Benzazoles; XI[1]. Synthesis of New Fused Benzimidazoles by 1,3-Dipolar Cycloaddition Reactions

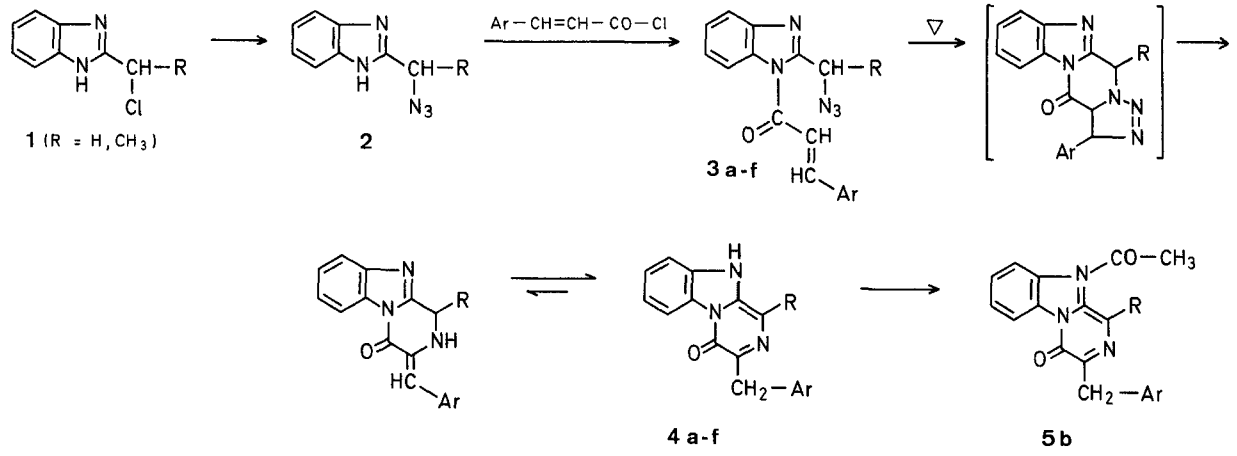
K. Hideg*, H. O. Hankovszky

Central Laboratory of Chemistry, University of Pécs, 7643 Pécs, P.O. Box. 99, Hungary

During our work in the field of benzazole compounds we aimed at developing syntheses of ring systems condensed with benzimidazole.

On reacting 2-chloromethylbenzimidazole (**1**, R = H) or 2-(α-chloroethyl)-benzimidazole (**1**, R = CH_3) with sodium azide the corresponding azido-compound **2** was formed. The azides **2** were acylated to products **3a–f** with β-aryl-α,β-unsaturated carboxylic acid chlorides in a pyridine solution. It is known that olefins conjugated with a strongly electron-attracting group are converted via a 1,3-dipolar cycloaddition reaction[2,3,4] into compounds with a triazoline ring[5]. The addition of azides is not regiospecific[6], and the stability of compounds with a triazoline ring is very varying.

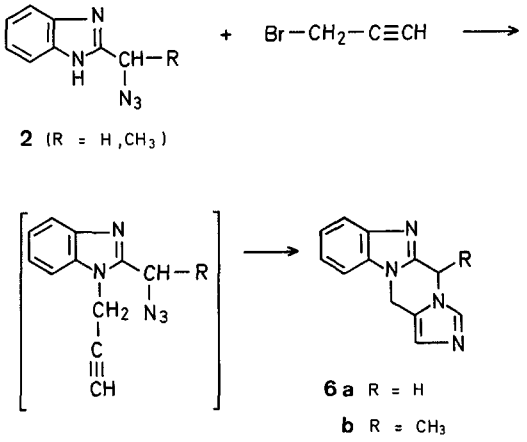
We have observed that, on heating toluene solutions of the acyl compounds **3a–f** for a short time, a solid substance is precipitated which shows in solution an intensive green fluorescence ($\lambda = 350$ nm). We presume that the reaction proceeds through an intermediate having a triazoline ring and the product is a substance of structure **4** formed through cleavage of nitrogen. It was impossible to determine unequivocally the position of the double bonds in the compounds **4** where R = H from the positions of the CH_2 signals in the ^{1}H-N.M.R. spectra [**4a**: 4.22 (s); **4b**: 4.16 (s) ppm].



	a	b	c	d	e	f
R	H	H	H	CH_3	CH_3	CH_3
Ar						

The fact that, in the N.M.R. spectrum of the derivative of **4b** acylated in pyridine by acetic anhydride (**5b**), the position of the methylene group remained unchanged [**5b**: 4.20 ppm (s)] supports the structure **5** which can be derived from the tautomer **4**. Also, the observation that the singlet signal of the methylene group is invariably present in the products **4d–f** and the methyl group appears as a (R = CH_3) singlet confirms the tautomeric structure **4**.

On reacting the azides **2** (R = H, CH_3) with 3-bromopropyne under alkylation of the NH group of benzimidazole, novel compounds having four condensed rings (**6a, 6b**) are formed as a result of a 1,3-dipolar cycloaddition reaction between the acetylene and the azido groups.



Melting points were measured by a Boetius micro-m.p. determining instrument, they have not been corrected. The I.R. spectra were measured in Nujol suspensions with a Zeiss Specord 71 type instrument. The N.M.R. spectra were established with a Perkin-Elmer R 12 instrument using tetramethylsilane (TMS) as internal standard. The compounds **1** (R = H, CH_3) used as starting substances[7,8,9] were prepared by the method of Phillips[10] from *o*-phenylenediamine and the corresponding halocarboxylic acid.

2-Azidomethyl- or 2-(α-Azidoethyl)-benzimidazoles 2 (R = H, CH_3); General Procedure:

To an aqueous solution (5 ml) of sodium azide (1.3 g, 0.02 mol), dimethylformamide (2 ml) and a solution of the respective compound **1** (0.01 mol) in ethanol (10 ml) are added. After being heated under reflux for 0.5 h the solvent is evaporated, the residue mixed with water, and extracted with chloroform. The combined extracts are dried with anhydrous sodium sulphate and evaporated in vacuum. The residue is crystallized from chloroform/*n*-hexane, filtered, and washed with ether (see Table 1).

***N*-Acylated 2-Azidoalkylbenzimidazoles (3a–f); General Procedure:**

To the solution of the azidobenzimidazole **2** (0.03 mol) in pyridine (30 ml), the β-aryl-α,β-unsaturated carboxylic acid chloride (0.036 mol) is added with stirring. After being stirred for 2 h at 20–40° the mixture is poured on to ice. The precipitated acid amide derivative is filtered and washed consecutively with water, ethanol, and finally with ether. The crude product is crystallized from acetone/*n*-hexane (see Table 1).

Pyrazino-benzimidazoles (4a–f); General Procedure:

After dissolving the acylated azidobenzimidazole **3a–f** (0.01 mol) in toluene (20 ml), the solution is refluxed for 1 h. On filtering

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Table 1. 2-Azidoalkylbenzimidazoles **2** and **3**

Compound	Yield [%]	m.p.	Molecular Formula[a]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
2 (R = H)	52	160–162°	$C_8H_7N_5$ (173.2)	2070 (N_3)	4.7 (s, 2H, —CH_2—); 7.1–7.8 (m, 4H_{arom})
2 (R = CH_3)	78	143–144°	$C_9H_9N_5$ (187.2)	2090 (N_3)	1.78 (d, 3H, —CH_3, J = 7 Hz); 4.98 (q, 1H, —CH<); 7.1–7.7 (m, 4H_{arom})
3a	84	115–116°	$C_{17}H_{13}N_5O$ (303.3)	2080 (N_3); 1685 (C=O)	4.74 (s, 2H, —CH_2—); 7.11 (d, 1H, =CH—, J = 15.6 Hz); 7.2–7.7 (m, 9H_{arom}); 7.92 (d, 1H, =CH—, J = 15.6 Hz)
3b	88	124–125°	$C_{17}H_{12}ClN_5O$ (337.8)	2080 (N_3); 1685 (C=O)	4.82 (s, 2H, —CH_2—); 7.1–7.8 (m, 8H_{arom}); 7.59 (d, 1H, =CH—, J = 15.6 Hz); 8.41 (d, 1H, =CH—, J = 15.6 Hz)
3c	75	122–124	$C_{21}H_{15}N_5O$ (353.4)	2090 (N_3); 1685 (C=O)	4.84 (s, 2H, —CH_2—); 7.1–8.4 (m, 11H_{arom} + =CH—); 8.80 (d, 1H, =CH—; J = 14.4 Hz)
3d	72	103–105°	$C_{18}H_{15}N_5O$ (317.4)	2090 (N_3); 1680 (C=O)	1.85 (d, 3H, —CH_3, J = 6.6 Hz); 5.23 (q, 1H, —CH<); 7.19 (d, 1H, =CH—, J = 15.6 Hz); 7.3–7.9 (m, 9H_{arom}); 7.99 (d, 1H, =CH—, J = 15.6 Hz)
3e	76	98–99°	$C_{18}H_{14}ClN_5O$ (351.8)	2090 (N_3); 1690 (C=O)	1.85 (d, 3H, —CH_3, J = 6.6 Hz); 5.23 (q, 1H, —CH<); 7.2–7.9 (m, 8H_{arom}); 7.23 (d, 1H, =CH—, J = 15.0 Hz); 8.43 (d, 1H, =CH—, J = 15.0 Hz)
3f	57	131–133°	$C_{22}H_{17}N_5O$ (367.4)	2080 (N_3); 1680 (C=O)	1.85 (d, 3H, —CH_3, J = 6.6 Hz); 5.28 (q, 1H, —CH<); 7.1–8.3 (m, 11H_{arom} + =CH—); 8.82 (d, 1H, =CH—, J = 15.6 Hz)

[a] All compounds gave satisfactory microanalyses (C ±0.18%, H ±0.24%, N ±0.21%).

Table 2. Fused Benzimidazoles **4** and **6**

Compound	Yield [%]	m.p.	Molecular Formula[a]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
4a	50	207–209°	$C_{17}H_{13}N_3O$ (275.3)	1630 (C=C)	4.22 (s, 2H, —CH_2—); 7.1–7.8 (m, 8H_{arom}); 7.8 (s, 1H, =CH—); 8.65 (d, 1H, =C—6H_{arom}, J = 7.2 Hz)
4b	49	217–219°	$C_{17}H_{12}ClN_3O$ (309.8)	1630 (C=C)	4.16 (s, 2H, —CH_2—); 7.1–7.6 (m, 7H_{arom} + =CH—); 8.62 (d, 1H, =C—6H_{arom}, J = 7.2 Hz)
4c	30	200–202°	$C_{21}H_{15}N_3O$ (325.4)	1630 (C=C)	4.42 (s, 2H, —CH_2—); 7.1–8.4 (m, 10H_{arom} + =CH—); 8.60 (d, 1H, =C—6H_{arom}, J = 7.2 Hz)
4d	67	217–218°	$C_{18}H_{15}N_3O$ (289.3)	1630 (C=C)	2.52 (s, 3H, —CH_3); 4.22 (s, 2H, —CH_2—); 7.0–7.5 (m, 8H_{arom}); 8.82 (d, 1H, =C—6H_{arom}, J = 7.2 Hz)
4e	50	215–216°	$C_{18}H_{14}ClN_3O$ (323.8)	1630 (C=C)	2.44 (s, 3H, —CH_3); 4.18 (s, 2H, —CH_2—); 6.9–7.6 (m, 7H_{arom}); 8.71 (d, 1H, =C—6H_{arom}, J = 8.4 Hz)
4f	65	226–228°	$C_{22}H_{17}N_3O$ (339.4)	1630 (C=C)	2.40 (s, 3H, —CH_3); 4.50 (s, 2H, —CH_2—); 7.1–8.1 (m, 10H_{arom}); 8.70 (d, 1H, =C—6H_{arom}, J = 7.2 Hz)
6a	52	256–257°	$C_{11}H_9N_5$ (211.2)[b]		5.16 (s, 2H, —CH_2—); 5.90 (s, 2H, —CH_2—); 7.3–7.8 (m, 4H_{arom}); 7.90 (s, 1H, =C—12H)
6b	70	213–214°	$C_{12}H_{11}N_5$ (225.3)		2.14 (d, 3H, —CH_3, J = 7.2 Hz); 5.50 (s, 2H, —CH_2—); 5.89 (q, 1H, —CH); 7.24 (s, 1H, =C—12H); 7.3–7.8 (m, 4H_{arom})

[a] All products gave satisfactory microanalyses (C ±0.19%, H ±0.24%, N ±0.28%).
[b] M.S.: m/e (relative intensity) = 211 ($M^{\oplus}$, 100).

the solution while hot, the precipitated product is separated and washed with toluene and ether. The product is crystallized from dimethyl sulphoxide/ethanol (see Table 2).

3-(1-Naphthyl)-10-acetyl-4-oxo-4,10-dihydropyrazino[3,4-*a*]benzimidazole (5b):

3-(1-Naphthyl)-4-oxo-4,10-dihydropyrazino[3,4-*a*]benzimidazole (**4b**; 0.31 g, 0.001 mol) is dissolved in anhydrous pyridine (5 ml) then acetic anhydride (5 ml) is added and the mixture allowed to stand for 3 h. After pouring the mixture on to ice, the precipitate is filtered and washed consecutively with water, ethanol, and ether; yield: 0.30 g (85%); m.p. 169–171°. The crude product is recrystallized from dimethyl sulphoxide/ethanol; m.p. 174–176°.

$C_{19}H_{14}ClN_3O_2$ (351.8)	calc.	C 64.87	H 4.01	Cl 10.08	N 11.94
	found	64.57	4.31	10.12	11.60

M.S.: m/e (relative intensity) = 351 ($M^{\oplus}$, 30), 316 (10), 309 (25), 274 (100), 246 (20).

I.R. (Nujol): ν_{max} = 1720, 1650, 1565 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2.78 (s, 3H, CH_3); 4.20 (s, 2H, CH_2); 7.1–7.7 (m, 7H_{arom}); 8.14 (s, 1H, =CH—); 8.70 ppm (d, 1H, =C-6—H_{arom}, J = 7.2 Hz).

Triazolo-pyrazino-benzimidazoles (6a, b); General Procedure:

2-Azidoalkylbenzimidazole (0.03 mol) is dissolved in ethanol (50 ml) containing potassium hydroxide (1.68 g, 0.03 mol). The solu-