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PALLADIUM ACETATE-CATALYZED ONE-POT SYNTHESIS OF MONO- AND DISUBSTITUED PYRIDINES

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Abstract – A Pd-catalyzed one-pot synthesis of mono- and disubstituted pyridines was developed. The substituted pyridines were obtained from ketones or an aldehyde and 1,3-diaminopropane using a combination of catalytic $Pd(OAc)_2$ and $Cu(OAc)_2$. High-concentration reaction conditions enabled this catalytic reaction to be acid-free.

Nitrogen heterocycles in natural products play important roles in specific biological activities. For example, the pyridine scaffold is present in a variety of natural products,[1] including fuzanine D (**1**),[2] *O*-methyl halfordinol (**2**),[3] lycopladine A (**3**),[4] and cananodine (**4**)[5] (Figure 1).

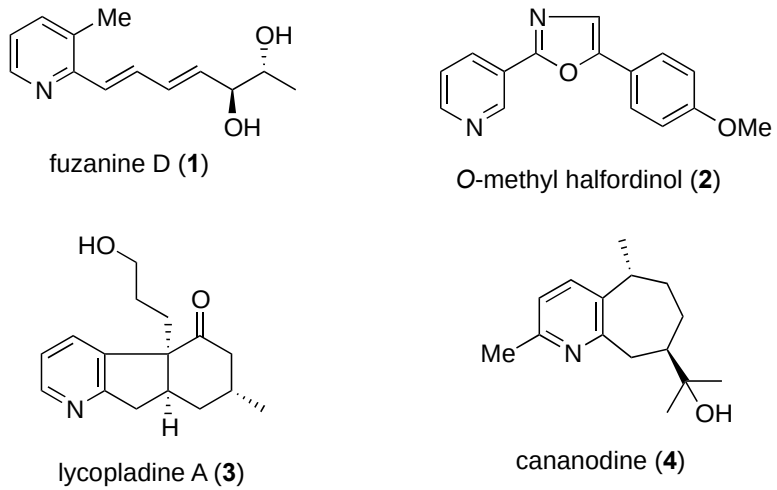
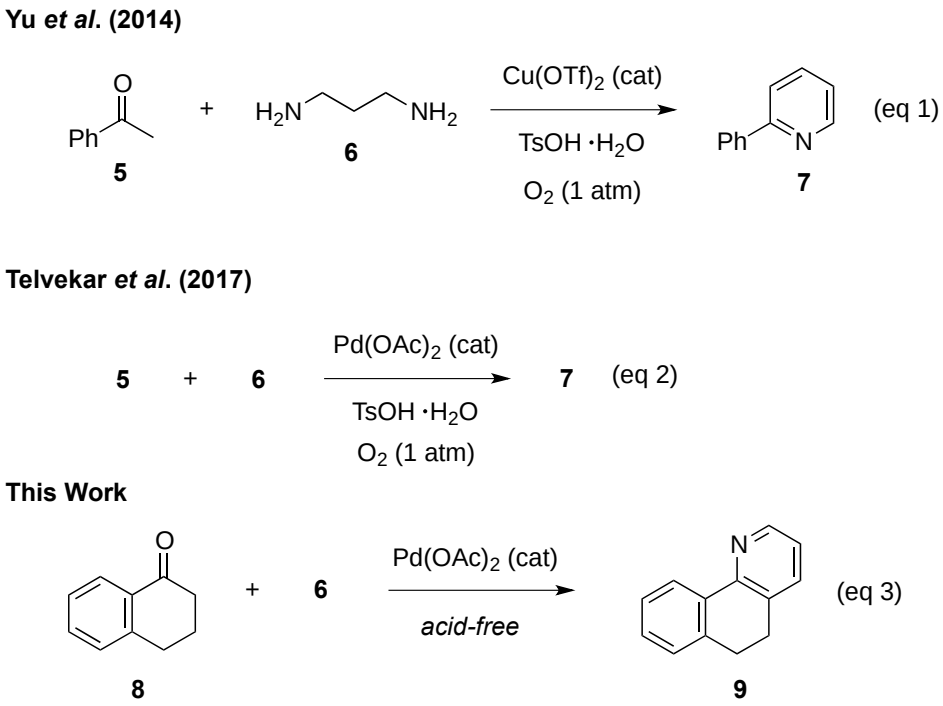


Figure 1

Recently, two research groups[6,7] independently reported the transition metal-catalyzed one-pot synthesis of pyridines using aryl ketones and 1,3-diaminopropane (**6**) in the presence of TsOH (Scheme 1, eqs 1 and 2). One of their experimental examples involved the synthesis of 2-phenylpyridine (**7**) from

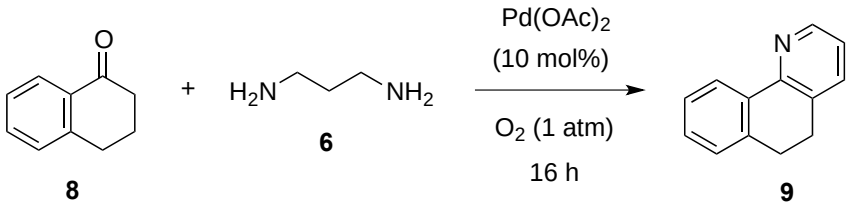
acetophenone (**5**) and 1,3-diaminopropane (**6**). The target product **7** was obtained in good yields. It occurred to us that analogous chemistry might be effected in one synthetic step without using TsOH by employing catalytic amounts of $Pd(OAc)_2$ under high-concentration reaction conditions (Scheme 1, eq 3).



Scheme 1

Our investigation began with an effort to optimize the reaction conditions for the one-pot synthesis of pyridines using $Pd(OAc)_2$. 3,4-Dihydronaphthalen-1(2*H*)-one (**8**) was selected as a model substrate for the optimization process. A number of reaction parameters, such as the additive, solvent, concentration, and temperature, were evaluated to optimize this reaction. The results are summarized in Table 1. Halogenated solvents, such as dichloromethane and dichloroethane, proved totally ineffective; however, THF gave **9** in 16% yield (Table 1, entry 1). Interestingly, toluene improved the yield (Table 1, entry 2). Performing the reaction using DMSO as a solvent provided **9** in 57% yield (Table 1, entry 3). The reaction conducted at higher concentrations and temperatures provided an inferior isolation yield of **9** compared to that obtained in entry 3 (Table 1, entry 4). Catalytic amounts of $Cu(OAc)_2$ proved to be an effective reoxidant (Table 1, entry 5). The best yield, 70%, was obtained when the transformation was performed under high concentrations (5 M solution) at 120 °C over 16 h under one atmosphere of oxygen (Table 1, entry 6). The control experiment clearly indicated that catalytic amounts of $Pd(OAc)_2$ were indispensable.

Tabel 1. Evaluation of reaction conditions for the pyridine synthesis[a]

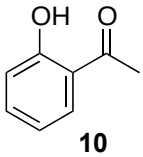
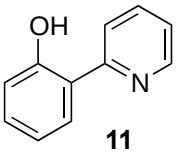
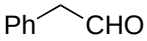
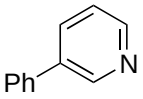
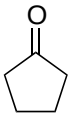
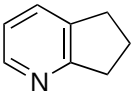
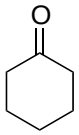
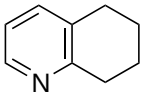
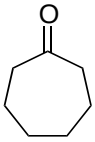
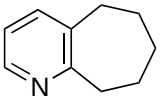
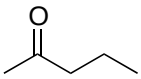
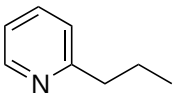
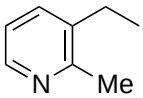
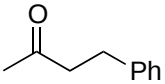
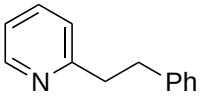
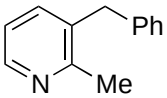
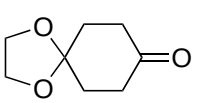
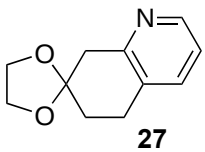


entry	additive (mol%)	solvent	conc (M)	temp (°C)	yield (%)
1	none	THF	1	100	16
2	none	toluene	1	100	33
3	none	DMSO	1	100	57
4	none	DMSO	5	120	39
5	$Cu(OAc)_2$ (20)	DMSO	1	120	63
6[b]	$Cu(OAc)_2$ (20)	DMSO	5	120	70[c]

[a] 3.0 equiv of 1,3-diaminopropane (**6**) were required. [b] Only 10% yield of **9** was obtaind in the absence of 10 mol% $Pd(OAc)_2$. [c] 46% under an atmosphere of air.

The scope and limitations of this catalytic process were next examined using various ketones and an aldehyde, and the results are incorporated into Table 2. Although each substrate was completely consumed, the conversion efficiency was moderate, probably because organic molecules were partially taken into the palladium complex. Acetophenone (**5**) provided 2-phenylpyridine (**7**) in 59% yield (Table 2, entry 1). Interestingly, 2-(pyridin-2-yl)phenol (**11**) was obtained from **10** with a chemical yield similar to that of **7** (Table 2, entry 2). We next examined whether aliphatic aldehyde can also be applied to this transformation. Although a low chemical yield was obtained, 2-phenylacetaldehyde (**12**) gave rise to 3-phenylpyridine (**13**) (Table 2, entry 3). Bicyclic pyridine **15** was produced using cyclopentenone (**14**) with a relatively low boiling point (Table 2, entry 5). Cyclohexanone (**16**) led to 5,6,7,8-tetrahydroquinoline (**17**) in 41% yield (Table 2, entry 5). Compound **19** had the same carbon skeleton as cananodine (**4**) and was also synthesized from cycloheptanone (**18**) in 55% yield (Table 2, entry 6). We tested the applicability of this process to aliphatic ketones. Pentan-2-one (**20**) furnished 2-propylpyridine (**21**) and 3-ethyl-2-methylpyridine (**22**) as an inseparable 2:5 mixture (Table 2, entry 7). The low yield was attributed to the low boiling point of **20**. 2-Phenethylpyridine (**24**) and 3-benzyl-2-methylpyridine (**25**) were afforded from 4-phenylbutan-2-one (**23**) in a 55% yield as a 5:4 mixture (Table 2, entry 8). Although the chemical yield and regioselectivity could be improved, it became clear that this methodology was applicable to aliphatic ketones for the preparation of 2- and 2,3-disubstituted pyridines. Bicyclic pyridine **27** was also obtained from acid sensitive compound **26** in a

Table 2. $Pd(OAc)_2$-catalyzed acid-free pyridine formation[a]

entry	substrate	product	time (h)	yield (%)
1	**5**	**7**	23	59
2	 **10**	 **11**	23	53
3	 **12**	 **13**	17	32
4	 **14**	 **15**	16	12
5	 **16**	 **17**	23	41
6	 **18**	 **19**	16	55
7	 **20**	 **21** (2 : 5)  **22**	15	13
8	 **23**	 **24** (5 : 4)  **25**	15	55
9	 **26**	 **27**	17	36

[a] All reactions were run in DMSO (5 M) using 10 mol% $Pd(OAc)_2$, 20 mol% $Cu(OAc)_2$, and 3 equiv 1,3-diaminopropane at 120 °C under O_2 (1 atm) atmosphere.

36% yield (Table 2, entry 9). It is particularly noteworthy that compound **27** was not obtained under reaction conditions reported in the literature.[7]

In conclusion, we developed a $Pd(OAc)_2$-catalyzed one-pot synthesis of mono- and disubstituted pyridines. This process proceeded without using strong acids, such as TsOH, and the present protocol could be adapted to substrates bearing acid-sensitive functional groups.

EXPERIMENTAL

NMR spectra were measured on Varian 400 MR at 400 MHz spectrometer. Chemical shifts were reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometer. Chemical shifts were reported relative to $CDCl_3$ (δ 77.2).

5,6-Dihydrobenzo[*h*]quinoline[8] **(9).** $Pd(OAc)_2$ (9.00 mg, 0.04 mmol) and $Cu(OAc)_2$ (14.6 mg, 0.08 mmol) were placed in a screw-top test tube, and a solution of 3,4-dihydronaphthalen-1(2*H*)-one (**8**) (58.6 mg, 0.40 mmol) in DMSO (0.08 mL) was added at room temperature. Then 1,3-diaminopropane (**6**) (0.10 mL, 1.20 mmol) was added to the reaction mixture. The test tube was filled with oxygen and then the resulting mixture was stirred at 120 °C for 16 h. After cooling down to room temperature, the palladium residue was removed by filtering through Celite. The organic solvent was removed under reduced pressure, and then the reaction was quenched by addition of 10% aqueous NH_3 solution. The solution was extracted three times with a 4:1 mixture of hexane and EtOAc. The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and filtered through Celite. The filtrate was concentrated to afford 5,6-dihydrobenzo[*h*]quinoline (**9**) (51.1 mg, 70%) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.6, 1.6 Hz, 1H), 8.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.37 (ddd, *J* = 7.4, 7.2, 1.2 Hz, 1H), 7.31 (ddd, *J* = 7.4, 7.2, 1.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 4.6 Hz, 1H), 2.93 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 147.9, 138.2, 135.7, 134.7, 131.9, 129.2, 127.9, 127.3, 125.0, 122.3, 28.2, 28.1.

2-Phenylpyridine[9] **(7).** ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.6 Hz, 1H), 7.52-7.49 (m, 2H), 7.30-7.23 (m, 2H), 7.04-6.98 (m, 2H), 6.94 (dd, *J* = 6.8, 1.6 Hz, 1H), 6.79-6.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 149.7, 139.4, 136.8, 129.0, 128.8, 126.9, 122.1, 120.6.

2-(Pyridin-2-yl)phenol[10] **(11).** ^1H NMR (400 MHz, $CDCl_3$) δ 14.39 (s, 1H), 8.54-8.50 (m, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.87-7.79 (m, 2H), 7.34-7.29 (m, 1H), 7.27-7.23 (m, 1H), 7.04 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.94-6.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 157.7, 145.8, 145.7, 137.7, 131.4, 126.1, 121.5, 119.0, 118.7, 118.5.

3-Phenylpyridine[9] **(13).** ^1H NMR (400 MHz, $CDCl_3$) δ 8.87-8.85 (m, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.88 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 7.61-7.57 (m, 1H), 7.52-7.46 (m, 2H), 7.42 (ddd, *J* = 6.8, 1.6, 1.4 Hz,

1H), 7.39-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.5, 138.0, 136.8, 134.5, 129.2, 128.2, 127.3, 123.7.

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridine[11] (15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.8 Hz, 1H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.02 (dd, *J* = 4.8, 2.8 Hz, 1H), 3.02 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.94 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.17-2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 147.5, 137.0, 132.2, 121.1, 34.3, 30.8, 23.2.

5,6,7,8-Tetrahydroquinoline[11] (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 4.8 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.01 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.92 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.77 (dd, *J* = 6.4, 6.4 Hz, 2H), 1.94-1.86 (m, 2H), 1.85-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 146.8, 136.8, 132.3, 120.9, 32.6, 28.8, 23.1, 22.7.

6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridine[12] (19). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.01 (dd, *J* = 7.4, 5.0 Hz, 1H), 3.07-3.01 (m, 2H), 2.79-2.75 (m, 2H), 1.91-1.84 (m, 2H), 1.74-1.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 146.2, 138.1, 136.4, 121.2, 39.5, 35.4, 32.6, 28.0, 26.5.

2-Propylpyridine[13] (21). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 1H), 7.57 (ddd, *J* = 7.6, 7.6, 2.0 Hz, 1H), 7.20-7.17 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 2.75 (dd, *J* = 7.6, 7.6 Hz, 2H), 1.80-1.70 (m, 2H), 0.96 (dd, *J* = 7.6, 7.6 Hz, 3H).

3-Ethyl-2-methylpyridine[14] (22). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 4.8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.07 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.54 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 146.5, 137.3, 135.5, 121.5, 25.8, 22.2, 14.0.

2-Phenethylpyridine[15] (24). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.53 (dd, *J* = 7.6, 7.0 Hz, 1H), 7.27-7.21 (m, 2H) 7.19-7.13 (m, 3H), 7.10-7.02 (m, 2H), 3.11-2.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 149.5, 141.7, 136.4, 128.6, 128.5, 126.1, 123.1, 121.3, 40.4, 36.2.

3-Benzyl-2-methylpyridine[16] (25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.2 Hz, 1H), 7.33-7.22 (m, 3H), 7.21-7.16 (m, 1H), 7.10-7.02 (m, 3H), 3.95 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 147.2, 139.2, 137.3, 134.3, 128.9, 128.7, 126.5, 121.4, 38.9, 22.7.

7,8-Dihydro-5*H*-spiro[quinoline-6,2'-[1,3]dioxolane][17] (27). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.0 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.04 (s, 4H), 3.14 (dd, *J* = 6.8, 6.8 Hz, 2H), 3.00 (s, 2H), 2.06 (dd, *J* = 6.8, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 147.4, 137.2, 129.6, 121.1, 107.6, 64.7, 38.6, 31.6, 31.0.

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