Origin of the Diastereoselectivity of the Heterogeneous Hydrogenation of a Substituted Indolizine

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ABSTRACT: In this work, the stereoselective heterogeneous hydrogenation of a tetrasubstituted indolizine was studied. Partial hydrogenation products were obtained in three steps from a substituted pyridine-2-carboxaldehyde prepared from commercial pyridoxine hydrochloride. The hydrogenation of the indolizine ring was shown to be diastereoselective, forming trans-6b and cis-9. Theoretical calculations (ab initio and DFT) were used to rationalize the unusual trans stereoselectivity for 6b, and a keto−enol tautomerism under kinetic control has been proposed as the source of diastereoselectivity.

Naturally occurring 5,6,7,8-tetrahydroindolizinones, bicyclic compounds characterized by a pyrrole ring fused to a 6-membered saturated chain, a bridgehead nitrogen atom, and a ketone moiety, are of rare occurrence in nature, even though their indolizidine saturated analogues are abundant in alkaloid chemistry. For instance, the isolation of the first natural 5,6,7,8-tetrahydroindolizinone was reported only in 1997, when polygonatine B (1) was isolated from the liliaceous plant Polygonatum sibiricum (Figure 1) and from Polygonatum kingianum (2). Polygonatine A (3), the hydroxymethyl parent of both 1 and 2, was also isolated from P. sibiricum. Both 1 and 2 exhibited antimicrobial and antifungal activities against a range of microorganisms.

Furthermore, (−)-rhazinicine (4), an alkaloid containing the 5,6,7,8-tetrahydroindolizin-5-one motif, showed an antitumor activity similar to that of taxol (Figure 1).

Unlike 5,6,7,8-tetrahydroindolizinones, whose preparations have been achieved by efficient procedures in the literature, there are only a few protocols reported for 5,6,7,8-tetrahydroindolizinone synthesis. More specifically, the synthesis of compounds containing a 5,6,7,8-tetrahydroindolizin-8-one core (also named 6,7-dihydro-8(5H)-indolizinone) has been scarcely explored, with most of the approaches relying on Friedel−Crafts acylation. To the best of our knowledge, there are no reports on 5,6,7,8-tetrahydroindolizinone preparation directly through partial hydrogenation of an indolizine.

Received: June 5, 2020  Published: August 11, 2020
In this work, we describe the results of a highly trans diastereoselective heterogeneous hydrogenation reaction of the tetrastituted indolizine 5 to prepare polyfunctionalized 5,6,7,8-tetrahydroindolizin-8-one 6 (Scheme 1). This trans-formation was rationalized by theoretical calculations, which suggested a keto−enol tautomerism as the source of the observed stereoselectivity, favoring the kinetic product. The starting material for our synthetic route was pyridoxine hydrochloride—a also known as vitamin B6—which, despite its polyfunctionalized structure, is a low-cost compound (>US $1 per gram).12 We envisaged that the presence of hydroxyl groups of different reactivities in vitamin B6 could potentially be explored for the preparation of new tetrahydroindolizinone and tetrahydroindolizine motifs.

The synthetic route developed for the synthesis of the 5,6,7,8-tetrahydroindolizinone 6 was carefully planned to avoid chromatographic purification in most of its steps. Furthermore, most of the sequence was carried out on a multigram scale through low cost and efficient reactions. Thus, functionalized pyridine-2-carboxaldehyde 7 was prepared in six steps and 77% overall yield by using a quite robust, modified procedure reported several decades ago by Korytnyk et al. (Scheme 1).13 The presence of the seven-membered cyclic acetal in 7 is essential, since it is key to the observed diastereoselectivity in the heterogeneous hydrogenation step, as will be discussed later. No chromatographic purification was required for the preparation of 7, which was sufficiently pure by NMR spectrum to be used in the next reaction step.

Scheme 1. Synthetic Approach to Tetrahydroindolizinone 6 and Tetrahydroindolizine 9

Scheme 2. Heterogeneous Hydrogenation of Indolizine 5

Scheme 3. Mechanistic Hypothesis for the Hydrogenation Step Using Rh/Al2O3 as Catalyst

In this work, we describe the results of a highly trans diastereoselective heterogeneous hydrogenation reaction of the tetrastituted indolizine 5 to prepare polyfunctionalized 5,6,7,8-tetrahydroindolizin-8-one 6 (Scheme 1). This transformation was rationalized by theoretical calculations, which suggested a keto−enol tautomerism as the source of the observed stereoselectivity, favoring the kinetic product. The starting material for our synthetic route was pyridoxine hydrochloride—a also known as vitamin B6—which, despite its polyfunctionalized structure, is a low-cost compound (>US $1 per gram).12 We envisaged that the presence of hydroxyl groups of different reactivities in vitamin B6 could potentially be explored for the preparation of new tetrahydroindolizinone and tetrahydroindolizine motifs.

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The Morita−Baylis−Hillman (MBH) reaction of compound 7 with methyl acrylate, a key step of our approach, was performed using a protocol developed by our laboratory involving the use of ultrasound to speed up the reaction.14 Adduct 8 was obtained in 85% yield after 64 h, and the crude product was used in the next reaction step without further purification. Then, we turned our attention to prepare indolizine 5. Several literature methodologies describe the synthesis of indolizines from MBH adducts.9,15 We initially opted to test some of them, and the best result was achieved by heating the MBH adduct to 100 °C in acetic anhydride medium. Some byproducts were formed in this step, and chromatographic purification was necessary to obtain pure 5 in 65% yield.

Once indolizine 5 was prepared, the performance of the partial hydrogenation reaction was evaluated by screening reaction parameters such as heterogeneous catalysts, H2 pressures, and solvents (see the Supporting Information for more details).5,15 When Rh/Al2O3 was used as a catalyst in ethyl acetate at 80 bar of H2 pressure and room temperature, starting material 5 was fully consumed after 48 h, furnishing a mixture of three main compounds (as determined by 1H NMR). Compound 6b could be separated and isolated in 30% yield, while alcohol 9 was obtained as an inseparable mixture (see the Supporting Information for full structural assignment) (Scheme 2).

Compound 6b and the mixture containing 9 were fully characterized by 1H, 13C{1H} NMR, 1H−1H COSY, 1H−13C HSQC, and 1H−13C HMBC experiments, and their relative
stereochemistries were assigned using $\text{J}_{\text{HH}}$ obtained directly from $^1\text{H}$ NMR spectra\textsuperscript{16} and NOE values\textsuperscript{17} obtained from NOESY experiments (see the Supporting Information for details).

Curiously, compound 6b was not further reduced under high pressures of $\text{H}_2$. Also, this compound shows a trans relationship between the hydrogen atoms at the 6–7 ring junction, and the other possible diastereomer (6a), which would have a cis relationship between these hydrogen atoms, was not observed. The hydrogenation of each individual double bond is expected to occur by cis addition of $\text{H}_2$. However, it is intriguing that the second double bond hydrogenation occurs preferentially at the opposite face of the first hydrogenation step to furnish 6b.

A plausible mechanistic rationale accounting for the formation of the products of this reaction is shown in Scheme 3.

Benzyl hydrogenolysis should occur quickly, even at low hydrogen pressure.\textsuperscript{18} Indeed, the disappearance of the typical aromatic protons of the benzyl group in the crude $^1\text{H}$ NMR spectrum was observed after only 1 h of reaction at 1 atm of $\text{H}_2$ pressure. Debenzylated intermediate 10 could be hydrogenated in either one of the two double bonds of the 6-membered ring. Supposing that the double bond in the $\alpha$ position to the nitrogen atom is hydrogenated preferentially (C5–C6 reduction), there is formation of enol 11, which in turn can furnish compound 6b via keto–enol tautomerism. Catalytic hydrogenation of either 11 or 12, which would come from C7–C8 reduction, could then furnish alcohol 9. Since formation of the stereocentric at position 7 occurs with protonation of 11, we sought to further study this step of the keto–enol equilibrium.

To elucidate the reason for the observed stereoselectivity of the hydrogenation step, theoretical calculations were carried out for compound 6 for both cis (6a) and trans (6b) relative stereochemistries (see the Supporting Information for details).

For both compounds 6a and 6b, the conformer of type 1 is the most stable at the B3LYP-D3/aug-cc-pVTZ level in EtOAc. Its geometrical representations are shown in Figure 2 and considered for further comparative calculations between these two diastereomers using DFT functionals and ab initio methods (Table S1, Supporting Information).

![Figure 2. Geometrical representations for the global minima of 6a and 6b obtained at the B3LYP-D3/aug-cc-pVDZ level in EtOAc, using the IEF-PCM implicit solvent model.](image)

The ab initio methods show that electron correlation is an important factor to be taken into account, since the HF method shows the opposite result in comparison to MP2, Grimme’s spin-component-scaled (SCS)\textsuperscript{19} MP2 and MP4 methods, which indicate that 6a should be more stable than 6b. Similarly, the B3LYP functional shows the opposite result, indicating that 6b should be 0.55 kcal mol$^{-1}$ more stable than 6a ($\Delta G$ values, Table S1, Supporting Information). When Grimme’s D3 dispersion correction\textsuperscript{16} is applied to the B3LYP method, 6a becomes more stable, hence indicating both electron correlation and dispersion corrections should be important parameters to account for the energy difference between 6a and 6b.

Based on these results, we applied Truhlar’s M06, M06-2X, and M11 functionals\textsuperscript{20,21} and Grimme’s B2PLYP functional\textsuperscript{22} including D3 dispersion correction for the latter. These functionals showed a considerable increase in $\Delta G$ values favoring 6a in comparison to B3LYP-D3. By considering the calculated $\Delta G$ values for these functionals, the approximate ratio between 6a and 6b (6a:6b) is calculated to be of 1:1 for B3LYP-D3, 2:1 for M06-2X, 3:1 for M06, 4:1 for M11, and 7:1 for B2PLYP-D3. Although these functionals show a higher stability for 6a, they are not in complete agreement with the experimental result, since 6a was not observed in any proportion. The MP2 ab initio method shows a 6a:6b ratio of 10:1 (1.38 kcal mol$^{-1}$; Table S1, Supporting Information).

However, the SCS-MP2, which is considered an improvement for the MP2 method,\textsuperscript{23} shows a smaller 5:1 ratio. Although of high accuracy, the SCS-MP2 approach cannot replace the CCSD(T) model,\textsuperscript{24} which has been termed as “the gold standard” in the literature,\textsuperscript{25} mainly when applied together with the CBS approximation.\textsuperscript{26} The CCSD(T) method, which scales as N$^7$ (N = basis set), was shown to be prohibitively expensive to be applied for 6a and 6b. However, we could apply the MP4(SDQ) method\textsuperscript{27} and the DLPNO-CCSDT-(T)/aug-cc-pVTZ\textsuperscript{28–30} level, which may be considered the highest levels applied in this work. The MP4(SDQ) showed a Gibbs free energy preference for 6a of 1.82 kcal mol$^{-1}$ (Table S1, Supporting Information). Such an energy difference would correspond to a ratio higher than 20:1. However, the DLPNO-CCSD(T) showed only a slight preference for 6a of 0.19 kcal mol$^{-1}$, which increases to 0.82 kcal mol$^{-1}$ when thermal Gibbs free energy corrections from the M11 functional are added. Thus, even high-level ab initio methods diverge in the energy difference between 6a and 6b, showing that 6a should be slightly more stable, even though it could not be observed experimentally. It is worth mentioning that keto–enol tautomerism has been shown to be a challenge for high level ab initio methods and DFT calculations in the gas phase and implicit solvent even for simpler molecular systems in previous benchmark studies.\textsuperscript{31}

Thus, although the cis isomer should be the most stable, the keto–enol tautomerism can have a high barrier in this molecular system, with the formation of the trans isomer controlled kinetically instead of thermodynamically. Indeed, it was observed that carboxylic acids can catalyze the keto–enol tautomerism and decrease the Gibbs free energy barrier of keto–enol interconversion by as much as 45 kcal mol$^{-1}$.\textsuperscript{32–34} Because the reaction in this work is being carried out in EtOAc, some residual acetic acid (AcOH) may be present in the reaction mixture, catalyzing the reaction, decreasing the barrier height, and possibly making 6b the favored kinetic product.

The keto tautomer (6a or 6b, see the Supporting Information) is more stable than the enol tautomer (11) by as much as 19 kcal mol$^{-1}$ (M11/aug-cc-pVDZ), and the uncatalyzed energy barrier in the stepwise mechanism can be as high as ~50–60 kcal mol$^{-1}$.\textsuperscript{32–34} In order to evaluate the kinetic product, we obtained the reaction barriers for formation of 6a and 6b from 11 catalyzed by AcOH (Figure 3). These calculations were carried out at the M11/aug-cc-pVDZ level, since this theoretical level showed similar results to the
DLPNO-CCSD(T)/aug-cc-pVTZ (Table S1, Supporting Information). Such calculations showed a $\Delta G^\ddagger$ value of 15.50 kcal-mol$^{-1}$ for 6b and 17.19 kcal-mol$^{-1}$ for 6a; hence, the barrier for 6a is 1.69 kcal-mol$^{-1}$ higher than that for 6b. Thus, 6b is the kinetic product and 6a is the thermodynamic one. Because 6a is not observed experimentally, these results suggest that the observed product 6b may be preferentially formed under kinetic control. Quantitatively, our computed difference in the activation barriers is probably somewhat underestimated, because it would correspond to a 6a:6b distribution of 5:95 at room temperature. Qualitatively, however, our results provide evidence for this reaction being under kinetic control, and this may be the reason why the diastereomer with cis stereochemistry is not observed experimentally.

The present work explored the heterogeneous hydrogenation of a polyfunctionalized indolizine (S), which was prepared by using a straightforward two-step sequence based on a Morita–Baylis–Hillman reaction with a known pyridine-2-carboxaldehyde. The partial hydrogenation step was shown to be highly diastereoselective, forming trans ketone 6b in 30% yield and cis alcohol 9 as an inseparable mixture of unassigned compounds. The intriguing experimental preference of trans diastereomer 6b was unveiled by applying high level ab initio and DFT theoretical calculations, which pointed out the establishment of a keto–enol tautomerism as the key step of the hydrogenation reaction. Under the experimental conditions, the kinetic (trans, 6b) isomer is favored in detriment of the thermodynamic (cis, 6a) isomer. The transition state for the trans isomer is more stable by 1.69 kcal-mol$^{-1}$ in comparison to the cis isomer. Lastly, the present work may help guide future experiments for the exploration of keto–enol tautomerism to efficiently select thermodynamic/kinetic diastereomers in heterogeneous hydrogenation reactions.

**EXPERIMENTAL SECTION**

**General Procedures.** All chemicals and solvents were of analytical grade, purchased from commercial sources, and used without further purification unless otherwise stipulated.

Unless otherwise noted, all reactions were performed under an ambient atmosphere in oven-dried open-flask glassware with magnetic stirring. Reaction progress was monitored by analytical thin-layer chromatography (TLC) performed on precoated silica gel 60 F254 (5–40 μm thickness) plates. The TLC plates were visualized with UV light (254 nm) and/or potassium permanganate or sulfuric vanillin followed by heating. When necessary, reaction products were purified by flash column chromatography using silica gel (230–400 mesh).

Figure 3. Energy diagram and transition state geometrical representations for the keto–enol tautomerization step for formation of 6a through TSa and 6b through TSb calculated at the M11/aug-cc-pV DZ level. The energies are given in kcal-mol$^{-1}$. Forming/breaking C=O$\cdots$H–O and C=O$\cdots$H–C bond distances are shown in angstroms.
preheated silicone oil bath (at ~90 °C) until complete dissolution of the starting material. Then, p-toluene sulfonic acid monohydrate (0.05 equiv, 125.1 mg, 0.658 mmol) was added to the solution under stirring, and the reaction mixture was maintained under these conditions for 14 h. After this time, the reaction mixture was allowed to cool to room temperature and then quenched by adding distilled H2O (50 mL) and NaH2PO4·H2O (75 mg). The resulting mixture was extracted with CH2Cl2 (4 × 50 mL), and the combined organic phases were dried with anhydrous Na2SO4, filtered, and concentrated under reduced pressure to furnish crude seven-membered cyclic acetal as a viscous brown oil in quantitative yield (4.14 g). This compound was sufficiently pure to be used in the next step without further purification.

1H NMR (400 MHz, CDCl3): δ 7.83 (s, 1H), 7.47–7.34 (m, 5H), 4.82 (s, 2H), 4.81–4.77 (m, 4H), 2.51 (s, 3H), 4.5 (s, 6H).

13C{1H} NMR (101 MHz, CDCl3): δ 151.1, 150.1, 141.8, 141.2, 136.0, 134.8, 128.8 (2C), 128.7, 128.2 (2C), 102.8, 75.4, 61.8, 59.4, 23.6. HRMS (ESI/Q-TOF) m/z: Calcd for C18H20NO4 [M + H]+: 314.1387, found 314.1384.

9-(Benzyloxy)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridine-8-carbaldehyde (7). A solution of S5 (1.07 g, 3.38 mmol) in anhydrous CH2Cl2 (70 mL) was prepared in a round-bottomed flask. The solution was cooled to 0 °C, and then, trichloroisocyanuric acid (1.0 equiv, 785 mg, 3.39 mmol) and TEMPO (0.01 equiv, 5.3 mg, 0.038 mmol) were carefully added to the reaction mixture under stirring. A change in the color of the reaction mixture was noticed within the first 5 min of reaction time (it became an orange suspension). After 30 min, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure, affording aldehyde 7 as a viscous yellow oil in quantitative yield (1.13 g). This compound was sufficiently pure to be used in the next step without further purification.

1H NMR (400 MHz, CDCl3): δ 10.15 (s, 1H), 8.29 (s, 1H), 7.45–7.34 (m, 5H), 5.01 (s, 2H), 4.88 (s, 2H), 4.78 (s, 2H), 1.44 (s, 6H). 13C{1H} NMR (101 MHz, CDCl3): δ 191.1, 153.7, 141.1, 140.6, 135.9, 129.0, 128.9 (4C), 103.0, 78.2, 61.9, 59.0, 23.6. HRMS (ESI/Q-TOF) m/z: Calcd for C18H20NO4 [M + H]+: 316.1387, found 316.1384.

Methyl 2-[9-(Benzyloxy)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-yl]heptanoate (5). In a round-bottomed flask, S3 (4.15 g; 13.1 mmol) was dissolved in anhydrous acetic anhydride (66 mL, 0.20 mol L−1) under stirring at room temperature and heated to 70 °C using a preheated silicone oil bath for 1 h. [CAUTION: This transformation, also known as the Boekelheide reaction, may proceed rather exothermically and vigorously. A reflux condenser should be adapted to the flask.] Then, the reaction mixture was allowed to reach room temperature, and the solvent was removed under reduced pressure. The resulting mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phases were dried with anhydrous Na2SO4, filtered, and concentrated under reduced pressure to furnish crude acetate as a viscous yellow oil in quantitative yield (5.03 g). This compound was sufficiently pure to be used in the next step without further purification.

1H NMR (500 MHz, CDCl3): δ 7.83 (s, 1H), 7.42–7.33 (m, 5H), 5.19 (s, 2H), 4.85 (s, 2H), 4.81 (s, 4H), 2.06 (s, 3H), 1.44 (s, 6H). 13C{1H} NMR (126 MHz, CDCl3): δ 170.7, 150.5, 147.7, 147.2, 141.8, 136.0, 135.9, 128.8 (2C), 128.7, 128.2 (2C), 102.8, 76.9, 62.4, 61.7, 59.8, 23.6, 20.9. HRMS (ESI/Q-TOF) m/z: Calcd for C18H19NO4 [M + H]+: 315.1649, found 315.1649.

Methyl 2-[9-(Benzyloxy)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-yl]heptanoate (5). NaH (60% dispersion in mineral oil) (1.8 equiv, 587 mg; 24.4 mmol) was added in a flame-dried round-bottomed flask under a nitrogen atmosphere, carefully dissolved in 80 mL of dry methanol at −10 °C (ethylene glycol/dry CO2 cryogenic bath), and left to stir for 45 min. This solution was transferred via cannula to a solution of S4 (4.86 g, 13.6 mmol) in 50 mL of CHCl3, at 0 °C and under stirring. The reaction mixture was left to warm to room temperature (30 min) and then stirred for 2 h. After this time, the reaction was quenched with saturated aqueous solution of NH4Cl (50 mL), and the resulting mixture was extracted with EtOAc (4 × 50 mL). The combined organic phases were dried with anhydrous Na2SO4, filtered, and concentrated under reduced pressure to afford crude MBH adduct 8 as a yellow oil in 85% yield (1.66 g, 4.17 mmol). Compound 8 was sufficiently pure to be used in the next step without further purification.

1H NMR (250 MHz, CDCl3): δ 8.10 (s, 1H), 7.42–7.35 (m, 5H), 6.28 (s, 1H), 5.85 (s, 1H), 5.61 (s, 1H), 4.96–4.70 (m, 6H), 3.67 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H). 13C{1H} NMR (63 MHz, CDCl3): δ 166.7, 152.1, 149.3, 142.2, 142.0, 141.5, 136.3, 135.7, 128.9 (2C), 128.8, 128.3 (2C), 126.7, 103.0, 76.5, 67.8, 62.0, 59.2, 23.8. HRMS (ESI/Q-TOF) m/z: Calcd for C18H20NO4 [M + H]+: 316.1387, found 316.1384.
H,11aH-[1,3]dioxepino[5,6-f]indolizine-9-carboxylate (6b) oil.

30:70 to a for C22H24NO5 [M + H]+ 382.1649, found 382.1679.

model).37 The global minima of integral equation formalism variant of the polarizable continuum conformer using an implicit solvent model, namely, the IEF-PCM each species. Solvent e

observation of a single negative frequency was used to characterize the atmosphere was replaced with H2 (80 bar) in a hydrogenation reactor.

for C15H22NO5 [M + H]+ 296.1492, found 296.1487.

(dd, J 11.5 Hz, 1H), 3.83 (ddd, J 10.1, 4.2, 3.1 Hz, 1H), 1.88 (ddd, J = 12.3, 9.8, 3.5 Hz, 1H), 1.56 (ddd, J = 12.3, 10.1, 4.2, 3.1 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H).13C{1H} NMR signals of 276.0842, found 276.0829.

Details).

δ 7.05 (m, 1H), 4.17 (dd, J 12.7, 9.8 Hz, 1H), 3.55 (s, 3H), 3.14 (dd, J 12.7, 3.5 Hz, 1H), 3.71 (dd, J = 12.3, 4.2 Hz, 1H), 2.65 (dd, J = 12.3, 4.2 Hz, 1H), 2.36 (t, J = 12.3 Hz, 1H), 1.88 (ddd, J = 12.3, 9.8, 3.5 Hz, 1H), 1.56 (ddd, J = 12.3, 10.1, 4.2, 3.1 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H).13C{1H} NMR (60 MHz, C6D6): δ 7.71 (d, J = 1.7 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 4.59 (dd, J = 12.7, 3.5 Hz, 1H), 3.71 (dd, J = 12.7, 9.8 Hz, 1H), 3.55 (s, 3H), 3.14 (dd, J = 11.8, 10.1 Hz, 1H), 2.92 (dd, J = 11.8, 3.5 Hz, 1H), 2.65 (dd, J = 12.3, 4.2 Hz, 1H), 2.36 (t, J = 12.3 Hz, 1H), 1.88 (ddd, J = 12.3, 9.8, 3.5 Hz, 1H), 1.56 (ddd, J = 12.3, 10.1, 4.2, 3.1 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H). HRMS (ESI/Q-TOF) m/z: Calcd for C12H15NaNO5 (acetal deprotection) [M + Na]+ 276.0842, found 276.0829.

Methyl (5aRS,11aSR)-3,3-Dimethyl-11-oxo-1H,3H,5H,5aH,6H,11aH-[1,3]dioxepino[5,6-f]indolizine-9-carboxylate (6b).13 H NMR (600 MHz, C6D6): δ 7.52 (d, J = 1.8 Hz, 1H), 7.07−7.05 (m, 1H), 4.17 (dd, J = 6.0, 1.3 Hz, 1H), 3.94 (dd, J = 13.0, 11.5 Hz, 1H), 3.83 (ddd, J = 12.7, 3.0, 1.3 Hz, 1H), 3.62 (s, 2H), 3.53 (dd, J = 12.6, 1.7 Hz, 1H), 3.38 (ddd, J = 12.6, 10.6 Hz, 1H), 3.13−3.02 (m, 2H), 2.17 (ddd, J = 10.5, 6.1, 3.9, 3.0 Hz, 1H), 1.42−1.35 (m, 1H), 1.26 (s, 3H), 1.09 (s, 3H).13C{1H} NMR (101 MHz, C6D6): δ 165.5, 131.2, 125.1, 117.6, 107.3, 102.0, 74.1, 62.8, 58.2, 51.0, 43.1, 42.6, 36.2, 25.4, 25.3. HRMS (ESI/Q-TOF) m/z: Calcd for C10H7NO (M + H)+ 280.0821, found 280.0845.

Computational Details. Conformers of compounds 6a and 6b were located through a Monte Carlo conformational search at the MMFF level with the Spartan 14 program,35 using a 10 kcal-mol−1 threshold and 5000 K initial temperature in the simulated-annaling algorithm. Optimizations and frequency calculations were carried out at the B3LYP-D3/aug-cc-pVDZ level using the Gaussian 09 program, revision D.01,36 for all conformers found in the Monte Carlo calculations. The lack of negative harmonic vibrational frequencies confirmed that all conformers are true energy minima, or the observation of a single negative frequency was used to characterize the geometry as a transition state. The same frequency calculations were used to evaluate thermodynamic corrections affording enthalpies and Gibbs free energies at ambient temperature and pressure for each species. Solvent effects were evaluated by optimizing each conformer using an implicit solvent model, namely, the IEF-PCM (integral equation formalism variant of the polarizable continuum model).77 The global minima of 6a and 6b were reoptimized by using several DFT functional and the HF and MP2 ab initio methods and the aug-cc-pVDZ basis set. MP4 single point calculations were carried out over the M11/aug-cc-pVDZ optimized geometries, and the enthalpy and Gibbs free energies were obtained from this same functional to add to MP2, MP4, and BP2LYP-D3 potential energies. DLPNO-CCSD(T)/aug-cc-pVTZ calculations were ran over the M11/aug-cc-pVDZ optimized geometries using the ORCA 4.2.1 program and were also corrected with the enthalpy and Gibbs free energies obtained from this same level.38

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