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Pyridine Activation via Copper(I)-Catalyzed Annulation toward Indolizines

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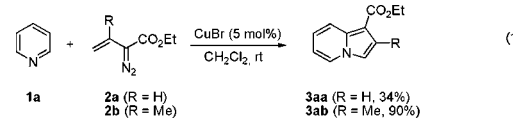
Abstract: The copper(I)-catalyzed regioselective [3 + 2] cyclization of pyridines toward alkenyldiazoacetates leading to functionalized indolizine derivatives is reported. A broad range of pyridine derivatives (including quinoline and isoquinoline) is compatible with this cyclization reaction. The process represents the first successful example of metal-catalyzed cyclization of a π-deficient heterocyclic system with alkenyldiazo compounds.

Pyridine derivatives play a pivotal role in coordination chemistry and catalysis. A number of complexes involving coordination of different metals to a great variety of pyridine-containing ligands have been reported in the literature.[1] In apparent contradiction with the easy formation of this sort of complex, transformations of the pyridine skeleton catalyzed by transition-metal complexes are very scarce and often suffer from harsh reaction conditions and/or limited substrate scope (for instance, pyridine itself proved to be particularly reluctant to partake in most of the reported catalytic processes).[2] For these reasons, the ability to efficiently functionalize pyridines and their derivatives (e.g., quinoline, isoquinoline, etc.) remains an important issue in synthetic chemistry.

On the other hand, the pyridine core is present in a huge number of relevant heteropolycycles. Among them, the indolizine framework is a common substructure in a number of biologically important natural products and pharmaceuticals[3] and is used to provide a high level of fluorescence.[4] Most synthetic strategies require starting from pyridinium *N*-methylides[5] or pyridines with specific C2 functionalization.[6] In contrast, only two annulation reactions of the pyridine ring that involve N-alkylation/nucleophilic cyclization have recently been reported.[7]

Continuing our interest in the design of new metal-catalyzed processes using copper as an eco-friendly, cheap transition metal, we found that pyridine itself and substituted pyridines do behave as noninnocent ligands. Specifically, herein we report the Cu(I)-catalyzed [3 + 2] cyclization of the pyridine ring toward alkenyldiazoacetates leading to substituted indolizines.[8]

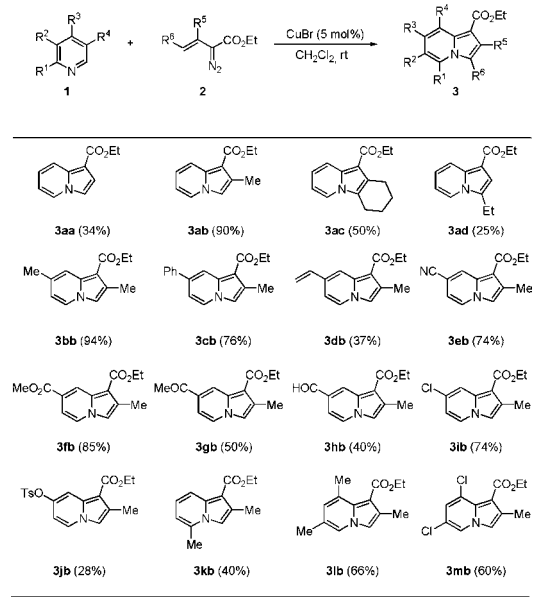
Thus, we found that stirring a mixture of pyridine (**1a**) (1 equiv), ethyl vinyldiazoacetate **2a** (1 equiv), and CuBr (5 mol %) in CH_2Cl_2 at room temperature led to complete disappearance of the starting diazo compound after 4 h (TLC, 5:1 hexane/ethyl acetate). Purification by column chromatography (SiO_2, 5:1 hexane/ethyl acetate) afforded indolizine **3aa** in 34% isolated yield (eq 1). This result seemed promising, as indolizines are highly sensitive to chromatographic media.[9,10] Encouraged by this initial result, we next addressed this heterocyclization using substituted vinyldiazoacetates. We found that the presence of a methyl substituent at C3 of the diazo ester had a large and favorable effect on the yield of the reaction. Thus, running the reaction of ethyl isopropenyldiazoacetate (**2b**) and **1a** under the same reaction conditions resulted in the isolation of pure indolizine **3ab** in 90% yield (eq 1). Moreover, the annulation of diazoacetates **2a** and **2b** to **1a** occurred with complete regioselectivity.



(1)

Next, we examined the scope of this new catalytic transformation of the pyridine ring. We were pleased to find that the copper(I)-catalyzed reaction of pyridines **1** and vinyldiazoacetates **2** allowed the preparation of indolizines with a variety of substitution patterns (Table 1).

Table 1. Cu(I)-Catalyzed Synthesis of Indolizine Derivatives **3** from Pyridines **1** and Ethyl Alkenyldiazoacetates **2**[a]



[a] Yields of isolated products after column chromatography are reported.

First, pyridine reacts with alkenyldiazoacetates with various substitution patterns, though with varying efficiency. Thus, the reaction yield increased in going from unsubstituted ($R^5 = R^6 =$ H) to substituted ($R^5 \neq$ H or R^5, $R^6 \neq$ H) diazo compounds (**3aa** vs **3ab** and **3ac**) and from β-substituted ($R^4 =$ Et) to α-substituted ($R^3 =$ Me) diazo compounds (**3ad** vs **3ab**).

The reaction tolerated substitution of various kinds at C4 of pyridine. Besides methyl and phenyl groups, which afforded indolizines **3bb** and **3cb** in 94 and 76% yield, respectively, a great variety of functionalization (vinyl, methoxycarbonyl, acyl, formyl, cyano) was compatible with the protocol, providing indolizines **3db**−**hb** in moderate to good yields (37−85%). Moreover, 4-chlo-

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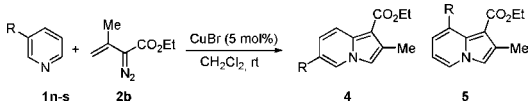
ropyridine (**1i**) furnished chloroindolizidine **3ib**, which is amenable to further elaboration by standard cross-coupling methods.[11] On the contrary, the reaction was rather ineffective in the case of electron-donor-substituted pyridines. In fact, 4-methoxy- and 4-dimethylaminopyridine led to complex mixtures of products, while 4-tosylpyridine (**1j**) afforded **3jb** in 28% yield. Substitution at C2 also makes the reaction sluggish, as illustrated for the annulation of 2-picoline (**1k**), which gave **3kb** in 40% yield. The [3 + 2] cyclization also proved to be amenable for disubstituted pyridines. Thus, treatment of 3,5-dimethylpyridine (**1l**) and 3,5-dichloropyridine (**1m**) with diazo compound **2b** under the above condition reactions afforded in moderate yields the indolizine derivatives **3lb** (66%) and **3mb** (60%).

The issue of the regioselectivity of the annulation of 3-substituted pyridines toward diazo compound **2b** was then addressed (Table 2). It was found that the ratio of isomers resulting from the cyclizations toward C6 (indolizines **4**) and C2 (indolizines **5**) is highly dependent on the nature of the substituent. Interestingly, the strong-acceptor nitro group not only was compatible but also directed the cyclization exclusively toward the regioisomer **4nb** in acceptable yield (64%). Standard electron-withdrawing groups also favored the cyclization through C6 of the pyridine ring, providing adducts **4** in preference over **5** (R = CN, **4ob**/**5ob** = 10; R = CO_2Et, **4pb**/**5pb** = 3) in 54−73% yield. On the contrary, this regioselective trend was reversed for 3-picoline and 3-X-pyridines (X = F, Cl), which yielded indolizines **5** as the major isomers in 45−60% yield.

Table 2. Cu(I)-Catalyzed Synthesis of Indolizine Derivatives **4** and **5** from 3-Substituted Pyridines **1n**−**s** and Ethyl Isopropenyldiazoacetate **2b**

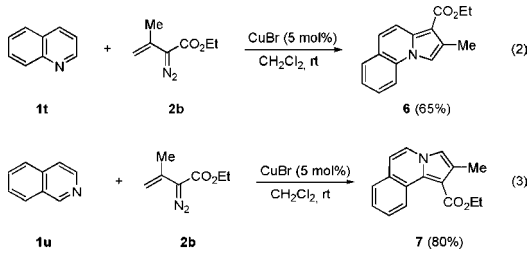


1n-s 2b 4 5

entry	1	R	4	5	4/5[a]	yield (%)[b]
1	**1n**	NO_2	**4nb**	**5nb**	**4nb** only	64
2	**1o**	CN	**4ob**	**5ob**	10:1	73
3	**1p**	CO_2Me	**4pb**	**5pb**	3:1	54
4	**1q**	Cl	**4qb**	**5qb**	1:1.5	45
5	**1r**	F	**4rb**	**5rb**	1:3	60
6	**1s**	Me	**4sb**	**5sb**	1:7	54[c]

[a] Estimated by ^{1}H NMR spectroscopy (400 MHz) of the crude reaction mixture. [b] Yield of isolated products after column chromatography. [c] Isolated as a nonseparable mixture of regioisomers.

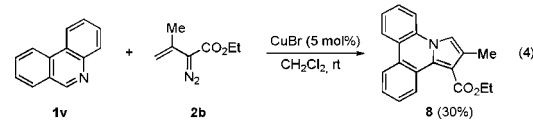
Interestingly, simple benzo-fused pyridines **1t**−**v** were found to work well, leading to more complex cycloadducts in variable yields. Thus, quinoline (**1t**) and isoquinoline (**1u**) afforded substituted pyrrolo[1,2-*a*]quinoline **6** and pyrrolo[2,1-*a*]isoquinoline **7** in yields of 65 and 80%, respectively, upon reaction with **2b** (eqs 2 and 3):



1t 2b 6 (65%)

1u 2b 7 (80%)

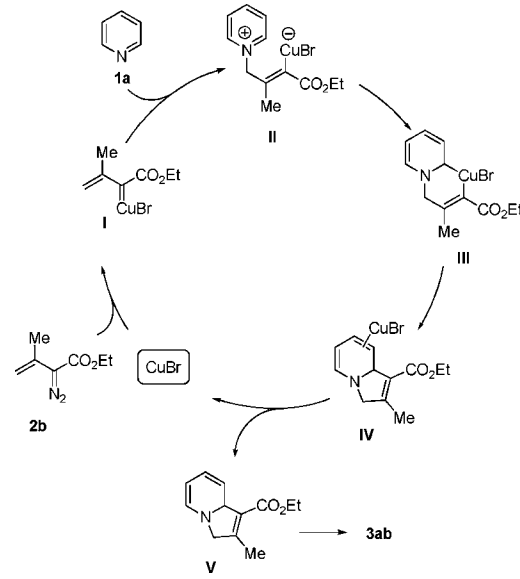
In contrast, the reaction with phenanthridine (**1v**) proved to be more challenging and provided the pyrrolo[1,2-*f*]phenanthridine structure **8** in only 30% yield (eq 4):



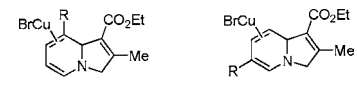
1v 2b 8 (30%)

A tentative rationale for this cyclization is illustrated in Scheme 1 for the cyclization of **1a** with diazo compound **2b**. Initially, decomposition of **2b** would form the copper(I) alkenylcarbene species **I**,[12] which then would evolve to the cuprate **II** by Michael-type addition of the pyridine nitrogen,[13] probably directed by pyridine−copper coordination. The cyclization of the latter would generate the copper(III) metallacycle **III**, which would undergo reductive elimination assisted by the proximal ring C−C double bond, giving rise to the Cu(I) complex **IV**.[14] Further metal decoordination would afford the dihydroindolizine **V**, thus concluding the catalytic cycle. Finally, oxidative aromatization would result in the formation of the corresponding indolizidine.[15]

Scheme 1. Proposed Mechanism for the Cu(I)-Catalyzed Synthesis of Indolizine Derivatives from Pyridines **1** and Diazo Compounds **2**



The selectivity of the cyclization observed in the case of 3-substituted pyridines is in accordance with this mechanistic model in the sense that the major regioisomer observed results from the more stable complex intermediate **IV**. In the case of 3-methylpyridine, the coordination involving the more electron-rich C3═C4 bond is preferred, whereas the coordination of copper through the less electron-poor, nonconjugated C4═C5 bond occurs for 3-nitropyridine (Figure 1). Theoretical calculations at the B3LYP/6-31G* level (see the Supporting Information) support this mechanistic model and predict that (i) the formation of **II** is the rate-determining step and (ii) the major complex **IV** observed is kinetically and thermodynamically favored over the other one.[16]



IV (R = Me) IV (R = NO_2)

Figure 1. Preferred intermediates **IV** for 3-X-pyridines (X = Me, NO_2).

In conclusion, direct annulation of pyridine derivatives to form indolizine derivatives has been accomplished in a regioselective manner. All of the heterocyclic substrates used were commercially

available and did not require additional purification.[17] A broad range of pyridine substrates is compatible with this operationally simple and mild copper-catalyzed cyclization, allowing heterocyclic nuclei as important as indolizidines and benzoindolines (pyrroloquinolines and -isoquinolines) to be readily obtained with a broad array of substitution and functionalization patterns. It is noteworthy that this is the first successful example of metal-catalyzed cyclization of a π-deficient heterocyclic system with alkenyldiazo compounds, in contrast to the extensive chemistry performed on π-excessive heterocycles.[18] From these results, it can be envisioned that copper will prove to be a suitable eco-friendly candidate for catalyzing transformations onto other nitrogen heterocycles rather than simply undergoing metal−ligand coordination.

Acknowledgment. This work is respectfully dedicated to the memory of Prof. José M. Concellón. We are grateful to the MICINN/FEDER (Grant CTQ2007-61048) and the Principado de Asturias (Grant IB 08-088). G.L. and L.R. thank the MICINN and European Union (Fondo Social Europeo) for predoctoral fellowships. We are also grateful to Dr. J. González for his assistance in the computational study.

Supporting Information Available: Experimental procedures and spectral and analytical data for compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Rh(II)- and Cu(I)-catalyzed [3 + 2] cyclizations of vinyldiazoacetates and *p*-nitroaniline-derived imines have been reported. See: Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. *J. Am. Chem. Soc.* **2003**, *125*, 4692.

(9) The easy decomposition of some indolizine derivatives is well-known (for example, see: Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074). In fact, we found that pure indolizine **3aa** undergoes partial decomposition during column chromatography (SiO_2, 5:1 hexane/ethyl acetate).

(10) The use of other solvents (THF, toluene, acetonitrile) and copper complexes ($[(MeCN)_4Cu][BF_4]$, CuCl, CuCN, $Cu(OTf)_2$) did not improve the yield of the process. On the other hand, no reaction at all occurred using $Rh_2(OAc)_4$.

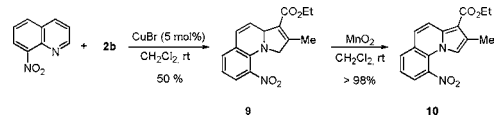
(11) For the synthesis of 3-arylindolizines from 3-chloroindolizines under Suzuki−Miyaura conditions, see: Xia, J.-B.; You, S.-L. *Org. Lett.* **2009**, *11*, 1187.

(12) The generation of copper(I) carbenes by the decomposition of diazoacetates is a well-documented process. For example, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

(13) The electrophilic reactivity at the vinylogous and carbenoid positions of vinylcarbenoids has been reported previously. For example, see: (a) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696. (b) Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535. (c) Davies, H. M. L.; Yokota, Y. *Tetrahedron Lett.* **2000**, *41*, 4851. (d) Sevryugina, Y.; Weaver, B.; Hansen, J.; Thompson, J.; Davies, H. M. L.; Petrukhina, M. A. *Organometallics* **2008**, *27*, 1750. For significant enhancement of vinylogous vs carbenoid reactivity in copper vinylcarbenoids, see: Yue, Y.; Wang, Y.; Hu, W. *Tetrahedron Lett.* **2007**, *48*, 3975. For a related intramolecular Michael-type addition of the pyridine nitrogen, see ref 6d.

(14) Reductive elimination involving copper(III) complexes has been proposed for C−C bond-forming reactions leading to either acyclic and cyclic adducts. For example, see: (a) Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. The generation of intermediate **IV** by direct attack of the vinyl anion on the iminium function of **II**, as found in related rhodium-catalyzed [3 + 2] cyclization reactions (ref 13b), cannot be ruled out.

(15) The dihydro derivative **9** was isolated in 50% yield from 8-nitroquinoline and diazo compound **2b**. Further treatment with MnO_2 (CH_2Cl_2, rt) quantitatively yielded the corresponding pyrroloquinoline **10**.



(16) As expected, stirring a 1:1:1 mixture of **2b**, pyridine, and pyridine-d_5 (5 mol% CuBr, CH_2Cl_2, rt) gave indolizine **3ab** and methyl 5,6,7,8-tetradeutero-2-methylindolizine-1-carboxylate as a 1:1 mixture (~50% conversion).

(17) 4-Tosylpyridine is available by tosylation of commercial 4-hydroxypyridine.

(18) (a) For a review of intermolecular reactions of electron-rich heterocycles with copper and rhodium carbenoids, see: Hedley, S. J.; Davies, H. M. L. *Chem. Soc. Rev.* **2007**, *36*, 1109. (b) The pyridine synthesis via rhodium carbenoid-induced ring expansion of isoxazoles has recently been reported. See: Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (c) For a recent rhodium-catalyzed [3 + 2] annulation of indoles, see: Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440.

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