Heterocyclic *N*-Oxide Reduction by Titanium Trichloride

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The *N*-oxide bond of heterocyclic *N*-oxides has been reduced by catalytic hydrogenation, complex hydrides, trivalent phosphorus compounds, various sulfur containing compounds, dissolving metals, metal ions, and electrolysis. This chemistry has been reviewed[1-4]. Brooks and Sternglanz have published an analytical method in which titanium trichloride reduced the *N*-oxide of pyridine 1-oxides[5]. Titanium trichloride has, however, never been used preparatively in such reductions. Various reductions in other systems by titanium trichloride have recently been reviewed[6].

We report now that aqueous titanium trichloride is an excellent synthetic alternative to available reagents for the reduction of certain *N*-oxides. Data for the heterocyclic *N*-oxides that we have reduced with titanium trichloride are summarized in the Table. Products were identified by comparison of their I.R. spectra and physical constants to those of known compounds. The yields which are recorded are for isolated, pure products. The reaction of titanium trichloride and heterocyclic *N*-oxides is exemplified in equations (*1*–*3*).

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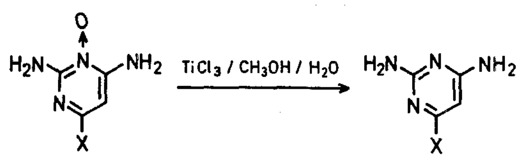
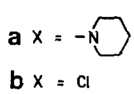
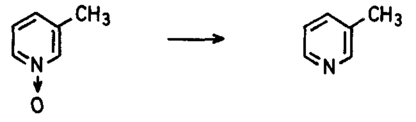
(*1*)



1a,b **2a,b**

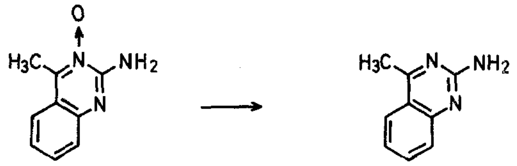


(2)



3 **4**

(*3*)



5 **6**

The compounds cited in the Table were rapidly reduced by dropwise addition of a 20% aqueous titanium trichloride solution[7] to an ice-cooled solution of the compound in either tetrahydrofuran or methanol. Typical experimental procedures for the two solvents are cited below.

2,4-Diamino-6-piperidinopyrimidine (2a):

A solution of 2,4-diamino-6-piperidinopyrimidine 3-oxide (0.50 g, 2.39 mmol) in methanol (20 ml) was stirred at 0°. A solution of 20% aqueous titanium trichloride was added dropwise at a rate that barely maintained the titanium trichloride color in the reaction flask. After 15 min, the color was no longer discharged. The mixture was concentrated *in vacuo* and partitioned between aqueous saturated sodium hydrogen carbonate and dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo* to give crystalline material; yield: 0.45 g (97%); m.p. 135–136°.

$C_9H_{15}N_5$	calc.	C 55.97	H 7.77	N 36.26
(193.2)	found	55.69	7.98	35.95

Table. Reductions of *N*-Oxides with Titanium Trichloride

Product[a]	Yield (%)	B.p. or m.p. (recryst. solvent)	Lit. b.p. or m.p.	Reaction solvent
2a	97	m.p. 135–136° C_2H_5OAc/C_6H_{12}	135.5–136.5°[8]	methanol
2b	78[b]	m.p. 200–201° CH_2Cl_2/CH_3OH	197–200°[8]	methanol
4	71	b.p. 77°/85 torr	143.8°/760 torr[9]	THF
6	83[b]	m.p. 157–158° CH_2Cl_2/C_6H_{12}	159–159.8°[10]	methanol
4-chloro-2-methyl-pyridine	79[b]	—		THF

[a] Products characterized by comparison of I.R. spectra.

[b] Product purified by column chromatography on silica gel using methanol/dichloromethane as eluent.

3-Picoline (4):

3-Picoline 1-oxide (10.0 g, 91.7 mmol) was dissolved in tetrahydrofuran (40 ml) and stirred at 0°. A 20% aqueous titanium trichloride solution[7] was added in the manner which was described above. The reaction mixture was then neutralized with 50% aqueous sodium hydroxide and filtered by pressure through Celite. The inorganic sludge was stirred and washed repeatedly with dichloromethane. The combined organic phases were washed with aqueous sodium hydrogen carbonate, dried over sodium sulfate, concentrated *in vacuo*, and distilled; yield: 6.05 g (71%); b.p. 77°/85 torr. The spectral properties of the distillate were identical to those of the known compound.

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