Benzimidazole Condensed Ring Systems. 5 [1]. Studies on the Synthesis of Pyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones

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The reaction of ethyl 1*H*-benzimidazole-2-acetate (**1**) with methyl or ethyl isocyantes **2a,b** resulted in excellent yields of the respective 2-methyl- or 2-ethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **3a,b**, while the reaction of **1** with phenyl isocyanate (**2c**) gave, unexpectedly, ethyl 2-(1-phenylcarbamoyl-1*H*,3*H*-benzimidazol-2-ylidene)-2-phenylcarbamoylacetate (**4**). Alkylation of **3** with trimethyl or triethyl phosphates **5a,b** led to the 5-methyl or 5-ethyl derivatives **6a-d**. Chlorination of **6** with sulfuryl chloride afforded the 4-chloro derivatives **7a-d**.

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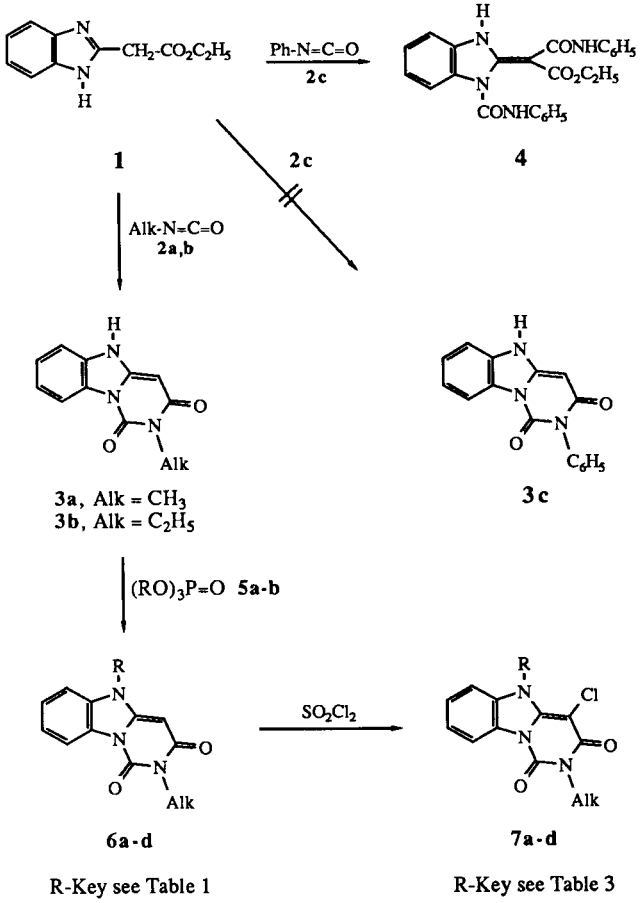
In the preceeding paper [1] we have described an efficient synthesis of 1,3-dioxo-2*H*,5*H*-pyrimido[1,6-*a*]benzimidazole-4-carbonitriles and 4-ethyl carboxylates through condensation of some 1*H*-benzimidazole-2-acetonitriles and ethyl 1*H*-benzimidazole-2-acetates, respectively, with ethoxycarbonyl isocyanate. We now report the extension of this condensation to alkyl and aryl isocyanates. Thus reacting ethyl 1*H*-benzimidazole-2-acetate (**1**) with methyl or ethyl isocyanates **2a,b** yielded the corresponding 2-methyl- or 2-ethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,-5*H*)-diones **3a,b** in appreciable yields. A trial to prepare 2-phenylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)dione (**3c**) by reacting **1** with phenyl isocyanate (**2c**) under similar conditions resulted in the uncyclized product **4**. The assigned structures were substantiated by ir and ^{1}H-nmr data. Mechanistically, the formation of **3** would involve the addition of **1** to **2** followed by intramolecular cyclization of the intermediate with elimination of ethyl alcohol (Scheme 2). In contrast, in case of phenyl isocyanate (**2c**) one molecule of **1** reacted with two molecules of the reagent. The cyclization which is limited to alkyl isocyanates provided a new facile route to 2-alkylpyrimido-[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones unsubstituted at C-4. Reacting **3** with trimethyl or triethyl phosphates **5a,b** afforded the respective N^5-methyl or N^5-ethyl derivatives **6a-d**. Out of these, compound **6d** has been previously obtained during the course of ethylating ethyl 1,3-dioxo(2*H*,-5*H*)pyrimido[1,6-*a*]benzimidazole-4-carboxylate with triethyl phosphate [1]. Treatment of **6a-d** with sulfuryl chloride easily gave the 4-chloro derivatives **7a-d** in excellent yields.

Scheme 1



R-Key see Table 1

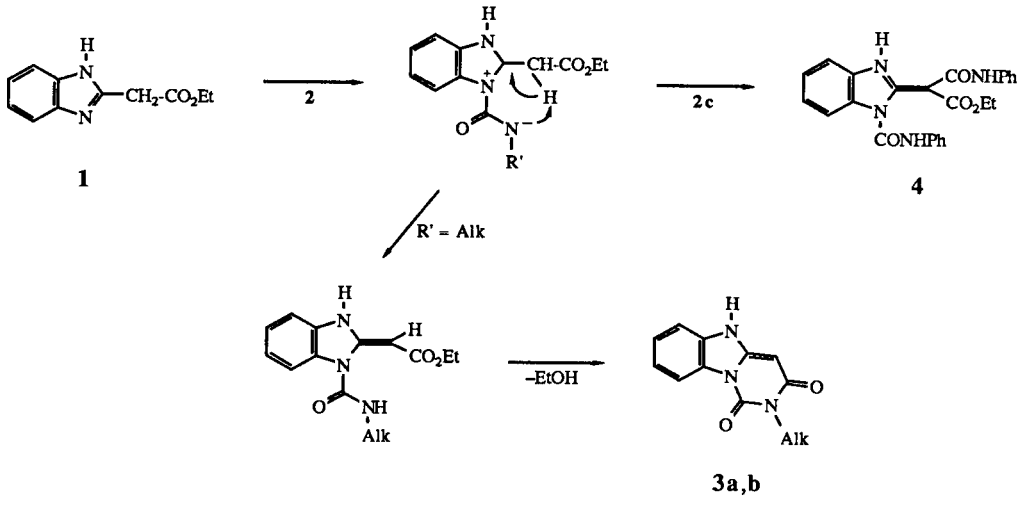
R-Key see Table 3

Compounds **6a-d**, **7c**, and **7d** were screened against P388 lymphocytic leukemia in mice according to a standard protocol [2] and were inactive.

EXPERIMENTAL

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer

Scheme 2



1 4 3a,b

Table 1

2,5-Dialkylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **6a-d**

Compound No.	Alk	R	Yield (%)	MP (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, % Calcd./Found C	H	N
6a	CH_3	CH_3	85	269-271	DMF	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33
						229.21	62.49	5.24	18.10
b	CH_3	C_2H_5	74	175-179	EtOH	$C_{13}H_{13}N_3O_3$	64.18	5.39	17.28
						243.27	64.35	5.44	17.19
c	C_2H_5	CH_3	71	252-254	DMF	$C_{13}H_{13}N_3O_2$	64.18	5.39	17.28
						243.27	64.47	5.46	17.26
d	C_2H_5	C_2H_5	80	184-186	DMF/H_2O	$C_{14}H_{15}N_3O_2$	65.35	5.87	16.33
						257.30	65.57	5.70	16.30

Table 2

^{1}H-NMR Data of 2,5-Dialkylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **6a-d**

Compound No.	Alk	R	^{1}H-NMR (δ ppm)
6a	CH_3	CH_3	3.2 (s, CH_3 at N-5), 3.5 (s, CH_3 at N-2), 5.4 (s, H at C-4), 7.1-7.5 (m, 3 aromatic H), 8.1 (d, H at C-9)
b	CH_3	C_2H_5	1.4 (t, J = 7 Hz, CH_3-ethyl), 3.4 (s, CH_3 at N-2), 4.0 (q, J = 7 Hz, CH_2-ethyl), 5.3 (s, H at C-4), 6.9-7.5 (m, 3 aromatic H), 8.3 (d, H at C-9)
c	C_2H_5	CH_3	1.5 (t, J = 7 Hz, CH_3-ethyl), 3.9 (s, CH_3), 4.4 (q, J = 7 Hz, CH_2-ethyl), 6.3 (s, H at C-4), 7.4-7.8 (m, 3 aromatic H), 8.4 (d, H at C-9) [a]
d	C_2H_5	C_2H_5	1.3 (t, J = 7 Hz, CH_3-ethyl at N-5), 1.4 (t, J = 7 Hz, CH_3-ethyl at N-2), 3.9 (q, CH_2-ethyl at N-5), 4.15 (q, CH_2-ethyl at N-2), 5.2 (s, H at C-4), 7.0-7.5 (m, 3 aromatic H), 8.2 (d, H at C-9)

[a] Trifluoroacetic acid was used as the solvent.

Table 3

4-Chloro-2,5-dialkypyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **7a-d**

Compound No.	Alk	R	Yield (%)	MP (°C)	Recrystallization solvent	Molecular formula Molecular weight	Analysis, % Calcd./Found C	H	Cl	N
7a	CH_3	CH_3	99	274-276	DMF	$C_{12}H_{10}ClN_3O_2$	54.66	3.82		15.94
						263.69	54.28	3.72		15.94
b	CH_3	C_2H_5	88	249-251	DMF	$C_{13}H_{12}ClN_3O_2$	56.22	4.35	12.77	15.13
						277.72	55.94	4.30	13.02	14.99
c	C_2H_5	CH_3	88	237-239	DMF/H_2O	$C_{13}H_{12}ClN_3O_2\cdot$	54.50	4.57		14.65
						½ H_2O	54.93	4.39		14.62
						286.73				
d	C_2H_5	C_2H_5	94	216-220	DMF	$C_{14}H_{14}ClN_3O_2$	57.64	4.84		14.40
						291.75	57.33	4.74		14.29

Table 4

^{1}H-NMR Data of 4-Chloro-2,5-dialkylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **7a-d**

Compound No.	Alk	R	^{1}H-NMR (200 MHz) (δ ppm)
7a	CH_3	CH_3	2.1 (s, CH_3 at N-2), 3.9 (s, CH_3 at N-5), 7.1-7.5 (m, 3 aromatic H), 8.1 (d, H at C-9)
b	CH_3	C_2H_5	1.35 (t, J = 7 Hz, CH_3-ethyl), 3.3 (s, CH_3 at N-2), 4.5 (q, J = 7 Hz, CH_2-ethyl), 7.2-7.6 (m, 3 aromatic H), 8.15 (d, H at C-9)
c	C_2H_5	CH_3	1.15 (t, J = 7 Hz, CH_3-ethyl), 3.9 (s, CH_3 at N-5), 3.95 (q, J = 7 Hz, CH_2-ethyl), 7.2-7.6 (m, 3 aromatic H), 8.15 (d, H at C-9)
d	C_2H_5	C_2H_5	1.2 (t, J = 7 Hz, CH_3-ethyl at N-2), 1.35 (t, J = 7 Hz, CH_3-ethyl at N-5), 4.0 (q, J = 7 Hz, CH_2-ethyl at N-2), 4.5 (q, J = 7 hz, CH_2-ethyl at N-5), 7.2-7.6 (m, 3 aromatic H), 8.15 (d, H at C-9)

using samples in potassium bromide disks, the ^{1}H-nmr spectra were recorded on a Varian EM-360 spectrometer using hexadeuteriodimethyl sulfoxide as the solvent (unless otherwise specified) and tetramethylsilane as the internal standard.

2-Methylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-dione (**3a**).

A solution of **1** (6.12 g, 30 mmoles) in acetonitrile (50 ml) was refluxed with methyl isocyanate (**2a**) (1.95 ml, 33 mmoles) for 5 hours. After cooling, the product was filtered, washed with acetonitrile and dried, yield 5.04 g (78%), mp >300° (dimethylformamide); ir: 3200-2500 bm, 1720 s (C_1=O), 1660 s (C_3=O), 1610 s, 1590 w cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 3.8 (s, CH_3), 6.4 (s, H at C-4), 7.4-7.9 (m, 3 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.28; H, 4.36; N, 19.43.

2-Ethylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-dione (**3b**).

This was likewise prepared from **1** (6.12 g, 30 mmoles) and ethyl isocyanate (**2b**) (1.5 ml, 33 mmoles), yield 4.54 g (66%), mp 277-280° dec (dimethylformamide-water); ir: 3200-2500 bm, 1710 s, 1670 s (C_1=O), 1650 s (C_3=O), 1610 s, 1560 w cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ 1.5 (t, J = 7 Hz, CH_3), 4.45 (q, J = 7 Hz, CH_2), 6.4 (s, H at C-4), 7.4-7.8 (m, 3 ArH), 8.5 (d, H at C-9).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.70; H, 4.87; N, 18.36.

Ethyl 2-(1-Phenylcarbamoyl-1*H*,3*H*-benzimidazol-2-ylidene)-2-phenylcarbamoylacetate (**4**).

Compound **1** (2.04 g, 10 mmoles) and phenyl isocyanate (**2c**) (2.4 ml, 22 mmoles) were refluxed in acetonitrile (15 ml) for 15 hours. Excess solvent was then removed under vacuum and the oily residue treated with ether to get the solid product, yield 2.78 g (63%), mp 168-170° (xylene); ir: 3400-2900 bm, 1650 s (CO), 1600 s, 1570 s cm^{-1}; ^{1}H-nmr: δ 1.2 (t, J = 7 Hz, CH_3), 4.25 (q, J = 7 Hz, CH_2), 6.7-7.7 (m, 14 ArH), 10.5 (s, NH), 11.4 (s, 2 NH).

Anal. Calcd. for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.61; N, 12.66. Found: C, 67.80; H, 5.38; N, 12.78.

2,5-Dialkylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **6a-d** (Table 1).

Compound **3a**, or **3b** (10 mmoles) was refluxed with trimethyl or triethyl phosphates **5a,b** (20 ml) for 1 hour in the presence of potassium carbonate (0.5 g). After cooling and addition of water the desired product was obtained; ir: 3100-3000 w, 1710 s (C_1=O), 1660 s (C_3=O), 1640-1560 (w-m) cm^{-1}; the ^{1}H-nmr data of the compounds are recorded in Table 2.

4-Chloro-2,5-dialkylpyrimido[1,6-*a*]benzimidazole-1,3(2*H*,5*H*)-diones **7a-d** (Table 3).

Sulfuryl chloride (2.02 ml, 25 mmoles) was carefully added to a suspension of the appropriate **6a-d** (10 mmoles) in dioxane (25 ml) and then warmed at 70-80°. After 15 minutes the mixture was

cooled and poured into cold water to precipitate the product; ir: 3100-2990 w, 1720 s ($C_1=O$), 1650 s ($C_3=O$), 1630-1610 (w-s) cm^{-1}. The ^1H-nmr data of the compounds are recorded in Table 4.

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REFERENCES AND NOTES

[1] For Part **4** see: E. A. M. Badawey, S. M. Rida, F. S. G. Soliman and T. Kappe, *J. Heterocyclic Chem.*, **26**, 405 (1989).

[2] Conducted by the National Cancer Institute, Bethesda, Maryland, USA.