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Stereoselective synthesis of allyl- and homoallylglycines

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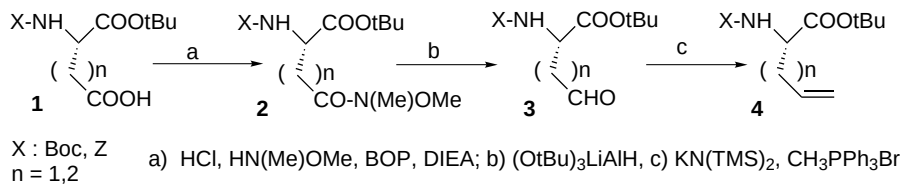
Abstract—A new method for the synthesis of *N*-protected allyl- and homoallylglycines was developed from aspartic and glutamic acid derivatives. The carboxylic side-chains of aspartic and glutamic derivatives was first transformed into the Weinreb amide by coupling with *N*,*O*-dimethylhydroxylamine and then reduced into the corresponding aldehyde. The latter could react with methyl-triphenylphosphonium bromide to yield the title compounds with 50% total yield.

Allyl- and homoallylglycines are of great importance, particularly with the publication of ring-closing olefin metathesis on allylglycine containing peptides to construct rigidified peptide systems.[1] Furthermore, these α-amino acids are also used as starting materials for the syntheses of, e.g. sulfur-containing trifunctional amino acids[2] or 3-amino-5-hydroxymethyl-γ-lactones.[3] Various publications reported the preparation of allyl- and homoallylglycines, including the reactions of alkyltrimethylsilanes with nitrones,[4] allylsilanes with glycidyl cation equivalents,[5] the direct alkylation of pseudoephedrine glycinamide,[6] the zinc mediated alkylation of oximes,[7] the enolate alkylation of diphenyloxazinones[8] or alkylation of aldimines and the ketimine derivatives of glycine esters.[9,10] These derivatives are commercially available but expensive. We decided to develop a new synthesis of allyl- and homoallylglycine derivatives by a simple route from easily available aspartic and glutamic acid derivatives. We recently published that Weinreb amide[11] of *N*-protected amino acids could be reduced with bulky hydrides such as tris(*tert*-butoxy)lithium aluminum hydride and that it was possible to synthesize *N* and side chain protected aspartyl and glutamyl aldehyde derivatives in fairly good conditions.[12] In this paper, we want to show that the carboxylic side-chain of aspartyl and glutamyl residues can also be reduced into aldehyde and then reacted with the ylide derived from CH_3PPh_3Br to produce enantiomerically pure allyl and homoallylglycine derivatives with an acceptable yield.

Previous syntheses of side-chain aldehyde function of *C*- and *N*-protected aspartyl or glutamyl derivatives have been reported. Several proceeded by reduction of the corresponding acid chloride with tri-*n*-butyltin hydride in the presence of tetrakis(triphenylphosphine)palladium(0),[13] by reduction of the corresponding oxazolidinone acid chloride with tri-*n*-butyltin hydride[14] or by hydrogenolysis of the same oxazolidinone in the presence of palladium barium sulfate.[15] Another paper related the regioselective reduction of dimethyl *N*,*N*-di-Boc-glutamate by DIBAL for the synthesis of (*S*)-α-amino arachidonic acid.[16]



Scheme 1. Synthetic pathway of allyl- and homoallylglycine.

Keywords: allylglycine; homoallylglycine; Weinreb amide; aspartic acid; glutamic acid.

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Table 1. Results

1	2: Yield (%)	$[\alpha]_D^{20}$ (MeOH, $c=1$)	3: Yield (%)[a]	4: Yield (%)[b]	$[\alpha]_D$ (MeOH, $c=1$)
Boc-(L)Glu-O*t*Bu	92	−21	95	48	−19
Boc-(L)-Asp-O*t*Bu	88	−11	93	50	−3
Z-(L)-Glu-O*t*Bu	89	−22	95	58	−15

[a] Yields of the crude.
[b] Yields of both steps (2→4) after a flash chromatography on silica gel.

Our synthesis strategy is illustrated in Scheme 1. Starting from *N*-protected *tert*-butyloxycarbonyl or benzyloxycarbonyl aspartic or glutamic acid *tert*-butyl ester, the side-chain carboxylic function is coupled with *N*,*O*-dimethylhydroxylamine in the presence of an activating agent. This acylation reaction proceeds in almost quantitative yield. The Weinreb amide can then be reduced with tris(*tert*-butoxy)lithium aluminum hydride in an anhydrous solvent at room temperature within 3 h. After a classical workup, the crude is allowed to react for 30 min to 1 h with the preformed ylide prepared by action of $KN(TMS)_2$ with CH_3PPh_3Br under argon. A classical workup followed by a flash chromatography yielded the target compounds with yields of about 50%.

The obtained results are summarized in Table 1 and their physical constants are reported.[17] Although Boc and *Z*-protection of the primary amine can be used in these syntheses, Fmoc protection has to be avoided because it is cleaved in the basic medium containing the ylide moiety. Benzyl esters of the α carboxylic function are reduced by the hydride; all attempts to reduce the Weinreb amide of the side-chain without protecting the α carboxylic function failed. So the use of bulky esters such as *tert*-butyl ester are highly recommended. If benzyloxycarbonyl group (*Z*) is used for the amine protection, the *tert*-butyl ester of the desired allylglycine derivative can easily and quantitatively be removed by TFA to generate the carboxylic function in order to incorporate the new residue in a peptidic sequence.

In a typical experiment, 300 mg of Boc-Glu[N(Me)OMe]-O*t*Bu (0.9 mmol) are dissolved in 10 mL of anhydrous THF. $LiAlH(OtBu)_3$ (2.7 mL, 2.7 mmol, 3 equivalents, 1 M in THF) were added and allowed to react at room temperature for 3 h under stirring. The mixture is then hydrolyzed with a solution of potassium hydrogenosulfate (5% in water). After a classical workup,[18] the aldehyde is obtained with a crude yield of 95%. To a suspension of methyltriphenylphosphonium (617 mg, 1.73 mmol, 2 equivalents) in anhydrous THF (5 mL) and under argon, were added 3.11 mL of $KN(TMS)_2$ (1.55 mmol, 1.8 equivalents, 0.5 M in toluene). After 30 min, a solution containing the aldehyde (240 mg, 0.84 mmol) was added to the yellow colored ylide solution via a cannula. The reaction was completed within 30–60 min (completion is followed on TLC with a AcOEt/hexane (3/7) eluent system). The reaction mixture was hydrolyzed with a saturated solution of ammonium chloride. The desired compound was extracted with diethylether (2×20 mL), the organic phases washed twice with water and brine (20 mL), dried over sodium sulfate, filtered and concentrated. After flash chromatography on silica gel with an eluent system AcOEt/hexane (1/9), the expected compound was obtained as an oil with a global yield of 48%.

In conclusion, we proposed a simple synthesis of allyl- and homoallylglycines from easily available aspartic and glutamic acid derivatives. The stereochemistry of the obtained allylic compound depends on the stereochemistry of the starting amino acid. No racemization by enolization can occur with the side-chain aldehyde function.

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17. Boc-homoallyl-Gly-O*t*Bu: M+H$^+$ 286, R_f: 0.59 (AcOEt/hex: 1/9); ^{1}H NMR (360 MHz, DMSO-d_6): δ (ppm) 1.40 (s, 18H, Boc+*t*Bu), 1.7–1.5 (m, 2H, $CH_2\beta$), 2.00 (m, 2H, $CH_2\gamma$), 3.72 (m, 1H, CHα), 4.93 (m, 2H, CHε), 5.71 (m, 1H, CHδ), 7.05 (d, 1H, NH).
Boc-allyl-Gly-O*t*Bu: M+H$^+$ 272, R_f: 0.4 (AcOEt/hex: 1/9); ^{1}H NMR (360 MHz, DMSO-d_6): δ (ppm) 1.30 (s, 18H, Boc+*t*Bu), 2.25 (m, 2H, $CH_2\beta$), 3.75 (m, 1H, CHα), 4.95 (m, 2H, $CH_2\delta$), 5.70 (m, 1H, CHγ), 7.00 (d, 1H, NH).
Z-Homoallyl-Gly-O*t*Bu: M+H$^+$ 320, R_f: 0.5 (AcOEt/hex: 1/9); ^{1}H NMR (360 MHz, DMSO-d_6): δ (ppm) 1.25 (s, 9H, *t*Bu), 1.64–1.46 (m, 2H, $CH_2\beta$), 1.95 (m, 2H, $CH_2\gamma$), 3.75 (m, 1H, CHα), 4.84 (m, 2H, $CH_2\varepsilon$), 4.91 (s, 2H, CH_2-Z), 5.64 (m, 1H, CHδ), 7.23 (s, 5H, ϕ-Z), 7.50 (d, 1H, NH).
Z-Homoallyl-Gly-OH: M+H$^+$ 264, ^{1}H NMR (360 MHz, DMSO-d_6): δ (ppm) 1.65–1.45 (m, 2H, $CH_2\beta$), 1.90 (m, 2H, $CH_2\gamma$), 3.80 (m, 1H, CHα), 4.83 (m, 2H, $CH_2\varepsilon$), 4.87 (s, 2H, CH_2-Z), 5.63 (m, 1H, CHδ), 7.20 (s, 5H, ϕ-Z), 7.45 (d, 1H, NH).
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