Hydrogenation on palladium-containing granulated catalysts
3.* Synthesis of aminobenzimidazoles by catalytic hydrogenation of dinitroanilines

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Efficient hydrogenation of *o*-aminonitrobenzenes on palladium-containing granulated carbon catalysts in carboxylic acid solutions was accompanied by cyclization into aminobenzimidazoles. A simple hydrogenation reactor with a fixed gauze holding a reusable granulated catalyst was designed. Acylated and sulfonylated 4(7)-aminobenzimidazoles were obtained. In terms of electronic and geometrical parameters, they are close analogs of biologically active imidazo[1,5,4-*e*,*f*][1,5]benzodiazepines.

Key words: hydrogenation, aminobenzimidazoles, *o*-aminonitrobenzenes, dinitroanilines, palladium-containing granulated catalysts.

Polyaminobenzene derivatives and their cyclization products (aminobenzimidazoles) are of considerable interest for various areas of clinical chemistry because of their structural similarity with purine bases. For instance, retigabine (a 1,2,4-triaminobenzene derivative) is an efficient anticonvulsant blocking ion channels.[2]

4-Sulfonylamino derivatives of 1,4-diamino-2,6-dinitrobenzenes are highly effective against sleeping sickness (*African trypanosomiasis*).[3]

4-Aminobenzimidazoles are used in the synthesis of many biologically active compounds, *e.g.*, imidazo[1,5,4-*e*,*f*][1,5]benzodiazepines, which are HIV-1 replication inhibitors.[4] 5-Aminobenzimidazoles[5] and their sulfonylamino derivatives are inhibitors of thrombases[6] and promising antagonists of NMDA receptors.[7]

A usual route to benzimidazoles containing an amino group in different positions of the benzene ring involves cyclization of nitrophenylenediamines followed by hydrogenation of the nitro group[5,6,8,9] or direct synthesis from appropriate triaminobenzenes.[10] However, the starting triaminobenzenes are readily oxidized in air and a major part of the product becomes lost during isolation when prepared by hydrogenation of dinitroanilines on both tin dichloride[11—13] and the Raney nickel.[10] In addition, triaminobenzenes form complexes with tin and nickel salts, which also hinders to obtain them in the individual state, especially when tin salts are removed with hydrogen sulfide.[13]

The same problems complicate the synthesis of aromatic and heterocyclic polyamines *via* hydrogenation of polyaminonitrobenzenes and fused furoxanes.[14]

Here we studied the possibility of "one pot" synthesis of aminobenzimidazoles from accessible dinitroanilines through catalytic hydrogenation of dinitroanilines to triaminobenzenes followed by their condensation with carboxylic acid derivatives.

Dinitroanilines **1a,b** were hydrogenated in the presence of a catalyst (2—5% Pd on granulated graphite Sibunit) in specially designed reactors[15] ensuring contact between a solution to be hydrogenated and a fixed layer of the catalyst. Earlier,[1] we have demonstrated that mononitroarenes and -heteroarenes can be smoothly hydrogenated on a fixed catalyst layer.

In this study, we used a reactor (Fig. 1) in which contact of the catalyst with a substrate to be hydrogenated is ensured by motion of its solution through a stainless steel box suspended in the reactor. A magnet was sealed in a teflon holder under the box and stirring in the stainless steel autoclave was carried out with a common magnetic stirrer. Such a reactor design is convenient for hydrogenation of small amounts of substrates in small autoclaves (40—700 mL).

To prevent deactivation of the catalyst, the reacting solution should be periodically removed from the reactor avoiding penetration of the ambient air and the reactor should be filled with a solvent. In this case, the catalyst can be recycled.

Hydrogenation of aminonitrobenzenes on supported palladium catalysts prevents complexation between the

* For Part 2, see Ref. 1.

† Deceased.

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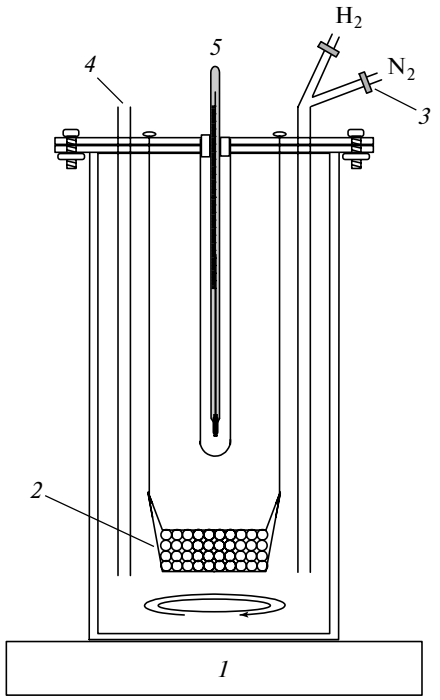


Fig. 1. The hydrogenation reactor (V = 40—400 cm^3): (*1*) magnetic stirring bar, (*2*) stainless steel box with Pd/Sibunit granules, (*3*) valve, (*4*) discharge outlet, (*5*) thermometer.

resulting polyaminobenzenes and heavy metals, thus facilitating isolation of the reaction products. As the consequence, the yields of the target triaminobenzenes **2a,b** were increased to 90%.

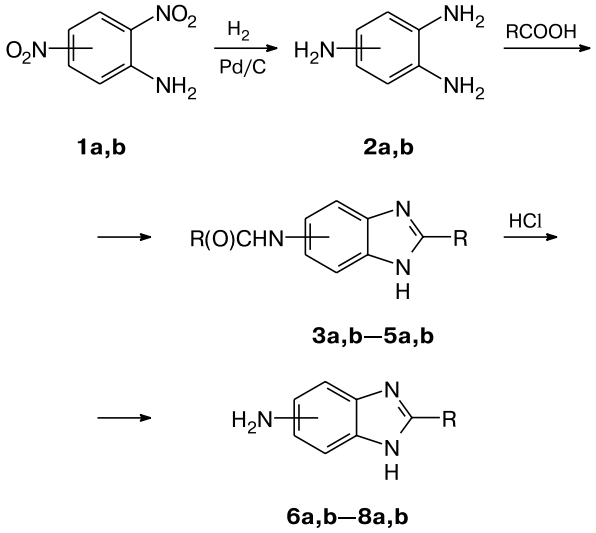
In hydrogenation, a mineral acid (*e.g.*, HCl in ethanol) can be added to a substrate. Protonated amino groups impart electron-withdrawing properties to the aromatic ring and are resistant to oxidation, which increases the yields of products isolated as dihydrochlorides.

In neutral alcoholic media, the target triaminobenzenes decompose rapidly: by more than 50% in an hour after the hydrogenation. Subsequent cyclization of dihydrochlorides of compounds **2** in carboxylic acids give the corresponding NH-acylated benzimidazoles **3**. The acyl group can be easily removed in boiling 10% HCl (Scheme 1).

Hydrogenation of 2,4- and 2,6-dinitroanilines in concentrated formic and acetic acids followed by heating the reaction mixture in the autoclave afforded the corresponding aminobenzimidazoles.

Both reaction steps can be easily combined in a hydrogenation reactor to prevent air contact; the total yields of aminobenzimidazoles are usually higher than in step-by-step isolation of intermediate products. In addition, the final products can be isolated in air. Apparently, acylation of the amino groups formed in the hydrogenation stabilizes an intermediate product and stimulates hydrogenation because of diminished electron-donating properties of the aromatic ring.

Scheme 1



1: 4-NO_2 (**a**), 6-NO_2 (**b**); **2:** 4-NH_2 (**a**), 3-NH_2 (**b**)

Compound	R	NHC(O)R	Compound	R	Position of the NH_2 group
3a	H	5-NHC(O)H	**6a**	H	5
3b	H	4-NHC(O)H	**6b**	H	4
4a	Me	5-NHC(O)Me	**7a**	Me	5
4b	Me	4-NHC(O)Me	**7b**	Me	4
5a	CF_3	5-NHC(O)CF_3	**8a**	CF_3	5
5b	CF_3	4-NHC(O)CF_3	**8b**	CF_3	4

As shown earlier,[16] hydrogenation of *o*-nitroanilines in acids in the presence of 10% Pd on powdered carbon also results in cyclization leading, however, to aminobenzimidazole *N*-oxide.

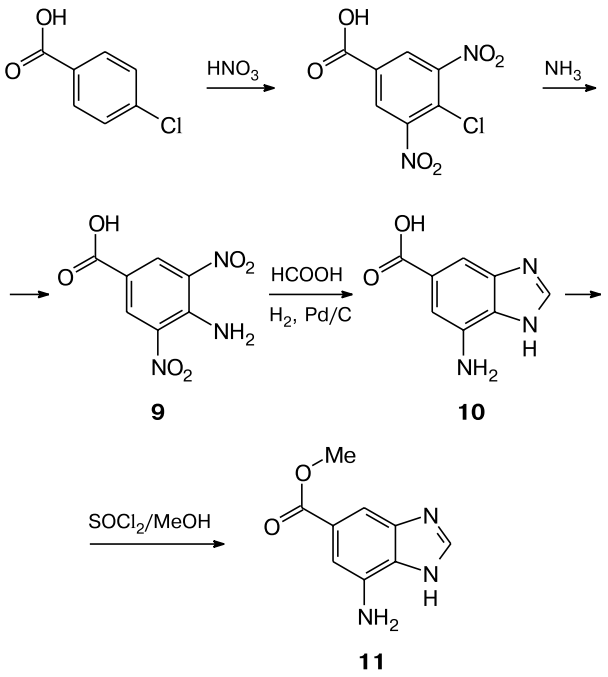
In the case of hardly available or high-melting carboxylic acids, their solutions with hydrogen chloride can be employed for simultaneous hydrogenation, cyclization, and deacylation. It should be emphasized that 4(7)-aminobenzimidazoles are much more stable in storage than 5(6)-aminobenzimidazoles, which are best isolated and stored as *N*-acylated derivatives.

Dinitroanilines can be hydrogenated in other cyclization solvents (*e.g.*, ethyl acetate). In this way, we obtained 4(7)-amino-2-methylbenzimidazole from 2,6-dinitroaniline (reactor charges up to 200 g).

This method is convenient for the synthesis of more complex 4-aminobenzimidazole-6-carboxylic acids (Scheme 2). Esterification of acid **10** was carried out in methanol in the presence of $SOCl_2$.

The starting 4-amino-3,5-dinitrobenzoic acid (**9**) was prepared by nitration of 4-chlorobenzoic acid followed by treatment with ammonia (for substitution of an amino group for the Cl atom) according to a slightly modified procedure.[17] The total yield was 80%.

Scheme 2



9 **10** **11**

This method is preparatively more convenient and substantially more efficient (97% yield) than a three-step synthesis involving hydrogenation of one nitro group with $SnCl_2$, cyclization, and hydrogenation of the other nitro group.[17]

Recently,[18] cyclization of 4-amino-3,5-dinitrobenzoate derivatives has been effected in one step in the presence of $SnCl_2$. However, the yields of 4-aminobenzimidazolecarboxylates did not exceed 30%, the benzene ring always containing a chlorine atom.

Starting from 2,4-dinitroaniline (**1a**), one can obtain hardly available 1,2,3,4-diimidazobenzene (**14**) in only three steps (Scheme 3).

We found that nitration of acylated aminobenzimidazoles **3a** and **4a** mainly occurs at position 4, yielding compounds **12** and **13** and small amounts of the 7-nitro isomer. This is in conflict with previous data[19] on exclusive nitration of 5-acetamido-2-methylbenzimidazole at position 6. The nitration of 4-acetamidobenzimidazole (**17a**) proceeded nonselectively (at positions 5 and 7) to give a 9 : 5 mixture of isomers **15a** and **15b**, respectively, in a high total yield (78%). The structure of isomer **15b** was proved by homonuclear $^1H—^1H$ NOESY data. The spectrum shows a cross-peak due to a coupling of the NH proton of the acetamido group with the H(5) proton of the aromatic ring. This cross-peak was not observed for isomer **15a** because a nitro group is *ortho* to the acetamido fragment.

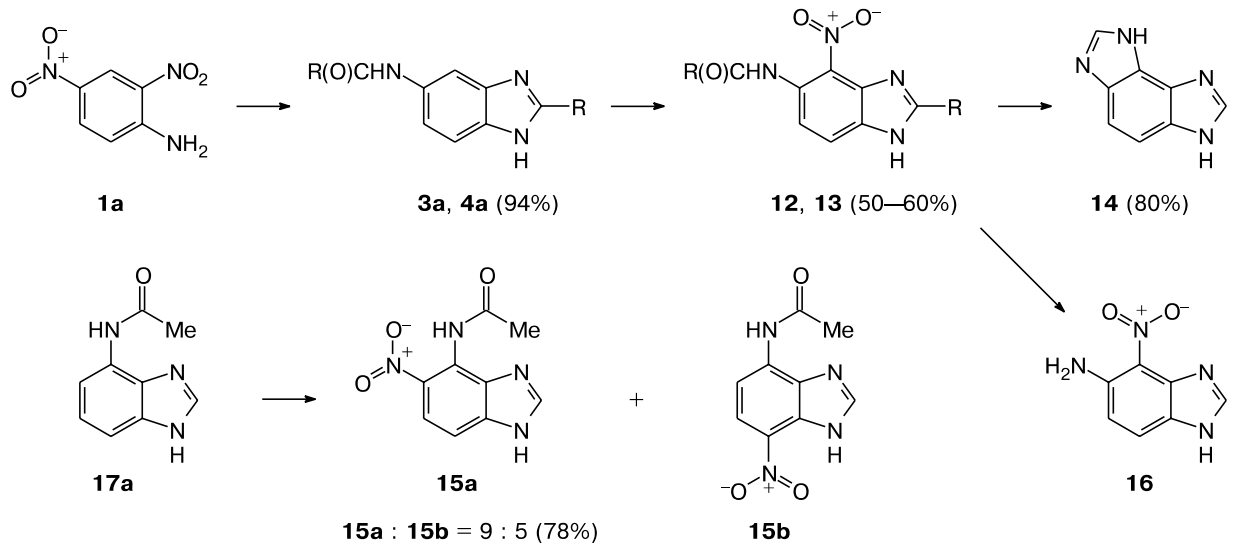
Acylation of 4(7)-aminobenzimidazoles simultaneously involved two centers (the amino group and the ring N atom), regardless of the stoichiometric ratio (Scheme 4). The acyl group at the ring N atom was easily eliminated by heating in $Et_3N—MeOH$.

In the case of 2-trifluoromethyl derivatives **19**, the acyl substituent at the ring N atom was eliminated more easily (even on re-heating of the reaction mixture).

The resulting 4-acylaminobenzimidazoles **17** can be stabilized by intramolecular hydrogen bonding that closes a seven-membered ring. In terms of electronic and geometrical parameters, they are close analogs of imidazo[1,5,4-*e*,*f*][1,5]benzodiazepines and hence can exhibit similar biological activity.[4]

Sulfonylated 4-aminobenzimidazoles **18**, which are analogs of highly biologically active compounds,[7,20] can

Scheme 3

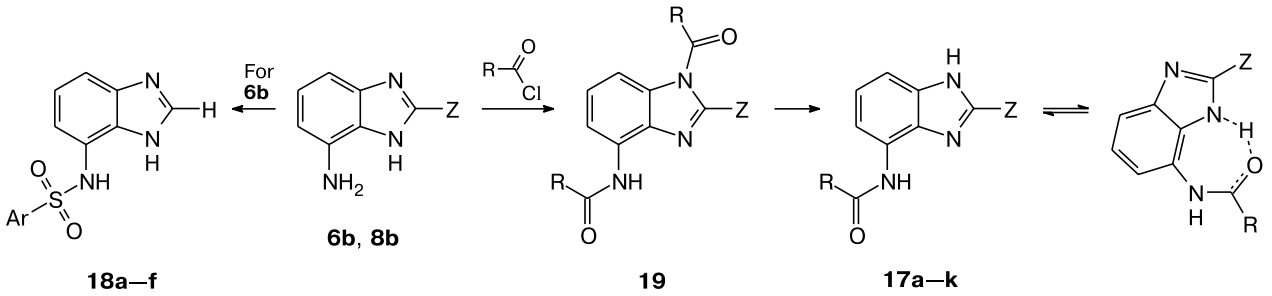


1a **3a**, **4a** (94%) **12**, **13** (50—60%) **14** (80%)

17a **15a** **15a** : **15b** = 9 : 5 (78%) **15b** **16**

R = H (**3a**, **12**), Me (**4a**, **13**)

Scheme 4



6b: Z = H; **8b:** Z = CF_3
17: Z = H; R = Me (**a**), 3-NCC_6H_4 (**b**), 4-NCC_6H_4 (**c**), 2-F-4-BrC_6H_3 (**d**), 4-$PhOC_6H_4$ (**e**);
Z = CF_3; R = Ph (**f**), 3,4-$OCH_2OC_6H_3$ (**g**), 2-furyl (**h**), 2-thienyl (**i**), 4-$CF_3C_6H_4$ (**j**), 3-$CF_3C_6H_4$ (**k**)
18: Ar = 3-Cl-4-FC_6H_3 (**a**), 3-$CF_3OC_6H_4$ (**b**), 4-$CF_3OC_6H_4$ (**c**), 4-NCC_6H_4 (**d**), 4-$PhOC_6H_4$ (**e**), 2-F-4-BrC_6H_3 (**f**)

be easily obtained by monosulfonylation of the amino group.

To conclude, we synthesized over 50 various 4(7)-acyl- and 4(7)-sulfonylaminobenzimidazoles*. Some of them can suppress cell proliferation by breaking *in vivo* polymerization of the cell tubulin according to our recent[21] test system on sea urchin embryos.

4(7)-Sulfonylaminobenzimidazoles **18** can be regarded as analogs of 4-sulfonylamino derivatives of 1,4-diamino-2,6-dinitrobenzenes, which inhibit tubulin polymerization in curing *African trypanosomiasis*.[3]

Experimental

NMR spectra were recorded on a Bruker DRX500 instrument (500.13 MHz) in DMSO-d_6 (unless otherwise specified). Mass spectra were recorded on Kratos MS-30 and Finnigan MAT instruments (direct inlet probe, EI, 70 eV). The course of the reactions was monitored by TLC on Silufol UV-254 plates.

* The comprehensive list of the structures and their spectra have been published on the website: www.chemblock.com (a search for compounds by structural fragment is possible).

2,6-Dinitroaniline was prepared according to a known procedure.[22] Commercial reagents were used. 2—5% Pd/Sibunit catalysts were prepared and regenerated as described earlier.[15]

The yields and physicochemical and spectroscopic characteristics of the compounds obtained are given in Tables 1 and 2.

4-Chloro-3,5-dinitrobenzoic acid (*cf.* Ref. 17). 4-Chlorobenzoic acid (20 g) was dissolved in H_2SO_4 (d = 1.835, 300 mL) at 70—100 °C and KNO_3 (66 g) was added. The reaction mixture was heated to 130—140 °C, kept for 1.5 h, cooled to ~20 °C, and poured onto ice. The yield of 4-chloro-3,5-dinitrobenzoic acid was 26 g (82.5%), m.p. 153—156 °C (*cf.* Ref. 17).

4-Amino-3,5-dinitrobenzoic acid (9) (*cf.* Ref. 17). 4-Chloro-3,5-dinitrobenzoic acid (97.6 g) was dissolved in methanol (200 mL) and aqueous 24% NH_3 (600 mL) was gradually added. The reaction mixture was stirred at ~20 °C for 2.5 h, refluxed for 3 h, and left for ~14 h. The precipitate that formed was filtered off and the filtrate was evaporated to dryness. The solid residue was combined with the precipitate and water (50 mL) and HCl (50 mL) were added. On stirring, the precipitate was filtered off and washed with water to neutral reaction. The yield of 4-amino-3,5-dinitrobenzoic acid (**9**) was 87 g (97%).[17]

Hydrogenation of dinitroanilines 1a,b in a solution of HCl in methanol (general procedure *A*). A stainless steel autoclave was charged with a solution of dinitroaniline **1a** or **1b** (20 mmol) in

Table 1. Reaction conditions (temperature (T), reaction time (t), pressure (P), and solvent) and the yields, melting points, spectroscopic characteristics, and elemental analysis data for compounds **2**—**8** and **10**—**16**

Compound	Yield (%) (method)	Reaction conditions				M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ (J/Hz)	MS, m/z (I_{rel} (%))
		T/°C	t/h	P/atm	Solvent		C	H	N			
2a··2HCl	81 (*A*)	50	4	60	MeOH	164—167[10] (EtOH)	—	—	—	—	6.77 (d, 1 H, H(3), J = 1.5); 6.95 (dd, 1 H, H(5), J = 8, J = 1.5); 7.17 (d, 1 H, H(6), J = 8); 5.50—8.10[a]	123 $[M]^+$ (100), 95 (83)
2b··2HCl	86 (*A*)	50	4	60	MeOH	>300[12] (H_2O—HCl)	—	—	—	—	6.75 (t, 1 H, H(5), J = 8.5); 7.25 (d, 2 H, H(4), H(6), J = 8.5); 6.00—8.50[a]	123 $[M]^+$ (100), 95 (33)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%) (method)	Reaction conditions				M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)	MS, *m*/*z* (I_{rel} (%))
		T/°C	*t*/h	*P*/atm	Solvent		C	H	N			
3a··HCO$_2$H	94 (*B*) 91 (*C*)	80 Reflux	4 3	70 —	HCOOH HCOOH	280—282 (H_2O)	52.38 52.17	4.42 4.38	20.87 20.28	$C_9H_9N_3O_3$	—[b]	161 [M]$^+$ (100), 133 (81), 105 (44)
3b	78 (*C*)	Reflux	2.5	—	HCOOH	173—174 (H_2O), 173—175[4,23]	—	—	—	—	See Ref. 4	See Ref. 4
4a	72.5 (*B*)	60—65	4	40	AcOH	239—241 (10% HCl)	63.54 63.47	5.81 5.86	22.28 22.21	$C_{10}H_{11}N_3O$	2.00 (s, 3 H, MeCO); 3.35 (s, 3 H, 2-Me); 7.18 (d, 1 H, H(4), *J* = 8.6); 7.31 (d, 1 H, H(5), *J* = 8.6); 7.92 (s, 1 H, H(7)); 9.78 (br.s, 1 H, AcNH); 12.00 (br.s, 1 H, H(1))	189 [M]$^+$ (64), 148 (21.6), 147 (100), 105 (21.4)
4b	83 (*B*)	60—65	4	40	AcOH	92—99[23,24] (H_2O—HCl)	63.38 63.47	5.75 5.86	22.30 22.21	$C_{10}H_{11}N_3O$	—	—
5a	85 (*C*)	Reflux	3	—	CF_3COOH	200 (decomp.)	40.48 40.42	1.65 1.70	14.16 14.14	$C_{10}H_5F_6N_3O$	7.60 (br.s, 1 H, H(4)); 7.75 (br.s, 1 H, H(5)); 8.15 (s, 1 H, H(7)); 11.42 (s, 1 H, CF_3CONH); 14.00 (br.s,1 H, H(1))	297 [M]$^+$ (100), 278 (15), 227 (19), 200 (87), 100 (61)
5b	63 (*C*)	Reflux	3	—	CF_3COOH	180—185	40.38 40.42	1.72 1.70	14.17 14.14	$C_{10}H_5F_6N_3O$	7.43 (t, 1 H, H(5), *J* = 8.4); 7.52 (d, 1 H, H(4), *J* = 8.4); 7.67 (d, 1 H, H(6), *J* = 8.4); 11.38 (s, 1 H, CF_3CONH); 14.08 (br.s, 1 H, H(1))	297 [M]$^+$ (46), 228 (100), 200 (30)
6a··2HCl	57.5 (*B*)	60—65 Reflux	4 2.5 1	40 — —	HCOOH HCOOH 10% HCl	223—225 (aqueous EtOH)	40.88 40.80	4.51 4.40	20.43 20.39	$C_7H_9Cl_2N_3$	7.33 (d, 1 H, H(2), *J* = 8.6); 7.62 (s, 1 H, H(7)); 7.81 (d, 1 H, H(5), *J* = 8.6); 9.43 (s, 1 H, H(1))	133 [M]$^+$ (100), 105 (39)
6b··2HCl	75 (*B*)	60—65 Reflux	4 2.5 1	40 — —	HCOOH HCOOH 10% HCl	229—231 (H_2O—HCl)	40.69 40.80	4.31 4.40	20.44 20.39	$C_7H_9Cl_2N_3$	6.10 (br.s, 3 H, N^+H_3); 6.72 (d, 1 H, H(6), *J* = 8.6); 6.96 (d, 1 H, H(4), *J* = 8.6); 7.24 (t, 1 H, H(5), *J* = 8.6); 9.40 (s, 1 H, H(2)); 14.87 (br.s, 1 H, H(1))	133 [M]$^+$ (100), 105 (24)
7a··2HCl	90 (*C*)	Reflux	3 1	— —	AcOH 10% HCl	>280[8] (decomp.) (MeOH)	43.57 43.65	5.07 5.04	19.19 19.09	$C_8H_{11}Cl_2N_3$	2.78 (s, 1 H, 2-Me); 7.33 (d, 1 H, H(6), *J* = 8.2); 7.62 (s, 1 H, H(4)); 7.72 (d, 1 H, H(7), *J* = 8.2); 9.00—13.00[a]	147 [M]$^+$ (100), 146 (73), 119 (16), 105 (51)
7b··2HCl	84 (*C*)	Reflux	1.5 1	— —	CF_3COOH 10% HCl	—[c]	43.74 43.65	5.01 5.04	19.20 19.09	$C_8H_{11}Cl_2N_3$	2.75 (s, 3 H, Me); 6.72 (d, 1 H, H(5), *J* = 8.2); 6.91 (d, 1 H, H(7), *J* = 8.2); 7.18 (t, 1 H, H(6), *J* = 8.2); 5.85—7.35[a]	147 [M]$^+$ (100), 146 (34), 105 (15)
8a··2HCl	87 (*C*)	Reflux	3 1	— —	CF_3COOH 10% HCl	275—295 (decomp.), 290[9]	35.17 35.06	2.83 2.94	15.44 15.33	$C_8H_8Cl_2F_3N_3$	7.40 (s, 1 H, H (7)); 7.90 (d, 2 H, H(4), H(5), *J* = 8); 10.20—10.5 (d)	201 [M]$^+$ (100), 181 (68), 154 (8), 105 (22)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%) (method)	Reaction conditions				M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ (*J*/Hz)	MS, *m*/*z* (I_{rel} (%))
		T/°C	*t*/h	*P*/atm	Solvent		C	H	N			
8b· ·2HCl	76 (*C*)	Reflux 1	3 —	— —	CF_3COOH 10% HCl	>350 (H_2O—HCl)	35.21 35.06	2.87 2.94	15.38 15.33	$C_8H_8Cl_2F_3N_3$	7.21 (d, 1 H, H(5), *J* = 8); 7.36 (t, 1 H, H(6), *J* = 8); 7.52 (d, 1 H, H(7), *J* = 8); 5.10—10.00[a]	201 $[M]^+$ (100), 181 (31), 162 (36), 105 (13)
10· ·2 HCl	97 (*B*)	70	4	70	HCOOH	260—263 (MeOH)	38.48 38.42	3.69 3.63	16.75 16.80	$C_8H_9Cl_2N_3O_2$	7.27 (s, 1 H, H(4)); 7.46 (s, 1 H, H(6)); 9.50 (s, 1 H, H(2)); 5.20—9.90[a]	177 $[M]^+$ (100), 105 (44)
11· ·2HCl	81	Reflux	6	—	MeOH, $SOCl_2$	141—142 (MeOH)	40.42 40.32	4.17 4.14	15.75 15.67	$C_9H_{11}Cl_3N_2O_3$	3.72 (s, 3 H, OMe); 7.29 (s, 1 H, H(4)); 7.48 (s, 1 H, H(6)); 9.50 (s, 1 H, H(2)); 7.20—11.50[a]	191 $[M]^+$ (100), 160 (44), 133 (35), 132 (55), 105 (17)
12	80	0	2	—	100% HNO_3	>300	46.21 46.06	2.87 2.93	39.33 39.32	$C_8H_6N_4O_3$	7.90 (br.s, 1 H, H(6)); 8.00 (d, 1 H, H(7), *J* = 8.4); 8.36 (s, 1 H, H(2)); 8.48, 8.50 (2 br.s, 1 H, COH)[d]; 10.42, 10.67 (2 br.s, 1 H, NH)[d]; 13.00 (br.s, 1 H, H(1))	206 $[M]^+$ (43), 178 (100), 132 (87), 105 (74)
13	50	0	2	—	100% HNO_3	289—291 (H_2O)	51.32 51.28	4.35 4.30	29.80 29.90	$C_{10}H_{10}N_4O_3$	2.10 (s, 3 H, Me); 2.45 (s, 3 H, MeCO); 7.40 (br.s, 1 H, H(4)); 7.80 (br.s, 1 H, H(5)); 10.23 (br.s, 1 H, NH); 12.70 (br.s, 1 H, H(1))	234 $[M]^+$ (28), 192 (100), 146 (70), 104 (15)
14	80 (*B*)	20 Reflux	5 2 1	30 — —	HCOOH HCOOH 10% HCl	321—324 (decomp.) (water—acetone)	53.18 53.16	3.94 3.82	44.36 44.28	$C_8H_6N_4$	7.76 (s, 2 H, H(8), H(9)); 9.10 (s, 2 H, H(2), H(6)); 13.50 (br.s, 2 H, H(1), H(5))	158 $[M]^+$ (100), 131 (12), 104 (12)
15a	50	20	1.5	—	100% HNO_3	300 (decomp.)	49.21 49.09	3.75 3.66	31.74 31.81	$C_9H_8N_4O_3$	2.12 (br.s, 3 H, Me); 7.50, 7.65 (br.s, 1 H, H(4))[d]; 7.83 (br.s, 1 H, H(5)); 8.49 (s, 1 H, H(2)); 10.15, 10.45 (2 br.s, 1 H, MeCONH)[d]; 12.80, 13.00 (2 br.s, 1 H, H(1))[d]	220 $[M]^+$ (13), 178 (100), 148 (45), 132 (50), 105 (70)
15b	29	20	1.5	—	100% HNO_3	230—240 (decomp.)	49.21 49.09	3.75 3.66	31.74 31.81	$C_9H_8N_4O_3$	2.29 (s, 3 H, Me); 8.15 (d, 1 H, H(5), *J* = 8.2); 8.28 (d, 1 H, H(6), *J* = 8.2); 8.40 (s, 1 H, H(2)); 10.45 (s, 1 H, MeCONH); 13.30 (s, 1 H, H(1))	220 $[M]^+$ (32), 178 (100), 148 (51), 132 (50), 105 (67)
16	88	Reflux	0.5	—	10% HCl	260 (subl.)	47.25 47.19	3.46 3.39	15.75 15.67	$C_7H_6N_4O_2$	6.81 (d, 1 H, H(6), *J* = 7.6); 7.71 (d, 1 H, H(7), *J* = 7.6); 7.82 (br.s, 2 H, NH_2); 7.89 (s, 1 H, H(2)); 12.56 (br.s, 1 H, H(1))	178 $[M]^+$ (100), 132 (55), 105 (42)

[a] The signals for the NH_2 group and sometimes for the H(1) atom are distributed between these values as a smooth convex line.
[b] The NMR spectrum is poorly resolved because of an impurity of formic acid in different stoichiometric ratios.
[c] No definite melting point.[23,24]
[d] The H(1) ↔ H(3) tautomerism.

Table 2. Yields, physicochemical and spectroscopic characteristics, and elemental analysis data for compounds **17—19**

Compound	Yield (%)	R_f	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)	MS, *m*/*z* (I_{rel} (%))
				C	H	N			
17a	67	0.55 (AcOEt—MeOH, 4 : 1)	260	61.70 61.75	5.11 5.18	23.87 23.99	$C_9H_9N_3O$	2.18 (s, 3 H, MeCO); 7.11 (t, 1 H, H(5), *J* = 7.9); 7.28 (d, 1 H, H(4), *J* = 7.9); 7.67 (br.s, 1 H, H(6)); 8.14 (s, 1 H, H(2)); 9.68 (s, 1 H, MeCONH); 12.21 (br.s, 1 H, H(1))	175 $[M]^+$ (43), 160 (3), 133 (100)
17b	47	0.4 (AcOEt—MeOH, 9 : 1)	125—127 (MeCN)	68.66 68.70	3.77 3.84	21.44 21.37	$C_{15}H_{10}N_4O$	7.21 (t, 1 H, H(5), *J* = 7.5); 7.46 (br.s, 2 H, H(4), H(6)); 7.78 (t, 1 H, H(5′), *J* = 8.6); 8.08 (d, 1 H, H(6′), *J* = 8.6); 8.20 (s, 1 H, H(2′)); 8.33 (d, 1 H, H(4′), *J* = 8.6); 8.48 (s, 1 H, H(2)); 10.20, 10.40 (2 br.s, 1 H, ArCONH)*; 12.10, 12.50 (2 br.s, 1 H, H(1))*	262 $[M]^+$ (50), 233 (22), 130 (98), 105 (40), 102 (100)
17c	44	0.4 (AcOEt—MeOH, 9 : 1)	242—243	68.77 68.70	3.91 3.84	21.45 21.37	$C_{15}H_{10}N_4O$	7.18 (t, 1 H, H(5), *J* = 7.5); 7.48 (d, 1 H, H(4), *J* = 7.5); 7.57 (d, 1 H, H(6), *J* = 7.5); 8.01 (d, 2 H, H(2′), H(6′), *J* = 8.6): 8.18 (d, 2 H, H(3′), H(5′), *J* = 8.6); 8.20 (s, 1 H, H(2)); 10.23 (s, 1 H, ArNH); 12.29 (br.s, 1 H, H(1))	262 $[M]^+$ (100), 233 (47), 160 (24), 130 (82)
17d**	26	0.8 (C_6H_6—AcOEt, 1 : 1)	230	50.38 50.32	2.65 2.71	12.66 12.58	$C_{14}H_9BrFN_3O$	7.21 (t, 1 H, H(5), *J* = 7.6); 7.38 (d, 1 H, H(4), *J* = 7.6); 7.57 (d, 1 H, H(3′), *J* = 10); 7.82 (br.s, 2 H, H(5′), H(6′)); 8.21 (s, 1 H, H(2)); 10.06 (s, 1 H, ArNH); 12.38 (br.s, 1 H, H(1))	335 $[M]^+$ (44), 333 (56), 307 (10), 305 (14), 205 (100), 203 (100), 177 (20), 175 (22), 132 (8)
17e	27	0.9 (C_6H_6—AcOEt, 1 : 1)	95—98	72.80 72.93	4.61 4.59	12.84 12.76	$C_{20}H_{15}N_3O_2$	7.12—8.07 (m, 12 H, H(4)—H(6), $C_6H_5OC_6H_4$); 8.20 (s, 1 H, H(2)); 9.92 (s, 1 H, ArCONH); 12.28 (br.s, 1 H, H (1))	329 $[M]^+$ (30), 197 (100), 160 (4), 141 (28), 132 (22)
17f	96	—	221—224	55.08 55.02	3.28 3.30	13.87 13.77	$C_{15}H_{10}F_3N_3O$	7.38 (t, 1 H, H(5), *J* = 8); 7.55—8.15 (m, 7 H, H(5), H(6), Ph); 10.19 (s, 1 H, ArCONH); 13.78 (br.s, 1 H, H(1))	305 $[M]^+$ (34.7), 105 (100), 79 (22), 77 (82)
17g	60	—	195—197 (water—EtOH)	55.10 55.02	2.81 2.89	12.13 12.03	$C_{16}H_{10}F_3N_3O_3$	6.12 (s, 2 H, OCH_2O); 7.08 (d, 1 H, H(4), *J* = 8); 7.37 (t, 1 H, H(5), *J* = 8); 7.54 (d, 1 H, H(6), *J* = 8); 7.58 (s, 1 H, H(6′)); 7.65 (d, 1 H, H(3′), *J* = 8.1); 7.72 (br.s, 1 H, H(2′)); 10.00 (s, 1 H, ArCONH); 13.75 (br.s, 1 H, H(1))	349 $[M]^+$ (17), 149 (100), 174 (17)
17h	99	—	182—184	52.81 52.89	2.75 2.73	14.27 14.23	$C_{13}H_8F_3N_3O_2$	6.72 (br.s, 1 H, H(4)); 7.38—7.84 (m, 5 H, H(5), H(6), H(2′)—H(4′)); 8.00 (s, 1 H, H(2)); 9.82 (br.s, 1 H, ArCONH); 13.90 (br.s, 1 H, H(1))	295 $[M]^+$ (100), 276 (3), 95 (55)
17i	75	—	163—166	50.27 50.16	2.51 2.59	13.50 13.50	$C_{13}H_8F_3N_3OS$	7.24 (br.s, 1 H, H(4′)); 7.36 (br.s, 1 H, H(3′)); 7.53 (br.s, 1 H, H(2′)); 7.67 (br.s, 1 H, H(4)); 7.85(s, 1 H, H(5)); 8.06 (s, 1 H, H(6)); 10.12 (s, 1 H, ArCONH); 13.74 (br.s, 1 H, H(1))	311 $[M]^+$ (49), 128 (10), 111 (100)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	R_f	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)	MS, *m*/*z* (I_{rel} (%))
				C	H	N			
17j	61	—	181—183 (water—EtOH)	51.44 51.48	2.48 2.43	11.27 11.26	$C_{16}H_9F_6N_3O$	7.38 (t, 1 H, H(5), *J* = 8); 7.56 (d, 1 H, H(4), *J* = 8); 7.72 (d, 1 H, H(6), *J* = 8); 7.92 (d, 2 H, H(2′), H(6′), *J* = 8.3); 8.25 (d, 2 H, H(3′), H(5′), *J* = 8.3); 10.40 (s, 1 H, ArCONH); 13.73 (br.s, 1 H, H(1))	373 $[M]^+$ (19), 354 (3), 173 (100), 145 (50)
17k	66	—	195—197 (water—EtOH)	51.41 51.48	2.51 2.43	11.31 11.26	$C_{16}H_9F_6N_3O$	7.31 (t, 1 H, H(5), *J* = 8); 7.54 (d, 1 H, H(4), *J* = 8); 7.66 (br.s, 1 H, H(6)); 7.78 (t, 1 H, H(5′), *J* = 8.3); 7.93 (d, 1 H, H(6′), *J* = 8.3); 8.29 (d, 1 H, H(4′), *J* = 8.3); 8.33 (s, 1 H, H(2)); 10.50 (s, 1 H, ArCONH); 13.72 (br.s, 1 H, H(1))	373 $[M]^+$ (19), 173 (100), 145 (51)
18a	78	0.64 (AcOEt—MeOH, 9 : 1)	234—236 (Pr^iOH)	47.85 47.93	2.70 2.78	12.93 12.90	$C_{13}H_9ClFN_3O_2S$	6.98 (br.s, 1 H, H(5)); 7.10 (m, 1 H, H(4)); 7.36 (br.s, 1 H, H(6)); 7.55 (t, 1 H, H(5′), *J* = 8); 7.73 (br.s, 1 H, H(4′)); 7.97 (br.s, 1 H, H(6′)); 8.12 (s, 1 H, H(2)); 10.06 (br.s, 1 H, $ArSO_2NH$); 12.20, 12.43 (2 s, 1 H, H(1))*	327 $[M]^+$ (19), 325 (50), 262 (12), 260 (34), 132 (100), 129 (18), 105 (42)
18b	93	0.80 (AcOEt—MeOH, 19 : 1)	149—151 (Pr^iOH—C_6H_6)	47.16 47.06	2.88 2.82	11.78 11.76	$C_{14}H_{10}F_3N_3O_3S$	6.90 (d, 1 H, H(4), *J* = 7.9); 7.05 (t, 1 H, H(5), *J* = 7.9); 7.32 (d, 1 H, H(6), *J* = 7.9); 7.58—7.80 (m, 4 H, H(2′), H(4′), H(5′), H(6′)); 8.14 (s, 1 H, H(2)); 12.44 (br.s, 1 H, H (1))	357 $[M]^+$ (18), 293 (6), 209 (22), 132 (100), 105 (37)
18c	78	0.75 (AcOEt—MeOH, 19 : 1)	226—228 (Pr^iOH)	47.09 47.06	2.93 2.82	11.94 11.76	$C_{14}H_{10}F_3N_3O_3S$	6.88 (br.s, 1 H, H(4)); 7.08 (t, 1 H, H(5), *J* = 7.9); 7.33 (d, 1 H, H(6), *J* = 7.9); 7.48 (d, 2 H, H(2′), H(6′), *J* = 8.6); 7.87 (d, 2 H, H(3′), H(5′), *J* = 8.6); 8.12 (s, 1 H, H(2)); 10.12 (br.s, 1 H, $ArSO_2NH$); 12.35 (br.s, 1 H, H(1))	357 $[M]^+$ (3), 293 (28), 194 (20), 132 (100)
18d	74	0.76 (AcOEt—MeOH, 19 : 1)	218—220 (C_6H_6)	56.28 56.36	3.42 3.38	18.85 18.78	$C_{14}H_{10}N_4O_2S$	6.92 (d, 1 H, H(4), *J* = 7.9); 7.08 (t, 1 H, H(5), *J* = 7.9); 7.36 (d, 1 H, H(6), *J* = 7.9); 7.92—8.00 (m, 4 H, H(2′), H(3′), H(5′), H(6′)); 8.13 (s, 1 H, H(2)); 12.42 (br.s, 1 H, H (1))	298 $[M]^+$ (22), 233 (25), 132 (100), 105 (73)
18e	94	0.75 (AcOEt—MeOH, 19 : 1)	240—242 (EtOH)	62.54 62.45	4.19 4.14	11.62 11.50	$C_{19}H_{15}N_3O_3S$	6.80 (d, 1 H, H(4), *J* = 7.5); 6.87—7.10 (m, 5 H, H (2″), H(3″), H(4″), H(5″), H(6″)); 7.24 (t, 1 H, H(5), *J* = 7.5); 7.32 (d, 1 H, H(6), *J* = 7.5); 7.45 (t, 2 H, H(3′), H(5′), *J* = 8); 7.80 (d, 2 H, H(2′), H(6′), *J* = 8); 8.15 (s, 1 H, H(2)); 10.00 (br.s, 1 H, $ArSO_2NH$); 12.30 (br.s, 1 H, H (1))	365 $[M]^+$ (12), 301 (24), 141 (20), 132 (100), 105 (47)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	R_f	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)	MS, *m/z* (I_{rel} (%))
				C	H	N			
18f	73	0.8 (AcOEt—MeOH, 19 : 1)	245—247 (EtOH)	42.28 / 42.17	2.57 / 2.45	11.47 / 11.35	$C_{13}H_9BrFN_3O_2S$	6.92 (d, 1 H, H(4), *J* = 7.5); 7.10 (t, 1 H, H(5), *J* = 7.5); 7.38 (d, 1 H, H(6), *J* = 7.5); 7.52 (d, 1 H, H(3′), *J* = 8); 7.67 (t, 1 H, H(2), *J* = 8); 7.72 (d, 1 H, H (5′), *J* = 10); 8.18 (s, 1 H, H(2)); 12.38 (br.s, 1 H, H (1))	371 $[M]^+$ (8), 369 (8), 351 (34), 349 (34), 287 (55), 285 (55), 179 (96), 132 (80), 105 (89), 76 (100)
19a	86	0.57 (AcOEt—MeOH, 9 : 1)	138—140	60.89 / 60.77	5.11 / 5.06	19.21 / 19.33	$C_{11}H_{11}N_3O_2$	2.18 (s, 3 H, 1-MeCO); 2.73 (s, 3 H, 4-MeCO); 7.34 (t, 1 H, H(6), *J* = 8.4); 7.83 (d, 1 H, H(7), *J* = 8.4); 8.07 (d, 1 H, H(5), *J* = 8.4); 8.85 (s, 1 H, H(2)); 9.88 (s, 1 H, MeCONH)	217 $[M]^+$ (61), 175 (75), 160 (33), 133 (100)

* The NH(1) ↔ NH(3) tautomerism.

** Isolated by column chromatography (dry column, C_6H_6—AcOEt). A diacyl derivative (0.107 g) with R_f 0.9 (C_6H_6—AcOEt, 1 : 1) and the starting acid (0.062 g) with R_f 0.7 (C_6H_6—AcOEt, 1 : 1) were also detected.

methanol (70 mL) and aqueous HCl (10 mL). Hydrogenation was carried out over a catalyst (2% Pd/C, 1 mL) placed in a gauze container. The container was immersed for 4—6 h (depending on the temperature and the pressure) in the solution stirred with a magnetic stirring bar. The hydrogen pressure was varied from 40 to 70 atm at 50—60 °C. On cooling, the catalyst was withdrawn from the reactor, the reaction mixture was filtered to remove catalyst particles, and the solvent was removed in a rotary evaporator. The residue was recrystallized from ethanol or dilute HCl. The yields of triaminobenzenes **2a,b** as dihydrochlorides were 80—85% (for more soluble nitrobenzenes, we employed more concentrated (3—4 times) solutions). For catalyst recycling, the gauze with the catalyst was placed in the same solvent as in the hydrogenation.

Hydrogenation and cyclization with carboxylic acids (general procedure *B*). A stainless steel autoclave (650 mL) was charged with dinitroaniline **1a** or **1b** (0.1 mol) and a carboxylic acid (200 mL). A gauze container containing a 2% Pd/C catalyst (7—10 mL) was placed in the autoclave in such a way that the catalyst was immersed in solution. The dinitroaniline was hydrogenated at 20—80 °C and a hydrogen pressure up to 30—80 atm for 4—6 h. The reaction mixture was stirred with a magnetic stirring bar. The autoclave was discharged, the reaction mixture was refluxed for 6 h to complete the cyclization, and the excess of the carboxylic acid was removed in a rotary evaporator. Recrystallization of the residue gave *N*-acylated benzimidazoles **3a,b**—**5a,b** (see Table 1). To eliminate the acetyl group, the product was dissolved in 10% HCl (200 mL), refluxed for 1 h, and cooled. The solvent was removed in a rotary evaporator. Dihydrochlorides of aminobenzimidazoles **6a,b**—**8a,b** were recrystallized from 10% HCl or ethanol.

Selected syntheses according to general procedure ***B*** are given below.

5(6)-Formamidobenzimidazole formate (3a · HCOOH). 2,4-Dinitroaniline (**1a**) (3.66 g, 20 mmol) in 85% formic acid (20 mL) was hydrogenated in a stainless steel autoclave over a 2% Pd/C catalyst for 4 h (hydrogen pressure 70—80 atm, 80 °C). The autoclave was discharged and the reaction mixture was refluxed for 6 h to complete the cyclization. The solvent was removed in a rotary evaporator in water aspirator vacuum and the residual acid was removed with methanol (2×5 mL). The resulting gray crystals were dissolved in methanol (20 mL) and refluxed with activated carbon for 1 h. The solution was filtered and evaporated to dryness to give grayish crystals (4.00 g, 94%). The compound obtained was used without additional purification for subsequent nitration.

For large amounts of the reagents, we employed an autoclave with a turbostirrer and a catalyst (50 mL) fixed in a net holder (see Ref. 15). For instance, hydrogenation of 2,4-dinitroaniline (90 g) in formic acid (450 mL) for 17 h (hydrogen pressure 55—70 atm, 50—70 °C) gave 5(6)-formamidobenzimidazole formate **3a** · HCOOH (97 g, 93%).

5(6)-Aminobenzimidazole (6a), dihydrochloride. 2,4-Dinitroaniline (**1a**) (2.34 g, 12.8 mmol) in 85% formic acid (20 mL) was hydrogenated in a stainless steel autoclave over a 5% Pd/C catalyst for 6 h (hydrogen pressure 40 atm, 60—65 °C). The autoclave was discharged and the reaction mixture was refluxed for 6 h to complete the cyclization. The solvent was removed in a rotary evaporator in water aspirator vacuum and the residual acid was removed with methanol (2×5 mL). The resulting gray crystals were dissolved in 10% HCl (20 mL) and the solution was refluxed for 30 min and evaporated to dryness. The black crystals that formed were twice refluxed in ethanol (10 mL) and filtered off to give grayish crystals (1.52 g, 57.5%).

7-Aminobenzimidazole-5-carboxylic acid (10), dihydrochloride. An autoclave was charged with 4-amino-3,5-dinitrobenzoic acid (**9**) (20 g, 88 mmol), 80% formic acid (250 mL), and a 2% Pd/C catalyst (10 mL). The autoclave was purged with hydrogen up to a pressure of 80 atm. The reaction mixture was stirred at ~20 °C for 2 h, heated to 70 °C, and kept at a hydrogen pressure of 70 atm for 4 h until the hydrogen absorption ceased. The reaction mixture was discharged hot and the formic acid was removed in a rotary evaporator. The residue was dissolved in 10% HCl (200 mL) and the resulting solution was refluxed for 1 h,

cooled, and concentrated in a rotary evaporator. The yield of 4(7)-aminobenzimidazole-5(6)-carboxylic acid (**10**) as dihydrochloride was 21.3 g (97%), m.p. 260—263 °C (MeOH).

Methyl 4(7)-aminobenzimidazole-5-carboxylate (11), dihydrochloride. A four-neck flask fitted with a stirrer, a condenser, a thermometer, and a dropping funnel was charged with methanol (250 mL) and the dihydrochloride of (4)7-aminobenzimidazole-5(6)-carboxylic acid (**10**) (21 g). Thionyl chloride (48 g) was added dropwise to the resulting ice-cooled (5—7 °C) suspension and the solution was refluxed for 6 h and left for ~14 h. The solvent was partially removed and the precipitate that formed was filtered off. The yield of methyl (4)7-aminobenzimidazole-5(6)-carboxylate (**11**) as dihydrochloride was 18 g (81%).

Cyclization of triaminobenzenes with carboxylic acids (general procedure *C*). Triaminobenzene dihydrochloride (0.1 mol) was dissolved in a carboxylic acid (100 mL) (HCOOH, AcOH, or CF_3COOH). The resulting solution was refluxed for 3—15 h and concentrated. The residue (a diacyl derivative of aminobenzimidazole) was dissolved in 10% HCl (300 mL) and the solution was refluxed for 1 h and concentrated to precipitation. The suspension was cooled and the crystals that formed were filtered off and dried.

This procedure was used to obtain compounds **3a,b**, **5a,b**, **7a,b**, and **8a,b**. Selected syntheses are given below.

5(6)-Formamidobenzimidazole formate (3a·HCOOH). 1,2,4-Triaminobenzene dihydrochloride (80 g) was refluxed in formic acid (400 mL) for 3 h. The acid was evaporated almost to dryness and the residue was dissolved in distilled water (200 mL). The solution was neutralized with concentrated aqueous ammonia and left for crystallization. The crystals that formed were filtered off and dissolved in distilled water (200 mL). The solution was refluxed with activated carbon, filtered hot, and cooled. The resulting crystals were filtered off and dried to give a powdery solid (55.2 g). The mother liquor was concentrated to crystallization in the hot solution and refluxed with a small amount of activated carbon for 3 h. The solution was filtered and cooled and the crystals that formed were filtered off and dried. An additional crop was 18.1 g. The total yield of 5(6)-formamidobenzimidazole formate was 73.3 g (91%).

4(7)-Amino-2-trifluoromethylbenzimidazole (8b), dihydrochloride. A four-neck flask fitted with a stirrer, a condenser, a dropping funnel, and a thermometer was charged with dilute (1 : 1) HCl (210 mL) and 1,2,3-triaminobenzene dihydrochloride (21 g, 0.107 mol). Trifluoroacetic acid (37 g, 27 mL, 0.324 mol) was gradually added. The reaction mixture was refluxed for 3 h until 1,2,3-triaminobenzene was completely consumed (TLC, Pr^iOH—AcOEt—aqueous NH_3 (7 : 9 : 4) as an eluent). Then the mixture was refluxed four times with a fresh portion of activated carbon to the formation of a transparent solution. The solvent was removed in a rotary evaporator. The residue was dissolved under heating in dilute (1 : 3) HCl with activated carbon. The solution was filtered and concentrated in a rotary evaporator. The residue was cooled and the crystals that formed were filtered off and dried. The yield of 4(7)-amino-2-trifluoromethylbenzimidazole (**8b**) as dihydrochloride was 22.4 g (76.3%).

5-Amino-2-trifluoromethylbenzimidazole (8a), dihydrochloride, was obtained analogously. The product was purified by reflux in butyl acetate for 1.5 h.

5(6)-Formamido-4(7)-nitrobenzimidazole (12). 5(6)-Formamidobenzimidazole (**3a**) (8.00 g, 38.6 mmol) was added in portions at −10 °C for 1.5 h to continuously stirred conc. HNO_3 (d = 1.516, 50 mL) so that the reaction temperature did not exceed −10 °C. After the cooling bath was removed, the reaction mixture was carefully poured at 0 °C into vigorously stirred water with ice (100 mL). The resulting crystalline solid was filtered off on a porous glass filter, thoroughly squeezed, and suspended in water (100 mL). The suspension was neutralized with concentrated aqueous ammonia to pH 7. The crystals were filtered off again, thoroughly washed with water, and dried in air and then *in vacuo* over P_2O_5 to give yellow crystals (6.4 g, 80%).

5(6)-Acetamido-2-methyl-4(7)-nitrobenzimidazole (13) was obtained analogously from 5(6)-acetamido-2-methylbenzimidazole (**4a**) (10 g). The yield was 6.2 g (50%), yellow crystals.

5(6)-Amino-4(7)-nitrobenzimidazole (16). 5(6)-Formylamino-4(7)-nitrobenzimidazole (**12**) (3.09 g, 15 mmol) was refluxed in 10% HCl (50 mL) for 30 min. The solvent was removed and the residue was dissolved in water (50 mL). Concentrated NH_4OH was added to a weakly basic reaction and the solution was neutralized with acetic acid. The crystals that formed were filtered off, thoroughly washed with water (5×10 mL), and dried to give red crystals (2.35 g, 88%).

1,2,3,4-Diimidazobenzene (14). 5(6)-Amino-4(7)-nitrobenzimidazole (**16**) (1.93 g) in formic acid (30 mL) was hydrogenated with stirring in a reactor over a 2% Pd/C catalyst (0.6 mL) for 5 h (hydrogen pressure 30 atm, ~20 °C). The catalyst was withdrawn and the solution was filtered and refluxed for 2 h to complete the cyclization. The solvent was removed and the residual formic acid was removed with methanol. The resulting solid was dissolved in methanol (10 mL) and refluxed with conc. HCl (1 mL) for 1 h. The solution was concentrated and the residue was dissolved in water (10 mL). The product was precipitated from the solution with acetone (70 mL). The crystals that formed were washed with acetone (3×10 mL) and dried to give grayish crystals (1.37 g, 80%).

Compound **14** was obtained analogously from compound **12**.

Nitration of 4(7)-acetamidobenzimidazole (17a). 4(7)-Acetamidobenzimidazole (**17a**) (0.88 g, 5 mmol) was added in portions at 0 °C for 10 min to stirred fuming HNO_3 (d = 1.52, 3.5 mL). The reaction mixture was kept at this temperature for 30 min, warmed to ~20 °C in 20 min, and left for 1 h. Ice with water (20 g) was added. After several minutes, the voluminous yellow precipitate that formed was filtered off, washed with ice water (2×10 mL), and dried to give yellow crystals. The yield of a mixture of 4(7)-acetamidonitrobenzimidazoles **15a,b** as nitrates was 1.19 g (84%). To a suspension of this mixture (1.13 g, 4 mmol) in water (5 mL), 15% aqueous NH_3 was added dropwise. The precipitate that formed was filtered off, washed with water, and dried to give yellow crystals. The yield of a mixture of acetamidonitrobenzimidazoles **15a,b** was 0.86 g (78.4%) (R_f 0.18 and 0.55, AcOEt—MeOH (9 : 1) as an eluent). The mixture of the nitro derivatives (0.6 g) was separated by column chromatography on silica gel 5/40 in benzene—AcOEt with increasing polarity and then in AcOEt—MeOH with increasing polarity. Fractions with equal R_f values were combined and evaporated to dryness. The residue was dried *in vacuo* to give 7-acetamido-4-nitrobenzimidazole (**15b**) (0.18 g) with R_f 0.55 and 7-acetamido-6-nitrobenzimidazole (**15a**) (0.32 g) with R_f 0.18 (AcOEt—MeOH, 9 : 1).

7-Acetamido-1-acetylbenzimidazole (19a). Acetic anhydride (1.25 g, 12 mmol, 1.13 mL) was added dropwise to a stirred suspension of the dihydrochloride of 4(7)-aminobenzimidazole

(**6b**) (1.03 g, 5 mmol) in anhydrous pyridine (3 mL). The reaction mixture was stirred at ~20 °C for 0.5 h and at 60—70 °C for 2 h. The solvent was removed *in vacuo* and ice water (5 mL) was added to the residue. The resulting precipitate was filtered off, washed with ice water (2×0.5 mL) to neutral reaction, and dried in oil pump vacuum while heating over P_2O_5. The yield of compound **19a** was 0.94 g (87%), white crystals, R_f 0.52 (AcOEt—MeOH, 9 : 1, twice).

4(7)-Acetamidobenzimidazole (17a). Anhydrous methanol (40 mL) and anhydrous triethylamine (2 mL) were added to 4(7)-acetamido-1-acetylbenzimidazole (**19a**) (4.5 g). The resulting solution remained homogeneous for 2—3 min and then a voluminous white precipitate formed. The precipitate was filtered off, washed with a required minimum amount of ice water, and dried to give white crystals. The yield of compound **17a** was 3.045 g (67%), R_f 0.55 (AcOEt—MeOH, 4 : 1).

Synthesis of compounds 17b—k *via* acylation of 4(7)-aminobenzimidazoles 6b and 8b (general procedure). 1) A mixture of an appropriate benzoic acid (2—2.5 mmol) and thionyl chloride (1.3—1.5 mmol) was refluxed for 3 h. Residual thionyl chloride was removed *in vacuo*. Benzene (1 mL) was added and residual SO_2 and HCl were removed *in vacuo*.

2) The resulting solution of substituted benzoyl chloride was diluted with anhydrous benzene (4 mL) and added dropwise to a stirred solution of 4(7)-aminobenzimidazole (2—2.5 mmol) in anhydrous pyridine (3—4 mL). The reaction mixture was left at ~20 °C for ~14 h, the solvents were removed *in vacuo*, and water (6—7 mL) was added to the residue. The precipitate of a dibenzoyl derivative that formed was washed with water (3×6 mL) and thoroughly dried *in vacuo* over P_2O_5.

3) Anhydrous methanol (5—10 mL) and anhydrous triethylamine (1 mL) were added to the dibenzoyl derivative obtained. The reaction mixture was refluxed for 1 h to complete homogenization. The solution was cooled, filtered, and concentrated. The residue was recrystallized from an appropriate solvent. In the case of compound **17e**, water treatment gave a viscous noncrystallizable oil. The product was extracted from the oil with CH_2Cl_2, the solvent was removed, and the residue was purified by column chromatography (see Table 2).

Synthesis of compound 17f *via* acylation of 4(7)-amino-2-trifluoromethylbenzimidazole (8b). Benzoyl chloride (0.7 g, 51 mmol) was added dropwise at ~20 °C to a solution of the dihydrochloride of 4(7)-amino-2-trifluoromethylbenzimidazole (**8b**) (0.7 g, 25.5 mmol) in anhydrous pyridine (5 mL). The reaction mixture was left for 20 h, heated at ~70 °C for 40 min, and cooled. The solvent was removed in water aspirator vacuum. A small amount of water was added to the residue. The crystals that formed were filtered off, repeatedly washed with hot water and acetonitrile, and dried to give compound **17f** (0.75 g).

Synthesis of compounds 18a—f by sulfonylation of benzimidazoles (general procedure). A solution of an appropriate arylsulfonyl chloride (2—3 mmol) in anhydrous pyridine (3—4 mL) was added to a suspension of the dihydrochloride of 4(7)-aminobenzimidazole (**6b**) (2—3 mmol) in anhydrous pyridine (5—7 mL). The reaction mixture underwent self-heating, turned red, and produced a voluminous precipitate. The mixture was heated at 100 °C for 3 h and the excess pyridine was removed *in vacuo*. Water (10—15 mL) was added to the residue and the resulting oil was crystallized by trituration. The crystals were filtered off, washed with water to neutral reaction, and recrystallized from an appropriate solvent. Whenever an oily product did not crystallize, it was extracted with *tert*-butyl methyl ether (3×25 mL). The extracts were combined, washed with water, and dried over calcined $MgSO_4$. On removal of the ether, the residue was crystallized by trituration.

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