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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Yong-Qing Yang, Meng-Chen Ji, Zheng Lu, Mao Jiang, Wei-Wei Huang & Xue-Zhi He (2016): Facile access to α,β-dehydroalanine and α,β-dehydroamino butyric acid derivatives from DL-serines and threonines, Synthetic Communications, DOI: 10.1080/00397911.2016.1149194

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1149194

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http://dx.doi.org/10.1080/00397911.2016.1149194

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Facile access to α,β-dehydroalanine and α,β-dehydroamino butyric acid derivatives from DL-serines and threonines

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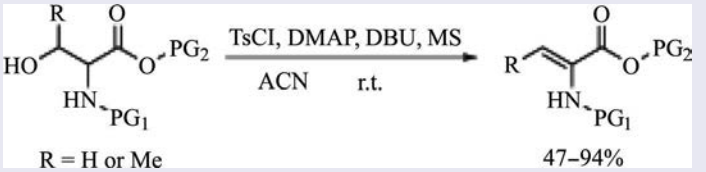
ABSTRACT

Not only α,β-dehydroamino acids are important constituents for a number of bioactive peptides in nature, but also they are important building blocks for a variety of synthetic amino acids in organic synthesis. Methods to prepare dehydroamino acids have been reported extensively in the literature; however, efficient and convenient protocols are still required. Here we have developed a convenient method to prepare dehydroalanine (ΔAla) and dehydroamino butyric acid (ΔAbu) derivatives derived from DL-serines and DL-threonines, respectively. 4-Toluenesulfonyl chloride (TsCl) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were employed in this procedure, which carried out activation of hydroxyl group and β-elimination in one pot. Because it is convenient and easy to handle, this method will attract the attention of synthetic chemists.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 12 January 2016

KEYWORDS
Dehydroamino acids; one pot; serine; threonine

Introduction

α,β-Dehydroamino acids (ΔAAs) are important components of many bioactive peptides[1] and are very useful precursors for synthetic amino acids[2] in organic chemistry. Their preparation procedures are common in the literature.[3] One main type of ΔAAs is α,β-dehydroalanine (ΔAla), which is derived from serine and cystein biosynthetically, via activation of β-hydroxyl or thiol group and posterior β-elimination. There are mainly two approaches to prepare ΔAAs from β-hydroxyl-amino acid derivatives. One is a two-step procedure, which is mild and high yielding. Under mild conditions, the hydroxyl group was converted to a leaving group, and then β-elimination occurred under basic conditions.[3c,3d,3j,3l,3o,3q] Chandrasekaran and coworkers have reported that O-Cbz serine derivatives could be converted to ΔAla in the presence of K_2CO_3 or tetrabutylammonium fluoride (TBAF) in good yield.[3n,3o] However, the protection of hydroxyl group has to be

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Supplemental data (Full experimental detail, IR, ^{1}H NMR, and EI-MS data) can be accessed on publisher's website

carried out at −50 °C for several hours.[3o] The other one is a one-pot procedure, and reagents such as $PhNTf_2/Et_3N$,[3f] Boc_2O/dimethylaminopyridine (DMAP),[3i,3p] $ClCOCHCl_2/Et_3N$[3g], and $SOCl_2$/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[3j] were employed. Depending on the configuration of β-hydroxyamino esters (2° or 3° OH), Wandless and coworkers have reported that $SOCl_2$/DBU can selectively transform them to *E* or *Z* isomers via cyclic sulfamidites in good to excellent yield.[3j] However, the harsh reaction conditions limit its application, because the solvent, dichloromethane (DCM), has to be distilled beforehand and the reaction temperature has to be kept low, initially at −78 °C and then raised to 0 °C. In terms of cost, convenience, and efficiency, new methods to prepare ΔAAs are still required. Here we describe a mild way to prepare dehydroalanine derivatives, starting from DL-serines in one pot. It is efficient and easy, and its application has been expanded to preparation of dehydroamino butyric acid (ΔAbu) derivatives with high regioselectivity.

Results and discussion

Our story starts from preparation of methyl 2-((*tert*-butoxycarbonyl)amino) -3-(tosyloxy) propanoate (**1**) (Fig. 1). It could be prepared from DL-serine under low temperature with pyridine[4] or a combination of triethylamine and trimethylamine hydrochlorate[5] as the base. This shows that sulfonylation of β-OH of serine is a subtle way.

For N-Boc-DL-serine-O-Me (**2**), we have employed TsCl as tosylating agent and triethylamine (Et_3N) as base at r.t., and the reaction ends up as a complex mixture. To our surprise, the major product was not **1** but N-Boc-dehydroalanine (ΔAla)-O-Me (**3**). This means that the major side reaction is β-elimination. This one-pot transformation to dehydroamino acid from amino acid derivatives aroused our interest. Experiments have been carried out to find out the optimal condition to obtain **3** from **2** (Table 1).

We started the investigation with DCM as the solvent. We found that with 1 equivalent of TsCl and triethylamine, in the presence of 10% DMAP, a small amount of dehydroamino acid was formed after 24 h with most of the substrate intact. Increasing the tosylating agent, the base, and the catalyst resulted in marked raise of the yield (entries 1–5). The highest yield in DCM is 80%, with 2 equivalents of TsCl, 5 equivalents of TEA, and 20% of DMAP. The effect of solvents was studied too. Among the commonly used solvents we tested, acetonitrile is the best (entries 5–10). Then we made an effort to study different organic bases. Tributylamine (p*K*a (H_2O) 10.89[6]) shared not only the structure but also the yield with triethylamine (p*K*a (H_2O)10.65,[6] p*K*a (CH_3CN) 18.82[7]). When pyridine was used, only 5% of product was isolated; we attributed this to its low basicity (p*K*a (CH_3CN) 12.53[7] vs. 17.95[7] of DMAP). The strongest base we tested was DBU (p*K*a (CH_3CN) 24.34[7]), and it gave the best result: the highest yield accompanied by reduced reaction time. As this reaction is a dehydration reaction, we thought that water could retard

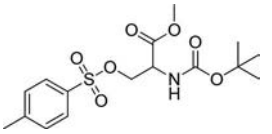
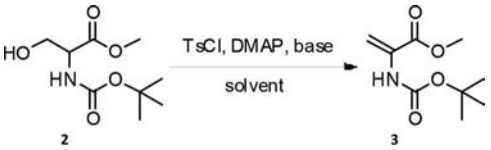


Figure 1. Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(tosyloxy)propanoate (**1**).

Table 1. Optimization of conditions for preparation of N-Boc-ΔAla-O-Me (**3**) from N-Boc-DL-Ser-O-Me (**2**).



2 3

Entry[a]	TsCl (eq.)	DMAP (eq.)	Base (eq.)	Solvent	Time (h)	Yield[b] (%)
1	1	0.1	Et_3N (1)	DCM	24	3
2	1	0.1	Et_3N (2)	DCM	24	10
3	1	0.2	Et_3N (2)	DCM	24	41
4	2	0.2	Et_3N (2)	DCM	24	45
5	2	0.2	Et_3N (5)	DCM	4	80
6	2	0.2	Et_3N (5)	THF	4	53
7	2	0.2	Et_3N (5)	DMF	4	66
8	2	0.2	Et_3N (5)	ACN	4	85
9	2	0.2	Et_3N (5)	DMSO	4	0
10	2	0.2	Et_3N (5)	Toluene	4	59
11	2	0.2	Et_3N (5)	DCE	4	80
12	2	0.2	Bu_3N (5)	ACN	4	80
13	2	0.2	NMM (5)	ACN	10	42
14	2	0.2	DIPEA (5)	ACN	10	84
15	2	0.2	Py (5)	ACN	10	5
16	2	0.2	DBU (5)	ACN	1	85
17	2	0.2	DBU (5)	ACN[c]	1	94

[a]Reaction temperature is 25 °C.
[b]Isolated yield.
[c]MS (4 Å) was added.

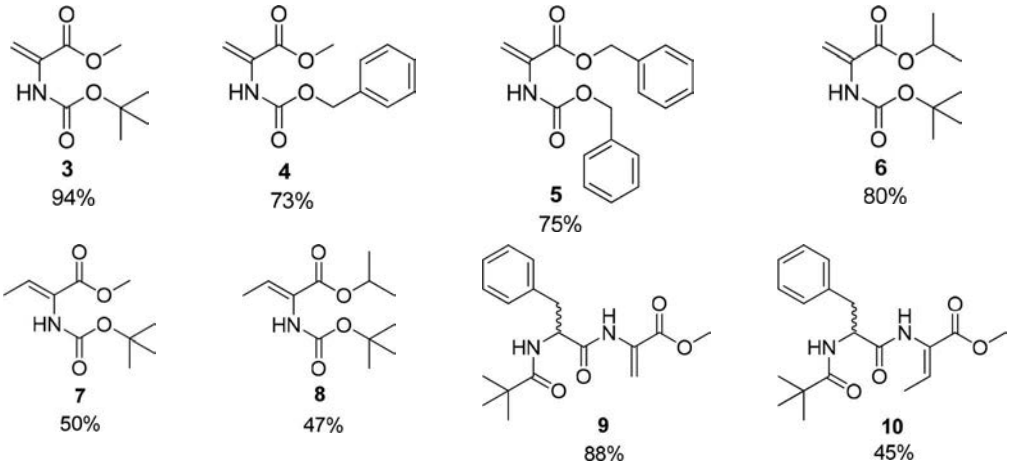
the desired reaction. A molecular sieve was added to eliminate trace amount of water in the reaction mixture, and finally we were gratified to see the yield come up to 94%.

With this optimal condition in hand, we set out to explore its application scope (Table 2). First, protection groups on amino and carboxylic acid affect the yield of the reaction (entries 3, 4, 5, and 6). Second, reaction of DL-threonines is more sluggish and has poorer yield compared to reaction of DL-serines (entries 3 versus 7, 6 versus 8), impeded by the steric hindrance upon S_N2 reaction in stage 1. Third, dehydration of both N-Boc-DL-Thr-O-Me and N-Boc-DL-Thr-O-Me gives all *Z*-isomers, which means that the β-elimination is highly regioselective (^{1}H NMR data of entries 7 and 8 are identical to reported data[30]).

To expand the scope of this reaction, the application to preparing dehydropeptide has been studied (Scheme 1). Under this condition, (±)-N-Boc-Phe-ΔAla-O-Me (**9**) could be obtained from N-Boc-L-Phe-L-Ser-O-Me (**11**) in excellent yield (88%). However, the chiral center of neighboring amino acid (phenylalanine) became racemized. For N-Boc-L-Phe-L-Thr-OMe (**12**), (±)-N-Boc-Phe-ΔAbu-OMe was obtained in 45%. It is likely that chiral center in the peptide is susceptible to basic conditions; with excessive base in the reaction system, the racemization occurred inevitably.

In summary, a convenient method to prepare α,β-dehydroalanine (or α,β-dehydroamino butyric acid) derivatives in one pot has been developed. All the reagents are easily accessible, and the procedure is easy to handle. Starting from DL-serine or threonine derivatives, the reaction could be completed in 1 h, with yields up to 94%. OH (1°) on DL-serine derivatives was eliminated faster than OH (2°) on DL-threonine derivatives. In the meanwhile, elimination on threonine derivatives gives only the *Z*-isomers.

Table 2. Exploration of scope of dehydration.



[a]Conditions: TsCl (2.0 eq), DMAP (0.2 eq), and MS (4 Å, 40 mg/mmol) were added to starting material in acetonitrile (0.2 M) at rt, followed by slow addition of DBU (5.0 eq).
[b]Isolated yield.

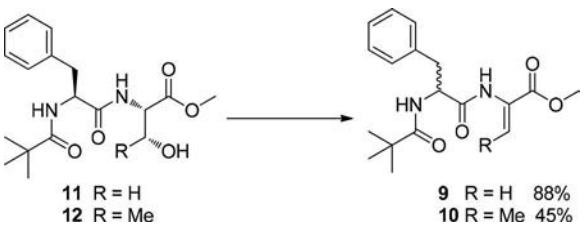
Application to dehydrodipeptide has also been carried out, with moderate to excellent yield but with racemization, so the method can only be employed to prepare racemic dehydropeptide.

Experimental

All reagents were purchased from commercial sources and were used without further treatment. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker 400 spectrometer. Infrared (IR) spectra were recorded on a JASCO FTIR spectrophotometer. Electron ionization–mass spectrometry (EI-MS) was acquired on an Agilent Technologies 5973 N instrument.

General procedure for preparation of dehydroamino acid (or dehydrodipeptide)

4-Toluenesulfonic chloride (TsCl) (2.0 eq) and 4-dimethylamino pyridine (DMAP) (0.2 eq) were added sequentially to the solution of N-Boc-DL-Ser-OMe (1.0 eq) in acetonitrile (0.2 M, containing MS (Molecular Sieve) (4 Å), 40 mg/mmol) at r.t., and 1,8-diazobicyclo[5.4.0]



Scheme 1. Preparation of dehydrodipeptide from dipeptide.

undec-7-ene (DBU) (5.0 eq) was added dropwisely to the solution, whose color darkened during the addition. The reaction was monitored by thin-layer chromatography (TLC). When starting material was consumed, the MS was filtered off and the solution was diluted with ethyl acetate and washed with saturated citric acid, water, and then brine. The organic phase was dried over anhydrous sodium sulfate. The crude product was obtained after concentration under reduced pressure, which was purified through flash chromatography.

Compound 3[30]

N-Boc-ΔAla-O-Me, yield 94%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (br s, 1H), 6.16 (s, 1H), 5.73 (d, $J = 1.6$ Hz, 1H), 3.83 (s, 3H), 1.48 (s, 9H). FT-IR (film) ν_{max} 3421, 2957, 2921, 1719, 1511, 1327, 1159 cm^{-1}. EI-MS *m/z* (%) 201 (M^+, 3.31), 57 (100), 41 (25.5), 59 (21.5), 145 (13.5), 101 (12.3), 43 (11.3), 55 (11), 56 (10.4).

Funding

The research is supported by Jiangsu University (No. 14JDG018, 10JDG042) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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