Zinc-promoted direct amination of nitropyridines with methoxyamine *via* vicarious nucleophilic substitution

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Direct amination of nitropyridines with methoxyamine in the presence of a stoichiometric amount of zinc(II) chloride under basic conditions proceeds to give aminonitropyridines.

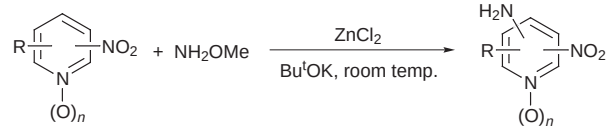
Direct amination of nitropyridine is a simple synthetic approach to aminonitropyridines, which are of great importance as intermediates of various biologically active compounds containing imidazopyridine, triazolopyridine *etc*.[1] The well-known Chichibabin amination,[2] in which the α-position of the pyridine ring is aminated by an alkali metal amide, fails to aminate nitropyridines.[3] Although oxidative direct amination of 3-nitropyridines using liquid ammonia/potassium permanganate has been reported,[4] 2- and 4-nitropyridines do not react in this system. On the other hand, alkylation of nitropyridines[5] and amination of nitrobenzenes[6] *via* vicarious nucleophilic substitution (VNS),[7] which has been extensively studied by Makosza, has been reported. However, little attention has been given to the VNS amination of nitropyridines.[8] Recently, we have found that alkoxyamines, in particular methoxyamine,[9] efficiently aminate nitrobenzenes in the presence of a copper catalyst *via* VNS.[10] As part of our investigations to develop new amination, we report here the direct amination of nitropyridines with methoxyamine in the presence of a stoichiometric amount of a zinc salt.

Treatment of 6-methoxy-3-nitropyridine with methoxyamine in the presence of a stoichiometric amount of zinc(II) chloride under strongly basic conditions in DMSO at room temperature gave 2-amino-6-methoxy-3-nitropyridine in 87% yield (Table 1, entry 1). The yield of the amination was strongly influenced by the combination of substrates and solvents used. In diethoxymethane (DEM), THF, DME, toluene and DMF, yields of 2-amino-6-methoxy-3-nitropyridine were 62, 59, 43, 19 and 0%, respectively (entries 2, 3, 4, 5 and 6). In DMF, the reaction with 2-chloro-3-nitropyridine also did not give the aminated products (entry 12). However, with 4-nitropyridine or 2-amino-3-nitropyridine, DMF was a good solvent (entries 7, 8 and 15). In general, DMSO was relatively favored in this reaction. DMSO may play a significant role in the activation of a Meisenheimer intermediate,[11] which result from nucleophilic attack of methoxyamine *ortho* or *para* to the nitro group.

4-Nitropyridine and 4-nitropyridine *N*-oxide were aminated with methoxyamine to afford 3-amino-4-nitropyridine and 3-amino-4-nitropyridine *N*-oxide, respectively (entries 7 and 8). The *N*-oxide provided the better result. The product is a precursor of 3,4-diaminopyridine, an important intermediate of many pharmaceuticals, which is presently synthesized from pyridin-4-ol *via* a tedious reaction sequence.[1c] Our methodology provides a new efficient route to 3,4-diaminopyridine from 4-nitropyridine *N*-oxide, which is cheaper than pyridin-4-ol. The use of other metallic halides as a promoter of the reaction with 4-nitropyridine *N*-oxide was examined. In the presence of titanium(IV) chloride, manganese(II) chloride, cobalt(II) chloride, nickel(II) chloride, copper(I) chloride or aluminum(III) chloride instead of zinc(II) chloride, the reaction gave 3-amino-4-nitropyridine *N*-oxide in 2, 8, 17, 0, 35 and 0% yields, respectively. The result with copper(I) chloride lacked reproducibility although it was similar to that with zinc(II) chloride. Thus zinc(II) chloride was found to be the best promoter of this amination. In the absence of zinc catalyst, the reaction did not proceed and starting material was recovered. The zinc(II) salt may act as an acceptor of an unshared electron pair from the nitrogen in pyridine ring or the oxygen of the *N*-oxide, and thus activates the substrate. A catalytic amount of zinc salt is insufficient to promote the amination since zinc also forms a coordination complex with the product as well as the substrate. This differs from the previously reported copper-catalyzed amination of nitrobenzenes with methoxyamine, in which interaction between the copper catalyst and methoxyamine was observed.[10]

An *ortho* selectivity with respect to the nitro group was observed in the case of 2-chloro-3-nitropyridine (entries 10 and 11). This selectivity is in good agreement with those observed in the amination of nitrobenzenes with methoxyamine.[10] We presume that in both cases (Scheme 1, X = C,N), *ortho* selectivity was observed because the neighboring nitro group in the σ-adduct **3**, derived from the *ortho* attack of methoxyamine on the nitroarene, assists in the elimination of the methoxy anion *via* a five-membered intermediate **4**.[6b] In contrast, Wozniak has reported that the same substrate was aminated by liquid ammonia/potassium permanganate with *para* selectivity to give mainly 6-amino-2-chloro-3-nitropyridine in 40% yield.

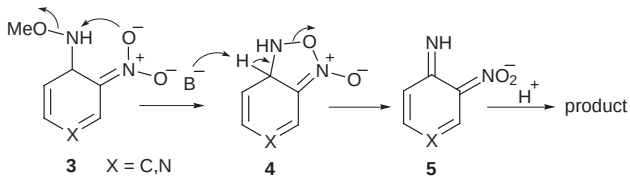
Table 1 Direct amination of nitropyridines **1** with methoxyamine[a]



1 **2**

Entry	R	*n*	Position of NO_2	Solvent	Position of amination	Yields[b] (%) of **2**
1	6-MeO	0	3	DMSO	2	87
2	6-MeO	0	3	DEM	2	62 (70)[c]
3	6-MeO	0	3	THF	2	59 (63)[c]
4	6-MeO	0	3	DME	2	43 (50)[c]
5	6-MeO	0	3	Toluene	2	19 (24)[c]
6	6-MeO	0	3	DMF	—	0
7	H	0	4	DMF	3	25
8	H	1	4	DMF	3	38
9	3-EtO	0	2	DMSO	5	7 (10)[c]
10	2-Cl	0	3	DME	4	34
11	2-Cl	0	3	DMSO	4/6	28/8
12	2-Cl	0	3	DMF	—	0
13	6-Cl	0	3	DEM	2/4	9/13
14[d]	2-NH_2	0	3	DMSO	6	58 (85)[c]
15[d]	2-NH_2	0	3	DMF	6	53
16[d]	2-NH_2	0	5	DEM	6	17 (26)[c]
17[d]	2-OH	0	5	DEM	6	9 (17)[c]

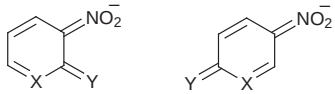
[a] Unless otherwise noted, the amination of **1** was carried out with methoxyamine (1.5 equiv.), zinc(II) chloride (1 equiv.) and potassium *tert*-butoxide (3 equiv.) in solvent at room temperature for 1–10 h. [b] Isolated yields. [c] Yields in parentheses are based on the conversion of **1**. [d] 4 equiv. of potassium *tert*-butoxide was used.



Scheme 1

He explained that the orientation of this reaction was controlled by the charge distribution.[4] However, neither charge control nor orbital control obtained by molecular calculations could explain our results.

It is noteworthy that the amination of 2-amino-3-nitropyridine, 2-amino-5-nitropyridine and 5-nitropyridin-2-ol in the presence of excess base (4 equiv.) proceeded (entries 14, 15, 16 and 17), despite no previous reports of VNS reactions of *o*- or *p*-nitroaniline and *o*- or *p*-nitrophenol. Under strongly basic conditions, *o*- or *p*-nitroaniline, *o*- or *p*-nitrophenol, 2-amino-3-nitropyridine, 2-amino-5-nitropyridine, 3-nitropyridin-2-ol and 5-nitropyridin-2-ol are easily deprotonated to form **6** or **7**. A

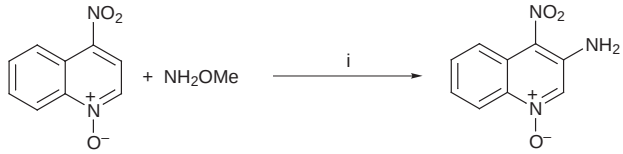


a X = C, Y = NH, O
b X = N, Y = NH, O

nucleophile cannot attack **6a** and **7a** because of the lack of an electrophilic carbon center. However nitropyridine derivatives **6b** and **7b** are susceptible to addition of a nucleophile at the α-position of the pyridine ring as well as to the Chichibabin reaction. Therefore, the amination of 2-amino-3-nitropyridine did not proceed with *ortho* selectivity but proceeded with *para* selectivity to give 2,6-diamino-3-nitropyridine (entries 14 and 15).

Similarly 4-nitroquinoline *N*-oxide was aminated, although in low yield (Scheme 2). This is important because, in spite of many reports of direct amination of bicyclic nitroarenes[12] with hydroxylamine or liquid ammonia/potassium permanganate, direct amination of 4-nitroquinoline derivatives has not been previously reported.

A typical experimental procedure is as follows. To a suspension of $ZnCl_2$ (1 mmol) and Bu^{t}OK (3 mmol) in DMSO



Scheme 2 *Reagents and conditions:* i, $ZnCl_2$, Bu^{t}OK, DMF, room temp., 21%.

(3 ml) was added dropwise a solution of the nitropyridine (1 mmol) and NH_2OMe (1.5 mmol) in DMSO (2 ml), and the mixture was stirred at room temperature. After 1–10 h, the reaction was quenched in saturated aq. NH_4Cl and the products were extracted with EtOAc. The combined organic layers were washed with water, dried, filtered and concentrated. The crude products were purified by silica gel thin layer chromatography to afford the pure aminonitropyridine.

In conclusion, we have developed a new direct amination of nitropyridines with methoxyamine in the presence of a stoichiometric amount of zinc salt. An *ortho* selectivity to the nitro group was observed, which is useful for the synthesis of many pharmaceuticals containing imidazopyridine, triazolopyridine and so on. The general, industrially practical method for direct amination of aromatic compounds has yet to be achieved, especially from the viewpoint of environmental protection. Further studies in this field are in progress in our laboratory.

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Notes and References

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