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Michael Addition of Amines and Thiols to Dehydroalanine Amides: A Remarkable Rate Acceleration in Water

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Received June 4, 2003

In water, the rate of Michael addition of amines and thiols to dehydroalanine amides was greatly accelerated, leading to shorter reaction times and higher yields. The scope of the new conditions was tested with a range of amines, thiols, and dehydroalanine amides. The ease and efficiency of this method provides an attractive route to the synthesis of natural and unnatural amino acid derivatives.

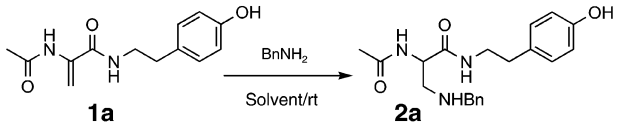
Introduction

Dehydroalanine amides are important constituents of many natural products, such as microcystins,[1a] lantibiotics,[1b] thiostrepton,[1c] and nocathiacins.[2] It has been postulated that the dehydroamino acids play an important role in defining the three-dimensional structure required for the biological activities of these agents.[3] Moreover, they are versatile synthetic precursors because dehydroalanine amide moieties can be readily transformed into various natural and unnatural amino acid derivatives.[4] In this paper, we describe our findings of the Michael addition of amines and thiols to dehydroalanine amides in water.

Although the Michael addition is one of the most powerful and widely used synthetic tools,[5] there are only a handful of reports on the Michael addition of nucleophiles to dehydroalanine derivatives.[4,6] This may be due to the fact that these dehydroalanine derivatives are generally very poor Michael acceptors.[6b]

While most Michael additions are performed in organic solvents, today's environmental concerns encourage the development of "greener" conditions where possible. Although the use of water as a reaction solvent has received considerable attention in synthetic organic chemistry,[7] Michael additions in water are relatively scarce.[8] Additionally, it may be possible by utilizing the unique physicochemical properties of water to realize reactivity and/or selectivity that cannot be attained in organic solvents.[9]

TABLE 1. Optimization of the Michael Addition with Benzylamine[a]



1a 2a

entry	amine equiv	solvent	time (h)	yield (%)[b]
1	10	DMF	48	0[c]
2	10	THF	48	0[c]
3	10	MeOH	120	77
4	10	1:1 DMF/H_2O	96	77
5	10	1:1 THF/H_2O	120	84
6	10	1:1 MeOH/H_2O	48	75
7	10	H_2O	15	91
8	5	H_2O	24	82
9	2	H_2O	48	76

[a] Reactions were run on a 0.5 mmol scale in 5 mL of solvent. [b] Isolated yields. [c] No detectable product was formed within this period.

(1) (a) Namikoshi, M.; Sivonen, K.; Evans, W. R.; Carmichael, W. W.; Rouhiainen, L.; Luukkainen, R.; Rinehart, K. L. *Chem. Res. Toxicol.* **1992**, *5*, 661−666 and references therein. (b) Jack, R. W.; Jung, G. *Curr. Opin. Chem. Biol.* **2000**, *4*, 310−317. (c) Anderson, B.; Hodgkin, D. C.; Viswamitra, M. A. *Nature* **1970**, *225*, 233−235.

(2) (a) Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. *J. Antibiot.* **1998**, *8*, 715−721. (b) Leet, J. E.; Li, W.; Ax, H. A.; Matson, J. A.; Huang, S.; Huang, R.; Cantone, J. L.; Drexler, D.; Dalterio, R. A.; Lam, K. S. *J. Antibiot.* **2003**, *56*, 232−242.

(3) (a) Palmer, D. E.; Pattaroni, C.; Nunami, K.; Chadha, R. K.; Goodman, M.; Wakamiya, T.; Fukase, K. *J. Am. Chem. Soc.* **1992**, *114*, 5634−5642. (b) Suzen, S. *Ankara Univ. Eczacilik Fak. Derg.* **1999**, *28*, 129−141. (c) Nomoto, S.; Sano, A.; Shiba, T. *Tetrahedron Lett.* **1979**, *6*, 521−522.

(4) (a) Gulzar, M. S.; Morris, K. B.; Gani, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1061−1062. (b) Choi, D.; Kohn, H. *Tetrahedron Lett.* **1995**, *36*, 7371−7373.

(5) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, England, 1992.

(6) (a) Labia, R.; Morin, C. *J. Org. Chem.* **1986**, *51*, 249−251. (b) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167−3173 and references therein.

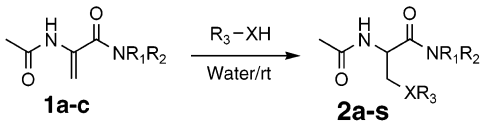
(7) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

(8) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Larpent, C.; Patin, H. *Tetrahedron* **1988**, *44*, 6107−6118. (c) Larpent, C.; Meignan, G.; Patin, H. *Tetrahedron* **1990**, *46*, 6381−6398. (d) Jenner, G. *Tetrahedron* **1996**, *52*, 13557−13568. (e) Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879−1882. (f) Keller, E.; Feringa, B. L. *Synlett* **1997**, 842−843. (g) Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107−3111. (h) Bensa, D.; Brunel, J.-M.; Buono, G.; Rodriguez, J. *Synlett* **2001**, 715−717.

(9) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971−11978 and references therein.

10.1021/jo034762z CCC: $25.00
Published on Web 11/27/2003

TABLE 2. Michael Addition of Amines and Thiols to Dehydroalanine Amides 1a−c[a]



entry	substrate/product	R_1	R_2	R_3XH	time (h)	yield (%)[b]
1	**1a/2a**	H	4-HO−$PhCH_2CH_2$	$BnNH_2$	15	91
2	**1a/2b**	H	4-HO−$PhCH_2CH_2$	$MeNH_2$	5	100
3	**1a/2c**	H	4-HO−$PhCH_2CH_2$	Me_2NH	3	99
4	**1a/2d**	H	4-HO−$PhCH_2CH_2$	$HOCH_2CH_2NH(Me)$	10	95
5	**1a/2e**	H	4-HO−$PhCH_2CH_2$	$HOCH_2CH_2NH(Bn)$	192	62
6	**1a/2f**	H	4-HO−$PhCH_2CH_2$	morpholine	15	100
7	**1a/2g**	H	4-HO−$PhCH_2CH_2$	BnNH(OH)	5	90
8	**1a/2h**	H	4-HO−$PhCH_2CH_2$	NH_3	168	98[c]
9	**1b/2i**	H	HO_2CCH_2	$MeNH_2$	3	100
10	**1b/2j**	H	HO_2CCH_2	Me_2NH	3	100
11	**1c/2k**	Et	Et	Me_2NH	36	90[d]
12	**1a/2l**	H	4-HO−$PhCH_2CH_2$	$Me_2NCH_2CH_2SH$	1	93
13	**1a/2m**	H	4-HO−$PhCH_2CH_2$	$H_2NCH_2CH_2SH$	1	97
14	**1a/2n**	H	4-HO−$PhCH_2CH_2$	$HO_2CCH_2CH_2SH$	1	88
15	**1a/2o**	H	4-HO−$PhCH_2CH_2$	$HO_3SCH_2CH_2SH$	1	85
16	**1a/2p**	H	4-HO−$PhCH_2CH_2$	Me_2CHSH	1	97
17	**1b/2q**	H	HO_2CCH_2	Me_2CHSH	1	100
18	**1c/2r**	Et	Et	Me_2CHSH	48	72[e]
19	**1c/2s**	Et	Et	$Me_2NCH_2CH_2SH$	72	91[e]

[a] Unless otherwise mentioned, the reactions were conducted in water using 10 equiv of amine or 3 equiv of thiol and 3 equiv of Et_3N. [b] Isolated yields. [c] Reaction was carried out in aqueous ammonium hydroxide (28−30% NH_3). [d] 20 equiv of amine was used. [e] These reactions were conducted using 6 equiv of thiol and 6 equiv of Et_3N.

Results and Discussion

Conditions for the Michael addition were optimized using dehydroalanine amide **1a** and benzylamine, and the results are summarized in Table 1. The reaction was conducted in anhydrous organic solvents such as DMF, methanol, and THF for comparison. As shown in Table 1, no detectable Michael adduct was formed in aprotic organic solvents such as DMF and THF even after 48 h (entries 1 and 2). As expected, the Michael addition of benzylamine to **1a** did take place in methanol but required 120 h for completion (entry 3).

Because water has been reported to have an unusual effect on the rate and outcome of many organic reactions, we decided to examine the effect of added water. To our surprise, when a mixture of **1a** and benzylamine was stirred in DMF/H_2O (1:1) or THF/H_2O (1:1), the Michael reaction occurred smoothly, albeit slowly, and provided the desired product **2a** in good yields (entries 4 and 5). In 50% aqueous methanol, the reaction was significantly faster, furnishing the Michael adduct **2a** in 75% yield (entry 6). In water, the addition of benzylamine to **1a** was complete in 15 h and provided the Michael adduct **2a** in 91% isolated yield (entry 7). Systematically reducing the number of equivalents of benzylamine led to somewhat longer reaction times but still provided very good isolated yields of the Michael adduct **2a** (entries 8 and 9). The dramatic rate acceleration in water may be attributed to several factors such as enforced hydrophobic interactions, stabilization of the activated complex through solvation or hydrogen bonding, and micellar catalysis.

With optimal conditions in hand, we next examined the generality of these conditions to other substrates using several amines and thiols. The results are summarized in Table 2. Generally, the Michael addition between dehydroalanine amides **1a**−**d** (Figure 1) and a variety of amines proceeded efficiently, furnishing moderate to excellent isolated yields of desired products. With dehydroalanine amide **1a**, additions were usually faster with hydrophilic amines (entries 2, 3, and 7) but slower with more sterically hindered amines (entries 5 and 6) and hydrophobic amines (entries 1 and 5). Thus, the Michael addition of sterically hindered *N*-benzylaminoethanol to **1a** was very slow and provided only a moderate yield of the product after 192 h. Even though ammonia is highly polar and sterically uncrowded, addition to **1a** was extremely slow, requiring 168 h for completion. This may be due to the relatively weaker nucleophilicity of ammonia compared to alkylamines in protic solvents. The Michael addition of amines to dehydroalanine amides **1b** and **1c** also proceeded smoothly to give the corresponding products in excellent isolated yields (entries 9−11).

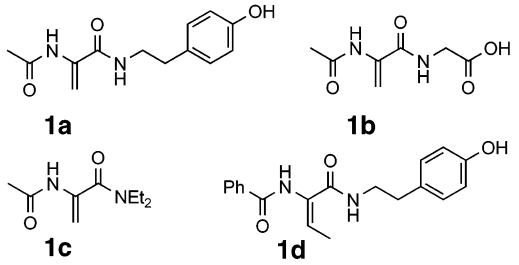
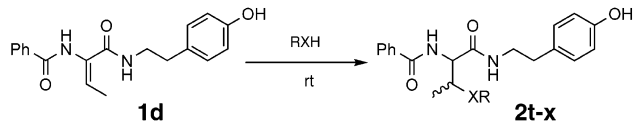


FIGURE 1. Dehydroalanine amides.

Having obtained excellent results with amines, we then examined the addition of thiols to dehydroalanine amides **1a**−**c**. Triethylamine was found to be essential to facilitate the reaction. The added base may play a dual role in improving the solubility of the dehydroalanine amides and acting as a base catalyst for the Michael addition of thiols. In general, the addition of thiols to dehydroalanine amides was faster than that of amines. We found that thiols containing both basic and acidic functional groups such as tertiary amine, primary amine, carboxylic acid,

TABLE 3. Michael Addition of Amines and Thiols to Dehydroalanine Amide 1d[a]

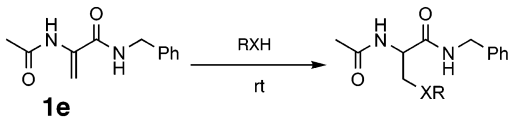


1d 2t-x

entry	RXH	time (h)	product	yield (%)[b]
1	$MeNH_2$	48	**2t**	96
2	Me_2NH	192	**2u**	95
3	pyrrolidine	144	**2v**	(100)[c]
4	Me_2CHSH	72	**2w**	97
5	$Me_2NCH_2CH_2SH$	48	**2x**	63

[a] Reactions were conducted in a 1:1 MeOH/H_2O solvent system using 50 equiv of the nucleophile. [b] Isolated yields. [c] Crude yield.

TABLE 4. Michael Addition of Amines and Thiols to Dehydroalanine Amide 1e[a]



1e 3a-d

entry	RXH	time (h)	product	yield (%)[b]
1	$MeNH_2$	6	**3a**	100
2	Me_2NH	3	**3b**	99
3	morpholine	60	**3c**	100
4	morpholine	26	**3c**	98[c]
5	CH_3SNa	1	**3d**	96

[a] Unless otherwise mentioned, the reactions were conducted in a 2:3 MeOH/H_2O solvent system using 10 equiv of the nucleophile. [b] Isolated yields. [c] 20 equiv of morpholine was used.

and sulfonic acid added to **1a** very efficiently and provided excellent isolated yields of Michael adducts (entries 12−16). Also, treatment of an aqueous solution of **1b** and **1c** with thiols produced the desired Michael adducts in moderate to excellent isolated yields (entries 17−19). Surprisingly, the addition of thiols to **1c** was slower, presumably because of the poor solubility of **1c** in water.

Dehydroalanine amide **1d** with two aromatic rings has very poor water solubility. Consequently, Michael additions with **1d** were carried out in 50% aqueous methanol, and the results are summarized in Table 3. Perhaps because of the presence of the extra methyl substituent on the olefin and reduced hydrophobic effects, the addition of amines/thiols to **1d** was slower, and as a result excess nucleophile was needed for completion in a reasonable time. Nevertheless, excellent yields of Michael adducts (**2t**−**x**) were obtained with both amines and thiols. The addition of nucleophiles to **1d** was nonselective, resulting in inseparable mixtures of diastereomers.

Choi and Kohn[5b] reported that the Michael addition of amines and sodium thiomethoxide to **1e** in methanol required an excess of the nucleophile (15−22 equiv) and 1−4 days for completion. Encouraging results with **1a**−**d** prompted us to examine the effect of water on the rate of the Michael addition to **1e**. The results in Table 4 clearly indicate that the inclusion of water in the reaction solvent increases the rate of the addition of nucleophiles to **1e** severalfold. For example, in 60% aqueous methanol, the addition of methylamine to **1e** was complete in 6 h, whereas dimethylamine addition took only 3 h for completion. However, the addition of morpholine to **1e** was slower and required 60 h for completion, but with excess morpholine the reaction was complete in 26 h and provided **3c** in very good isolated yield. Sodium thiomethoxide addition to **1e** was complete in 1 h and produced the desired product **3d** in an excellent yield.

In conclusion, the Michael addition of amines and thiols to dehydroalanine amides in the presence of water is efficient and high yielding. Reaction rates tend to be faster as the proportion of water in the solvent is increased. The ease and efficacy of this method provides an attractive route to the synthesis of natural and unnatural amino acid derivatives from readily available dehydroalanine amides. Application of these findings to the preparation of natural product analogues will be disclosed elsewhere.[10]

Experimental Section

General Procedure for the Addition of Amines to Dehydroalanine Amides (1a−e). A mixture of **1** (0.5 mmol) and amine (5 mmol) in water (5 mL) was stirred at room temperature until the reaction was complete. The reaction mixture was then freeze-dried to give the desired product **2**. Alternatively, the reaction mixture was acidified with aq HCl (1 N, 5 mL) and purified on a C-18 reverse-phase column using MeOH/water mixtures. Product-containing fractions were combined, concentrated, and freeze-dried to give **2**.

2-Acetylamino-3-benzylamino-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2a): purified using 10 and 15% MeOH/water; white powder (0.1826 g, 91%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (1H, br s), 9.34 (1H, br s), 8.50 (1H, d, J = 7.9 Hz), 8.16 (1H, t, J = 5.6 Hz), 7.59−7.55 (2H, m), 7.45−7.40 (3H, m), 6.96 (2H, d, J = 8.2 Hz), 6.68 (2H, d, J = 8.2 Hz), 4.65−4.60 (1H, m), 4.18−4.13 (2H, m), 3.73 (1H, br s), 3.25−3.17 (3H, m), 3.06−2.99 (1H, m), 2.58 (2H, t, J = 7.5 Hz), 1.91 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.0, 168.4, 155.6, 131.5, 130.1, 129.4, 129.1, 128.9, 128.5, 115.0, 50.0, 49.5, 47.0, 40.7, 34.0, 22.8; HRMS calcd for $C_{20}H_{26}N_3O_3$ (M + H) 356.1974, found 356.1969. Anal. Calcd for $C_{20}H_{25}N_3O_3\cdot 0.31H_2O\cdot 1.1HCl$: C, 59.89; H, 6.71; N, 10.48; Cl, 9.72. Found: C, 59.76; H, 6.83; N, 10.58; Cl, 9.96.

2-Acetylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-methylaminopropionamide (2b): white powder (0.1402 g, 100%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (1H, t, J = 5.5 Hz), 7.86 (1H, d, J = 7.9 Hz), 6.98 (2H, d, J = 8.6 Hz), 6.66 (2H, d, J = 8.6 Hz), 4.30−4.26 (1H, m), 3.45−3.13 (4H, m), 2.62−2.55 (4H, m), 2.22 (3H, s), 1.84 (3H, m); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.6, 169.1, 155.5, 129.4, 129.3, 114.9, 52.8, 52.0, 40.4, 35.4, 34.1, 22.5; HRMS calcd for $C_{14}H_{22}N_3O_3$ (M + H) 280.1661, found 280.1663. Anal. Calcd for $C_{14}H_{21}N_3O_3\cdot 0.2H_2O\cdot 0.1CH_3NH_2$: C, 59.26; H, 7.57; N, 15.18. Found: C, 59.26; H, 7.51; N, 15.36.

2-Acetylamino-3-dimethylamino-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2c): white powder (0.1452 g, 99%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (1H, br s), 8.06 (1H, t, J = 5.7 Hz), 7.90 (1H, d, J = 8.2 Hz), 6.98 (2H, d, J = 8.2 Hz), 6.66 (2H, d, J = 8.2 Hz), 4.33−4.29 (1H, m), 3.23−3.16 (2H, m), 2.57 (2H, t, J = 7.3 Hz), 2.40−2.36 (1H, m), 2.32−2.28 (1H, m), 2.12 (6H, s), 1.83 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.6, 168.8, 155.5, 129.4, 129.3, 114.9, 60.6, 50.8, 45.1, 40.4, 34.1, 22.4; HRMS calcd for $C_{15}H_{24}N_3O_3$ (M + H) 294.1818, found 294.1815. Anal. Calcd for $C_{15}H_{23}N_3O_3\cdot 0.1H_2O\cdot 0.1(CH_3)_2NH$: C, 60.91; H, 7.97; N, 14.49. Found: C, 60.58; H, 8.04; N, 14.35.

(10) Naidu, B. N.; Li, W.; Sorenson, M. E.; Connolly, T. P.; Wichtowski, J. A.; Zhang, Y.; Kim, O. K.; Matiskella, J. D.; Lam, K. S.; Bronson, J. J.; Ueda, Y. *Tetrahedron Lett.* In press.

2-Acetylamino-3-[(2-hydroxyethyl)methylamino]-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2d): purified using water followed by 5 and 10% MeOH/water; white solid (0.177 g, 95%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (1H, br s), 9.25 (1H, br s), 8.38 (1H, d, J = 8.6 Hz), 8.21 (1H, br s), 6.98 (2H, d, J = 8.2 Hz), 6.68 (2H, d, J = 8.5 Hz), 5.36 (1H, br s), 4.74−4.70 (1H, m), 3.74 (2H, t, J = 4.9 Hz), 3.60−3.11 (6H, m), 2.81 (3H, s), 2.60 (2H, t, J = 7.5 Hz), 1.91 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.0, 168.2, 155.7, 129.4, 129.0, 115.1, 58.2, 56.4, 55.0, 47.9, 40.7, 34.0, 22.7; HRMS calcd for $C_{15}H_{26}N_3O_4$ (M + H) 324.1923, found 324.1927. Anal. Calcd for $C_{15}H_{25}N_3O_3\cdot0.5H_2O\cdot1.1HCl$: C, 51.59; H, 7.33; N, 11.28; Cl, 10.47. Found: C, 51.83; H, 7.24; N, 11.27; Cl, 10.61.

2-Acetylamino-3-[benzyl(2-hydroxyethyl)amino]-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2e): purified using 10−30% MeOH/water; white solid (0.158 g, 62%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (1H, s), 8.13 (1H, t, J = 5.5 Hz), 7.88 (1H, d, J = 8.2 Hz), 7.30−7.26 (4H, m), 7.24−7.20 (1H, m), 6.99 (2H, d, J = 8.5 Hz), 6.67 (2H, d, J = 8.2 Hz), 4.43−4.38 (2H, m), 3.61 (2H, d, J_{AB} = 13.9 Hz), 3.45−3.39 (2H, m), 3.32 (1H, s), 3.23−3.16 (2H, m), 2.70 (1H, dd, J = 12.8, 7.3 Hz), 2.61−2.42 (4H, m), 1.84 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.6, 168.9, 155.5, 139.1, 129.34, 129.30, 128.6, 127.9, 126.6, 115.0, 58.7, 58.3, 56.1, 55.4, 51.1, 40.5, 34.1, 22.5; HRMS calcd for $C_{22}H_{30}N_3O_4$ (M + H) 400.2236, found 400.2244. Anal. Calcd for $C_{22}H_{29}N_3O_4$: C, 66.14; H, 7.31; N, 10.51. Found: C, 65.93; H, 7.29; N, 10.27.

2-Acetylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-morpholin-4-ylpropionamide (2f): white solid (0.1783 g, 100%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (1H, br s), 8.05 (1H, t, J = 5.5 Hz), 7.92 (1H, d, J = 8.2 Hz), 6.99 (2H, d, J = 8.6 Hz), 6.66 (2H, d, J = 8.2 Hz), 4.39−4.35 (1H, m), 3.46−3.42 (5H, m), 3.29−3.23 (1H, m), 3.20−3.13 (1H, m), 2.66 (1H, t, J = 4.7 Hz), 2.57 (2H, t, J = 7.2 Hz), 2.47−2.29 (6H, m), 1.83 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.5, 168.9, 155.5, 129.4, 129.3, 114.9, 67.2 (morpholine), 66.0, 59.8, 53.1, 45.9 (morpholine), 49.9, 40.3, 34.1, 22.5; HRMS calcd for $C_{17}H_{24}N_3O_4$ (M − H) 334.1767, found 334.1781. Anal. Calcd for $C_{17}H_{25}N_3O_4\cdot0.2H_2O\cdot0.25$morpholine: C, 59.91; H, 7.61; N, 12.62. Found: C, 59.53; H, 7.77; N, 12.62.

2-Acetylamino-3-(benzylhydroxyamino)-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2g): acidified with TFA and purified using 10−50% MeOH/water; white solid (0.2185 g, 90%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45−8.55 (2H, br s), 7.98 (1H, d, J = 7.9 Hz), 7.89 (1H, t, J = 5.5 Hz), 7.34−7.25 (5H, m), 6.99 (2H, d, J = 8.2 Hz), 6.67 (2H, d, J = 8.2 Hz), 4.53−4.48 (1H, m), 3.90 (2H, s), 3.25−3.18 (2H, m), 3.02−2.95 (1H, m), 2.86−2.79 (1H, m), 2.59 (2H, t, J = 7.5 Hz), 1.86 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.1, 169.3, 155.6, 129.4, 129.3, 127.9, 127.1, 115.0, 63.5, 60.7, 50.6, 40.6, 34.2, 22.5; HRMS calcd for $C_{20}H_{26}N_3O_4$ (M + H) 372.1923, found 372.1918.

2-Acetylamino-3-amino-*N*-[2-(4-hydroxyphenyl)ethyl]-propionamide (2h): white powder (0.132 g, 98%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (1H, br s), 7.94−7.87 (2H, m), 7.79 (1H, t, J = 5.6 Hz), 6.99−6.97 (2H, m), 6.68−6.65 (2H, m), 4.12−4.08 (1H, m), 3.29−3.17 (3H, m), 3.03−2.97 (1H, m), 2.70−2.56 (3H, m), 1.86 (1H, s), 1.81 (2H, s); HRMS calcd for $C_{13}H_{19}N_3O_3$ (M + Na) 288.1324, found 288.1311. Anal. Calcd for $C_{13}H_{19}N_3O_3\cdot0.2H_2O$: C, 58.06; H, 7.27; N, 15.63. Found: C, 57.72; H, 7.27; N, 15.43.

(2-Acetylamino-3-methylaminopropionylamino)acetic acid (2i): white powder (0.12 g, 100%); ^{1}H NMR (300 MHz, CD_3OD) δ 4.63 (1H, dd, J = 7.02, 5.80 H), 3.77 (2H, br s), 2.98 (2H, m), 2.54 (3H, s), 2.48 (3H, s), 2.05 (3H, s); HRMS calcd for $C_8H_{16}N_3O_4$ (M + H) 218.1141, found 218.1135. Anal. Calcd for $C_8H_{15}N_3O_4\cdot0.25CH_3NH_2\cdot0.4H_2O$: C, 42.68; H, 7.40; N, 19.61. Found: C, 42.70; H, 7.20; N, 19.43.

(2-Acetylamino-3-dimethylaminopropionylamino)acetic acid (2j): white powder (0.131 g, 100%); ^{1}H NMR (300 MHz, CD_3OD) δ 4.61 (1H, dd, J = 8.2, 6.10 Hz), 3.77 (2H, d, J = 1.5 Hz), 2.74 (2H, m), 2.69 (6H, s), 2.38 (6H, s), 2.05 (3H, s); HRMS calcd for $C_9H_{18}N_3O_4$ (M + H) 232.1297, found 232.1292. Anal. Calcd for $C_9H_{17}N_3O_4\cdot0.5(CH_3)_2NH\cdot0.4H_2O$: C, 46.02; H, 8.23; N, 18.78. Found: C, 45.82; H, 8.38; N, 18.57.

2-Acetylamino-3-dimethylamino-*N*,*N*-diethylpropionamide (2k): purified using 5−20% MeOH/water; white powder (0.120 g, 90%); ^{1}H NMR (500 MHz, CD_3OD) δ 5.19−5.15 (1H, m), 3.50−3.35 (4H, m), 3.18−3.13 (2H, m), 2.76 (6H, s), 2.04 (3H, s), 1.25 (3H, t, J = 7.2 Hz), 1.15 (3H, t, J = 7.2 Hz); ^{13}C NMR (125.77 MHz, CD_3OD) δ 172.2, 168.9, 59.6, 46.4, 44.1, 42.2, 40.9, 21.6, 13.5, 12.0; HRMS calcd for $C_{11}H_{24}N_3O_2$ (M + H) 230.1869, found 230.1865.

***N*-{1-[2-(4-Hydroxyphenyl)ethylcarbamoyl]-2-methylaminopropyl}benzamide (2t).** To a suspension of **1d** (0.10 g, 0.31 mmol) in MeOH (3 mL) was added methylamine (2.15 mL, 40 wt % in H_2O, 15.5 mmol). The resulting solution was stirred at room temperature for 48 h and concentrated to yield **2t** as a green solid (0.108 g, 96%): ^{1}H NMR (300 MHz $CDCl_3$) δ 8.01 (1H, t, J = 4.0 Hz), 7.86−7.79 (2H, m), 7.64 (1H, d, J = 5.9 Hz), 7.51−7.39 (4H, m), 7.03 (2H, d, J = 8.4 Hz), 6.73 (2H, d, J = 8.4 Hz), 4.52 (1H, dd, J = 3.1, 5.7 Hz), 3.54−3.47 (2H, m), 3.27 (1H, dd, J = 6.6, 3.30 Hz), 2.74 (2H, t, J = 6.8 Hz), 2.47 (3H, s), 1.11 (0.9H, d, J = 6.6 Hz), 0.96 (2.1 H, d, J = 6.6 Hz); LCMS calcd for $C_{20}H_{26}N_3O_3$ (M + H) 356 20, found 356.14. Anal. Calcd for $C_{20}H_{25}N_3O_3\cdot0.5H_2O$: C, 65.91; H, 7.19; N, 11.53. Found: C, 65.99; H, 7.26; N, 11.50.

***N*-{2-Dimethylamino-1-[2-(4-hydroxyphenyl)ethylcarbamoyl]propyl}benzamide (2u).** To a suspension of **1d** (0.10 g, 0.31 mmol) in MeOH (2 mL) was added dimethylamine (3.0 mL, 40 wt % in H_2O, 15.5 mmol). The resulting solution was stirred at room temperature for 8 days and concentrated to yield **2u** as a pale brown solid (0.113 g, 95% yield): ^{1}H NMR (300 MHz $CDCl_3$) δ 7.85−7.79 (2H, m), 7.52−7.38 (4H, m), 7.02−6.95 (2H, m), 6.75−6.69 (2H, m), 6.39−6.33 (1H, m), 4.63 (0.3H, d, J = 8.4 Hz), 4.47 (0.7H, d, J = 5.5 Hz), 3.53−3.46 (2H, m), 2.90 (1H, t, J = 6.4 Hz), 2.75−2.68 (2H, m), 1.00 (0.3H, d, J = 6.9 Hz), 0.90 (0.7H, d, J = 6.6 Hz); HRMS calcd for $C_{21}H_{28}N_3O_3$ (M + H) 370.2131, found 370.2141. Anal. Calcd for $C_{21}H_{27}N_3O_3\cdot0.6H_2O$: C, 66.33; H, 7.47; N, 11.05. Found: C, 66.23; H, 7.10; N, 11.39.

***N*-{1-[2-(4-Hydroxyphenyl)ethylcarbamoyl]-2-pyrrolidin-1-ylpropyl}benzamide (2v).** To a suspension of **1d** (0.10 g, 0.31 mmol) in MeOH (2 mL) was added pyrrolidine (1.3 mL, 15.5 mmol) followed by water (2.0 mL). The resulting solution was stirred at room temperature for 6 days and concentrated to yield **2v** as a white powder (0.122.5 g, 100%, 85−90% purity): ^{1}H NMR (300 MHz $CDCl_3$) δ 8.61 (1H, t, J = 4.8 Hz), 7.83−7.78 (2H, m), 7.53−7.39 (4H, m), 7.02−6.96 (2H, m), 6.79−6.71 (3H, m), 4.69 (1H, t, J = 3.7 Hz), 3.60−3.47 (2H, m), 3.06−2.97 (1H, m), 2.93 (1H, dd, J = 6.6, 3.66 Hz), 2.74 (2H, t, J = 6.6 Hz), 2.67−2.57 (3H, m), 1.68−1.59 (4H, m), 1.05 (0.9H, d, J = 6.8 Hz), 0.93 (2.1H, d, J = 6.8 Hz); HRMS calcd for $C_{23}H_{30}N_3O_3$ (M + H) 396.2287, found 396.2287.

General Procedure for the Addition of Thiols to Dehydroalanine Amides 1a−e. A mixture of **1** (0.5 mmol), thiol (1.5 mmol), and Et_3N (1.5 mmol) in water (5 mL) was stirred at room temperature until the reaction was complete. The reaction mixture was then freeze-dried to give the desired product **2**. Alternatively, the reaction mixture was acidified with aq HCl (1 N, 5 mL) and purified on a C-18 reverse phase column using MeOH/water mixtures. Product-containing fractions were combined, concentrated, and freeze-dried to give **2**.

2-Acetylamino-3-(2-dimethylaminoethylsulfanyl)-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2l): purified using water followed by 5% MeOH/water; white solid (0.1861 g, 93%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.53 (1H, s), 9.16 (1H, br s), 8.26 (1H, t, J = 5.7 Hz), 8.21 (1H, d, J = 8.2 Hz), 6.99 (2H, d, J = 8.2 Hz), 6.68 (2H, d, J = 8.2 Hz), 4.42−4.38 (1H, m), 3.27−3.17 (4H, m), 2.89−2.86 (2H, m), 2.82 (1H, dd, J = 13.4, 5.2 Hz), 2.75 (6H, s), 2.64−2.58 (3H, m), 1.87 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 169.7, 169.2, 155.6, 129.4, 129.2, 115.0, 55.5, 52.2, 41.9, 41.7, 40.5, 34.1, 33.5, 25.0, 22.4; HRMS

calcd for $C_{17}H_{28}N_3O_3S$ (M + H) 354.1852, found 354.1849. Anal. Calcd for $C_{17}H_{27}N_3O_3S \cdot 0.3H_2O \cdot 1.1HCl$: C, 51.18; H, 7.25; N, 10.53; Cl, 9.77; S, 8.04. Found: C, 50.95; H, 7.45; N, 10.48; Cl, 9.66; S, 8.08.

2-Acetylamino-3-(2-aminoethylsulfanyl)-*N*-[2-(4-hydroxyphenyl)ethyl]propionamide (2m): purified using water followed by 5% MeOH/water; white solid (0.1794 g, 97%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (1H, br s), 8.26 (1H, t, J = 5.7 Hz), 8.21 (1H, d, J = 8.6 Hz), 8.17 (3H, br s), 6.98 (2H, d, J = 8.2 Hz), 6.68 (2H, d, J = 8.5 Hz), 4.41−4.36 (1H, m), 3.26−3.15 (2H, m), 3.00−2.93 (2H, m), 2.83−2.71 (3H, m), 2.61−2.57 (3H, m), 1.86 (3H, s); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 169.8, 169.3, 155.6, 129.4, 129.2, 115.0, 52.2, 40.6, 38.2, 34.1, 33.4, 28.3, 22.5; HRMS calcd for $C_{15}H_{24}N_3O_3S$ (M + H) 326.1539, found 326.1538. Anal. Calcd for $C_{15}H_{23}N_3O_3S \cdot 0.4H_2O \cdot 1.05HCl$: C, 48.57; H, 6.75; N, 11.33; Cl, 10.04; S, 8.64. Found: C, 48.89; H, 6.69; N, 11.36; Cl, 10.38; S, 8.62.

3-{2-Acetylamino-2-[2-(4-hydroxyphenyl)ethylcarbamoyl]ethylsulfanyl}propionic acid (2n): purified using 5 and 10% MeOH/water; white solid (0.192 g, 88%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13−8.10 (2H, m), 6.98 (2H, d, J = 8.2 Hz), 6.66 (2H, d, J = 8.6 Hz), 4.37−4.33 (1H, m), 3.25−3.14 (2H, m), 2.74−2.64 (7H, m), 2.61−2.55 (3H, m), 2.40 (2H, t, J = 7.3 Hz), 1.84 (3H, s), 1.02 (6H, t, J = 7.3 Hz); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 173.6, 170.0, 169.1, 155.6, 129.4, 129.2, 115.0, 52.4, 45.2, 40.6, 35.3, 34.1, 33.5, 27.0, 22.4, 10.1; HRMS calcd for $C_{16}H_{23}N_2O_5S$ (M + H) 355.1328, found 355.1316. Anal. Calcd for $C_{16}H_{22}N_2O_5S \cdot 0.85H_2O \cdot 0.83Et_3N$: C, 55.54; H, 8.03; N, 8.74; S, 7.07. Found: C, 55.93; H, 7.92; N, 8.69; S, 7.46.

2-{2-Acetylamino-2-[2-(4-hydroxyphenyl)ethylcarbamoyl]ethylsulfanyl}ethanesulfonic acid (2o). The reaction mixture was quenched with aq $NaHCO_3$ (1 M, 3 mL) and purified using 5% MeOH/water: white solid (0.20 g, 85%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.15 (1H, s), 8.90 (1H, br s), 8.11 (1H, t, J = 5.7 Hz), 8.06 (1H, d, J = 8.6 Hz), 6.99 (2H, d, J = 8.2 Hz), 6.66 (2H, d, J = 8.2 Hz), 4.35−4.31 (1H, m), 3.25−3.15 (2H, m), 3.12−3.07 (3.34H, m), 2.76−2.54 (8H, m), 1.84 (3H, s), 1.17 (5H, t, J = 7.3 Hz); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 169.9, 169.1, 155.5, 129.4, 129.3, 115.0, 52.4, 51.7, 45.7, 40.6, 34.1, 33.7, 27.1, 22.4, 8.5; HRMS calcd for $C_{15}H_{21}N_2O_6S_2$ (M − H) 389.0841, found 389.0841. Anal. Calcd for $C_{15}H_{22}N_2O_6S_2 \cdot 0.4Na \cdot 0.9H_2O \cdot 0.6Et_3N$: C, 46.80; H, 6.94; N, 7.63; S, 13.43; Na, 1.93. Found: C, 46.99; H, 6.79; N, 7.65; S, 13.82; Na, 1.89.

2-Acetylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-isopropylsulfanylpropionamide (2p): white solid (0.158 g, 97%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.16 (1H, s), 8.11−8.04 (2H, m), 6.98 (2H, d, J = 8.2 Hz), 6.66 (2H, d, J = 8.2 Hz), 4.35−4.31 (1H, m), 3.26−3.14 (2H, m), 2.98−2.90 (1H, m), 2.74 (1H, dd, J = 13.2, 6.1 Hz), 2.61−2.56 (3H, m), 1.84 (3H, s), 1.18 (3H, d, J = 6.2 Hz), 1.17 (3H, d, J = 6.2 Hz); ^{13}C NMR (125.77 MHz, DMSO-d_6) δ 170.0, 169.0, 155.5, 129.4, 129.3, 114.9, 52.7, 40.5, 34.2, 34.1, 32.2, 23.2, 23.1, 22.4; HRMS calcd for $C_{16}H_{25}N_2O_3S$ (M + H) 325.1586, found 325.1597. Anal. Calcd for $C_{16}H_{24}N_2O_3S \cdot 0.2H_2O$: C, 58.58; H, 7.50; N, 8.54; S, 9.77. Found: C, 58.97; H, 7.73; N, 8.64; S, 9.48.

(2-Acetylamino-3-isopropylsulfanylpropionylamino)-acetic acid (2q): white powder (0.182, 100%); ^{1}H NMR (300 MHz, CD_3OD) δ 4.57 (1H, dd, J = 8.6, 4.88 Hz), 3.77 (2H, dd, J = 55.2, 17.4 Hz), 3.18 (6H, q, J = 7.3 Hz), 3.09 (1H, dd, J = 13.7, 5.2 Hz), 3.00 (1H, m), 2.80 (1H, dd, J = 13.7, 8.8 Hz), 2.05 (3H, s), 1.31 (9H, t, J = 7.3 Hz), 1.28 (6H, dd, J = 11.9, 6.7 Hz); HRMS calcd for $C_{10}H_{19}N_2O_4S$ (M + H) 263.1066, found 263.1059.

2-Acetylamino-*N*,*N*-diethyl-3-isopropylsulfanylpropionamide (2r): purified using 20% MeOH/water; white solid (0.0931 g, 72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (1H, d, J = 7.9 Hz), 5.06−5.01 (1H, m), 3.58−3.47 (2H, m), 3.40−3.33 (1H, m), 3.28−3.21 (1H, m), 2.95−2.83 (2H, m), 2.76 (1H, dd, J = 13.4, 5.8 Hz), 1.98 (3H, s), 1.24−1.20 (9H, m), 1.11 (3H, t, J = 7.0 Hz); HRMS calcd for $C_{12}H_{24}N_2O_2S$ (M + NH_4 + CH_3CN) 319.2168, found 319.2168. Anal. Calcd for $C_{12}H_{24}N_2O_2S$: C, 55.35; H, 9.29; N, 10.75; S, 12.31. Found: C, 55.43; H, 9.10; N, 10.69; S, 12.19.

2-Acetylamino-3-(2-dimethylaminoethylsulfanyl)-*N*,*N*-diethylpropionamide (2s): purified using 5−20% MeOH/water; white solid (0.156 g, 91%); ^{1}H NMR (500 MHz, CD_3OD) δ 4.99−4.94 (1H, m), 3.51−3.33 (6H, m), 3.07−2.90 (3H, m), 2.92 (6H, s), 2.82−2.76 (1H, m), 1.99 (3H, s), 1.24 (3H, t, J = 7.0 Hz), 1.13 (3H, t, J = 7.0 Hz); ^{13}C NMR (125.77 MHz, CD_3OD) δ 172.9, 171.2, 58.0, 50.5, 43.7, 43.60, 43.55, 42.2, 34.8, 27.7, 22.5, 14.9, 13.2; HRMS calcd for $C_{13}H_{28}N_3O_2S$ (M + H) 290.1902, found 290.1903. Anal. Calcd for $C_{13}H_{27}N_3O_2S \cdot 0.4H_2O \cdot 1.25HCl$: C, 45.63; H, 8.56; N, 12.28; S, 9.37; Cl, 12.95. Found: C, 45.89; H, 8.25; N, 12.32; S, 9.34; Cl, 12.59.

2-Acetylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-isopropylsulfanylbutyramide (2w). To a suspension of **1d** (0.10 g, 0.31 mmol) in MeOH (2.5 mL) was added 2-propanethiol (1.44 mL, 15.5 mmol) followed by H_2O (2.5 mL) and Et_3N (2.9 mL, 15.5 mmol). The resulting mixture was stirred at room temperature for 72 h and then concentrated to give **2w** as a white powder (0.1206 g, 97%, 95% purity): ^{1}H NMR (300 MHz $CDCl_3$) δ 7.81 (2H, d, J = 6.9 Hz), 7.52−7.42 (4H, m), 7.09 (2H, d, J = 8.4 Hz), 6.93 (1H, t, J = 5.5 Hz), 6.75 (2H, d, J = 8.4 Hz), 4.67 (1H, dd, J = 6.2, 2.9 Hz), 3.60−3.48 (3H, m), 3.31−3.17 (1H, m), 2.78 (2H, t, J = 6.9 Hz), 1.39 (3H, d, J = 6.6 Hz), 1.29 (3H, d, J = 6.9 Hz), 1.14 (3H, d, J = 6.9 Hz); HRMS calcd for $C_{22}H_{29}N_2O_3S$ (M + H) 401.1899, found 401.1904.

2-Acetylamino-3-(2-dimethylaminoethylsulfanyl)-*N*-[2-(4-hydroxyphenyl)ethyl]butyramide (2x). To a suspension of **1d** (0.10 g, 0.31 mmol) in MeOH (2.5 mL) was added 2-dimethylaminoethanethiol hydrochloride (2.19 g, 15.5 mmol) and Et_3N (2.19 mL, 15.5 mmol) followed by water (2.5 mL). The resulting solution was stirred at room temperature for 48 h. The reaction was then quenched with 1 N aq HCl (15 mL) and purified by C-18 reverse phase chromatography, eluting with 30−50% CH_3CN/H_2O containing 0.1% HCl, to give a solid. This was suspended in H_2O and filtered to yield pure **2x** as a white solid (0.0857 g, 63%): ^{1}H NMR (300 MHz $CDCl_3$) δ 8.18 (1H, t, J = 5.5 Hz), 7.80 (2H, dd, J = 6.9, 5.1 Hz), 7.54−7.40 (3H, m), 7.15 (1H, d, J = 8.8 Hz), 7.08 (1H, d, J = 8.4 Hz), 7.03 (1H, d, J = 8.4 Hz), 6.86 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 8.4 Hz), 5.01 (1H, dd, J = 8.8, 4.4 Hz), 4.59 (1H, dd, J = 6.2, 2.9 Hz), 3.67−3.52 (1H, m), 3.50−3.36 (1H, m), 3.33−3.22 (1H, m), 3.16−3.00 (1H, m), 2.94−2.89 (2H, m), 2.83−2.74 (2H, m), 2.39 (6H, s), 1.15 (3H, dd, J = 11.0, 7.3 Hz); HRMS calcd for $C_{23}H_{32}SN_3O_3$ (M + H) 430.2164, found 430.2163. Anal. Calcd for $C_{23}H_{31}N_3O_3S \cdot 0.02HCl \cdot 0.5H_2O$: C, 62.88; H, 7.35; N, 9.56; S, 7.30; Cl, 0.16. Found: C, 63.03; H, 7.58; N, 9.55; S, 7.59; Cl, 0.15.

Acknowledgment. We thank Dr. Gene Dubowchik for valuable suggestions in the preparation of this paper.

Supporting Information Available: Description of experimental procedures and analytical data for dehydroalanine amides (**1a**−**e**) and Michael adducts **3a**−**d**, ^{1}H NMR spectra for **1b**−**e**, **2g**, **2k**, **2q**, **2v**, **2w**, and **3a**−**d**, and the ^{13}C NMR spectrum for **2k**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034762Z