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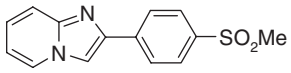
Abstract—α-Diazoketones undergo smooth coupling with 2-aminopyridines in the presence of 10 mol % of copper(II) triflate to produce the corresponding 2-substituted imidazo[1,2-*a*]pyridines (IPs) in excellent yields with high selectivity. $Rh_2(OAc)_4$ is also found to be an equally effective catalyst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



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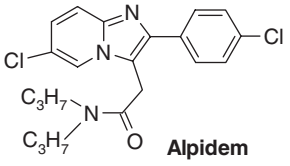

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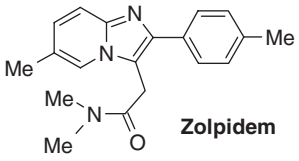

Zolpidem

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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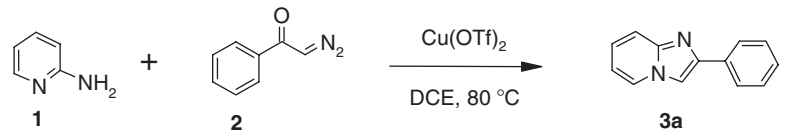
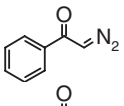
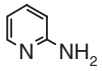
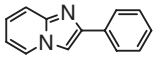
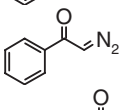
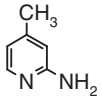
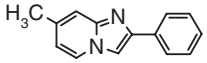
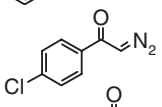
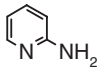
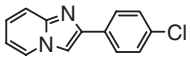
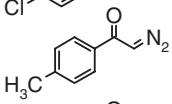
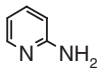
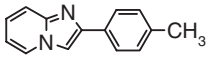
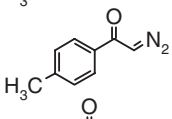
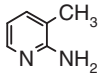
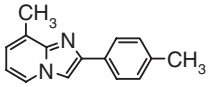
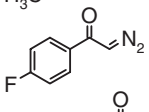
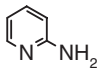
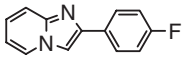
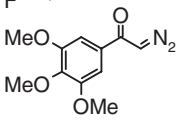
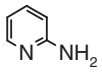
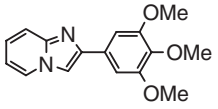
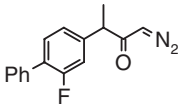
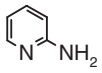
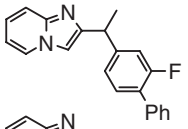
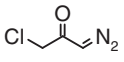
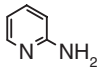
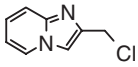
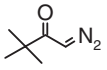
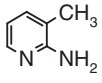
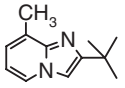
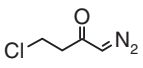
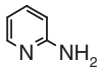
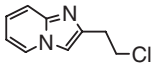
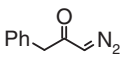
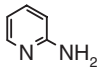
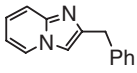
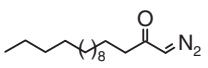
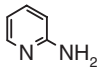
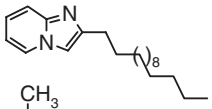
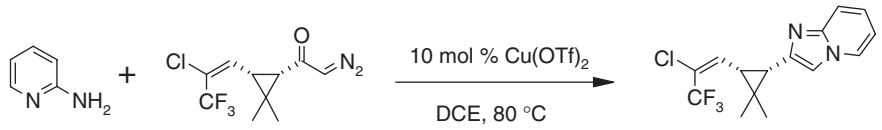


Scheme 1.

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.



Scheme 2.

Both aromatic and aliphatic diazoketones participated well in this conversion (Table 1). In all cases, the reactions proceeded efficiently in the presence of 10 mol % $Cu(OTf)_2$ at 80 °C in dichloroethane and the products were obtained in high yields with high selectivity. No side product arising from a Wolff rearrangement was observed under these reaction conditions. Other side products such as α-keto-*O*-triflates (the products of OTf insertion) arising from $Cu(OTf)_2$ were not detected under these conditions. To determine the efficiency of this procedure, we also performed the reaction with various other copper salts such as $Cu(OAc)_2$, $Cu(BF_4)_2$, $CuBr_2$, and $Cu(acac)_2$. Among these catalysts, $Cu(OTf)_2$ was found to be the most effective. As solvent, dichloroethane gave the best conversion. Alternatively, 5 mol % of $Rh_2(OAc)_4$ was found to be an equally effective catalyst for this transformation. Other Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $InBr_3$, and $InCl_3$ failed to give the desired products. Similarly, Bronsted acids such as Montmorillonite K10, heteropoly acids, PMA, and Amberlyst-15 also did not give the expected product. The reaction may proceed via initial formation of an imine followed by nitrogen insertion which would result in the formation of the imidazo[1,2-*a*]pyridine (Scheme 3).

The structures of the products were established by ^1H NMR, ^{13}C NMR, IR, and high resolution mass spectroscopy (HRMS). The scope and generality of this procedure is illustrated with respect to various α-diazoketones and 2-aminopyridines and the results are presented in Table 1.[15]

In summary, we have described a novel and efficient protocol for the synthesis of 2-aryl- and 2-alkylimidazo[1,2-*a*]pyridines (IP) via the coupling of α-diazoketones with 2-aminopyridines. In addition to its simplicity and mild reaction conditions, this method provides high yields of products with high selectivity making it a useful and attractive strategy for the preparation of biologically relevant 2-susbtituted imidazo[1,2-*a*]pyridines in a single step operation.

Acknowledgment

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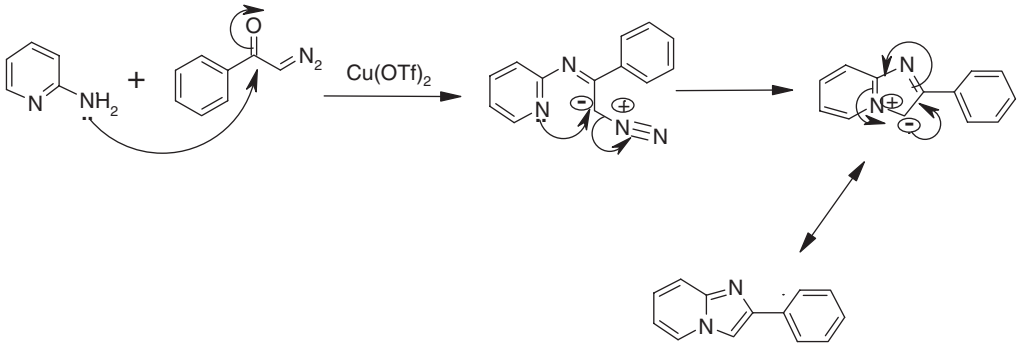

Scheme 3.

12. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds from Cyclopropanes to Ylides*; Wiley-Inter-Science: New York, 1998.
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15. *General procedure*: A mixture of α-diazoketone (1 mmol), 2-aminopyridine (1 mmol) and $Cu(OTf)_2$ (0.1 mmol) in dichloroethane (10 mL) was stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2×15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2–8) afforded the pure imidazo[1,2-*a*]pyridine. Compound **3a**: Gray solid, mp 131–133 °C; IR (KBr): *v* 2924, 2854, 1740, 1629, 1500, 1471, 1366, 1269, 1200, 1140, 1073, 1024, 915, 740, 692, 498, 426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, $J = 6.7$ Hz, 1H), 7.91 (d, $J = 7.5$ Hz, 2H), 7.82 (s, 1H), 7.63 (d, $J = 9.0$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 1H), 7.14 (dd, $J = 6.7$, 9.0 Hz, 1H), 6.74 (t, $J = 6.7$ Hz, 1H); ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 145.6, 131.9, 128.7, 127.9, 126.0, 125.5, 124.7, 117.4, 116.2, 108.1; ESIMS: *m*/*z*: (M^++H): 195; HRMS calcd for $C_{13}H_{11}N_2$ (M^++H): 195.0922; found, 195.0921. Compound **3i**: Brown semi-solid, IR (KBr): *v* 3415, 3112, 2925, 2854, 1645, 1523, 1452, 1342, 1274, 1149, 1019, 759, 712, 622, 436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, $J = 6.4$ Hz, 1H), 7.75 (br s, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.19 (dt, $J = 1.4$, 7.1 Hz, 1H), 7.69 (t, $J = 7.1$ Hz, 1H), 4.74 (s, 2H); ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 145.1, 130.9, 127.9, 122.5, 121.7, 110.4, 108.1, 41.3; ESIMS: *m*/*z*: (M^++H): 167; HRMS calcd for $C_8H_8N_2Cl$ (M^++H): 167.0376; found, 167.0375. Compound **3n**: Brown solid, mp 64–65 °C; IR (KBr): *v* 2917, 2849, 1699, 1524, 1464, 1299, 1177, 939, 761, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, $J = 6.4$ Hz, 1H), 7.27 (br s, 1H), 6.45 (d, $J = 8.5$ Hz, 1H), 6.15 (t, $J = 8.5$ Hz, 1H), 2.73 (t, $J = 7.1$ Hz, 2H), 1.60 (s, 3H, CH_3), 1.65–1.67 (m, 2H), 1.45–1.10 (m, 24H), 0.83 (t, $J = 8.5$ Hz, 3H); ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 145.6, 137.9, 129.2, 128.7, 122.9, 110.2, 108.0, 32.5, 30.1, 30.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 27.3, 25.7, 24.1, 19.3, 16.7, 13.3; ESIMS: *m*/*z*: (M^++H): 343; HRMS calcd for $C_{23}H_{39}N_2$ (M^++H): 343.3113; found: 343.3124. Compound **3p**: Colorless solid, mp 134–135 °C, IR (KBr): *v* 3188, 3079, 2965, 1685, 1652, 1583, 1535, 1437, 1298, 1144, 1055, 951, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.10 (br s, 1H); 8.23 (dd, $J = 0.7$, 1.9 Hz, 1H), 8.21 (dd, $J = 0.7$, 1.9 Hz, 1H), 7.69 (dt, $J = 1.9$, 6.8, Hz, 1H), 7.14 (dd, $J = 0.9$, 9.4 Hz, 1H), 7.01 (ddd, $J = 1.1$, 2.4, 4.9 Hz, 1H), 2.19 (dt, $J = 0.7$, 8.4 Hz, 1H), 1.86 (d, $J = 8.4$ Hz, 1H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 168.2, 151.7, 147.3, 138.6, 130.3, 119.6, 114.7, 35.5, 31.1, 28.7, 28.5, 14.7; ESIMS: *m*/*z*: (M^++H): 315; HRMS calcd for $C_{15}H_{15}N_2F_3Cl$ (M^++H): 315.0875, found, 315.0882.