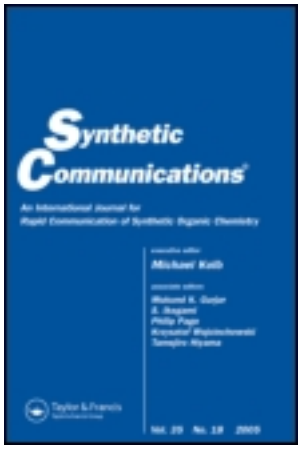
This article was downloaded by: [Georgetown University]
On: 13 September 2013, At: 11:53
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Thiol-Containing Amino Acids Through Alkylation of Glycinate Ketimine

Jian Zhi [a] , Yuli Xiao [a] & Aiguo Hu [a]

[a] Key Laboratory for Ultrafine Materials of Ministry of Education, School of Materials Science and Engineering, East China University of Science and Technology, Shanghai, China

Accepted author version posted online: 06 Sep 2011.Published online: 11 Nov 2011.

To cite this article: Jian Zhi , Yuli Xiao & Aiguo Hu (2012) Synthesis of Thiol-Containing Amino Acids Through Alkylation of Glycinate Ketimine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:6, 914-920, DOI: 10.1080/00397911.2010.533803

To link to this article: http://dx.doi.org/10.1080/00397911.2010.533803

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms &

Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [Georgetown University] at 11:53 13 September 2013

Synthetic Communications®, 42: 914–920, 2012
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.533803

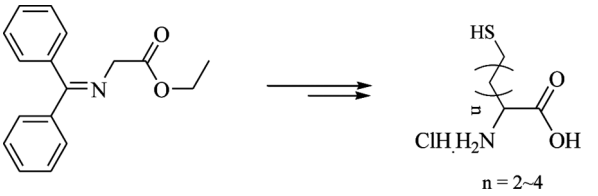
Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF THIOL-CONTAINING AMINO ACIDS THROUGH ALKYLATION OF GLYCINATE KETIMINE

Jian Zhi, Yuli Xiao, and Aiguo Hu

Key Laboratory for Ultrafine Materials of Ministry of Education, School of Materials Science and Engineering, East China University of Science and Technology, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *A general synthetic route for the synthesis of thiol-containing amino acids through alkylation of glycinate ketimine followed by hydrolysis was developed in this work. The common problems associated with the instability of ketimines and thioesters were solved by optimization of both synthetic and purification conditions. A series of thiol-containing amino acids were obtained in good yields. This method could be readily extended to the synthesis of other thiol-containing amino acids, which are important intermediates in pharmaceutical research and medical applications.*

Keywords Alkylation; ketimine; thiol-containing amino acids

Downloaded by [Georgetown University] at 11:53 13 September 2013

INTRODUCTION

Thiol-containing amino acids and their derivatives have been regarded as versatile tools that enable medicinal chemists and agrochemists to design new drugs and peptides. As a reactive member of natural amino acids, cysteine, the simplest thiol-containing amino acid, is commonly tapped as a nucleophile in enzyme active sites. Homocysteine, which has an additional methylene group, is an excitatory amino acid that markedly enhances the vulnerability of neuronal cells to excitotoxic and oxidative injury in vitro and in vivo.[1] Elevated plasma homocysteine (Hcy) levels in human blood are associated with great risk of venous and arterial thrombosis.[2] Thiotyrosine

Received August 19, 2010.

Address correspondence to Aiguo Hu, Key Laboratory for Ultrafine Materials of Ministry of Education, School of Materials Science and Engineering, East China University of Science and Technology, Shanghai 200237, China. E-mail: hagmhsn@ecust.edu.cn

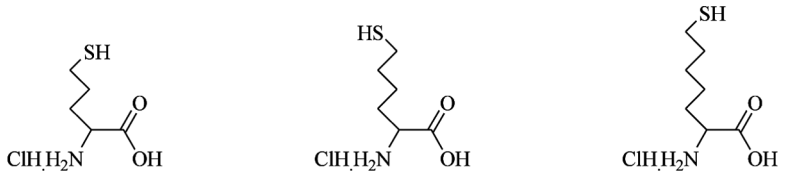
Downloaded by [Georgetown University] at 11:53 13 September 2013

derivatives, (*S*)-4′-mercaptophenylalanine (Tty) and 3-*N*-(4′-mercaptophenyl)-(*S*)-2,3-diaminoproprionate (Aty), have been prepared and incorporated into polyalanine peptides.[3] Upon photocleavage of the S-S bond, the peptide can then commence to fold into an α-helical conformation. Furthermore, thiol-containing amino acids are employed to synthesize cyclic peptides, which are applied to build peptide dendrimers.[4]

Several approaches have been reported for the synthesis of thiol-containing amino acids. Sano et al. reported a microbial transformation method for L-cysteine production using *Pesudomonas thiazolinophilum* (AJ3854).[5] Broxterman et al. successfully synthesized sulfur-containing trisfunctional amino acids by radical addition of thioacetic acid to unsaturated amino acids. The thioester moiety can be easily converted to a free mercapto group by hydrolysis.[6] Escher et al. have successfully obtained 4′-mercaptophenylalanine by chlorosulfonation of L-phenylalanine followed by tin–HCl reduction.[7] Most of these synthetic strategies were complex and difficult to control. All these methods are developed for preparation of specific thiol-containing amino acids, which limits their medical and biological application beyond laboratory synthesis. Thus, a simple, effective, and universal synthesis of thiol-containing amino acids with desired structure would meet the great demand of clinical and biochemical usage and so is of great interest.

Herein, we report a simple, mild, and general method for preparation of thiol-containing α-amino acids with diverse alkyl groups (Fig. 1). The procedure is based on the alkylation of a single starting material, benzophenone glycine ketimine (Schiff base) **1**, which is commercially available, with various alkylation agents. The alkylation products (i.e., thioester ketimines) can be easily hydrolyzed to obtain the final amino acids **4**. A number of higher homologs of glycine have been successfully prepared by this alkylation path,[8–10] however, synthesis of thiol-containing amino acids is difficult because of the susceptibility of thiol or thioester groups to the alkylation conditions, and a general synthetic strategy for thiol-containing amino acids through the alkylation route has not been reported yet. We employed ω-bromo-α-thioesters as the alkylation agents, and after incorporation of this moiety onto glycine ketimine starting material, the acetyl group was successfully cleaved through hydrolysis to give the desired amino acids.

ω-Bromo-α-thioesters were synthesized in good yields through reaction of commercially available α,ω-dibromoalkanes with thioacetic acid under basic conditions



2-amino-5-mercaptopentanoic acid hydrochloride — **4a**

2-amino-6-mercaptohexanoic acid hydrochloride — **4b**

2-amino-7-mercaptoheptanoic acid hydrochloride — **4c**

Figure 1. Structures of thiol-containing amino acids **4a**–**4c**.

Table 1. Alkylation of ketimines **1** with different bromoalkyl thioesters[a]

Entry	Alkylbromide	Solvent	Base	Yield[c]
1	**2a**	DMF	NaH	45
2	**2b**	DMF	NaH	62
3	**2c**	DMF	NaH	47
4	**2c**	Toluene	NaH	Trace
5	**2c**	Toluene	DBU[b]	Trace
6[d]	**2b**	DCM/Toluene	KOH	Trace

[a]Reactions were carried out at 40 °C (Entries 1–3), 110 °C (entry 4), 90 °C (entry 5) and 25 °C (entry 6).
[b]DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.
[c]Isolated yield.
[d]The alkylation was run under phase-transfer conditions with 50% aqueous KOH as base, dichloromethane (DCM) and toluene (7:3) as solvent, and tetrabutylammonium bromide as catalyst.

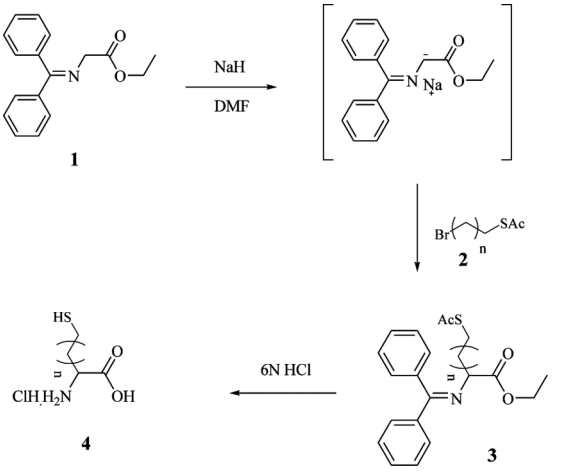
Downloaded by [Georgetown University] at 11:53 13 September 2013

and were isolated by fractional distillation. An initial trial on the synthesis of thiol-containing amino acids involved generation of an anionic synthon from **1** either in the presence of a strong base or under various phase-transfer conditions.[11,12] The anion was allowed to react with ω-bromo-α-thioesters to give α-substituted amino acids. The main disadvantage of this route is the instability of the thioesters groups toward aqueous basic conditions. A complex mixture was obtained after alkylation, which was difficult to purify because of the lability of the ketimine group during silica-gel chromatography.[13]

After screening several alkylation conditions (Table 1) to conquer these limitations and extend the scope and generality of the method, one approach developed by Ansari et al. was proven to be suitable for this purpose.[14] The ketimines **3** (benzophenone Schiff base) with an α-substituted alkyl thioester were obtained in good yields by adding 1.2 equivalents bromoalkyl thioester derivatives **2** in *N,N*-dimethylformamide (DMF) to a solution of **1** in DMF with sodium hydride (NaH) as base. The reaction processed smoothly at 40 °C. To avoid hydrolysis of ketimine intermediates on silica gel, Florisil, as the neutral adsorbent, was used in the flash chromatography. After these treatments, pure intermediates **3** were obtained and characterized with NMR and high-resolution mass spectroscopy (HR-MS). The ketimine protecting group as well as the thioester group at the end of the alkyl chain were successfully hydrolyzed by refluxing with 6 N HCl under a nitrogen atmosphere, and the amino acids with a thiol group were obtained in quantitative yields (Scheme 1).

The structures of **4a–4c** were confirmed with ^{1}H NMR, ^{13}C NMR and MS analysis. The free thiol groups (-SH) are visible in the 1.6–2.1 ppm region as triplets or multiplets, which is consistent with literature data in similar structures.[15] ^{13}C NMR spectra showed the resonance of carboxyl group at ca. δ 170 ppm, that of the α-carbon at 53 ppm, and the methylene group adjacent to the thiol group for all the products. Other methylene groups appeared between 23 and 30 ppm. All the spectra were clean, indicative of complete removal of both ketimine and thioester protection groups. Molecular ion peaks were found in the MS for all these products, and all were in good agreement with predicted patterns in MS, which further confirmed the structures of **4a-4c**.

All the alkylation reactions were conducted with slight excess (1.2–1.5 eq.) of **2a–2c** and monitored with thin-layer chromatography (TLC). It was found that even



Scheme 1. Synthesis of α-substituted thiol-containing amino acids **4a–4c**, wherein n = 2 to 4.

after prolonged reaction time, no dialkylation product was observed. We speculated that the second alkylation was hindered by the steric effect. Thus, to facilitate the purification of thiol-containing ketimines on column chromatography, a large excess of **2a–2c** was used to guarantee full conversion of **1**.

In conclusion, we have developed an effective and general synthesis of thiol-containing amino acids through alkylation of a glycinate ketimine followed by hydrolysis. The present method is a new route for the synthesis of amino acid derivatives with thiol groups. This method could be readily extended to the synthesis of other thiol-containing amino acids with desired structures, which have fascinating applications in biology and gene chemistry.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled over Na under nitrogen prior to use. *N,N*-Dimethylformamide (DMF) was dried over 4 Å molecular sieves and distilled under vacuum. Column chromatography was performed with Florisil (200–300 mesh). TLC analysis was performed on 0.25 mm thick silica gel plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 FT-NMR spectrometer in $CDCl_3$ or D_2O. Mass spectra were generated with Micromass LCT (ESI-TOF). FTIR was recorded from KBr pallets for solid samples or neat for liquid samples on a Nicolet Magna 5700 FTIR spectrometer. Ethyl *N*-(diphenylmethylene) glycinate (**1**) was prepared according to the literature procedure.[13]

ω-Bromo-α-thioesters 2a–2c

Thioacetic acid (3-bromopropyl) ester (2a). This compound was prepared according to the literature procedure with minor modification.[16] Thioacetic acid (8.28 g, 7.77 ml, 0.11 mol) was added to a solution of KOH (6.21 g, 0.11 mol) in

Downloaded by [Georgetown University] at 11:53 13 September 2013

dry, degassed THF (60 ml) containing 1,3-dibromopropane (12.24 ml, 0.12 mol). The mixture was stirred under nitrogen overnight at room temperature. The mixture was then concentrated and 13.71 g of **2a** was obtained after fraction distillation as a light yellow oil (bp 110–120 °C, 1.5 mmHg, 58% yield). ^{1}H NMR ($CDCl_3$, δ): 2.05 (t, $J = 6.8$ Hz, 2H), 2.27 (s, 3H), 2.93 (t, $J = 6.9$ Hz, 2H), 3.38 (t, $J = 6.5$ Hz, 2H).

Thioacetic acid (4-bromobutyl) ester (2b)[17]. Following the same procedure, **2b** was obtained after distillation as a light yellow oil (bp 80–90 °C, 1.0 mmHg, 43% yield). ^{1}H NMR ($CDCl_3$, δ): 1.66–1.73 (m, 2H), 1.84–1.92 (m, 2H), 2.29 (s, 3H), 2.86 (t, $J = 7.2$ Hz, 2H), 3.37 (t, $J = 6.6$ Hz, 2H).

Thioacetic acid (5-bromopentyl) ester (2c). Following the same procedure, **2c** was obtained after distillation as a light yellow oil (bp 110–115 °C, 1.0 mmHg, 62% yield). ^{1}H NMR ($CDCl_3$, δ): 1.51–1.56 (m, 2H), 1.58–1.64 (m, 2H), 1.89 (t, $J = 7.2$ Hz, 2H), 2.34 (s, 3H), 2.89 (t, $J = 7.2$ Hz, 2H), 3.41 (t, $J = 6.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$, δ): 27.29, 28.74, 28.83, 30.67, 32.19, 33.46, 196.86. IR (thin film): 2934.9, 2859.1, 1691.4, 1432.9, 1353.4, 1134.4 cm^{-1}. HRMS (ESI) calcd. for $C_7H_{13}BrOS$ (M^+) 223.9870, found 223.9874.

Glycine Ketimine 1

A solution of **1** (1.0 g, 3.75 mmol) in dry DMF (5 ml) was added to a stirred suspension of NaH (0.098 g, 4.1 mmol; 60% oil dispersion) in 15 ml dry DMF under nitrogen. The mixture was stirred gently at 40 °C for 30 min. The flask was removed from the heating bath, and a solution of ω-bromo-α-thioester (4.5 mmol, 1.2 eq) dissolved in a minimum amount of DMF was slowly added. After the addition, the reaction mixture was gently stirred until the starting material disappeared (checked by TLC). The reaction was stopped, and a small quantity of ethanol (2 mL) was added to destroy unreacted NaH. The solution was concentrated, and the residue was partitioned between water and ether. The ether fraction was dried ($MgSO_4$), filtered, and concentrated to yield a yellow liquid. Flash chromatography on Florisil gave monoalkylated Schiff bases (**3a–c**).

Ethyl 5-(acetylthio)-2-((diphenylmethylene)amino)pentanoate (3a). Flash chromatography (5% ethyl acetate–petroleum ether) gave a pale yellow oil **3a**, 0.65 g, 45% yield. ^{1}H NMR ($CDCl_3$, δ): 1.26–1.31 (m, 5H), 1.99 (q, $J = 7.4$ Hz, 2H), 2.32 (s, 3H), 2.83 (t, $J = 7.2$ Hz, 2H), 4.06 (t, $J = 6.49$ Hz, 1H), 4.17–4.22 (m, 2H), 7.18–7.69 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 14.23, 26.04, 28.89, 30.63, 32.74, 60.96, 64.88, 128.83, 131.03, 139.02, 170.75, 172.01, 192.21, 195.72. IR (thin film): 3058.6, 2932.8, 2858.1, 1738.0, 1690.8, 1623.7, 1445.4, 1353.4, 1278.8, 1184.6, 1135.9, 700.9, 629.0 cm^{-1}. HRMS (ESI) calcd. for $C_{22}H_{25}NO_3S$ (M^+) 383.1555, found 383.1553.

Ethyl 6-(acetylthio)-2-((diphenylmethylene)amino)hexanoate (3b). Flash chromatography (5% ethyl acetate–petroleum ether) gave a light yellow oil **3b**, 0.92 g, 62% yield. ^{1}H NMR ($CDCl_3$, δ): 1.26–1.30 (m, 5H), 1.52 (m, 2H), 1.94 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 3H), 2.84 (t, $J = 7.3$ Hz, 2H), 4.05 (t, $J = 6.5$ Hz, 1H), 4.15–4.24 (m, 2H), 7.17–7.72 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 14.25, 25.21, 28.91, 29.29, 30.62, 33.11, 60.89, 65.25, 128.76, 131.22, 139.13, 170.54, 172.25, 192.54, 195.89. IR (thin

Downloaded by [Georgetown University] at 11:53 13 September 2013

film): 3061.5, 2925.0, 2854.4, 1736.9, 1691.0, 1448.0, 1361.4, 1277.5, 1184.6, 1135.3, 700.1, 628.8 cm^{-1}. HRMS (ESI) calcd. for $C_{23}H_{27}NO_3S$ (M^+) 397.1712, found 397.1703.

Ethyl 7-(acetylthio)-2-((diphenylmethylene)amino)heptanoate (3c). Flash chromatography (5% ethyl acetate–petroleum ether) gave light yellow oil **3c**, 0.73 g, 47% yield. ^1H NMR ($CDCl_3$, δ): 1.24–1.27 (m, 7H), 1.52 (m, 2H), 1.91 (q, $J = 7.0$ Hz, 2H), 2.29 (s, 3H), 2.81 (t, $J = 7.3$ Hz, 2H), 4.02 (t, $J = 6.5$ Hz, 1H), 4.15–4.20 (m, 2H), 7.17–7.70 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 14.26, 25.53, 28.54, 29.04, 29.39, 30.64, 33.47, 60.82, 65.35, 128.73, 131.22, 139.09, 170.34, 172.36, 192.53, 195.89. IR (thin film): 3058.6, 2932.4, 2857.8, 1736.5, 1691.0, 1446.2, 1355.0, 1278.0, 1135.4, 701.2, 628.7 cm^{-1}. HRMS (ESI) calcd. for $C_{24}H_{29}NO_3S$ ($M^+ + K$) 450.1505, found 450.1501.

Downloaded by [Georgetown University] at 11:53 13 September 2013

Hydrolysis

Schiff bases **3a–c** (2 mmol) were suspended in 6 N HCl. The mixture was refluxed under nitrogen overnight, cooled, and washed several times with ether, and the layers were separated. The water fraction was concentrated to yield **4a–c**.

2-Amino-5-mercaptopentanoic acid hydrochloride (4a). White powder, 0.372 g, 100% yield. ^1H NMR (D_2O, δ): 1.59–1.72 (m, 2H), 1.92–2.01 (m, 2H), 2.13 (m, 1H), 2.51 (t, $J = 6.9$ Hz, 3H), 3.98 (t, $J = 6.3$ Hz, 1H). ^{13}C NMR (D_2O, δ): 23.01, 28.40, 40.03, 52.56, 169.86. IR (KBr): 3180.7, 2931.6, 2550.0, 1737.4, 1633.9, 1503.5, 1450.8, 1220.1, 1124.0, 1007.7 cm^{-1}. HRMS (ESI) calcd. for $C_5H_{11}NO_2S$ ($M^+ + H$) 150.0588, found 150.0560.

2-Amino-6-mercaptohexanoic acid hydrochloride (4b). White powder, 0.396 g, 100% yield. ^1H NMR (D_2O, δ): 1.39–1.47 (m, 2H), 1.55–1.56 (m, CH_2, 2H), 1.58 (m, 1H), 1.81–1.91 (m, 2H), 2.47 (t, $J = 6.7$ Hz, 2H), 3.99 (t, $J = 5.9$ Hz, 1H). ^{13}C NMR (D_2O, δ): 22.81, 23.18, 29.12, 32.27, 52.77, 172.09. IR (KBr): 3000.3, 2958.8, 2536.6, 1737.6, 1581.7, 1495.6, 1461.3, 1206.6, 1129.8, 1018.5 cm^{-1}. HRMS (ESI) calcd. for $C_6H_{13}NO_2S$ ($M^+ + H$) 164.0745, found 164.0688.

2-Amino-7-mercaptoheptanoic acid hydrochloride (4c). White powder, 0.428 g, 100% yield. ^1H NMR (D_2O, δ): 1.31–1.36 (m, 4H), 1.53 (q, $J = 6.7$ Hz, 2H), 1.62 (t, $J = 7.3$ Hz, 1H), 1.87 (m, 2H), 2.46 (t, $J = 7.0$ Hz, 2H), 3.99 (t, $J = 6.2$ Hz, 1H). ^{13}C NMR (D_2O, δ): 23.50, 26.87, 29.56, 32.46, 52.85, 172.25. IR (KBr): 3056.4, 2932.1, 2531.1, 1737.9, 1640.9, 1599.3, 1498.1, 1449.1, 1217.9, 1122.2, 1009.2 cm^{-1}. HRMS (ESI) calcd. for $C_7H_{15}NO_2S$ ($M^+ + H$) 178.0901, found 178.0858.

ACKNOWLEDGMENT

This work was supported by the National Special Fund for State Key Laboratory of Bioreactor Engineering of China (2060204).

REFERENCES

1. Kruman, I. I.; Culmsee, C.; Chan, S. L.; Lruman, Y.; Guo, Z.; Penix, L.; Mattson, M. P. Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J. Neurosci.* **2000**, *20*, 6920.
2. Lauricella, A. M.; Quintana, I. L.; Kordich, L. C. Effects of homocysteine thiol group on fibrin networks: Another possible mechanism of harm. *Throm. Res.* **2002**, *107*, 75.
3. Lu, H. S. M.; Volk, M.; Kholodenko, Y.; Gooding, E.; Hochstrasser, R. M.; DeGrado, W. F. Aminiothiotyrosine disulfide, an optical trigger for initiation of protein folding. *J. Am. Chem. Soc.* **1997**, *119*, 7173.
4. Zhang, L.; Tam, J. P. Synthesis and application of unprotected cyclic peptides as building blocks for peptide dendrimers. *J. Am. Chem. Soc.* **1997**, *119*, 2363.
5. Sano, K.; Yokozeki, K.; Tamura, F.; Yasuda, N.; Noda, I.; Mitsugi, K. Microbial conversion of D,L-2-amino-delta^2-thiazoline-4-carboxylic acid to L-cysteine and L-cystine: Screening of microorganisms and identification of products. *Appl. Environ. Microbiol.* **1977**, *34*, 806.
6. Broxterman, Q. B.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. Synthesis of (optically active) sulfur-containing trifunctional amino acids by radical addition to (optically active) unsaturated amino acids. *J. Org. Chem.* **1992**, *57*, 6286.
7. Escher, E.; Bernier, M.; Parent, P. Angiotensin II analogues, part II. Synthesis and incorporation of the sulfur-containing aromatic amino acids: L-(4-SH)Phe, L-(4-SO_2NH_2)Phe, L-(4-SO_3-)Phe, and L-(4-S-CH_3)Phe. *Helv. Chim. Acta* **1983**, *66*, 1355.
8. Hoppe, D. Chain-extended and α-branched a-amino acids by alkylation of metalated α-[(bis alkythio) methylene amino] acid esters. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 426.
9. Yamada, S.-I.; Oguri, T.; Shioiri, T. Asymmetric synthesis of α-amino acid derivatives by alkylation of a chiral Schiff base. *J. Chem Soc., Chem. Commun.* **1976**, 136.
10. Stork, G.; Leong, A. Y. W.; Touzin, A. M. Alkylation and Michael additions of glycine ethyl ester. Use in α-amino acid synthesis and as acyl carbanion equivalent. *J. Org. Chem.* **1976**, *41*, 3491.
11. Bey, P.; Vevert, J. P.; Doesselaer, V. V.; Kolb, M. Direct synthesis of α-halogenomethyl-α-amino acids from the parent α-amino acids. *J. Org. Chem.* **1979**, *44*, 2732.
12. Yamashita, T.; Mitsui, H.; Watanabe, H.; Nakamura, N. The enantioface differentiating methylation of the N-benzylidene-DL-phenylalanine methyl ester in the presence of chiral lithium amides. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 961.
13. O'Donnell, J. M.; Boniece, J. M.; Earp, S. E. The synthesis of amino acids by phase transfer reactions. *Tetrahedron Lett.* **1978**, 2641.
14. Ansari, A. M.; Ugwu, S. O. Efficient synthesis of α-substituted amino acid ester: Alkylation and hydrogenation removal of Schiff's base protecting group. *Synth. Commun.* **2008**, *38*, 2330.
15. Takoi, K.; Degueil, M.; Shinkaruk, S.; Thibon, C.; Maeda, K.; Ito, K.; Bennetau, B.; Dubourdieu, D.; Tominaga, T. Identification and characteristics of new volatile thiols derived from the hop (*Humulus luplus* L.) cultivar Nelson Sauvin. *J. Agric. Food. Chem.* **2009**, *57*, 2493.
16. Block, E.; Dikarer, E. V.; Glass, R. S.; Jin, J.; Li, B.; Li, X. J.; Zhang, S.-Z. Synthesis, structure, and chemistry of new, mixed group 14 and 16 heterocycles: Nucleophile-induced ring contraction of mesocyclic dications. *J. Am. Chem. Soc.* **2006**, *128*, 14949.
17. Savarin, C.; Srogl, J.; Liebeskind, L. S. Thiol ester−boronic acid cross-coupling: Catalysis using alkylative activation of the palladium thiolate intermediate. *Org. Lett.* **2000**, *2*, 3229.

Downloaded by [Georgetown University] at 11:53 13 September 2013