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Halogenation of Pyridinium-N-(2'-pyridyl)aminide: An Easy Synthesis of Halo-2-aminopyridines.

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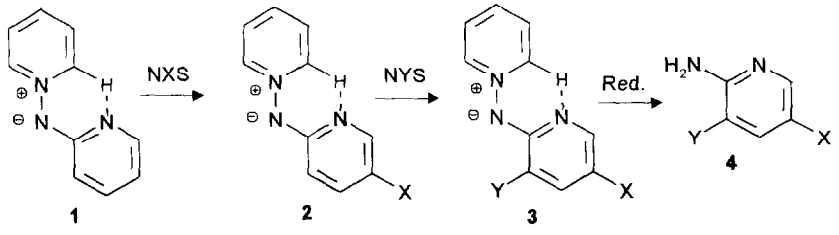
Abstract: The regioselective halogenation of pyridinium-N-(2'-pyridyl)aminide **1** with N-chloro, bromo or iodosuccinimide under mild conditions is described. The method, combined with a reduction of the N-N bond, allows an easy preparation of 5-halo and 3,5-dihalo-2-aminopyridines **4**.

It is a well-known axiom in heterocyclic chemistry that electrophilic substitution of π-deficient azines and diazines occurs with great difficulty, if at all. However, N-oxides[1] or other systems with electron-donating substituents,[2] such as amino groups, can easily be involved in electrophilic processes i.e. the halogenation. On the other side, halo-2-aminopyridines are intermediates of interest in the synthesis of relevant biologically active molecules,[3] being the direct halogenation of the corresponding 2-aminopyridine the more common method of preparation. Different halogenation systems have been employed, but in most cases the use of the aggressive molecular halogen is required.[4] More recently, new halogenation reagents such as tetrabutylammonium tribromide ($TBABr_3$) have been developed, allowing the formation of 5-bromo-2-aminopyridine in high yield.[5] N-Halosuccinimides, (NXS) have also been used as one of the mildest sources of X^+, being a safe alternative to the use of molecular halogen. They have been currently applied in the synthesis of haloarenes[6], but little attention has been paid to their use in azine ring halogenations.[7]

Pyridinium N-(2'-pyridyl)aminide (**1**) is an interesting example of a stable heterocyclic betaine, in which there is a π-deficient pyridinium fragment linked to a π-excessive 2-iminopyridine moiety. The negative charge on the exocyclic nitrogen facilitates the reaction of the pyridine nucleus towards

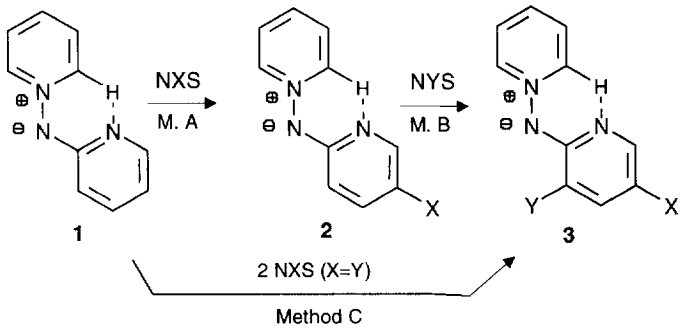


Scheme 1 NXS: N-Xsuccinimide; NYS: N-Ysuccinimide.

electrophiles. In a recent paper,[8] we had described the easy preparation of the betaine **1** from 2,4-dinitrophenyl pyridinium halide and 2-pyridylhydrazine, together with some of the reactions with halogens, but in most cases the formation of mixtures of 5′- and 3′,5′-disubstituted derivatives was not successfully controlled.

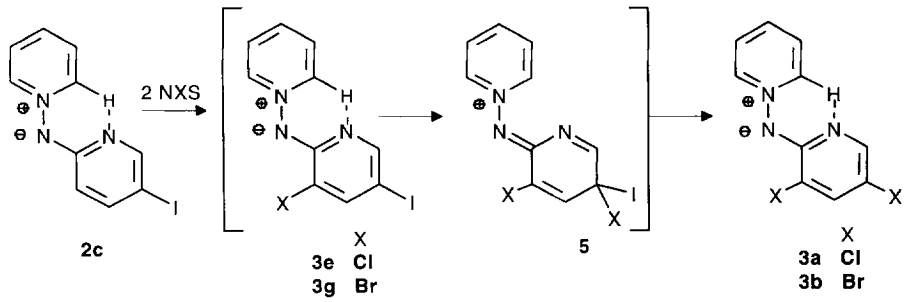
In this communication we report the use of different NXS in the preparation of haloaminides **2** and **3** (Scheme 1), which were easily reduced to obtain the 2-aminopyridines **4**.

As indicated in Scheme 2, three methods were used to prepare the haloderivatives **2** and **3**. The 5′-haloaminides **2a-c** were satisfactorily obtained by reaction, at low temperature (-20°C, with X = Cl, Br and 20°C with X = I), of equimolar amounts of **1** and the corresponding N-halosuccinimide (NXS, X = Cl, Br or I) (Method A). Traces of dihalo derivatives were detected in some reaction mixtures (X = Cl, 5%, Br, 15%, I, 0%). The haloderivatives **2** were halogenated again by treatment with an alternative NYS, at room temperature, and the dihaloaminides **3** were obtained (Method B). When the process was carried out at room temperature, using a two molar excess of NXS, the 3′,5′-dihaloaminides **3** (X = Y) were obtained in one step (Method C). Fluorination was tried with N-fluoro-N-methyl-*p*-toluenesulphonamide without success.



Scheme 2. Halogenation methods.

The use of Method B in the preparation of **3**, was not always straightforward, producing the expected compounds in the preparation of **3a, b, c** (X = Y = Cl, Br, I), **3d** (X = Cl; Y = Br) and **3e** (X= Cl Y = I), but when the method was tested to halogenate the iododerivative **2c**, ipso substitution was

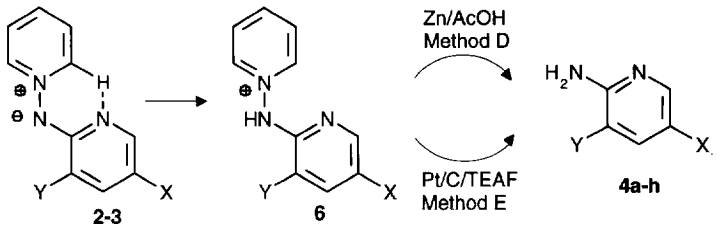


Scheme 3. Ipso substitution on **2c**.

observed, the dihaloderivatives **3a** and **b** being isolated in 50% yield. Although a free-radical substitution

cannot be discarded, the simplest explanation seems to be the process going through an electrophilic ipso substitution[9] (Scheme 3), facilitated both by the electron donating character of the aminide nitrogen and by the good electrofugal ability of the iodo substituent.

In a preceding communication,[8a] we described the N-N bond fission using Zn /acetic acid (Method



Scheme 4. Reduction of aminides **2, 3.**

Table 1. Compounds **2**, **3** and **4** obtained.

Comp.	Precursor	Reagent[a]	Method	X	Y	Yield (Lit. Yield)
2a	**1**	NCS	A	Cl	H	78
2b	**1**	NBS	A	Br	H	71(14)[b]
2c	**1**	NIS	A	I	H	90(61)[b]
3a	**2a**	NCS	B	Cl	Cl	80
3a	**1**	NCS	C	Cl	Cl	55[c]
3a	**2c**	NCS	B	Cl	Cl	55[d]
3b	**2b**	NBS	B	Br	Br	85[b]
3b	**1**	NBS	C	Br	Br	73(75)[b]
3b	**2c**	NBS	B	Br	Br	50[b,d]
3c	**2c**	NIS	B	I	I	64[b]
3c	**1**	NIS	C	I	I	61(70)[b]
3d	**2a**	NBS	B	Cl	Br	96
3e	**2a**	NIS	B[e]	Cl	I	50
3f	**2b**	NCS	B	Br	Cl	53
4a	**2a**	Zn/H^+	D	Cl	H	79[f]
4b	**3a**	Zn/H^+	D	Cl	Cl	88[f]
4c	**3b**	Zn/H^+	D	Br	H	75[g]
4c	**2b**	TEAF, Pt/C	E	Br	H	63[g]
4d	**3b**	TEAF, Pt/C	E	Br	Br	72[h]
4e	**2c**	TEAF, Pt/C	E	I	H	81[i]
4e	**3c**	TEAF, Pt/C	E	I	H	71[i]
4f	**3d**	TEAF, Pt/C	E	Cl	Br	86[j]
4g	**3e**	TEAF, Pt/C	E	Cl	H	87[f]
4h	**3f**	TEAF, Pt/C	E	Br	Cl	78[k]

[a] NCS = N-Chlorosuccinimide, NBS = N-Bromosuccinimide, NIS = N-Iodosuccinimide, TEAF = Triethylammonium formate. [b] Described in reference **8b**, by halogenation with 1 mole of the corresponding halogen.[c] The product was obtained as hydrochloride.[d] Ipso substitution.[e] The method was performed at reflux temperature, for 3 hours.[f] Described in ref. 11.[g] Described in ref. 12. [h] Described in ref. 13. [i] Described in ref. 14. [j] Described in ref. 15. [k] Described in ref. 16.

D), as a way to produce the substituted 2-aminopyridines **4** from the corresponding aminides. In that way,the 5´-chloro and 3´,5´-dichloro-2-aminopyridines **4a** and **4b** were satisfactorily obtained. However, when the method was applied to bromo or iodo derivatives, extensive dehalogenation was observed, being regioselective in the case of the aminide **3b**, where the bromo in the 3-position was selectively cleaved. As an alternative, reduction using formic acid/triethylamine, in the presence of platinum on carbon, has been described[10] as a chemoselective method for nitrogen functionalities without alteration of C-Hal bonds. The use of the method with aminides **2** and **3** (Method E) produced the expected halo-2-aminopyridines, except for iodo derivatives, in which the 3-I was easily cleaved. When the method was applied to compounds **3b** and **3d**, control of temperature -which should not be higher than 90ºC- proved to be essential to prevent cleavage of the 3-Br group in the final product. All results obtained are summarized in Table 1.

In conclusion, the pyridinium-N-(2'-pyridyl)aminide **1** can be regioselectively halogenated with N-chloro, bromo or iodosuccinimide under mild conditions. The method, combined with a reduction of the N-N bond, allows an easy preparation of 5-halo and 3,5-dihalo-2-aminopyridines **4**. The methodology is being extended to the preparation of different 2-aminoazine derivatives.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. IR spectra (KBr) were recorded using a Perkin Elmer 700 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Unity (300 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Elemental analyses were carried out on a Heraeus Rapid CHN analyzer and are within 0.4% of the theoretical values for all new compounds described.

Halogenation of pyridinium aminides. Method A: To a solution of Pyridinium N-(2´-pyridyl)aminide (**1**) (1 mmol) in dichloromethane (5 mL) stirred at -20ºC, a solution of the corresponding NXS (1 mmol) in the same solvent (10 mL) was added dropwise. After 1 hour of stirring, the solvent was evaporated and the residue was purified by column chromatography on silica gel with ethanol as eluent. The solid was recrystallized from the suitable solvent.

Method B: Similar to procedure A, except starting with the corresponding 5´-Haloaminides **2a-c**. The addition of the NYS solution was performed at room temperature (25ºC) and stirring was kept for 24 hours, except for Y = I, which needed 72 hours.

Method C: As described for procedure A, but a two molar excess of NXS was used. The addition of the NXS was performed at room temperature (25ºC) and stirring was kept for 24 hours, except for Y = I which needed 72 hours.

Reduction of pyridinium aminides. Method D. A solution of the corresponding haloaminides hydrobromides (1 mmol) in glacial acetic acid (15 mL) and Zinc dust (10 mmol) was stirred at room temperature for 5 hours. When almost all the Zn had disappeared, another portion of Zn (10 mmol) was added and the mixture was kept on stirring for 24 hours more. The resulting suspension was passed through a celite column, and eluted with acetic acid (2 x 2 mL). The eluate was evaporated *in vacuo* and the product was crystallized and identified.

Method E. Platinum on activated carbon (5%, 0.075 mg) was suspended into a solution of the corresponding aminide (0.31 mmol) in acetonitrile (3 mL) and cooled in an ice bath. Formic acid (98%, 0.5 mL) in acetonitrile (1.5 mL) was added, and then triethylamine (4.5 mL) in the same solvent (3 mL) was dropwise added. The reaction mixture was refluxed for 3-4 hours, and when cool, it was filtered. With

3b and **3d**, the temperature had to be maintained below 90ºC. The filtrate was evaporated and the residue dissolved in water, made basic with sodium carbonate and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (EtOAc/hexane 8:2). The corresponding 2-aminopyridine was purified and identified.

2a Mp 130-131° (red prisms, acetone). ^{1}H NMR: 8.90 (d, 2H, J = 5.8 Hz, H2 and H6); 7.79 (t, 1H, J =7.6 Hz, H4); 7.67 (t, 2H, J = 7.3, H3 and H5); 7.62 (d, 1H, J = 2.7 Hz, H6´); 7.24 (dd, 1H, J = 9.1 and 2.8 Hz, H4´); 6.33 (d, 1H, J = 9.1 Hz, H3´). Anal calcd for $C_{10}H_8ClN_3$: C, 58.52; H, 3.93; N, 20.49; Cl, 17.05. Found: C, 58.32; H, 3.99; N, 20.60; Cl, 17.21.

3a Mp 150-152° (orange plates, acetone/ethanol)^{1}H NMR: 8.73 (dd, 2H, J = 6.8 and 1.3 Hz, H2 and H6); 8.04 (t, 1H, J =7.6 Hz, H4); 7.81 (t, 2H, J = 6.8, H3 and H5); 7.53 (d, 1H, J = 2.3 Hz, H6´); 7.50 (d, 1H, J = 2.3 Hz, H4´). Anal calcd for $C_{10}H_7Cl_2N_3$: C, 50.21; H, 2.95; N, 17.58; Cl, 29.26. Found: C, 50.35; H, 3.09; N, 17.59; Cl, 29.46.

3d Mp 150-154° (yellow plates, dichloromethane/diethyl ether). ^{1}H NMR: 8.70 (d, 2H, J = 7.0 Hz, H2 and H6); 8.01 (at, 1H, J =7.7 Hz, H4); 7.78 (at, 2H, J = 7.7 Hz, H3 and H5); 7.59 (d, 1H, J = 2.2 Hz, H6´); 7.54 (d, 1H, J = 2.2 Hz, H4´). Anal calcd for $C_{10}H_7ClBrN_3$: C, 42.41; H, 2.49; Br, 27.80; Cl, 12.36; N, 14.85. Found C, 42.29; H, 2.30; Br, 27.65; Cl, 12.50; N, 14.53.

3e Mp 140-142° (yellow plates, acetone). ^{1}H NMR: 8.77 (d, 2H, J = 7.1 Hz, H2 and H6); 8.11 (t, 1H, J =7.3 Hz, H4); 7.90 (t, 2H, J = 7.5 Hz, H3 and H5); 7.48 (d, 1H, J = 2.3 Hz, H6´); 7.33 (d, 1H, J = 2.3 Hz, H4´). Anal calcd for $C_{10}H_7ClIN_3$: C, 36.26; H, 2.13; Cl, 10.57; I, 38.35; N, 12.69. Found C, 336.50; H, 2.32; Cl, 10.50; I, 38.13; N, 14.43.

3f Mp 156-159° (yellow plates, dichloromethane/diethyl ether). ^{1}H NMR: 8.73-8.68 (m, 2H, H2 and H6); 8.02 (t, 1H, J =7.3 Hz, H4); 7.79 (t, 2H, J = 7.3 Hz, H3 and H5); 7.56 (d, 1H, J = 2.2 Hz, H6´); 7.53 (d, 1H, J = 2.2 Hz, H4´). Anal calcd for $C_{10}H_7ClBrN_3$: C, 42.41; H, 2.49; Br, 27.80; Cl, 12.36; N, 14.85. Found C, 42.58; H, 2.40; Br, 27.68; Cl, 12.48; N, 14.97.

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