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A Novel Synthetic Methods for α-Amino Acids from Allyl Ethers *via N*-Allylcarbamates

Young Hoon Jung and Ji Deuk Kim

Laboratory of Organomedicinal Chemistry, College of Pharmacy, Sungkyunkwan University, Suwon 440-746, Korea

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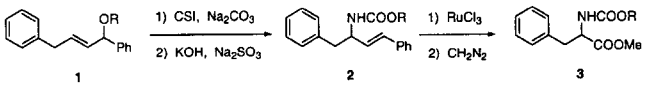
Protected α-Phenyl glycine **17** and phenylalanine **18** and **19** have been synthesized through an efficient three-step sequence from the corresponding allyl ethers **5**, **7**, and **10**. The key intermediate in this synthesis is the corresponding allylic amines prepared by reaction of allyl ethers with chlorosulfonyl isocyanate.

Key words: α-Amino acids, Chlorosulfonyl isocyanate (CSI), Allyl ethers, *N*-Allylcarbamates, α-Phenylglycine, Phenylalanine.

INTRODUCTION

Proteinogenic and non-proteinogenic α-amino acids are valuable starting materials for the construction of biologically active natural products and biologically selective and degradable drugs. Therefore, much attention has been paid to the development of concise and flexible synthetic approaches to α-amino acids, allowing facile incorporation of functional groups and structural variability. Among the approaches reported in this field, Strecker amino synthesis (Williams, 1989), Ugi reaction (Ugi *et al.*, 1982) and reductive amination of keto acid (Harada *et al.*, 1985) are representative methods for the synthesis of α-amino acids. Oxazolone route synthesis (Rao *et al.*, 1975), alkylation of glycine enolates, electrophillic amination of amide or ester enolate (Oppolzer *et al.*, 1988), alkylation of diacyliminium (Mooiweer *et al.*, 1989) and halogenation of enolates followed by nucleophilic substitution of the halogen also have been used (Barrett *et al.*, 1998). Another method used widely for synthesis of α-amino acids is the oxidation of double bond in protected various allylic amines which are fundamental building blocks in organic chemistry (Hayashi *et al.*, 1989).

Recently we reported upon a novel synthetic method for *N*-allylcarbamates from cinnamyl alkyl ethers using chlorosulfonyl isocyanate (CSI) (Kim *et al.*, 2000). N-Allylcarbamates are a protected form of allylic amines and the carbamates, in particular can be used as protective groups for amino acids to minimize racemization in peptide synthesis (Greene *et al.*, 1999). In connection with these studies, we now report the novel synthetic methods for α-amino acids from allyl ethers via N-allylcarbamates (Scheme 1)



1 2 3

Scheme 1. Synthetic approach to α-amino acids from allyl ethers

MATERIALS AND METHODS

Commercially available reagents were used without additional purification unless otherwise stated. All anhydrous solvent were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus and were not corrected. Nuclear magnetic resonance spectra (^1H, and ^{13}C NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer and chemical shifts are reported as part per million (ppm) from the internal standard, tetramethylsilane (TMS). Resonance pattern are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation b is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer and reported as cm^{-1}. Thin layer chromatography was

Correspondence to: Young Hoon Jung, Sungkyunkwan University Laboratory of Organomedicinal Chemistry, College of Pharmacy 300 Chonchon-Dong, Changan-Ku, Suwon 440-746, Kyonggi-Do, Korea
E-mail: yhjung@skku.ac.kr

carried out using plates coated with Kieselgel $60F_{254}$ (Merck). Flash column chromatography was carried out on silica gel 60 (230-400 mesh, Merck).

General procedure for the synthesis of cinnamyl methyl ether (5)

To a solution of cinnamyl alcohol (**4**) (0.5 g, 3.73 mmol) in THF (15 ml) was added NaH (60%, 0.22 g, 5.59 mmol, 1.5eq). The reaction mixture was warmed to 45°C under N_2 and CH_3I (0.35 ml, 5.59 mmol, 1.5eq) was added dropwise. The reaction mixture was stirred at 45 ~50°C for 1h and cooled to room temperature. H_2O (10 ml) was added and the solution was extracted with EtOAc (20 ml). The organic layer was washed with H_2O and brine. The organic was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:15) to afford 0.513 g (92.9%) of **5** as a colorless oil. R_f: 0.45 (EtOAc:hexane=1:6); ^1H NMR (500MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.37-7.34 (m, 2H), 7.30-7.27 (m, 1H), 6.65 (d, 1H, *J*=16Hz), 6.33 (dt, 1H, *J*=16Hz, 6Hz), 4.13 (d, 2H, *J*=6Hz), 3.43 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): 137.44, 133.15, 129.30, 128.41, 127.21, 126.68, 73.82, 58.72; IR (neat): cm^{-1} 3059, 2821, 1450, 1380.

Methyl 4-phenylbut-2-enyl ether (7)

4-Phenylbut-2-en-1-ol (**6**) (Rose *et al.*, 1974) was converted to **7** as a colorless oil in 82.2% yield. R_f: 0.34 (EtOAc:hexane=1:15); ^1H NMR (500MHz, $CDCl_3$): δ 7.30-7.28 (m, 2H), 7.21-7.20 (m, 3H), 5.88 (dt, 1H, *J*= 15Hz, 6Hz), 5.64 (dt, 1H, *J*=15Hz, 6Hz), 3.91 (d, 2H, *J*=6Hz), 3.41 (d, 2H, *J*=6Hz), 3.34 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 140.69, 133.80, 129.30, 129.15, 128.32, 126.81, 73.70, 58.56, 39.45; IR (neat): cm^{-1} 3027, 2826, 1453.

1,4-Diphenylbut-2-enyl methyl ether (10a)

To a solution of 4-phenylbut-2-en-1-ol (**6**) (1.6 g, 10.80 mmol) in CH_2Cl_2 (40 ml) was added Celite and PCC (3.49 g, 16.19 mmol). The reaction mixture was stirred at room temperature for 2h under N_2 and the solvent was concentrated. The result oil was dissolved in Et_2O and filtered through Celite. The solvent was removed and the oil obtained was redissolved in Et_2O (9 ml) and cooled to -20°C under N_2. PhMgBr (3.0 M solution in Et_2O, 2.92 ml, 10.51 mmol) was added dropwise below -10°C. The solution was stirred at 0~5°C for 1 h, quenched with s-NH_4Cl, then extracted with Et_2O (20 ml). The organic layer was separated and washed with H_2O and brine. The organic was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc: Hexane=1:6) to afford 1.430 g (59.1%) of 1,4-diphenylbut-2-en-1-ol (**9**) as a pale yellow oil.

9 was converted to **10a** as a colorless oil in 78.4% yield. R_f: 0.38 (EtOAc:hexane=1:15); ^1H NMR (500MHz, $CDCl_3$): δ 7.38-7.27 (m, 7H), 7.23-7.18 (m, 3H), 5.88 (dt, 1H, *J*=15Hz, 6.5Hz), 5.67 (ddt, 1H, *J*=15Hz, 7Hz, 3.5Hz), 4.64 (d, 1H, *J*=7Hz), 3.42 (dd, 2H, *J*=6.5Hz, 3.5 Hz), 3.33 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 142.06, 140.69, 132.82, 132.68, 129.30, 129.16, 128.27, 127.46, 126.82, 84.89, 57.01, 39.43; IR (neat): cm^{-1} 3029, 2931, 1452.

Benzyl 1,4-diphenylbut-2-enyl ether (10b)

To a solution of **9** (0.6 g, 2.68 mmol) in THF (16 ml), DMF (4 ml) was added NaH (60%, 0.16 g, 4.01 mmol) at 0°C. BnBr (0.38 ml, 4.01 mmol) was added dropwise under N_2. The reaction mixture was stirred at room temperature for 12 h. H_2O (10 ml) was added and the solution was extracted with EtOAc (20 ml). The organic layer was washed with H_2O and brine. The organic was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:30) to afford 0.570g (67.8%) of **10b** as a colorless oil. R_f: 0.32 (EtOAc:hexane=1:15); ^1H NMR (500MHz, $CDCl_3$): δ 7.45-7.28 (m, 12H), 7.26-7.24 (m, 3H), 5.92 (dt, 1H, *J*= 15Hz, 6.5Hz), 5.78 (dd, 1H, *J*=15Hz, 7Hz), 4.91 (d, 1H, *J*=7Hz), 4.58 (t, 2H, *J*=5Hz), 3.47 (d, 2H, *J*= 6.5Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 142.24, 140.78, 139.26, 133.03, 132.76, 129.21, 129.11, 128.41, 128.24, 127.68, 126.84, 82.24, 70.75, 39.50; IR (neat): cm^{-1} 3062, 3030, 1680, 1451.

General procedure for the synthesis of methyl *N*-(1-phenylallyl)carbamate (11) and methyl *N*-cinnamylcarbamate (12)

To a suspension of Na_2CO_3 (0.56 g, 3.54 mmol, 2.25 eq) in anhydrous CH_2Cl_2 (7 ml) was added CSI (0.31 ml, 3.54 mmol, 1.5eq) and a solution of cinnamyl methyl ether (**5**) (0.35 g, 2.36 mmol) in CH_2Cl_2 (3 ml) at 20°C under N_2. The reaction mixture was stirred at 20°C for 30 min, quenched with H_2O (10 ml), then extracted with EtOAc (5 ml × 2). The organic layer was added to a solution of Na_2SO_3 (25%) and KOH (10%) and the solution was stirred at room temperature for overnight. The organic layer was separated and washed with H_2O and brine. The organic was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:6) to afford 0.107 g (23.7%) of **11** as a white solid and 0.288 g (63.8%) of **12** as a white solid.

Methyl *N*-(1-phenylallyl)carbamate (11)

R_f: 0.37 (EtOAc:hexane=1:3); ^1H NMR (500MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.04-5.97 (m, 1H), 5.38-5.30 (bs, 1H), 5.24 (dd, 1H, *J*=10Hz, 1.5Hz), 5.23 (dd, 1H, *J*=16.5Hz, 1.5Hz), 5.10-5.00 (bs, 1H), 3.68 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 156.91, 141.41, 138.35, 129.43, 128.38, 127.71, 116.45, 57.73, 52.96; IR (CH_2Cl_2): cm^{-1} 3320, 1701, 1531, 1243; mp: 45~48°C.

Methyl *N*-cinnamylcarbamate (12)

R_f: 0.30 (EtOAc:hexane=1:3); ^{1}H NMR (500MHz, $CDCl_3$): 7.37-7.23 (m, 5H), 6.53 (d, 1H, J=15.5Hz), 6.20 (dt, 1H, J=15.5Hz, 6Hz), 5.90-5.80 (bs, 1H), 3.97 (dd, 1H, J=6Hz, 5.5Hz), 3.70 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 157.71, 137.26, 132.32, 129.29, 128.39, 127.09, 126.66, 52.93, 43.84; IR (KBr): cm^{-1} 3334, 1694, 1539, 1281; mp: 58~60°C.

Methyl *N*-(1-benzylallyl)carbamate (13) and Methyl *N*-(4-phenylbut-2-enyl)carbamate (14)

4-Phenylbut-2-enyl methyl ether (7) was converted to **13** as a colorless in 33.2% and **14** as a white solid in 36.4% yield.

Methyl *N*-(1-benzylallyl)carbamate (13)

R_f: 0.39 (EtOAc:hexane=1:5); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.84-5.78 (m, 1H), 5.12 (dt, 1H, J= 17Hz, 1.5Hz), 5.11 (dt, 1H, J=12Hz, 1.5Hz), 4.70-4.60 (br, 1H), 4.55-4.45(br, 1H), 3.63 (s, 3H), 2.86 (d, 2H, J= 6.5Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 157.01, 138.48, 137.77, 130.21, 129.11, 127.33, 115.72, 54.62, 52.83, 42.06; IR (nujol): cm^{-1} 3333, 1693, 1539, 1255.

Methyl *N*-(4-phenylbut-2-enyl)carbamate (14)

R_f: 0.32 (EtOAc:hexane=1:5); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.22-7.16 (m, 3H), 5.77 (dt, 1H, J=15Hz, 6.5Hz), 5.53 (dt, 1H, J=15Hz, 5Hz), 4.80-4.70 (bs, 1H), 3.80-3.75 (bs, 1H), 3.69 (s, 3H), 3.36 (d, 2H, J=6.5Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 157.58, 140.64, 132.34, 129.24, 129.18, 128.22, 126.87, 52.82, 43.49, 39.30; IR (nujol): cm^{-1} 3352, 1695, 1462, 1390; mp: 60~61°C.

Methyl *N*-(1-benzylcinnamyl)carbamate (15)

1,4-Diphenylbut-2-enyl methyl ether (**10a**) was converted to **15** as a white solid in 74.1% yield. R_f: 0.40 (EtOAc:hexane=1:3); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.39-7.21 (m, 10H), 6.47 (dd, 1H, J=16Hz, 1Hz), 6.14 (dd, 1 H, J=16Hz, 6Hz), 4.80-4.75 (bs, 1H), 4.70-4.60 (bs, 1 H), 3.68 (s, 3H), 2.96 (d, 2H, J=6.5Hz), 3.70 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 156.99, 137.73, 137.32, 131.15, 130.30, 129.20, 128.34, 127.39, 127.20, 54.39, 52.92, 42.49; IR (CH_2Cl_2): cm^{-1} 3318, 1690, 1537, 1284; mp: 113~115°C.

Benzyl *N*-(1-benzylcinnamyl)carbamate (16)

1,4-Diphenylbut-2-enyl benzyl ether (**10b**) was converted to **16** as a white solid in 70.4% yield. R_f: 0.31 (EtOAc:hexane=1:6); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.34-7.21 (m, 15H), 6.46 (d, 1H, J=16Hz), 6.14 (dd, 1H, J=16Hz, 6Hz), 5.10 (s, 2H), 4.90-4.80 (bs, 1H), 4.75-4.65 (bs, 1H), 2.97 (d, 2H, J=6.5Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 156.32, 137.68, 137.29, 131.24, 130.27, 129.25, 128.83, 128.34, 127.39, 127.13, 67.47, 54.46, 42.47; IR (CH_2Cl_2): cm^{-1} 3324, 1693, 1531, 1256; mp: 102-104°C.

General procedure for the synthesis of *N*-methoxycarbonyl α-phenylglycine methyl ester (17)

To a solution of methyl *N*-(1-phenylallyl)carbamate (**11**) (0.1 g, 0.52 mmol) in CH_3CN (3 ml), CCl_4 (3 ml), H_2O (4.5 ml) was added $NaIO_4$ (1.12 g, 5.23 mmol, 10eq) and $RuCl_3 \cdot xH_2O$ (5 mg, 5%). The reaction mixture was stirred at room temperature for 1h, the reaction was poured into CH_2Cl_2/H_2O (10 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5ml × 3). The organic was dried over $MgSO_4$ and concentrated. The result dark oil was redissolved in Et_2O and filtered through Celite. The solvent was removed and the oil obtained was treated with excess CH_2N_2 in Et_2O at 0 and concentrated. The residue was purified by column chromatography (EtOAc:Hexane=1:3) to afford 0.087 g (74.4 %) of **17** as a white solid. R_f: 0.26 (EtOAc:hexane=1:3); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.35-7.30 (m, 5H), 5.95-5.90 (bs, 1H), 5.37 (d, 1H, J=7.5Hz), 3.71 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 172.11, 156.75, 137.35, 129.49, 129.26, 127.87, 58.61, 53.48, 53.10; IR (CH_2Cl_2): cm^{-1} 3335, 1747, 1723, 1522; mp: 108~110°C.

***N*-Methoxycarbonyl phenylalanine methyl ester (18)**

Methyl *N*-(1-benzylallyl)carbamate (**13**) was converted to **18** as a colorless oil in 70.9% yield. R_f: 0.27 (EtOAc: hexane=1:3); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.30-7.23 (m, 3H), 7.12-7.11 (m, 2H), 5.30-5.20 (bs, 1H), 4.64 (dd, 1H, J=13.5Hz, 6Hz), 3.71 (s, 3H), 3.65 (s, 3H), 3.12 (dd, 1H, J=13.5Hz, 6Hz), 3.07 (dd, 1H, J=13.5Hz, 6Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 172.82, 157.01, 136.49, 129.76, 129.30, 127.83, 55.48, 53.01, 52.99, 38.92; IR (neat): cm^{-1} 3338, 1746, 1722, 1531.

***N*-Methoxycarbonyl phenylalanine methyl ester (18)**

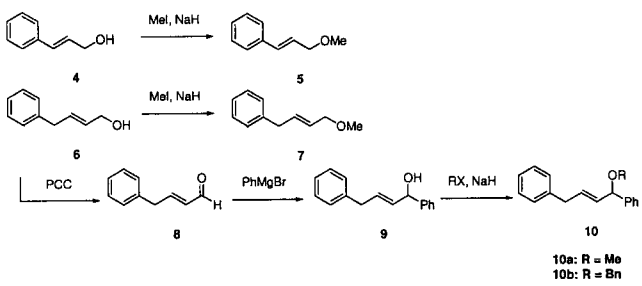
Methyl *N*-(1-benzylcinnamyl)carbamate (**15**) was converted to **18** as a colorless oil in 71.3% yield.

***N*-Cbz-phenylalanine methyl ester (19)**

Benzyl *N*-(1-benzylcinnamyl)carbamate **16** was converted to **19** as a white solid in 79.4% yield. R_f: 0.28 (EtOAc: hexane=1:3); ^{1}H NMR (500MHz, $CDCl_3$): δ 7.40-7.21 (m, 8H), 7.12-7.10 (m, 2H), 5.30-5.25 (bs, 1H), 5.11 (s, 2 H), 4.70 (dd, 1H, J=13.5Hz, 6 Hz), 3.73 (s, 3H), 3.15 (dd, 1H, J=13.5Hz, 6Hz), 3.09 (dd, 1H, J=13.5Hz, 6Hz); ^{13}C NMR (125MHz, $CDCl_3$): δ 172.71, 156.35, 136.96, 136.40, 129.97, 129.84, 129.42, 129.23, 128.89, 127.85, 67.68, 55.53, 53.03, 38.92; IR (CH_2Cl_2): cm^{-1} 3340, 1750, 1723, 1520, 1215; mp: 132~135°C.

RESULTS AND DISCUSSION

The preparations of allyl ethers as a starting material of

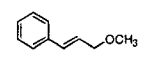
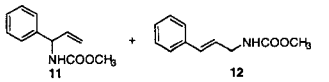
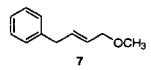
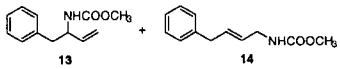
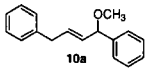
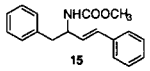
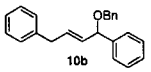
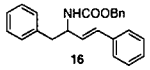


Scheme 2. Preparation of allyl ethers

CSI reaction were carried out as shown in scheme 2. Cinnamyl methyl ether (**5**) was obtained from cinnamyl alcohol (**4**) by methylation in 92.9% yield. Methyl 4-phenylbut-2-enyl ether (**7**) was prepared from 4-phenylbut-2-en-1-ol (**6**) in the same way in 82.2% yields. **6** was oxi-dized with PCC to give aldehyde **8** which was attacked by phenylmagnesium bromide to afford the alcohol **9** in 59.1% overall yield of two steps. **9** was converted to the corresponding ethers in 78.4% yield for methyl ether **10a** and in 67.8% yield for benzyl ether **10b** respectively.

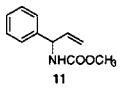
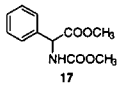
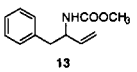
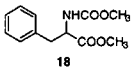
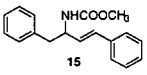
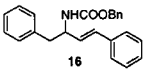
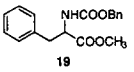
Conversions of allyl ethers to the corresponding N-protected allylic amines with CSI were shown in Table I. Initially, we examine the reaction of cinnamyl methyl ether (**5**) with CSI to afford the internal allylic amine (**11**) and terminal product (**12**) as a 1:2.7 mixture of regio-isomers and 4-phenylbut-2-enyl methyl ether (**7**) gave **13** and **14** in a comparable ratio of 1:1.1. In order to improve the isomer ratio of the internal allylic amine, we introduced the phenyl ring at the allylic position in the same direction as the alkoxy moiety. The reaction of 1,4-diphenylbut-2-enyl methyl ether (**10a**) with CSI gave the only product, methyl *N*-(1-benzylcinnamyl)carbamate (**15**), due to the steric hindrance of phenyl ring and the

Table I. Conversions of allyl ethers to the corresponding *N*-protected allylic amines with CSI

	Allyl Ethers	Allylic amines	Yield (%)[a] (ratio)
1	 5	 11 + 12	87.5 1 : 2.7
2	 7	 13 + 14	69.6 1 : 1.1
3	 10a	 15	65.1
4	 10b	 16	70.4

[a]Isolated yield of pure material

Table II. Conversions of allylic amines to the corresponding protected α-amino acids

	Allyic amines	Amino acid methyl esters	Yield (%)[a]
1	 11	 17	74.4
2	 13	 18	70.9
3	 15	18	71.3
4	 16	 19	79.4

[a]Isolated yield of pure material

formation of a stable conjugated product (entry 3). In the case of benzyl ethers (**10b**), the results were similar to those obatained in the methyl case (entry 4). None of the product derived from attack at the benzylic position was observed.

Oxidation of allylic amines with $RuCl_3$ (Rychnovsky *et al.*, 1992) and esterification with diazomethane gave corresponding *N*-protected α-amino acid methyl esters. The results were shown in Table II. Allylic amine **11** gave a protected α-phenyl glycine in 74.4% overall yield and **13**, **15** and **16** gave the corresponding protected phenyl alanine in 70.9%, 71.3% and 79.4% overall yields repectively.

In conclusion, we developed the novel synthetic method of α-amino acids from allyl ethers using CSI reaction, oxidation and esterification. This synthetic method can be applied to a more complex amino acid formation.

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