INFLUENCE OF THE 2-ARYL GROUP ON THE *IPSO* ELECTROPHILIC SUBSTITUTION PROCESS OF 2-ARYLIMIDAZO[1,2-*A*]PYRIDINES

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Abstract. A systematic study of electrophilic substitution reactions of 3-nitroso-2-arylimidazo[1,2-*a*]pyridine confirmed that the nitroso group may be *ipso*-substituted by bromine (NBS in DMF) and that bromine in turn may be substituted by the nitroso group. Electronic influence of the aryl sustituent at the imidazopyridine 2-position during the *ipso*-electrophilic process was experimentally assessed and confirmed by molecular orbital calculations. An *ipso* electrophilic substitution of bromine in 3-bromo-2-phenylimidazo[1,2-*a*]pyridine by a nitro group gave different nitro substituted imidazo[1,2-*a*]pyridine derivatives depending on the nitric acid concentration.

Introduction

The imidazo[1,2-*a*]pyridine ring system has attracted considerable attention due to the wide variety of biological applications.[1] In fact, products containing the imidazo[1,2-*a*]pyridine moiety, for example zolpidem, are already commercially marketed.[2] The system is also fluorescent.[3] On the other hand, the ease of functional group introduction followed by appropriate manipulation has made the system a valuable *synthon* for the construction of more complex derivatives.[4]

Both theoretical calculations and experimental data[5] have shown that position 3 of the imidazo[1,2-*a*]pyridine system is the most reactive towards electrophiles. There are fewer reports of the electrophilic substitution reactions when the position 3 is already occupied. The formation of 3-chloro-5-methylimidazo[1,2-*a*]pyridine by treatment of 3-bromo-5-methylimidazo[1,2-*a*]pyridine with chlorine (NCS) was explained in terms of an *ipso* electrophilic process.[6] In an early report,[7] treatment of 3-nitroso-2-phenylimidazo[1,2-*a*]pyridine with bromine/water resulted in substitution of the nitroso group by bromine. In this case, water may assist the elimination of the nitroso group. More recently, Russian chemists [8] reported the *ipso*-substitution of a nitroso group by bromine (bromine in $CHCl_3$), and the reverse process, i.e. bromine displacement by nitroso (38.4% yield), was also observed. This is an interesting result since the nitroso ion is a better leaving group than the bromonium ion.[9]

3-Nitrosoimidazopyridine derivatives have been investigated as intermediates in synthesis[10] and in biological evaluations as antiretroviral agents.[11] Interest in these compounds comes from the suggestion that they may be useful in the treatment of CNS disorders.[12] Thus, a systematic investigation on the *ipso*-electrophilic substitution reaction involving 3-nitroso- and 3-bromo-2-arylimidazo[1,2-*a*]pyridine was undertaken.

Results and Discussion

Several 2-arylimidazo[1,2-*a*]pyridines **1** were prepared following literature protocols.[13] Substituents on the aryl moiety were selected in order to study their electronic influence on the *ipso* electrophilic process. Treatment of products **1a**-e with sodium nitrite in acetic acid at room temperature afforded the 2-aryl-3-nitrosoimidazo[1,2-*a*]pyridines, **2** (Table 1).

As anticipated, nitrosation reaction times were very short for derivatives with aryl containing electron donating substituents. For example, complete nitrosation of 2-(4′-methoxyphenyl)imidazo[1,2-*a*]pyridine (**2b**) took less than one minute. By contrast, nitrosation of 2-(4′-nitrophenyl)imidazo[1,2-*a*]pyridine (**2f**) required 24 h for completion.

Table-1: Preparation of 3-nitroso-2-arylimidazo[1, 2-*a*]pyridines (**2**)

Compound	Aryl	Yield (%)	Mp (°C)	Lit. Mp (°C)
2a	C_6H_5	83	168 – 169	164 [8,14]
2b	4-$MeOC_6H_4$	76	239-241	237 – 239 [15]
2c	4-BrC_6H_4	80	227 – 229	[a]
2d	4-ClC_6H_4	75	224 - 225	227-228 [16]
2e	4-FC_6H_4	74	232 – 234	[b]
2f	4-$NO_2C_6H_4$	70	235 – 237	237 – 239 [14]

[a] Not reported in the literature. [b] Compound **2e** is a new product

Then the *ipso* electrophilic substitution reaction on the nitroso derivatives **2** was carried out using NBS in freshly distilled DMF. Indeed, the nitroso group was substituted in variable yields by bromine. The mixture was analyzed by HPLC (reverse phase conditions) to get a more accurate account of the substitution reaction. It was observed that 3-nitroso-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (**2f**) was again the least reactive substrate, and the reaction was completed by addition of a three-fold excess of NBS. The 2-aryl-3-bromoimidazo[1,2-*a*]pyridines **3** were also prepared by treating **1** with NBS in DMF. The structure of the products was confirmed by comparison of their mp's with those reported in the literature and by their spectroscopic data. Yields are summarized in Table 2.

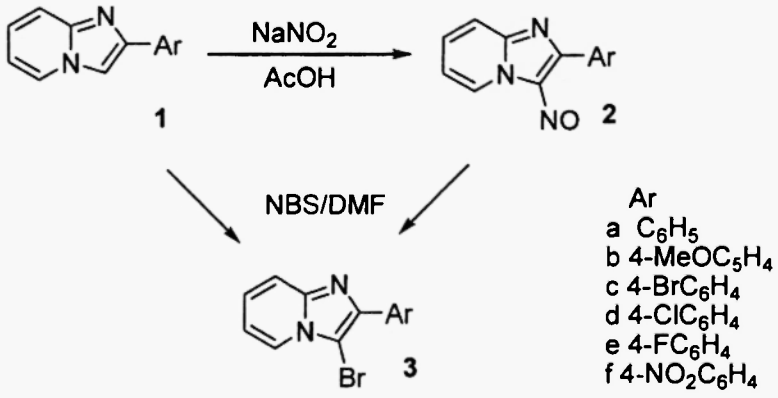


Table-2: 3-Bromo-2-arylimidazo[1,2-*a*]pyridines (**3**) from 2-arylimidazo[1,2-*a*] pyridine (**1**) and from 3-nitroso-2-arylimidazo[1,2-*a*]pyridines (**2**)

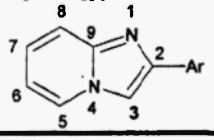
Compound	Yield (%) From imidazo[1,2-*a*]pyridine **1**	Yield (%) From nitroso derivative **2**	Mp (°C)	Lit. mp (°C)
3a	83	53	88 – 90	84-85 [17]
3b	87	79	105 – 106	101-103 [18]
3c	91	33	159 – 161	156-157 [18]
3d	75	49	146 - 148	[a]
3e	72	72	113 – 115	[b]
3f	67	40	233 – 235	223-223.5 [19]

[a] Not reported in the literature. [b] Compound **3e** is a new product.

The substitution of bromine by nitroso carried out on product **3a** was relatively inefficient.[9] However, addition of water to the reaction medium considerably improved the transformation and the nitroso derivative **2a** was isolated in 80% yield. Thus, an equilibrium is probably established within the process and displacement to either side becomes dependant on the reaction conditions.

A low level computational Hartree-Fock study (with a 3-21G basis set) was carried on 2-árylimidazo[1,2-*a*]pyridines to estimate the π-electron density at position 3, and the results are summarized in Table 3. The calculations confirmed the experimental fact that the position 3 is the most electron-rich.

Table-3: 2π-Electron populations of 2-arylimidazo[1,2-*a*]pyridines using HF/3-21G



Atom number	H	2-phenyl	2-(4'-F)Ph	2-(4'-Cl)Ph)	2-(4'-Br)Ph	2-(4'-Me)Ph	2-(4'-NO_2)Ph	2-(4'-MeO)Ph
1	1.22319	1.24238	1.24613	1.24366	1.24309	1.24363	1.23872	1.24798
2	1.02904	1.02035	1.02185	1.02912	1.02725	1.01705	1.04527	1.01199
3	**1.15772**	**1.16546**	**1.16704**	**1.15873**	**1.16003**	**1.16941**	**1.13970**	**1.17652**
4	1.52283	1.51937	1.51900	1.51917	1.51924	1.51913	1.51916	1.51902
5	0.98899	0.98872	0.98877	0.98953	0.98936	0.98843	0.99155	0.98733
6	1.06806	1.06870	1.06676	1.06429	1.06536	1.06986	1.05816	1.07145
7	0.98564	0.98064	0.97803	0.97705	0.97798	0.98113	0.97426	0.98036
8	1.01444	0.98064	1.02131	1.02042	1.02043	1.02115	1.01869	1.02290
9	1.01010	1.00004	0.99782	0.99806	0.99862	0.99994	0.99809	0.99831

In Figure 1, the HOMO also shows that the position 3 is the richest in electron density. Figure 2 shows the most stable conformation of 2-aryl-3-nitrosoimidazopyridine, as obtained from the calculations. The result agrees well with the X-ray diffraction structure of the same molecule published in reference 12. This molecular arrangement would explain the marked influence of the aromatic substituent on the *ipso* electrophilic process. Interestingly, the nitroso group adopts a sp^2 hybridization with the oxygen atom pointing toward hydrogen 5 of the imidazopyridine system. Thus, it can be suggested that the low field chemical shift observed for the H-5 atom may be caused by an anisotropic effect.

Fig. 1 **2-Phenylimidazo[1,2-*a*]pyridine HOMO. The high electron density at carbon 3 MO is notable.**

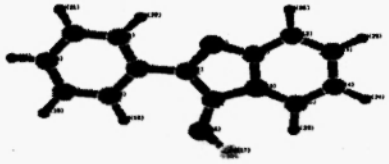
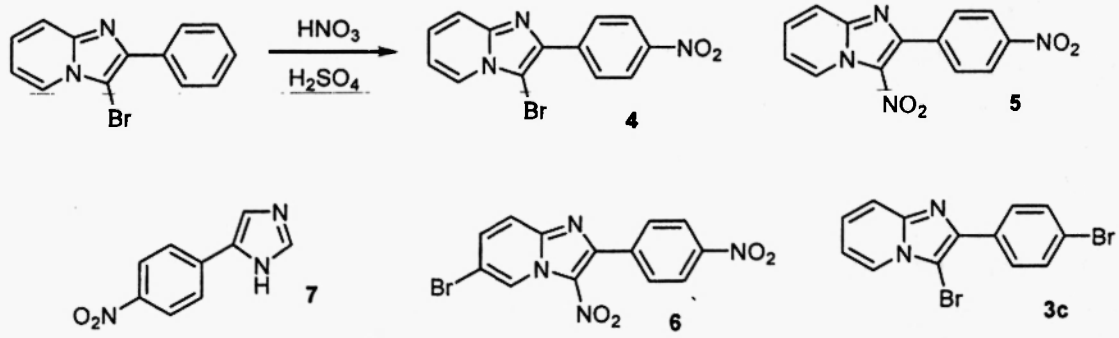


Fig. 2 **Most stable conformation obtained for 2-phenyl-3-**

3-Bromo-2-phenylimidazo[1,2-*a*]pyridine (**3a**) was then treated under typical nitration conditions (HNO_3/H_2SO_4) at low temperature. A mixture of the nitrated products, namely 2-(4′-nitrophenyl)-3-bromoimidazo[1,2-*a*]pyridine (4) and 2-(4'-nitrophenyl)-3-nitroimidazo[1,2-*a*]pyridine (**5**) was obtained together with a minor product for which structure **6** was proposed. The finding of compound 4 confirmed the observation made previously by Italian chemists that the first site of nitration is the *para*-position of the phenyl substituent [13] and such behavior is comparable to that of the phenylimidazolium ion.[14] Similarly, treatment of dibromo derivative **3c** with one equivalent of nitric acid led to the 3-bromo-4′-nitro derivative 4, whereas an excess of nitric acid (3 molar equivalents) gave a mixture of dinitro derivative **5** and traces of **6**. Compound **5** was also obtained by treatment of 4 with nitric acid (one equivalent). However, treatment of **5** with NBS did not produce compound **6**. Compound **5** is derived from the *ipso* substitution process. Analysis of the ^{1}H-NMR spectra of these compounds clearly distinguishes the H-5 resonance, which in the case of products **3** is displaced upfield (δ 8.14-8.40), whereas for product **5** it is shifted downfield (δ 9.4-9.5).



Conclusion

The position 3 of 2-arylimidazo[1,2-*a*]pyridines is reactive enough to allow *ipso* electrophilic substitution reactions (nitroso by bromine). Such process is influenced by the substituent present in the 2-aryl moiety. This was demonstrated both experimentally and by electron density calculations. Similarly, bromine may be *ipso*-substituted by nitro, with product distribution depending on acid concentration. An unexpected bromination on the electron deficient pyridine moiety of the imidazopyridine system was detected during nitration.

Experimental

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectral data were recorded al 300 and 75 MHz, respectively, using a Bruker DPX 300 MHz NMR spectrometer. Mass spectra were obtained with a Jeol JMSAX505HA instrument. The HPLC analyzes were performed on a HPCHEM apparatus using a reverse phase column ODS Ultrasphere (d = 4.6 mm, length 150.0 mm) eluting with CH_3CN/H_2O 1:1.

3-Nitroso-2-arylimidazo[1,2-*a*]pyridine. General procedure. An 2-arylimidazo[1,2-*a*]pyridine was dissolved in glacial acetic acid (1 mmol/5 mL) at room temperature. Sodium nitrite (2 equivalents) dissolved in water (1 mmol/1mL) was added to the imidazopyridine solution. The flask was placed in an ice/water bath and stirred. Progress of the reaction was monitored by tlc (ethyl acetate/hexane 1:1). At the end, the colored precipitate was collected by filtration and washed with water.

2-(4′-Bromophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (2c): a light green solid, isolated in 80% yield; mp 227-229 °C; IR (KBr): ν_{max} 3037, 1454, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6 + $(CD_3)_2CO$): δ H_5 9.88 (d, $J_{5,6}$ = 6.7, 1H), $H_{2'}$ 8.61 (d, $J_{2',3'}$ = 8.8, 2H), H_7 and H_8 8.05-7.94 (m, 2H), $H_{3'}$ 7.76 (d, $J_{2',3'}$ = 8.8, 2H) and $H_{6'}$, 7.49 (dd, $J_{5,6}$ = 6.7, $J_{6,7}$ = 6.9, 1H). MS (70 eV) m/z (%): $M+2^+$ 303 (23), M^+ 301 (23), 195 (17), 194 (100). 192 (26).

2-(4′-Fluorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (2e): a green solid, 74% yield; mp 232-234 °C; IR (KBr): ν_{max} 3062, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ H_5 9.9 (d, $J_{5,6}$ = 6.7, 1H), $H_{2'}$ 8.68 (m, 2H), H_7 and H_8 8.05-7.94 (m, 2H), H_6 7.46 (dd, $J_{5,6}$ = 6.7, $J_{6,7}$ = 6.8, $J_{6,8}$ = 1.5, 1H), and $H_{3'}$ 7.33 (dd, $J_{2',3'}$ = 7.8, $J_{3',F}$ = 8.0, 2H); MS (70 eV) m/z (%): 241 (M^+, 100), 212 (33), 210 (37), 187 (23). *Anal.* Calcd. for $C_{13}H_8N_3OF$: C, 43.63; H, 3.66. Found: C, 43.70; H, 3.45.

General procedure of the ipso-electrophilic substitution on 3-nitroso-2-arylimidazo[1,2-a]pyridines.
An 2-aryl-3-nitrosoimidazo[1,2-*a*]pyridine was dissolved in warm (50 °C) DMF. At the same temperature, $NaHCO_3$ (5 molar equivalents) was added, followed by dropwise addition of NBS dissolved in DMF. Then the temperature was raised and kept at 70 °C until reaction was completed. The mixture was allowed to cool to room temperature and then water was added. The solid formed was collected by filtration and washed with water. Following a similar procedure, treatment of the corresponding 2-arylimidazo[1,2-a]pyridine with NBS (1.15 equivalents) furnished the corresponding 2-aryl-3-bromoimidazo[1,2-*a*]pyridine.

3-Bromo-2-(4'-fluorophenyl)imidazo[1,2-*a*]pyridine (3e): a light yellowish powder; mp 113-115 °C; IR (KBr): ν_{max} 3033, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ H_5 and $H_{2'}$ 8.16-8.08 (m, 3H), H_8 7.62 (d, $J_{7,8}$ = 9.1, 1H), H_7 7.25 (m, 1H), $H_{3'}$ 7.16 (dd, $J_{2',3'}$ = 8.8 and $J_{3,F}$ = 8.8 , 2H) and H_6 6.92 (dd , $J_{5,6}$ = 6.8, $J_{6,7}$ = 6.8, 1H); ^{13}C NMR ($CDCl_3$): δ 164.3, 161.1, 145.3, 141.7, 129.5, 128.9, 125.2, 123.9, 117.5, 115.5, 115.2, 113.1, 91.4: MS (70 eV) m/z (%): 292 (M^++2, 67), 290 (M^+,67), 211 (100), 210 (52). *Anal.* Calcd. for $C_{13}H_8N_2BrF$: C, 53.60; H, 2.75. Found: C, 54.00; H, 2.78.

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