2-Amino-X-Nitrobenzimidazoles as Precursors of Food-Borne Carcinogens: A New Approach to IQ Synthesis

Maroš Bella,[a] Viktor Milata,[a]* and Lyudmila I. Larina[b]

[a]Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského street 9, 812 37 Bratislava, Slovak Republic

[b]A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky street, Irkutsk 664033, Russian Federation

*E-mail: viktor.milata@stuba.sk

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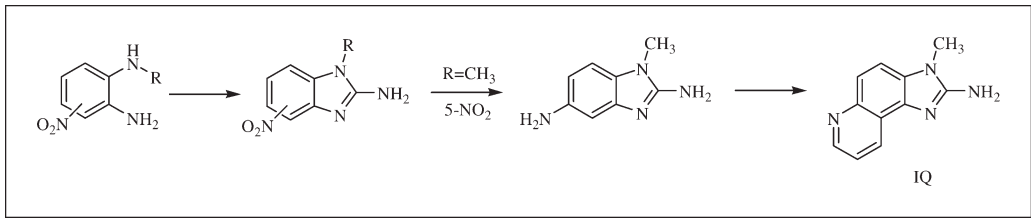

Cyclization of (non)-methylated nitro-*o*-phenylenediamines with cyanogen bromide provided nitro-substituted 2-aminobenzimidazoles in good up to excellent yields. Catalytic hydrogenation of 2-amino-1-methyl-5-nitrobenzimidazole yielded 2,5-diamino-1-methylbenzimidazole, which on treatment with 1,1,3,3-tetramethoxypropane in methanol and subsequently after removal of methanol in polyphosphoric acid afforded food-borne carcinogen 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) in 20% yield.

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INTRODUCTION

There exist many reactions leading to fused substituted pyridine ring such as Bischler–Napieralski, Camps, Combes, Conrad–Limpach, Doebner, Knorr, Meth–Cohn, Pfitzinger, and Riehm reactions [1]. 3-Substituted pyridines, especially those of them which have fused benzene ring, are suitable precursors for quinolone drugs of the nalidixic acid type [2]. Some of the reactions also yielded unsubstituted parent heterocycles such as Skraup [3], Doebner–von Miller [4], Friedländer [5], extended Gould–Jacobs reaction [6] or no-named protocols like exploitation of ynones such as propynal [7] prepared by chromium trioxide oxidation from propynol [8] enhanced by Veliev [9]; or 3-alkoxyacrolein prepared by trihalogenmethane Sydnes' method [10], 3-alkoxy/aminoacrolein like in Breitmaier's reaction [11]; or their equivalent like 1,1,3,3-tetralkoxypropane–malonodialdehyde method [12].

Compounds containing a benzimidazole moiety attached to a heterocyclic system are important chemical substances having a number of significant biological activities against several viruses such as HIV, herpes (HSV-1), influenza, and Epstein-Barr [13].

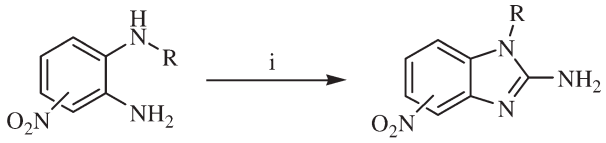
Although chemistry of imidazoquinolines is relatively old and due to this fact also well reviewed [14], special attention has been paid after discovery of carcinogenic activity of imidazoquinolines bearing aminogroup in position 2 of the imidazole ring found in thermally treated meat food [15]. In the early 1980's, a large group of heterocyclic compounds was isolated from thermally processed meats and cooked food (broiled sun-dried sardines and fishes, fried beef, hamburgers, potatoes): pyrolysates of various amino acids and proteins, with strong mutagenic and carcinogenic activity, even higher than that of aflatoxin B_1.

The simplest synthetic route for accessing these cancerogens by heterocyclic synthesis is the construction of the 2-aminoimidazole ring from corresponding precursors. Thus, 5,6- or 7,8-diaminoquinolines became important precursors for the preparation of carcerogens such as IQ and MeIQ mostly after action of cyanogen bromide [16]. Another possibility is the amination of appropriate *N*-methylbenzimidazole by sodium amide [17] or phenylazide [18]. Futher approach uses methylation of 2-aminoimidazoquinoline [19].

RESULTS AND DISCUSSION

Till now, reversal synthetic approach, for example, fusion of the pyridine ring to a 2-aminobenzimidazole ring is unknown. Within this respect, we have decided to explore the preparation of nitro-substituted 2-aminobenzimidazoles **2**, as potential precursors for food-borne carcinogens or their analogs, by convenient cyclization of nitro-*o*-phenylenediamines **1** with cyanogen bromide (Scheme 1). Synthesis of nitro-*o*-phenylenediamines **1** as starting materials for the above mentioned cyclization is summarized in this journal published by us [20]. Preparation of nonmethylated 2-aminonitrobenzimidazoles **2a**,**b** by treatment of nitro-*o*-phenylenediamines **1a**,**b** with cyanogen bromide

Scheme 1



1a-f **2a-f**

a: R = H, 3-NO_2 **a**: R = H, 4-NO_2
b: R = H, 4-NO_2 **b**: R = H, 5-NO_2
c: R = CH_3 3-NO_2 **c**: R = CH_3 4-NO_2
d: R = CH_3,4-NO_2 **d**: R = CH_3,5-NO_2
e: R = CH_3,5-NO_2 **e**: R = CH_3,6-NO_2
f: R = CH_3,6-NO_2 **f**: R = CH_3,7-NO_2

Reagents and conditions: (i) BrCN (1.4 eq.), MeOH, reflux, 2-6 h, then 30% NaOH

has already been reported [21]. Described ring closure is conducted at room temperature in methanol, methanol/water, or dioxan/water as solvents. However, to our surprise, analogical synthesis of 1-methyl-2-aminobenzimidazoles **2c–f** starting from *N*-methyl nitro-*o*-phenylenediamines **1c–f** has not been described in the literature so far. In this article, we report the cyclization of appropriate components (**1a–f** and BrCN) in refluxing methanol to afford desired products **2a–f** (Scheme 1). Compounds **2a**,**b** were isolated in about 50% yields after two crystallizations from water, but derivative **2b** was obtained as a monohydrate, which was confirmed by elemental analysis and DTA-TGA analysis, respectively. 1-Methyl-2-aminobenzimidazoles **2c–f** were obtained in good yields and high purity so no further purification was necessary.

All prepared 2-aminobenzimidazoles **2a–f** are fully characterized by multinuclear ^{1}H-, ^{13}C-, and ^{15}N-NMR spectroscopy and 2D experiments HSQC, HMBC and NOESY (Tables 1–3). Prototropic rearrangements of almost all NH-benzazoles in solutions proceed so quickly on the NMR time scale that varying solution temperatures does not cause changes in the spectra [22–25]. In these cases, the time-averaged signals are observed in the spectra. It should be noted that unlike methylated analogs, aminobenzimidazoles **2a**,**b** exist in tautomeric equilibria. The introduction of the nitro and amino groups into the benzimidazole ring leads to significant changes of chemical shifts. The ^{1}H- and ^{13}C-NMR spectra of **2a,b** compounds show broadening of some signals caused by prototropic exchange. The availability of the prototropic exchange in NH-benzimidazoles **2a**,**b** did not allow detection of nitrogen signals N-1 and N-3 in the ^{15}N-NMR spectra (Table 3). In the ^{15}N-NMR spectra of *N*-methyl-substituted benzimidazoles **2c–f** (no tautomerism), it was possible to identify all four ^{15}N-NMR signals of the benzimidazole system (Table 3).

To obtain the food-borne carcinogen **4** (IQ), we have decided to apply malonodialdehyde dimethylacetal (1,1,3,3-tetramethoxypropane) methodology to diamine **3**. This construction of the pyridine ring exploits different reactivity of two aminogroups of diamine **3**: less reactive 2-aminoimidazole versuss aniline-like type in position 5 of the benzimidazole ring. The above mentioned diamine **3** was prepared from 5-nitro-1-methyl-2-aminobenzimidazole (**2d**) by catalytic hydrogenation on Raney-nickel in methanol. Resulted diamine **3** has not been isolated but used directly into ring closure after filtering off the catalyst. After the reflux of diamine **3** with 1,1,3,3-tetramethoxypropane in methanol, the solvent was evaporated under reduced pressure and replaced by PPA. Simple heating in PPA at 120°C furnished 2-aminoimidazo[4,5-*f*]quinoline **4** in 20% yield (Scheme 2). Angular anelation of the pyridine ring was confirmed by coupling constants of the benzene ring. All spectral data and physical properties of amine **4** are in accordance with previously obtained ones [16,17b].

Presented synthesis of the nitro-substituted 2-aminobenzimidazoles **2** is direct, simple, and convenient method for the preparation of compounds **2a–f** from corresponding 1,2-phenylenediamines **1**. Also this synthesis can be extended to the synthesis of typical food carcinogen 2-aminoimidazo[4,5-*f*]quinoline **4** type of compounds, exploiting pyridine ring fusion in last reaction step using malondialdehyde method.

Table 1

^{1}H-NMR chemical shifts (ppm) and coupling constants *J* (Hz) of 2-aminobenzimidazoles **2a–f** (solvent DMSO-d_6).

Comp.	4-H	5-H	6-H	7-H	NH	N—CH_3	NH_2
2a	–	7.68 (d, ^3J = 8.1)	7.11 (dd, ^3J = 8.1; 7.3)	7.50 (d, ^3J = 7.3)	11.49	–	6.49
2b	7.93 (d, ^4J = 2.3)	–	7.87 (dd, ^3J = 8.6; ^4J = 2.3)	7.18 (d, ^3J = 8.6)	11.35	–	6.90
2c	–	7.76 (dd, ^3J = 8.3; ^4J = 1.0)	6.98 (dd, ^3J = 8.3; 7.7)	7.48 (dd, ^3J = 7.7; ^4J = 1.0)	–	3.56 s	7.30
2d	7.92 (d, ^4J = 2.2)	–	7.88 (dd, ^3J = 8.7; ^4J = 2.2)	7.31 (d, ^3J = 8.7)	–	3.58 s	6.94
2e	7.18 (d, ^3J = 8.8)	7.93 (dd, ^3J = 8.8; ^4J = 2.3)	–	8.06 (d, ^4J = 2.3)	–	3.59 s	7.20
2f	7.47 (d, ^3J = 8.8)	7.10 (dd, ^3J = 8.8; ^4J = 8.2)	7.49 (d, ^3J = 8.2)	–	–	3.51 s	6.88

Table 2

^{13}C-NMR chemical shifts (ppm) and coupling constants J_{C-H} (Hz) of 2-aminobenzimidazoles **2a–f** (solvent DMSO-d_6).

Comp.	2-C	3a-C	4-C	5-C	6-C	7-C	7a-C	N—CH_3
2a[a]	157.6	131.0[b]	146.3[b]	114.0	119.5	119.6[b]	126.9[b]	–
				^1J = 166.9	^1J = 162.5	^1J = 163.6		
2b[a]	158.8	140.0[b]	106.0	146.3[b]	116.2	111.1	139.9[b]	–
			^1J = 170.0		^1J = 166.2	^1J = 164.4		
2c	159.1	134.1 d	138.6 d	116.7 dd	116.8 d	112.8 dd	138.5 d	28.8 q
		^3J = 9.2	^3J = 7.4	^1J = 164.8; ^3J = 6.6	^1J = 165.1	^1J = 163.3; ^3J = 8.9	^3J = 6.3	^1J = 140.2
2d	158.2	140.3 m[c]	109.5 dd	142.7 d	114.7 dd	107.0 d	141.8 d	29.0 q
			^1J = 166.6; ^3J = 4.4	^3J = 5.5	^1J = 166.9; ^3J = 3.7	^1J = 165.9	^3J = 9.1	^1J = 140.1
2e	159.6	134.6[b]	113.4 d	117.8 dd	149.6 d	103.5 dd	138.9 dd	28.8 q
			^1J = 164.4	^1J = 165.9; ^3J = 3.7	^3J = 8.8	^1J = 168.1; ^3J = 4.8	^3J = 9.2; ^3J = 5.2	^1J = 140.4
2f	158.0	127.4 d	120.3 dd	120.1 d	114.9 dd	146.7 d	134.1 d	32.6 q
		^3J = 4.8	^1J = 161.8; ^3J = 8.1	^1J = 164.0	^1J = 166.2; ^3J = 7.7	^3J = 9.2	^3J = 10.3	^1J = 140.8

[a] Measured at 60°C.
[b] Broad signal.
[c] Multiplet.

EXPERIMENTAL

^{1}H-, ^{13}C-, and ^{15}N-NMR spectra of the studied compounds were recorded on Bruker DPX-400 and AV-400 spectrometers (400.13, 100.61, and 40.56 MHz, respectively) at room temperature or 60°C using DMSO-d_6 as a solvent. ^{1}H, ^{13}C, and ^{15}N chemical shifts (δ in ppm) were measured with accuracy of 0.01, 0.05, and 0.1 ppm, respectively, and referred to TMS (^{1}H, ^{13}C) and nitromethane (^{15}N). ^{1}H-^{1}H, ^{13}C-^{1}H, and ^{15}N-^{1}H coupling constants (J in Hz) are accurate to 0.1 Hz. Some ^{1}H-NMR signals were assigned using ^{1}H-^{1}H two-dimensional (2D) spectra (NOESY), whereas the ^{13}C- and ^{15}N-NMR signal assignment was made on the basis of 2D NMR methods HSQC-GP ^{1}H-^{13}C, HMBC-GP ^{1}H-^{13}C, and HMBC-GP ^{1}H-^{15}N, correspondently, and also with account data reported in refs. 22–27. Two-dimensional inverse ^{1}H-detected heteronuclear shift correlation spectra were obtained with standard pulse sequences [28]. HMBC spectra were recorded with an acquisition time of 0.2 s, a spectral width of 6000 Hz, 1024 points in the ^{1}H dimension and 17 and 20 kHz spectral width for ^{15}N and ^{13}C dimension, 512 increments and, aiming at long-range coupling constant of 5 and 10 Hz for ^{15}N and ^{13}C, respectively, with a relaxation delay of 2 s.

Melting points were determined on Koffler's apparatus using a digital thermometer (DT012C) and are uncorrected. The reaction monitoring and purity of products were accomplished by TLC on silica-gel plates (Fluka). Stains were visualized by UV light (254 and 366 nm) or by iodine vapors. Elemental analyses were determined with a Thermo Fingion CHNS(O) 1112 instrument.

Table 3

^{15}N-NMR chemical shifts (ppm) and coupling constants J_{NH} (Hz) of 2-aminobenzimidazoles **2a–f** (solvent DMSO-d_6).

Comp.	1-N	3-N	NH_2	NO_2
2a[a]	–	–	−318.4, $^1J_{NH}$ = 88.6	−8.8
2b[a]	–	–	−317.2, $^1J_{NH}$ = 88.4	−7.8
2c	−262.5	−186.5	−316.8, $^1J_{NH}$ = 88.9	−8.6
2d	−258.1	−186.3	−319.5, $^1J_{NH}$ = 87.9	−7.6
2e	−261.6	−181.2	−315.9, $^1J_{NH}$ = 89.6	−7.9
2f	−260.1	−186.6	−320.8, $^1J_{NH}$ = 87.4	−8.9

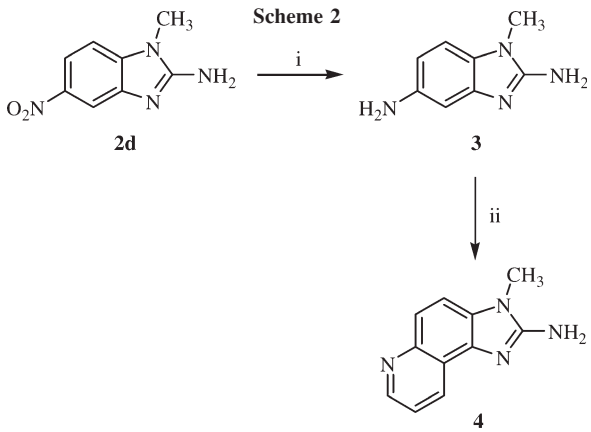
[a] We cannot accumulate these signals on account of prototropy exchange in solution, and the ^{15}N-NMR chemical shifts can be in field of 185–205 ppm, see refs. 22–24.

General procedure for preparation of 2-amino-4-nitrobenzimidazole (2a) and 2-amino-5-nitrobenzimidazole (2b). A mixture of nitro-*o*-phenylenediamine **1a** or **1b** (1.0 g, 6.52 mmol) and cyanogen bromide (0.95 g, 8.96 mmol, 1.4 eq) was refluxed in methanol (25 mL) for 4 h (TLC $CHCl_3$:MeOH 10:1). After cooling, reaction mixture was alkalized with 30% NaOH solution, and solvent was evaporated under reduced pressure. The rest was recrystallized twice from water with addition of charcoal to afford compounds **2a** (0.62 g, 55%) and **2b** (0.65 g, 53%), respectively.

2-Amino-4-nitrobenzimidazole (2a) Yellow-orange needles, mp 282–287°C ([21b] 275–279°C). Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.39; N, 31.45. Found: C, 47.21; H, 3.37; N, 31.49.

2-Amino-5-nitrobenzimidazole monohydrate (2b) Yellow solid, mp 126–130°C ([21a] 222–223°C (hemihydrate)). Anal. Calcd. for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.91; H, 4.09; N, 28.58.

Scheme 2



Reagents and conditions: (i) H_2, RaNi, MeOH, r.t., overnight; (ii) 1,1,3,3-tetramethoxypropane, MeOH, reflux, 2h; removal of MeOH then PPA, 120 °C, 30 min. 20%

General procedure for preparation of methylated 2-aminonitrobenzimidazoles (2c–f). A mixture of *N*-methylated nitro-*o*-phenylenediamine **1c–f** (0.25 g, 1.5 mmol) and cyanogen bromide (0.22 g, 2.1 mmol, 1.4 eq) was refluxed in methanol (7.5 mL) until all starting material was consumed (2–6 h, TLC $CHCl_3$:MeOH 10:1). After cooling, reaction mixture was charcoaled, filtered into a beaker, and alkalized with 30% NaOH solution. Separated crystals or solids were collected by suction, washed with water to remove rests of inorganic materials, and dried to give compounds **2c** (0.27 g, 94%) **2d** (0.27 g, 94%), **2e** (0.24 g, 83%), and **2f** (0.23 g, 80%), respectively.

2-Amino-1-methyl-4-nitrobenzimidazole (2c) Golden-brown needles, mp 300–304°C. Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.10; H, 4.18; N, 29.19.

2-Amino-1-methyl-5-nitrobenzimidazole (2d) Yellow solid, mp 342–350°C. Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.96; H, 4.21; N, 29.13.

2-Amino-1-methyl-6-nitrobenzimidazole (2e) Yellow solid, mp 305–309°C. Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.09; H, 4.17; N, 29.12.

2-Amino-1-methyl-7-nitrobenzimidazole (2f) Brown solid, mp 290–296°C. Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.13; H, 4.16; N, 29.17.

2-Amino-3-methylimidazo[4,5-f]quinoline (4) To a suspension of 2-aminobenzimidazole **2d** (1.92 g, 10 mmol) in methanol (100 mL), freshly activated Raney nickel catalyst (prepared from 4 g of RaNi alloy) was added, and reaction mixture was stirred vigorously under hydrogen atmosphere (200 kPa) overnight. After the reduction was complete, 1,1,3,3-tetramethoxypropane (2.46 g, 15 mmol) was added, and the catalyst was filtered off. The filtrate was slowly heated with magnetic stirring in an oil bath till the temperature in the oil bath reached 100°C within 2 h. Thereafter reaction mixture was allowed to cool, and the solvent was evaporated under reduced pressure. To the rest, polyphosphoric acid (40 g) was added, and the resulting mixture was mechanically stirred with a glass rod while the temperature in the oil bath was raised to 120°C and stirring continued at this temperature for 30 min. After cooling, reaction mixture was diluted with ice-water (150 mL), charcoaled, filtered into a beaker, and alkalized with concentrated ammonia. This mixture was extracted with toluene (3 × 50 mL) and ethyl acetate (3 × 50 mL). Combined extracts were dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was recrystallized from acetone-methanol to give white crystals, 0.4 g (20%), mp > 300°C ([17b] >320°C); NMR spectra were in accordance with previously published ones [16,17b].

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