SELECTIVE REDUCTION OF 2′-NITROANILIDES

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Hydrogenation of 2′-nitro-2,2,2-trifluoroacetanilide in ether over palladium-on-charcoal gives 2′-aminotrifluoroacetanilide that readily cyclizes to 2-trifluoromethylbenzimidazole in methanol solution.[1] If the reaction is performed in ethanol with palladium-on-charcoal as a catalyst, two products are obtained—2-trifluoromethylbenzimidazole and 1-hydroxy-2-trifluoromethylbenzimidazole. The latter product can be made to predominate by the addition of an acid catalyst and can be readily separated from 2-trifluoromethylbenzimidazole by its solubility in sodium bicarbonate. Until this finding, the instances of occurrence of *N*-hydroxyimidazole derivatives by catalytic hydrogenation in the literature were rare, though the production of *N*-oxides by this route has been described several times (FIGURE 1). It was found[2,6] that hydrogenation of an *o*-nitro-*N*-alkylanilide gave the benzimidazole *N*-oxide, but the reaction could not be extended to *N*-oxides unsubstituted at the 1-position (i.e., those capable of tautomerizing to an *N*-hydroxybenzimidazole). An exception to this rule was *o*-nitroformanilide that, in ethanol, gave a low yield of 1-hydroxybenzimidazole. Other workers have reported that sodium borohydride–platinum mixtures cause the same reaction.[3,5] None of the other known methods for the introduction of an *N*-oxy function were applicable to the production of 2-perfluoroalkyl-1-oxyimidazole derivatives (e.g., direct oxidation and hydrosulfide reduction[4]), and this prompted us to look further into the catalytic hydrogenation of *o*-nitroanilides and *o*-nitroperfluoroalkanoanilides, in particular.

In general, 1-hydroxy-2-(2,2-difluoroalkyl)benzimidazoles and imidazopyridines can be prepared by reduction—preferably by hydrogenation—of the corresponding 2′-nitroanilide. They are high-melting solids, considerably more acidic than the corresponding imidazoles (TABLE 1) and less soluble in nonpolar solvents. They exhibit a characteristic broad continuous hydroxyl absorption stretching down to below 2400 cm^{-1} (in contrast to the imidazoles, which have a broad "saw-toothed" absorption down to about 2650 cm^{-1}).

If the cyclodehydration to give an *N*-hydroxyimidazole occurs at the hydroxylamine stage (which seems probable), then the reason for the rapid ring closure in the case of perfluoroalkanoanilides is the high positive charge density on the carbon atom of the amide carbonyl group that induces attack by the nucleophilic nitrogen of the hydroxylamine group (FIGURE 2). The use of a nonpolar aprotic solvent decreases yields, and solvents such as ethanol maximize yields (FIGURE 3). Addition of mineral acid also favors hydroxyimidazole formation, presumably by protonation of the carbonyl group, giving rise to a full formal positive charge on the carbon atom. Any substitution on the benzo ring that tends to lower this positive charge density lessens the chance of *N*-hydroxyimidazole formation in favor of the desoxy compound. This latter reaction is believed to occur by cyclodehydration of an intermediate, 2-aminoperfluoroanilide, rather than deoxygenation of a hydroxyimidazole, because

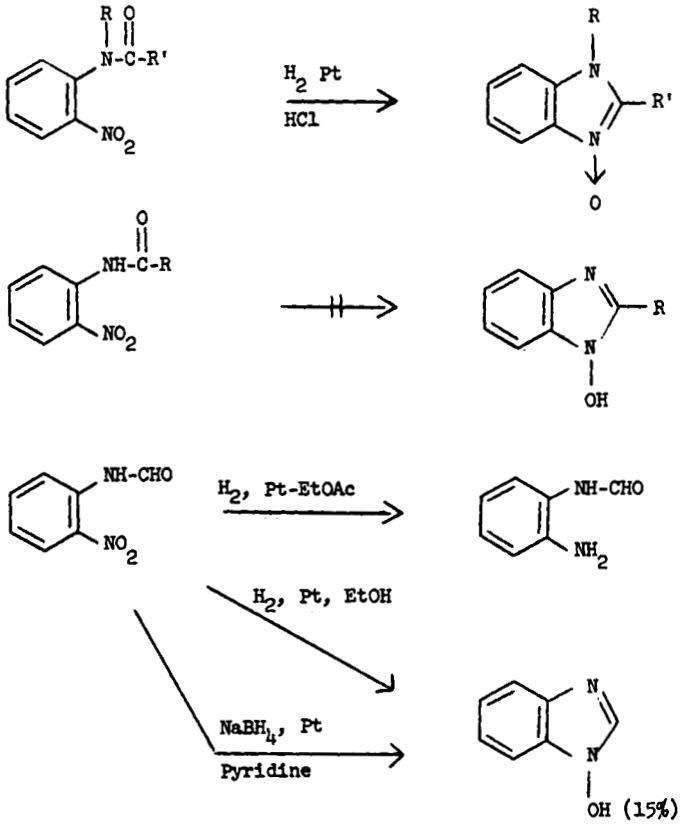


FIGURE 1. Catalytic hydrogenation of 2′-nitroanilides.

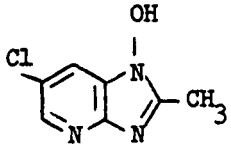
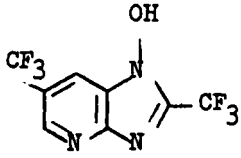
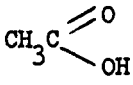
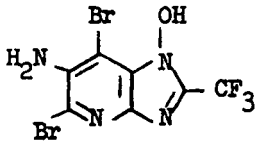
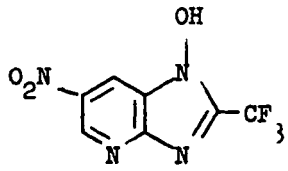
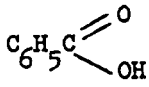
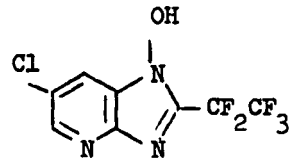
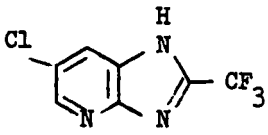
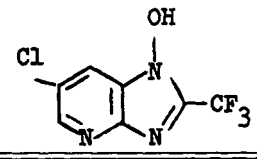
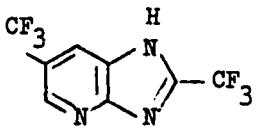
these are resistant to reduction depending on the electron-withdrawing power of the substituents. The ease of cyclization of 2′-aminoanilides follows a similar pattern. (The half-life of 2′-amino-2,2,2-trifluoroacetanilide in methanol is 12 hr,[1] though 2′-amino-6′-nitro-4-trifluoromethyl-2,2,2-trifluoroacetanilide requires heating at steambath temperatures in concentrated sulfuric acid to affect cyclization.) Conversely, substituents that increase the positive charge enhance the possibility of *N*-hydroxyimidazole formation (FIGURE 4). If the 2′-nitroperfluoroalkanoanilide contains a basic group in some part of the molecule, a mole equivalent of acid is required to permit the formation of any *N*-hydroxy compound. Without the addition of a mole of acid, the principal product is the corresponding azo compound (FIGURE 5), and addition of triethylamine to the reaction of a neutral substrate produces a similar result. However (FIGURE 6), if the substituents on the benzo or hetero portion of the molecule are such that a large positive charge occurs on the carbonyl carbon, then cyclization to hydroxyimidazole occurs quite readily in neutral solution (less readily in basic solution) after an initial induction period. The reaction then speeds up because of the formation of the usually strongly acidic hydroxyimidazole acting as an acid catalyst.

The rate of reduction of the nitro group to hydroxylamine, although faster than that of hydroxylamine to amino, is not critical; actually, the rate of cyclization of the hydroxylamine (that, in turn, is dependent on the carbonyl carbon positive charge density) is the dominant factor (FIGURE 7). The fact that one nitro group can be reduced and cyclized in the presence of another bears this out. Although it is necessary to terminate hydrogen uptake after 2 mole equiv have been absorbed to achieve optimum yields of the desired compounds, a marked decrease in the rate of hydrogen uptake is usually observed at this stage.

As already mentioned, the presence of a strongly electronegative 2,2-disubstitution on the acyl group is the driving force for cyclization at the hydroxylamine stage of reduction; however, this is not a sufficient condition, as attempts

TABLE 1

pK_a VALUES IN 66% DIMETHYLFORMAMIDE

	pKa		pKa
	7.3		5.1
	6.9		
	6.9		4.55
	6.5		
	5.65		7.3
	5.5		7.1

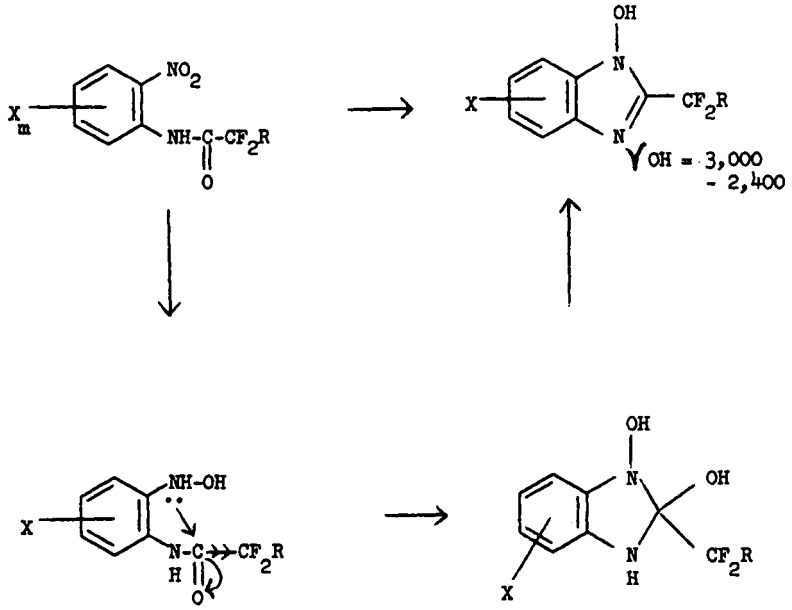


FIGURE 2. Reaction intermediates.

to reduce 2′-nitrotrichloroacetanilide gave intractable mixtures from which no *N*-hydroxyimidazole could be readily isolated. It may therefore be inferred that steric effects may also operate (FIGURE 8). The trifluoromethyl group approximates the size of a methyl group which, however, has no electron-withdrawing properties. If the positive charge on the acetyl carbonyl group could be affected by benzo-substitution, then one might expect the possibility of cyclization of a 2′-nitroacetanilide to a 1-hydroxy-2-methylbenzimidazole. In fact, 2′,6′-dinitro-4-trifluoromethylacetanilide can be reduced to 1-hydroxy-2-methyl-4-nitro-6-trifluoromethylbenzimidazole in good yield, lending some support to the above hypothesis. The corresponding benzoyl compound also gives the *N*-hydroxybenzimidazole in good yield, although the yield of 6-chloro-1-hydroxy-2-methylimidazo[4,5-b]pyridine is somewhat decreased.

The oxygen function in all the 2-perfluoroalkylbenzimidazoles and imidazopyridines we have examined exists as a hydroxyl group rather than the possible tautomeric *N*-oxide. The broad intense hydroxyl absorption at approximately 2500 cm^{-1} in the infrared spectrum occurs in all of the compounds examined, both in the solid state and in solution. Also, acylation and alkylation reactions invariably give the *O*- rather than the *N*-derivative (FIGURE 9). Methylation with diazomethane or methyl iodide and base gives stable *O*-methyl derivatives that are generally low-melting solids or liquids. The acetyl compounds can be prepared by reaction with acetic anhydride catalyzed by a small amount of sulfuric acid and followed by quenching in water; the resulting acetates can be recrystallized from ethanol without decomposition, although the infrared carbonyl absorption at approximately 1800 cm^{-1} suggests a mixed-anhydride character for these compounds. Aroyl esters are even more stable while exhibiting the same high-frequency carbonyl absorption. Methanesulfonate esters,

preparable by reaction of the *N*-hydroxyimidazole and methanesulfonyl chloride in pyridine, are less stable but in some cases can be recrystallized from ethanol without decomposition. The esters, in general, react with amines as mixed anhydrides to give the *N*-hydroxyimidazole and the corresponding amide.

The existence of some *N*-oxide form can be inferred when it is possible to hydrogenolyze the oxygen function. 1-Hydroxy-2-trifluoromethylbenzimidazole can be hydrogenolyzed to 2-trifluoromethylbenzimidazole in approximately 28 hr in ethanol over palladium-on-carbon. 1-Hydroxy-6-chloro-2-trifluoromethylimidazo[4,5-b]pyridine is unaffected by the same conditions in 5 days. Hydrogenation over platinum at 60 psi for 5 days produced approximately a 2% loss of substrate; the products were identified as 2-trifluoromethylimidazo[4,5-b] pyridine and its 1-hydroxy derivative, suggesting the route shown in FIGURE 10. It was therefore not possible to hydrogenolyze the very acidic hydroxyl group of **I** until the chlorine atom had been removed; the resulting **II** then has enough *N*-oxide character to allow hydrogenolysis to **III**.

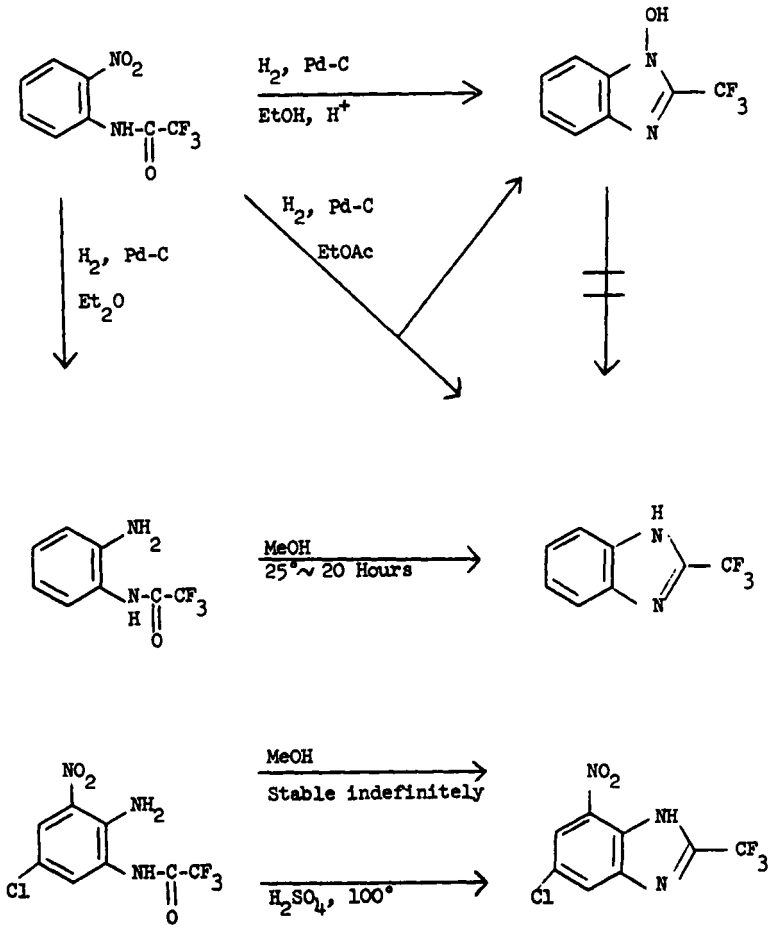


FIGURE 3. Solvent effects.

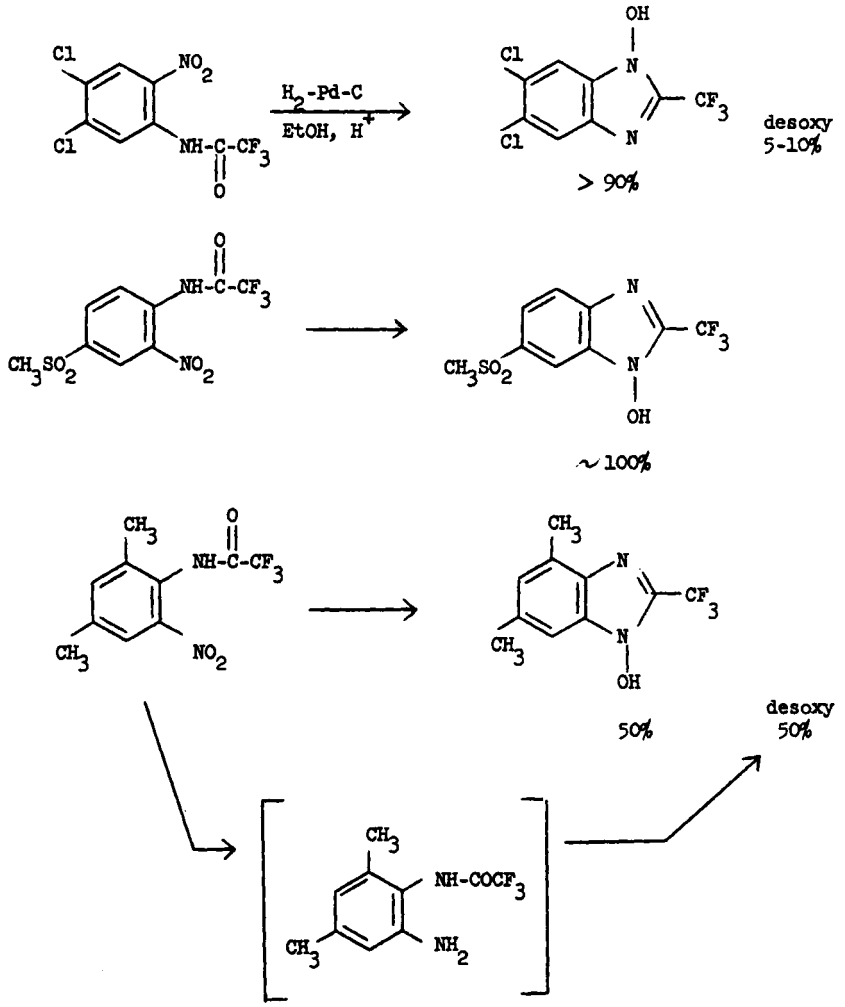


FIGURE 4. Substituent effects.

METHODS AND MATERIALS

The following are exemplary; more complete experimental details and physical data may be found elsewhere.[7]

4'-Methanesulfonyl-2'-Nitro-2,2,2-Trifluoroacetanilide

4-Methanesulfonyl-2-nitroaniline (2.16 g, 0.01 M), chloroform (3.5 ml), and trifluoroacetic anhydride (4 ml) were stirred until homogeneous (3 hr). The chloroform solution was washed with water, filtered, and evaporated. The

resulting solid (3.2 g) crystallized from chloroform, mp 140° C (rapid heating).

Anal. Calcd for $C_9H_7F_3N_2O_5S$: C, 35.40; H, 1.98; N, 9.26. Found: C, 35.60; H, 2.21; N, 9.00.

1-Hydroxy-6-Methanesulfonyl-2-Trifluoromethylbenzimidazole

4'-Methanesulfonyl-2'-nitro-2,2,2-trifluoroacetanilide (3.12 g, 0.01 M), 5% palladium-on-carbon (300 mg), ethanol (100 ml), and 0.05 ml concentrated hydrochloric acid hydrogenated on a Parr apparatus (initial pressure 50 psi) until hydrogen uptake ceased. The filtrate was evaporated to 10 ml and then diluted with aqueous sodium bicarbonate (10%, 12 ml) and water (40 ml). The solution was stirred for 0.5 hr and filtered (Norite). The filtrate was

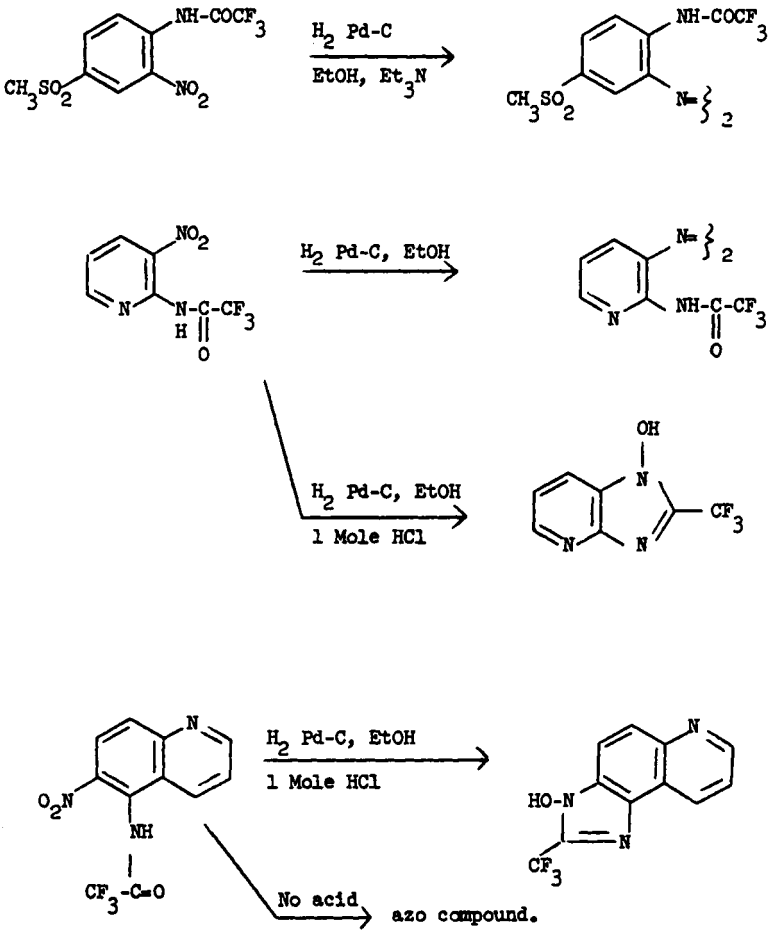


FIGURE 5. Effect of organic base.

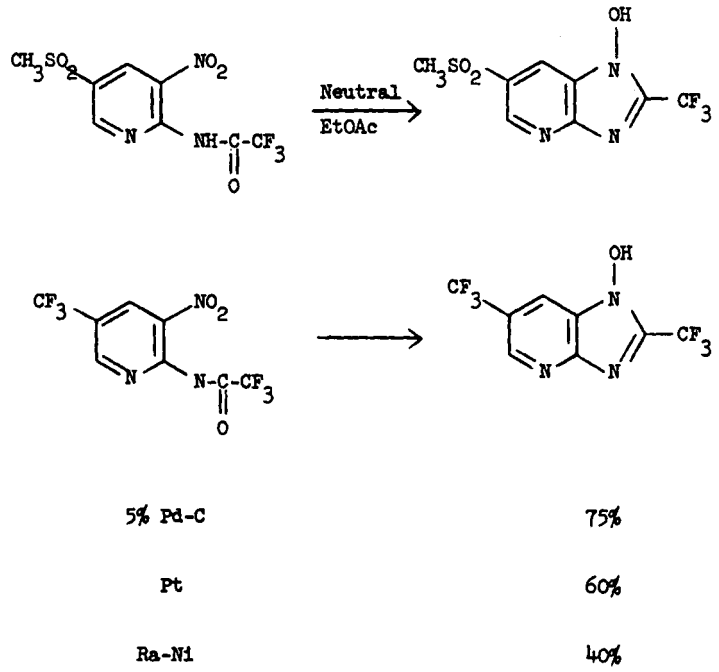


FIGURE 6. Substituent effect overcomes basic center effect. Catalyst efficiency.

acidified to pH = 2 and filtered to give a white solid (2.7 g), mp 198–200° C; recrystallized from acetone, mp 205° C (decn).

Anal. Calcd for $C_9H_7F_3N_2O_3S$: C, 38.64; H, 2.55; N, 10.01. Found: C, 38.91; H, 2.73; N, 10.26.

1-Hydroxy-2-Trifluoromethylimidazo[4,5-b]Pyridine

2-Amino-3-nitropyridine (1.4 g, 0.01 M), chloroform (25 ml), and trifluoroacetic anhydride (2 ml) were stirred at 25° C for 3 hr; the chloroform solution was washed with water, filtered, and evaporated. The residue was dissolved in 100 ml ethanol and 2 ml concentrated hydrochloric acid and hydrogenated over 200 mg of 5% palladium-on-carbon. The filtered solution was evaporated, taken up in sodium bicarbonate solution (2%, 50 ml), filtered (Norite), and acidified to pH = 2 with concentrated hydrochloric acid. The resulting precipitate was recrystallized from acetone to give 1.3 g colorless prisms, mp 261–2° C.

Anal. Calcd for $C_7H_4F_3N_3O$: C, 41.39; H, 1.98; N, 20.70. Found: C, 41.59; H, 2.03; N, 20.69.

1-Methylcarbamyloxy-2-Trifluoromethylimidazo[4,5-b]Pyridine

1-Hydroxy-2-trifluoromethylimidazo[4,5-b]pyridine (3 g) in chloroform (20 ml) and methylisocyanate (3 ml) were stirred for 16 hr at 25° C and

filtered to give 3.5 g white solid that crystallized from chloroform, mp 225° C (dec.). $\nu C = 0$ 1800 cm^{-1}.

Anal. Calcd for $C_9H_7F_3N_4O_2$: C, 41.55; H, 2.71; N, 21.53. Found: C, 41.26; H, 2.74; N, 21.32.

2',6'-Dinitro-4'-Trifluoromethylacetanilide

2,6-Dinitro-4-trifluoromethylaniline (20 g), acetic anhydride (50 ml), and sulfuric acid (0.05 ml) were refluxed for 2 hr. The mixture was evaporated to dryness *in vacuo*, and the residue recrystallized from ethanol–acetone to give 22 g, mp 251–252° C.

Anal. Calcd for $C_9H_6F_3N_3O_5$: C, 36.87; H, 2.06; N, 14.33. Found: C, 37.17; H, 2.00; N, 14.61.

1-Hydroxy-2-Methyl-4-Nitro-6-Trifluoromethylbenzimidazole

2',6'-Dinitro-4'-trifluoromethylacetanilide (5.0 g) in ethanol (200 ml) and sulfuric acid (0.05 ml) was hydrogenated over 5% palladium-on-carbon (0.5

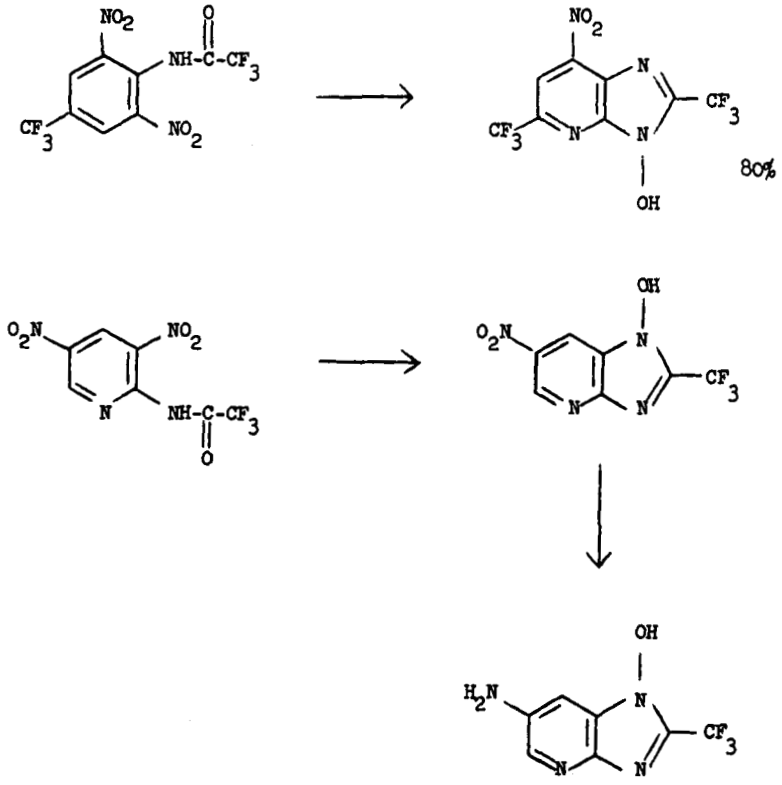


FIGURE 7. Reductive cyclization in the presence of other nitro groups.

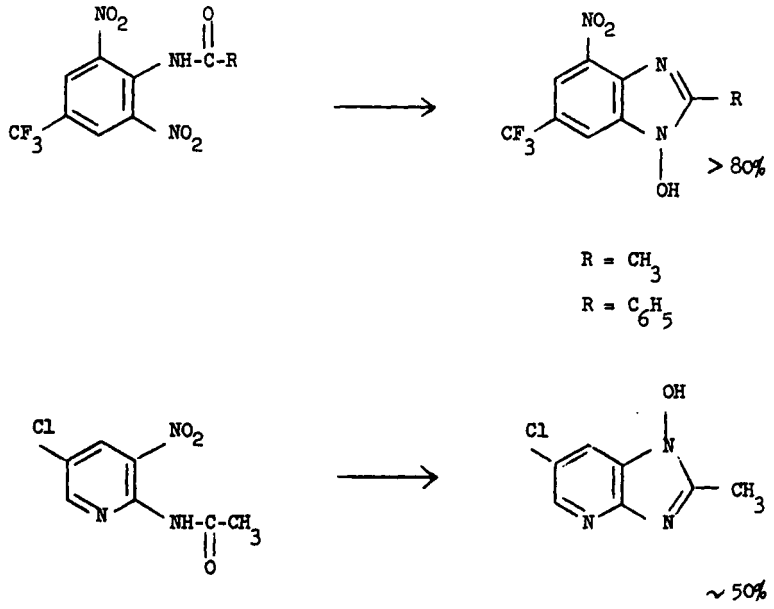


FIGURE 8. *N*-Hydroxyimidazole formation without perfluoroalkyl side chain.

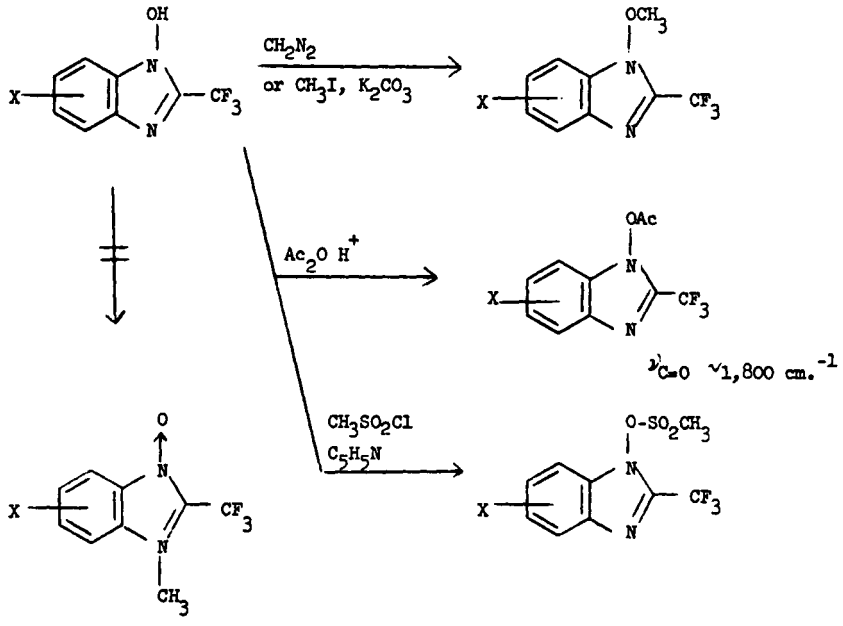


FIGURE 9. Functionalization on oxygen.

g) to 2 mole equiv uptake. The filtrate was evaporated, and the residue recrystallized from ethanol (4.3 g), mp 256° C (decn.).

Anal. Calcd for $C_8H_6F_3N_3O_3$: C, 41.39; H, 2.32; N, 16.09. Found: C, 41.20; H, 2.17; N, 15.93.

1-Hydroxy-2-phenyl-4-nitro-6-trifluoromethylbenzimidazole similarly prepared, mp 275–6° C (from acetone).

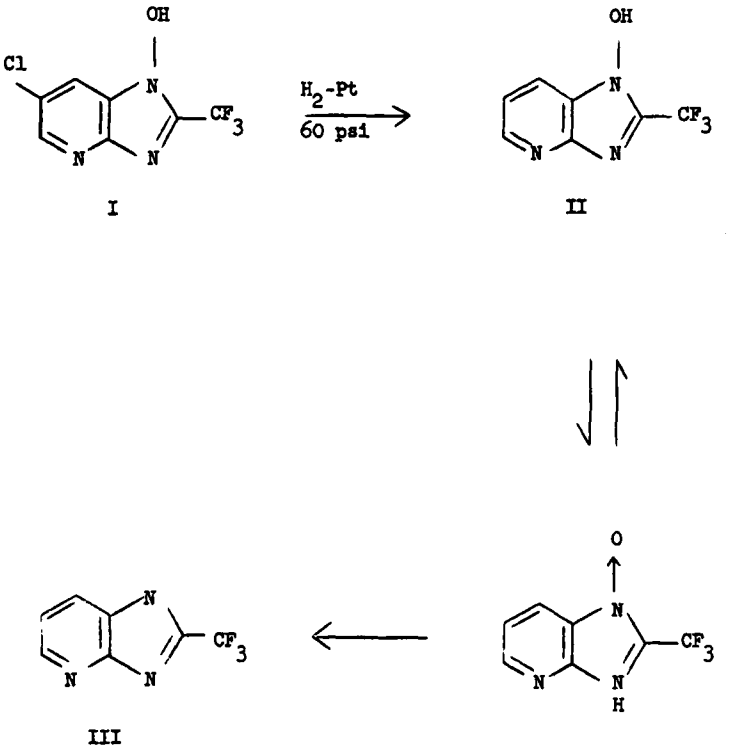


FIGURE 10. Attempted hydrogenolysis of oxy function.

2-Acetamido-5-Chloro-3-Nitropyridine

2-Amino-5-chloro-3-nitropyridine (10 g) in acetic anhydride (30 ml) and acetic acid (20 ml) were refluxed for 4 hr, poured into 200 ml water, and the precipitate filtered after 1 hr. The solid crystallized from ethanol (8 g), mp 175–6° C.

Anal. Calcd for $C_7H_6ClN_3O_3$: C, 39.00; H, 2.81; N, 19.49. Found: C, 39.20; H, 3.00; N, 19.73.

6-Chloro-1-Hydroxy-2-Methylimidazo[4,5-b]Pyridine

2-Acetamido-5-chloro-3-nitropyridine (4.3 g), ethanol (100 ml), concentrated hydrochloric acid (3 ml) were hydrogenated over 700 mg of 5% palladium-on-carbon. The filtrate was evaporated, and the residue shaken with 5% $NaHCO_3$(50 ml) and filtered to give 2.5 g of a pale-brown solid that crystallized from ethanol, mp 250–1° C (decn.).

Anal. Calcd for $C_7H_6ClN_3O$: C, 45.79; H, 3.29; N, 22.89. Found: C, 45.66; H, 3.27; N, 22.69.

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4. Von Niementowski, S. 1910. Chem. Ber. **43:** 3018.
5. Takahashi, S. 1969. French Patent 1,555,336 (1-24-69).
6. Schulenberg, J. W. 1969. U.S. Patent 3,431,274 (3-4-69).
7. Doherty, G. O. P. & K. H. Fuhr. 1971. Belgian Patent 764,571 (12-21-70).