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Iron-Catalyzed Indolizine Synthesis from Pyridines, Diazo Compounds, and Alkynes

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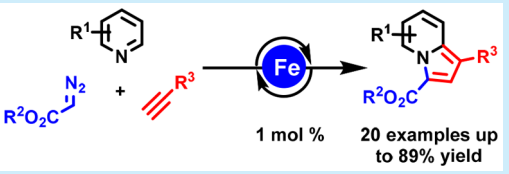
Supporting Information

ABSTRACT: The iron(III)-catalyzed synthesis of indolizines from commercially available alkyne, pyridine, and diazo precursors is reported. This mild, expedient method is tolerant of various solvents and proceeds with as little as 0.25 mol % [Fe(TPP)Cl]. Significantly, this multicomponent reaction is compatible with electrophilic alkynes; control experiments demonstrate the importance of the catalyst in promoting pyridinium ylide formation over background reactivity.

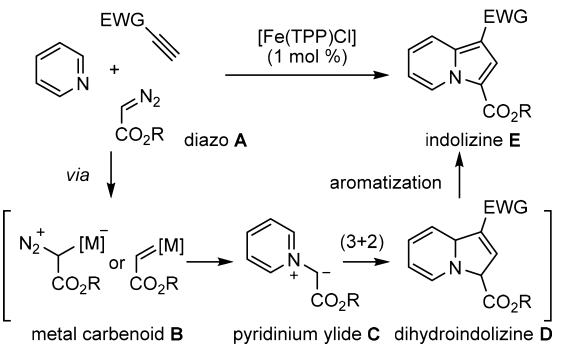


Catalytic multicomponent reactions that give direct access to indolizines from commercially available precursors are highly desirable. The strong demand for this heterocycle reflects its versatile photochemical properties[1−5] and biological activity.[6,7] In turn, this has stimulated much innovation in indolizine synthesis.[8−11] Exploiting the abundance of commercially available pyridines would be attractive, especially if they are used directly without the need for prior functionalization. An initial report of rhodium(II)-catalyzed indolizine synthesis involved transformation of pyridine-tethered diazo precursors via metal carbenoids and ylides in the presence of electrophilic alkynes; just one example from this report involved a three-component transformation from a simple pyridine.[12] The synthesis of indolizines by combination of alkenes, diazo reagents, and quinolines or pyridines was described very recently, although a large amount of catalyst (20 mol % CuF_2 and PPh_3) was required and poor yields were obtained from reactions involving pyridines.[13] A general method involving alkynes and catalytically generated pyridinium ylides is yet to be reported.

We recently described the efficient synthesis of alkaloid-inspired spirotetrahydroindolizines by combination of pyridines, diazo compounds, and alkenes using an iron(III) catalyst.[14] We were keen to investigate whether indolizines could be accessed by performing the related reaction with electrophilic alkynes. Marshaling the greater reactivity of these dipolarophiles is a potential challenge, however. In the ideal reaction pathway (Scheme 1), diazo precursor **A** is converted to electrophilic metal carbenoid **B**, which is intercepted by the pyridine to give ylide **C**. Subsequent addition to the electrophilic alkyne and cyclization give dihydroindolizine **D**, which undergoes aromatization to generate the target indolizine **E**. Clearly, direct addition of the pyridine to the alkyne is a potential competing pathway, but once formed, pyridinium ylides are expected to be significantly more nucleophilic than pyridines.[15]

Herein we report the catalytic synthesis of indolizines by one-pot condensation of commercially available pyridine, alkyne, and diazo ester precursors. The commercially available [Fe(TPP)Cl] (TPP = tetraphenylporphyrin) catalyst is derived from cheap and abundant iron and successfully operates with loadings as low as 0.25 mol % at mild temperatures in various solvents. Characterization of background reaction products underlines the remarkable capacity of this catalyst to promote a pathway via highly reactive metal carbenoid and pyridinium ylides.

Scheme 1. Envisaged Reaction Pathway for Indolizine Synthesis via Catalytically Generated Pyridinium Ylides



Initially, reaction of pyridine (3 equiv), ethyl diazoacetate (EDA) (1.5 equiv), and ethyl propiolate (1 equiv) using [Fe(TPP)Cl] as the catalyst (1 mol %) at ambient temperature was investigated. Reagents were combined in a vessel open to air without additional oxidant. To our satisfaction, these reaction conditions returned an excellent yield of the target indolizine **1** (89%; Table 1, entry 1). The same reaction was performed in a variety of solvents (e.g., acetone, ethyl acetate, toluene, etc.), from which consistently good yields of indolizine **1** were obtained (70−82%; entries 2−5).[16]

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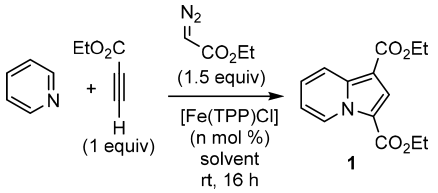
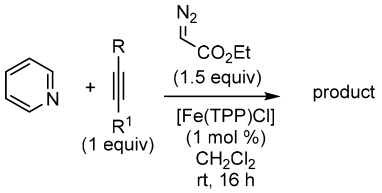
Table 1. Initial Reaction Optimization

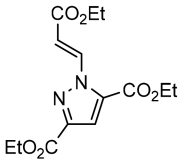
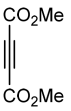
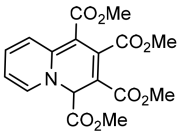
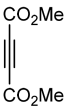
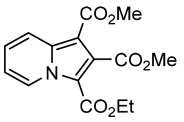
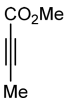
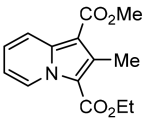


entry	pyridine (equiv)	Fe(TPP)Cl (mol %)	solvent	yield (%)[a]
1	3	1	CH_2Cl_2	89
2	3	1	CH_3CN	80
3	3	1	acetone	82
4	3	1	toluene	79
5	3	1	EtOAc	70
6	3	1	H_2O	13
7	3	1	H_2O/EtOH (2:8)	82
8	1	1	CH_2Cl_2	87
9	1	0.25	CH_2Cl_2	82
10	1	0.1	CH_2Cl_2	27

[a]Isolated yields after column chromatography.

Table 2. Further Optimization of Indolizine Synthesis



entry	alkyne	change from std. conditions	product (yield %)
1		no catalyst, (1.3 equiv pyridine)[a]	 **2** (49%)
2		(3 equiv pyridine)[a]	 **3** (66%)
3		-20 °C[b]	 **4** (53%)
4		-20 °C[b]	 **5** (34%)

[a]Reactions were performed by addition of EDA (1.5 equiv) to a solution of pyridine (as specified), alkyne (1.0 equiv), and [Fe(TPP)-Cl] (1 mol %) in CH_2Cl_2 at room temperature. [b]EDA (1.5 equiv) and pyridine (1.0 equiv, 0.6 mmol) were added to a solution of alkyne (1.0 equiv) and [Fe(TPP)Cl] (1 mol %) in CH_2Cl_2 at the specified temperature.

The yield of indolizine **1** was not significantly reduced when pyridine was used in a 1:1 ratio to alkyne (87%; Table 1, entry 8). Subsequently, reducing the amount of catalyst to 0.25 mol % also gave **1** in good yield (82%; entry 9), but a poor yield (27%) was obtained if the catalyst was used at 0.1 mol % (entry 10). For the rest of this study, reactions were compared using the most productive conditions, specifically 1 mol % catalyst in dichloromethane.

In the absence of catalyst, the same combination of reagents furnished 3*H*-pyrazole derivative **2** in significant yield (49%; Table 2, entry 1). Presumably, cycloaddition between EDA and the alkyne gives an initial 1*H*-pyrazole product,[17] which undergoes subsequent 1,4-conjugate addition with a further equivalent of ethyl propiolate. The lack of product **2** when [Fe(TPP)Cl] (1 mol %) was present reinforces the notion of a catalytic pathway via metal carbenoid and pyridinium ylide.

When ethyl propiolate was replaced with more electrophilic dimethyl acetylenedicarboxylate, an exothermic reaction occurred prior to addition of EDA, which may be identified as the deleterious reaction between alkyne and pyridine. Specifically, 4*H*-quinolizine **3** (66%, entry 2) was isolated as the main product from this reaction mixture, which is consistent with reported preparation of this molecule.[18] Indolizine **4** was obtained in 4% yield from the same reaction. The yield of **4** improved to 53% upon coaddition of pyridine and EDA to a mixture of catalyst and alkyne at −20 °C and subsequent warming to room temperature (entry 3). Methyl 2-butynoate, pyridine, and EDA gave indolizine **5** in 34% yield using these conditions (entry 4).

Indolizines were readily obtained using these improved reaction conditions and a variety of commercially available pyridines. For example, reaction of 4-methoxypyridine gave indolizine **6** in excellent yield (77%; Scheme 2). Pyridines with various 4-substitutents also gave indolizine products. 4-Acetylpyridine gave the corresponding indolizine **7** in excellent yield (75%). Reaction of 4-pyridines with other electron-withdrawing substituents (CF_3, CN) gave the corresponding indolizines **8** (57%) and **9** (45%), respectively. Indolizines **10** (74%) and **11** (59%) were obtained from 4-methylpyridine and 4-phenylpyridine precursors, respectively. 2-Methylpyridine also reacted well to give indolizine **12** in 58% yield.

3-Substituted pyridines also reacted in good yields, and the resulting indolizine products were obtained as mixtures of regioisomers corresponding to substitution at either the 6- or 8-position. 3-Formylpyridine gave a 1:1 mixture of indolizine regioisomers **13a** and **13b** in 51% yield. Indolizines were produced with a slight preference for substitution at the 8-position from reaction of either 3-methylpyridine (69% yield; **14a**:**14b** = 5:3) or 3-fluoropyridine (**15a** 33% and **15b** 19%). A more significant preference was observed in the reaction of 3-methoxypyridine, from which the 8-methoxyindolizine isomer **16a** was obtained as the major product (68%), whereas 6-methoxyindolizine **16b** was isolated from the same reaction in 4% yield. The influence of electron-donating substituents on the products of addition to pyridinium species has been noted previously.[19] Interestingly, reaction of 3-bromopyridine gave the indolizine product arising from protodebromination, **1** (60%; Scheme 3A).

We sought to further explore this dehalogenation. The same indolizine product **1** was obtained in the noncatalyzed route

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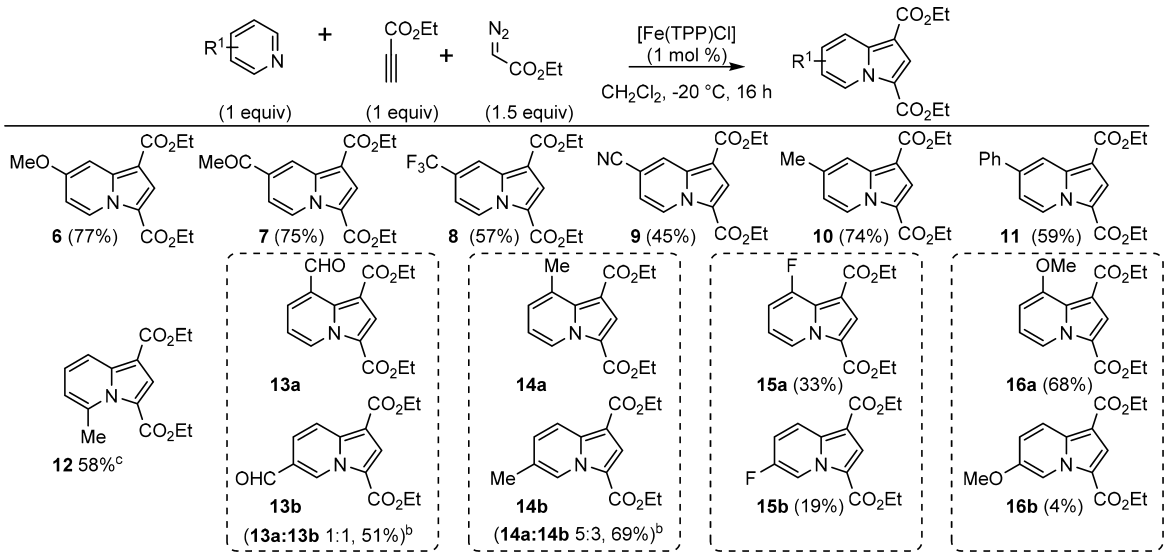
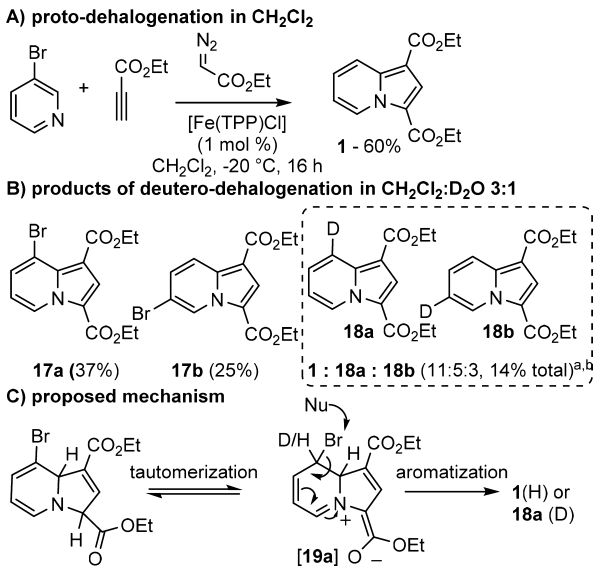
Scheme 2. Indolizine Products Incorporating Various Pyridines[a]



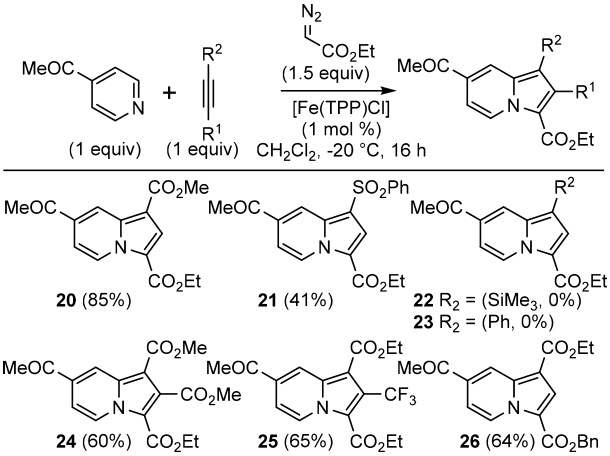
[a]Reactions were performed using pyridines (1.0 equiv, 0.6 mmol), ethyl propiolate (1.0 equiv), EDA (1.5 equiv), and [Fe(TPP)Cl] (1 mol %) in CH_2Cl_2 at −20 °C followed by warming to room temperature for 16 h. Yields after chromatography are shown. [b]Product ratios were estimated by relative integration of peaks corresponding to the indolizine 6- or 8-position by ^{1}H NMR spectroscopy. [c]5 equiv of 2-methylpyridine was used.

Scheme 3. Dehalogenation Observed During the Reaction of 3-Bromopyridine in (A) CH_2Cl_2 or (B) CH_2Cl_2/D_2O (3:1); (C) Proposed Debromination Mechanism to Form 1 or 18a



[a]Reaction conditions: 3-bromopyridine (1.0 equiv, 1.74 mmol), ethyl propiolate (1.0 equiv), EDA (1.5 equiv), and [Fe(TPP)Cl] (1 mol %) in CH_2Cl_2/D_2O (3:1) at room temperature for 16 h; the combined yield for the inseparable mixture of **1** and **18ab** is shown. [b]The product ratio was estimated by relative integration of protons at the indolizine 5-, 6-, and 8-positions by ^{1}H NMR spectroscopy.

Scheme 4. Indolizine Products of Various Alkynes[a]



[a]Reactions were performed using 4-acetylpyridine (1.0 equiv, 0.6 mmol), alkynes (1.0 equiv), EDA (1.5 equiv), and [Fe(TPP)Cl] (1 mol %) in CH_2Cl_2 at −20 °C followed by warming to room temperature for 16 h. Yields after chromatography are shown.

using K_2CO_3 to generate the ylide by deprotonation of a pyridinium salt (40%; Scheme S1A),[20,21] absolving the iron catalyst from involvement in this process. Performing the catalytic reaction in a biphasic mixture of CH_2Cl_2 and D_2O (3:1) gave indolizine products with bromine at the 6- or 8-position (**17a** 37% and **17b** 25%, respectively; Scheme 3B) along with a mixture of proto- and deuterodebrominated products (**1** and **18ab**, 14%); deuterium was incorporated in a similar ratio (**18a**:**18b** = 5:3) to the brominated coproducts (**17a** and **17b**). On the basis of these observations, we speculate that the initial dihydropyridine cycloadduct undergoes tautomerization and deuterium exchange to form an intermediate (e.g., [**19a**]) from which bromine is collected by an external nucleophile (e.g., pyridinium ylide) to furnish **1** or deuterated analogue **18a** (Scheme 3C). Formation of **18b** from the dihydropyiridine precursor of **17b** via an analogous pathway is envisaged (Scheme S2).[20] A related dehalogenation mechanism has been noted for other N-heterocycles.[22,23]

Generally, electron-deficient alkynes were required to produce indolizines in acceptable yields. For example, methyl propiolate and phenylsulfonylacetylene reacted with 4-acetylpyridine to give indolizines **20** and **21** in 85% and 41% yield, respectively (Scheme 4), but the target heterocycles (**22**,

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23) were not obtained from the reaction with trimethylsilylacetylene or phenylacetylene.

Disubstituted alkynes such as dimethyl acetylenedicarboxylate or ethyl 3-trifluoromethylpropiolate gave the corresponding indolizines **24** in 60% yield and **25** in 65% yield. Alternative benzyl diazoacetate ester performed equally well in the reaction with ethyl propiolate to produce indolizine **26** in 64% yield.

In conclusion, a general and expedient one-pot synthesis of indolizines has been developed. The reaction uses commercially available pyridine, alkyne and diazo ester precursors, while the catalyst is derived from cheap and abundant iron. Significantly, the iron-catalyzed route via pyridinium ylides is compatible with electrophilic alkynes by outcompeting potentially significant background reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03252.

Supplementary tables and schemes and detailed experimental and compound characterization data (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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