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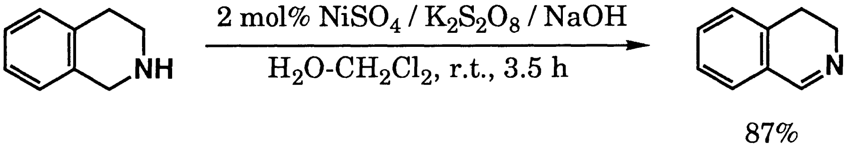
Oxidation of Secondary Amines with $NiSO_4$-$K_2S_2O_8$

Shigekazu YAMAZAKI
Toyama Industrial Technology Center, 150, Futagami, Takaoka, Toyama 933

The catalytic system consisting of $NiSO_4$ and $K_2S_2O_8$ has been found to be effective for the oxidation of secondary amines to imines. 1,2,3,4-Tetrahydroisoquinoline was oxidized to 3,4-dihydroisoquinoline as the main product with a small amount of isoquinoline. N-Benzylaniline gave N-benzylideneaniline and a N-N coupling dimer.

Selective transformation of functional groups of organic compounds is important in synthetic chemistry. The utilization of stoichiometric metal oxidants such as manganese dioxide and chromium compounds has been general method of choice for this purpose. The stoichiometric use as well as disposal of these reagents is, however, undesirable from economical and environmental viewpoints. As a result, there has been much recent interest in the catalytic system by these metal reagents.1)

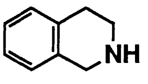
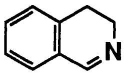
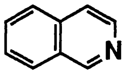
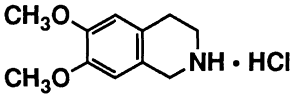
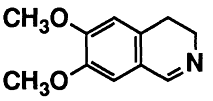
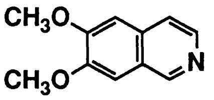
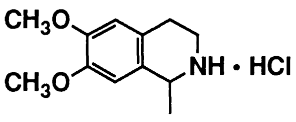
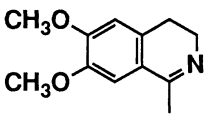
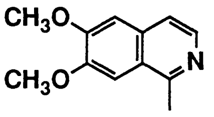
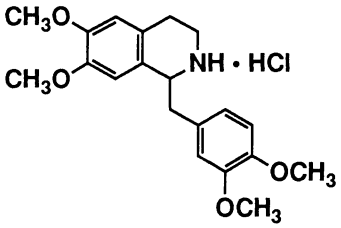
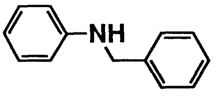
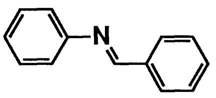
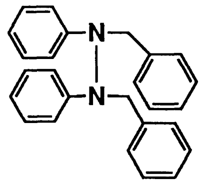
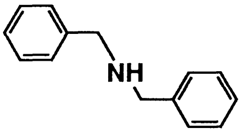
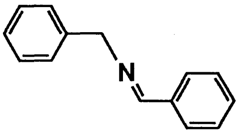
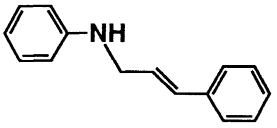
We previously reported that the catalytic system consisting of nickel(II) sulfate and $K_2S_2O_8$ in an aqueous alkaline solution was efficient for the dehydrogenation of allylic alcohols to the corresponding unsaturated carbonyl compounds,2) the dehydrogenation of primary amines to nitriles,3) and the synthesis of nitriles from aldehydes and aqueous ammonia.4) Here I report that this system has been found to be also effective for the catalytic dehydrogenation of secondary amines to imines.



Stoichiometric oxidations of secondary amines to imines have been well documented with several oxidizing reagents such as MnO_2,5) $Hg(OAc)_2$,6) Fremy's salt,7) diphenylselenium bis(trifluoloacetate),8) and so on.9) But there are a few reports on catalytic oxidations of secondary amines to imines by ruthenium10) or cobalt complexes11) as catalysts.

At first 1,2,3,4-tetrahydroisoquinoline was examined as the substrate. Solutions of 1,2,3,4-tetrahydroisoquinoline (0.300 g, 2.25 mmol) in CH_2Cl_2 (10 mL) and of $K_2S_2O_8$ (0.85 g, 3.1 mmol) /

Table 1. Nickel-Catalyzed Oxidation of Secondary Amines with $K_2S_2O_8$[a]

Amine	$K_2S_2O_8$/NaOH (equiv.)	Time / h	Product (Yield / %)[b]
	1.4/2.4	3.5	 (87)  (1)
	2.0/2.4	1	 (60)  (6) c)
	3.0/3.6	18	 (29)  (11) d)
	2.0/2.4	24	No Reaction
	2.0/4.0	24	 (45)  (23) c)
	2.0/3.0	24	 (6) e)
	2.0/4.0	24	No Reaction

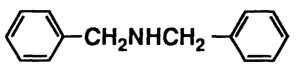
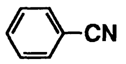
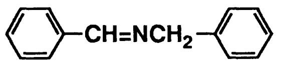
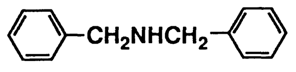
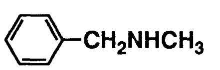
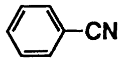
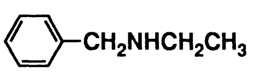
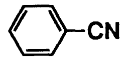
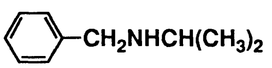
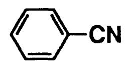
a) Reaction conditions: a mixture of the amine in CH_2Cl_2, 2 mol% 0.050 M aqueous $NiSO_4$, and $K_2S_2O_8$/NaOH in H_2O was stirred vigorously at room temperature. b) Determined by GC. c) Isolated yield. d) The starting amine (9%) was recovered. e) The starting amine (94%) was recovered.

NaOH (0.22 g, 5.5 mmol) in H_2O (20 mL) were mixed and stirred to which a 0.050 M aqueous solution of $NiSO_4$ (0.90 mL, 0.045 mmol) was added. Fine black precipitates deposited immediately, and the resulting mixture was stirred vigorously at room temperature. The black color was almost disappeared after 3.5 h. The mixture was filtered through a short Celite column to remove insoluble materials. The organic materials in the filtrate were separated by extraction with CH_2Cl_2. The products in the CH_2Cl_2 extract were analyzed by gas chromatography. As a result, 3,4-dihydroisoquinoline was obtained as the major product in 87% yield along with a small amount of isoquinoline (1% yield).

The use of other organic solvents such as benzene, hexane, diethyl ether, and acetonitrile gave almost the same results as those with the case in CH_2Cl_2. The use of a large excess amount of the oxidant and a long reaction period resulted in a decreased amount of 3,4-dihydroisoquinoline, while the formation of isoquinoline increased.

The results of the oxidation of some substituted 1,2,3,4-tetrahydroisoquinoline derivatives are summarized in Table 1. 3,4-Dihydroisoquinolines thus obtained are useful intermediates for the synthesis of more complex isoquinoline alkaloids.[5c,12] An alkyl substituent at the 1-position in 1,2,3,4-tetrahydroisoquinoline serves to slow down the reaction rate. Thus, no reaction took place with norlaudanosine.

Table 2. Nickel-catalyzed oxidation of N-benzylamines with $K_2S_2O_8$[a)]

Amine	Time / h	Product[b)] (Yield / %)
	24	 (59)  (31)  (3)
	24	 (19)
	5	 (8)
	48	 (19)

a) Reaction conditions: amine (2.5 mmol), 0.050 M aqueous $NiSO_4$ (2.0 mL, 0.10 mmol), and $K_2S_2O_8$ (2.7 g, 10 mmol) / NaOH (0.80 g, 20 mmol) in H_2O (50 mL) at room temperature. b) Determined by GC.

The oxidation of N-benzylaniline proceeded smoothly under the conditions described above, and N-benzylideneaniline and N,N'-dibenzyl-N,N'-diphenylhydrazine[13] were obtained in 45% and 23% yield respectively (Table 1). No such N-N coupling dimer was detected in the stoichiometric nickel peroxide oxidation of N-benzylaniline.[14)] On the other hand, the rate of reaction with dibenzylamine was very slow, where only 6% of N-benzylidenebenzylamine was obtained in 24h and 94% of the amine was recovered. The reaction of N-(*trans*-3-phenyl-2-propenyl)aniline did not react at all under the conditions.

Interestingly, the oxidation of dibenzylamine in the absence of organic solvent proceeded smoothly, and benzonitrile was obtained as the main product (59% yield) along with a considerable amount of N-benzylidenebenzylamine (31% yield). The oxidation of other N-alkyl benzylamines also gave benzonitrile but in low yield (Table 2).

Further application of this catalytic system for the synthesis of heterocyclic compounds is currently under investigation.

References

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13) The oxidation products were identified by comparison of physical data with those of commercial or reported samples. N,N'-Dibenzyl-N,N'-diphenylhydrazine: Mp 125 °C (lit.[14)] 127 °C); ^{1}H-NMR ($CDCl_3$) δ= 4.77 (s, 4H), 6.6-7.4 (m, 20H); ^{13}C-NMR ($CDCl_3$) δ= 56.71, 113.40, 118.92, 126.91, 128.47, 129.27, 138.46, 147.98; Anal. ($C_{26}H_{24}N_2$) C, H, N.

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