SYNTHESIS AND TRANSFORMATIONS OF 2-AMINO-1- (4,5-DI - HYDRO-1*H*-IMIDAZOL-2-YL)BENZIMIDAZOLES. A ROUTE TO 2,3 -DIHYDROBENZO[4,5]IMIDAZO[1,2-*c*]IMIDAZO[1,2-*a*][1,3,5] - TRIAZINE RING SYSTEM

Franciszek Sączewski,* Tomasz Dębowski, and Jacek Szmigiel

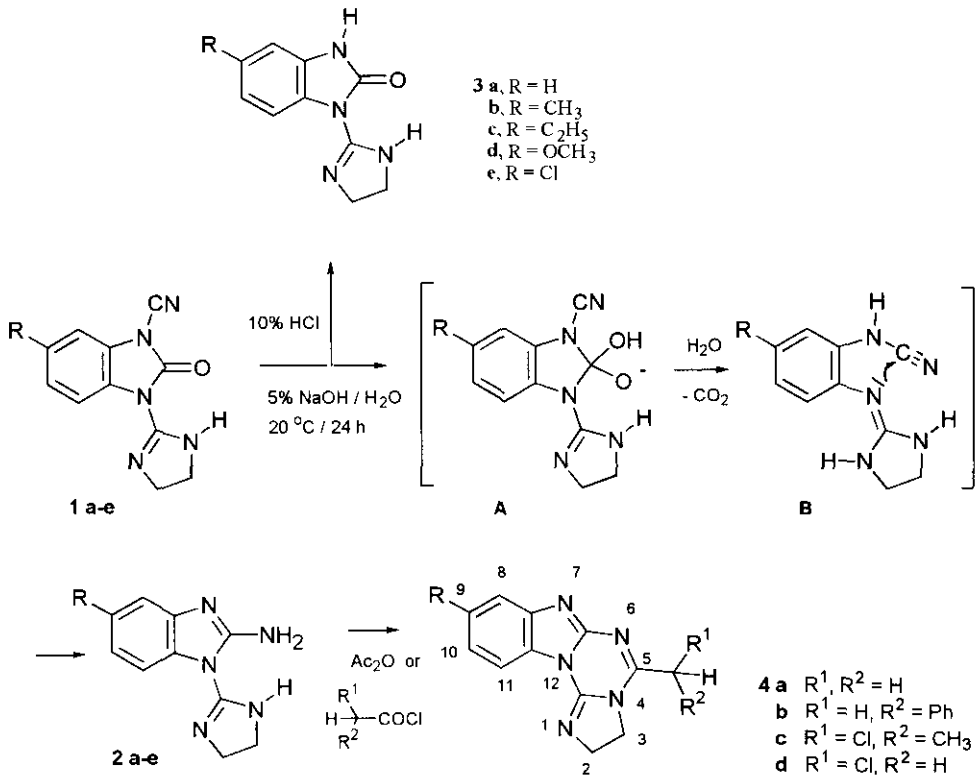
Department of Organic Chemistry, Medical University of Gdańsk, Poland

Abstract - Starting from 3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-oxo-2,3-dihydro-benzimidazole-1-carbonitriles (**1a-e**) the 2-amino-1-(4,5-dihydro-1*H*-imidazol-2-yl)benzimidazoles (**2a-e**) and 1-(4,5-dihydro-1*H*-imidazol-2-yl)-2-oxo-2,3-dihydrobenzimidazoles (**3a-e**) have been synthesized. Cyclocondensation of **2a** with acetic anhydride or acyl chlorides gave novel functionalized 2,3-dihydro-benzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*]triazines (**4a-d**).

2-Aminobenzimidazoles occur in a broad spectrum of drugs and pharmacological agents[1] with antihistaminic,[2] hypotensive,[3] anthelmintic,[4,5] antiviral,[6] antitumor,[7] antibacterial,[8,9] antiaggregatory,[10] antiarrythmic,[11] analgesic,[12] or antiinflammatory properties.[13] There has been widespread interest in their chemistry, although many simple 2-aminobenzimidazoles are still not readily available.[14]

In connection with our studies on novel antihypertensive aryliminoimidazolines (clonidine, moxonidine) analogs with the exocyclic nitrogen atom incorporated into an azole ring system, we have previously described the facile methods for preparation of the 1-(4,5-dihydro-1*H*-imidazol-2-yl)benzimidazoles[15] and the 3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-oxo-2,3-dihydrobenzimidazole-1-carbonitriles of type **1**.[16] However, attempts to prepare 2-amino-1-(4,5-dihydro-1*H*-imidazol-2-yl)benzimidazoles (**2**) by the direct heteroalkylation of 2-amino-benzimidazoles with an imidazoline derivative possessing a good leaving group (Cl, CH_3S or $NHNO_2$) at the position C-2 have failed. Thus, we wish to describe herein a possible entry to 2-aminobenzimidazole derivatives (**2**) and their application to the synthesis of novel functionalized 2,3-dihydrobenzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*] [1,3,5]triazine ring system (**4**) (Scheme 1).

Treatment of the carbonitriles (**1a-e**) with aqueous 5% NaOH at room temperature for 24 h affords the corresponding 2-aminobenzimidazole derivatives (**2a-e**) and 2-oxo-2,3-dihydrobenzimidazoles (**3a-e**).



Scheme 1

Products (**2**) and (**3**) thus obtained can be easily separated as the former compounds deposit from the reaction mixture and are simply filtered. Compounds (**2**) are obtained upon neutralization of the filtrate with 10% HCl.

Mechanistically, the formation of **2** can be rationalized by invoking the initial nucleophilic attack of an hydroxide anion at the carbon atom of the C=O group of **1** leading to the intermediate (**A**) followed by the imidazoline ring scission and subsequent loss of CO_2 molecule which results in the formation of the *N*-acylcyanamide (**B**). This process is completed by an intramolecular nucleophilic attack of the exocyclic nitrogen atom to the cyano carbon in **B** to give the final product (**2**).

Transformation of carbonitriles (**1**) into 2-aminobenzimidazoles (**2**) was rather unexpected in view of the previous findings that 2-oxo-2,3-dihydrobenzimidazoles were stable under Schotten-Baumann reaction conditions,[14,17] and the hydrolysis of their 1,3-diacetyl or 1,3-diarylsulfonyl derivatives under basic conditions led to the exclusive formation of the parent 2-oxo-2,3-dihydrobenzimidazoles.[18] Therefore, we have estimated the reactivity of **1** using *ab initio* MO calculations.[19] In general, the reaction with hard reagent would be the electrostatically -controlled reaction and positive charges at each electrophilic center

must be considered. For the two electrophilic sites in **1a** the following charges were calculated: 0.52 e (the cyano carbon atom) and 1.04 e (the carbon atom of the carbonyl group). In this viewpoint, the nucleophile (OH^-) can easily approach the later site giving rise to the formation of the intermediate (**A**).

Presence of the electron-donating CH_3O group in benzimidazole ring of **1d** caused a dramatic decrease in the yield of product (**2d**) (cf. Table 1). Assuming that, by analogy to aromatic amides, in the alkaline hydrolysis of 2-oxobenzimidazoles (**1**) the rate-determining step is the attack of hydroxide ion at the carbonyl atom, the OCH_3 group is predicted to increase the free energy of the transition state, and hence, decrease the rate of this reaction.

The common IR feature of the products (**2**) and (**3**) is the lack of C≡N vibrations at 2250-2270 cm^{-1}. The IR spectra of **3**, in contradistinction to these of **2**, exhibit C=O vibrations at 1708-1728 cm^{-1}. Physical and spectroscopic properties of the 2-oxobenzimidazoles (**3**) prepared herein are identical with these described by us elsewhere.[20]

Table 1. 2-Aminobenzimidazoles (**2a-e**), 2-oxobenzimidazoles (**3a-e**) and 2,3-dihydrobenzo[4,5]imidazo[1,2- *c*]imidazo[1,2-*a*][1,3,5]triazines (**4a-d**).

Product	R	R^1	R^2	Yield (%)	mp (^{0} C) (solvent)	Molecular Formula	Analysis % Calcd (Found) C	H	N
2a	H	-	-	45	204 - 207 (EtOH)	$C_{10}H_{11}N_5$	59.68 (59.44	5.51 5.29	34.80 35.02)
2b	CH_3	-	-	47	224 - 226 (DMF/H_2O)	$C_{11}H_{13}N_5$	61.37 (61.14	6.08 6.33	32.54 32.38)
2c	C_2H_5	-	-	52	200 - 203 (MeOH)	$C_{12}H_{15}N_5$	62.86 (63.11	6.59 6.54	30.55 30.29)
2d	OCH_3	-	-	7	195 - 198 (H_2O)	$C_{11}H_{13}N_5O$	57.12 (57.33	5.66 5.34	30.29 30.55)
2e	Cl	-	-	67	220 - 223 (MeOH)	$C_{10}H_{10}N_5Cl$	50.96 (50.82	4.28 4.39	29.72 29.56)
3a	H	-	-	23	196 - 198 (EtOH)	$C_{10}H_{10}N_4O$	59.39 (59.11	4.98 4.88	27.71 28.02)
3b	CH_3	-	-	25	188 - 190 (MeOH)	$C_{11}H_{12}N_4O$	61.09 (61.22	5.59 5.78	25.91 26.87)
3c	C_2H_5	-	-	19	179 - 182 (MeOH)	$C_{12}H_{14}N_4O$	62.59 (62.71	6.13 6.34	24.33 24.59)
3d	OCH_3	-	-	49	194 - 196 (MeOH)	$C_{11}H_{12}N_4O_2$	56.89 (56.79	5.21 5.33	24.13 23.99)
3e	Cl	-	-	11	178 - 180 (DMF/H_2O)	$C_{10}H_9N_4OCl$	50.75 (51.01	3.83 3.88	23.68 23.54)
4a	H	H	H	48	285 - 288 (MeOH)	$C_{12}H_{11}N_5$	63.98 (64.13	4.92 5.15	31.09 31.01)
4b	H	H	Ph	63	238 - 241 (DMF)	$C_{18}H_{15}N_5$	71.74 (71.54	5.02 5.12	23.24 23.19)
4c	H	Cl	CH_3	51	240 (MeOH)	$C_{13}H_{12}N_5Cl$	57.04 (57.33	4.42 4.27	25.59 25.69)
4d	H	Cl	H	71	260 (DMF)	$C_{12}H_{10}N_5Cl$	55.49 (55.28	3.88 4.14	26.97 27.15)

Table 2. Spectroscopic data of compounds (**2 a - e**) and (**4 a - e**)

Product	IR ((cm^{-1}, KBr)	^{1}H NMR (DMSO - d_6)	^{13}C NMR (DMSO - d_6)
2a	3264, 1680, 1664, 1616, 1600, 1488, 1452, 1264	3.5 (m , 2H, CH_2), 3.8 (m, 2H, CH_2), 6.9 - 7.3 (m, 3H, CH), 7.4 - 7.6 (m, 1H, CH), 7.7 (s, 2H, NH_2)	43.72, 52.3, 111.58, 115.29, 118.95, 122.64, 130.64, 142.82, 154.09, 156.47
2b [1]	3312, 3088, 1664, 1620, 1488, 1445, 1276	2.3 (s, 3H, CH_3), 3.5 (m, 2H, CH_2), 3.8 (m, 2H, CH_2), 6.8 (dd, J = 8.1, 1.2 Hz, 1H, CH), 6.9 (s, 1H, NH), 7.0 (d, J = 1.2 Hz, 1H, CH), 7.4 (d, J = 8.1 Hz, 1H, CH), 7.6 (s, 2H, NH_2)	21.02, 43.64, 52.22, 111.1, 115.66, 119.71, 128.63, 131.57, 143.05, 154.2, 156.5
2c	3336, 1680, 1516, 1424, 1299, 1268	1.2 (t, J = 7.5 Hz, 3H, CH_3), 2.6 (q, J = 7.5 Hz, 2H, CH_2), 3.2 - 3.6 (m, 2H, CH_2), 3.7 - 3.9 (m , 2H, CH_2), 6.8 (dd, J = 8.2, 1.5 Hz, 1H, CH), 6.9 (s, 1H, NH), 7.0 (d, J = 1.5 Hz, 1H, CH), 7.4 (d, J = 8.2 Hz, 1H, CH), 7.6 (s, 2H, NH_2)	16.34, 28.32, 43.68, 52.23, 111.26, 114.5, 118.7, 128.87, 138.4, 143.1, 154.31, 156.6
2d	3296, 1668, 1640, 1616, 1488, 1424, 1200	3.4 - 3.6 (m , 2H, CH_2), 3.7 (s, 3H, CH_3), 3.8 - 3.9 (m, 2H, CH_2), 6.5 (dd, J = 6.2, 2.4 Hz, 1H, CH), 6.8 (d, J = 2.4 Hz, 1H, CH), 6.9 (s, 1H, CH), 7.4 (d, J = 6.8 Hz, 1H, CH), 7.7 (s, 2H, NH)	43.67, 52.23, 55.29, 110.26, 105.69, 111.65, 124.85, 144.03, 154.74, 155, 155.47
2e	3392, 3184, 1664, 1600, 1504, 1472, 1408	3.5 - 4.0 (m, 4H, CH_2), 6.9 (d, J = 8.3 Hz, 1H, CH), 7.0 (s, 1H, NH), 7.2 (s, 1H, NH), 7.5 (d, J = 8.3 Hz, 1H, CH), 7.8 (s, 2H, NH)	43.6, 51.9, 112.54, 114.71, 118.42, 126.97, 129.63, 144.27, 155.21, 156.14
4a	2960, 1696, 1616, 1568, 1440, 1392, 1248	2.4 (s, 3H, CH_3), 3.9 - 4.1 (m, 2H, CH_2), 4.1 - 4.2 (m, 2H, CH_2), 7.2 - 7.4 (m, 2H, CH), 7.6 - 7.7 (m, 1H, CH), 7.9 - 8.0 (m, 1H, CH)	21.5, 46.06, 51.29, 113.06, 118.4, 122.58, 124.5, 127.92, 138.81, 143.05, 150.05, 157.7
4b	2900, 1692, 1615, 1563, 1440, 1323, 1280	3.9 - 4.0 (m, 2H, CH_2), 4.0 (s, 2H, CH_2), 4.1 - 4.2 (m, 2H, CH_2), 7.2 - 7.4 (m, 7H, CH), 7.6 - 7.7 (m, 1H, CH), 7.9 - 8.0 (m, 1H, CH)	40.63, 45.94, 51.42, 113.15, 118.46, 122.76, 124.57, 127.07, 127.93, 128.6, 129.41, 134.3, 138.81, 143.06, 145.16, 158.63
4c	2960, 1696, 1616, 1568, 1536, 1440, 1152	1.8 (d, J = 6.3 Hz, 3H, CH_3), 4.0 - 4.2 (m, 2H, CH_2), 4.2 - 4.4 (m, 2H, CH_2), 5.2 (q, J = 6.3 Hz, 1H, CH), 7.3 - 7.5 (m, 2H, CH), 7.6 - 7.8 (m, 1H, CH), 7.9 - 8.1 (m, 1H, CH)	20.63, 45.77, 51.73, 53.06, 113.32, 118.78, 123.33, 124.82, 128.01, 143.07, 144.9, 149.96, 156.85
4d [2]	2912, 1696, 1616, 1568, 1536, 1428, 1280	4.1 (m, 2H, CH_2), 4.3 (m, 2H, CH_2), 4.7 (s, 2H, CH_2), 7.3 - 7.5 (m, 2H, CH), 7.6 - 7.8 (m, 1H, CH), 8.0 - 8.1 (m, 1H, CH)	

[1] MS (70 eV) *m z* = 215 (M^+, 100 %), 214 (26), 147 (13), 131 (5). [2] MS (70 eV) *m z* = 259 (M^+, 100 %), 260 (M + 1, 45), 261 (M + 2, 80), 258 (46), 223 (12), 224 (36), 225 (16), 156 (13), 157 (33), 130 (11), 129 (13), 102 (13)

We further found that the compound (**2a**) subjected to the reaction with acetic anhydride in the presence of triethylamine in boiling THF, undergoes *N*-acetylation reaction followed by a cyclocondensation process giving rise to the formation of 5-methyl-2,3-dihydrobenzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*][1,3,5]triazine (**4a**). Similarly, the reactions of **2a** with a variety of acyl chlorides afford the corresponding derivatives (**4b-d**).

Structures of the products (**2**, **3** and **4**) are confirmed by elemental analyses, IR, ^{1}H- and ^{13}C-NMR as well as MS spectral data presented in Table 2.

EXPERIMENTAL

Melting points were determined using a Boetius apparatus and are uncorrected. IR spectra were recorded on a Specord M80 spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer in DMSO-d_6 as solvent, locked on solvent deuterium and referenced to residual solvent protons. MS spectra were measured with a LKB 9000S spectrometer at 70 eV.

2-Amino-1-(4,5-dihydro-1*H*-imidazol-2-yl)benzimidazole (2a) and 1-(4,5-dihydro-1*H*-imidazol-2-yl)-2-oxo-2,3-dihydrobenzimidazole (3a):

A suspension of a nitrile (**1a**)[16] (0.5 g, 2.2 mmol) in aqueous 5% NaOH (20 mL) was stirred at rt for 24 h. The crude product (**2a**) that precipitated was collected by filtration, washed with H_2O and purified by recrystallization from EtOH (0.2 g; 45%). The alkaline filtrate was treated with 10% HCl (pH = 6), then, the pH of the solution was adjusted to 9 with 10% Na_2CO_3. Product (**3a**) that deposited was collected by suction, washed with H_2O and purified by recrystallization from EtOH (0.1 g, 23%).

Analogously were prepared compounds **(2b-e)** and **(3b-e).**

5-Methyl-2,3-dihydrobenzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*][1,3,5]triazine (4a):

To a suspension of 2-aminobenzimidazole (**2a**) (0.5 g, 2.43 mmol) in anhyd THF (15 mL) were succesively added triethylamine (0.68 mL, 4.9 mmol) and acetic anhydride (0.51 mL, 4.9 mmol). The reaction mixture was refluxed for 2 h, and after cooling, the solvent was removed under reduced pressure. The crude residue thus obtained was recrystallized from MeOH to give 0.27 g (48%) of the compound (**4a**).

5-Benzyl-2,3-dihydrobenzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*][1,3,5]triazine (4b):

To a suspension of 2-aminobenzimidazole (**2a**) (0.5 g, 2.48 mmol) in anhyd THF (15 mL) were added succesively triethylamine (0.69 mL, 4.96 mmol) and phenylacetyl chloride (0.65 mL, 4.96 mmol). The reaction mixture was refluxed for 2 h and after cooling to rt, the solvent was removed under reduced pressure. The solid residue was purified by recrystallization from DMF to give 0.47g (63%) of the compound (**4b**).

Analogously were prepared compounds (**4c**) and (**4d**).

Physico-chemical properties of the compounds (**2, 3**, and **4**) are given in Table 1 and the corresponding spectral data of **2** and **4** in Table 2.

ACKNOWLEDGEMENTS

We thank the Committee for Scientific Research (Grant KBN No 4 P05F 050 10) for financial support of this work.

REFERENCES

1. For recent review see: W. Nawrocka, *Boll. Chim. Farm.*, 1996, **135**, 18.
2. M. Menzer, G. Laban, H. G. Kazmirowski, P. Meisel, and E. Kretzschmar, *Ger.* (East) DD 281,383 (*Chem. Abstr.*, 1991, **114**, 185508k).
3. M. Paal, W. Stenzel, R. Brueckner, and B. Arman, *Ger. Offen.* DE 4.027.592 (*Chem. Abstr.*, 1992, **116**, 235629q).
4. E. Rovina, R. Sanchez-Alonso, J. Fueyo, M. P. Baltar, J. Bos, R. Inglesias, and M. L. Sanmartin, *Arzneim. Forsch. Drug Res.*, 1993, **43**, 689.
5. B. J. Banks, Ch. Dutton, and G. A. Crossman, *PTC Int. Appl.* W0 93,18010 (*Chem. Abstr.*, 1994, **120**, 107014f).
6. C. J. Paget, K. Kisner, R. L. Stone, and D .G. Ce Long, *J. Med. Chem.*, 1969, **12**, 1010.
7. E.A.M. Badawey, A.A. Haazza, S.M. Rida, and H. T. Y. Fahmy, *Arch. Pharm.*, 1993, **325**, 565.
8. M.G. Vigavita, T. Trevitera, C. Zappala, A. Trovato, M.T. Monoforte, R. Barbera, and F. Pizzimenti, *Il Farmaco*, 1990, **45**, 223.
9. E. Alcade, L. Perez-Garcia, I. Dinares, G. H. Coombs, and J. Frigola, *Eur. J. Med. Chem.*, 1992, **27**, 171.

10. P. Caroti, C. Ceccotti, F. Da Settimo, G. Primofiore, J. S. Franzone, J. S. Reboani, and C. Cravanzola, *Il Farmaco,* 1989, **44**, 227.

11. W. Spinelli, M.W. Winkley, T. T. Nguyen, and J. F. Moubarak, *J. Med. Chem.,* 1992, **35**, 705.

12. K. Taniguchi, S. Shigenoga, and T. Ogahara, *Chem. Pharm. Bull.,* 1993, **41**, 301.

13. A. Da Settimo, G. Primofiore, F. Da Settimo, and A. M. Mariani, *Il Farmaco,* 1992, **47**, 1293.

14. M. R. Grimmet, In *Comprehensive Heterocyclic Chemistry*, Vol. 5, ed. by A. R. Katritzky, and C. W. Rees, Pergamon Press, 1984, pp. 345-498.

15. A. R. Katritzki and F. Sączewski, *Synthesis,* **1990**, 561.

16. F. Sączewski and T. Dębowski, *Tetrahedron Lett.,* 1993, **34**, 2846.

17. O. Kym and L. Ratner, *Ber.,* 1912, **45**, 3238.

18. J. Sawlewicz and J. Jasińska, *Ann. Soc. Chim. Polon.,* 1964, **38**, 1073.

19. Formal charges were calculated at *ab initio* level using 6.31G* basis set as implemented into a SPARTAN program, version 5.0, 1977, Wavefunction Inc. 18401 Von Karman Ave., Suite 370, CA 92612, USA, installed on SGI O2 workstation.

20. F. Sączewski, T. Dębowski, J. Petrusewicz, and H. Trzeciak, *Arch. Pharm.*, in press.

Received, 13th May, 1998