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N-Methylimidazole Promotes the Reaction of Homophthalic Anhydride with Imines

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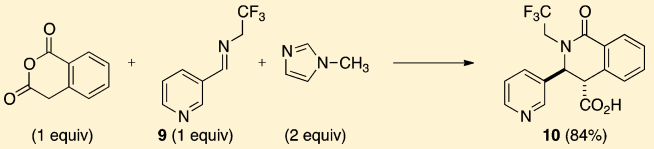
Supporting Information

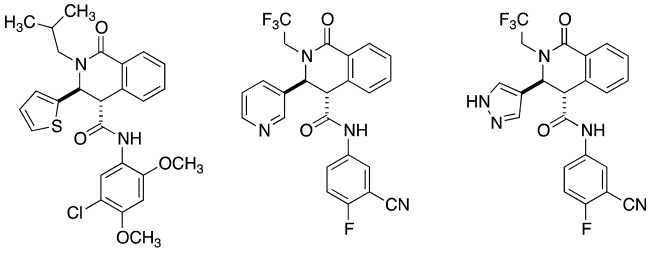
ABSTRACT: The addition of *N*-methylimidazole (NMI) to the reaction of homophthalic anhydride with imines such as pyridine-3-carboxaldehyde-*N*-trifluoroethylimine (**9**) reduces the amount of elimination byproduct and improves the yield of the formal cycloadduct, tetrahydroisoquinolonic carboxylate **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.



1 **2** **3**

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

Scheme 1. Formal Cycloaddition of Homophthalic Anhydride with Aldimines

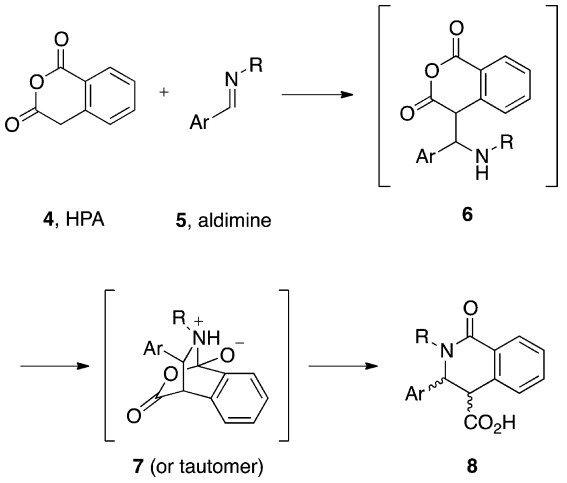


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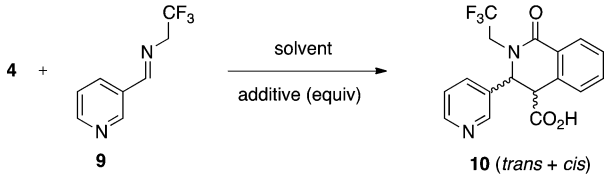
Table 1. Effect of Additives and Solvent on the Apparent Yield of 1-Oxo-2-(2,2,2-trifluoroethyl)-3-(3-pyridyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids 10



base (equiv)	pK_a[a]	solvent	NMR yield (*trans*:*cis*)
no base		$CHCl_3$	47% (2.2:1)
pyridine (1.0)	5.2	〃	45% (1:1)
DABCO (1.0)	8.8	〃	[b]
2,4,6-collidine (1.0)	7.6	〃	[b]
N,*N*-diethylaniline (1.0)	6.6	〃	[b]
N-methylmorpholine (1.0)	7.4	〃	[b]
4-(dimethylamino)pyridine (1.0)	9.2	〃	55%
4-(dimethylamino)pyridine (1.0)	〃	CH_3CN	[b]
4-(4-morpholino)pyridine (1.0)	8.0	$CHCl_3$	47%
4(1-pyrrolidino)pyridine (1.0)	9.6	〃	36%
HOAc (1.0)	4.8	〃	50% (4:1)
N-methylimidazole, NMI (1.0)	7.0		63%
NMI (1.5)	〃	〃	68%
NMI (0.5)	〃	〃	65%
NMI (2.0)	〃	〃	78%
NMI (5.0)	〃	〃	53%
NMI (neat)	〃	〃	[b]
NMI (1.0)	〃	toluene	[b]
NMI (1.0)	〃	CH_2Cl_2	66%
NMI (1.0)	〃	14 other solvents[c]	[b]

[a]Approximate pK_a of conjugate acid. [b]Poor yield and/or messy reaction mixture. [c]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.

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 cycloaddition 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$^+$),[8] 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-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids found in the literature.[4] Also apparent was the multiplet for trifluoroethylamine at 3.2 ppm, indicative of the elimination pathway (Scheme 2), and some unreacted 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 −C$\underline{H}_2$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, dibenzodihydroisocoumarin 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

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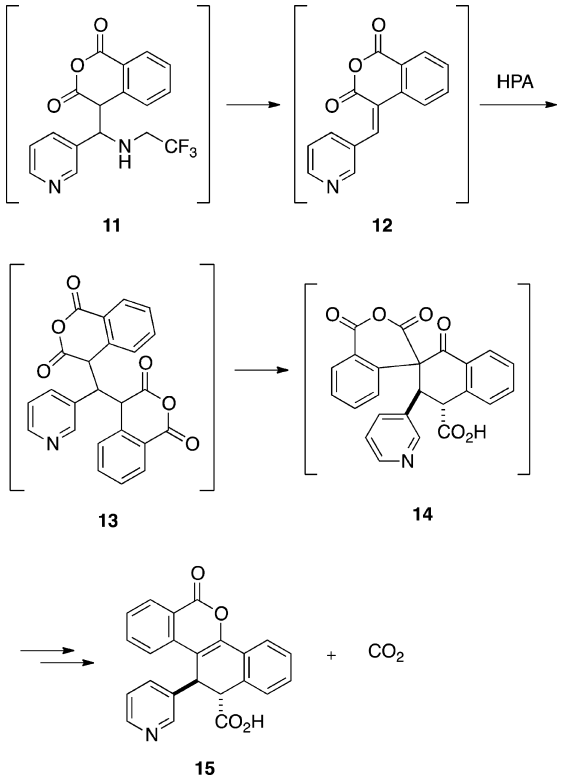
Scheme 2. Proposed Knoevenagel Byproduct 12 and Intermediates Leading to Dibenzodihydroisocoumarin 15



Experimental Section). This type of HPA adduct has been reported previously[9] and is a downstream result of the undesired Knoevenagel pathway illustrated in Scheme 2.

According to the mechanism proposed in Scheme 2, Knoevenagel product **12** can form from Mannich adduct **11** by loss of 2,2,2-trifluoroethylamine. Conjugate addition of a second equiv of HPA leads to two-to-one adduct **13**, and then intramolecular C-acylation onto one of the anhydride carbonyl groups gives spiroanhydride **14** as a potential mixture of up to four diastereomers. Decarboxylation and O-cyclization furnishes **15**. Spiro anhydrides **14** 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 −30 °C, the Knoevenagel pathway was suppressed almost

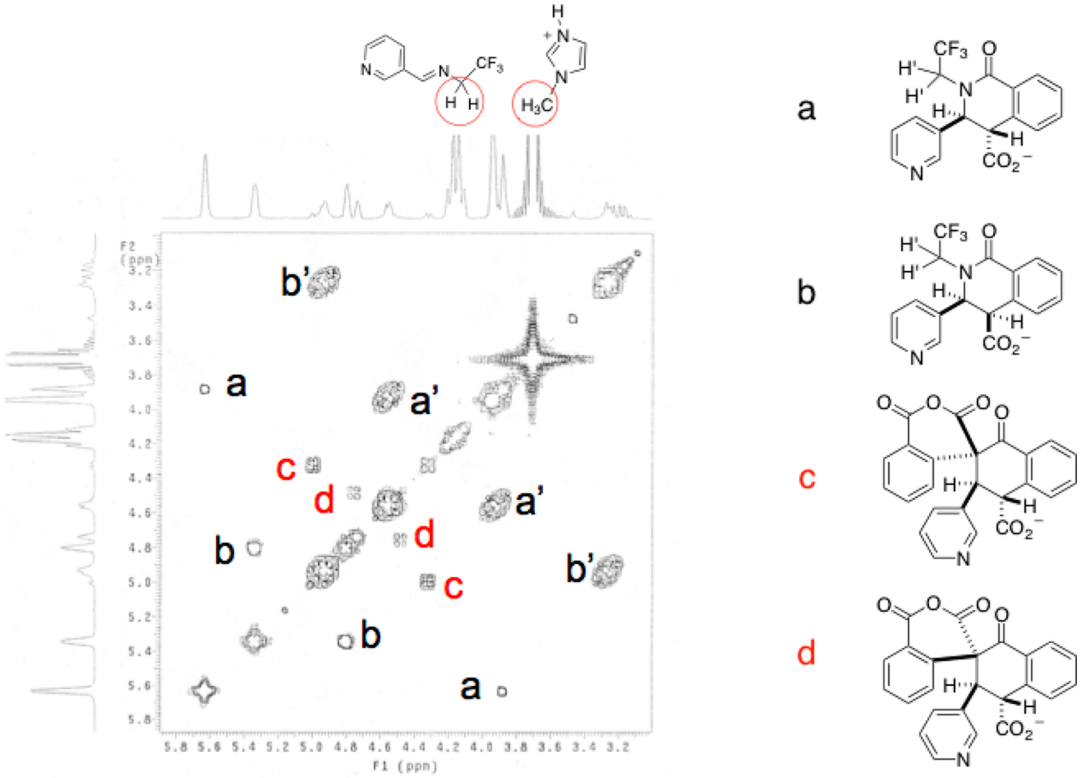


Figure 1. Reaction of homophthalic anhydride with NMI and imine **9** after 40 min. gCOSY cross-peaks for the wide doublets from the two spiro anhydride ring H's are designated, respectively, c (red) and d (red). Cross-peaks for the respective ring proton doublets (a and b) and the $-C\underline{H}_2CF_3$ doublets-of-quartets (a' and b') signals for *trans*- and *cis*-**10** are also designated.

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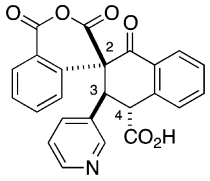
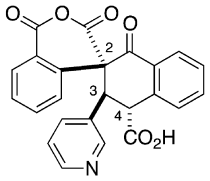


14: 2*S**,3*S**,4*R** (major)

H-3, H-4 Calculated: 4.19 and 4.81 (J = 11.5 Hz)

Observed: 4.21 and 4.83 (J = 12.0 Hz)



14: 2*R**,3*S**,4*R** (minor)

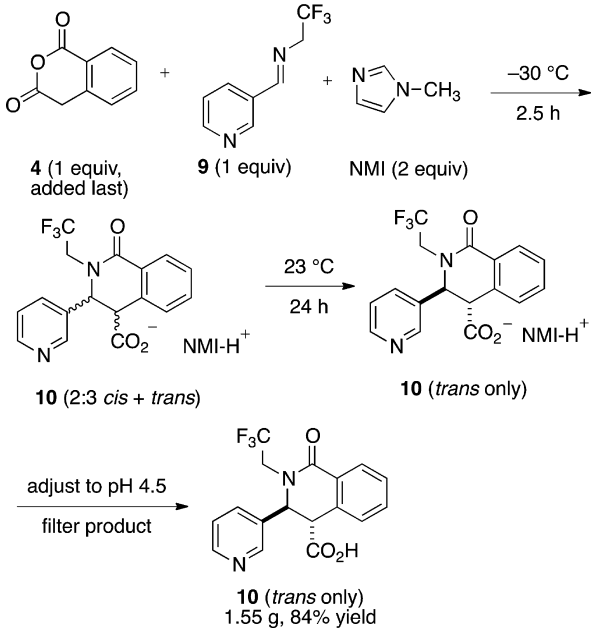
H-3, H-4 Calculated: 4.63 and 4.30 (J = 12.4 Hz)

Observed: 4.59 and 4.37 (J = 12.6 Hz)

Figure 2. Calculated and observed chemical shifts and vicinal coupling constants for the spiro anhydrides **14**.

entirely (Scheme 3). The reaction mixture was then stirred (NMI is still present) for a day, during which time the *cis*/*trans* mixture

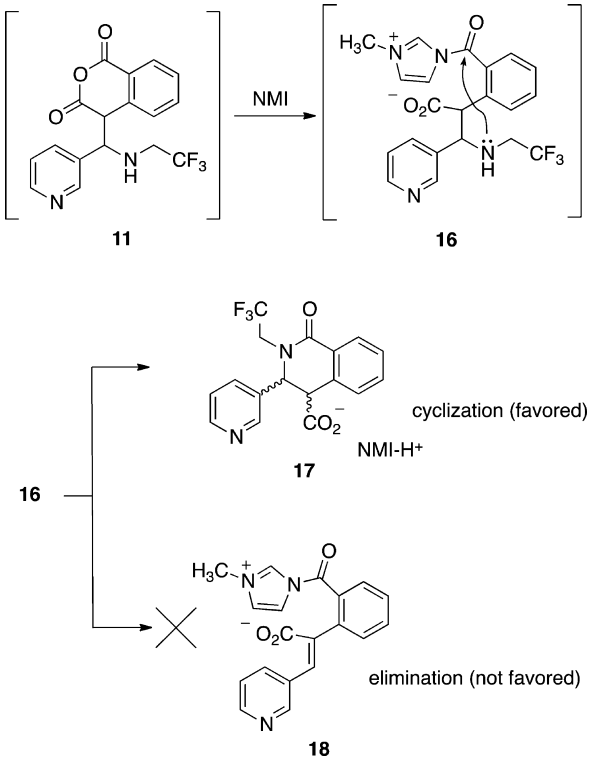
Scheme 3. Optimized Conditions for Gram-Scale Synthesis of 10



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**,

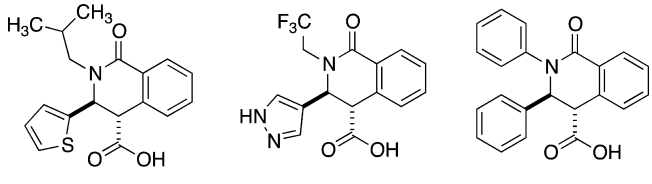
Scheme 4. Proposed Role of NMI in the Reaction of HPA with Aldimines



acting as an acyl transfer promoter,[10,11] 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 and related pyridines also promote the reaction (Table 1), possibly as a result of their well-established acyl transfer promoting property,[12,13] 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

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



19 (85%) **20** (64%) **21** (60%)

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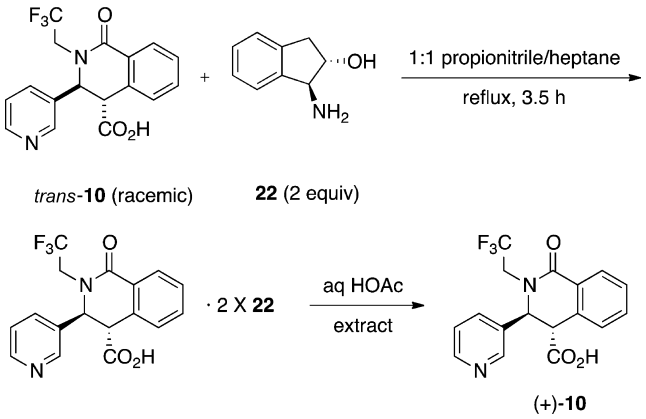
partners is described in the Experimental Section. Products **19** and **20** are the precursors to carboxanilides **1** and **3**, respectively. Compound **21** has been reported previously.[14,15]

Finally, we developed an unusual, but effective, procedure for resolving racemic *trans*-**10** (Scheme 5) to provide the desired

Scheme 5. Resolution of Racemic 10



(+)-(3*S*,4*S*) enantiomer. A suspension of racemic **10** and 2 equiv of commercial (1*S*,2*S*)-(+)-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 (1*R*,2*R*)-(+)-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 (2*R*,3*R*) 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 aldimines 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 ^{1}H NMR Spectroscopy with BHT as Internal Standard. This example of the standard procedure used no additive. A stirred solution of aldimine **9** (50.0 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-d_4. 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 ^{1}H NMR spectroscopy. The well-separated H-3 signals for respective *trans*- and *cis*-tetrahydroisoquinolone carboxylate products **10** appear at 5.67 ppm (d, J = 0.9 Hz) and 5.41 ppm (d, 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 *trans*/*cis* 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-ylmethylene)ethanamine (9). Aqueous sodium hydroxide (11.8 g, 295 mmol) was added slowly to a cooled (ice bath) mixture of 2,2,2-trifluoroethylamine 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 imine **9** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, 1 H, J = 2.1 Hz), 8.72 (dd, 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); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.0, 152.5, 150.71, 134.8, 130.8, 124.3 (q, J = 275 Hz), 123.8, 61.6 (q, J = 29.7 Hz); HR-ESI-MS $[M + H]^+$ calcd for $C_8H_8F_3N_2$, 189.0634; found, 189.0635.

(3*S,4*S**)-1-Oxo-3-(pyridin-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (Racemic *trans*-10).** A solution of aldimine **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 reaction 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 × 15 mL) and pumped to dryness, affording carboxylic acid *trans*-**10** (1.55 g, 84%), mp 229.1−230.5 °C: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.40 (dd, 1 H, J = 4.8 and 1.5 Hz), 8.36 (d, 1 H, J = 2.1 Hz), 8.11−8.08 (m, 1 H), 7.56−7.45 (m, 3 H), 7.32 (dd, 1 H, J = 8.1 and 4.8 Hz), 7.23−7.26 (m, 1 H), 5.67 (d, 1 H, J = 1.5 Hz), 4.57 (dq, 1 H, J = 15 and 9.0 Hz), 4.18 (d, 1 H, J = 1.5 Hz), 4.12 (dq, 1 H, J = 15 and 9.0 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 172.1, 164.6, 149.4, 148.2, 134.8, 134.4, 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 $[M + H]^+$ calcd for $C_{17}H_{14}F_3N_2O_3$, 351.0949; found, 351.0951.

2-Methyl-*N*-(thiophen-2-ylmethylene)propan-1-amine. Thiophene-2-carboxaldehyde (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: ^{1}H NMR (300 MHz, MeOH-d_4) 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); ^{13}C NMR (75.4 MHz, MeOH-d_4, δ 155.7, 141.5, 131.4, 129.1, 127.3, 68.5, 29.2, 19.6; HR-ESI-MS $[M + H]^+$ calcd for $C_9H_{14}NS$, 168.0849; found, 168.0850.

(3*S,4*S**)-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-methyl-*N*-(thiophen-2-ylmethylene)propan-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

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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 (85%) of carboxylic acid **19**, mp 165−168 °C: ^{1}H NMR (300 MHz, DMSO-d_6) 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 (td, 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 = 3.3 and 1.5 Hz), 6.86 (dd, 1 H, J = 4.8 and 3.3 Hz), 5.55 (d, 1 H, J = 1.5 Hz), 4.23 (d, 1 H, J = 1.5 Hz), 3.81 (dd, J = 13.2 and 9.3 Hz), 2.68 (dd, 1 H, J = 13.2 and 5.4 Hz), 1.97−2.11 (m, 1 H), 0.90 (d, 3 H, J = 6.9 Hz), 0.82 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 172.2, 163.2, 143.7, 134.5, 132.3, 130.4, 129.4, 128.4, 127.5, 127.0, 126.6, 125.9, 58.2, 52.8, 51.0, 27.3, 20.6 (2 C); HR-ESI-MS [M + H]$^+$ calcd for $C_{18}H_{20}NO_3S$, 330.1167; found, 330.1161.

(*E*)-*N*-((1*H*-Pyrazol-4-yl)methylene)-2,2,2-trifluoroethanamine. Solid 4-pyrazolecarboxaldehyde hydrochloride (10.0 g, 76 mmol), prepared by the literature method,[16] was added to a cooled (ice bath) solution of 2,2,2-trifluoroethylamine hydrochloride (15.2 g, 113 mmol) in 36 mL of acetonitrile, followed by triethylamine (31.5 mL, 226 mmol). The resulting reaction mixture was allowed to warm to 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 mL of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 mL). Concentration of the ether supernatant gave 12.0 g (90%) of the aldimine as a white foam. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.42 (d, 1 H J = 1.5 Hz), 8.06 (br s, 2 H), 4.12 (qd, 2 H, J = 9.6 and 1.5 Hz); ^{13}C NMR (100.6 MHz, MeOH-d_4) δ 161.1, 138.6 (br), 131.2 (br), 125.1 (q, J = 274 Hz), 119.5, 60.7 (q, J = 30.5 Hz); HR-ESI-MS [M + H]$^+$ calcd for $C_6H_7F_3N_3$, 178.0587; found, 178.0588.

(3*S,4*S**)-1-Oxo-3-(1*H*-pyrazol-4-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (20).** Homophthalic anhydride **4** (0.271 g, 1.67 mmol) was added to a solution of (*E*)-*N*-[(1*H*-pyrazol-4-yl)methylene]-2,2,2-trifluoroethanamine (0.296 g, 1.67 mmol) and *N*-methylimidazole (0.982 g, 3.34 mmol) in 5 mL of dichloromethane and 1 mL of acetonitrile at −30 °C as described above. The reaction mixture was stirred at −30 °C for 2.5 h and at 23 °C for 48 h, and then concentrated. The residue was purified by column chromatography on silica by using 20:1 hexanes/acetic acid and then 12:8:1 hexanes/ethyl acetate/acetic acid as the eluant to afford title compound **20** as a white solid (0.365 g, 64% yield), mp 268.5−270.3 °C: ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.05 (d, 1 H, J = 7.5), 7.54 (td, 1 H, J = 7.5 and 1.0 Hz), 7.47 (td, 1 H, J = 8.0 and 1.5 Hz), 7.32 (d, 1 H, J = 7.5 Hz), 7.26 (br s, 2 H), 5.11 (d, 1 H, J = 1.5 Hz), 4.68 (dq, 1 H, J = 15.5 and 9.5 Hz), 4.13 (d, 1 H, J = 1.5 Hz), 3.83 (dq, 1 H, J = 15.5 and 9.5 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 172.2, 165.3, 135.1, 133.0, 132.0, 129.8, 128.3, 128.2, 127.8, 124.8 (q, J = 278 Hz), 119.4, 117.0, 56.2, 51.0, 46.5 (q, J = 34 Hz); HR-ESI-MS [M + H]$^+$ calcd for $C_{15}H_{13}F_3N_3O_3$, 340.0909; found, 340.0900.

(3*S,4*S**)-1-Oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (21).**[13,14] Homophthalic anhydride **4** (0.895 g, 5.52 mmol) was added to a solution of the commercial *N*-benzylideneaniline (1.00 g, 5.52 mmol) and *N*-methylimidazole (0.900 g, 11.0 mmol) in 16.2 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 48 h, concentrated, and then chromatographed on silica by using a gradient eluent of 20:1 hexanes/acetic acid through 12:8:1 hexanes/ethyl acetate/acetic acid to afford 1.14 g (60%) of carboxylic acid **21**. A sample crystallized from methanol had mp 224.2−226.5 °C, lit.[14] mp 203−204 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.21 (s, 1 H), 8.00 (d, 1 H, J = 6.9 Hz), 7.22−7.46 (m, 13 H), 5.71 (s, 1 H), 4.24 (s, 1 H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 172.5, 163.1, 142.8, 139.7, 134.3, 132.8, 130.2, 129.6, 129.3 (2 C), 129.1 (2 C), 128.5, 127.9, 127.8, 127.0, 126.8 (2 C), 126.7 (2 C), 64.8, 51.6; HR-ESI-MS [M + H]$^+$ calcd for $C_{22}H_{18}NO_3$, 344.1289; found, 344.1293.

(11*S,12*R**)-6-Oxo-11-(pyridin-3-yl)-11,12-dihydro-6*H*-dibenzo[*c*,*h*]chromene-12-carboxylic Acid (15).** The *N*-methylimidazolium salt of **15** was obtained serendipitously from a large-scale preparation of **10**. A stirred solution of aldimine **9** (14.5 g, 77.3 mmol) and *N*-methylimidazole (12.3 mL, 155 mmol) in 618 mL of dichloromethane was treated with homophthalic anhydride (12.5 g, 77.3 mmol) in one portion. The solution was stirred for 16 h, and then concentrated. Trituration of the residue over 16 h with 200 mL of ether gave a supernatant that, upon standing, deposited 580 mg of *N*-methylimidazolium salt of **15** as a tan solid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.50 (d, 1 H, J = 2.4 Hz,), 8.29−8.33 (m, 2 H), 8.03 (s, 1 H), 7.93 (dd, 1 H, J = 1.5 and 7.65 Hz), 7.76 (dt, 1 H, J = 1.5 and 8.1 Hz), 7.67 (d, 1 H, J = 7.8 Hz), 7.61 (td, 1 H, J = 2.1 and 7.8 Hz), 7.54 (dt, 1 H, J = 1.2 and 7.5 Hz), 7.43 (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 (t, 1 H, J = 1.5 Hz), 5.28 (s, 1 H), 3.98 (d, 1 H, J = 1.5 Hz), 3.80 (s, 3 H); C^{13} NMR (75.6 MHz, DMSO-d_6) δ 173.1, 161.3, 149.7, 148.7, 148.4, 138.2, 136.4, 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, 33.35. A sample crystallized from isopropanol gave free acid **15** (*i*-PrOH solvate), mp 170−171.3 °C: HR-ESI-MS [M + H]$^+$ calcd for $C_{23}H_{16}NO_4$, 370.1079; found, 370.1059. These crystals were suitable for single-crystal X-ray analysis.

2,2,2-Trifluoroethylamine. A mixture of 10 mg of 2,2,2-trifluoroethylammonium chloride, 15 mg of solid sodium hydroxide, and 1.5 mL of dichloromethane-d_2 was stirred for 10 min. The supernatant, which contains the free base, was examined by NMR spectroscopy: ^{1}H NMR (300 MHz, dichloromethane-d_2) δ 3.20 (app sextet, 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 (1*S*,2*S*)-(+)-*trans*-1-amino-2-indanol (**22**) in 270 mL of 1:1 propionitrile/heptane was heated at reflux (82 °C internal temperature) for 3.5 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 propionitrile/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: ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.33 (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 9:1 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: $[\alpha]_D^{20}$ + 60 (*c* 1.00, MeOH); analysis by chiral HPLC (Chiral Pak IC, 250 × 4.6 mm, 5 μ; mobile phase 80:20 hexane/isopropanol with 0.1% trifluoroacetic acid; flow rate 4 mL/min; enantiomers baseline separated) indicated an *er* > 99.9. Anal. Calcd for $C_{17}H_{13}F_3N_2O_3$: C, 58.29; H, 3.74; F, 16.27; N, 8.00. Found: C, 58.20; H, 3.86; F, 16.00; N, 7.82.

By the identical procedure, but using instead (1*R*,2*R*)-(−)-*trans*-1-amino-2-indanol, 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: $[\alpha]_D^{20}$ − 61 (*c* 1.00, MeOH).

Determination of Absolute Stereochemistry 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 (also contains 0.5 *i*-PrOH of crystallization), mp 112−114 °C: ^{1}H NMR (500 MHz, MeOH-d_4) 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 Hz), 5.60 (s, 1 H), 4.83−4.86 (m, 1H), 4.24−4.24 (m, 2 H), 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, 1.5 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.[17] 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 pseudoequatorial. The remaining rings were essentially perfectly planar. Rotation about the C_4−CO_2H and C_3−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 (2*S*,3*S*,4*R*) diastereomer was calculated to lie 3.3 kcal/mol lower in free energy than the minor (2*R*,3*S*,4*R*) 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 into chemical shift values according to the equation $d = (31.8440 - S))/1.0205$, 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 ^{13}C 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.

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Notes

The authors declare no competing financial interest.

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