Amino Acids (2009) 37:603–607
DOI 10.1007/s00726-008-0179-6

ORIGINAL ARTICLE

Facile syntheses of L-β-haloalanine derivatives from L-cysteine or L-cystine

Feiyan Tao · Yinggang Luo · Qingchun Huang · Yan Liu · Bogang Li · Guolin Zhang

Received: 1 August 2008 / Accepted: 1 September 2008 / Published online: 5 October 2008

Abstract L-β-Haloalanines are physiologically active unnatural amino acids and they are useful intermediates for the synthesis of natural and unnatural amino acids, *S*-linked glycopeptides, and lanthionines. In general L-β-haloalanines were prepared predominantly from L-serine via functional group transformation. Here we reported an alternative approach for the preparation of L-β-haloalanines via halogenation of protected L-cysteine esters which was obtained from L-cysteine or L-cystine, respectively. The mercapto group of protected L-cysteine esters was efficiently transformed to halo groups by triphenylphosphine/*N*-halosuccinimides. It has been proved to be a versatile desulfurization strategy via this functional group transformation.

Keywords L-β-Haloalanine · Cysteine · Cystine · Halogenation · Desulfurization · Functional group transformation

Introduction

Optical active unnatural amino acids play important roles in living organisms. Thus the development of novel methods for synthesizing these unnatural amino acids is of great interest for organic chemists and medicinal chemists (Williams 1989). L-β-Haloalanines are physiologically active unnatural amino acids and they are important intermediates for the syntheses of natural and unnatural amino acids, medicines and pesticides owing to their further functionality (Soper et al. 1977). Incorporation of these unnatural amino acids into peptides or non-peptides plays an important role in peptide ligand-receptor interaction and also has a crucial role in the rational design of bioactive peptides and their non-peptide mimetics. In general, L-β-haloalanines were prepared by chemical synthesis from L-serine (Fisher and Raske 1907), and optical resolution and preferential crystallization of racemic β-chloroalanine (Inoue and Murayama 1986; Ohoka et al. 1987). L-β-Chloroalanine can also be chemicoenzymatically prepared from the reductive amination of 3-chloropyruvate catalyzed by alanine dehydrogenase (Kato et al. 1993). The peptides containing β-chloroanaline were also readily prepared on resin by converting a protected hydroxyl group of serine to a chloro group with triphenylphosphine dichloride and the following intramolecular substitution of the chloro group of β-chloroanaline with the thiol group of cysteine offers thioether linked peptides which were widely utilized as a stable disulfide surrogate to replace the native disulfide bridges of bioactive cyclic peptides, such as hormones, neurotransmitters, and neuromodulators, to prolong their biological activities (Yu et al. 1998). β-Bromoalanine derivatives were used to prepare lanthionines which are a group of non-standard amino acids consists of two alanines linked by a thioether bridge (Zhu and Schmidt 2003). *S*-Linked glycopeptides, naturally occurring *O*-glycosidic or *N*-glycosidic peptides modified by the replacement of the anomeric oxgen by sulfur, were also efficiently prepared from β-bromoalanine and γ-bromohomoalanine which were generated directly by bromination of serine and homoserine residues, respectively (Zhu and Schmidt 2004). The bromine group of the bromoalanine-containing peptides was displaced by a thiol

F. Tao · Y. Luo (✉) · Q. Huang · Y. Liu · B. Li · G. Zhang
Center for Natural Products Research,
Chengdu Institute of Biology,
Chinese Academy of Sciences,
610041 Chengdu, People's Republic of China
e-mail: yinggluo@cib.ac.cn

group of the sulfur-containing lipid to synthesize *S*-farnesylated and *S*-palmitoylated peptides via S_N2 displacement (Pachamuthu et al. 2005).

All of these chemical syntheses of haloalanine derivatives were prepared from serine residue. From structural view, L-cysteine is a thiol analogue of L-serine which contains a hydroxyl group. L-Cysteine is known to be biosynthesized by the sequential reaction of two enzymes, serine acetyltransferase and *O*-acetylserine (thiol) lyase, using L-serine as the starting material (Wirtz and Hell 2006). These biochemical reactions are irreversible in vivo (http://www.genome.ad.jp/kegg/pathway/map/map00272.html). In continuation of our studies on the convenient preparation of unnatural amino acids (Tao et al. 2004), we envisioned that the mercapto group of L-cysteine can be displaced by other groups via functional group transformation to give unnatural amino acids. The mercapto group of thiols were efficiently converted to alkyl halides in high to excellent yields when treated with triphenylphosphine (Ph_3P)/*N*-halosuccinimide (NXS, halogen: Br, Cl, and I) (Iranpoor et al. 2001), Ph_3P/2,3-dichloro-5,6-dicyanobenzoquinone (Iranpoor et al. 2002), sulfuryl chloride/Ph_3P (Still et al. 1982), Ph_3P/iodine (Oae and Togo 1981), chlorocarbonylsulphenyl chloride/Ph_3P (Clive and Denyer 1972), or Ph_3P/carbon tetrachloride (Weiss and Snyder 1968). However there is no report on the formation of haloamino acid derivatives using these simple, mild, and efficient methods for the conversion of thiols to alkyl halides because of the much more polarity of sulfur-containing amino acids. Herein we reported the results of an alternative approach to prepare haloalanines via halogenation of protected L-cysteine esters using L-cysteine or L-cystine as starting materials, respectively. The mercapto group of protected L-cysteine esters was efficiently transformed to halo groups by triphenylphosphine/*N*-halosuccinimides. It has been proved to be a versatile desulfurization strategy via this functional group transformation.

Materials and methods

General

Melting points were recorded on an X-6 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer Spectrum One spectrometer using KBr disc and ν_{max} is given in cm^{-1}. NMR spectra were recorded on a Bruker Avance 600 spectrometer (^1H NMR: 600 MHz; ^{13}C NMR: 150 MHz) at room temperature. The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard and the coupling constants (*J*) are given in Hz. ESIMS spectra were obtained on a Bio TOF IIIQ mass spectrometer. Optical rotations were record on Perkin Elmer 341 automatic polarimeter at 20°C. Column chromatography (CC) was performed on self-packed open column with silica gel (200–300 mesh) from Qingdao Ocean Chemical Engineering Company (QOCEC). TLC analyses were carried out on plates precoated with 10–40 μ of silica gel GF254 from QOCEC and were visualized under an ultraviolet lamp, by spraying 8% phosphomolybdic acid-ethanol solution (w/v), 5% vanillin-H_2SO_4 (w/v), or ninhydrin solution followed by heating, or by iodine (I_2).

All reagents were purchased commercially and used without purification. Anhydrous solvents were prepared according to the standard protocols for purification of laboratory chemicals (Armarego and Chai 2003).

*Preparation of Boc-Cys-OMe (**3a**, R = Me, P = Boc)*

Boc-Cys-OMe was prepared successfully from cysteine (**1**) according to the reported procedures (Cowling 1975; Threadgill and Gledhill 1989).

*Preparation of Fmoc-Cys-OEt (**3b**, R = Et, P = Fmoc)*

Fmoc-Cys-OEt was obtained from cystine (**4**) according to the reported procedures (Benoiton 1968; Carpino and Han 1972; Krajewski et al. 2003; Kelleman et al. 2003; Swali et al. 2002).

*Preparation of Cbz-Cys-OEt (**3c**, R = Et, P = Cbz)*

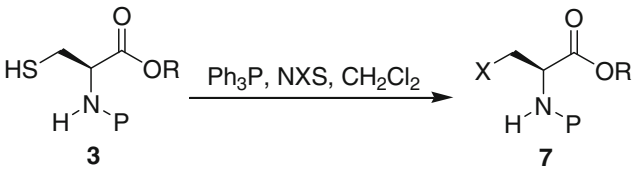
Cbz-Cys-OEt was successfully prepared by the reported procedures from cystine (**4**) (Benoiton 1968; Olsen et al. 1985).

General procedures for the preparation of L-β-haloalanine derivatives

The haloalanine derivatives (**7**) were prepared according to Iranpoor et al. (2001) with some modifications. To the solution of NXS (0.28 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Ph_3P (84 mg, 0.32 mmol) with stirring at room temperature. To this halogenating reagents mixture, *N*-protected cysteine esters **3** (0.2 mmol) was added and the reaction mixture was stirred at appropriate temperature (for the exact temperature, see Table 1). After completion of the reaction on the basis of TLC analysis, the reaction mixture was filtered to remove the solid. The solvent of the filtrate was evaporated under reduced pressure to give a residue which was separated by flash chromatography over silica gel using petroleum ether and ethyl acetate as eluent to give the title compounds.

L-N-Boc-β-chloroalanine methyl ester (**7a**, entry 1 in Table 1): white solid, m. p. 59–60°C, $[\alpha]_D^{20} = +39.2$ (*c* 0.5,

Table 1 Coversion of the mercapto group to halo groups by triphenylphosphine/*N*-halosuccinimides



3 7

Entry	Substrate **3**		Product **7**			Reaction time (h)	Reaction temperature	Isolated yield (%)
	R	P	R	P	X			
1	Me	Boc	Me	Boc	Cl	12	r. t.	83.0
2			Me	Boc	Br	6	r. t.	39.0[a]
3	Et	Fmoc	Et	Fmoc	Cl	48	r. t.	80.0
4			Et	Fmoc	Br	22	r. t.	71.0[b]
5	Et	Cbz	Et	Cbz	Cl	4	Reflux	84.7
6			Et	Cbz	Br	12	Reflux	76.2[b]

[a] This low isolated yield may be due to the instability of *N*-Boc-bromoalanine in the process of separation over silica gel

[b] The large protection group such as Fmoc may decrease the lability of bromoalanine on silica gel (Couturier et al. 2006), thus the yields of Fmoc or Cbz-protected bromoalanine are higher than that of Boc-protected bromoalanine

$CHCl_3$) ($[\alpha]_D^{21}$= + 37.8 (*c* 1.5, $CHCl_3$) from Kenworthy et al. 2004). ^{1}H NMR ($CDCl_3$): δ 5.42 (1H, brs), 4.71 (1H, m), 3.97 (1H, dd, *J* = 11.1, 2.0 Hz), 3.85 (1H, dd, *J* = 11.1, 2.8 Hz), 3.81 (3H, s), and 1.46 (9H, s). ESIMS (positive mode): *m/z* 260 ($[M_{Cl}^{35} + Na]^+$) and 262 ($[M_{Cl}^{37} + Na]^+$). IR ν_{max}: 3,436, 2,980, 1,716, 1,634, 1,508, 1,369, 1,167, and 1,064 cm^{-1}. The NMR data are in accordance with those reported (Kenworthy et al. 2004).

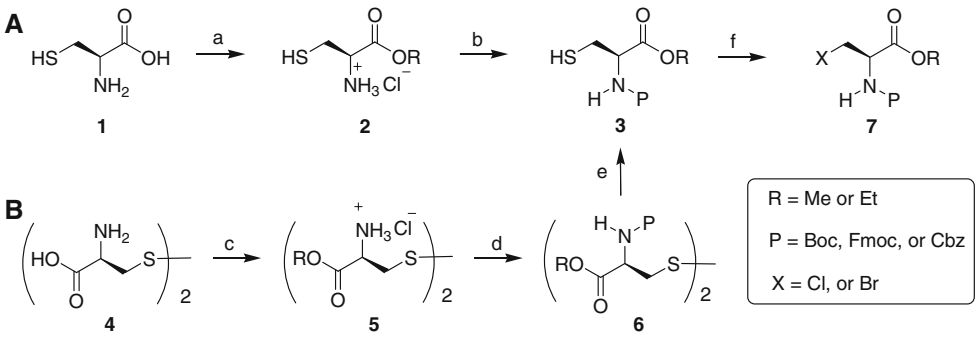
L-N-Boc-β-bromoalanine methyl ester (**7b**, entry 2 in Table 1): white solid, m. p. 48–50°C, $[\alpha]_D^{20}$ = + 21.3 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 5.40 (1H, brs), 4.75 (1H, m), 3.83 (1H, m), 3.80 (3H, s), 3.71 (1H, dd, *J* = 9.2, 3.0 Hz), and 1.46 (9H, s). ESIMS (positive mode): *m/z* 304 ($[M_{Br}^{79} + Na]^+$) and 306 ($[M_{Br}^{81} + Na]^+$). IR ν_{max}: 3,436, 2,928, 1,717, 1,632, 1,502, 1,369, and 1,166 cm^{-1}. The NMR data are in accordance with those reported (Savithri et al. 1996).

L-N-Fmoc-β-chloroalanine ethyl ester (**7c**, entry 3 in Table 1): white solid, m. p. 126–127°C, $[\alpha]_D^{20}$ = + 21.4 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.77 (2H, d, *J* = 7.7 Hz), 7.61 (2H, m), 7.43 (2H, m), 7.32 (2H, m), 5.72 (1H, d, *J* = 7.3 Hz,), 4.75 (1H, m), 4.41 (2H, d, *J* = 7.2 Hz), 4.31 (2H, q, *J* = 7.1 Hz), 4.25 (1H, t, *J* = 7.2 Hz), 4.00 (1H, dd, *J* = 11.4, 3.0 Hz), 3.91 (1H, dd, *J* = 11.4, 3.0 Hz), and 1.32 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 168.7, 155.6, 143.8, 143.6, 141.3, 127.8, 127.1, 125.1, 120.0, 67.4, 62.4, 54.9, 47.1, 45.3, and 14.1. ESIMS (positive mode): *m/z* 396 ($[M_{Cl}^{35} + Na]^+$) and 398 ($[M_{Cl}^{37} + Na]^+$). IR ν_{max}: 3,436, 3,315, 2,931, 1,748, 1,688, 1,529, 1,383, 1,345, 1,260, 1,215, 1,104, 1,032, and 736 cm^{-1}. HRESIMS (positive mode): calcd for $C_{20}H_{20}ClNO_4$ *m/z* ($[M_{Cl}^{35} + Na]^+$) 396.0973, found 396.0978, error −1.14 ppm.

L-N-Fmoc-β-bromoalanine ethyl ester (**7d**, entry 4 in Table 1): white solid, m. p. 125–126°C, $[\alpha]_D^{20}$ = + 38.8 (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.77 (2H, d, *J* = 7.6 Hz), 7.61 (2H, d, *J* = 6.0 Hz), 7.41 (2H, t, *J* = 7.6 Hz), 7.33 (2H, td, *J* = 7.3, 2.0 Hz), 5.71 (1H, d, *J* = 7.1 Hz), 4.79 (1H, t, *J* = 4.0 Hz), 4.42 (2H, q, *J* = 7.2 Hz), 4.29 (3H, m), 3.84 (1H, dd, *J* = 10.4, 3.0 Hz), 3.76 (1H, dd, *J* = 10.4, 3.0 Hz), and 1.33 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 168.8, 155.5, 143.8, 143.6, 141.3, 127.8, 127.1, 125.1, 120.0, 67.4, 62.4, 54.3, 47.1, 33.8, and 14.2. ESIMS (positive mode): *m/z* 440 ($[M_{Br}^{79} + Na]^+$) and 442 ($[M_{Br}^{81} + Na]^+$). IR ν_{max}: 3,432, 3,327, 2,930, 1,728, 1,703, 1,538, 1,449, 1,277, 1,182, 1,153, 1,090, 1,031, and 756 cm^{-1}. HRESIMS (positive mode): calcd for $C_{20}H_{20}BrNO_4$ *m/z* ($[M_{Br}^{79} + Na]^+$) 440.0468, found 440.0467, error 0.26 ppm.

L-N-Cbz-β-chloroalanine ethyl ester (**7e**, entry 5 in Table 1): white solid, m. p. 55–56°C, $[\alpha]_D^{20}$ = + 32.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.31–7.37 (5H, m), 5.68 (1H, d, *J* = 5.8 Hz), 5.14 (2H, s), 4.74 (1H, t, *J* = 3.7 Hz), 4.27 (2H, q, *J* = 7.2 Hz), 3.99 (1H, dd, *J* = 11.0, 2.4 Hz), 3.89 (1H, dd, *J* = 11.0, 2.8 Hz), and 1.30 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 168.8, 155.6, 136.0, 128.6, 128.3, 128.1, 67.3, 62.3, 54.9, 45.3, and 14.1. ESIMS (positive mode): *m/z* 308 ($[M_{Cl}^{35} + Na]^+$) and 310 ($[M_{Cl}^{37} + Na]^+$). IR ν_{max}: 3,331, 2,978, 2,926, 1,746, 1,693, 1,527, 1,350, 1,329, 1,269, 1,219, 1,074, 1,038, 923, 780, 733, 697, 582, and 522 cm^{-1}. HRESIMS (positive mode): calcd for $C_{13}H_{16}ClNO_4$ *m/z* ($[M_{Cl}^{35} + Na]^+$) 308.0660, found 308.0649, error 3.58 ppm.

L-N-Cbz-β-bromoalanine ethyl ester (**7f**, entry 6 in Table 1): white solid, m. p. 68–69°C, $[\alpha]_D^{20}$ = + 43.2 (*c* 0.7,



Scheme 1 Reaction reagents and conditions: **a** MeOH, HCl (gas), reflux, 75%; **b** $(Boc)_2O$, NEt_3, CH_2Cl_2, 97%; **c** EtOH, $SOCl_2$, reflux, 94.6%; **d** for Cbz-protected **6**: Cbz-Cl, $NaHCO_3$, 86%; for Fmoc-protected **6**: Fmoc-OSu, Na_2CO_3, 82.5%; **e** Zn, HOAc, 98.6% for Cbz-protected **3**; 97.7% for Fmoc-protected **3**; **f** Ph_3P, NXS, CH_2Cl_2

$CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.32–7.37 (5H, m), 5.68 (1H, d, J = 6.0 Hz), 5.14 (2H, s), 4.78 (1H, t, J = 3.7 Hz), 4.27 (2H, q, J = 6.6 Hz), 3.83 (1H, dd, J = 10.8, 3.1 Hz), 3.75 (1H, dd, J = 10.8, 3.1 Hz), and 1.31 (3H, t, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 168.8, 155.6, 136.0, 128.6, 128.3, 128.1, 67.3, 62.4, 54.3, 33.8, and 14.2. ESIMS (positive mode): m/z 352 ($[M^{79}_{Br} + Na]^+$) and 354 ($[M^{81}_{Br} + Na]^+$). IR ν_{max}: 3,337, 2,977, 2,915, 1,743, 1,693, 1,525, 1,367, 1,348, 1,319, 1,217, 1,074, 1,034, 779, 738, 697, 577, and 490 cm^{-1}. HRESIMS (positive mode): calcd for $C_{13}H_{16}BrNO_4$ m/z ($[M^{79}_{Br} + Na]^+$) 352.0155, found 352.0155, error −0.06 ppm.

Results and discussion

The key intermediate **3**, *N*-protected L-cysteine esters, can be obtained from L-cysteine (**1**) or L-cystine (**4**), respectively (Routes A and B, Scheme 1). Based on the known procedure of Cowling, esterification of L-cysteine catalyzed by HCl (gas) in methanol offers the amino ester **2** in high yield (Cowling 1975). The amino group of **2** was protected in high yield according to Threadgill et al. (Threadgill and Gledhill 1989) to offer the desired protected L-cysteine esters **3** (Route A, Scheme 1). The *N*-protected L-cysteine esters **3** also can be prepared from L-cystine (**4**) (Route B, Scheme 1). Esterification of **4** affords the desired product **5** in high yields (Benoiton 1968). *N*-Cbz-protected **6** was obtained from **5** based on the procedure of Benoiton (1968). Whereas Fmoc-protected **6** was prepared from **5** based on the reported procedures (Carpino and Han 1972; Krajewski et al. 2003; Kelleman et al. 2003; Swali et al. 2002). Reduction of the disulfide ether **6** gave the expected *N*-protected L-cysteine esters **3** in high yields (Olsen et al. 1985).

With the protected L-cysteine esters **3** in our hands, we tried the functional group transformation from mercapto group to halo groups using the known halogenating reagents mentioned above. The protected L-cysteine ester **3a** (R = OMe, P = Boc) was reacted with different halogenating reagents. To our surprise and delight the halogenated L-alanine **7a** (R = OMe, P = Boc) was obtained in high yield using the complex of triphenylphosphine/*N*-halosuccinimides as halogenating reagent (entry 1, Table 1). The optical rotation of **7a** was in good agreement with the published value, which suggested that no racemization happened in the reaction and work-up processes. To expand and validate this functional group transformation, the L-cysteine esters **3** with various protected groups were prepared in high yields. All these protected L-cysteine esters **3** were converted to corresponding halogenated alanine derivatives **7** in high yields (entries 1 and 3–6, Table 1) except in the case of entry 2 (Table 1). This low isolated yield of entry 2 may be due to the instability of bromoalanine bearing a small protection group in the process of separation over silica gel (Couturier et al. 2006). The results suggested that the complex of triphenylphosphine/*N*-halosuccinimides is a useful halogenating reagent and this method has been proved to be a versatile desulfurization strategy via this functional group transformation.

In summary, we herein reported an alternative approach to L-β-haloalanine derivities from L-cysteine or L-cystine, respectively. The mercapto group of protected L-cysteine esters was efficiently transformed to halo groups by triphenylphosphine/*N*-halosuccinimides in high yields. It has been proved to be a versatile desulfurization strategy via this functional group transformation.

Acknowledgments Financial support from the "Western Light" of the Chinese Academy of Sciences is gratefully acknowledged.

References

Armarego WLF, Chai CLL (2003) Purification of laboratory chemicals, 5th edn. Butterworth-Heinemann, New York

Benoiton L (1968) Conversion of β-chloro-L-alanine to α-carbobenzoxy-DL-diaminopropionic acid. Can J Chem 46:1549–1552

Carpino LA, Han GY (1972) 9-Fluorenylmethoxycarbonyl amino-protecting group. J Org Chem 37:3404–3409. doi:10.1021/jo00795a005

Clive DLJ, Denyer CV (1972) Desulphurization of alkyl chlorocarbonyl disulphides: a method for replacement of -SH by -Cl. J Chem Soc Chem Commun 1972:773–774. doi:10.1039/c39720000773

Couturier C, Blanchet J, Schlama T, Zhu J (2006) Aziridinium from N, N-dibenzyl serine methyl ester: Synthesis of enantiomerically pure β-amino and α, β-diamino esters. Org Lett 8:2183–2186. doi:10.1021/ol060700u

Cowling DT (1975) Bonding of enzymes, enzyme derivatives and other compounds to polymeric materials. US3884761

Fisher E, Raske E (1907) Verwandlung des L-serins in D-alanin. Chem Ber 40:3717–3724. http://www.genome.ad.jp/kegg/pathway/map/map00272.html

Inoue O, Murayama A (1986) Optical resolutions of β-chloro-DL-alanine. JP86-152645

Iranpoor N, Firouzabadi H, Aghapour G (2001) A facile conversion of thiols to alkyl halides by triphenylphosphine/*N*-halosuccinimides. Synlett 7:1176–1178. doi:10.1055/s-2001-15157 (and references cited therein)

Iranpoor N, Firouzabadi H, Aghapour G, Vaez zadeh AR (2002) Triphenylphosphine/2, 3-dichloro-5, 6-dicyanobenzoquinone as a new, selective and neutral system for the facile conversion of alcohols, thiols and selenols to alkyl halides in the presence of halide ions. Tetrahedron 58:8689–8693. doi:10.1016/S0040-4020(02)01089-X

Kato Y, Fukumoto K, Asano Y (1993) Enzymatic synthesis of L-β-chloroalanine using amino acid dehydrogenase. Appl Microbiol Biotechnol 39:301–304. doi:10.1007/BF00192082

Kelleman A, Mattern RH, Pierschbacher MD, Goodman M (2003) Incorporation of thioether building blocks into an $\alpha_v\beta_3$-specific RGD peptide: synthesis and biological activity. Biopolymers 71:686–695. doi:10.1002/bip.10586

Kenworthy MN, Kilburn JP, Taylor RJK (2004) Highly functionalized organolithium reagents for enantiomerically pure α-amino acid synthesis. Org Lett 6:19–22. doi:10.1021/ol0360039

Krajewski K, Long YQ, Marchand C, Pommier Y, Roller PP (2003) Design and synthesis of dimeric HIV-1 integrase inhibitory peptides. Bioorg Med Chem Lett 13:3203–3205. doi:10.1016/S0960-894X(03)00679-6

Oae S, Togo H (1981) Facile conversion of aliphatic sulfonic acids, sulfinic acids, thiols, sulfonates, thiolsulfonates, and disulfides to the corresponding alkyl iodides by triphenylphosphine/iodine. Synthesis 1981:371–373. doi:10.1055/s-1981-29453

Ohoka M, Kato T, Mita R, Kawashima N, Higuchi C (1987) A process for producing β-chloroalanine. WO 8204043

Olsen RK, Kini GD, Hennen WJ (1985) Conversion of thiosulfinate derivatives of cystine to unsymmetrical cystines and lanthionines by reaction with tris(dialkylamino)phosphines. J Org Chem 50:4332–4336. doi:10.1021/jo00222a026

Pachamuthu K, Zhu XM, Schmidt RR (2005) Reversed approach to *S*-farnesylation and *S*-palmitoylation: Application to an efficient synthesis of the *C*-terminus of lapidated human *N*-Ras hexapeptide. J Org Chem 70:3720–3723. doi:10.1021/jo0482357

Savithri D, Leumann C, Scheffold R (1996) Synthesis of a building block for a nucleic-acid analog with a chiral flexible peptide backbone. Helv Chim Acta 79:288–294. doi:10.1002/hlca.19960790128

Soper TS, Jones WM, Lerner B, Torp M, James MM (1977) Inaction of bacterial D-amino acid transaminase by β-chloro-D-alanine. J Biol Chem 252:3170–3175

Still IW, Kutney GW, McLean D (1982) Convenient method for the conversion of thiols and disulfides to the corresponding chlorides. J Org Chem 47:560–561. doi:10.1021/jo00342a037

Swali V, Matteucci M, Elliot R, Bradley M (2002) The stereospecific synthesis of 'orthogonally' protected lanthionines. Tetrahedron 58:9101–9109. doi:10.1016/S0040-4020(02)01091-8

Tao F, Luo Y, Wei Q, Zhang G (2004) Efficient preparation of L-cysteic acid and its esters. Amino Acids 27:149–151. doi:10.1007/s00726-004-0124-2

Threadgill MD, Gledhill AP (1989) Synthesis of peptides containing *S*-(*N*-alkylcarbamoyl)cysteine residues, metabolites of *N*-alkylformamides in rodents and in humans. J Org Chem 54:2940–2949. doi:10.1021/jo00273a031

Weiss RG, Snyder EI (1968) Stereochemistry of chloride formation from alcohols and thiols by use of triphenylphosphine and carbon tetrachloride. Chem Commun 1968:1358–1359. doi:10.1039/c19680001358

Williams RM (1989) Synthesis of optically active α-amino acids. Pergamon Press, Oxford

Wirtz M, Hell R (2006) Functional analysis of the cysteine synthase protein complex from plants: structural, biochemical and regulatory properties. J Plant Physiol 163:273–286. doi:10.1016/j.jplph.2005.11.013

Yu L, Lai YH, Wade JV, Coutts SM (1998) A simple and efficient method for the syntheses of thioether cyclic peptides. Tetrahedron Lett 39:6633–6636. doi:10.1016/S0040-4039(98)01397-5

Zhu XM, Schmidt RR (2003) Efficient synthesis of differently protected lanthionines via β-bromoalanine derivatives. Eur J Org Chem 2003:4069–4072. doi:10.1002/ejoc.200300336

Zhu XM, Schmidt RR (2004) Efficient synthesis of *S*-linked glycopeptides in aqueous solution by a convergent strategy. Chem Eur J 10:875–887. doi:10.1002/chem.200305163 and references cited therein