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Graphical Abstract

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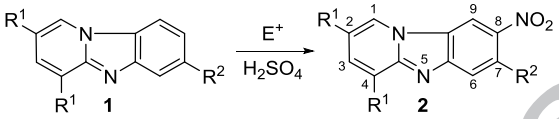

E = NO_2, Br, Cl; R_1 = H or CH_3
R_2 = NO_2, CF_3, CN, $C(O)NH_2$, $C(O)OC_2H_5$, Cl, COOH

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Reaction of substituted pyrido[1,2-*a*]benzimidazoles with electrophilic agents

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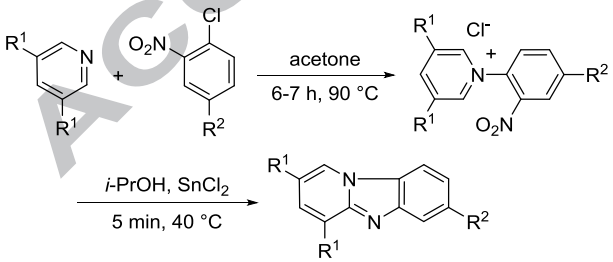
ABSTRACT

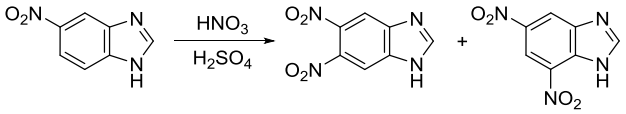
The reactivity of substituted pyrido[1,2-*a*]benzimidazoles towards electrophilic aromatic substitution has been studied. An unusual introduction of an electrophilic species at the *ortho* position with respect to an electron-withdrawing group was found, and investigated. Changing the substituent nature from a *meta* director to an *ortho*/*para* director did not alter the selectivity of electrophilic substitution. Assignment of the proton and carbon spectra for the products of S_EAr reactions were carried out using 1D and 2D NMR and the structures of selected nitro- and dinitropyrido[1,2-*a*]benzimidazoles were confirmed by single crystal X-ray diffraction.

Substituted pyrido[1,2-*a*]benzimidazoles (PBI) are an important class of heterocyclic compounds which possess a broad spectrum of biological activities that include: antibacterial,[1-4] antifungal,[5] anticancer,[6-8] antimalarial,[9] and perforin inhibition activity.[10] Therefore, it is expected that new PBIs would also show high pharmacological activity. In order to expand the structural variety of this class of compounds, we have studied the functionalization of previously reported[11] substituted pyrido[1,2-*a*]benzimidazoles by S_EAr reactions (Scheme 1).



Scheme 1. Synthesis of 2,4-R^1-7-R^2-pyrido[1,2-*a*]benzimidazoles.

It was expected that incorporation of an electrophilic moiety at the *ortho* position with respect to the electron-withdrawing substituent would be observed for azaheterocycles of this type, in a similar manner to the nitration of 5(6)-nitrobenzimidazoles (Scheme 2).[12-19]



Scheme 2. Nitration of 5(6)-nitrobenzimidazole.

Introduction of the nitrogroup was initially examined using pyrido[1,2-*a*]benzimidazole **1a** and potassium nitrate in H_2SO_4 (Table 1, entry 1). It was observed that a single dinitrosubstituted product formed within 1 hour at 20 °C in 91 % yield. This indicated that the process had occurred with high selectivity and that compound **1a** was highly reactive under electrophilic substitution conditions. In comparison, the reaction with nitrobenzimidazole occurred in 2 h under reflux conditions and was noted to have low regioselectivity.[14,15,19]

High resolution mass spectrometry allowed the determination of the molecular formula as $C_{11}H_6N_4O_4$, which corresponded to the assumed dinitro derivative (*m/z* $[M+H]^+$ 259.0468). The ^1H NMR spectrum indicated that the hydrogen atom at position 8 had been substituted by a nitro group. The observed signals, namely, a doublet at δ 9.39, a doublet at δ 7.87, a doublet of doublets of doublets at δ 7.85, and a triplet of doublets at δ 7.30, were assigned to the H^1, H^4, H^3 and H^2 protons, respectively. The singlet at δ 8.54 was assigned to H^6, while the singlet at δ 9.48 belonging to H^9 showed a NOE with the H^1.

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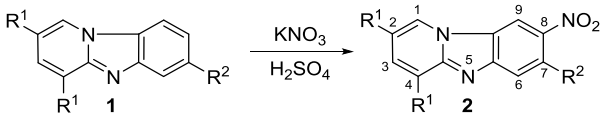
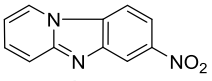
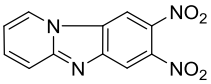
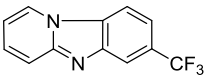
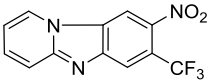
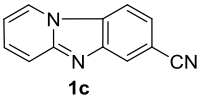
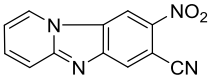
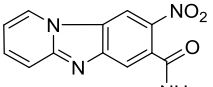
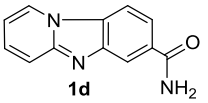
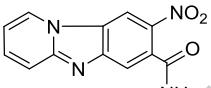
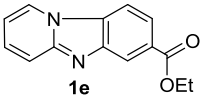
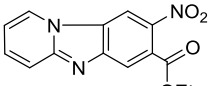
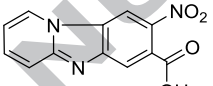
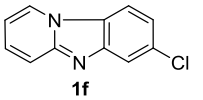
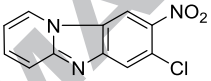
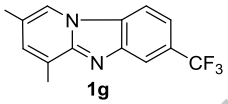
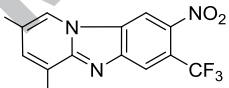
Table 1

Synthesis of 2,4-R^1-7-R^2-8-nitropyrido[1,2-*a*]benzimidazoles[a,b]



Entry	Substrate	Product	Yield[c] (%)
1	 **1a**	 **2a**	91[a]; 95[b]
2	 **1b**	 **2b**	92[a]; 96[b]
3	 **1c**	 **2c**  **2d**	49[a] (**2c**) + 44[a] (**2d**) 41[b] (**2c**) + 51[b] (**2d**)
4	 **1d**	 **2d**	88[a]; 90[b]
5	 **1e**	 **2e**  **2h**	94 (**2e**)[a] 88 (**2e**)[b] + 7 (**2h**)[b]
6	 **1f**	 **2f**	94[a]; 96[b]
7	 **1g**	 **2g**	95[a]; 97[b]

[a] Reaction conditions: substrate (1 mmol) and KNO_3 (1.1 mmol), H_2SO_4, r.t., 1 h.

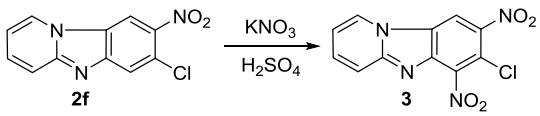
[b] Reaction conditions: substrate (1 mmol) and KNO_3 (1.1 mmol), H_2SO_4, 30 ºC, 1.5 h.

[c] Isolated yield.

Similar outcomes were observed in the cases of PBIs **1b-g** (Table 1). The product yields were generally exellent. Changing the substituent nature from *meta*- directors in **1a-e** (entries 1-5) to *ortho*/*para* directors in **1f** as well as the introduction of two methyl groups to the pyridine moiety **1g** did not change the selectivity of nitro group introduction. Nitration of non-substituted pyrido[1,2-*a*]benzimidazoles and benzimidazo[1,2-*a*]quinolines have been reported to also occurr at position 8.[20-23]

The low yield of product **2c** (49%) could be explained by partial hydrolysis of the cyano group and formation of a mixture of compounds (**2c**, **2d)**. Separation of these compounds was carried out by heating in a 2:1 isopropanol−DMF solution at reflux in which nitrile **2c** was insoluble. Increasing the reaction temperature to 30 ºC and the time to 1.5 h increased the yields of **2a,b,d,f,g** by 2-4 %, whereas the yields of **2c,e** decreased to 41% and 88%, respectively. The decrease in yield was due to increased hydrolysis of the cyano and ester functional groups, giving 8-nitropyrido[1,2-*a*]benzimidazole-7-carboxamide **2d** and 8-nitropyrido[1,2-*a*]benzimidazole-7-carboxylic acid **2h**, respectively. The hydrolysis products were isolated and their structures confirmed by NMR and HRMS.

The substituent nature at the C-7 position was found to influence the introduction of a second nitro group into nitro products **2**. 7-Chloro-6,8-dinitropyrido[1,2-*a*]benzimidazole **3** was synthesized in 6 h at 100 ºC in 94 % yield (Scheme 3). However, under similar conditions, introduction of a second nitro group onto compounds **2b-e** did not occur.



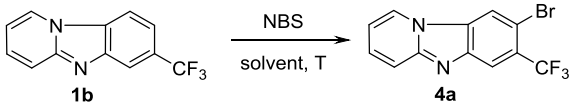
Scheme 3. Nitration of 7-chloro-8-nitropyrido[1,2-*a*]benzimidazole.

Halogenation is another reaction often used for the functionalization of aromatic compounds. Halosuccinimides in acetic acid[24-25] or sulfuric acid[26-28] are widely used for the efficient electrophilic introduction of halogen atoms onto arenes. Therefore, we began by examining synthesis of bromo-substituted PBIs by the reaction of **1b** with *N*-bromosuccinimide (NBS) in acid solvents at various temperatures (Table 2).

When the reaction was carried out in acetic acid, a considerable amount of the substrate remained unreacted. Increasing the temperature did not significantly increase the yield of the brominated PBI. The highest yield of **4a** was observed using sulfuric acid at 30 °C. Increasing the temperature decreased the amount of product formed due to side reactions. Therefore, the time was increased to 9 hours, giving **4a** in 89% yield.

According to the NMR spectroscopic data for compound **4a**, the C-8 position of the heterocyclic system was also the reactive center for bromination. These conditions were subsequently used to incorporate Br and Cl atoms onto a series of substituted PBI (Table 3).

Table 2
Screening of reaction conditions[a]

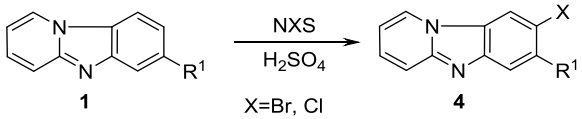


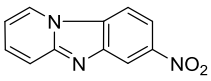
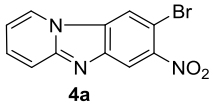
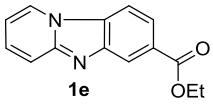
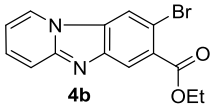
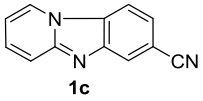
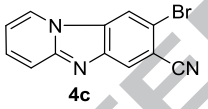
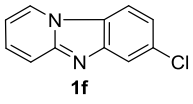
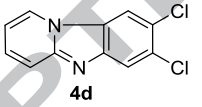
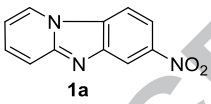
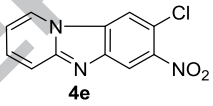
Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	AcOH	30	3	47
2	AcOH	60	3	53
3	AcOH	90	3	65
4	H_2SO_4	30	3	73
5	H_2SO_4	60	3	65
6	H_2SO_4	90	3	15
7	H_2SO_4	30	9	89

[a] Reagents and conditions: **1a** (2.0 mmol), NBS (2.2 mmol), solvent (20 mL).

[b] Isolated yield.

Table 3
Halogenation of 7-R^1-pyrido[1,2-*a*]benzimidazoles[a]



№	Substrate	Product	Yield[b] (%)
1			89
2			87
3			53
4			80
5			71

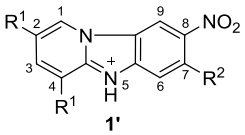
[a] Reagents and conditions: **1** (2.0 mmol), NBS or NCS (2.2 mmol), H_2SO_4 (20 mL), 30 ºC, 9 h.

[b] Isolated yield.

The high regioselectivity of the reaction of substituted pyrido[1,2-*a*]benzimidazoles with electrophilic agents was explained using an approach based on assessment of the distribution of the frontier electron density (FED) proposed by Fukui.[29] The effectiveness for the estimation of reactivity of condensed polyazaheterocycles in S_EAr reactions has been demonstrated by Breza and Milata[30] who carried out quantum-chemical modeling, in which contributions of the possible reaction centers in the HOMO of the protonated substrate were assessed. Good correlations for this parameter with the experimental data for nitration of various benzazoles were obtained.

Quantum-chemical calculations (see ESI) were carried out for PBI cations (**1'**), the formation of which occurred as a result of protonation of the imine nitrogen atom in the acidic reaction media. The distribution of electron density in the HOMO **1'** are shown in Table 4.

Table 4
HOMO frontier electron density indices of PBI's



HOMO FED*	R			
	H	NO_2	CF_3	Cl
C(1)	0.096	0.108	0.107	0.051
C(2)	0.043	0.054	0.046	0.001
C(3)	0.044	0.040	0.047	0.069
C(4)	0.092	0.109	0.103	0.020
C(6)	0.118	0.124	0.106	0.037
C(7)	0.013	0.009	0.016	0.168
C(8)	**0.230**	**0.199**	**0.227**	**0.184**
C(9)	0.107	0.095	0.091	0.002

As seen from the calculation results, the greatest coefficient of the HOMO of structure (**1'**) was at the C-8 atom. This was found to be true for both unsubstituted and substituted PBIs. Therefore, according to Fukui's theory,[29] the 8-position of the PBI was the preferred center for electrophilic attack. This agreed well with the experimental data (Table 1).

The structures of compounds **2a** (Figure 1), **1b**, and **2b** were also determined by single crystal X-ray diffraction.

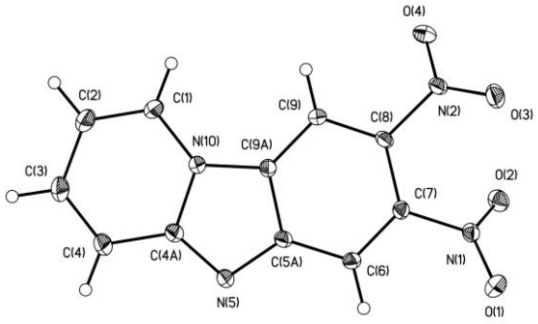


Figure 1. Molecular structure of 7,8-dinitropyrido[1,2-*a*]benzimidazole **2a.** Ellipsoids are drawn at the 50% probability level.

Single crystals of **2a** were obtained by gradual cooling of a solution of the compound in DMF or a 1:1 *i*-PrOH–DMF mixture. Yellow needle-like crystals were obtained in the first case, whereas crystallization from *i*-PrOH-DMF gave red prismatic crystals. According to X-ray diffraction data, the yellow crystals were solvates of the dinitro compound with DMF molecules. Therefore, single crystals of compounds **1b**, **2a**, and **2b** were obtained from *i*-PrOH–DMF solvent system.

The bond lengths and angles in the three compounds (**1b**, **2a**, and **2b)** were found to be very close to the mean values in substituted imidazo[1,2-*a*]pyridines (IP) (except for the C(5A)-C(9A) bond) and pyrido[1,2-*a*]benzimidazoles (PBI). The mean values were calculated from 105 (IP) and 13 (PBI) substituted heterocycles selected from the Cambridge Structural database (CSD). The smallest bond lengths in structures **1b**, **2a** and **2b** were observed between the N(5) and C(4A) atoms: 1.3303(16), 1.3351(17), 1.3396(17), respectively. The largest distances were found between the C(2)-C(3) and C(4)-C(4A) pyridine ring atoms 1.4139(18)–1.4255(18) Å respectively. Introduction of a nitro group to position 8 did not affect the bond length distribution, except for the N(5)–C(5a) bond, which was 0.013(3) and 0.008 (3) Å shorter in **2b** and **2a** than in the mono-substituted compound. The nitro group in the crystal of **2b** deviated from the plane of the heterocyclic system by 44.60 (14)°, which is most likely the result of steric interactions between the -NO_2 and -CF_3

groups. Both nitro groups in the structure of **2a** were outside the plane of the heterocyclic ring, with interplane angles being 42.80(14)° and 38.33 (14)° for the groups at positions 7 and 8. The *ortho* arrangement of the two NO_2 groups results in the O (2) ... O (3) (2.722 (2) Å) intramolecular contact between them. The molecules in all three crystal structures are involved in π-stacking to give infinite stacks in **1b** and **2b** and dimers in **2a**. The most compact packing was observed in **2b**, with a minimum C ... C distance of 3.350 (2) Å in comparison with 3.439 (2) Å in **1b** and 3.380 (2) Å in **2a**. All other shortened interatomic distances in the crystals were due to weak nonspecific interactions.

The C(8) atom of the pyrido[1,2-*a*]benzimidazole system were found to be the reactive center for attack by a nitronium cation and halonium ion, instead of C(9), as might be expected on the basis of the electronic effects of electron-withdrawing group. The nature or absence of a substituent at the benzene moiety of a PBI did not affect the selectivity of electrophilic aromatic substitution. The obtained results allowed us to refine the data that we previously reported[31] concerning the orientation of 7-(trifluoromethyl)pyrido[1,2-*a*]benzimidazole nitration.

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