Pergamon

Bioorganic & Medicinal Chemistry 8 (2000) 37–42

BIOORGANIC & MEDICINAL CHEMISTRY

Reactions of a Series of 1-Aminobenzimidazoles and 1-Amino-3-methylbenzimidazolium Chlorides with 2,4-Pentanedione

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Received 14 June 1999; accepted 19 August 1999

Abstract—Reactions of a series of 1-aminobenzimidazoles and 1-amino-3-methylbenzimidazolium chlorides with 2,4-pentanedione were carried out and pyridazino[1,6-*a*]benzimidazoles and 2-pyrazolylanilines were generated. The product ratios of these compounds remarkably depended on the reaction conditions and on the electronic character of the substituent at the benzene moiety. The possible mechanisms involved in these reactions are discussed.

Introduction

In order to elucidate the chemical carcinogenesis of arylaminating carcinogens, we have examined electrophilic amination of nucleic acid components.[1] To date, we have generated all isomers of ring-nitrogen mono-aminated bases and nucleosides of nucleic acid components.[2–6] As a model for the imidazole moiety of purines, we also examined electrophilic amination of a series of benzimidazole derivatives.[7] In a report on the utilization of *N*-aminated derivatives, we previously described the formation of pyridazinopurine derivatives, new tricyclic compounds, by the reaction of 7- or 9-aminoadenine derivatives with 2,4-pentanedione[8] (Scheme 1). In the case of 7-aminoadenines, 5-pyrazolylpyrimidines were also obtained as by-products. This study was carried out to elucidate the reaction mechanisms responsible for formation of these products using a series of 1-aminobenzimidazole and 1-amino-3-methylbenzimidazolium chloride derivatives.

Results and Discussion

Reactions of 1-aminobenzimidazoles (1) with 2,4-pentanedione

Each 1-aminobenzimidazole (**1a**–**c**) was dissolved in a large excess of 2,4-pentanedione and refluxed for 4 h. Products were then separated and identified (Scheme 2 and Table 1). From compounds **1a,b**, pyridazino[1,6-*a*]benzimidazoles (**3a,b**) were obtained in yields of 78 and 97%, respectively, as already reported.[9] Compound **1c** has an electron-withdrawing substituent at the benzene moiety, and when it was allowed to react with 2,4-pentanedione, no product corresponding to compound **3** was produced, although 2-pyrazolylaniline (**4c**) was obtained in a low yield of 17%. In this case, the starting material, **1c**, remained, indicating that the reaction had proceeded slower than with **1a,b**. The structures of compounds **3a,b** and **4c** were determined from spectroscopic data (details of **4c** will be described later). Assignments of ^{1}H and ^{13}C NMR signals of these compounds were carried out by means of HMBC correlations. In the reaction of **1** with 2,4-pentanedione in the presence of a catalytic amount of $ZnCl_2$, compound **1a** afforded a quantitative yield of **3a**, however, compound **1b** gave **3b** and **5b**, each in a 27% yield.

Compound **5b** will be formed from compound **4b** by further reaction of its amino group with 2,4-pentanedione to form a Schiff base. In the case of **1c**, the starting material was completely consumed and the reaction gave several products, however, only one product, **5c**, was identified with a very low yield (details of the structure will be described later). These results suggested that the types and ratios of the products remarkably depended on the substituent at the benzene moiety and on the presence or absence of a Lewis acid. With respect to the reaction of **1c**, we used a 1:1 mixture of 1-amino-5-nitrobenzimidazole and 1-amino-6-nitrobenzimidazole because of the difficulty in separating these two isomers. It was interesting that compound **1c** gave only

Keywords: *N*-aminobenzimidazole; 2,4-pentanedione; pyridazinobenzimidazole; chemical carcinogenesis.
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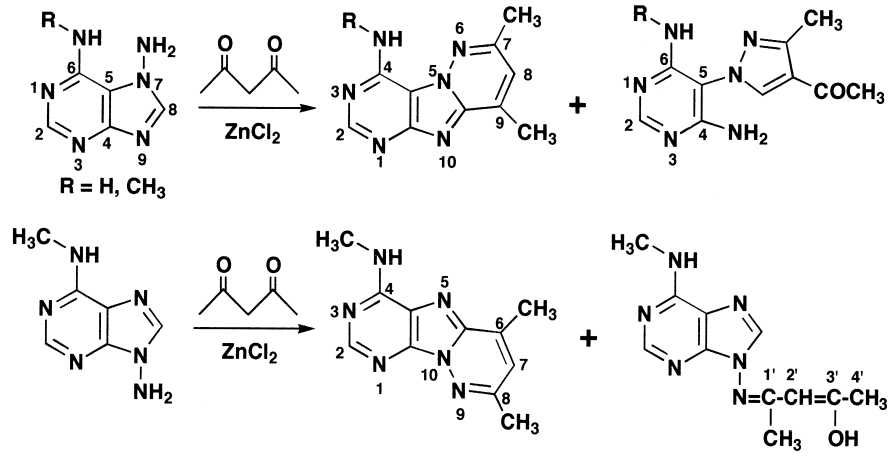
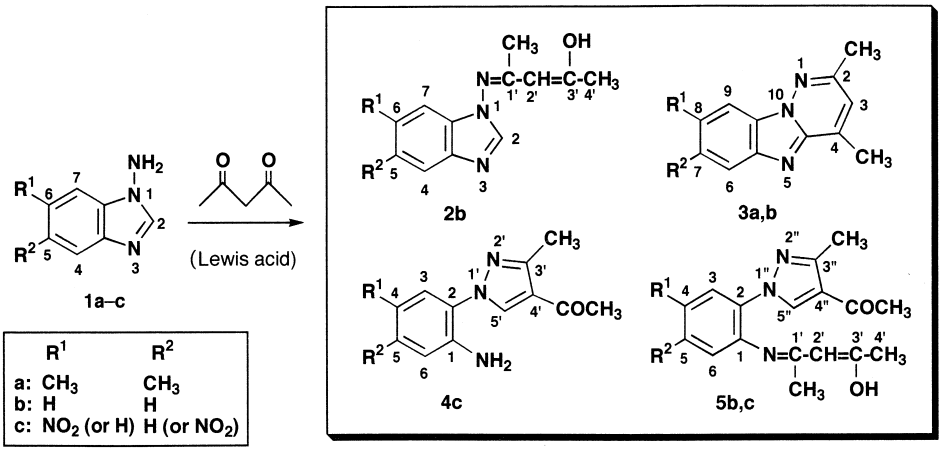
PII: S0968-0896(99)00254-0



Scheme 1. Reactions of *N*-aminoadenines with 2,4-pentanedione.



Scheme 2. Reactions of 1-aminobenzimidazole derivatives with 2,4-pentanedione.

the 4-nitro derivative of **4** (R^1=NO_2, R^2=H) when **1c** was allowed to react with 2,4-pentanedione in the absence of a Lewis acid, whereas in the presence of $ZnCl_2$, the reaction gave only the 5-nitro derivative of **5** (R^1=H, R^2=NO_2). These results indicated that the reactivity of 1-amino-5-nitrobenzimidazole and 1-amino-6-nitrobenzimidazole toward 2,4-pentanedione was altered by the presence of $ZnCl_2$. The effect of another Lewis acid, $AlCl_3$, on the reaction of **1b** was also examined, and results showed that the yield of **5b** was lower than with $ZnCl_2$ (Table 1). With respect to the tautomeric structures of **5b,c**, the ^{1}H NMR spectra showed that they are in the enol form as is **2b**, as shown in Scheme 2.

HPLC study of reaction pathways

The reaction pathway of **1b** with 2,4-pentanedione was examined using HPLC. Compound **1b** was allowed to react with 2,4-pentanedione under the same reaction conditions described above. Identification and quantification of products **1b**, **2b**, **3b** and **5b** were carried out at the appropriate times. In the absence of a Lewis acid, the reaction mixture after 30 min contained starting material **1b** and products **2b** and **3b**. After 2 h, the starting material had been totally consumed and product **3b** was the major product along with a smaller amount of **2b**. In the presence of $ZnCl_2$, the reaction mixture contained no starting material after 30 min, and product **2b** was the major product with smaller amounts of products **3b** and **5b**. After 2 h, a decreased amount of product **2b** and an increased amount of products **3b** and **5b** were noted. No product corresponding to compound **4** was observed, suggesting that the amino group of product **4**, once formed, was converted to Schiff base **5** very quickly by further reaction with 1,2-pentanedione.

These results strongly suggested that the Schiff base product **2b** is the first to yield products **3b** and **5b**. For further confirmation of the reaction pathway, compound **2b** was obtained as an oil from the reaction mixture in which **1b** and 2,4-pentanedione were refluxed for 30 min (Table 1). Compound **2b** was then allowed to react with 2,4-pentanedione in the presence or absence of $ZnCl_2$, and product analyses were carried out using HPLC. In the absence of $ZnCl_2$, a decreased amount of **2b** and an increased amount of **3b** were obtained after 30 min, but after 2 h, only compound **3b** was observed. In the presence of $ZnCl_2$, products **3b** and **5b** appeared after 30 min with a decreased amount of **2b**, and after

Table 1. Reactions of 1-aminoobenzimidazoles (**1**) with 2,4-pentanedione and yields of products[a]

Starting material	Lewis acid	Reaction time (h)	Yields of products (%)[b]				Comments
			2	**3**	**4**	**5**	
1a	None	4		78			
1b	None	4		97			
1c[c]	None	4			17[d]		f
1a	$ZnCl_2$	4		100			
1b	$ZnCl_2$	4		27		27	
1c[c]	$ZnCl_2$	4				6[e]	g
1b	None	0.5	23	5			f
1b	$AlCl_3$	4		25		5	
2b	None	4		88			
2b	$ZnCl_2$	4		18		21	

[a]A solution of **1** or **2** (0.5 mmol) in 1,2-pentanedione (10 mL) was refluxed for 0.5 or 4 h in the presence or absence of a Lewis acid (10 mg).
[b]Isolation yield.
[c]A 1:1 mixture (R^1=NO_2, R^2=H and R^1=H, R^2=NO_2) was used (Scheme 2).
[d]R^1=NO_2, R^2=H.
[e]R^1=H, R^2=NO_2.
[f]Starting material remained.
[g]Unidentified products were included.

2 h, products **3b** and **5b** predominated with only a trace amount of **2b** remaining.

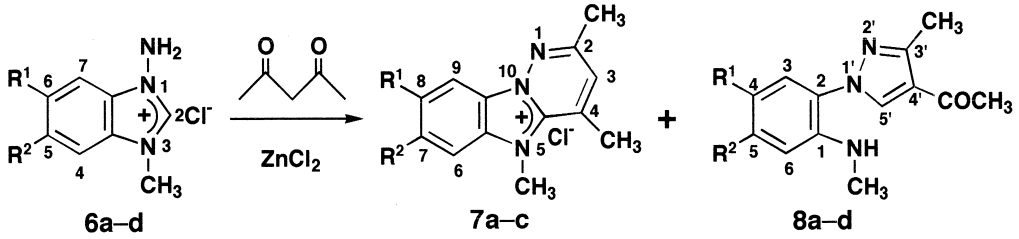
Reactions of 1-amino-3-methylbenzimidazolium chlorides (6) with 2,4-pentanedione

Similar reactions were carried out with 2,4-pentanedione and compounds **6**, the quaternary salts of **1** (Table 2). Since these reactions did not proceed well without $ZnCl_2$, this Lewis acid was included in the reactions. Four derivatives of 1-amino-3-methylbenzimidazolium chlorides (**6a–d**) were employed. Although the yields of products were low, 2,4,5-trimethylpyridazino[1,6-*a*]benzimidazolium chlorides (**7a–c**) and 2-(4-acetyl-3-methylpyrazol-1-yl)-*N*-methylanilines (**8a–c**) were obtained from **6a–c**. In contrast, compound **6d**, which has an electron-withdrawing substituent at the benzene moiety, produced **8d** and no **7d**. These results were similar to those obtained with **1c**, as shown in Table 1. Structures of products **8** were determined mainly by means of ^1H and ^{13}C NMR spectroscopies and HMBC correlation analyses. Unequivocal structural determination of **8** was carried out with products **8c,d**, and the structures of **8a,b** were determined by comparing their spectroscopic data with those of **8c,d**. Unequivocal structural determination of product **7** was not successful because **7** is a quaternary ammonium salt and its purification and crystallization could not be achieved. However, there is strong evidence for the structure of **7** in that the UV spectrum of **7c** in H_2O (λ_{max} 236 and 309 nm) was quite similar to that of **3b** in acidic media (the protonation site may be at N5 and the λ_{max} were 235 and 308 nm). Moreover, spots of both **3** and **7** on TLC fluoresced a light blue and purplish blue color, respectively, when exposed to UV light.

Proposed reaction mechanisms

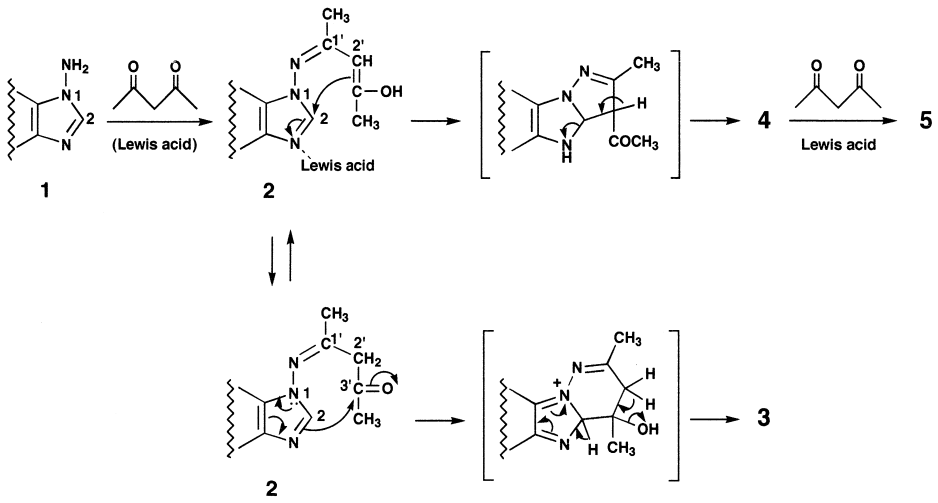
In the reaction of 1-aminobenzimidazoles (**1**) with 2,4-pentanedione, the initial step of the reaction is the formation of Schiff base product **2** (Scheme 3). Products **3** and **4** will be formed by cyclization at C2 and C3′ and subsequent aromatization, and by cyclization at C2 and C2′ and subsequent C2–N3 bond cleavage of the imidazole ring, respectively. Product **5** is formed by the further reaction of **4** with 2,4-pentanedione. When the electron density of the imidazole moiety is decreased by the introduction of an electron-withdrawing substituent at the benzene moiety (compound **1c**) or by the presence of a Lewis acid, the reaction pathway forming compound **4** or **5** is favored. Similarly, in the reaction of 1-amino-3-methylbenzimidazolium chlorides **6** with 2,4-pentanedione, a Schiff base is formed initially and its cyclization at C2 and C2′ gives **8** (Scheme 4). For formation of **7**, the carbanion at C2 may attack the carbonyl carbon of the side chain to form **7**, although we have no evidence supporting the participation of the carbanion in this reaction as yet. Formation of similar types of cationic tricyclic system using other procedures[10] and description of similar types of reaction mechanisms[11] have been reported by others.

Table 2. Reactions of 1-amino-3-methylbenzimidazolium chlorides (**6**) with 2,4-pentanedione and yields of products

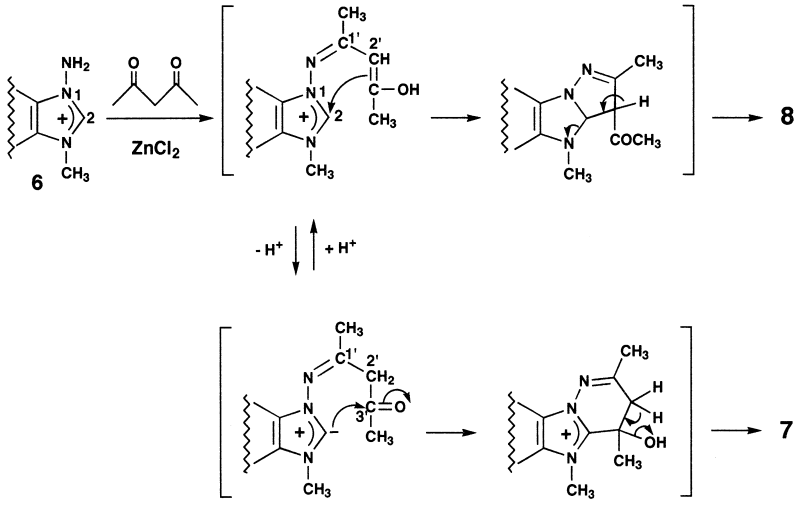


	R^1	R^2	Isolation yields (%)	
a:	CH_3	CH_3	7	8
b:	CH_3	H	a	17
c:	H	H	5	14
d:	H	NO_2	None	34

[a]A product was formed but not isolated.



Scheme 3. Proposed reaction mechanisms.



Scheme 4. Proposed reaction mechanisms.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on JEOL EX 270, GSX 400 and ALPHA 500 spectrometers, and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained with JEOL AX 505HA and SX 102A spectrometers. UV spectra were recorded on a Shimadzu UV-2100 spectrophotometer and p*K*a values were estimated from pH-dependent UV spectral changes. HPLC analyses were carried out using a Shimadzu LC-10AD apparatus equipped with a photodiode array UV detector SPD-M6A. A Merck LiChrospher 100RP-18(e) column (4×250 mm) was used and eluted with a solvent system of 1/15 M phosphate buffer (pH 6.8)–MeOH (a linear gradient of 20% MeOH at 0 min to 70% MeOH at 40 min at a flow rate of 0.8 mL/min). Melting points (Mp) were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Preparative thin-layer chromatography (PLC) was carried out with Merck silica gel 60 PF_{254} plates. 1-Aminobenzimidazole[12] and 1-amino-5,6-dimethylbenzimidazole[13] were prepared as previously reported. 1-Amino-3-methylbenzimidazolium chloride derivatives[14] were also prepared as previously described.

Preparation of a 1:1 mixture of 1-amino-5-nitrobenzimidazole and 1-amino-6-nitrobenzimidazole (1c). 5-Nitrobenzimidazole (82 mg, 0.5 mmol) was dissolved in 5 mL of water containing KOH (84 mg, 1.5 mmol). Then, 5 mL of water containing hydroxylamine-*O*-sulfonic acid (170 mg, 1.5 mmol) and $NaHCO_3$ (126 mg, 1.5 mmol) were added to this solution, and the mixture was heated at 60 °C for 2 h. The reaction mixture was then neutralized with acetic acid and the solvent was removed by evaporation to dryness. Products were extracted from the residue with MeOH and separated by repeated PLC (silica gel, $CHCl_3$:MeOH = 85:15). Colorless crystals of a 1:1 mixture of 1-amino-5-nitobenzimidazole (5-NO_2) and 1-amino-6-nitobenzimidazole (6-NO_2) were obtained in a 44 mg (49%) yield. The extent of recovery of the starting material was 28 mg (34%). ^{1}H NMR ($CDCl_3$) (pairs of signals having the same heights were observed) δ 4.99 and 5.02 (each s, each 2H, NH_2 of 5-NO_2 and 6-NO_2), 7.57 and 7.84 (each d, each 1H, each J = 9.0 Hz, 7-H of 5-NO_2, 4-H of

6-NO_2), 8.15 and 8.22 (each s, each 1H, 2-H of 5-NO_2 and 6-NO_2), 8.22 and 8.29 (each dd, each 1H, each $J=2.2$, 9.0 Hz, 6-H of 5-NO_2, 5-H of 6-NO_2), 8.46 and 8.70 (each d, each 1H, each $J=2.2$ Hz, 4-H of 5-NO_2, 7-H of 6-NO_2); MS m/z 178 (M^+). HRMS m/z M^+ calcd for $C_7H_6N_4O_2$: 178.0491; found: 178.0491.

General procedure for the reactions of 1-aminobenzimidazoles (1) with 2,4-pentanedione

Each 1-aminobenzimidazole derivative (**1a**–**c**, 0.5 mmol) was dissolved in 2,4-pentanedione (10 mL) and the solution was refluxed for 4 h in the presence or absence of $ZnCl_2$ (10 mg). After the reaction, 2,4-pentanedione was removed by evaporation and the residues were subjected to PLC (silica gel, $CHCl_3$:MeOH = 95:5).

2,4,7,8-Tetramethylpyridazino[1,6-*a*]benzimidazole (3a).[9] ^{1}H NMR ($CDCl_3$) δ 2.46 and 2.48 (each s, each 3H, 7- and 8-CH_3), 2.59 (s, 3H, 2-CH_3), 2.69 (s, 3H, 4-CH_3), 6.89 (s, 1H, 3-H), 7.70 (s, 1H, 6-H), 7.87 (s, 1H, 9-H); ^{13}C NMR ($CDCl_3$) δ 16.9 (q, 4-CH_3), 20.6 and 20.8 (each q, 7- and 8-CH_3), 21.5 (q, 2-CH_3), 111.4 (d, 9-C), 119.8 (d, 6-C), 121.3 (d, 3-C), 129.3 (s, 5a-C), 132.1 (s, 7-C), 135.0 (s, 8-C), 136.6 (s, 4a-C), 141.5 and 142.6 (each s, 4- and 9a-C), 149.4 (s, 2-C); MS m/z 225 (M^+).

2,4-Dimethylpyridazino[1,6-*a*]benzimidazole (3b).[9] Recrystallization from $CHCl_3$–hexane gave colorless plates. Mp 139–141 °C; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, 2-CH_3), 2.70 (s, 3H, 4-CH_3), 6.92 (s, 1H, 3-H), 7.42 (t, 1H, $J=7.3$ Hz, 7-H), 7.52 (t, 1H, $J=7.3$ Hz, 8-H), 7.96 (d, 1H, $J=7.3$ Hz, 6-H), 8.11 (d, 1H, $J=7.3$ Hz, 9-H); ^{13}C NMR ($CDCl_3$) δ 16.9 (q, 4-CH_3), 21.6 (q, 2-CH_3), 111.8 (d, 9-C), 120.2 (d, 6-C), 122.2 (d, 3-C), 122.4 (d, 7-C), 125.5 (d, 8-C), 130.8 (s, 5a-C), 136.8 (s, 4a-C), 142.7 (s, 9a-C), 143.3 (s, 4-C), 150.0 (s, 2-C); UV λ_{max} nm, (pH 1) 235, 308, (H_2O and pH 12) 243, 316; pK_a 4.3; MS m/z 197 (M^+). Anal. calcd for $C_{12}H_{11}N_3$: C, 73.03; H, 5.62; N, 21.30. Found: C, 73.33; H, 5.70; N, 21.16.

2-(4-Acetyl-3-methylpyrazol-1-yl)-4-nitroaniline (4c). Recrystallization from MeOH gave yellow needles. Mp 218–220 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.44 (s, 3H, 3′-CH_3), 2.45 (s, 3H, $COCH_3$), 6.96 (d, 1H, $J=9.0$ Hz, 6-H), 7.03 (br s, 2H, NH_2), 8.06 (dd, 1H, $J=2.4$, 9.0 Hz, 5-H), 8.21 (d, 1H, $J=2.4$ Hz, 3-H), 8.96 (s, 1H, 5′-H); ^{13}C NMR (Me_2SO-d_6) δ 13.7 (q, CH_3), 28.5 (q, CO*C*H_3), 115.3 (d, 6-C), 121.0 (s, 4′-C), 121.2 (d, 3-C), 122.2 (s, 2-C), 125.1 (d, 5-C), 135.5 (s, 4-C), 136.9 (d, 5′-C), 148.9 (s, 1-C), 150.4 (s, 3′-C), 192.5 (s, *C*OCH_3); MS m/z 260 (M^+), 245 (M^+-CH_3). Anal. calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.02; H, 4.68; N, 21.20.

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*-(3-hydroxy-1-methyl-2-butenylidene)aniline (5b). Recrystallization from MeOH gave brown plates. Mp 161–163 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H, 1′-CH_3), 2.09 (s, 3H, 3′-CH_3), 2.38 (s, 3H, $COCH_3$), 2.55 (s, 3H, 3″-CH_3), 5.20 (s, 1H, 2′-H), 7.29 (m, 1H, 5-H), 7.40 (m, 2H, 3- and 6-H), 7.71 (m, 1H, 4-H), 8.14 (s, 1H, 5″-H), 12.30 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 14.0 (q, 3″-CH_3), 19.2 (q, 1′-CH_3), 28.5 (q, CO*C*H_3), 29.2 (q, 4′-C), 98.3 (d, 2′-C), 122.3 (s, 4″-C), 125.7 (d, 4-C), 127.9 and 128.2 (each d, 3- and 6-C), 128.5 (d, 5-C), 131.2 (s, 2-C), 135.1 (d, 5″-C), 135.7 (s, 1-C), 151.8 (s, 3″-C), 160.6 (s, 1′-C), 192.7 (s, *C*OCH_3), 197.0 (s, 3′-C); MS m/z 297 (M^+), 282 (M^+-CH_3), 254 (M^+-COCH_3), 240 ($M^+-CH=C(OH)$-CH_3). Anal. calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.54; H, 6.42; N, 14.15.

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*-(3-hydroxy-1-methyl-2-butenylidene)-5-nitroaniline (5c). Recrystallization from MeOH gave a yellow flocculi. Mp 200–202 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.01 (s, 3H, 3′-CH_3), 2.08 (s, 3H, 1′-CH_3), 2.43 (s, 3H, $COCH_3$), 2.45 (s, 3H, 3″-CH_3), 5.43 (s, 1H, 2′-H), 7.74 (d, 1H, $J=9.0$ Hz, 3-H), 8.26 (dd, 1H, $J=2.3$, 9.0 Hz, 4-H), 8.43 (d, 1H, $J=2.3$ Hz, 6-H), 8.96 (s, 1H, 5″-H), 12.49 (br s, OH); MS m/z 342 (M^+), 327 (M^+-CH_3), 299 (M^+-COCH_3), 285 ($M^+-CH=C(OH)$-CH_3). HRMS m/z M^+ calcd for $C_{17}H_{18}N_4O_4$: 342.1328; found: 342.1328. Anal. calcd for $C_{17}H_{18}N_4O_4 \cdot 2/3H_2O$: C, 57.62; H, 5.50; N, 15.81. Found: C, 57.32; H, 5.17; N, 15.78.

1-(3-Hydroxy-1-methyl-2-butenylideneamino)benzimidazole (2b). ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H, 1′-CH_3), 2.19 (s, 3H, 3′-CH_3), 5.38 (s, 1H, 2′-CH), 7.34 (m, 3H, 5-, 6-H and 4- or 7-H), 7.81 (dd, 1H, $J=1.8$, 6.7 Hz, 7- or 4-H), 7.94 (s, 1H, 2-H), 12.28 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 17.1 (q, 1′-CH_3), 29.5 (q, 4′-C), 99.2 (d, 2′-C), 108.9 and 121.0 (each d, 4- and 7-C), 123.2 and 124.4 (each d, 5 and 6-C), 133.8 and 141.3 (each s, 3a- and 7a-C), 142.8 (d, 2-C), 161.1 (s, 1′-C), 198.4 (s, 3′-C); MS m/z 215 (M^+), 200 (M^+-CH_3), 198 (M^+-OH).

General procedure for the reactions of 1-amino-3-methylbenzimidazolium chlorides (6) with 2,4-pentanedione

Each 1-amino-3-methylbenzimidazolium chloride derivative (**6a**–**d**, 0.5 mmol) was dissolved in 2,4-pentanedione (10 mL) and the solution was refluxed for 4 h in the presence of $ZnCl_2$ (10 mg). After the reaction, 2,4-pentanedione was removed by evaporation and the residues were subjected to PLC (silica gel, $CHCl_3$ then $CHCl_3$:MeOH = 85:15).

2,4,5,7,8-Pentamethylpyridazino[1,6-*a*]benzimidazolium chloride (7a). ^{1}H NMR (Me_2SO-d_6) δ 2.51 (s, 3H, 8-CH_3), 2.53 (s, 3H, 7-CH_3), 2.71 (s, 3H, 2-CH_3), 2.95 (s, 3H, 4-CH_3), 4.38 (s, 3H, 5-CH_3), 7.90 (s, 1H, 3-H), 8.09 (s, 1H, 6-H), 8.19 (s, 1H, 9-H); ^{13}C NMR (Me_2SO-d_6) δ 18.2 (q, 4-CH_3), 19.8 (q, 8-CH_3), 20.5 (q, 7-CH_3), 20.9 (q, 2-CH_3), 33.3 (q, N-CH_3), 112.6 (2d, 6- and 9-C), 125.6 (s, 9a-C), 130.2 (d, 3-C), 130.8 (s, 5a-C), 134.0 (s, 4-C), 136.4 (s, 8-C), 138.7 (s, 4a-C), 140.1 (s, 7-C), 155.5 (s, 2-C).

2,4,5-Trimethylpyridazino[1,6-*a*]benzimidazolium chloride (7c). ^{1}H NMR (Me_2SO-d_6) δ 2.73 (s, 3H, 2-CH_3), 2.97 (s, 3H, 4-CH_3), 4.43 (s, 3H, N-CH_3), 7.81 (t, 1H, $J=7.9$ Hz, 8-H), 7.95 (t, 1H, $J=7.9$ Hz, 7-H), 7.98 (s, 1H, 3-H), 8.30 (d, 1H, $J=7.9$ Hz, 9-H), 8.42 (d, 1H, $J=7.9$ Hz, 6-H); ^{13}C NMR (Me_2SO-d_6) δ 18.2 (q, 4-CH_3), 20.8 (q, 2-CH_3), 33.3 (q, N-CH_3), 113.0 (d, 9-C), 113.2 (d, 6-C), 126.2 (d, 8-C), 127.1 (s, 9a-C), 129.7 (d,

7-C), 131.0 (d, 3-C), 132.1 (s, 5a-C), 134.0 (s, 4-C), 139.6 (s, 4a-C), 155.7 (s, 2-C). UV λ_{max} nm; (H_2O) 236, 309.

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*,4,5-trimethylaniline (8a). ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H, 4-CH_3), 2.28 (s, 3H, 5-CH_3), 2.45 (s, 3H, $COCH_3$), 2.55 (s, 3H, 3′-CH_3), 2.84 (s, 3H, N-CH_3), 5.20 (br s, 1H, NH), 6.61 (s, 1H, 6-H), 6.93 (s, 1H, 3-H), 8.02 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, 3′-CH_3), 18.5 (q, 4-CH_3), 20.0 (q, 5-CH_3), 28.7 (q, CO*C*H_3), 30.4 (q, N-CH_3), 113.3 (d, 6-C), 121.3 (s, 4′-C), 123.2 (s, 2-C), 124.4 (s, 4-C), 125.2 (d, 3-C), 134.6 (d, 5′-C), 138.2 (s, 5-C), 141.4 (1-C), 151.7 (s, 3′-C), 192.4 (s, *C*OCH_3); MS *m*/*z* 257 (M^+), 242 (M^+-CH_3), 214 (M^+-COCH_3).

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*,4-dimethylaniline (8b). ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, 4-CH_3), 2.46 (s, 3H, $COCH_3$), 2.56 (s, 3H, 3′-CH_3), 2.83 (s, 3H, N-CH_3), 5.22 (br s, 1H, NH), 6.69 (d, 1H, J = 8.3 Hz, 6-H), 6.97 (s, 1H, 3-H), 7.10 (d, 1H, J = 8.3 Hz, 5-H), 8.04 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, 3′-CH_3), 20.1 (q, 4-CH_3), 28.7 (q, CO*C*H_3), 30.4 (q, N-CH_3), 111.9 (d, 6-C), 121.4 (s, 4′-C), 124.8 (d, 3-C), 125.3 and 125.9 (each s, 2- and 4-C), 130.3 (d, 5-C), 134.6 (d, 5′-C), 141.3 (1-C), 151.8 (s, 3′-C), 192.4 (s, *C*OCH_3); MS *m*/*z* 243 (M^+), 200 (M^+-COCH_3).

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*-methylaniline (8c). Recrystallization from MeOH gave light brown needles. Mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, $COCH_3$), 2.57 (s, 3H, 3′-CH_3), 2.86 (s, 3H, N-CH_3), 5.44 (br s, 1H, NH), 6.73 (ddd, 1H, J = 1.2, 7.3, 7.3 Hz, 4-H), 6.77 (dd, 1H, J = 1.2, 7.3 Hz, 3-H), 7.14 (dd, 1H, J = 1.2, 7.3 Hz, 6-H), 7.30 (ddd, 1H, J = 1.2, 7.3, 7.3 Hz, 5-H), 8.05 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q, 3′-CH_3), 28.7 (q, CO*C*H_3), 30.2 (q, N-CH_3), 111.8 (d, 3-C), 116.3 (s, 4-C), 121.5 (s, 4′-C), 124.2 (d, 6-C), 125.3 (s, 2-C), 129.8 (d, 5-C), 134.7 (d, 5′-C), 143.5 (s, 1-C), 151.9 (s, 3′-C), 192.4 (s, *C*OCH_3); UV λ_{max} nm, (pH 1) 264, (H_2O and pH 12) 239, 300; MS *m*/*z* 229 (M^+). HRMS *m*/*z* M^+ calcd for $C_{13}H_{15}N_3O$: 229.1214; found: 229.1215. Anal. calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.96; H, 6.48; N, 18.09.

2-(4-Acetyl-3-methylpyrazol-1-yl)-*N*-methyl-5-nitroaniline (8d). Recrystallization from $CHCl_3$–hexane gave orange plates. Mp 176–179 °C; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H, $COCH_3$), 2.59 (s, 3H, 3′-CH_3), 2.97 (s, 3H, N-CH_3), 6.44 (br s, 1H, NH), 7.29 (d, 1H, J = 8.5 Hz, 3-H), 7.57 (dd, 1H, J = 2.4, 8.5 Hz, 4-H), 7.59 (d, 1H, J = 2.4 Hz, 6-H), 8.15 (s, 1H, 5′-H); ^{13}C NMR ($CDCl_3$) δ 14.3 (q, 3′-CH_3), 28.8 (q, CO*C*H_3), 30.1 (q, N-CH_3), 106.4 (d, 6-C), 110.9 (d, 4-C), 122.2 (s, 4′-C), 123.3 (d, 3-C), 128.9 (s, 2-C), 134.3 (d, 5′-C), 143.9 (s, 1-C), 148.4 (s, 5-C), 152.5 (s, 3′-C), 192.1 (s, $COCH_3$); MS *m*/*z* 274 (M^+), 259 (M^+-CH_3). Anal. calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.83; H, 5.25; N, 20.40.

Acknowledgement

We would like to thank Professor Emeritus Y. Kawazoe of Nagoya City University for his helpful advice and encouragement.

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