An Advantageous Synthesis of 2-Substituted Benzimidazoles Using Polyphosphoric Acid. 2-(Pyridyl)-1*H*-benzimidazoles, 1-Alkyl-(1*H*-benzimidazol-2-yl)pyridinium Salts, their Homologues and Vinylogues

Ermitas Alcalde,* Immaculada Dinarés, Lluïsa Pérez-García, Tomàs Roca
Laboratorio de Química Orgánica, Facultad de Farmacia, Universidad de Barcelona, E-08028-Barcelona, Spain

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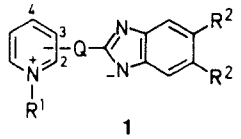
The title 2-substituted benzimidazoles are prepared by a highly efficient one-pot procedure, cyclodehydration of the corresponding accessible carboxylic acids and 1,2-arylenediamines, using polyphosphoric acid as the catalyst and solvent in a condensation of the type found in the Phillips benzimidazole synthesis. The method has been adapted and proved to be extremely useful for 1-alkyl-(1*H*-benzimidazol-2-yl)pyridinium tetrafluoroborates with a methylene and vinylene interannular moiety.

During the course of our investigation on heterocyclic betaines and organic substrates with a dipolar character **1**,[1-4] where the π-excessive ring is a benzimidazole, we have found that their precursors the 2-(pyridyl)-1*H*-benzimidazoles **2** and 1-alkyl-(1*H*-benzimidazol-2-yl)-pyridinium salts **3** with several interannular moieties may be efficiently prepared using polyphosphoric acid (PPA) as the catalyst and solvent in a condensation of the type found in the Phillips benzimidazole synthesis.[5]



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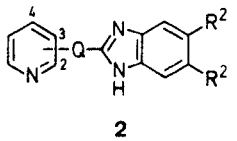

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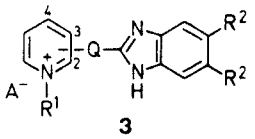
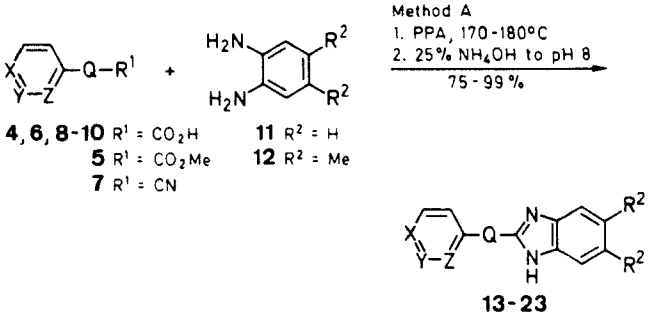


3

Q = –, $-CH_2-$, $-CH=CH-$

Since the discovery of Hein et al.[5] that PPA-induced cyclocondensation of benzoic acids and 1,2-phenylenediamines was a convenient route to 2-arylbenzimidazoles, the utility of PPA as a catalyst for synthesis of benzimidazoles has received little attention,[5-10] although a recent report[11] on "phosphonium anhydride" reagent did show good yields of several 2-arylbenzimidazoles. Moreover, despite the main use of PPA as catalyst and solvent for cyclodehydrations,[6] only a few quaternary ammonium salts have been used[7,12] – via reaction with PPA – as precursor for the synthesis of indolium, quinolinium, isoquinolinium and benzodiazepinium salts.

In the present work, new 2-pyridyl-1*H*-benzimidazoles **13–23** were prepared by Method A (Scheme 1). 4-Pyridinecarboxylic acid (**4**), 3-pyridylacetic acid (**6**), derivatives methyl 4-pyridylacetate (**5**) and 2-pyridineacetonitrile (**7**), and 3-pyridylacrylic acids **8–10** were easily accessible. Condensation of the pyridylcarboxylic acid analogues or derivatives, **4–10** with 1,2-arylenediamines **11, 12** in the presence of PPA at 170–180 °C then afforded the title compounds **13–23** in high yield (Table).



4, 6, 8-10 R^1 = CO_2H **11** R^2 = H
5 R^1 = CO_2Me **12** R^2 = Me
7 R^1 = CN

13-23

Compound	Q	Type	X	Y	Z
4, 13, 14	–	4-pyridyl	N	CH	CH
5, 15, 16	CH_2	4-pyridyl	N	CH	CH
6, 17, 18	CH_2	3-pyridyl	CH	N	CH
7, 19, 20	CH_2	2-pyridyl	CH	CH	N
8, 21	(*E*)-CH=CH	4-pyridyl	N	CH	CH
9, 22	(*E*)-CH=CH	3-pyridyl	CH	N	CH
10, 23	(*E*)-CH=CH	2-pyridyl	CH	CH	N

[a] R^2 = H for **13, 15, 17, 19** and R^2 = Me for **14, 16, 18, 20–23**

Scheme 1

The process was also found to be adaptable for cyclization of several quaternary salts, the pyridinium acetic and 3-pyridiniumacrylic acids **24–26**. In this way, 1-alkyl-(1*H*-benzimidazol-2-yl)pyridinium tetrafluoroborates **27–29** were obtained by Method B (Scheme 2) in high yields (Table). Different reaction conditions were experimented, and the best result is described (Method B). Notwithstanding, choice of the alkaline medium and later treatment with aqueous tetrafluoroboric acid is the most critical point in the process. It is noteworthy that the reaction temperature was of crucial importance, and at 160 °C better yields were found. At higher temperatures, due to dealkylation of the pyridinium salts present in the reaction mixture, compounds **15, 21** and **22** were isolated along with the title pyridinium salts **27–29**.

Physical data of the new compounds **15–23** and **27–29** are listed in Table 1. The structures of all of them have been unambiguously characterized on the basis of their ^1H NMR data. All of them gave satisfactory elemental analysis.

The above mentioned procedures provide a simple and a facile entry into a variety of benzimidazoles conveniently substituted in position 2. These methods can easily be adapted to more elaborated systems, and further studies are in progress.

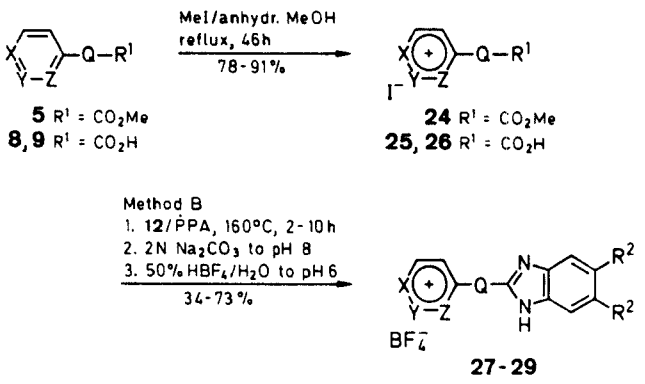
4-Pyridine carboxylic acid 99% (**4**), 3-pyridylacetic acid > 99% (**6**), 2-pyridylacetonitrile > 95% (**7**), 1,2-phenylenediamine (**11**)

Table. Compounds **15–23** and **27–29** Prepared

Substrate	Diamine	Time (h)	Product	Yield[b] (%)	R_f (solvent system)[c]	mp (°C) (solvent)[d]	Molecular Formula[e] or Lit. mp. (°C)	^{1}H NMR (DMSO-d_6)[f] δ, J (Hz)	MS (70 eV) m/z (%)
4	**11**	4	**13**[a]	80	0.6 (A)	221–223	224–225		
4	**12**	4	**14**[a]	81	0.7 (A)	240–241	241–243		
5	**11**	4.5	**15**	91	0.4 (A)	189 (CH_2Cl_2/EtOH)	$C_{13}H_{11}N_3$ (209.2)	4.23 (s, 2H), 7.13 (m, 2H), 7.34 (d, 2H, J = 4.7), 7.51 (m, 2H), 8.51 (d, 2H, J = 4.7), 12.44 (br, 1H)	209 (92)
5	**12**	2.5	**16**	75	0.4 (A)	161[g]	$C_{15}H_{15}N_3 \cdot H_2O$ (255.3)	2.26 (s, 6H), 4.17 (s, 2H), 7.26 (s, 2H), 7.30 (d, 2H, J = 5.7), 8.48 (d, 2H, J = 5.7), 12.15 (br, 1H)	237 (100)
6	**11**	7.5	**17**	85	0.6 (B)	149–150 (MeCN)	$C_{13}H_{11}N_3$ (209.2)	4.23 (s, 2H), 7.12 (m, 2H), 7.33 (dd, 2H, J = 7.5, 4.4), 7.49 (m, 2H), 7.73 (d, 1H, J = 7.5), 8.45 (m, 1H), 8.60 (s, 1H)	209 (74)
6	**12**	2.5	**18**	91	0.5 (A)	148–149 (EtOAc)	$C_{15}H_{15}N_3 \cdot H_2O$ (255.3)	2.25 (s, 6H), 4.17 (s, 2H), 7.25 (s, 2H), 7.31 (dd, 1H, J = 7.7, 4.7), 7.70 (d, 1H, J = 7.7), 8.44 (d, 1H, J = 4.7), 8.57 (s, 1H)	237 (89)
7	**11**	5	**19**	90	0.7 (C)	145–147[h]	$C_{13}H_{11}N_3 \cdot 0.5H_2O$ (218.2)	4.32 (s, 2H), 7.10 (m, 2H), 7.25 (m, 1H), 7.37 (d, 1H, J = 7.8), 7.46 (m, 2H), 7.74 (m, 1H), 8.49 (d, 1H, J = 5.0), 12.31 (br, 1H)	209 (100)
7	**12**	5	**20**	99	0.5 (C)	105–107[h]	$C_{15}H_{15}N_3 \cdot 2H_2O$ (273.3)	2.25 (s, 6H), 4.26 (s, 2H), 7.20 (m, 1H), 7.22 (s, 2H), 7.33 (d, 1H, J = 7.7), 7.73 (m, 1H), 8.48 (d, 1H, J = 4.1)	237 (100)
8	**12**	1	**21**	99	0.3 (D)	208–210[h]	$C_{16}H_{15}N_3 \cdot H_2O$ (267.3)	2.30 (s, 6H), 7.36 (br, 2H), 7.43 (d, 1H, J = 16.4), 7.53 (d, 1H, J = 16.4), 7.59 (dd, 2H, J = 4.6, 1.6), 8.58 (dd, 2H, J = 4.6, 1.6)	249 (35)
9	**12**	1.75	**22**	99	0.7 (C)	214–216[h]	$C_{16}H_{15}N_3 \cdot 0.5H_2O$ (258.3)	2.29 (s, 6H), 7.31 (s, 2H), 7.31 (d, 1H, J = 16.6), 7.44 (dd, 1H, J = 7.9, 4.7), 7.60 (d, 1H, J = 16.6), 8.12 (dt, 1H, J = 7.9, 1.9), 8.51 (dd, 1H, J = 4.7, 1.9), 8.79 (d, 1H, J = 1.9)	249 (32)
10	**12**	1.25	**23**	95	0.6 (C)	223–225[h]	$C_{16}H_{15}N_3 \cdot H_2O$ (267.3)	2.30 (s, 6H), 7.31 (s, 2H), 7.31 (m, 1H), 7.57 (d, 1H, J = 16.9), 7.60 (m, 1H), 7.64 (d, 1H, J = 16.0), 7.82 (td, 1H, J = 8.3, 1.8), 8.62 (d, 1H, J = 3.7), 12.46 (br, 1H)	249 (44)
24	**12**	10	**27**	73	0.1 (C)	198 (Et_2O/acetone)[i]	$C_{16}H_{18}BF_4N_3$ (339.1)	2.27 (s, 6H), 4.29 (s, 3H), 4.49 (s, 2H), 7.26 (s, 2H), 8.05 (d, 2H, J = 5.5), 8.87 (d, 2H, J = 5.5), 12.28 (br, 1H)	[j]
25	**12**	2.5	**28**	37	0.1 (C)	240–242 (*i*-PrOH)	$C_{17}H_{18}BF_4N_3$ (351.2)	2.32 (s, 6H), 4.27 (s, 3H), 7.39 (s, 2H), 7.71 (d, 1H, J = 16.2), 7.86 (d, 1H, J = 16.2), 8.30 (d, 2H, J = 6.7), 8.88 (d, 2H, J = 6.7), 12.8 (br, 1H)	[j]
26	**12**	2	**29**	34	0.1 (C)	287–289 (EtOH)	$C_{17}H_{18}BF_4N_3 \cdot H_2O$ (369.2)	2.30 (s, 6H), 4.36 (s, 3H), 7.36 (s, 2H), 7.56 (d, 1H, J = 16.6), 7.65 (d, 1H, J = 16.6), 8.12 (dd, 1H, J = 8.6, 6.2), 8.79 (d, 1H, J = 8.6), 8.87 (d, 1H, J = 6.2), 9.32 (s, 1H), 12.68 (br, 1H)	[j]

[a] Compounds **13** and **14** have been previously described following a different procedure[13] (ca. 78% yield).
[b] Yields were not optimized.
[c] solvent systems: A, $CHCl_3$/MeOH (8 : 2); B, EtOH/H_2O (9 : 1); C, MeOH/Et_2O (8 : 2); D, $CHCl_3$/MeOH (9 : 1); detection by UV light.
[d] Uncorrected measured with a CTP-MP hot-plate apparatus
[e] Satisfactory microanalysis obtained: C ±0.4, H ±0.4, N ±0.4.
[f] Recorded on a Varian Gemini 200 MHz spectrometer.
[g] Flash chromatography (CH_2Cl_2/EtOH, 95 : 5), the residue recristallized from acetone.
[h] Recrystallization was not necessary.
[i] Compound **27** is unstable in solution.
[j] Not measured.

and 50% aqueous HBF_4 were purchased from Fluka Chemical Co. 3-(3-Pyridyl)acrylic acid 99% (**9**) and 4,5-dimethyl-1,2-phenylenediamine 99% (**12**) were purchased from Aldrich Chemical Co. Polyphosphoric acid > 84% was purchased from Janssen Chimica. Analytical TLC plates Alugram Ref: 8181333 were purchased from Macherey Nagel. Silica gel (230–400 mesh) was



5 $R^1 = CO_2Me$
8, 9 $R^1 = CO_2H$

24 $R^1 = CO_2Me$
25, 26 $R^1 = CO_2H$

27-29

Compound	Q	Type	X	Y	Z
24, 27	CH_2	1-methyl-4-pyridinio	NMe^+	CH	CH
25, 28	(*E*)-CH=CH	1-methyl-4-pyridinio	NMe^+	CH	CH
26, 29	(*E*)-CH=CH	1-methyl-3-pyridinio	CH	NMe^+	CH

Scheme 2

purchased from SDS. Reagent quality solvents were used without further purification. Methyl 4-pyridylacetate **(5)**,[14] and 4-(methoxycarbonylmethyl)-1-methylpyridinium iodide **(24)**[15] were prepared as in the literature. Microanalyses were obtained using a Carlo Erba model 1160 element analyser. Mass spectra were obtained using a Finnigan model TSQ-70 and Hewlett-Pakard 5988A spectrometers with DEI ionization. IR spectra were obtained using a Perkin-Elmer 1430 spectrometer. ^1H NMR spectra using a Varian Gemini 200 MHz spectrometer. ^{13}C NMR spectra using a Varian Gemini 50.3 MHz spectrometer. NMR spectra were determined in DMSO-d_6, using the central peak of DMSO-d_6 as internal standard.

2-(4-Pyridyl)-, 2-(3-Pyridyl)-, and 2-(2-Pyridyl)-1*H*-benzimidazoles 13–23; General Procedure:

Method A: In a dry, N_2-filled three-necked flask fitted with stirrer, 1,2-arylenediamine **11** or **12** (40 mmol) and the carboxylic acid or derivative **4–10** (40 mmol) were suspended in PPA (25 g) and this suspension was heated in a bath at 170–180 °C for the time given in Table 1. The cooled mixture was poured into ice-water (150 mL) and the resulting solution was then neutralized to pH 8 with 25% NH_4OH. The precipitated product was filtered, washed with H_2O (3 × 50 mL), dried at 40 °C/50 mbar and recrystallized (Table 1).

^{13}C NMR chemical shifts (DMSO-d_6) of some typical examples are given below.

Compound **16**: δ = 20.1 ($2CH_3$), 34.3 (CH_2), 116.0 (C-4,7), 124.6 (C-3',5'), 130.2 (C-5,6), 147.2 (C-4'), 150.2 (C-2',6'), 151.5 (C-2).

Compound **21**: δ = 20.0 ($2CH_3$), 115.2 (C-4,7), 121.0 (C-3',5'), 122.5 (=CH-Bz), 130.5 (=CH-Py), 131.1 (C-5,6), 138.0 (C-3a,7a), 143.2 (C-4'), 149.2 (C-2), 150.2 (C-2',6').

1-Alkyl-(1*H*-benzimidazol-2-yl)pyridinium Tetrafluoroborates 27–29; General Procedure:

Method B: In a dry, N_2-filled three-necked flask fitted with stirrer, 1,2-arylenediamine **12** (5 mmol) and 1-methyl-4-(methoxycarbonylmethyl)pyridinium iodide (**24**; 1.47 g, 5 mmol) or 3-pyridiniumacrylic acids **25** or **26** (5 mmol) were suspended in PPA (20 g) and this suspension we heated in a bath at 160 °C for the time given in Table 1. The cooled mixture was poured into ice-water (50 mL) and the resulting solution was treated with 2 N Na_2CO_3 to pH 8. This solution was then made acid with 50% HBF_4/H_2O to reach pH 6 and the solid was filtered, washed with H_2O (2 × 10 mL), dried at 60 °C/50 mbar and recrystallized (Table).

^{13}C NMR chemical shifts (DMSO-d_6) of compounds **27** and **28** are given below.

Compound **27**: δ = 20.0 ($2CH_3$), 31.9 (CH_2), 47.8 (CH_3-N+), 114.1 (C-4',7'), 128.7 (C-3,5), 130.2 (C-5',6'), 135.9 (C-3a'-7a'), 146.2 (c-2,6), 148.6 (C-4), 153.0 (C-2').

Compound **28**: δ = 20.0 ($2CH_3$), 47.2 (CH_3-N+), 115.3 (C-4',7'), 123.9 (C-3,5), 127.0 (=CH-Bz), 128.9 (=CH-Py), 132.1 (C-5',6'), 137.8 (C-3a',7a'), 145.1 (C-2,6), 147.9 (C-2'), 151.0 (C-4).

(*E*)-3-(4-Pyridyl)acrylic Acid (8) and (*E*)-(2-Pyridyl)acrylic Acid (10):

In a dry, N_2-filled three-necked flask fitted with stirrer, 4-pyridinecarbaldehyde or 2-pyridinecarbaldehyde (3.20 g, 30 mmol) and malonic acid (7.18 g, 70 mmol) were dissolved in pyridine (12 mL) and piperidine (0.3 mL) and this solution was heated at 90 °C for 1.5 h, then at 130 °C for 3 h and the mixture was then worked up.

To the suspension was then added Et_2O (15 mL), and the white precipitate was filtered and washed with Et_2O (10 mL) to give **8**; yield: 3.9 g (86%); mp 230 °C.

$C_8H_7NO_2$ calc. C 64.42 H 4.73 N 9.39
found 64.31 4.60 9.30

^1H NMR (DMSO-d_6): δ = 6.46 (d, 1 H, =CH$_A$–CO_2H), 7.23 (d, 1 H, Py–CH$_B$=), 7.36 (d, 2 H, H-3,5), 8.3 (d, 2 H, H-2,6).

The mixture was evaporated and the oily residue treated with $CHCl_3$ (40 mL), the resultant solid was filtered and washed with $CHCl_3$ (2 × 5 mL) to give **10**; yield: 1.80 g (40%); mp 198–200 °C.

$C_8H_7NO_2$ calc. C 64.42 H 4.73 N 9.39
found 64.23 4.55 9.29

^1H NMR (DMSO-d_6): δ = 6.56 (d, 1 H, =CH$_A$–CO_2H), 7.36 (d, 1 H, Py–CH$_B$=), 6.93–7.70 (m, 3 H, H-3,4,5), 8.33 (d, 1 H, H-6).

(*E*)-2-[Carboxyvinyl]-1-methylpyridinium Iodides 25 and 26:

A solution of MeI 823.78 g, 167.5 mmol) in anhydr. MeOH (50 mL) was added dropwise to a stirred suspension of 4- or 3-pyridylacrylic acid **8** or **9** (5 g, 33.5 mmol) in anhydr. MeOH (250 mL) at ≤ 10 °C and the mixture was then refluxed for 46 h. The mixture was evaporated and the residue worked up. The crude product **25** was dissolved in H_2O (150 mL) and washed with EtOAc (9 × 50 mL). The aqueous solution was evaporated to dryness to give **25**; yield: 8.87 g (91%); mp 229 °C.

$C_9H_{10}INO_2 \cdot 0.5\ H_2O$ calc. C 36.00 H 3.66 N 4.66
found 36.40 3.41 4.58

^1H NMR (DMSO-d_6): δ = 4.2 (s, 3 H, CH_3), 6.83 (d, 1 H, =CH$_A$–CO_2H), 7.48 (d, 1 H, Py$^+$–CH$_B$=), 8.10 (d, 2 H, H-3,5), 8.73 (d, 2 H, H-2,6).

The crude product **26** was washed with Et_2O (3 × 50 mL) and recrystallized from H_2O to give **26**; yield: 8.05 g (81%); mp 208–210 °C.

$C_9H_{10}INO_2 \cdot H_2O$ calc. C 34.95 H 3.88 N 4.53
found 35.11 3.66 4.75

^1H NMR (DMSO-d_6): δ = 4.23 (s, 3 H, CH_3), 6.66 (d, 1 H, =CH$_A$–CO_2H), 7.46 (d, 1 H, Py$^+$–CH=), 7.9 (m, 1 H, H-5), 8.5–8.8 (m, 2 H, H-4,6), 9.16 (s, 1 H, H-2).

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