δ 7.34 (s, 5H), 4.46 (s,

(8) Vogel, A. *Textbook of Practical Organic Chemistry*, 4th ed.; Longman: London, UK, 1978; p 498.

2H), 4.21−4.07 (m, 4H), 3.87 (d, J = 9.8 Hz, 2H), 3.65 (bs, 2H), 3.12 (s, 3H), 1.32 (t, J = 7.2 Hz, 6H). ^{13}C NMR: δ 164.8, 137.2, 129.2, 128.6, 127.9,62.5, 57.9, 48.0, 45.0, 39.5, 16.8. IR (neat): 3326, 1636 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_3O_4P\cdot 1/2H_2O$: C, 49.76; H, 7.31; N, 12.44. Found: C, 50.12; H, 7.42; N, 12.51.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-(4-trifluoromethyl-2-pyrimidylamino)urea, 14g,** was prepared from mesylate **12a** (0.77 g, 2.54 mmol), 2-hydrazino-4-(trifluoromethyl)pyrimidine **13g** (0.475 g, 2.66 mmol), and NaH (0.111 g, 2.79 mmol) in THF (60 mL). The usual workup and purification afforded **14g** as a mixture of two rotamers in 68% yield. ^{1}H NMR for rotamer 1: δ 8.61−8.58 (m, 1H), 7.78 (d, J = 11.0 Hz, 1H), 7.0 (m, 1H), 4.26−4.11 (m, 4H), 3.77 (d, J = 9.5 Hz, 2H), 3.09 (s, 3H), 2.3 (bs, 1H), 1.36−0.89 (m, 6H). ^{1}H NMR for rotamer 2: δ 8.61−8.58 (m, 1H), 8.25 (bs, 1H), 7.0 (m, 1H), 4.26−4.11 (m, 4H), 3.67 (d, J = 22.02 Hz, 2H), 2.58 (s, 3H), 2.3 (bs, 1H), 1.36−0.89 (m, 6H). ^{13}C NMR (mixture): δ 167.5, 164.3, 163.1, 161.0, 159.0, 157.3, 156.6, 123.5, 117.9, 108.6, 64.0, 63.2, 61.3, 47.2, 44.0, 36.4, 16.7. ^{31}P NMR: δ 22.15, 18.73. IR (neat): 3251, 1670 cm^{-1}. Anal. Calcd for $C_{12}H_{19}N_5O_4F_3P$: C, 37.39; H, 4.97; N, 18.18. Found: C, 37.50; H, 5.08; N, 18.48.

***N*-(Diethylphosphonomethyl)-*N*-methyl-*N*′-(2-thienylcarboxamido)urea, 14h**, was prepared from mesylate **12a** (0.77 g, 2.54 mmol), NaH (0.111 g, 2.79 mmol), and 2-thiophenecarboxylic hydrazide **13h** (0.433 g, 3.05 mmol) in THF (60 mL). The usual workup and purification afforded **14h** as a mixture of two rotamers in 30% yield. ^{1}H NMR (mixture): δ 8.08 (bs, 1H), 7.72 (m, 1H), 7.51−7.41 (m, 1H), 7.07−6.96 (m, 2H), 4.26−4.07 (m, 4H), 3.77−3.66 (m, 2H), 3.05 (s) and 2.52 (s, 3H total), 1.38−1.22 (m, 6H). ^{13}C NMR (mixture): δ 166.8, 162.2, 160.5, 158.8, 136.7, 131.3, 129.7, 128.1, 64.1, 63.1, 60.8, 46.9, 43.7, 37.1, 36.1, 16.7. IR ($CHCl_3$): 3251, 1641 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_3O_5SP\cdot 1/2H_2O$: C, 40.22; H, 5.86; N, 11.73. Found: C, 39.76; H, 5.81; N, 10.83.

***N*-(Diethylphosphonomethyl)-*N*,*N*′-dibenzylurea, 15a**. Mesylate **12b** (0.7 g, 1.84 mmol) in THF (20 mL) was added dropwise at 0 °C to a suspension of NaH (0.081 g, 2.02 mmol) in THF (20 mL). After the addition is complete, **13a** (0.235 g, 2.21 mmol) in THF (20 mL) was added over a period of 20 min. The reaction was stirred at 0 °C for 1 h and then at room temperature for 20 h. Solvent was evaporated, and the residue was taken into ethyl acetate (50 mL), washed with water (1 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography to afford **15a** in 74% yield. ^{1}H NMR: δ 7.4−7.15 (m, 10H), 5.87 (t, J = 5.1 Hz, 1H), 4.62 (s, 2H), 4.41 (d, J = 5.5 Hz, 2H), 4.18−4.04 (m, 4H), 3.61 (d, J = 8.8 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 159.0, 139.8, 137.4, 129.1, 128.8, 127.9, 127.4, 63.0, 51.5, 45.4, 44.7, 41.5, 16.7. IR (neat): 3352, 1636, 1541 cm^{-1}. Anal. Calcd for $C_{20}H_{27}N_2O_4P$: C, 61.51; H, 6.97; N, 7.18. Found: C, 61.42; H, 7.22; N, 7.10.

***N*-(Diethylphosphanomethyl)-*N*,*N*′-dibenzyl-*N*′-aminourea, 15f**. Mesylate **12b** (0.81 g, 2.13 mmol) in THF (20 mL) was added dropwise to a suspension of NaH (0.094 g, 2.34 mmol) in THF (20 mL) at 0 °C. After the addition was complete, **13f** (0.313 g, 2.56 mmol) in THF (20 mL) was added over a period of 20 min. The reaction was sonicated[9] at 0 °C for 2 h. The solvent was evaporated, and the residue was taken into ethyl acetate (50 mL), washed with water (1 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography (hexanes/ethyl acetate 1:4) to afford **15f** in 67% yield. ^{1}H NMR: δ 7.4−7.2 (m, 10H), 4.80 (s, 2H), 4.54 (s, 2H), 4.19−4.05 (m, 4H), 3.80 (d, J = 9.8 Hz, 2H), 3.67 (bs, 2H), 1.31 (t, J = 7.0 Hz, 6H). ^{13}C NMR: δ 164.3, 137.7, 137.0, 129.0, 128.6, 128.1, 62.5, 58.1, 53.7, 44.9, 41.8, 16.8. IR (neat): 3472, 1645 cm^{-1}. Anal. Calcd for $C_{20}H_{28}N_3O_4P$: C, 59.23; H, 6.96; N, 10.37. Found: C, 58.92; H, 7.02; N, 10.35.

3-Methyl-5-ethoxy-2-oxazolone, 16. Mesylate **1a** (1.5 g, 6.27 mmol) in THF (20 mL) was added over a period of 30 min to a suspension of NaH (0.3 g, 7.5 mmol) in THF (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then at room temperature for 32 h. Solvent was removed under vacuo, and the residue was taken into ethyl acetate (100 mL), washed with sat. NaCl (1 × 15 mL), dried ($MgSO_4$), and evaporated. The product was purified by flash chromatography (hexanes:ethyl acetate 2:3) to give oxazolone **16** in 50% yield. mp 63−64 °C ^{1}H NMR: δ 5.6 (s, 1H), 4.0 (q, J = 7.0 Hz, 2H), 3.16 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 151.9, 148.5, 91.5, 68.4, 30.7, 14.7. IR ($CHCl_3$): 1772, 1681 cm^{-1}. M/S (m/z) 144.1, 116.1, 83.1, 44.0. Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.29; N, 9.79. Found: C, 50.12; H, 6.09; N, 9.85.

If the same reaction mixture was sonicated at 0 °C, the starting material disappeared in 5 h and **16** was produced in 83% yield after purification. Single crystals of **16** suitable for X-ray structure determination were grown by allowing a solution of **16** in dichloromethane to evaporate very slowly.

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Supporting Information Available: ^{1}H NMR spectra for compounds **12a, 12b**, and **14h**, ^{13}C NMR spectra for **12b** and **14h**, and details of the X-ray structure determination data for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction flask was immersed in a Bransonic 220 Ultrasonic bath (125 W) filled with ice−water and irradiated until the reaction was complete.