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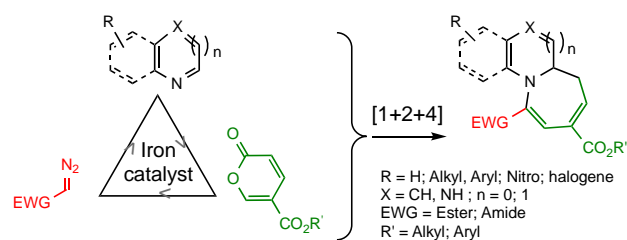
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# Iron Catalyzed Dearomatization of Pyridines into Annelated Azepine Derivatives in a One-step, Three-component Reaction

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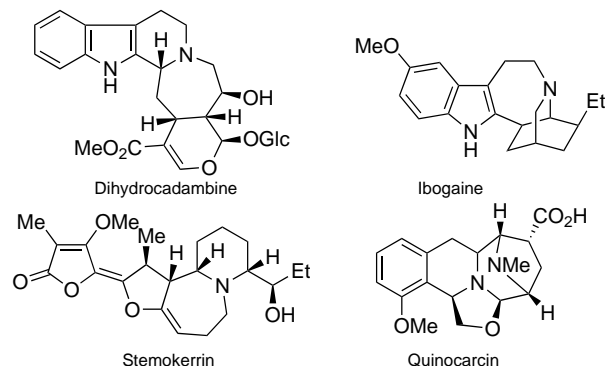
Supporting Information Placeholder



- \* Rare fused azepine moiety
- \* Only N<sub>2</sub> and CO<sub>2</sub> as byproducts
- \* 10 minutes reaction time
- \* Broad scope > 35 examples

**ABSTRACT:** Commercially available Fe(TTP)Cl catalyzes three-component dearomative formal cycloaddition reactions between pyridines, diazo compounds and coumalates. Diversely substituted annelated seven-membered N-heterocycles could be generated in less than ten minutes, in one step at room temperature. The reaction is compatible to gram scale. The extension to benzimidazoles in place of pyridines has been successfully demonstrated. The mechanism of this reaction has been carefully examined by computational studies that corroborate the observed regioselectivities.

Organic chemists are continuously discovering and improving methodologies to build complex molecules. Some colleagues from the pharmaceutical industry recently stated: “*Drug molecules typically contain amines and N-heterocycles as well as unprotected polar groups, which present significant synthesis challenges. More synthetic methods are needed which tolerate these functionalities*”.<sup>1</sup> In the expending world of azaheterocyclic compounds,<sup>2</sup> (polycyclic) seven-membered azepan and azepine derivatives are key structural fragments found in natural products isolated from fungi, plants and marine sponges (Figure 1).<sup>3</sup> These motifs possess a wide range of biological activities leading to various applications in medicine and pharmacology.<sup>4</sup> As a result, many approaches have been developed to construct the 7-membered core,<sup>5</sup> among which nucleophilic substitution, lactamisation, ring reorganization, ring closing metathesis, cycloadditions, including the use of azomethine ylides.<sup>6</sup>



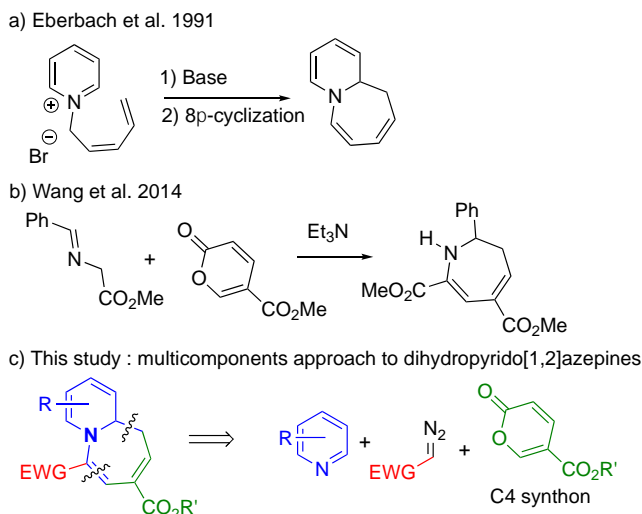
**Figure 1. Natural Products Containing Fused Azepine Moiety**

In comparison to other 7-membered N-heterocycles, dihydropyrido[1,2- $\alpha$ ]azepines synthesis remains underexplored and efficient and general approaches are still to be discovered.

The first but unsuccessful approach toward pyrido[1,2- $\alpha$ ]azepines was reported by Jones.<sup>8</sup> In a more recent approach, Xia prepared a pyridinium[1,2- $\alpha$ ]azepine ruthenium complex that only led to the azepino-pyridinium salt after deprotection with tetrafluoroboric acid.<sup>9</sup> Eberbach and co-workers reported and studied the 8 $\pi$ -electrocyclization of conjugated butadienylpyridinium ylides into dihydropyrido[1,2- $\alpha$ ]azepines (Figure 2a).<sup>10</sup>

Altogether, the existing methods require multiple steps to access the desired compounds, with moderate yields or difficulties to isolate intermediates. Therefore, searching for an efficient, easily adaptable method to synthesize dihydropyrido[1,2-*a*]azepines is still highly desirable.

Azomethine ylides have been used as C-N-C partners to build N-heterocycles.<sup>6,11</sup> Among others, dihydroazepines have also been synthesized from iminoesters and pyrones (Figure 2 b).<sup>12</sup> Pyridinium ylides which are stable dipoles are known to be versatile partners in [4+3] cycloadditions.<sup>13</sup> The possible salt-free preparation of pyridinium ylides by *in situ* reaction of pyridines with diazo compounds in the presence of metal catalyst is even more interesting in terms of sustainability.<sup>14</sup>



**Figure 2. Pathways to Pyrido[1,2-*a*]azepines**

Methyl coumalate, a 4-carbomethoxy pyrone, has demonstrated a wide range of partner-dependent reactivities. In addition to photoinduced intramolecular [2+2] electrocycloaddition leading to cyclobutenyl synthons,<sup>15</sup> it could deliver 2  $\pi$ - or 4  $\pi$ -electrons in cycloadditions with dienes, dienophiles, or dipoles.<sup>16</sup> It is an excellent electrophile that participates in cascade reactions<sup>17</sup> or can be converted into a nucleophilic species *via* the transient addition of organocatalysts.<sup>18</sup> As a cherry on the cake, coumalic acid is produced from the dimerization of malic acid,<sup>19</sup> providing a basis for sustainable synthesis of more complex molecules.

In this context, we developed a simple and general method to access diversely functionalized annelated azepines in a one-step multicomponent reaction, starting from commercially available compounds (Figure 2c).

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**

Entry	Catalyst (mol%)	Temp.	Time	<b>4a</b> (%) <sup>b</sup>
1	Fe(TTP)Cl (1) <sup>c</sup>	r.t	10 min	73
2	Fe(TTP)Cl (1)	r.t	10 min	61 <sup>d</sup>
3	Fe(TTPOMe)Cl (1) <sup>e</sup>	r.t	10 min	73
4	Fe(TTPF)Cl (1) <sup>f</sup>	r.t	10 min	58
5	Cu(OAc) <sub>2</sub> (10)	r.t	4 h	23
6	Cu(OAc) <sub>2</sub> (10)	r.t	12h	27
7	Cu(OAc) <sub>2</sub> (10)	50 °C	4 h	22 <sup>g</sup>

<sup>a</sup> All reactions were carried out with pyridine **1a** (1 mmol), **2a** (1.2 mmol), **3a** (1 mmol), Fe(TTP)Cl (1 mol%), DCM (3 mL), r.t. 10 min.

<sup>b</sup> Yield after purification by flash-chromatography. <sup>c</sup> Fe(TTP)Cl : 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphyrin iron (III) chloride <sup>d</sup> Reaction on 1 gram scale <sup>e</sup> Fe(TTPOMe)Cl : 5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphyrin iron (III) chloride <sup>f</sup> Fe(TTPF)Cl : 5,10,15,20-Tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin iron (III) chloride. <sup>g</sup> Reaction in dichloroethane

To initiate the study, pyridine **1a**, ethyl diazoacetate **2a** and methyl coumalate **3a** were mixed in DCM in the presence of 1 mol% of 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphyrin iron (III) chloride (Fe(TTP)Cl) as catalyst. To our delight, the desired dihydropyridoazepine **4a**, was isolated in 73% yield after 10 minutes (Table 1, entry 1). No other product was detected. A concentration-dependance study was carried out and 0.33 M seems the optimal concentration. We also divided per two or doubled the

amount of catalyst without improvement (see SI, Table S1). Substitution of DCM by other solvents did not provide better results. Toluene or THF afforded compound **4a** in yield reaching 70% whereas EtOH led to 63% of **4a**.

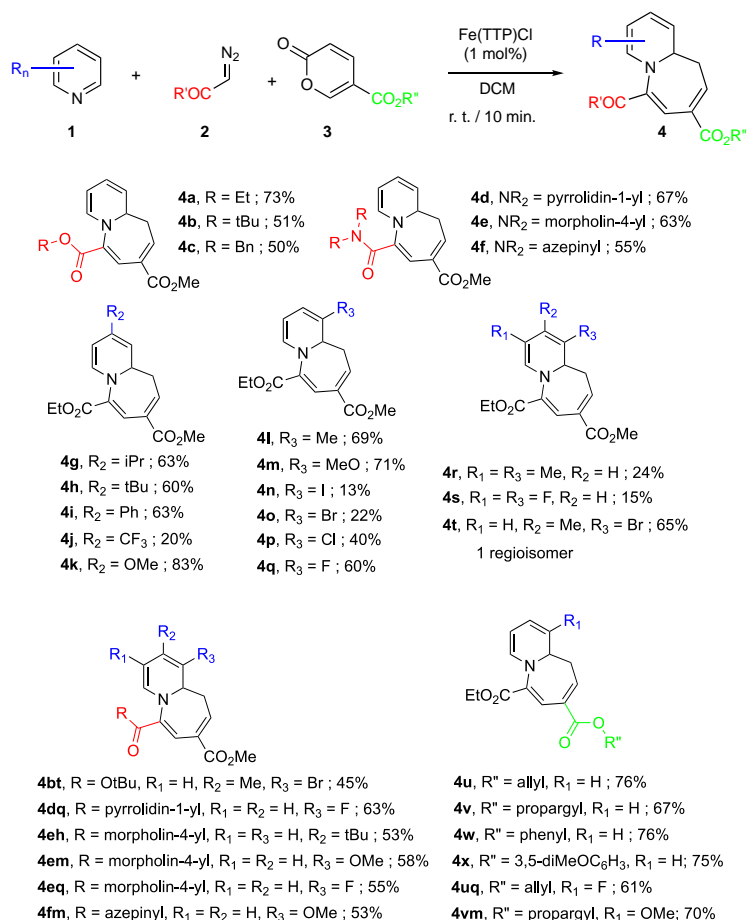
Different metal salts were investigated and selected results are summarized in Table 1 (see SI, Table S1). Various iron-based catalysts such as 5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-porphyrin iron (III) chloride (Fe(TTPOMe)Cl) and 5,10,15,20-Tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin iron (III) chloride (Fe(TTPF)Cl) or FeCl<sub>3</sub> were tested. While similar results were observed with Fe(TTP)Cl and Fe(TTPOMe)Cl, the use of Fe(TTPF)Cl reduced the yield in **4a** down to 58% (Table 1, entries 1-4). Unfortunately, FeCl<sub>3</sub> did not lead to the formation of **4a** even with 1 h reaction time or increasing its quantity up to 10 mol% (see SI). Initial results with copper diacetate (II) were encouraging, giving **4a** in a moderate 23% yield, however all attempts to improve the conversion were unsuccessful (Table 1, entries 5-7). The use of catalysts based on palladium, rhodium, silver or chromium did not allow the formation of the desired compound even with longer reaction time (See SI, Table S1).

In summary, we chose the following conditions: pyridine, diazoacetate **2a** (1 equiv), coumalate **3a** (1.2 equiv.) and Fe(TTP)Cl (1 mol %) in DCM and tested at the gram scale. It delivered 2.1 g (61% yield) of the desired dihydropyridoazepine **4a** in less than 10 min (Table 1, entry 2).

Starting from commercially available benzyl 2-diazoacetate **2b** and *tert*-butyl 2-diazoacetate **2c** (Table 2), the desired dihydropyridoazepines **4b** and **4c** were obtained in moderate yield, whereas diazo amides **2d-f** led to the expected fused azepines **4d**, **4e** and **4f** in yield up to 67%.

Pyridines **1g-k** with substituents in para position were first tested for their symmetry and low steric hindrance. Isopropyl or *tert*butyl groups had no significant influence and the desired compounds **4g-h** were obtained in yields around 65 %. The use of 4-phenylpyridine **1i** as substrate led to the corresponding dihydropyridoazepine **4i** in 63%. However, the presence of the strongly electron-withdrawing trifluoromethyl group significantly decreased the reactivity of **1j**. The same trend was observed with 4-cyano group as no reaction occurred. Gratifyingly, the dihydropyridoazepine **4k** bearing a 4-methoxy group could be isolated in 83% yield after precipitation. Altogether, these results suggest that electronic density on the nitrogen atom of the nucleophilic pyridine has a strong influence on the overall reactivity and electron-neutral or donating substituents are preferred. Although the conversion of the reactants was sometimes almost quantitative, unfortunately the stability of the products should be mentioned as a drawback of this efficient dearomative reaction. For example, **4k** degraded over silica or alumina column chromatography.

**Table 2. Scope and Limitations Varying Pyridines 1, Diazo Compounds 2 and Coumalates 3<sup>a,b</sup>**



<sup>a</sup> Reaction conditions : pyridines **1** (1 mmol), diazo compounds **2** (1.2 mmol), coumalates **3** (1 mmol), Fe(TTP)Cl (1 mol%), DCM (3 mL), r.t., 10 min. <sup>b</sup> Isolated yields

Subsequently, we tested pyridines **1l-q** substituted in meta position. Interestingly, products **4l-q** were obtained as single regioisomers. Indeed, although positions 2 or 6 of pyridines **1l-q** could be engaged to fuse the rings, the cyclization took place exclusively at position 2. Yields for products presenting a methyl or a methoxy group (**4l-m**) are comparable to the one of **4q** bearing a fluorine atom (60 to 71%). Electronic effects seem to be less pronounced than steric ones. Indeed, from iodide to fluoride (compare yields from **4n** to **4q**), the smaller the atomic radius of the halogen is, the higher the isolated yield. These results could be attributed to steric hindrance but may also be explained by the possible insertion of iron into the carbon-halogen bond. When 3-(trifluoromethyl)pyridine was used, no bicyclic product could be isolated. To complete the study, we checked ortho-substituted pyridines. Unfortunately, 2-methyl- and 2-fluoro pyridine did not react at all, proving the strong steric influence appearing during the cyclisation.

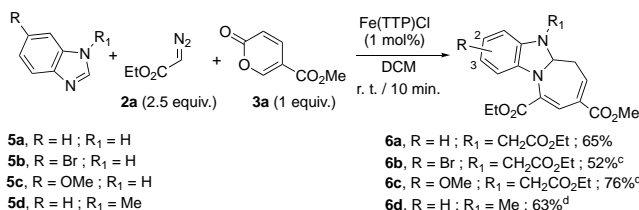
We turned our attention toward polysubstituted pyridines. We first investigated symmetrically disubstituted ones such as 3,5-dimethyl- and 3,5-difluoropyridine. The corresponding dihydropyridoazepines **4r** and **4s** were isolated in low yields. These results were attributed to steric hindrance in the case of **1r** and to a strong decrease of nucleophilicity for **1s**. Positively, the 3-bromo-4-methylpyridine **1t** led to the formation of dihydropyridoazepine **4t** in 65 % yield with a total regioselectivity. Finally, we varied both pyridines and diazo compounds, the desired dihydropyridoazepines **4bt** to **4fm** were isolated as expected.

The third reactant of this three-component reaction, namely pyrone **3**, could also be varied by changing the nature of the ester, introducing various alkyls or aryls instead of methyl group (see Table 2). As representatives, coumalates bearing allylic, propargylic or phenolic ester function were prepared from coumalic acid and the corresponding alcohols using EDC. The coumalates **3u-x** reacted smoothly giving the expected dihydroazepines **4u-x** in yields from 67 to 76%. The reaction supported the double functionalization on both pyridine **1** and coumalate **3** leading to **4uq** and **4vm** in 61 and 70% yields respectively.

We also investigated the replacement of pyridine **1** by benzimidazole **5**. Using the previously optimized conditions, compound **6a** resulting from both N-H insertion and cyclization reaction was isolated with a modest 23% yield together with unreacted **3a**. In order to fully consume starting materials, the quantity of ethyl diazoacetate **2a** was increased to 2.5 equivalents. In these conditions, the tricyclic fused azepine **6a** was isolated in 65% yield (Table 3).

Subsequently, we explored the influence of the substituents on the regioselectivity and efficiency of the reaction. The 5-bromo-, and 5-methoxybenzimidazole **5b-c** were tested as representatives. The reaction proceeded well leading to products **6b-c** as an almost equimolar mixture of two regioisomers. Brominated tricyclic benzimidazolo azepine **6b** was obtained with a slightly lower yield compared to the methoxy substituted product **6c** (52 vs 76 % yields respectively). The N-methylbenzimidazole **5d** required only one equivalent of **2a** and reacted cleanly to provide the expected tricyclic fused azepine in 63% isolated yield (Table 3).

**Table 3. Scope and Limitations in Benzimidazole Series<sup>a,b</sup>**



<sup>a</sup> Reaction conditions : benzimidazoles **5** (1 mmol), **2a** (2.5 equiv.), **3a** (1 equiv.), Fe(TPP)Cl (1 mol%), r.t., DCM (3 mL). <sup>b</sup> Isolated yields. <sup>c</sup> mixture of regioisomers - **6b** 2/3 ratio : 47/53 - **6c** 2/3 ratio : 43/57. <sup>d</sup> 1 equiv. of **2a**.

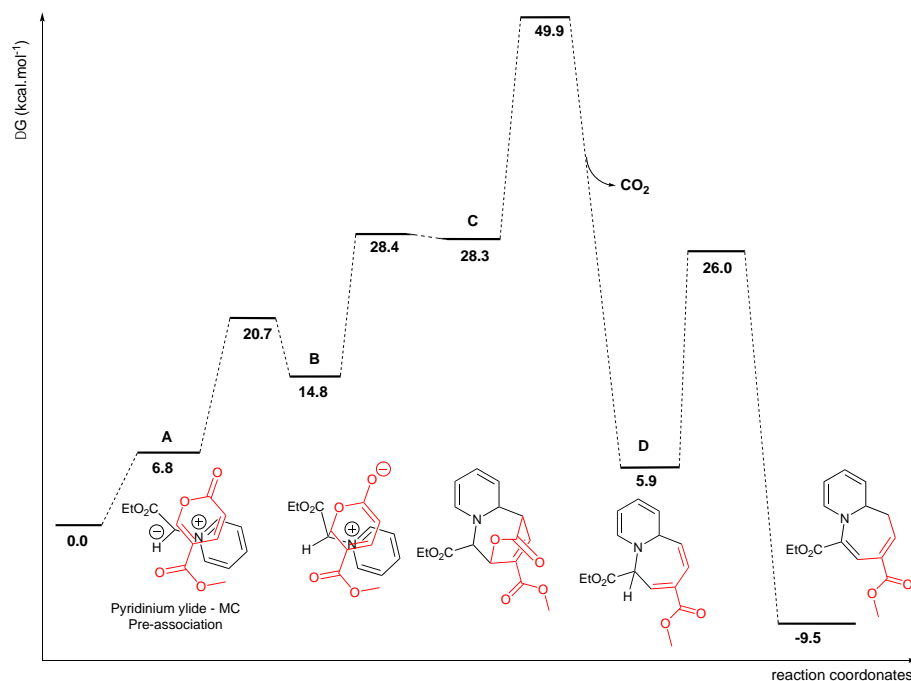
Concerning the mechanism of the reaction, a pyridinium ylide is stated to be catalytically produced from the reaction between **1a** and **2a** in the presence of Fe(TPP)Cl.<sup>43–48</sup> Then, two plausible pathways could be envisaged for the observed cyclization between **3a** and the pyridinium ylide, i.e. a concerted [4+3] cycloaddition or a two-step asynchronous addition-cyclization.

Based on previous reactivity observed for **3a**, we privileged a two-step process. On the other hand, the total regioselectivity observed with 3-substituted pyridines preferentially supported a concerted mechanism, or at least a pre-organized association between the two reactants. To discriminate these two pathways, we carried out DFT calculation (Figure 3, see also SI, Table S2).

A preassociative dipole-dipole complex **A** linking the substrates was found to align the two separate polar molecules (+ 6.8 kcal/mol to access **A**). The first C-C bond is created through a transition state lying at 20.7 kcal/mol above reactants. This 1,6-addition leads to an enolate **B** in an endothermic reaction (8 kcal/mol). It rapidly undergoes an intramolecular endothermic C-C bond formation leading to the lactone-bridged nitrogen tricyclic compound **C** that presents a strain of 28.3 kcal/mol.

Surprisingly, the concerted [4+2] retro Diels-Alder reaction that expulses CO<sub>2</sub>, requires the highest energy to convert **C** into azepine **D** but releases 22.4 kcal/mol by decongestion of the structure. Intermediate **D** stands at 0.9 kcal/mol lower than complex **A**. The last step is the formation of the highly conjugated dihydropyridoazepine **4a** via a 1-5 hydrogen shift. This step which maximizes  $\pi$ -electrons conjugation is the driving force of the observed reaction which releases 9.5 kcal/mol.

The total regioselectivity observed with 3-substituted pyridines, leading to products **4m-r**, could be justified by the development of steric hindrance that appears during the initial approach of the two reacting molecules (see Figure S1 and S2). The absence of reactivity observed for substituted 2-pyridines could similarly be explained by the stronger steric interactions that appear for such substrates.



**Figure 3. Computed Pathway for the Formation of 4a**

In summary, we have developed a multicomponent domino reaction to quickly access fused bicyclic [6+7] dihydropyridoazepines or tricyclic [6+5+7] fused benzimidazolo azepines starting from commercially available substrates, renewable feedstock and Fe(TTP)Cl as catalyst. A wide range of pyridines, benzimidazoles, diazo compounds and coumalates were used and more than 35 compounds were successfully synthesized. A total regioselectivity was observed for 3-substituted pyridines. The proposed mechanism was rationalized by DFT calculations. This dearomatization process leads to the formation of molecules previously reported as difficult to synthesize. The reaction appeared scalable up to the gram scale and releases only CO<sub>2</sub> and N<sub>2</sub> as by products.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. It contains information regarding experimental procedures, optimization table, characterization of organic molecules, and mechanistic studies (PDF).

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

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