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J. Liu
Z. Wang
A. Levin
T. J. Emge
Paul R. Rablen
Swarthmore College, prablen1@swarthmore.edu

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N-Methylimidazole Promotes the Reaction of Homophthalic Anhydride with Imines

Jian Liu,† Zheng Wang,† Aaron Levin,† Thomas J. Emge,† Paul R. Rablen,‡ David M. Floyd,† and Spencer Knapp*†

†Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey, 610 Taylor Road, Piscataway, New Jersey 08854, United States
‡Department of Chemistry and Biochemistry, Swarthmore College, Swarthmore, Pennsylvania 19081, United States

Supporting Information

ABSTRACT: The addition of N-methylimidazole (NMI) to the reaction of homophthalic anhydride with imines such as pyridine-3-carboxaldehyde-N-trifluoroethylimine (9) reduces the amount of elimination byproduct and improves the yield of the formal cycloadduct, tetrahydroisoquinolonic carboxylate 10. Carboxanilides of such compounds are of interest as potential antimalarial agents. A mechanism that rationalizes the role of NMI is proposed, and a gram-scale procedure for the synthesis and resolution of 10 is also described.

INTRODUCTION

Malaria persists as a global health risk, with roughly 200 million cases of the disease reported in 2012, accompanied by an estimated 627 000 deaths.1 Antimalarial drugs remain among the most effective tools for defeating the Plasmodium agent, and new treatments are continually required as resistance to more traditional drugs such as artemisinin sets in.2 Phenotypic screening has proven to be a good source of lead compounds for this purpose, and a recent campaign examining more than 300 000 compounds for activity against P. falciparum in human erythrocytes revealed among the actives a series of tetrahydroisoquinolonic carboxanilides related to 1.3 Hit-to-lead studies have further identified carboxanilides 2 and 3 as worthy of further development.

We have undertaken an investigation of methods to improve existing syntheses of this class of compounds and can report that N-methylimidazole has proven beneficial as a promoter of the formal cycloaddition reaction of homophthalic anhydride with aldimines.

RESULTS AND DISCUSSION

A variety of methods have been described for the synthesis of 1-oxo-2-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids 8 by formal cycloaddition of homophthalic anhydride (HPA) 4 with aldimines 5 (Scheme 1).4 The reaction is commonly thought to proceed by way of a Mannich intermediate 6, the amino group of which subsequently closes upon the anhydride carbonyl group in a Perkin-analogous process leading to lactam acid 8.5 Alternatively, a more direct cycloaddition pathway leading to intermediate 7 or its tautomer has been considered.6 The reaction often goes well without additives or catalysts, but various improvements have been recommended.4,6,7 In our specific case with the N-2,2,2-trifluoroethylimine derived from pyridine-3-carboxaldehyde (i.e., 9, Table 1), the...
Table 1. Effect of Additives and Solvent on the Apparent Yield of 1-Oxo-2-(2,2,2-trifluoroethyl)-3-(3-pyridyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids 10

<table>
<thead>
<tr>
<th>base (equiv)</th>
<th>pK_a</th>
<th>solvent</th>
<th>NMR yield (trans/cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no base</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pyridine (1.0)</td>
<td>5.2</td>
<td>CHCl_3</td>
<td>47% (2.2:1)</td>
</tr>
<tr>
<td>DABCO (1.0)</td>
<td>8.8</td>
<td>&quot;</td>
<td>45% (1:1)</td>
</tr>
<tr>
<td>2,4,6-collidine (1.0)</td>
<td>7.6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>N,N-diethylaniline (1.0)</td>
<td>6.6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>N-methylmorpholine (1.0)</td>
<td>7.4</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4-(dimethylamino)pyridine (1.0)</td>
<td>9.2</td>
<td>&quot;</td>
<td>55%</td>
</tr>
<tr>
<td>4-(dimethylamino)pyridine (1.0)</td>
<td>&quot;</td>
<td>CH_3CN</td>
<td>&quot;</td>
</tr>
<tr>
<td>4-(4-morpholino)pyridine (1.0)</td>
<td>8.0</td>
<td>CHCl_3</td>
<td>47%</td>
</tr>
<tr>
<td>4(1-pyrrolidino)pyridine (1.0)</td>
<td>9.6</td>
<td>&quot;</td>
<td>36%</td>
</tr>
<tr>
<td>HOAc (1.0)</td>
<td>4.8</td>
<td>&quot;</td>
<td>50% (4:1)</td>
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<td>N-methylimidazole, NMI (1.0)</td>
<td>7.0</td>
<td>&quot;</td>
<td>63%</td>
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<tr>
<td>NMI (1.5)</td>
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<td>68%</td>
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<td>&quot;</td>
<td>65%</td>
</tr>
<tr>
<td>NMI (2.0)</td>
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<td>&quot;</td>
<td>78%</td>
</tr>
<tr>
<td>NMI (5.0)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>53%</td>
</tr>
<tr>
<td>NMI (neat)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>toluene</td>
<td>&quot;</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>66%</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>14 other solvents</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

"Approximate pK_a of conjugate acid.  "Poor yield and/or messy reaction mixture.  "Solvents tried: methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, n-butyl acetate, ethyl lactate, dimethyl carbonate, diethyl carbonate, tetrahydrofuran, acetone, tert-butanol, acetonitrile, propionitrile, and diethoxymethane.

The reaction under several literature conditions led to large amounts of an elimination pathway (see 12, Scheme 2) and associated downstream educts and other byproducts, accompanied by only modest yields of desired product 10. Aldimines of basic heterocyclic carboxaldehydes were generally troublesome as cycladdition partners. We, therefore, set about screening solvents and additives, including various weak bases and acyl transfer promoters, as displayed in Table 1.

By examining the crude reaction products by proton NMR spectroscopy in the presence of a known amount of an internal standard, 2,6-di-tert-butyl-4-methylphenol (BHT), and integrating the appropriate signals, the approximate reaction yields of the desired trans and cis products (10, combined) could be determined. Apparent yields for the reaction in chloroform solution without additive or with an equiv of acetic acid hovered around 50%. Among the various additives examined, 4-(N,N-dimethylamino)pyridine led to a slight improvement (55%), whereas other amines of similar or lower basicity gave poorer yields and/or messier reactions. N-Methylimidazole (NMI), on the other hand, with a pK_a ~ 7.0 (for NMI·H^+), gave an improved yield (63%) at 1 equiv, and this could be increased to 78% at 2 equiv. Greater or lesser amounts of NMI did not help further. A wide variety of solvents were also screened. Of these, only dichloromethane gave yields comparable to those with chloroform, and thus, dichloromethane was selected as the preferred solvent and 2 equiv of NMI as the preferred additive. The reaction of HPA 4 and imine 9 with 2 equiv of NMI in dichloromethane-d_2 solution was monitored in situ by proton NMR spectroscopy at room temperature. Within 2.5 min, formation of the cis and trans products 10 (~1:2:1 respectively, as their NMI salts) was complete, according to the presence of diagnostic signals for their H-3 and H-4 protons. In particular, trans-10 shows narrow doublets (J < 1 Hz) at 5.6 and 3.9 ppm, and cis-10 shows wider doublets (J = 6 Hz) at 5.3 and 4.8 ppm. These values are fully consistent with our spectra of isolated cis/trans mixtures and those reported for analogous 1-oxo-2-alkyl-3aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids found in the literature. Also apparent was the multiplet for trifluoroethyamine at 3.2 ppm, indicative of the elimination pathway (Scheme 2), and some unaerected imine 9. In addition, two sets of (initially) unassigned wide doublets were observed at 4.21 and 4.83 ppm (J = 12.0 Hz), and at 4.59 and 4.37 ppm (J = 12.6 Hz) in a 3:1 respective ratio. A gCOSY spectrum of the reaction mixture taken after 40 min of reaction time in situ (Figure 1) shows the expected cross-peaks for coupling of all eight doublets in the region of 3–6 ppm, as well as cross-peaks for the geminal dq signals (two each) for the −CH_3·CF_3 substituents of cis- and trans-10.

Over the next 24 h at room temperature in dichloromethane-d_2 solution, the cis/trans mixture of products 10 isomerized exclusively to the more stable trans-10 (as the NMI salt), a process promoted by NMI that we also observed later in gram-scale runs. The wide doublets disappeared, and a new singlet at 5.3 ppm became evident and grew in further over 48 h. From a later gram-scale reaction, we isolated this same byproduct, dibenzodihydrosoconumarin carboxylic acid 15 (diagnostic singlet at 5.3 ppm) as its NMI salt, and confirmed its structure and trans stereochemistry by X-ray crystallography (see the
Experimental Section). This type of HPA adduct has been reported previously and is a downstream result of the undesired Knoevenagel pathway illustrated in Scheme 2.

According to the mechanism proposed in Scheme 2, Knoevenagel product can form from Mannich adduct by loss of 2,2,2-trifluoroethylamine. Conjugate addition of a second equiv of HPA leads to two-to-one adduct, and then intramolecular C-acylation onto one of the anhydride carbonyl groups gives spiroanhydride as a potential mixture of up to four diastereomers. Decarboxylation and O-cyclization furnishes Spiro anhydrides have not been previously observed in reactions of this type, but could account for the unassigned wide doublets observed by proton NMR early in the reaction course.

Calculational determination [Gaussian 09, B3LYP/6-31G(d)] of the structures of the two trans isomers of 14 was carried out, along with a calculation of the expected chemical shifts and coupling constants of the ring methines. The results are displayed in Figure 2, and the calculated structures and methodological details are provided in the Experimental Section and the Supporting Information. A close match is obtained between the calculated chemical shifts of the two trans-14 isomers and the observed values, and the respective calculated, unusually wide, vicinal coupling constants also match quite well with the observed J values. On the basis of these calculational results, the proton NMR observations over the time course of the reaction, and on the presumed mechanism (Scheme 2) for formation of 15, the wide doublets are assigned to pseudo-trans-diaxial vicinal H’s of intermediate trans spiro anhydrides 14.

An additional change in reaction conditions was made for the gram-scale preparation of 10: by conducting the initial reaction at °C, the Knoevenagel pathway was suppressed almost

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**Figure 1.** Reaction of homophthalic anhydride with NMI and imine 9 after 40 min. gCOSY cross-peaks for the wide doublets from the two spiro anhydride ring H’s are designated, respectively, c (red) and d (red). Cross-peaks for the respective ring proton doublets (a and b) and the –CH₂CF₃ doublets-of-quartets (a’ and b’) signals for trans- and cis-10 are also designated.
entirely (Scheme 3). The reaction mixture was then stirred (NMI is still present) for a day, during which time the cis/trans mixture was cleanly converted to all-trans. NMI is well-suited for this isomerization at room temperature; analogous treatment of the mixture with triethylamine led to no isomerization. Adjustment of the pH to near the isoelectric point of the product (∼pH 4.5) caused it to precipitate, and filtration gave 10 in 84% overall yield.

**Scheme 3. Optimized Conditions for Gram-Scale Synthesis of 10**

- 4 (1 equiv, added last) + 9 (1 equiv) + NMI (2 equiv) → 10 (2:3 cis + trans)
- 10 (trans only) 1.85 g, 84% yield

was cleanly converted to all-trans. NMI is well-suited for this isomerization at room temperature; analogous treatment of the mixture with triethylamine led to no isomerization. Adjustment of the pH to near the isoelectric point of the product (∼pH 4.5) caused it to precipitate, and filtration gave 10 in 84% overall yield.

What is the role of NMI in this formal cycloaddition, and how does it improve the reaction? Possibly, NMI benefits the reaction by affecting the balance between Perkin-analogous ring closure and the main side reaction, Knoevenagel-type elimination (Scheme 4). Should NMI intercept Mannich intermediate 11, acting as an acyl transfer promoter, the resulting activated N-acylimidazolium intermediate, 16, is well-suited for ring closure to give desired product 17. In contrast, the elimination process would be suppressed, inasmuch as full alignment and conjugation of the newly forming π-bond with the π systems of the benzo ring and the carbonyl group, a situation obtaining in 11, is weakened by σ bond rotation in 16. Furthermore, enolization of the anhydride carbonyl group, should this be prelude to elimination, is favored in 11, but not for the carbonyl group in 16. 4-((N,N-Dimethylamino)pyridine)pyridine and related pyridines also promote the reaction (Table 1), possibly as a result of their well-established acyl transfer promoting property, whereas organic bases without this characteristic, such as N-methylmorpholine, N,N-diethylaniline, and 2,4,6-collidine, are ineffective.

We also applied the new reaction conditions (−30 °C, 2 equiv of NMI in dichloromethane solution) for the gram-scale synthesis of three other 1-oxo-2-alkyl/aryl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids of interest to us: 19, 20, and 21 (Chart 1). Preparation of the appropriate aldimine coupling was calculated and observed chemical shifts and vicinal coupling constants for the spiro anhydrides 14.

**Chart 1. Additional Examples of NMI Promoted HPA/Aldimine Cycloadditions**

<table>
<thead>
<tr>
<th>chemistry</th>
<th>structure</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(85%)</td>
</tr>
<tr>
<td>20</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(64%)</td>
</tr>
<tr>
<td>21</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(60%)</td>
</tr>
</tbody>
</table>
partners is described in the Experimental Section. Products 19 and 20 are the precursors to carboxanilides 1 and 3, respectively. Compound 21 has been reported previously.4,15

Finally, we developed an unusual, but effective, procedure for resolving racemic trans-10 (Scheme 5) to provide the desired (+)-(35,4S)-enantiomer. A separation of racemic 10 and 2 equiv of commercial (15S,2S)-(+)−1-amino-2-indanol (22) in a 1:1 mixture of heptane and propionitrile was digested at reflux, cooled, and then filtered. The resulting solid was subjected to another digestion, and then the collected product was analyzed by proton NMR spectroscopy. Integration indicated that this salt comprises a two-to-one complex of 22 with 10. Acidification with acetic acid, extraction, and then exhaustive concentration produced (+)-10 (71% overall), mp 134−137 °C, enantiomerically pure according to chiral HPLC analysis. Likewise, the use of (1R,2R)-(+)−1-amino-2-indanol afforded 71% of the (−)-enantiomer of 10, mp 135−137 °C, also enantiomerically pure according to chiral HPLC analysis. The absolute configuration of the (−)-10 enantiomer was established unambiguously as (2R,3R) by X-ray crystallographic analysis of its salt with (R)-(−)-2-amino-1-phenylethanol. Details of these procedures are provided in the Experimental Section and in the Supporting Information.

■ CONCLUSION

N-Methylimidazole is effective as an additive in the formal cycloaddition reactions of aldimes with homophthalic anhydride, increasing both the yield and the selectivity (cyclization versus elimination), and also promoting the isomerization of cis/trans mixtures of product to all-trans. NMI may act in this instance as an acyl transfer agent, intercepting the Mannich intermediate, e.g., 11, and promoting its ring closure. 1-Oxo-2-alkyl/aryl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids 10, 19, 20, and 21 have been prepared on a gram scale by this method.

■ EXPERIMENTAL SECTION

Estimation of Crude Cycloaddition Yields by 1H NMR Spectroscopy with BHT as Internal Standard. This example of the standard procedure used no additive. A stirred solution of alidine 9 (5.0 mg, 0.270 mmol, 1 equiv) in 2 mL of chloroform was treated with homophthalic anhydride 4 (43.7 mg, 0.270 mmol, 1 equiv) in one aliquot. After 16 h, the reaction was concentrated and the residue was dissolved in 2 mL of MeOH-d₄. Approximately 0.333 molar equiv of 2,6-di-tert-butyl-4-methylphenol (BHT) was added in this case, 20.5 mg (0.093 mmol, 0.344 equiv), and the resulting solution was analyzed by 1H NMR spectroscopy. The well-separated H-3 signals for respective trans- and cis-tetrahydroisoquinolinecarboxylic acid products 10 appear at 5.67 ppm (δ J = 0.9 Hz) and 5.41 ppm (δ J = 6.0 Hz), and the methyl (3 H) singlet of BHT appears at 2.23 ppm. The measured integral of the latter is corrected by the deviation of the molar equivalent amount of BHT from 0.333; here, 3.22 (measured) is corrected to 3.11. The sum of the measured integrals of the respective H-3 signals, in this case, 1.00 and 0.46, is divided into the corrected integral of BHT to give the apparent crude yield (here, 1.46:3.11 = 47%). Analogous measurements on reactions with added promoters gave the cycloadduct cis/trans ratios and the apparent yields shown in Table 1. In several cases, the initial cis/trans mixtures of 10 isomerized over the 16 h to all-trans.

(E)-2,2,2-Trifluoro-N-(pyridin-3-ylmethyl)ethanamine (9). Aqueous sodium hydroxide (11.8 g, 295 mmol) was added slowly to a cooled (ice bath) mixture of 2,2,2-trifluoroethyamine hydrochloride (39.8 g, 295 mmol), 3-pyridinecarboxaldehyde (21 g, 196 mmol), and toluene (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then at 23 °C for 15 h. The toluene layer was separated, and the aqueous layer was washed with additional toluene (6 × 50 mL). The combined organic solution was dried over sodium sulfate and concentrated to afford 34.57 g (94%) of the title compound as a yellow oil:1H NMR (300 MHz, CDCl₃) δ 8.12 (d, 1 H, J = 4.8 ppm, 1 H); 8.08 (d, 1 H, J = 4.8 and 1.8 Hz), 8.41 (br s, 1 H), 8.20 (dt, 1 H, J = 7.8 and 1.8 Hz), 7.39 (dd, 1 H, J = 8.1 and 4.8 Hz), 4.18 (qd, 2 H, J = 9.3 and 1.5 Hz).13C NMR (75.4 MHz, CDCl₃) δ 164.0, 152.5, 150.7, 134.8, 130.8, 124.3 (q, J = 275 Hz), 123.8, 61.6 (q, J = 297 Hz); HR-ESI-MS [M + H]⁺ calc for C₇H₆F₃N₂O₂, 189.0634; found, 189.0635.

(35S,4S)−1-Oxo-3-(pyrindin-2-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (Racemic trans-10). A solution of alidine 9 (1.00 g, 5.3 mmol) and N-methylimidazole (0.87 g, 10.6 mmol) in 16 mL of dichloromethane was stirred for 40 min at 23 °C, and then was cooled to −30 °C (internal temperature) by using a dry ice acetone bath. Solid homophthalic anhydride (0.86 g, 5.3 mmol) was added in one aliquot, and the solid was observed to dissolve in less than 1 min. The reaction mixture was stirred for 2.5 h at −30 °C, and then the cooling bath was removed and the reaction mixture was allowed to come to room temperature and stirred for a total of 48 h. Saturated aqueous sodium chloride solution (30 mL) was added, and the resulting mixture was brought to pH 4.5 (monitored by pH meter) by addition of concentrated hydrochloric acid (37%, ~0.88 mL). The resulting suspension was stirred for 12 h and then filtered. The precipitate was collected by filtration, and the solid product was washed with ice cold water (2 × 50 mL) and pumped to dryness, affording carboxylic acid trans-10 (1.55 g, 84%), mp 229.1−230.5 °C.13C NMR (300 MHz, MeOD-d₄) δ 8.40 (dd, 1 H, J = 4.8 and 1.5 Hz), 8.38 (m, 1 H, J = 7.8 and 4.8 Hz, 8.36 (m, 1 H, J = 8.1 and 4.8 Hz), 8.21 (dd, 1 H, J = 9.3 and 1.5 Hz).13C NMR (75.4 MHz, DMSO-d₆) δ 172.1, 164.6, 149.4, 148.2, 134.8, 134.8, 133.5, 130.3, 128.9, 128.6, 128.0, 126.7 (q, J = 210 Hz), 124.1, 123.9, 61.3, 51.0, 47.2 (q, J = 24.6 Hz); HR-ESI-MS [M + H]⁺ calc for C₉H₈F₃N₂O₃, 351.0949; found, 351.0951.

2-Methyl-N-(thiophen-2-ylmethyl)propan-1-amine. Thio-phen-2-carbazaldehyde (6.70 g, 60.6 mmol) was added to a solution of isobutylamine (8.91 mL, 90 mmol) in 28 mL of acetonitrile, and the solution was stirred at 23 °C for 15 h. Concentration afforded 9.6 g (96%) of the title compound as a yellow oil:1H NMR (300 MHz, MeOD-d₄) δ 8.34 (d, 1 H, J = 1.2 Hz), 7.51 (dt, 1 H, J = 5.1 and 1.2 Hz), 7.41 (dd, 1 H, J = 3.6 and 1.2 Hz), 7.09 (dd, 1 H, J = 4.8 and 3.6 Hz), 3.34 (dd, 1 H, J = 6.6 and 1.2 Hz), 1.95 (app nonet, 1 H, J = 6.6 Hz), 0.92 (d, 6 H, J = 6.6 Hz).13C NMR (75.4 MHz, MeOD-d₄) δ 155.7, 141.5, 131.4, 129.1, 127.3, 68.5, 29.2, 19.6; HR-ESI-MS [M + H]⁺ calc for C₁₃H₁₃NS, 168.0849; found, 168.0850.

(35S,4S)−2-Isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (19). Homophthalic anhydride (0.969 g, 5.98 mmol) was added to a solution of 2-thiophen-2-ylmethyl)propane-1-amine (1.00 g, 5.98 mmol) and N-methylimidazole (0.982 g, 12.0 mmol) in 17.6 mL of dichloromethane at −30 °C as described above. The reaction mixture was stirred at −30 °C for 2.5 h and then at 23 °C for 24 h, concentrated, and then
chromatographed on silica by using 20:1 hexanes/acetic acid and then 12.8:1 hexanes/ethyl acetate/acetic acid as the eluant to afford 1.67 g (86%) of carboxylic acid 19, mp 165–166 °C. 1H NMR (300 MHz, DMSO-d6) δ 13.16 (s, 1 H), 7.92 (dd, 1 H, J = 7.8 and 1.5 Hz), 7.49 (td, 1 H, J = 7.2 and 1.5 Hz), 7.42 (dd, 1 H, J = 7.5 and 1.5 Hz), 7.35 (dd, 1 H, J = 7.2 and 1.5 Hz), 7.26 (dd, 1 H, J = 4.8 and 1.5 Hz), 6.99 (dd, 1 H, J = 3.5 and 1.5 Hz), 6.81 (dd, 1 H, J = 7.5 and 1.5 Hz), 5.85 (dt, 1 H, J = 1.5 and 7.6 Hz), 7.34 (dt, 1 H, J = 1.5 and 7.5 Hz), 7.30 (dd, 1 H, J = 1.5 and 7.5 Hz), 7.20–7.24 (m, 2 H), 7.15 (1 H, J = 15 Hz), 5.28 (d, 1 H, J = 1.5 Hz), 3.98 (d, 1 H, J = 15 Hz), 3.80 (s, 3 H), C15 NMR (75.4 MHz, DMSO-d6) δ 173.1, 161.3, 149.7, 148.7, 138.4, 138.1, 136.1, 136.0, 135.5, 132.6, 131.3, 130.3, 130.1, 129.01, 128.8, 128.3, 128.1, 124.0, 123.5, 122.7, 121.2, 121.1, 110.4, 51.6, 37.4, 33.5. A sample crystallized from isopropanol gave free acid 15 (i-ProH solvate, mp 170–171 °C; HR-ESI-MS [M + H]+ calcd for C17H17NO4, 370.1079; found, 370.1059. These crystals were suitable for single crystal X-ray analysis.

1,2,2-Trifluorooxalylamine. A mixture of 10 g of 2,2,2-trifluoroethyloxycarbonyl chloride, 15 g of solid sodium hydride, and 1.5 mL of dichloromethane-d2 was stirred for 10 min. The supernatant, which contains the free base, was examined by NMR spectroscopy: 1H NMR (300 MHz, dichloromethane-d2) δ 6.30 (app septet, 2 H, J = 8.7 Hz), 1.31 (br s, 2 H).

Resolution of racemic 10. A suspension of racemic 10 (9.0 g, 25.7 mmol, prepared as described above) and 7.68 g (50 mmol, 1.95 equiv) of (15S)-(+)-trans-1-amino-2-iodanisol (22) in 270 mL of 1-propiolone/heptane was stirred at reflux (82 °C) for 1.5 h. The resulting suspension was cooled to 23 °C over 3 h and filtered, and the solids were washed with 102 mL of 1:1 propiolone/heptane. The solids were digested again with 270 mL of the same solvent mixture, and after filtration and rinsing as before, the recovered solids were dried at 50 °C for 15 h to afford 7.70 g of the chiral 2:1 salt, mp 176–178 °C. 1H NMR (500 MHz, MeOH-d4) δ 8.83 (d, 2 H, J = 5.0 Hz), 8.01 (dd, 1 H, J = 7.5 and 1.5 Hz), 7.55 (dd, 1 H, J = 7.0 and 3 Hz), 7.42 (td, 1 H, J = 7.5 and 1.5 Hz), 7.34–7.40 (m, 3 H), 7.20–7.30 (m, 7 H), 7.14 (dd, 1 H, J = 7.5 and 0.5 Hz), 5.60 (s, 1 H), 4.30–4.40 (m, 1 H), 3.75 (s, 1 H), 4.20–4.30 (m, 5 H), 3.75 (s, 1 H), 3.28 (dd, 2 H, J = 16 and 6.5 Hz), 2.82 (dd, 2 H, J = 16 and 6.5 Hz). This product was dissolved in 300 mL of 91/8 water/acetic acid and stirred for 15 h. Extraction with ethyl acetate (4 × 100 mL), followed by concentration in vacuo at 95 °C to remove traces of acetic acid, gave 3.2 g (71% of theoretical) of resolved (+)-10, mp 134–137 °C; [α]D 20 + 60 (c 1.00, MeOH); analysis by chiral HPLC (Chiral Pak IC, 250 × 4.6 mm, S μl; mobile phase: 80:20 hexane/isopropanol with 0.1% trifluoroacetic acid; flow rate 4 mL/min; enantiomers baseline separated) indicated an ε 99.9. Anal. Calc. for C17H15F2NO3 Si: 58.39, C: 73.47, F: 26.70, N: 80.00. Found: C: 58.10, H: 7.36, F: 16.00, Si: 7.82.

The identical procedure, but using instead (1R,2R)-(−)-trans-1-amino-2-iodanisol, racemic trans acid 10 (234 mg, 0.66 mmol) was converted to its 2:1 salt (173 mg, 80%), mp 176–178 °C. Liberation of (+)-10 as above gave 82 mg (70% overall from racemic 10), mp 135–137 °C; [α]D 20 + 61 (c 1.00, MeOH).

Determination of Absolute Stereocchemistry of Resolved (+)-10. A mixture of (+)-10 (200 mg, 0.57 mmol) and (R)-(-)-2-amino-1-phenylethanol (80 mg, 0.58 mmol) in 2 mL of 1:1 isopropyl alcohol/heptane was heated at reflux to produce a clear solution. The solution was allowed to cool and rest at 23 °C overnight. The resulting crystals were collected by filtration and washed with a small amount of 1:1 isopropyl alcohol/heptane to afford 109 mg of the 1:1 salt (contains 0.5 %PrOH of crystallization), mp 112–114 °C. 1H NMR (500 MHz, MeOH-d4) δ 8.34 (dd, 2 H, J = 4.5 and 1.5 Hz), 8.08 (dd, 1 H, J = 7.5 and 1.5 Hz), 7.55 (dt, 1 H, J = 8.0 and 1.5 Hz), 7.29–7.45 (m, 6H), 7.25–7.28 (m, 1 H), 7.27 (dd, 1 H, J = 8 and 5 Hz), 7.14 (d, 1 H, J = 7.5 Hz), 5.60 (s, 1 H), 4.83–4.86 (m, 1H), 4.24–4.24 (m, 2H), 3.80–3.95 (m, 0.25 H, IPA), 3.77 (s, 1H), 3.09 (dd, 1 H, J = 12.5 and 1.5 Hz), 2.96 (dd, 1 H, J = 13 and 9.5 Hz), 1.14 (d, 1 H, IPA, J = 6 Hz). These crystals proved suitable for X-ray analysis (see the Supporting Information).

Calculational Studies. All calculations were carried out by using the Gaussian 09 software package. The geometries of the two diastereomers of 14 were optimized by using the B3LYP/6-31G(d) level of theory, followed by frequency calculations at the same level. The
structures have little conformational flexibility of consequence, and only one significant conformation of either structure was located, in which the ring pucker places the pyridyl substituent pseudoaxial. The remaining rings were essentially perfectly planar. Rotation about the C3−CO2H and C3−pyridyl was deemed unlikely to make a significant difference either for the energy or for the computed NMR properties of the C-3 and C-4 protons, and so was not explored. The major (2S,3S,4R) diastereomer was calculated to lie 3.3 kcal/mol lower in free energy than the minor (2R,3S,4R) diastereomer at 298 K.

Proton NMR properties were computed according to the procedures recommended by Bally and Rablen and co-worker.18,19 Chemical shifts were computed by using GIAO/WP04/cc-pVDZ and a simulated chloroform solvent (SCRF). Magnetic shielding values were converted to the chemical shift according to the equation $\delta = (31.8440 - S)/10205$, where $S$ is the magnetic shielding and $d$ the chemical shift. Coupling constants were computed in the gas phase at B3LYP/6-31G(d,p)u+1s and scaled by 0.916.20,21

### ASSOCIATED CONTENT

**Supporting Information**

1H and 13C NMR spectra of new compounds; calculated coordinates, chemical shifts, and coupling constants; and crystallographic details and CIF’s for $(-)-10$ (CCDC 1007451) and $15$ (CCDC 1007452). This material is available free of charge via the Internet at http://pubs.acs.org.

### AUTHOR INFORMATION

Corresponding Author

*E-mail: spencer.knapp@rutgers.edu.

Notes

The authors declare no competing financial interest.

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