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Facile Determination of the Optical Purity of α-N-Boc-Amino Aldehydes[1]

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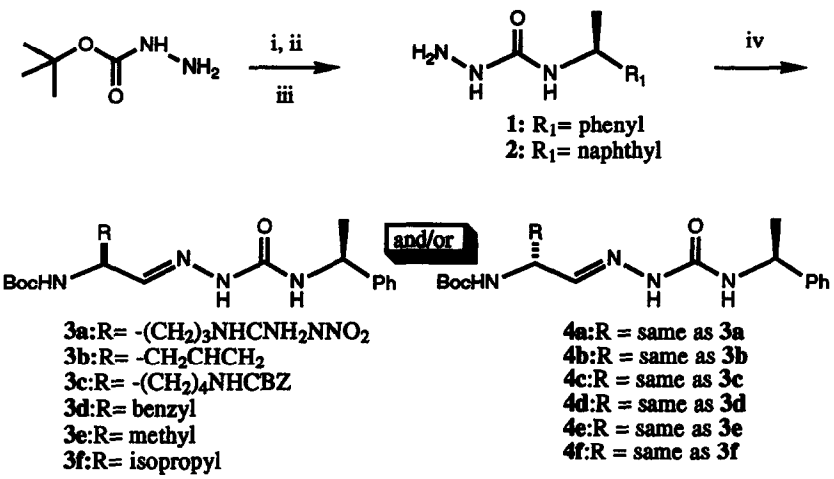
Abstract: A facile ^{1}H NMR spectroscopic method is presented for the determination of the optical purity of α–amino aldehydes, via derivatization with optically pure semicarbazides .

Optically pure α–amino aldehyde derivatives are synthetically useful as intermediates for the preparation of enzyme inhibitors and other valuable derivatives.[2] The determination of optical purity of α–amino aldehyde derivatives by conventional methods is often difficult or inaccurate. For example, a precise method has been reported for the determination of the optical purity of α-Boc-leucinal; this procedure involves reduction of the aldehyde to the alcohol, followed successively by oxidation to the acid, removal of the Boc group, reaction with dansyl chloride and analysis of the resulting derivative using chiral chromatography.[3] We have prepared several α–amino aldehyde derivatives in connection with our work, and therefore desired a facile and accurate way to measure their optical purity.[4] The application of chiral solvents or chiral shift reagents[5,6] is complicated by the fact that α–amino aldehyde derivatives can exist as mixtures of free aldehyde, hydrated aldehyde, and (as in the case of argininal derivatives) as cyclic guanidinocarbinol forms.[2] The known chiral derivatizing reagents[6] have not been shown to be useful for the determination of the optical purity of the title compounds by NMR, to our knowledge. We prepared the optically active semicarbazide derivatives[7] (see Scheme 1) with the expectation that diastereomeric semicarbazones derived from them would have distinct ^{1}H or ^{13}C NMR signals, depending on the absolute stereochemistry of the R group.

We prepared α–Boc-Nᵍ-nitro-(L)-argininal and α–Boc-Nᵍ-nitro-(D)-argininal, starting from the corresponding acid, using the published procedure.[4,8] We prepared the optically pure semicarbazide **1** using the general procedure for the synthesis of semicarbazides, which has been developed in our laboratory.[4,8] We then used the semicarbazide **1** to prepare the corresponding semicarbazones of α–Boc-Nᵍ-nitro-(L)-argininal and α–Boc-Nᵍ-nitro-(D)-argininal (see Scheme 1).[9] The product of the reaction of **1** with α–Boc-Nᵍ-nitro-(L)-argininal was expected to be **3a** and the product of the reaction of **1** with α–Boc-Nᵍ-nitro-(D)-argininal was expected to be **4a**. Though the ^{13}C NMR spectra were identical, the ^{1}H NMR spectra (400 MHz) clearly show distinct Boc peaks at δ1.45 and 1.46 ppm.[10] To confirm this slight difference, mixtures of **3a** and **4a** were prepared in various ratios and ^{1}H NMR spectra were obtained (see Figure 1). These experiments confirmed the difference in the Boc *t*-butyl chemical shifts, and showed that as little as 1% of a diastereomer could be detected. No indication of racemization was observed which would have been attributable to the synthesis of the aldehyde or its conversion to the semicarbazone. With this result in hand we decided to investigate the

derivatization of a racemic aldehyde. We prepared the racemic aldehyde α-N-Boc-allyl glycinal, using the same procedure that we have previously employed.[8] Racemic α-N-Boc-allyl glycinal was allowed to react with **1** to give a mixture of diastereomeric semicarbazones **3b** and **4b**. The ^1H NMR (in $CDCl_3$) spectrum shows resolution of the methyl doublet, and of the Boc signals (at δ1.42 and 1.44 ppm) of these diastereomers. Integration shows the expected 1:1 ratio of the diastereomers, demonstrating that the isomer ratio was not changed during the isolation of the semicarbazone mixture.[10] The derivative **2** was prepared but the semicarbazones derived from **2** did not show any overall advantages to those derived from **1** for the spectroscopic determination of optical purity of the title compounds.

Scheme 1



i) carbonyl diimidazole, DMF. ii) (S)1-arylethylamine. iii) trifluoroacetic acid/ dichloromethane, 1:1. iv) BocNHCHR-CHO/ NaOAc in EtOH/H_2O.

We also prepared the enantiomer of **1** (from the commercially available (R)-1-phenethylamine) so that diastereomeric pairs of the derivatives could be prepared from a single optically pure title compound. To further investigate the scope and limitations of this technique we prepared the derivatives **3c**, **3d**, **3e**, **3f**, and the diastereomers **4c**, **4d**, **4e**, and **4f** (as the enantiomers of the structures shown).[7,8,9] These compounds showed similar distinct chemical shifts as seen with the corresponding semicarbazones, above. This suggests that these observations may hold true for many of the title compounds, making this a generally useful technique for many of these important synthetic intermediates. The use of compound **1** and its enantiomer allows for the facile validation of the utility of this technique for other title compounds.

The chemical shift differences that we have observed are independent of concentration, between the range of 0.1 and 2%. The solvent deuteromethanol was chosen because of the polar nature of these semicabazones (the solubility of **4a** in chloroform, for example, is minimal). The semicarbazones (**3b**, and **4b**) show the identical spectral nonequivalence of Boc resonance between diastereomers in

deuterochloroform or deuteromethanol. It is possible that an intramolecular hydrophobic interaction between the aromatic ring of the semicarbazone and the *t*-butyl group, or a hydrogen bonding interaction, is responsible for the spectral nonequivalence of the diastereomeric semicarbazones. More studies will be required before firm conclusions can be made in regard to the mechanistic basis of the spectral nonequivalence.

Figure 1

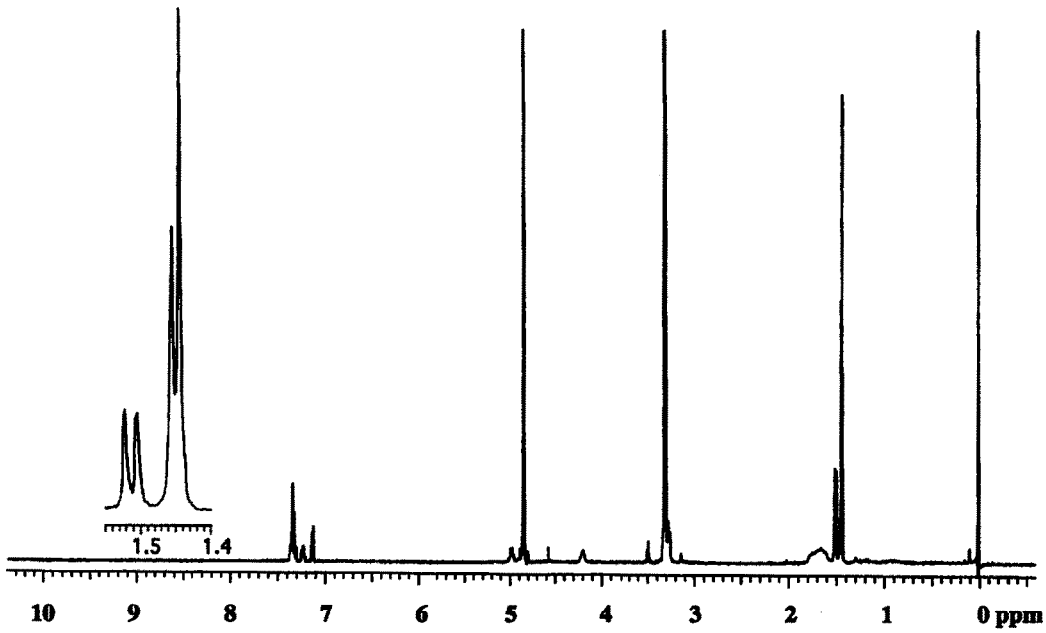


Figure 1. A ^{1}H NMR (400 MHz) spectrum of 2:1 mixture of **3a** and **4a** in deuteromethanol. The insert shows an expansion of the region between 1.40 and 1.55 ppm.

In conclusion, we have demonstrated that the optical purity of several α-Boc-amino-aldehydes can be readily determined by their reaction with chiral semicarbazides, and their subsequent analysis by ^{1}H NMR. The semicarbazides are easily prepared, stable, crystalline compounds. The multiple forms that are normally observed with argininal derivatives are converted to a single derivative, thus dramatically simplifying the determination of optical purity of these compounds. In the cases that we have examined, the diastereomers' methyl doublet, or the Boc singlet, or both, are distinct in their ^{1}H NMR spectra. We find that the integration of the Boc singlet is most convenient for quantification. We were surprised that the ^{1}H NMR resonance of the Boc group would be most affected by the presence of an apparently remote chiral center. Though the exact mechanistic cause of the observed chemical shift nonequivalence is not clear at this time, we have found that the reagents **1** or **2** to be very convenient for the determination of optical purity of the synthetically useful title

compounds. We routinely use **1** for that purpose in our laboratory. High performance liquid chromatography should also be useful for the more accurate quantification of optical purity using the semicarbazones, for those researchers who prefer that technique.

Acknowledgment: We would like to thank Aileen M. Murphy for the initial synthesis of **1**.

References and Notes:

1. This was presented, in part, at the XIIth International Symposium on Medicinal Chemistry, in Basel, Switzerland: September, 1992.

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7. The general procedure is exemplified by the synthesis of the semicarbazide **1**, as follows; A solution of carbonyldiimidazole (6.7 g, 41.3 mmol) was dissolved in 100 mL DMF, while maintaining a dry nitrogen atmosphere. A solution of t-butyl carbazate (5.45 g, 41.3 mmol) in 100 mL DMF was added dropwise over 30 minutes. (S)-Methylbenzylamine (5g, 41.3 mmol) was added followed by dropwise addition of TEA (6.2 mL). The reaction was allowed to stir at room temperature for one hour. Water was added and the solution was extracted three times with ethyl acetate. The combined organics were washed with 1N HCl, H_2O, $NaHCO_3$, and brine, then dried ($MgSO_4$), filtered and concentrated to an oil. The resulting crude N-4-Boc-(S)-Methylbenzyl semicarbazide was dissolved in 50% TFA/DCM at 0°C. The ice bath was removed and the solution was allowed to stir for one hour at rt. The reaction was concentrated to an oil under vacuum. This oil was dissolved in toluene and concentrated to a small volume . Ether and hexane were added to turbidity and this mixture cooled in an ice-bath to facilitate the crystallization of product. The mixture was filtered to give 5.1 grams in the first crop (44% yield) of pure product as white needles (mp= 132-133° C), an additional crop of product could be isolated from the mother liquor (~4 grams). ^1H NMR ($CDCl_3$, TMS) δ= 1.50 (d, 3H, J= 7 Hz), 4.98 (m, 1H), 5.92 (d, 1H, 7Hz) 7.27 (m, 5H). ^{13}C NMR (CD_3OD) d= 21.47, 48.78, 124.9, 125.5, 126.0, 127.6, 128.1, 144.2, 160.5. Anal. Calcd. for $C_{11}H_{14}N_3F_3O_3$: C, 45.05; H, 4.81; N, 14.33. Found: C, 44.95; H, 4.81; N, 14.47.

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9. This general procedure is exemplified by the synthesis of **3a**; A mixture α–Boc-N^g-nitro-(L)-argininal (50 mg, 0.18 mmole), **1** (61 mg, 0.20 mmole) and NaOAc trihydrate (41 mg, 0.3 mmole) was dissolved in 0.4 mL of 3:1 ethanol: water and refluxed for 30 min. This mixture was allowed to cool, then poured into water and extracted several times with ethyl acetate. The combined organic phase was extracted with water and saturated NaCl, dried ($MgSO_4$) and concentrated to a small volume. This solution was treated with ether and the resulting white solid was isolated by filtration. (The precipitation must be done rapidly to avoid the possibility of selective crystallization of one diastereomer.) This gave 40mg (50% yield) of pure **3a**, mp= 164-166° C. ^1H NMR (CD_3OD, TMS) δ= 1.45 (s, 9H), 1.51 (d, 3H, J=7 Hz), 1.6-1.8 (m, 4H), 3.26 (t, 2H), 4.18 (bs, 1H), 4.97 (q, 1H, J=7 Hz), 7.31 (d, 1H, J= 8 Hz), 7.34 (m, 5H). Anal. Calcd for $C_{20}H_{32}N_8O_5$: C, 51.71; H, 6.94; N, 24.12. Found: C, 51.60; H, 6.95; N, 24.02.

10. All NMR spectra were obtained using a Varian XL-400 instrument in the indicated solvent at 22° C with tetramethylsilane as the internal standard (δ= 0.00).

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