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$Cu(OTf)_2$-catalyzed synthesis of imidazo[1,2-*a*]pyridines from α-diazoketones and 2-aminopyridines

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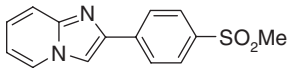
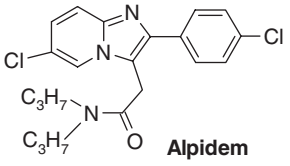
Abstract—α-Diazoketones undergo smooth coupling with 2-aminopyridines in the presence of 10 mol % of copper(II) triflate to produce the corresponding 2-substituted imidazo[1,2-*a*]pyridines (IPs) in excellent yields with high selectivity. $Rh_2(OAc)_4$ is also found to be an equally effective catalyst for this transformation.

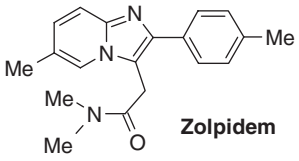
Imidazo[1,2-*a*]pyridines (IPs) have received considerable interest from the pharmaceutical industry because of their interesting therapeutic properties,[1] including antibacterial,[2] antifungal,[3] antiviral,[4] antiulcer,[5] and anti-inflammatory behavior.[6] They have also been characterized as selective cyclin-dependent kinase inhibitors,[7] calcium channel blockers,[8] β-amyloid formation inhibitors,[9] and benzodiazepine receptor agonists,[10] and they constitute a novel class of orally active nonpeptide bradykinin B_2 receptor antagonists.[11] Drug formulations containing imidazo[1,2-*a*]pyridines such as alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (antiulcer) are currently available.



Zolimidine



Alpidem



Zolpidem

The ready availability, relative stability, and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base, and transition metal catalysis conditions make them useful intermediates in organic synthesis.[12] Interestingly, α-diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H and X–H insertion reactions, and cyclization reactions.[13] These reactions are chemoselective, which allow new carbon-carbon and carbon-hetero atom bond formation under mild conditions.[14] However, there have been no reports on the coupling of α-diazoketones with 2-aminopyridines to generate biologically potent imidazo[1,2-*a*]pyridines (IPs).

In this Letter, we report a novel and efficient method for the synthesis of substituted imidazo[1,2-*a*]pyridines (IPs) via the coupling of 2-aminopyridines and α-diazoketones using a catalytic amount of copper(II) triflate under mild conditions. Accordingly, treatment of diazoacetophenone with 2-aminopyridine in the presence of 10 mol % $Cu(OTf)_2$ in dichloroethane (DCE) at 80 °C afforded 2-phenylimidazo[1,2-*a*]pyridine **3a** in 94% yield (Scheme 1).

This remarkable catalytic activity of copper(II) triflate provided the incentive for further study of reactions with other α-diazocarbonyl compounds. Interestingly, various α-diazoketones reacted smoothly with several 2-aminopyridines to give the corresponding 2-aryl- and 2-alkylimidazo[1,2-*a*]pyridine derivatives as the products of nitrogen insertion. The *cis*-cyhalothric acid derived diazoketone also gave the nitrogen insertion product (Table 1, entry **p**, Scheme 2).

Keywords: α-Diazoketones; Carbene insertion reactions; Imidazo[1,2-*a*]pyridines.
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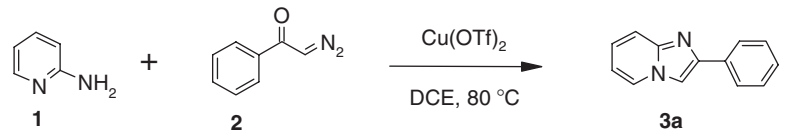
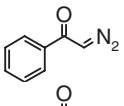
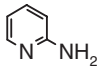
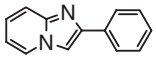
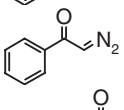
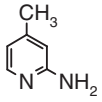
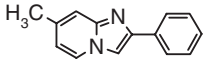
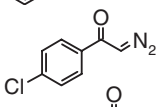
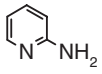
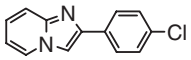
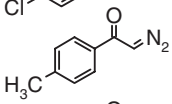
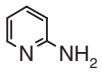
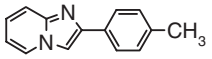
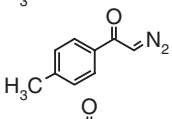
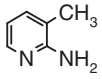
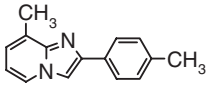
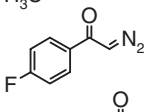
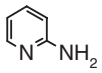
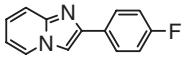
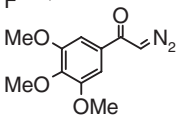
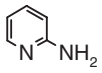
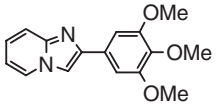
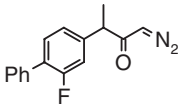
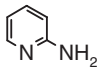
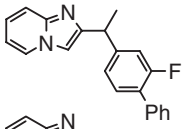
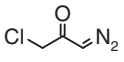
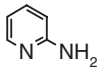
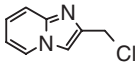
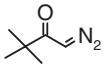
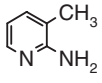
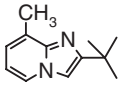
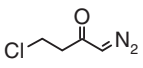
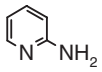
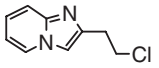
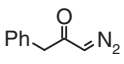
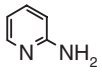
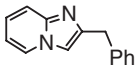
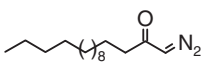
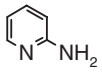
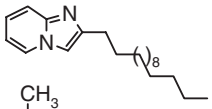


Scheme 1.

Table 1. $Cu(OTf)_2$-catalyzed synthesis of imidazo[1,2-*a*]pyridines from α-diazoketones and 2-aminopyridines

Entry	Diazoketone	2-Aminopyridine	Product[a]	Time (h)	Yield[b] (%)
a				2.0	94
b				2.5	92
c				2.5	91
d				3.0	87
e				2.5	90
f				2.5	91
g				2.0	92
h				3.0	95
i				3.0	90
j				2.0	91
k				2.5	88
l				2.5	90
m				3.0	89
n				2.5	87
o				3.0	86
p				2.5	90

[a] All products were characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.