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PRACTICAL SYNTHESIS OF METHYL Z-2-(N-ACETYLAMINO)BUT-2-ENOATE. AN INTERMEDIATE TO D- AND L-2-AMINOBUTYRIC ACID

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Abstract: Treatment of inexpensive L- or DL-threonine methyl ester with acetic anhydride and either pyridine or anhydrous sodium acetate at reflux results in dehydration yielding the N,N-diacetamide of the title compound in >80% yield. Monodeacetylation of the diacetamide with 0.1 equiv of triethylamine in methanol affords the title monoacetamido derivative 1 in nearly quantitative yield.

D- and L-2-aminobutyric acid are compounds of potential commercial importance. These nonessential amino acids are present in a variety of peptide and peptidomimetic derivatives with interesting biological activity.[1] The L-isomer, (S)-(+)-2-aminobutyric acid, can serve as an intermediate for the manufacture of the tuberculostatic drug ethambutol[2] while the D-isomer is the key building block for a new high-potency sweetener[3]. State-of-the-art asymmetric hydrogenation technology provides access to these α-amino acids, with very high selectivity for a single enantiomer. For

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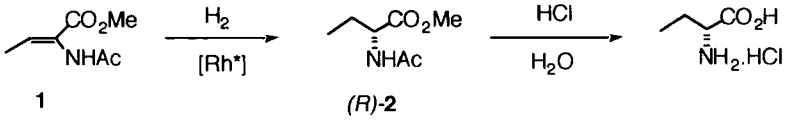
example, using rhodium catalysts bearing chiral DuPHOS ligands[4], either enantiomer of 2-aminobutyric acid can be prepared from the acetamidocrotonate 1 in 99% enantiomeric excess. This is illustrated for the case of (*R*)-2-aminobutyric in eq. 1:

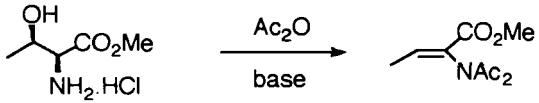


1 (*R*)-2 (1)

Unfortunately, large scale manufacture of the necessary dehydroamino acid 1 has proven problematic. One attractive route to 1 would be the selective dehydration of the inexpensive L- or DL-threonine, a transformation which is well precedented on a laboratory scale. Existing procedures include both *step-wise* and *direct* dehydration protocols. In the step-wise approach, the hydroxyl group is first converted into an isolated intermediate bearing a better leaving group such as p-toluenesulfonate[5,6] which then undergoes base-induced elimination in a separate step. The direct approach typically utilizes expensive reagents such as diisopropylcarbodiimide[7], N,N-carbonyldiimidazole[8], or DAST[9] (diethylaminosulfur trifluoride). An alternative one-pot procedure uses commercially viable diethyl chlorophosphate and sodium hydride but product isolation appears to require chromatography[10]. A general problem which must be addressed in any synthetic route to 1 is its high water solubility which precludes extractive work-up. In this paper we describe an improved procedure for the direct dehydration of threonine esters using very inexpensive reagents. This new procedure is fully amenable to large scale manufacture.[11]

When a solution of threonine methyl ester in 1:1 volume pyridine/acetic anhydride was heated at reflux for 2 h (eq. 1) a single product was obtained upon extractive work-up. This was

shown by elemental analysis and ^1H NMR to be methyl 2-N,N-diacetylaminocrotonate 3. It was also evident from the NMR that the 3 is formed as a single diastereomer.

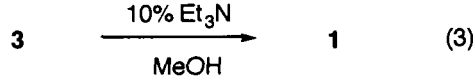


(2)

3

Subsequent investigation revealed that a variety of other weak bases besides pyridine could be utilized in eq. 2. Of the bases examined, anhydrous sodium acetate is especially advantageous from the standpoint of product isolation and allows the straightforward synthesis of 3 in >80% yield after distillation.

Since monoacetamides of dehydroamino acids are commonly utilized as substrates for asymmetric hydrogenation reactions, we next investigated the selective mono-deacetylation of 3. This is readily accomplished by heating a methanol solution of 3 in the presence of a catalytic amount of triethylamine (eq. 3).

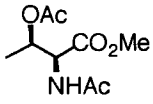


(3)

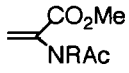
The crystalline monoacetamide 1 could be isolated by simply distilling off the volatiles at reduced pressure. Comparison of the ^1H NMR spectrum of the product with those reported[12] for the Z and E compounds clearly indicates that 1 is formed as the Z stereoisomer. (On this basis we also tentatively assign the stereochemistry of 3 as Z.)

The detailed mechanism for the dehydration process of eq. 2 remains unknown. However, several relevant observations can be noted. It is assumed that this process requires prior conversion of the threonine hydroxyl to the O-acetyl derivative thus providing a better leaving group. Consistent with this expectation, an authentic sample of O,N-diacetyl threonine 4 was cleanly dehydrated to 3

when heated in 1:1 pyridine/acetic anhydride (2 h, reflux). In contrast, when the O,N-diacetyl derivative was heated in pyridine at reflux without any added acetic anhydride, elimination occurred only slowly (<10% reaction after 2 h) suggesting that diacetylation of the amine nitrogen facilitates the dehydration process. However, complicating this proposal[13] is the observation that dehydration of serine methyl ester hydrochloride in refluxing acetic anhydride/sodium acetate (under identical conditions to those used for prepartion of 3) gives a roughly 1:1 mixture of monoacetamide 5a and diacetamide 5b.



4



5a, R = H
5b, R = Ac

The highly stereoselective formation of the Z stereoisomer 3 was further probed by carrying out the elimination on a sample of N-acetyl-*allo*-threonine methyl ester. We were surprised to find that the product was again the Z diastereomer, 3. Thus eq. 2 is stereoselective but not stereospecific. Possible explanations for this observation are that dehydration of threonine and *allo*-threonine proceed through a common intermediate or that both isomers are initially formed but that the E diastereomer isomerizes to Z under the reaction conditions. Distinguishing between these possibilities must await studies of the authentic E diastereomer under these conditions.

EXPERIMENTAL

Methyl 2-(N,N-diacetylamino)-Z-but-2-enoate, 3. A mixture of L-threonine methyl ester hydrochloride (17.0 g, 0.100 mol) and anhydrous sodium acetate (50.0 g, 0.610 mol) in acetic anhydride

(150 mL) was heated at reflux for 2 h. Volatiles were removed with a rotary evaporator connected to a vacuum pump. The residue was taken up in ether (250 mL) and water (250 mL). The ether layer was separated and further washed with water (50 mL). The ether was distilled off on a rotary evaporator and the residue was subjected to simple distillation into a receiver containing a few crystals of hydroquinone to afford 3 (16.34 g, 82%) as a pale yellow liquid, b.p. 88-92 ° C at 0.5 torr. Anal. for $C_9H_{13}NO_4$. Calcd: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.14; H, 6.66; N, 6.90. ^1H NMR ($CDCl_3$/TMS): δ 1.80 (d, J = 7, 3 H), 2.32 (s, 6 H), 3.80 (s, 3 H), 7.22 (q, J = 7, 1 H). ^{13}C NMR ($CDCl_3$/TMS): δ 13.37, 25.44, 52.35, 130.66, 140.36, 163.52, 171.73.

Methyl 2-(N-acetylamino)-Z-but-2-enoate, 1. A solution of 3 (14.45 g, 72.54 mmol) and triethylamine (1.0 g, 10 mmol) in methanol (200 mL) was heated at reflux overnight. The volatiles were removed at reduced pressure to afford a yellow liquid (13.43 g) which crystallized over the course of several hours. The product was triturated with hexane and dried in high vacuum to afford 1 (11.09 g, 97%) as an off-white solid, m.p. 53-54°C, of adequate purity for asymmetric hydrogenation under the conditions of eq. 1. Dissolution of the crude product in ether (20 mL/gram) and cooling the resulting solution to -25°C to provide 1 as snow-white needles, m.p. 59-60°C, Anal. for $C_7H_{11}NO_3$ Calcd: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.30; H, 7.04; N, 8.75. ^1H NMR($CDCl_3$/TMS): δ 1.77 (d, J = 8, 3 H), 2.13 (s, 3 H), 3.76 (s, 3 H), 6.81 (q, J = 8, 1 H). ^{13}C NMR: δ 14.52, 23.19, 52.27, 126.44, 134.27, 165.17, 168.75.

***(R)*-(-)-2-N-Acetylaminobutanoic Acid Methyl Ester, *(R)*-2.** In a nitrogen filled glove box a Fisher-Porter apparatus was charged with 1 (8.26 g, 70.6 mmol), methanol (100 mL), and cyclooctadiene-

(*R,R*)-(methylDuPHOS)rhodium(I) trifluoromethanesulfonate (5 mg, 0.01%). The bottle was flushed several times with hydrogen and was then pressured to 30 psi. After 3 h hydrogen uptake had ceased but stirring was continued overnight. Filtration through a short bed of silica followed by removal of solvent at reduced pressure afforded (*R*)-2 with spectroscopic properties identical to those reported earlier.[4] $[\alpha]_D^{25}$ -24.6 ° (c = 1, chloroform). Capillary column gas chromatographic analysis on Chiracel XE60-S-val indicated that product was formed in 98.9% ee (140 ° C isothermal, major peak 23.0 min, minor peak 23.5 min).

A sample of the product was quantitatively deprotected following the literature protocol[4] (6 N HCl, reflux, 6 h). The crystalline (R)-2-aminobutyric acid hydrochloride so obtained was reprotected (methanol/HCl reflux; pyridine/acetic anhydride, 25 ° C). The enantiomeric excess of the reprotected (*R*)-2 was determined using the above protocol to be 98.2%

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13) Differences in the dehydration of serine and threonine may result from threonine having to adopt a conformation where the methyl group must be syn-periplanar to a large group for elimination to occur thus incurring a substantial non-bonded interaction as the reaction proceeds through the transition state.

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