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On the racemisation of aspartic anhydride during its preparation

Frédéric Buron, Geoffrey Deguest, Laurent Bischoff,* Corinne Fruit and Francis Marsais

Laboratoire de Chimie Organique Fine et Hétérocyclique, IRCOF-INSA Rouen, CNRS UMR 6014, BP 08, 76131 Mont-Saint-Aignan Cedex, France

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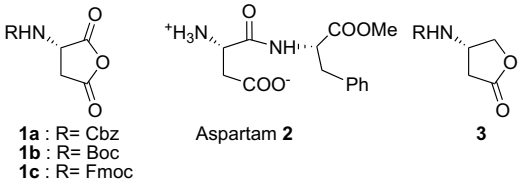
Abstract—Due to the possible differentiation of both carboxyl groups, N-protected aspartic anhydride is a useful starting material in synthesis. However, most methods published in the literature for its formation lead to partial racemisation, which is generally not mentioned. Herein we report a comparison between the main methods published, with accurate measurements of the enantiomeric purity of this compound.

1. Introduction

N-protected aspartic anhydride **1** was first described more than 70 years ago.[1] It has generally been used as a synthon with potential differentiation of both acid moieties, thus avoiding selective protection and activation sequences. Regioselective nucleophilic opening of the latter was achieved with alcohols,[2] amines,[3] hydrides[4] and carbon nucleophiles.[5] Frequently described syntheses using this reagent lead to either aspartam **2**[6] or lactone **3**[4] (Scheme 1).



Scheme 1. N-protected aspartic anhydride and products arising from this reactant.

Despite the usefulness of this molecule, little has been published concerning the racemisation of the α-carbon during the dehydration of the diacid. As we have encountered this problem during the preparation of *N*-Cbz aspartic anhydride **1a**,[5b] we have further examined the stereochemical outcome of the dehydration of *N*-Cbz aspartic acid, using standard literature procedures.

2. Results and discussion

2.1. Determination of optical purities

Unfortunately, the literature lacks reliable values of enantiomeric purities for these compounds. The anhydride itself is commercially available from Aldrich®, its $[\alpha]_D$ value is given in methanol. However, since N-protected aspartic anhydride reacts with methanol, this measurement must be taken as soon as the anhydride is solubilised. Indeed, the specific rotation of a methanol solution of *N*-Cbz aspartic anhydride, that is, $[\alpha]_D^{20} = -25$ (*c* 1, MeOH); $t = 1$ min; slowly decreased overnight. Methanol evaporation gave a compound whose NMR spectrum was consistent with the α-monoester *Z*-Asp(OH)-OMe. In addition, two different crystalline forms were described[7] for the *N*-Cbz anhydride and their common $[\alpha]_D$ value was given in glacial acetic acid.

Searching for a reliable method to measure the racemisation of the title compound led us to hydrolyse it in water under mild conditions. Thus, whatever the regioselectivity of the nucleophilic opening with water, N-protected aspartic acid will be the only product resulting from the hydrolysis. This allowed us a comparison with an authentic sample of enantiomerically pure N-protected aspartic acid. No racemisation occurred during the opening step, since enantiomeric excesses of up to 100% could be measured after the hydrolysis of the anhydride (Scheme 2).

These racemisations were measured using a chiral Chiracel OD column, eluting with [heptane–*i*-PrOH–TFA = 80:20:0.5]. Retention times were 5.98 min for the (*S*)-enan-

* Corresponding author. Fax: +33 235 5229 62; e-mail: laurent.bischoff@insa-rouen.fr

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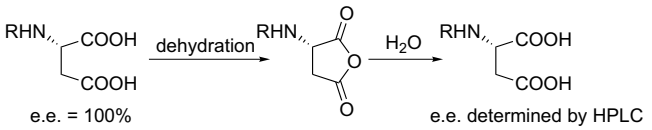

Scheme 2. Determination of enantiomeric purity after re-opening to the diacid.

tiomer, and 7.51 min for the (*R*)-enantiomer, first determined from racemic and L-enantiomer of *N*-Cbz aspartic acid.

2.2. Dehydration procedures

Many published reports account for the use of N-protected aspartic anhydride, but seldom give unambiguous enantiomeric ratios of the latter. In view of this study, we have examined most dehydration procedures reported in the literature, as listed in Table 1.

Dehydration protocols using acetic anhydride are the most commonly employed methods for obtaining **1a** (entries 1–7). The original reference[1] describes the use of Ac_2O, but does not actually provide an accurate protocol in terms of time and temperature. Our results suggest that racemisation depends on time, temperature and on the molar excess of acetic anhydride. The least racemising conditions were obtained with a low amount of Ac_2O, either neat (entries 1–3), or in ethyl acetate solution (entry 4). Increasing the temperature, reaction times or excess amounts of acetic anhydride resulted in higher racemisations, up to 40% ee (entries 2, 5 and 6).

Nevertheless, the same dehydration carried out during a very short period of time under microwave irradiation avoided such racemisation and gave the anhydride with a good 92% ee (entry 7).

Table 1. Formation of *N*-Cbz aspartic anhydride **1a** using different dehydration protocols described in the literature

Entry	Experimental conditions	ee[a]	Ref.
1	Ac_2O (0.7 ml for 1 g Cbz-Asp), 45 °C 15 min then rt 2 h	92	7
2	Ac_2O 3 M equiv, 100 °C 5 min	40	8
3	Ac_2O 2.1 M equiv, 50–60 °C 2.5 h	80	9
4	Ac_2O 1.5 M equiv, AcOEt (1 M), 54 °C, 2 h	84	10
5	Ac_2O 8.5 M equiv, 25 °C, 24 h	45	11
6	Ac_2O 30 M equiv, rt, 48 h then 50–55 °C, 2 h	76	12
7	Ac_2O 3 M equiv, microwaves, 210 W, 1 min	92	13
8	DCC 1 M equiv, rt, 12 h	96	2
9	Boc_2O 1 M equiv, 0.6 equiv pyridine, CH_2Cl_2 (0.5 M), rt 8 h	86	14
10	TFAA 1.4 M equiv, AcOEt (0.26 M), 35 °C, 1 h	100	15
11	Commercially available material (Aldrich)	100	

[a] Enantiomeric excesses of *N*-Cbz aspartic acid were measured after subsequent hydrolysis, using a HPLC Chiracel OD chiral column.

Table 2. Dehydration of *N*-Fmoc aspartic acid

Entry	R	Experimental conditions	ee
1	Fmoc	TFAA 1.4 M equiv, AcOEt (0.26 M), 35 °C, 1 h	86
2	Fmoc	DCC 1 M equiv, rt, 12 h	100

More reactive dehydrating agents were also proposed for this transformation. Dehydration with dicyclohexyl carbodiimide (DCC) afforded a nearly enantiomerically pure material (entry 8), whereas the stereogenic centre seemed slightly more sensitive to treatment with di-*tert*-butyl dicarbonate Boc_2O in the presence of pyridine (entry 9).

Treatment with trifluoroacetic anhydride in ethyl acetate under moderate heating was published on a kg-scale.[15] Using this method on a 1 g scale, afforded enantiomerically pure material. Eventually, we verified a sample of commercially available anhydride, the latter exhibiting a complete enantiomeric purity.

On the basis of these results, we checked whether the least racemising procedures would be applicable to similar *N*-Fmoc anhydride, in order to use it in solid-phase peptide synthesis (Table 2). *N*-Fmoc aspartic acid readily dehydrated in the presence of TFAA, but unexpected, partial racemisation was observed. Finally, dehydration of the latter with DCC gave an excellent enantiomeric excess. Apparently, *N*-Fmoc anhydride is more sensitive to racemisation in acidic medium than *N*-Cbz anhydride.

3. Conclusion

Despite what is generally assumed, the dehydration of N-protected aspartic acid often leads to high rates of racemisation. This work allows a choice of the experimental conditions for the preparation of this reagent, taking into account the enantiomeric purity obtained through different methods.

4. Experimental

4.1. Procedures for non-racemising dehydration

4.1.1. TFAA protocol.[15] To a solution of *N*-Cbz aspartic acid (1 g, 3.74 mmol) in ethyl acetate (14 mL) was added trifluoroacetic anhydride (0.73 mL, 5.24 mmol). After heating for 1 h at 35 °C, concentration in vacuo afforded pure *N*-Cbz aspartic anhydride (0.93 g, 100%).

4.1.2. DCC protocol.[2] To a solution of *N*-Cbz aspartic acid (1 g, 3.74 mmol) in THF (7 mL) was added dicyclohexylcarbodiimide (772 mg, 3.74 mmol) at −5 °C. After stirring overnight at room temperature, DCU was precipitated at 0 °C and removed by filtration. Concentration in vacuo afforded pure *N*-Cbz aspartic anhydride (0.93 g, 100%).

4.2. Determination of the rates of racemisation

Re-opening by mild aqueous hydrolysis was carried out by stirring a water suspension (20 mL for 200 mg) of the anhydrides in water at room temperature for three hours, and freeze-drying of the solution. An aliquot was dissolved in a mixture of heptane and isopropanol (80:20). Enantiomeric excesses were measured on a chiral Chiracel OD column, eluting with [heptane–*i*-PrOH–TFA = 80:20:0.5] at a flow rate of 1 ml/min, measuring at 254 nm. Retention times were 5.98 min for the (*S*)-enantiomer and 7.51 min for the (*R*)-enantiomer, first determined from commercially available racemic and (L)-aspartic acid.

With *N*-Fmoc aspartic acid, retention times were 10.79 min for the (*S*)-enantiomer and 15.32 min for the (*R*)-enantiomer.

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