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A NEW ROUTE TO 6-SUBSTITUTED 2,3-DIAMINOPYRIDINES

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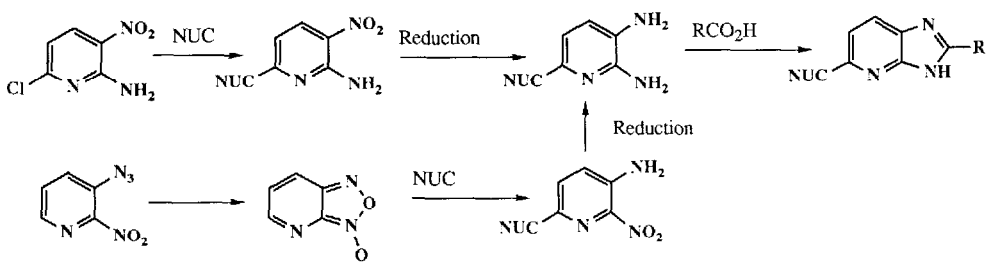
Summary: 2,3-Diaminopyridine reacts with cyclohexanone to form dihydro-4-azabenzimidazole-2-spirocyclohexane. Reaction of this intermediate with a variety of nucleophiles (e.g., water, phenylmercaptan, ethanol, dimethylamine, and diethylmalonate) in the presence of MnO_2 results in addition to the 5-position. Subsequent acidic hydrogenation affords 6-substituted-2,3-diaminopyridines, key synthons for the synthesis of bicyclic heterocycles.

2,3-Diaminopyridines are important intermediates for the synthesis of heterocycles useful in pharmaceutical research. A recent such example has been the utility of these intermediates for the synthesis of azabenzimidazole angiotensin II antagonists.[1] Despite the synthetic importance of substituted 2,3-diaminopyridines, the scope of methodologies to prepare these key synthons is narrow and, as summarized below, is focused on introducing functionality into the 6-position of nitropyridine derivatives.[2]



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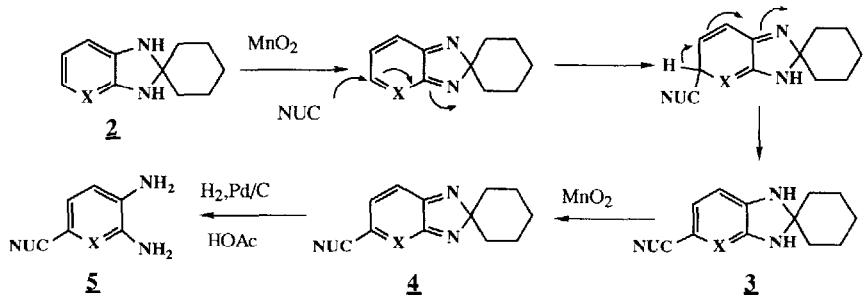
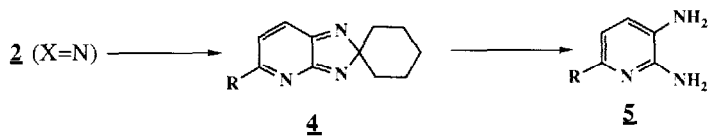
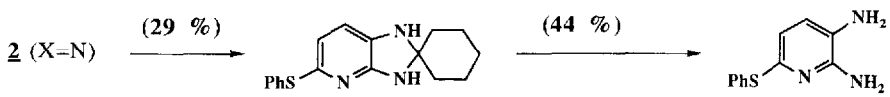
We report now a novel approach to 6-substituted 2,3-diaminopyridines based upon the reported observation that phenylenediamine reacts with cyclohexanone to form dihydrobenzimidazole-2-spirocyclohexane (2, X=CH).[3] The reactivity of this intermediate has been extensively explored and reviewed by Suschitzky.[4] In the presence of a mild oxidizing agent, this intermediate reacts with nucleophiles via a facile 1,4 addition to give the substituted isobenzimidazole-2-spirocyclohexane 4 (X=CH). Hydrogenation of 4 under acidic conditions yields the desired phenylenediamine 5 (X=CH).



We reasoned that because of the structural similarity of the azaisobenzimidazole-2-spirocyclohexane 4 (X=N) and the pyrido-2,3-furoxan intermediate 1, and the propensity of pyridine to undergo 1,2 addition-elimination reactions, that the Suschitzky reaction scheme could be adapted to prepare 6-substituted-2,3-diaminopyridines such as 5 (X=N). We therefore reacted 2,3-diaminopyridine with cyclohexanone in the same fashion to prepare the dihydro-4-azabenzimidazole-2-spirocyclohexane 2 (X=N) in 47% yield. As predicted, this compound readily reacted with water, dimethylamine, ethanol, and diethylmalonate, in the presence of MnO_2 and an appropriate solvent, to form the substituted intermediates 4 (X=N). However, an exception occurred when the sodium salt of phenylmercaptan was the nucleophile, the product 3 (X=N) did not further oxidize to 4 (X=N) and the dihydro-4-azabenzimidazole-2-spirocyclohexane (6, below) was isolated in 29% yield.



R	% Yield (mp)		% Yield (mp), TFA Salt	
HO-	30	(153-4°C)	21	(amorphous)
$(CH_3)_2N$-	70	(162-4°C)	80	(111-4°C)
CH_3CH_2O-	44	(128-9°C)	62	(130-2°C)
$(EtO_2C)_2CH$-	58	(103-5°C)	39	(117-9°C)

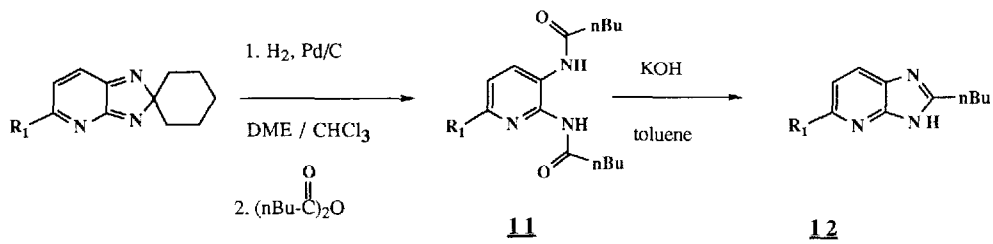


mp= 263-5° mp= 114-5°

Attempts to liberate the substituted diaminopyridines, 5, using Suschitzky's conditions

(hydrogenation in acetic acid) gave very poor yields when the nucleophile was dimethylamine, ethanol, or water. The desired products appear to be unstable under these conditions. However, replacement of acetic acid with trifluoroacetic acid resulted in improved yields, presumably because the TFA salts were more resistant to oxidation. The mild reducing condition provided by chloroform in ethanol was investigated; [5, 6] while moderately successful, it was not as general as the TFA procedure. It should be noted that 6-phenylsulfide-2,3-diaminopyridine was likewise prepared by acidic hydrolysis of dihydro-azabenzimidazole-spirocyclohexane 6.

A major advantage of this methodology is that unstable electron-rich diamines such as 6-hydroxy-2,3-diaminopyridine can be directly converted to azabenzimidazoles by a modification of this method. Thus, for example, hydrogenation of the azaisobenzimidazole-2-spirocyclohexanes, below, in a dimethoxyethane/anhydride mixture afforded the protected derivatives 11, which could be converted to the azabenzimidazoles 12 in good yield.



11 12

R	% Yield (mp)	% Yield (mp)
$(CH_3)_2N$-	49 (amorphous)	42 (128-131°C)
CH_3CH_2O-	62 (107-8°C)	85 (syrup)

Preparation of dihydro-4-azabenzimidazole-2-spirocyclohexane, 2 (X=N).
Molecular sieves (50 g, 4Å) were added to a solution of 2,3-diaminopyridine (50 g, 0.46 mol) and cyclohexanone (135 g, 1.37 mol) in sulfolane (450 ml). The reaction mixture was heated at 130° for 72 hours. The molecular sieves were filtered off while the reaction was hot. As the filtrate cooled to room temperature, the product crystallized from solution. Filtration, followed by an ether wash, afforded the product as pale golden platelets, 47 g (47%, mp= 217-21° C) (Lit. mp = 212-14°C).[7]

General procedure for the reaction of nucleophiles with dihydro-4-azabenzimidazole-2-spirocyclohexane.
Manganese dioxide (12 g, 138 mmol) was added to a solution of 2 (X=N), (6 g, 31.7 mmol) and the nucleophile (1 equivalent when the nucleophile was not the solvent) in the specified solvent.[8] The reaction mixture was stirred at room temperature until reaction was complete by tlc (2-18 hours). When the nucleophile was ethanol, refluxing significantly increased the yield. Excess manganese dioxide was removed by filtration through supercel, and the filtrate was evaporated *in vacuo* to give the crude 4-azaisobenzimidazole-2-spirocyclohexane 4 which was purified by chromatography on silica gel or crystallization.[9, 10]

General procedure for the hydrogenation of the appropriate 5-substituted-4-azaisobenzimidazole-2-spirocyclohexanes

The 5-substituted-4-azaisobenzimidazole-2-spirocyclohexane (1 mmol) was dissolved in trifluoroacetic acid (2 ml). A catalytic amount of 10% Pd/C (.025 g) was added and the reaction mixture was hydrogenated at atmospheric pressure for one hour. Removal of the catalyst by filtration, followed by evaporation of the solvent and chromatography on silica gel, using methylene chloride/methanol as eluent afforded the 6-substituted-2,3-diaminopyridine as their TFA salts.

General procedure for the preparation of azabenzimidazoles

The appropriate 5-substituted-4-azaisobenzimidazole-2-spirocyclohexane (10 mmol) and anhydride (40 mmol) were dissolved in a mixture of 1,2-dimethoxyethane (80 ml) and chloroform (8 ml). A catalytic amount of 10% Pd/C (0.3 g) was added and the reaction mixture was hydrogenated at atmospheric pressure overnight. Removal of the catalyst by filtration, followed by evaporation of the solvent and chromatography on silica gel, using ethyl acetate/hexanes as eluent afforded the amides 11 in good yield.

The amides 11 (5.29 mmol) were refluxed for three hours in a mixture of 2N aqueous potassium hydroxide (7.9 ml) and ethanol (30 ml). Ethanol was evaporated and the residue was partitioned between methylene chloride and water. The organic layer was dried ($MgSO_4$), filtered and evaporated to give a mixture of monoamides. These amides were dissolved in toluene (50 ml). Aqueous 2N potassium hydroxide (2.65 ml) was added and the reaction mixture was heated at reflux overnight while removing water with a Dean-Stark trap. The solvent was distilled off at atmospheric pressure. The residue was heated *in vacuo* at 140°C for three hours to complete the reaction. The crude reaction product was partitioned between methylene chloride and water. The organic phase was dried ($MgSO_4$), filtered and evaporated. Chromatography on silica gel, eluting with methylene chloride and methanol afforded the azabenzimidazole in good yield.

References

1. Roberts, D. A. ; Russell, S.T. ; Ratcliffe, A. H. ; Gibson, K.H. ; Wood, R. (ICI) ; Eur. Pat. Appl. EP 0 399 731 (1990).
2. Kotovskaya, S. K. ; Mokrushina, G. A. ; Postovskii, I. Ya. ; Polyakova, M. V. Khim Geterotsikl Soedin, **1981**, *5*, 654-7.
3. Staab, H. A.; Vogtle, F. Chem Ber., **1965**, *98*, 2681.
4. Suschitsky, H. Croatica Chemica Acta, **1986**, *59(1)*, 57-77.
5. Secrist, J. A.; Logue, M. N. J. Org. Chem., **1972**, *37*, 335.
6. Lyle, R. E; LaMattina, J. L. Synthesis, **1974**, 726-727.
7. Dubey, P.; Ratnam, C. V. Indian Journal of Chemistry, **1980**, *19B*, 863-865.
8. Ethanol was the solvent when the nucleophile was dimethylamine, ethanol or sodium phenylmercaptide. Toluene was the solvent for diethylmalonate. Finally, benzene was used as solvent when water was the nucleophile.
9. The dimethylamino, ethoxy, and diethylmalonate substituted 4 were purified by chromatography, eluting respectively with methylene chloride/methanol, 19 : 1; ethylacetate/hexanes, 2 : 1; ether/hexanes, 1:1. The hydroxy substituted 4 was recrystallized from pet. ether.
10. All new compounds gave satisfactory nmr and high resolution mass spectral data.

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