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Simple conversion of fully protected amino acids to zwitterions

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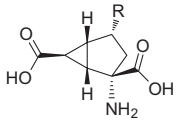
ABSTRACT

An operationally simple and efficient method under mild acidic conditions was developed to convert fully protected amino acids to the corresponding zwitterions without either isoelectric precipitation or ion exchange chromatography.

Protecting groups are widely used in multi-step synthetic organic chemistry.[1] Judicious selection of protecting groups and subsequent development of efficient methods for their removal can greatly enhance the overall synthetic efficiency. Synthesis of unnatural amino acids frequently involves multiple protecting groups, and final manipulations of synthetic amino acids into their zwitterionic form typically involve isoelectric precipitation or laborious ion exchange chromatography.[2] Reported here is a novel and efficient method to convert fully protected amino acids to their corresponding zwitterionic forms in an operationally simple and high-yielding manner.

Recent work pertaining to the preparation of conformationally constrained glutamic acid analogs from our laboratories has led to the discovery of several group II selective metabotropic glutamate receptor (mGlu) agonists, such as (1*R*,2*S*,5*S*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**1**, LY354740, Fig. 1),[3] and a mixed mGlu2 agonist/mGlu3 antagonist, (l*R*,2*S*,4*R*,5*S*,6*S*)-2-amino-4-methyl-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid (**2**, LY541850).[4] To obtain the desired final products in the zwitterionic form, the fully protected amino acids were hydrolyzed under prolonged (24–48 h) strongly acidic (48% HBr)[3] or strongly basic (3 N NaOH) conditions[4] at an elevated temperature (100 °C) followed by either isoelectric precipitation[3] or anion exchange column chromatography (AG1-X8 resin, acetate form, eluents: 10% AcOH in water).[4] These procedures are both time consuming and labor intensive. To overcome these operational issues, we have redesigned the protecting groups on these amino acids, and envisioned a simple and universal deprotection–isolation methodology that does not require laborious ion exchange chromatography.



1, R = H (LY354740)
2, R = Me (LY541850)

Figure 1.

We reasoned that, since protecting groups, such as *t*-butyl ester, and *t*-butyloxycarbonyl (Boc) carbamate, can each be removed under relatively mild acidic conditions, fully protected compound **3**[5] might be cleanly converted to its corresponding deprotected zwitterion with a mild acid followed by isoelectric precipitation. Following several preliminary trials, we found that in the presence of excess $MeSO_3H$ in aqueous acetone at 60 °C for 18 h, all the protecting groups on **3** were cleanly cleaved (Scheme 1).[6] Next we tried to obtain the zwitterion through isoelectric precipitation, but were disappointed to find that the methanesulfonic acid salt of **2** was maintained throughout this process. Therefore, we resorted to cation exchange chromatography (Dowex 50X8-100 resin, H^+ form, eluents: 10% pyridine in water) to convert the salt to the zwitterionic form. Although the overall process with $MeSO_3H$ led to a high yield (94%) of zwitterionic **2**, lengthy and laborious ion exchange chromatography was still involved, greatly impeding access to compounds of this type.

We have previously used a 10% aqueous AcOH solution as an eluent in the aforementioned anion exchange chromatography[4] and have found that evaporation of this eluent under reduced

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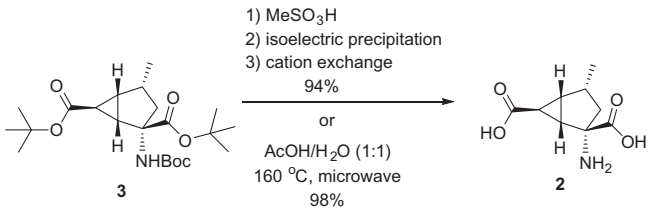
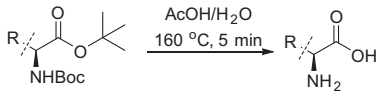


Scheme 1.

Table 1



R	R	Yield (%)	e (%)
BocHN	H_2N	84[a]	93
HO	HO	84	71
		73	88
HO	HO	81	91
N Boc	HN	82	96

[a] Acetic acid salt was obtained.

pressure consistently produces the final amino acids in its zwitterionic form. We reasoned that if AcOH could be employed to simultaneously remove both *t*-butyl ester and Boc protecting groups, we might be able to avoid ion exchange chromatography altogether and obtain zwitterionic amino acids after solvent removal. Thus, after adjusting both the reaction temperature and $AcOH/H_2O$ ratio, we were delighted to find that, by heating the mixture of **3** in $AcOH/H_2O$ (1:1, v/v) at 160 °C in a microwave for only 5 min, this fully protected glutamate analog **3** was cleanly converted to zwitterion **2** in a 98% yield after simple evaporation of solvents (AcOH and water) without any further purification or manipulation![7] Although this reaction worked equally well under conventional heating at lower temperatures, the reaction time was much longer. This straightforward and fast microwave procedure greatly reduced operational tediousness for this conversion, and enabled us to rapidly prepare and isolate additional unnatural amino acids of this type.[8] Finally, it is interesting to mention that the widely used trifluoroacetic acid (TFA) worked comparably under identical conditions. However, it yielded the TFA salt of **2** (^{19}F NMR spectroscopy) after the evaporation of volatiles.

We further applied these AcOH conditions to the deprotection of select natural amino acids to demonstrate the operational simplicity and usefulness of this reaction to access these amino acids in their zwitterionic form. Following the typical procedure, most protected amino acids[9] were cleanly converted to the zwitterionic form in moderate to high yields (Table 1).[10] Varying degrees of epimerization were observed with these amino acids,[11] which might constitute a limitation for this method.

In summary, an operationally simple and efficient method was developed to convert appropriately fully protected amino acids to their corresponding zwitterionic forms in high yields without involving either isoelectric precipitation or ion exchange chromatography. This method has been applied in the ongoing amino acid based research efforts in order to access these unnatural amino acids quickly and efficiently.

References and notes

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5. Synthesis of this compound **3** will be reported in due course.
6. *Experimental*: A solution of **3** (1.70 g, 4.13 mmol) in acetone (0.23 M, 18 mL) and water (4 M, 1.0 mL) was treated with methanesulfonic acid (21.69 mmol, 1.42 mL). The reaction was heated to 60 °C for 18 h with stirring. Cooled to room temperature and concentrated in vacuo. The pH was adjusted to approximately 2 with 1 N aqueous NaOH solution. The solution was concentrated to reduce the aqueous volume. The pH was further adjusted to 3 and the solid was collected via vacuum filtration. The filter cake was washed with isopropyl alcohol. The solid was dried overnight at 50 °C under vacuum. Proton NMR showed the material to be the methanesulfonic acid salt. It was combined with the filtrate, and adjusted to pH ~2. This mixture was loaded on a cation exchange column (Dowex 50X8-100, H^+ form). The resin was then washed with water, 50% aq THF, and water. Finally the product was eluted from the column with 10% aqueous pyridine. Eluents containing products were concentrated to a white crystalline solid. Additional water was added and the mixture was concentrated in *vacuo* (3 times, to remove any residual pyridine) to get the product **2** (0.82 g, 94%).
7. *A typical procedure is shown here*: A mixture of **3** (0.8 g, 1.94 mmol) in acetic acid (0.2 M, 9.7 mL) and water (0.2 M; 9.7 mL) was heated to 160 °C in a Biotage Initiator microwave for 5 min. After cooled to rt, the reaction mixture was concentrated in vacuo. Water was added and removed in vacuo (twice) to remove the residual acetic acid. The residual was washed with ^iPrOH to afford **2** (0.44 g, 98%) as a white solid after drying.
8. Application of these conditions to the syntheses of other [3.1.0]-bicyclic amino acid analogs for the group II metabotropic glutamate receptor will be published in due course.
9. These fully protected amino acids were either commercially available or synthesized through the standard protecting group manipulations.
10. The deprotection followed the procedure for **3**. Isolation of final amino acids was not optimized for best recovery.
11. The enantiomeric purity of the zwitterionic amino acids after deprotection was determined by a chiral HPLC (column: 4.6 × 100 mm Chirobiotic T, solvent: 70/30 (v/v) 3A $EtOH/H_2O$ containing 0.2% formic acid, flow rate: 1 mL/min, isocratic, detection: 205 nm).