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THE REACTION OF N-MONO AND N,N-DISUBSTITUTED HYDROXYLAMINES WITH PALLADIUM CATALYST

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The Palladium catalyzed reactions of N,N-disubstituted and N-substituted hydroxylamines give the corresponding nitrones and azoxy compounds highly efficiently. The former reactions are performed in the presence of alkenes to give the cycloadducts which are valuable intermediates regio and stereoselectively.

We have explored various new reactions, which include alkyl group exchange reactions[1] and hydrolysis reactions[2], by the activation of amines with metal catalysts. These reactions involve dehydrogenation processes which are deeply concerned with the metabolism of amines. In relation to the alternative deamination process which involves the oxidation with molecular oxygen[3], the catalytic oxidation of hydroxylamines is of interest. We wish to report efficient palladium catalyzed transformations of N,N-disubstituted and N-monosubstituted hydroxylamines to the corresponding nitrones and azoxy compounds, respectively as depicted in eq 1-2.

$$R^1CH_2\underset{\underset{OH}{|}}{N}R^2 \xrightarrow{Pd} R^1CH=\overset{+}{N}(\overset{-}{O})-R^2 + H_2 \qquad (1)$$

$$2\ R^1NHOH \xrightarrow{Pd} R^1-\overset{+}{N}(\overset{-}{O})=N-R^1 + H_2 + H_2O \qquad (2)$$

Although nitrones are valuable intermediates to construct various biologically active nitrogen compounds[4], their preparative methods are limited to few reactions. The condensation of N-monosubstituted hydroxylamines with aldehydes is the general and efficient method which involves a carbon-carbon bond formation[5]. However, cyclic nitrones cannot be derived from this method, and hence the oxidation of hydroxylamines with stoichiometric oxidants has been used[6]. Therefore, the catalytic oxidation of hydroxylamines under mild conditions has been waited to be developed.

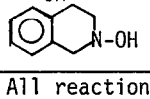
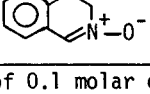
Treatment of N,N-disubstituted and cyclic hydroxylamines with palladium black at 80-110°C gives the corresponding nitrones along with hydrogen. The catalytic activity of various metal complexes has been examined for the reaction of N,N-dibutylhydroxylamine in hexane at 65°C. The

reaction products are N-butylidene butylamine-1-oxide, butylamine, dibutylamine, and tributylamine. Palladium black and $RhCl(PPh_3)_3$ gave the nitrone in 98 % yield. Other palladium complexes, such as $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(MeCN)_2$ produced the nitrone and the amines. Ruthenium and rhodium complexes, such as Ru black, $RuCl_3$, $Ru(OAc)_3$, $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$, $RhCl_3 \cdot 3H_2O$, $Rh(OAc)_3$ gave the amines along with a small amount of the nitrone. The corresponding nitrones were obtained in high yields upon treatment of N,N-disubstituted hydroxylamines with a solvent such as hexane, toluene, tetrahydrofuran, and water or without a solvent. However, cyclic nitrones could not be obtained by using non-polar solvents. For the isolation of cyclic nitrones water is the best solvent among examined. Thus, 1,2,3,4-tetrahydropyridine-1-oxide (1) was obtained as a monomer. Noteworthy is that the stoichiometric oxidation of N-hydroxypiperidine gives the dimer of the nitrone (HgO)[6a] or the trimer ($K_3[Fe(CN)_6]$)[6b].

A representative example is the isolation of 1. A mixture of N-hydroxypiperidine (0.505 g, 5.0 mmol) and Pd black (0.020 g, 0.20 mmol) in water (1 mL) was heated at 80°C for 12 hr under argon. To the reaction mixture was added CH_2Cl_2 (50 mL), and the solution was filtered off. The filtrate was dried ($MgSO_4$), and concentrated to give crude 1 (0.350 g). Recrystallization from petroleum ether gave the pure nitrone (0.280 g, 56 %). Mp 110-113°C(dec)[7], NMR ($CDCl_3$) δ, 1.35-2.20 (m, 4H), 2.35-2.65 (m, 2H), 3.65-4.15(m, 2H), 7.16(t, J = 4.3 Hz, 1H). IR ($CHCl_3$), 2960, 2865, 1622, 1543, 1378, 1268 cm^{-1}. The other typical examples of the nitrone formation are summarized in Table 1.

The 1,3-dipolar cycloaddition of nitrones to alkenes is of interest to construct five-membered heterocyclic compounds[8]. Especially the cycloadducts of cyclic nitrones provide valuable key intermediates for natural product synthesis[4]. The palladium catalyzed reaction of

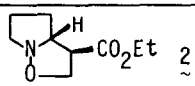
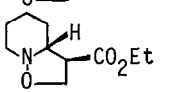
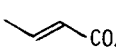
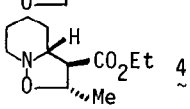
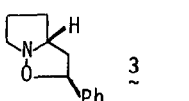
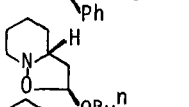
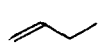
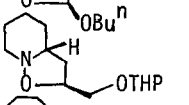
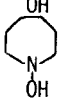
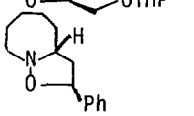
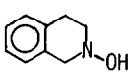
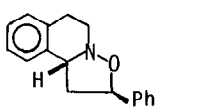
Table 1. Palladium Catalyzed Preparation of Nitrones[a)]

Hydroxylamine	Solvent	Temp. (°C)	Conv.[b)c)] (%)	Nitrone[e)]	Yield[f)] (%)	mp or bp[g)]
$(C_4H_9)_2N\text{-}OH$	Toluene	110	95	$C_3H_7CH{=}N^+(O^-)C_4H_9$	84[g)]	95-100°C/2mm
$(PhCH_2)_2N\text{-}OH$	Toluene	110	90[d)]	$PhCH{=}N^+(O^-)CH_2Ph$	87[h)]	81-83°C
$PhCH_2N(OH)(CH_2)_2CO_2Et$	Toluene	110	95	$PhCH{=}N^+(O^-)(CH_2)_2CO_2Et$	80[h)]	-
	water	80	95		67[g)]	105-110°C/1mm
	water	80	67	 1	57[i)]	110-113°C
	water	80	90		80[g)]	160-165°C/1mm

a) All reactions were carried out in the presence of 0.1 molar equivalent of Pd-black under argon. b) Determined by GLC analysis using internal standards. c) Reaction time is 12 hr. d) Reaction time is 36 hr. e) All products exhibited satisfactory spectra and analytical data. f) Isolated yields. g) Kugelrohl distillation. h) Preparative TLC (SiO_2). i) Recrystallization (petroleum ether).

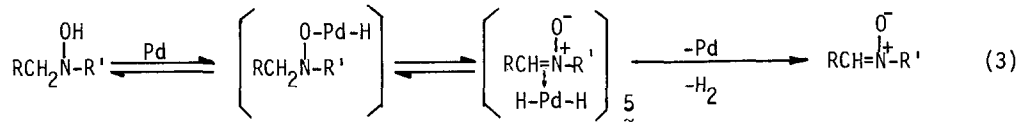
cyclic hydroxylamines in the presence of alkenes gives cycloadducts in high yields. The examples are summarized in Table 2. Apparently, the yields of the cycloadducts are higher than those obtained by isolation of nitrones followed by addition. Importantly, the cycloaddition of cyclic nitrones proceeds regioselectively. Thus, the palladium catalyzed reaction of N-hydroxypyrrolidine in the presence of ethyl acrylate gave 3-carboethoxy cycloadduct (2) in 59 % isolated yield, while with styrene 2-phenyl cycloadduct (3) was obtained in 73 % yield regioselectively. Generally, alkenes with an electron-withdrawing substituent give 3-substituted five-membered rings (Entries 1-3), while those with an electron-donating substituent[9] and aryl group give 2-substituted adducts (Entries 4-8). Furthermore, the cycloaddition proceeds stereoselectively[10]. Typically, the palladium catalyzed reaction of N-hydroxypiperidine with ethyl crotonate gave 2-methyl-3-carboethoxyhexahydropyridinoisoxazole (4) in 85 % isolated yield. The trans, trans-stereochemistry was confirmed by the NMR analysis ($J_{H^2H^3}$ = 6.0 Hz, $J_{H^3H^4}$ = 6.0 Hz).

Table 2. Palladium Catalyzed Reactions of Hydroxylamines in the Presence of Alkenes.[a)]

Entry	Hydroxylamine	Alkene	Temp. (°C)	Adduct[b)]	Yield[c)] (%)
1			100	 2	59
2			100		73
3			100	 4	85
4			110	 3	73
5			100		64
6			110		66
7			110		61
8			110		55[d)]

a) A mixture of a hydroxylamine (3.0 mmol), an alkene (6.0 mmol), and palladium black (0.3 mmol) was allowed to react for 12 hr under argon. b) All products exhibited satisfactory spectral data. c) Isolated yields by Kugelrohl distillation. d) Preparative TLC (SiO_2).

The reaction can be rationalized by eq 3. The oxidative addition of palladium to the O-H bond of hydroxylamines followed by elimination of [PdH] species gives 5 which undergoes reductive coupling to give nitrones and hydrogen.



(3)

The palladium catalyzed reaction of N-monosubstituted hydroxylamines in the presence of triethylamine gives the corresponding azoxy compounds efficiently[11]. The treatment of N-arylhydroxylamines with palladium black at 20°C for 12 hr gives azoxybenzenes along with arylamines (20-30 %). The addition of 0.10 molar equivalent of triethylamine retards the formation of amines[12], and azoxybenzenes are generally obtained in over 95 % yields. Similar treatment of N-monosubstituted hydroxylamines bearing an α-hydrogen gives azoxy compounds and aldoximes in the ratio of 75:25. The reaction can be explained by the similar oxidative addition followed by β-elimination to give a nitroso intermediate which undergoes nucleophilic reaction with the starting hydroxylamines[12].

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References and Notes

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7) The mp of the dimer is 126-127°C[6a], and the trimer is oil[6b].
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12) The effect of triethylamine may be due to retard the transfer hydrogenation of [PdH] species to the hydroxyamine by assisting the decomposition of the hydride complex.

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