for $C_6H_7O_4N$: C, 41.63; H, 4.08; N, 8.09. Found: C, 41.71; H, 3.97; N, 7.82.

Preparation of α-L-Aspartyl-L-phenylalanine Methyl Ester Hydrochloride 9. L-Phenylalanine (7.4 g, 0.045 mol) was stirred in 90 mL of water. The pH of this solution was adjusted to 10.2 (0–2 °C) with 50% NaOH. Then a solution of pure NCA 7 (8.3 g, 0.048 mol) in 8 mL of THF was added in 15 min with vigorous stirring. The pH was maintained at 10.0–10.2 by the addition of 7 N NaOH solution. The reaction mixture was then stirred at 0–2 °C for 2 h (pH 10.0–10.2). One equivalent of 37% hydrochloric acid (9.7 g) was added at the end of the hold period. Liquid chromatography indicated an 80–82% yield of aspartyl ester 8 based on L-phenylalanine. This clear solution was extracted twice with 50-mL portions of ethyl acetate. To the aqueous solution, 4.2 g of 37% HCl (0.043 mol) was added. The solution was concentrated in vacuo to a total weight of 31.1 g. Another 8.4 g (0.085 mol) of 37% HCl was added, and the reaction slurry was held at 40 °C for 6 h to convert 8 to α-L-aspartyl-L-phenylalanine hydrochloride **10**. Solid (NaCl) was collected and washed with 2.6 g (0.026 mol) of 37% HCl and 7.5 g of methanol. Seed crystals were added to the combined filtrate and washings. The resulting solution was stirred at ambient temperature for 68 h. The thick slurry was cooled to 0–2 °C, and the solid was collected by filtration and washed with 7 mL of cold water. The dry weight of **9** was 9 g (55% yield[7] based on L-phenylalanine). This material was then neutralized with sodium hydroxide to give aspartame 1,[2a] $[\alpha]^{20}_D$ 30.3° (*c* 1.0, HOAc), authentic sample, $[\alpha]^{20}_D$ 30.1° (*c* 1.0, HOAc).

Registry No. 1, 22839-47-0; 7, 21933-62-0; 8, 22839-82-3; 9, 5910-52-1; L-aspartic acid, 56-84-8; β-methyl-L-aspartate hydrochloride, 16856-13-6; phosgene, 75-44-5; L-phenylalanine, 63-91-2.

(7) The HPLC analysis of the mother liquor indicated the presence of a 2:2:1 ratio of **8**, **9**, and diacid **10**. A small amount of phenylalanine and diester **11** were also observed. It is likely that recycling the mother liquor would raise the overall yield of **9** above the current 55%.

N-Methyloxazolinium Salts: Diastereomer Ratios by ^{1}H NMR

Mark. J. Kurth,* Edward G. Brown, and Owen H. W. Decker

Department of Chemistry, University of California, Davis, Davis, California 95616

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The oxazoline heterocycle is very useful in synthesis, particularly as a transient chiron[1,2] in enantioselective methodology,[3,4] The expanding structural complexity of chiral products made available by the numerous oxazoline-based synthetic methods complicates the analytical problem of assessing the enantioselectivity obtained in these various transformations. As is inherent to all enantioselective methods employing a transient chiron, the chiral products obtained in each oxazoline-based variant are diastereomeric in nature. Thus, prior to liberation of the transient chiron, they accommodate a variety of methods for assessing the degree of asymmetric induction (i.e., diastereoselectivity).

The two analytical methods most successfully used in oxazoline-based studies are high-pressure liquid chromatography (HPLC) and ^{1}H NMR. Of the two, HPLC has generally been the analytical tool of choice because it is versatile, sensitive, and reliable. Unfortunately, its application to a broad range of substrates can be complicated, and often requires experimentation with a large number of column and solvent variations. This is particularly true for nonrigid oxazolines in which the chiral centers are separated by several atoms.

Given the ease of sample preparation and the availability of high-field instrumentation, direct ^{1}H NMR analysis of oxazoline diastereomers would appear to be an attractive alternative. We find, however, that only rarely are baseline-resolved diastereomeric resonances observed (vide infra). Indeed most ^{1}H NMR derived ratios have been determined by chiral lanthanide-induced shift (LIS) studies on the enantiomers after the transient chiron has been removed.[5] LIS studies, although versatile, are limited by the vicissitudes of fortune and the paramagnetic line broadening inherent in the method.[6] This loss of resolution due to line broadening is particularly troublesome in the assessment of product ratios from highly enantioselective methods.

Our aza-Claisen work,[4] which generates oxazolines with chiral centers separated by two or three atoms required a rapid, general method for diastereomer ratio determination. While HPLC resolves a number of these diastereomers, we have found that baseline resolution via HPLC is capricious, particularly when the chiral centers are separated by three atoms. Faced with the time-consuming prospect of generating a unique HPLC protocol for each new substate, we set out to develop a rapid and reliable ^{1}H NMR method of assessing oxazoline-based diastereomer ratios.

In the course of developing our aza-Claisen procedure, we prepared a series of *N*-allyloxazolinium salts. In each case, a number of significant chemical shift changes were noted in the ^{1}H NMR spectrum of the salt relative to the unalkylated oxazoline. While downfield shifts were anticipated for protons proximal to the delocalized charge,[7] a number of more remote protons displayed unexpected shifts. These "aberrant" chemical shift changes may be the result of restricted rotation about the C(2)–C(α) bond caused by conformational restraints imparted by the N-allyl substituent.[8] Extending this observation to diastereomeric oxazolines, we reasoned that *N*-alkylation would amplify the conformational bias of each diastereomer and might, therefore, afford baseline resolution of peaks in the ^{1}H NMR.

This proved to be the case. For example, the 360 MHz ^{1}H NMR spectrum of a diastereomeric mixture of N-allyloxazolinium salts **1** displayed a number of base-line-resolved resonances (Table I). In contrast, a diastereomeric mixture of (4*S*,1′*R*)- and (4*S*,1′*S*)-4,5-dihydro-4-(1-methylethyl)-2-(1-phenylethyl)oxazole gave no base-line-resolved ^{1}H NMR resonances.

Although *N*-allyl salts could be used to determine diastereomer ratios in several cases, generally they were not useful due to the complexity of their ^{1}H NMR spectra. We therefore turned to the *N*-methyl derivatives and were delighted to find that these salts not only afforded much simpler NMR spectra, but also were formed faster, under

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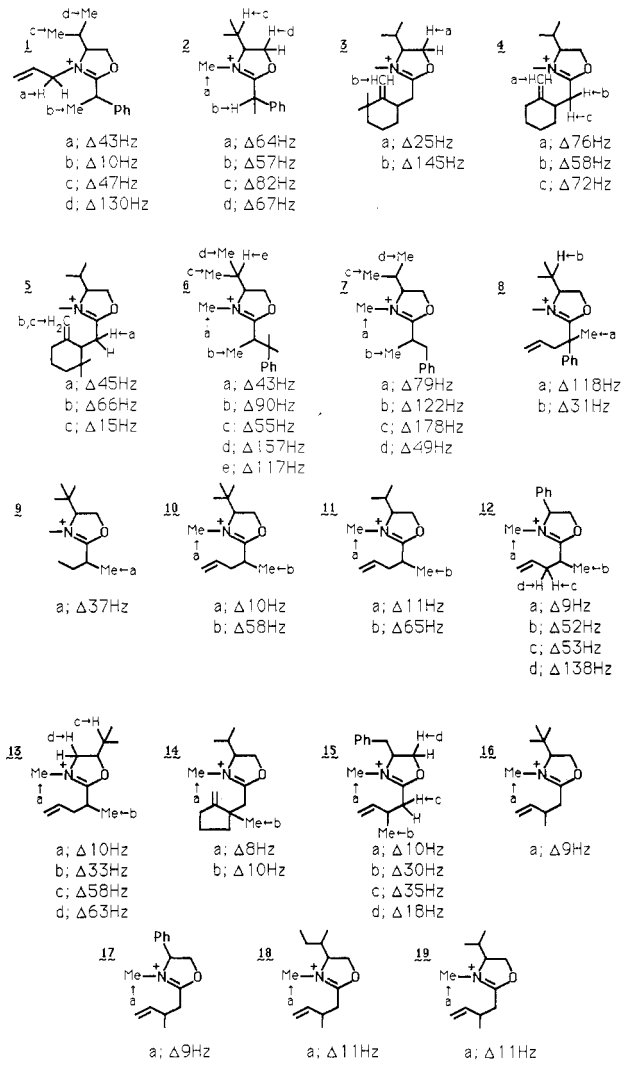
Table I. ^{1}H NMR[a] Chemical Shift Differences[b] in Diastereomeric Oxazolium Salts[c]



[a] Data collected on a Nicolet NTCFT-1180 spectrometer (360 MHz). [b] Only chemical shift differences (Δ) for baseline resolved (Δ ≥ 8 Hz) diastereomeric resonances are listed here. [c] See the supplemental material for a complete listing of ^{1}H NMR data for these oxazolium salts.

milder conditions, by using inexpensive dimethyl sulfate.[9]

Inspection of the Table I reveals that striking differences in chemical shifts between diastereomeric *N*-methyloxazolinium salts are common. It should be kept in mind that this table does not list all the resolved diastereomeric resonances. In many cases, a coincident overlap of resolved diastereomer resonances with other resonances in the spectrum made overall ratio-determination by base-line resolution of peaks impossible on the 360-MHz spectrometer.

Generally, we found the most useful resonance differences to be: (i) Those due to the *N*-methyl group. In 13 of the 18 *N*-methyloxazolinium salts listed in Table I, the separation of methyl peaks was >8 Hz and could be integrated accurately. (ii) Those due to a C-α methyl group. Base-line resolutions of peaks were obtained in 8 of the 9 examples listed. The average separation between methyl resonances was about 60 Hz, but extended as high as 122 Hz in **7**. (iii) Those due to the exocyclic methylene resonances of oxazolines bearing alicyclic substituents. In all four cases, base-line resolution of peaks was obtained. The method is not limited to oxazolines bearing C(4) substituents. Compound **13** demonstrates that the technique is also applicable to C(5) chiral oxazolines.

N-Methyloxazolinium salts were prepared in essentially quantitative yield by treating the oxazoline with 1.2 equiv of dimethyl sulfate, a procedure which is amenable to analytical scale preparations (<5 mg). The crude product is taken up in chloroform-*d* and analyzed by ^{1}H NMR. While these salts are reasonably stable, they are susceptible to base-catalyzed hydrolysis[10] and should be prepared just prior to analysis. With proper care in their preparation and storage, we find that chloroform-*d* solutions of these salts are stable for at least one week at 0 °C. Furthermore, at room temperature, D_2O solutions of these salts hydrolyze over several hours whereas addition of lithium deuterioxide causes complete hydrolysis in just a few minutes.

In conclusion, we find that this method permits rapid, accurate determinations of oxazoline diastereomer ratios. Further studies which rely upon this new analytical technique are currently in progress in these laboratories.

Experimental Section

General. Analytical samples were prepared by GLC using a 5 ft × $^3/_8$ in. column packed with 5% SE-30 on Chromasorb W, 30/60 mesh. A Nicolet NT-360 360 MHz spectrometer was used for NMR experiments. Elemental analyses for all new compounds were performed by the University of California, Berkeley, Analytical Laboratories.

Preparation of (4*S*,1′*R*)- and (4*S*,1′*S*)-4,5-Dihydro-4-(1-methylethyl)-2-(1-phenylethyl)-3-(2-propenyl)oxazolinium 4-Methylbenzenesulfonate (1a and 1b). An approximately equimolar mixture of (4*S*,1′*R*)- and (4*S*,1′*S*)-4,5-dihydro-4-(1-methylethyl)-2-(1-phenylethyl)oxazole (0.033 g, 0.15 mmol) was heated 16 h with 2-propenyl 4-methylbenzenesulfonate (0.035 g, 0.17 mmol) at 85 °C. Cooling, trituration with Et_2O (3 × 2 mL), and evaporation at 1 torr gave 0.028 g, 0.066 mmol, 44% of a viscous yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.61 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.69 (d, *J* = 7.1 Hz, 3 H), 1.72 (d, *J* = 6.9 Hz, 3 H), 2.17 (m, 1 H) , 2.34 (s, 6 H), 2.38 (m, 1 H), 4.17 (dd, *J* = 7.1, 15.6 Hz, 1 H), 4.28 (dd, *J* = 8.2 Hz, 16.3 Hz, 1 H), 4.50 (dd, *J* = 6.4, 15.6 Hz, 1 H), 4.55 (q, *J* = 6.9 Hz, 1 H), 4.67 (dd, *J* = 9.1, 5.7 Hz, 1 H), 4.73–4.83 (m, 2 H), 4.83–4.92 (m, 3 H), 5.14 (t, *J* = 12.7 Hz, 1 H), 5.24–5.37 (m, 3 H), 5.46 (dd, *J* = 9.5, 10.4 Hz, 2 H), 5.75 (m, 2 H), 7.14 (d, *J* = 8.0 Hz, 4 H), 7.20–7.45 (m, 10 H), 7.79 (d, *J* = 8.0 Hz, 4 H); IR ($CHCl_3$) 3000, 2920, 1632, 1460, 1380, 1165, 1125, 1015, 820, 690, 670 cm^{-1}.

Procedure for the Preparation of *N*-Methyloxazolium Salts. To the appropriate mixture of diastereomeric oxazolines (5 mg) in a 5-mL flask was added dimethyl sulfate (1.2 equiv). The flask was centrifuged briefly, then stirred 1.5 h. The resulting clear colorless viscous oils, composed of diastereomeric mixtures, were directly subjected to NMR and IR analyses.

(4*S*,2′*R*)-2-((3,3-Dimethyl-2-methylenecyclohexyl)-methyl)-4,5-dihydro-3-methyl-4-(1-methylethyl)oxazolium Methyl Sulfate (3a). ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 7.5 Hz, 3 H), 1.06 (s, 3 H), 1.11 (s, 3 H), 1.20–1.30 (m, 1 H), 1.48–1.79 (m, 5 H), 2.30 (qqd, *J* = 7.5, 6.3, 4 Hz, 1 H), 2.76 (dd, *J* = 16.7, 9.2 Hz, 1 H), 2.76–2.85 (m, 1 H), 3.20 (dd, *J* = 16.7, 9.1 Hz, 1 H), 3.44 (s, 3 H), 3.73 (s, 3 H), 4.60 (dd, *J* = 9.2, 6.6 Hz, 1 H), *4.64* (br s, 1 H), 4.79 (ddd, *J* = 10.6, 6.7, 4 Hz, 1 H), 4.85 (br s, 1 H), 5.21 (dd, *J* = 10.6, 9.3 Hz, 1 H).

(4*S*,2′*S*)-2-((3,3-Dimethyl-2-methylenecyclohexyl)-methyl)-4,5-dihydro-3-methyl-4-(1-methylethyl)oxazolium

(9) Most reported *N*-methyl oxazolinium salts have been prepared from iodomethane. See for example: (a) Oehlschager, A. C.; Wong, J. W.; Verigin, V. G.; Pierce, H. D. *J. Org. Chem.* **1983**, 48, 5009. (b) Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778.

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Methyl Sulfate (3b). ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 7.4 Hz, 3 H), 1.06 (s, 3 H), 1.09 (s, 3 H), 1.19–1.29 (m, 1 H), 1.49–1.75 (m, 4 H), 1.88–1.96 (m, 1 H, 2.31 (qqd, J = 7.4, 6.8, 4 Hz, 1 H), 2.85–2.94 (m, 2 H), 3.05 (dd, J = 20.9, 9.3 Hz, 1 H), 3.44 (s, 3 H), 3.73 (s, 3 H), 4.23 (br s, 1 H), 4.53 (dd, J = 9.3, 6.7Hz, 1 H), 4.76 (br s, 1 H), 4.77 (ddd, J = 10.7, 6.7, 4 Hz, 1 H), 5.17 (dd, J = 10.7, 9.3 Hz, 1 H); IR ($CHCl_3$) 3090, 2960, 2455, 1650, 1470, 1445, 1395, 1380, 1220, 1000, 895 cm^{-1}.

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Registry No. **1a**, 98901-10-1; **1b**, 98876-59-6; **2a**, 98877-34-0; **2b**, 98876-63-2; **3a**, 98876-65-4; **3b**, 98876-67-6; **4a**, 98901-12-3; **4b**, 98876-69-8; **5a**, 98876-71-2; **5b**, 98876-73-4; **6a**, 98876-75-6; **6b**, 98876-77-8; **7a**, 98876-79-0; **7b**, 98876-81-4; **8a**, 98876-83-6; **8b**, 98876-85-8; (±)-**9a**, 98876-87-0; (±)-**9b**, 98876-89-2; (±)-**10a**, 98876-91-6; (±)-**10b**, 98876-93-8; **11a**, 98876-94-9; **11b**, 98876-95-0; **12a**, 98876-97-2; **12b**, 98876-99-4; (±)-**13a**, 98877-01-1; (±)-**13b**, 98877-03-3; **14a**, 98877-05-5; **14b**, 98877-07-7; **15a**, 98877-09-9; **15b**, 98877-11-3; (±)-**16a**, 98877-13-5; (±)-**16b**, 98877-15-7; **17a**, 98877-16-8; **17b**, 98877-17-9; **18a**, 98877-19-1; **18b**, 98877-21-5; **19a**, 98877-23-7; **20a**, 98876-60-9; **20b**, 98876-61-0; **24a**, 98877-40-8; **24b**, 98877-41-9; **25a**, 98877-24-8; **25b**, 98877-25-9; **26a**, 98877-42-0; **26b**, 98877-43-1; (±)-**27a**, 98877-26-0; (±)-**27b**, 98877-27-1; **30a**, 98877-28-2; **30b**, 98877-29-3; (±)-**31a**, 98877-30-6; (±)-**31b**, 98877-31-7; **33a**, 98877-32-8; **33b**, 98877-44-2; (±)-**34a**, 98877-35-1; (±)-**34b**, 98877-36-2; **36a**, 98877-37-3; **36b**, 98877-38-4; **37a**, 98877-39-5; 2-propenyl 4-methylbenzenesulfonate, 4873-09-0.

Supplementary Material Available: Spectral data for N-methyloxazolium salts **2**, **4–19** and their oxazoline precursors (11 pages). Ordering information is given on any current masthead page.

Broadened Scope of Translocative Rearrangements. Substituted 1,2,3-Triazolo[1,5-*a*]-1,3,5-triazines

Fred T. Oakes and Nelson J. Leonard*

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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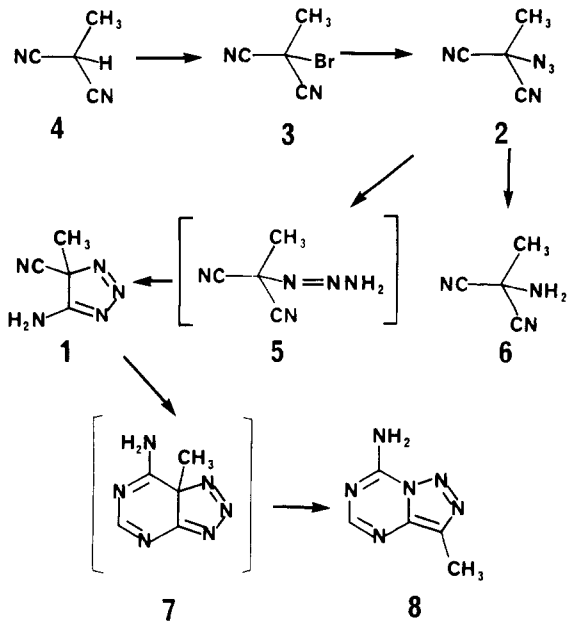
We have previously reported "translocative rearrangements" in which the overall result that occurs during a reaction with formamidine is the removal of a C≡N group from the quaternary carbon of a heterocycle and its translocation to a ring nitrogen two atoms removed, where it becomes attached as a ≥CNH_2 function. Generality has been shown to the extent that 4-substituted 5-amino-4-cyano-4*H*-imidazoles are converted to 8-substituted 4-aminoimidazo[1,5-*a*]-1,3,5-triazines by treatment with formamidine at 20 °C.[1] It was of interest to learn whether the scope of the reaction could be broadened to include the conversion of 4-substituted 5-amino-4-cyano-4*H*-1,2,3-triazoles to 8-substituted 4-amino-1,2,3-triazolo-[1,5-*a*]-1,3,5-triazines. In this category, 5-amino-4-cyano-4-methyl-4*H*-1,2,3-triazole (**1**) was considered a representative candidate for translocative rearrangement.

Scheme I



Several synthetic routes were examined for the preparation of **1**, including approaches through 2-azido-2-cyanopropionitrile (**2**). This proved to be the most acceptable precursor, prepared successfully from 2-bromo-2-cyanopropionitrile (**3**), which was available in turn from the bromination of 2-methylmalononitrile (**4**) (Scheme I).[2] More direct approaches to 2-azido-2-cyanopropionitrile (**2**) from 2-methylmalononitrile (**4**) resulted in diversions. For example, a previous report of the reaction of the sodium salt of 2-methylmalononitrile with *p*-toluenesulfonyl azide in methanol detailed a condensation, rearrangement, and methanolysis that led ultimately to 4-methyl-2-[(4-toluenesulfonyl)amino]-5-imidazolone.[3] The sodium salt of **4**, when treated with benzyl azide in methanol, gave a product consistent with the loss of one cyano group and the formation of the aromatized compound, 5-amino-1-benzyl-4-methyl-1,2,3-triazole. Reaction of the same sodium salt with trimethylsilyl azide in tetrahydrofuran or in methanol did not give promising results. Also, reaction of the highly explosive 2-azido-2-sodiomalonitrile with methyl iodide failed to provide a route to **2**.

The successful synthesis of 5-amino-4-cyano-4-methyl-4*H*-1,2,3-triazole (**1**) was patterned after one described by Hohenlohe–Oehringen for the preparation of 5-amino-4,4-diphenyl-4*H*-1,2,3-triazole.[4] 2-Azido-2-cyanopropionitrile was hydrogenated in ethyl acetate–ethanol using 10% Pd/C catalyst. Ring closure of the putative intermediate[4] triazene **5** or a tautomer gave the substituted triazole **1**. A competing loss of nitrogen from **5** occurred to a nearly equal extent and yielded 2-amino-2-cyanopropionitrile (**6**). The two products, after filtration and evaporation, were readily separable by trituration with chloroform. Filtration followed by a chloroform wash of the insoluble solid afforded analytically pure **1**, while evaporation and distillation of the filtrate provided **6**.

When 5-amino-4-cyano-4-methyl-4*H*-1,2,3-triazole (**1**) was treated with formamidine at room temperature, a $C_5H_6N_6$ product was obtained that had spectroscopic properties satisfactory for the assigned structure **8**, which would result by way of the presumed intermediate **7**

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