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Complete List of Authors:	Lee, Seokjoo; Michigan State University, Department of Chemistry Jena, Rashmi; Michigan State University, Department of Chemistry Odom, Aaron; Michigan State University, Department of Chemistry

ARTICLE

Substituted Pyridines from Isoxazoles: Scope and Mechanism

Seokjoo Lee, Rashmi Jena, and Aaron L. Odom*

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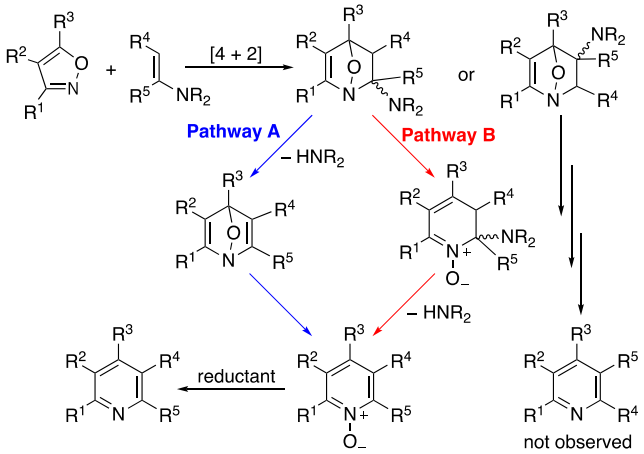
Treatment of isoxazoles with enamines leads to an inverse electron-demand hetero-Diels-Alder reaction that produces substituted pyridines in the presence of $TiCl_4(THF)_2$ and titanium powder. The reaction is highly regioselective with only a single isomer of the product observed by GC/MS and tolerant of many common functional groups. The transformation was examined computationally, and it was found that $TiCl_4$ (or a similar Lewis acid) likely acts to catalyze the reaction. After the initial [4 + 2]-cycloaddition, the oxaza-[2.2.1]-bicycle produced likely ring opens before amine loss to give an *N*-oxide. The pyridine is then obtained after reduction with $TiCl_4$ and titanium powder.

Introduction

The alteration of one pharmacologically active heterocyclic core into another core is an exciting method for the production of new compounds with biological activity that has drawn substantial recent interest with possibilities for late-stage functionalization.[1, 2] In a recent example, one can "delete" a nitrogen atom from a heterocyclic structure.[3, 4] This type of core structure editing, or "scaffold hopping", is an intriguing method for taking biologically active compounds and switching out the core while leaving the substituents the same or adding complexity.[5-9] This type of "hopping" is often discussed as a conceptual or in silico method for drug design, but synthetic methods for leaving peripheral substituents more or less in place and changing the core are an intriguing synthetic area. Ordinarily, chemists think of starting with a core structure and building complexity upon it, so these methods of changing a core through ring expansion, contraction, or other alteration offer a quite different strategy for rapid exploration of structural relationships to biological activity.

An applicable methodology that has been reported, but not substantially developed, is the reaction of isoxazoles with electron-rich olefins in an inverse electron-demand hetero-Diels-Alder[10] reaction to give pyridines. This reaction takes substituted isoxazoles (or isoxazole itself) and exchanges the core for pyridine with net removal of the oxygen atom. In addition, new substituents are added in a regioselective manner to the ring.

A simple outline for the reaction is shown in Scheme 1. In a simplified description of the proposed mechanism, the substituted isoxazole undergoes initial [4 + 2]-cycloaddition with the enamine to form a [2.2.1]-oxazabicyclic intermediate. The only product observed from the reaction has R^5 in the α-position, adjacent to the pyridine nitrogen; consequently, the alternative cycloaddition shown to the right is unfavorable. From the [2.2.1]-bicyclic compound, one can imagine two major pathways: (A) initial loss of amine followed by ring opening and (B) initial ring opening followed by loss of amine. Reduction occurs in situ to give the pyridine directly.



Scheme 1. The inverse-electron demand hetero-Diels Alder reaction of isoxazole with enamine can be used to give pyridines after in situ reduction. The reaction mechanism can be divided into two major pathways depending on whether ring-opening or amine loss occurs first.

The reaction was originally reported by Ohta and coworkers in 1989 using $TiCl_4$/Zn as the reductant; however, the methodology has been little used since this report.[11] In fact, this original paper for this intriguing reaction has only been referenced 5 times in over 30 years.[12-16] In previous work, we have developed a new one-pot, multicomponent method for the synthesis of some isoxazoles, and we were interested in their applications to pyridine synthesis,[17, 18] with possible applications to biologically-active pyridine studies ongoing in our research group.[19] Here, we report a reoptimization of the conditions that make the reaction more reliable in our hands and which use more "bench stable" reagents with an easier reaction setup. In addition, we report a computational study on

Michigan State University, Department of Chemistry, 578 S. Shaw Ln, East Lansing, Michigan 48824

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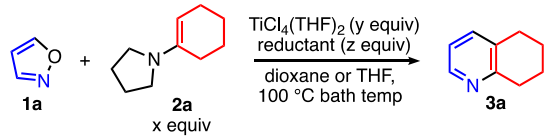
the mechanism of the reaction that suggests $TiCl_4$ may have a catalytic role as well as act as the precursor to the reductant.

Results and Discussion

Reoptimization of the Reaction and Substrate Scope

The original report by Ohta and coworkers proposed that the reaction of isoxazoles with enamines provided pyridine-*N*-oxide products that could be reduced with $TiCl_4$ and zinc.[11] In place of the fuming liquid $TiCl_4$, (Table 1) we investigated commercially available and more bench stable $TiCl_4(THF)_2$. In addition to zinc dust, we tried conditions with Ti powder, Al pellets, Mg turnings, Sn powder, and Reike Zn. In the test reaction, and other reactions where comparisons were made, Ti powder gave the highest yields, generally the same or slightly higher than those reported in the original paper (for the few products that overlap between the previous study and this one), and the reaction was quite reliable with this combination of reagents.

Table 1 Optimization of pyridine synthesis using $TiCl_4(THF)_2$ and reductants



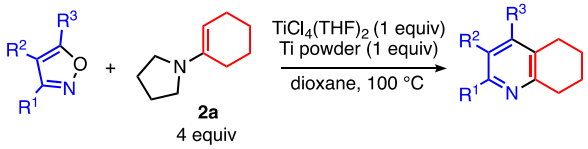
Entry	x / y / z	Reductant	GC % Yield
1	4 / 1 / 1	Ti powder	80
2	3 / 1 / 1	Ti powder	69
3	2 / 1 / 1	Ti powder	58
5	4 / 2 / 1	Ti powder	69
6	4 / 1 / 2	Ti powder	68
7	2 / 1 / 1	Zn dust	61
8	2 / 1 / 1	Al pellets	45
9	2 / 1 / 2.2	Mg turning	38
10	4 / 1 / 1	Sn powder	65[a]
11	4 / 2 / 1.5	Rieke Zn	53[a]
12	4 / 2 / 1.2	Ti powder	53[a]
13	4 / 2 / 1.2	Zn dust	46[a]

[a]THF was used in place of dioxane as solvent.

With these conditions in hand, we investigated the scope of the reaction with a variety of isoxazoles and enamines. First, with 1-pyrrolidino-1-cyclohexene, a large series of isoxazoles was investigated (Table 2). The [4 + 2]-cycloaddition involves addition to the nitrogen and 5-position of the isoxazole to the enamine double bond. As a result, substituents on the 5-position (R^3) prevent reactivity. It appears that large substituents in the 4-position (R^2) may also lead to reduced yield. (For example, see Table 2, entry 2 vs entry 8.) This is perhaps due to steric protection of the 5-position by a large group on the 4-position, but some substitutions certainly are tolerated, like methyl, ethyl, bromo, and to a lesser extent aryl.

Dimethylfurazane, 3,4-dimethyl-1,2,5-oxadiazole (**1h**), reacts with enamine under these conditions to give a substituted pyrazine (Table 2, entry 9). A variety of substituents in the 3- and 4-positions are tolerated including alkyls, aryls, acylamines, and halides. An ester group in either the 3- or 5-position gave only a trace amount of product under these conditions.

Table 2 Pyridine synthesis with 1-pyrrolidino-1-cyclohexene

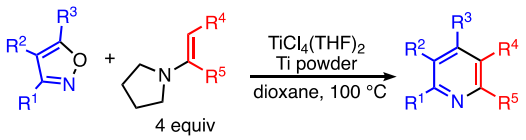


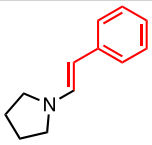
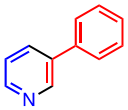
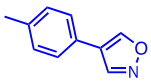
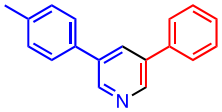
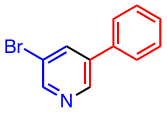
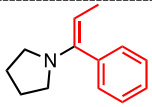
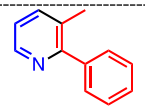
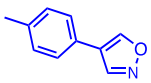
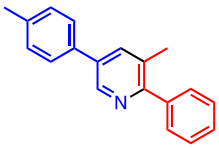
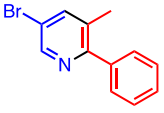
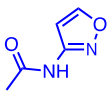
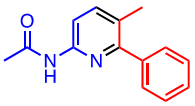
Entry	Heterocycle	Product	Isolated % Yield
1	**1a**	**3a**	76
2	**1b**	**3b**	41
4	**1c**	**3c**	70
5	**1d**	**3d**	21
6	**1e**	**3e**	73
7	**1f**	**3f**	72
8	**1g**	**3g**	82
9	**1h**	**3h**	19

The reaction appears to be selective. We never observed another isomer of the product by GC/MS in any of the reactions, which is readily explicable as nucleophilic addition of the β-carbon of the enamine builds up negative charge stabilized by electronegative nitrogen (vide infra). A couple of different

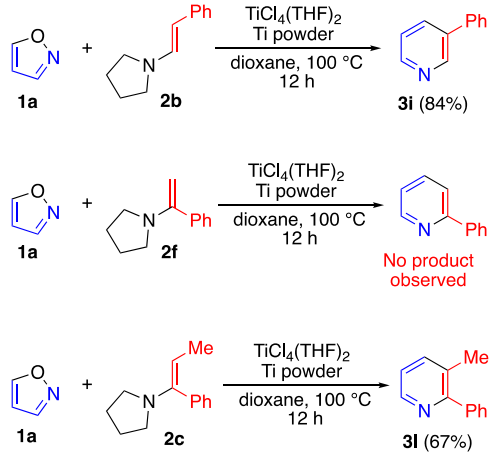
monoaryl enamines were tried in the reaction (Table 3), and the carbon adjacent to the pyrrolidinyl of the enamine (R^5) invariably is one of the α-carbons of the product pyridine.

Table 3 Pyridine synthesis using $TiCl_4(THF)_2$ and Ti powder



Entry	Heterocycle	Enamine	Product (% Yield)
1	 **1a**	 **2b**	 **3i** (84)
	 **1b**		 **3j** (80)
2	 **1c**		 **3k** (86)
4	 **1a**	 **2c**	 **3l** (67)
5	 **1b**		 **3m** (77)
6	 **1c**		 **3n** (84)
7	 **1d**		 **3o** (65)

1-Phenyl-1-(1-pyrrolidinyl)ethene (**2b**) was found to give good yields when paired with several different isoxazoles (Table 3, Scheme 2). In contrast to intuition regarding steric influences in the two different isomers, this enamine is more reactive than 2-phenyl-1-(1-pyrrolidinyl)ethene (**2f**). Enamine **2f** is also less reactive than 2-methyl-1-phenyl-1-(1-pyrrolidinyl) (**2c**). These results are consistent with the findings of Mayr and coworkers on the nucleophilicity of enamines as a function of substitution patterns, and it appears that more nucleophilic enamines are preferred for the reaction.[20] Similarly, Houk and coworkers found slightly higher barriers for enamines without substitution on one side of the olefin in 1,3-dipolar cycloadditions with phenylazide.[21]



Scheme 2. Reactions of parent isoxazole (**1a**) with enamines **2b, 2f**, and **2c**. The terminal enamine **2f** is unreactive and thought to be less nucleophilic.[20]

Finally, we investigated a couple of di(aryl)enamines (**2d** and **2e**) as well (Table 4). These are particularly good substrates for the reaction, providing good yields with parent isoxazole, along with mono- and disubstituted isoxazoles.

In further explorations, we investigated the effect of the secondary amine used to generate the enamine. It was found that pyrrolidine gave superior reactivity to piperidine and morpholine. Again, this is consistent with Mayr's findings associated with the nucleophilicity of enamines, where nucleophilicity with secondary amine was found to go as pyrrolidine > piperidine > morpholine. In some cases, pyrrolidine-based enamines have been found to have rate constants many orders of magnitude larger than morpholine derivatives, so the effect of the secondary amine can be quite substantial![20]

DFT examination of the reaction mechanism

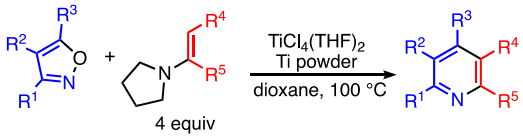
The mechanism of the reaction was investigated using Density Functional Theory, B3LYPD3 with aug-cc-pVDZ. In the initial investigation, gas phase calculations were carried out, and a summary of those findings are in the SI. Here, we will discuss the mechanism of pyridine-*N*-oxide formation with and without $TiCl_4$ involvement with the SMD universal continuum solvent model of the experimental solvent, 1,4-dioxane.

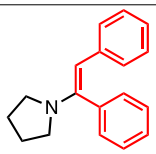
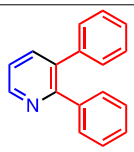
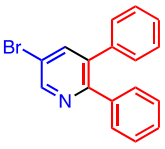
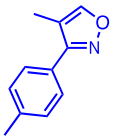
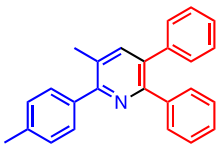
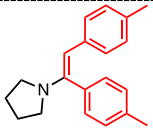
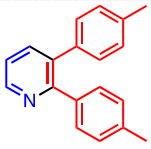
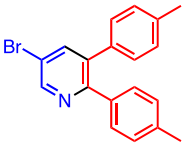
In the calculations, we considered formation of endo and exo isomers; however, the two are quite close in energy in all cases. To simplify the figures and the discussion, we will discuss the endo isomers, but the exo isomer is typically within ~3 kcal/mol in energy. A discussion of the energy differences between endo and exo can be found in the SI.

In the modelling, we chose to use isoxazole with H_2N-CH=CH_2 as the reactants. As discussed above, the use of NH_2 as the amine was an expedient one for the calculations, but one would expect the barriers, particularly those related to the nucleophilicity of the enamine and basicity of the amine, to be lower with pyrrolidine, as used experimentally. As a result, the trends observed here likely hold for the experimental reaction, but the numerical values for the barriers likely differ from experiment.

In the calculations with $TiCl_4$, the metal center was moved between various donor atoms to find the lowest energy structures and transition states. In practice, there may be a variety of different Lewis acids in solution, especially other titanium halides like $TiCl_3$. Nevertheless, we only investigated the strongest Lewis acid in solution, $TiCl_4$, as a catalyst.

Table 4 Pyridine synthesis with 1-(1,2-diarylethenyl)-1-pyrrolidine



Entry	Heterocycle	Enamine	Product (% Yield)
1	 **1a**	 **2d**	 **3p** (90)
2	 **2c**		 **3q** (88)
3	 **1g**		 **3r** (91)
4		 **2e**	 **3s** (67)
5			 **3t** (84)

The first step in the synthesis is the critical [4 + 2]-cycloaddition of the enamine with and without $TiCl_4$. In Fig. 1, $TiCl_4$ is abbreviated as "[M]" to simplify the drawings. In the absence of $TiCl_4$, it was found that the highest barrier to reaction was the [4 + 2]-cycloaddition (TS1), which occurred in a concerted manner with a barrier of 42 kcal/mol. The product of cycloaddition was found to be substantially higher in energy than the starting materials, 31 kcal/mol (I1).

The pathway changed significantly in the presence of the Lewis acid (blue path, Fig. 1). The reaction of the enamine with the isoxazole was found to occur in a stepwise fashion, first with C–C then C–N bond formation. The barriers (TS1A_M and TS1B_M) for this stepwise addition were substantially smaller than in the absence of Lewis acid at <19 kcal/mol. The product of cycloaddition (I1_M) was also greatly stabilized by the addition of the Lewis acid at only ~17 kcal/mol higher than starting materials (SM).

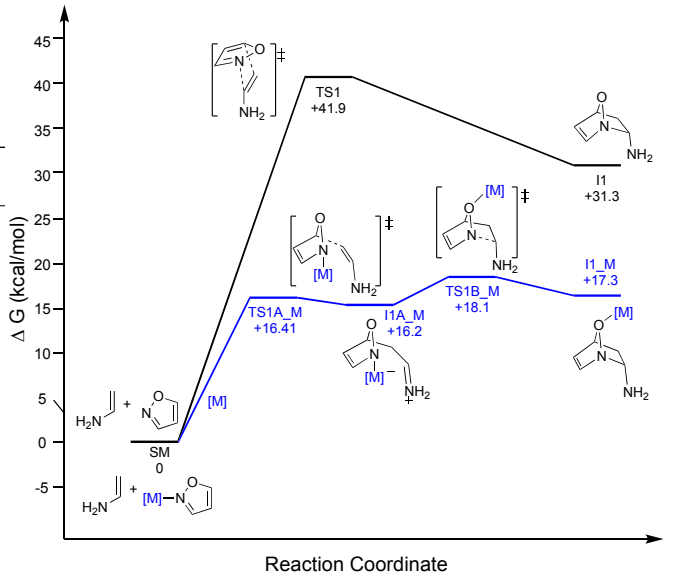


Fig. 1. Calculated pathway to the endo cycloaddition product between enamine and isoxazole with (blue) and without (black) $TiCl_4$. [M] = $TiCl_4$. Free energies are in kcal/mol under standard conditions. The two paths are referenced to starting materials as 0 kcal/mol, i.e., enamine + isoxazole for the pathway without Lewis acid and enamine + $TiCl_4$(isoxazole) for the pathway with Lewis acid. Calculations were done using B3LYPD3 with aug-cc-pVDZ with an SMD solvent model for 1,4-dioxane.

After the initial cyclization product is formed (I1 or I1_M), we investigated two possible pathways: (1) initial amine loss followed by ring opening shown in Fig. 2 and (2) ring opening followed by amine loss shown in Fig 3.

First discussing the pathway involving initial amine loss followed by ring opening (Fig. 2), the ground and transition state structures for the system containing the $TiCl_4$ and the one without the Lewis acid had quite similar structures, although the energies of the pathway with the Lewis acid were somewhat lower throughout. In Fig. 2 and Fig. 3 (the other pathway), transition state 2 (TS2) is for amine loss and transition state 3 (TS3) is for ring opening. In Fig. 2, to distinguish from the opposing ring-opening followed by amine loss mechanistic path, the intermediates and transition states unique to this pathway are labelled α.

The most noticeable and important finding is that the transition states for amine loss both with and without Lewis acid are exceedingly high when this step occurs before ring opening (Fig. 2). In fact, the transition state for NH_3 elimination was found to be >60 kcal/mol from the cycloaddition intermediate **I1** with the Lewis acid making little difference in this energy. Consequently, this pathway looks to be energetically untenable. Obviously, this should be compared with the pathway involving ring opening first, followed by amine loss (Fig. 3).

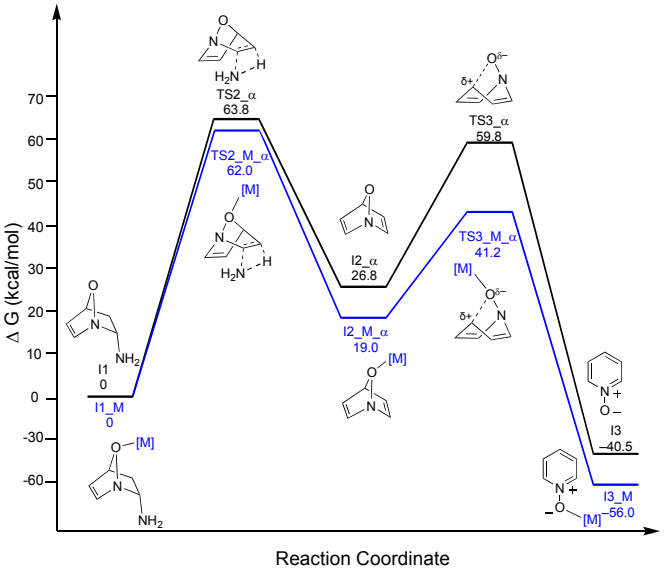


Fig. 2. Calculated pathway starting with the cycloaddition product **I1** for amine loss first followed by ring opening with (blue) and without (black) $TiCl_4$. [M] = $TiCl_4$. Energies are in kcal/mol under standard conditions. Transition states and intermediates unique to this mechanistic path are labelled α. Calculations were done using B3LYPD3 with aug-cc-pVDZ with an SMD solvent model for 1,4-dioxane.

The calculated free energies (kcal/mol) for the pathway with ring opening followed by amine loss are shown in Fig. 3. Notably, ring opening barriers (35.9 and 27.3 kcal/mol with and without $TiCl_4$) are similar from the ones in Fig. 2 (33.0 and 22.2 kcal/mol with and without $TiCl_4$), and these barriers seem far more reachable than that for initial amine loss (>60 kcal/mol). Note that calculations on the ring opening step with pyrrolidine in place of NH_2 leads to a somewhat lower energy barrier (21 kcal/mol) in the presence of $TiCl_4$. Once the ring is open, one can reason that concomitant aromatization of the pyridine ring may aid in amine loss and give a much lower barrier for this step. Without $TiCl_4$, the amine loss after ring open has a more reasonable barrier of 27.4 kcal/mol.

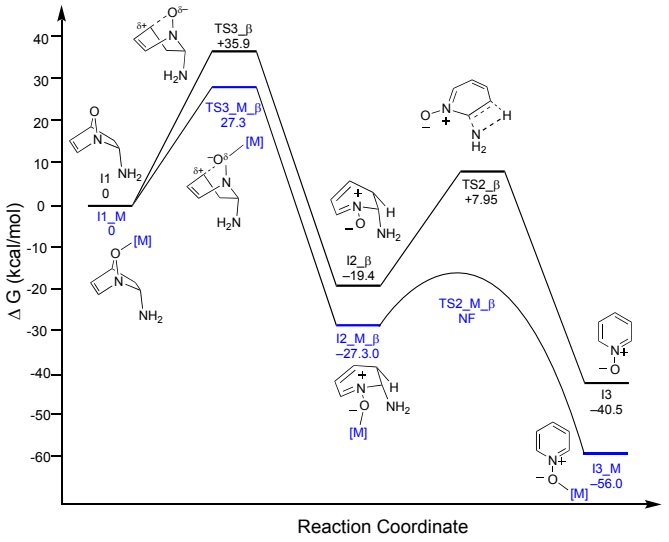


Fig. 3. Calculated pathway starting with the cycloaddition product **I1** for ring opening first followed by amine loss with (blue) and without (black) $TiCl_4$. [M] = $TiCl_4$. Energies are in kcal/mol under standard conditions. Transition states and intermediates unique to this mechanistic path are labelled β. Calculations were done using B3LYPD3 with aug-cc-pVDZ with an SMD solvent model for 1,4-dioxane.

After many attempts, we were unable to locate the transition state for amine loss after ring opening in the presence of $TiCl_4$ (TS2_M_β); however, since every transition state and intermediate with the Lewis acid bound has been lower in energy, we would assume it has a lower energy than TS2_β. If the metal-complexed transition state were higher in energy, it is possible that the metal could be lost prior to amine loss and go through the TS2_β transition state. Calculations to estimate the energy required for loss of $TiCl_4$ from I2_M_β to give I2_β, suggest that ΔG° for decoordination of the Lewis acid is only 13 kcal/mol for the endo isomer and 10 for the exo. In other words, crossing from the metal coordinated path in Fig 3 from I2_M_β to I2_β seems energetically reasonable.

As a result, the calculations suggest that a Lewis acid can alter the pathway of the reaction somewhat leading to a lower energy, stepwise cycloaddition pathway. In addition, the most likely mechanistic pathway is one where the O–C bond is cleaved first, opening that ring prior to amine loss. The higher energy amine loss is then aided by aromatization of the pyridine ring.

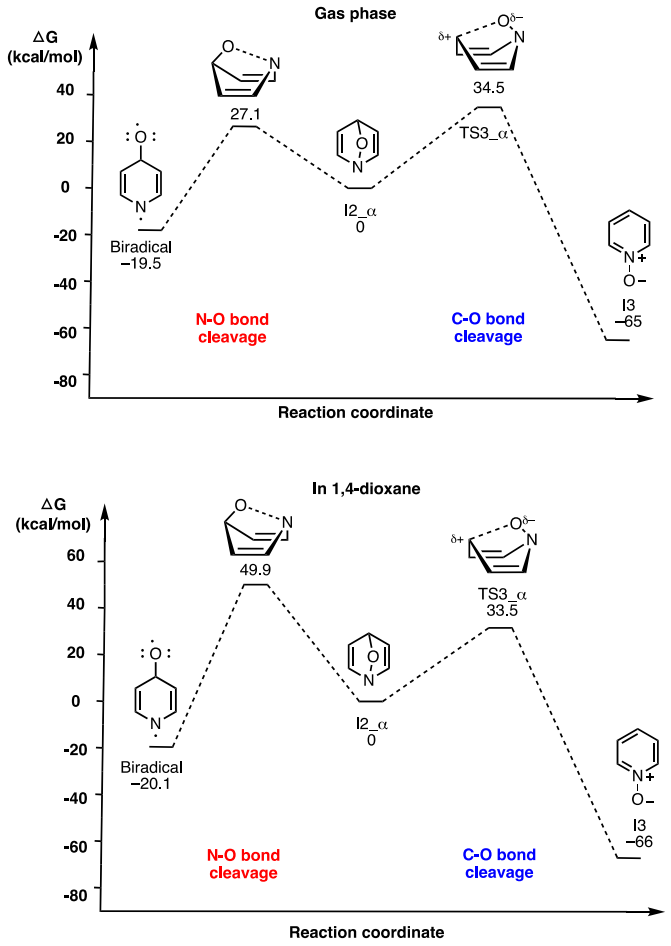


Fig. 4. Computational investigation (B3LYPD3 with aug-cc-pVDZ) of homolytic N–O bond cleavage versus heterolytic C–O bond cleavage in intermediate I2_α. The N–O bond is expected to be weak due to lone pair bond weakening, and in the gas phase the barrier to cleave this bond is smaller (top). Use of an SMD solvent model for 1,4-dioxane leads to a lower energy heterolytic C–O bond cleavage (bottom).

In addition to the above, we were curious about an unusual aspect of this reaction. Namely product formation involves cleavage of an O–C bond adjacent to what one would assume is a much weaker N–O bond (Fig. 4). Compounds like peroxides, hydrazines, hydroxylamines, and F_2 have lower bond dissociation enthalpies due to lone pair bond weakening.[22-24] However, product formation requires breakage of the adjacent C–O bond instead. The two cleavages are quite different as N–O cleavage would be expected to occur homolytically, while C–O cleavage should be heterolytic; however, the relative barriers associated with the two processes are less than obvious. Indeed, in the gas phase it was found that homolytic cleavage of the N–O bond in I2_α to form a diradical has a substantially lower barrier (+27.1 kcal/mol) than heterolytic cleavage of the O–C bond (+34.5 kcal/mol). In 1,4-dioxane, the situation is reversed with the O–C heterolytic cleavage having a barrier of 33.5 kcal/mol and the homolytic N–O cleavage requiring a very high 49.9 kcal/mol. It seems likely that the presence of solvent helps to stabilize the incipient charges associated with the heterolytic transition state.

Conclusions

Using an inverse-electron demand hetero-Diels-Alder reaction an isoxazole core can be converted to a pyridine by reaction with an enamine. The reaction was found to work well with $TiCl_4(THF)_2$ and titanium powder in the presence of dioxane to give a single observable regioisomer for the product. The scope of the reaction is good but limited to isoxazoles without substitution in the 5-position. More nucleophilic enamines give much better reactivity, with those derived from pyrrolidine better than piperidine and morpholine derivatives.

The mechanism was investigated using DFT (B3LYPD3, aug-cc-PVDZ, SMD-dioxane). It was found that the [4 + 2]-cycloaddition (Fig. 1) between the isoxazole and enamine was concerted in the absence of $TiCl_4$ but had a high energy transition state (~40 kcal/mol). In the presence of the Lewis acid, the reaction was nonconcerted with a much more energetically accessible transition state energy (<19 kcal/mol).

The preferred pathway computationally involved the initial ring opening of the oxaza-[2.2.1]-bicycle formed after the cycloaddition to give an imine-*N*-oxide that could then lose amine to aromatize the pyridine ring (Fig. 3). This pathway was energetically preferred over initial amine loss followed by ring opening.

Based on the pathway discussed, it might be possible to isolate the pyridine-*N*-oxide from the reaction. Attempts to run the reaction with the same conditions described, but without $TiCl_4$, gave no discernible reaction by GC/MS. If $TiCl_4$ is used without a reductant present (e.g., titanium powder or zinc), then the reaction proceeds to give pyridine(!), but in lower yields. The question then becomes, "what is the reductant if no titanium powder (or another stoichiometric reductant) is added?" Running the reaction in a solvent that is unlikely to act as a radical donor, benzene, gave pyridine as well. It is postulated that the electron-rich enamine may be acting as the reductant in the absence of titanium powder. It might be that the side reaction of the enamine starting material acting as reductant contributes to the far better yields for the reaction when using an excess of this reagent.

Based on these results, it is difficult to pinpoint the moment of reduction in the reaction. While pyridine-*N*-oxide may be produced by the reaction as suggested by Ohta and coworkers, a lack of build-up of this intermediate suggests that its reduction is faster than its production. However, it is also possible that the imine-*N*-oxide intermediate (I2_M_β, Fig. 3) is reduced prior to amine loss and pyridine-*N*-oxide is never produced.

Overall, the reaction of isoxazoles with enamine is a fascinating reaction that allows conversion of an isoxazole core to pyridines, with additional substitution possibly being added in the process. The reaction is highly regiospecific and fairly general, tolerating many common functional groups.

Author Contributions

R.J. and S. L. equally divided the computational work and carried out the DFT calculations. S. L. carried out all the experimental work, including isolation and characterization of compounds. A.L.O.

conceived the project and designed many of the experiments. A.L.O. wrote the initial draft of the article, and all authors reviewed and edited the article.

Conflicts of interest

There are no conflicts to declare.

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