Heterocycles of biological importance. Part 6[1]. The formation of novel biologically active pyrimido[1,2-*a*]benzimidazoles from electron deficient alkynes and 2-aminobenzimidazoles

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Dedicated to Professor Branko Stanovnik on his 65th birthday

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Abstract

2-Aminobenzimidazole (**1a)** and its 5,6-dimethyl derivative **1b** react with phenylpropynenitrile (**2)** to give 2-amino-4-phenylpyrimido[1,2-*a*]benzimidazoles **8a,b** in excellent yields. Of these compounds, 2-amino-7,8-dimethyl-4-phenylpyrimido[1,2-*a*]benzimidazole (**8b)** has been shown to possess diuretic properties. Acetylenic aldehydes **9a,b** also react with **1a,b** to give pyrimido[1,2-*a*]benzimidazoles **13a-13d** in good yield.

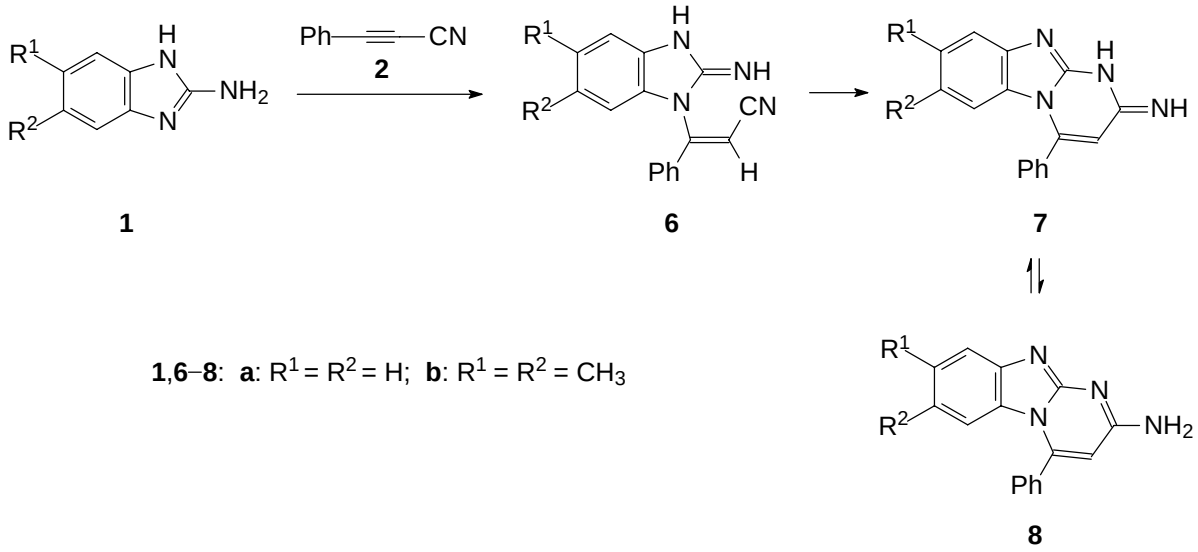
Keywords: 2-Aminobenzimidazole, pyrimido[1,2-*a*]benzimidazole, Michael addition, diuretic

Introduction

The usefulness of allenic and acetylenic nitriles as starting materials in heterocyclic syntheses has been amply demonstrated[2-12]. Recently, we have synthesized pyrimido[1,2-a]benzimidazoles from allenic nitriles and 2-aminobenzimidazoles and shown that such heterocycles are of great potential interest[1]. We now report that pyrimido[1,2-a]benzimidazoles are formed similarly from the reaction of acetylenic nitriles and acetylenic aldehydes with 2-aminobenzimidazoles.

Results and Discussion

When 3-phenylpropynenitrile (**2**) was allowed to react with 2-aminobenzimidazole (1a) and its 5,6-dimethyl derivative **1b**, we found that 2-amino-4-phenylpyrimido[1,2-*a*]benzimidazoles **8a**,**b** were obtained in high yield. The reaction of **2** and the benzimidazoles very likely proceeds by initial attack of the imino ring nitrogen of the benzimidazole to the acetylenic *β*-carbon, followed by cyclisation to give compounds **8** (Scheme 1).



Scheme 1

There is no indication whatsoever of initial attack of the 2-amino group of **1a**,**b** on C-3 of **2**. When 5,6-dimethyl substituted benzimidazole **1b** was used, a solid product **8b** precipitated from the reaction mixture immediately at reflux in *N*,*N*-dimethylformamide as solvent. This indicated that the conjugate addition is the rate determining step in pyrimidobenzimidazole formation, and cyclisation takes place immediately to give compound **8b** which precipitated from the reaction mixture.

The IR, ^{1}H NMR, ^{13}C NMR and the mass spectral data of the products are consistent with the structures assigned to **8a**,**b**. These products showed twin streching bands in the IR spectra at 3440, 3301 and 3442, 3303 cm^{-1} for NH_2 as well as intense stretching bands for C=N between 1653-1650 cm^{-1} and for C=C at 1600 cm^{-1}**.**

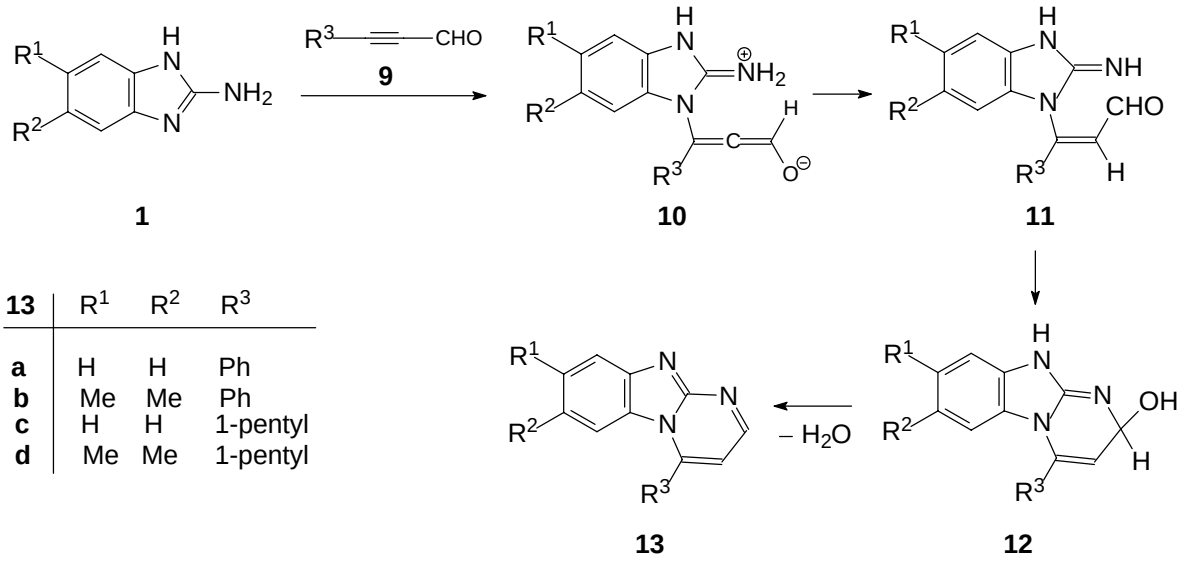
The NMR spectra of **8a**,**b** showed signals for two shielded aryl-protons each, one of which gives rise to a sharp singlet at δ = 6.15 ppm (**8a**) and 6.10 ppm (**8b**) and is attributed to 3-H. The other one, which appears as a multiplet at δ 6.13 ppm (for **8a**) and as a singlet at δ 5.87 ppm in the 7,8-dimethyl compound **8b**, is attributed to 6-H.

The shielding effect observed for 6-H is most likely due to the anisotropy of the phenyl group attached to C-4 which cannot be coplanar with the molecular skeleton and therefore exerts an

upfield shift on 6-H. The same effect has been observed also by *Al-Jallo* and others[13] for related systems.

The ^{13}C-NMR-spectra of **8a**,**b** display two low-field signals for C-2 (δ = 153.6 for **8a** and 153.5 for **8b**) and the guanidine-like carbon C-10a (δ = 160.5 for **8a** and 161.5 for **8b**), whereas the signals for the enamine-β-carbon-like C-3 are shifted upfield: δ = 99.6 (**8a**) and 98.9 (**8b**). All other carbon and proton signals fall into the expected shift ranges (see Experimental).

Similarly acetylenic aldehydes **9a,b** reacted by conjugate addition to **1** giving 4-pentyl and 4-phenylpyrimido[1,2-*a*]benzimidazoles **13a-d** by elimination of water via intermediates **10**, **11**, and **12** (Scheme 2).



13	R^1	R^2	R^3
a	H	H	Ph
b	Me	Me	Ph
c	H	H	1-pentyl
d	Me	Me	1-pentyl

Scheme 2

The structural assignment of **13a-d** is based on the following characteristical spectral data. The ^{1}H-NMR signals for 2-H are found at pronouncedly low field between δ = 8.56 and 8.80 ppm as expected, whereas 3-H gives rise to resonances between 6.60 and 6.98 ppm. Again, the anisotropy exerted by the non-coplanar 4-phenyl group in **13a**,**b** gives rise to significant upfield shifts for 6-H compared to 4-pentyl substitution (in **13c**,**d**): δ = 6.71 (for **13a**) and 6.43 (for **13b**) in contrast to 8.16 (for **13c**) and 7.76 (for **13d**), respectively. The ^{13}C-NMR spectra show signals for C-2 between 154.7 and 156.0 ppm, and for the quaternary carbon C-10a at 151.0–151.4 ppm, which is 10 ppm upfield compared to **8a**,**b**. Again, C-3 signals are relatively upfield in the range of 105.9–108.4 ppm. All other carbon and proton chemical shifts fall into the range of expectation (see Experimental).

Biological activity of compound 8b

2-Amino-7,8-dimethyl-4-phenylpyrimido[1,2-*a*]benzimidazole (**8b)** was subjected to various biological activity tests[14]. It was found that it was completely non toxic to mice at concentrations of up to 300 milligrams per kilogram by weight used in the experiment when administered orally or peritoneally. As a metabolic agent, it possesses diuretic properties.

Test 1. Acute toxicity

Mice were dosed at 300mg/kg p.o. and 200mg/kg i.p. for observation of acute toxic symptoms or autonomic effects during the subsequent 72 hours. When none were noted; pharmacological evaluation proceeded employing doses and concentrations for each test based on appropriate multiples of doses required by suitable reference compounds. When acute toxicity was observed initially, the minimal toxic dose was determined and pharmacological screening doses were reduced proportionally. Since no abnormal responses were observed for the 300mg/kg (p.o.) and 200mg/kg (i.p.) doses, the compound was regarded non-toxic.

Test 2. Diuretic properties

Rats were hydrated and given the test drug p.o., the score refers to the multiple of that day's control sodium excretion (mceq/100g rat) produced by a test drug, e.g. if the control sodium excretion is 150 mceq (usual) and the test drug produces more than twice that amount, say 450 mceq, the score is 450/150 = 3.0 (Table 1, mceq = microgramequivalent).

Table 1. Effect of compound **8b** on the metabolic system

N°	Test	Dose[a]	Criterion	Response
1.	Hypocholesterolemic (mice)	400	>15	0
2.	HP-Beta-Lipoprotein (mice)	400	>20	0
3.	Hypoglycemic (mice)	100	>20	0
4.	Diuretic (rat)	20	>2	3.5
5.	Diuretic [b] (rat)	10		1.2
	"	20		3.6 ED_{100}[c]
	"	20		2.1 MED[d]

[a] milligrams per kilogram of weight.

[b] With reference to spironolactone (= 7*α*-Acetylthio-3-oxo-17 *α* -pregn-4-ene-21,17*β*-carbolactone).

[c] ED_{100} = Dose which is always active in the test system.

[d] MED = Minimum Effective Dose.

Experimental Section

General Procedures. Elemental and spectroscopic analyses were performed at Institut fuer Chemie at Universitaet Duisburg-Essen in Duisburg, Germany. Melting points were determined with a Reichert Thermovar microscope and are uncorrected. The infrared (IR) spectra (potassium bromide pellets) were measured with a Varian Cary 2290 and a Perkin-Elmer 298 spectrophotometer. The 300 MHz and 75 MHz ^{13}C NMR spectra were performed on a Bruker WM 300 instrument with tetramethylsilane as internal standard. Mass spectra were obtained with a MAT 311A instrument using EI at 70 eV and direct inlet. Purities of the samples were checked by tlc. Alumina of activity 5 for column chromatography was prepared by mixing 15 ml of distilled water and 100g of neutral alumina which had been preheated for 4 hours at 120°C. Combustion analyses were performed with CHN elemental analyzer "Carlo Erba" Model 1106. Phenylpropynenitrile (**2)** was prepared as previously reported.[15]

Preparation of 2-amino-4-phenylpyrimido[1,2-*a*]benzimidazoles (8a,b). Phenylpropynenitrile (**2**, 1.27g, 10 mmol) was heated under reflux with 2-aminobenzimidazole (**1a**, 1.33g, 10 mmol) or 5,6-dimethyl-2-aminobenzimidazole (**1b**, 1.61g, 10 mmol) in *N*,*N*-dimethylformamide (50 mL). A solid precipitated after 3 hours (from **2** and **1a**) or immediately (from **1b** and **2**).

2-Amino-4-phenylpyrimido[1,2-*a*]benzimidazole (8a). Yield 1.97g (76%) of colorless crystals (DMSO), no melt below 300°C (Lit. [16]: 364-366°C); IR: ν/cm^{-1} 3440, 3303 (NH_2), 3054 (aryl. C-H), 1653 (C=N), 1600 (C=C), 1533 (NH_2 def). NMR data: δ_H (DMSO-d_6) 6.13 (1H, 6-H), 6.15 (1H, s, 3-H), 6.75 (1H, m, 7-H), 7.15 (1H, m, 8-H), 7.50 (1H, m, 9-H), 7.40 (2H, s, NH_2 deuterium exchangable), 7.63-7.69 (5H, m, Ph). δ_C (DMSO-d_6) 99.6 (C-3), 112.5 (C-6), 117.6 (C-9), 118.7 (C-8), 123.9 (C-7), 127.7 (C-5a), 128.5 (Ph-C3, C5), 129.3 (Ph-C2, C6), 130.8 (Ph-C4), 132.6 (Ph-C1), 144.7 (C-9a), 147.7 (C-4), 153.6 (C-2), 160.5 (C-10a). MS: *m*/*z* (%) = 260 (M^+, 100), 259 (23), 220 (18), 133 (8), 116 (4), 104 (5), 90 (9), 77 (5). Anal. Calcd. for $C_{16}H_{12}N_4$: C, 73.85; H, 4.61; N, 21.54. Found: C, 73.41; H, 4.58; N, 21.22.

2-Amino-7,8-dimethyl-4-phenylpyrimido[1,2-*a*]benzimidazole (8b). Yield 2.50g (87%), colorless crystals (DMSO), no melt below 300°C; ir: ν /cm^{-1} 3442, 3301 (NH_2), 3050 (aryl C-H), 1650 (C=N), 1600 (C=C), 1529 (NH_2 def). NMR data: δ_H (DMSO-d_6) 1.95 (3H, s, 7-CH_3), 2.25 (3H, s, 8-CH_3), 5.87 (1H, s, 6-H), 6.10 (1H, s, 3-H), 7.27 (2H, s, NH_2 deuterium exchangable), 7.65 (1H, s, 9-H), 7.59-7.70 (5H, m, Ph). δ_C (DMSO-d_6) 19.84 (8-CH_3), 20.06 (7-CH_3), 98.91 (C-3), 112.94 (C-6), 117.94 (C-9), 126.29 (C-7), 126.51 (C-8), 128.39 (Ph-C3, C5), 129.06 (Ph-C2, C6), 130.50 (Ph-C4), 132.03 (C-5a), 132.61 (Ph-C1), 143.13 (C-9a), 147.50 (C-4), 153.50 (C-2), 161.5 (C-10a). MS: *m*/*z* (%) = 288 (M^+, 100), 287 (34), 273 (15), 160 (6), 144 (7), 136 (6), 128 (5). Anal. Calcd. for $C_{18}H_{16}N_4$: C, 75.00; H, 5.56; N, 19.44. Found: C, 74.86; H, 5.53; N, 19.15.

4-Phenylpyrimido[1,2-*a*]benzimidazole (13a). 2-Aminobenzimidazole (**1a**, 2.53g, 19 mmol) was heated under reflux with phenylpropargylaldehyde (**9a**, 2.80g, 19 mmol) in ethanol (25 mL) for 6 days. Removal of solvent gave a dark brown oil which partially solidified on standing at room temperature. Purification of 5.33g of this crude product by column chromatography on neutral alumina (300 g, activity 5) eluting with hexane/ethyl acetate (2:8) gave a crystalline

residue. Crystallization from dichloromethane/hexane gave 3.98g (75%) of colorless crystals, mp 178–180°C; ir: ν /cm^{-1} 3047 (aryl. C-H), 1622 (C=N) and 1603 (C=C). NMR data: δ_H ($CDCl_3$) 6.71 (1H, m, 6-H), 6.75 (1H, m, 3-H), 7.02 (1H, m, 7-H), 7.50 (1H, m, 8-H), 7.59 – 7.75 (5H, m, Ph), 8.00 (1H, m, 9-H), 8.80 (1H, m, 2-H). δ_C ($CDCl_3$) 108.4 (C-3), 114.7 (C-6), 119.7 (C-9), 121.1 (C-8), 125.9 (C-7), 127.1 (C-5a), 128.5 (Ph-C3, C5), 129.5 (Ph-C2, C6), 131.2 (Ph-C4), 132.2 (Ph-C1), 144.4 (C-9a), 149.6 (C-4), 151.4 (C-10a), 156.0 (C-2). MS: *m*/*z* (%) = 245 (M^+, 100), 244 (65), 243 (9), 123 (7), 122 (11), 116 (3), 90 (5). Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found C, 78.17; H, 4.52; N, 17.09.

7,8-Dimethyl-4-phenylpyrimido[1,2-*a*]benzimidazole (13b). 2-Amino-5,6-dimethylbenzimidazole (**1b**, 3.0g, 19 mmol) was heated under reflux with phenylpropargylaldehyde (**9a**, 2.8g, 19 mmol) in ethanol (25 mL) for 7 days. Removal of solvent gave a crude product (5.6g) which was purified by column chromatography on neutral alumina (300g, activity 5) eluting with ethyl acetate to give a crystalline compound which was crystallized from dichloromethane/hexane to give 3.4g (61%) of colorless crystals, mp 178–179°C; ir: ν /cm^{-1} 3054 (aryl C-H), 2966 (aliph. C-H), 1610 (C=N), 1594 (C=C). NMR data: δ_H ($CDCl_3$) 2.17 (3H, s, 7-CH_3), 2.39 (3H, s, 8-CH_3), 6.43 (1H, s, 6-H), 6.71 (1H, m, 3-H), 7.59 – 7.74 (5H, m, Ph), 7.75 (1H, s, 9-H), 8.75 (1H, m, 2-H). δ_C ($CDCl_3$) 20.3 (8-CH_3), 20.7 (7-CH_3), 108.0 (C-3), 114.7 (C-6), 119.5 (C-9), 125.5 (C-7), 129.9 (C-8), 128.6 (Ph-C3, C5), 129.5 (Ph-C2, C6), 131.2 (Ph-C4), 132.3 (Ph-C1), 135.2 (C-5a), 143.2 (C-9a), 149.1 (C-4), 151.0 (C-10a), 155.0 (C-2). MS: *m*/*z* (%) = 273 (M^+, 100), 272 (39), 270 (4), 259 (5), 258 (22), 257 (4), 256 (6), 168 (4), 143 (4), 137 (3), 129 (8), 116 (3) Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found C, 79.09; H, 5.56; N, 15.31.

4-Pentylpyrimido[1,2-*a*]benzimidazole (13c). 2-Aminobenzimidazole (**1a**, 2.66g, 20 mmol) was refluxed with oct-2-ynal (**2b**, 2.48 g, 20 mmol) in ethanol (50 mL) for 3 days. Removal of solvent gave an oily crude product. Column chromatography on neutral alumina (activity 5) eluting with dichloromethane/methanol (7:3) gave a crude product as solid. Crystallisation from dichloromethane/hexane gave 4.43 g (86%) of colorless crystals, mp 117–119°C; ir: ν /cm^{-1} 3055 (aryl C-H), 2960 (aliph C-H), 619 (C=N), 1595 (C=C). NMR data: δ_H (DMSO-d_6) 0.91 (3H, m, *CH*$_3$-C_4H_8), 1.37 – 1.56 (4H, m, CH_3-*C*$_2$*H*$_4$-C_2H_4), 1.83 (2H, m, C_3H_7-*CH*$_2$-CH_2), 3.41 (2H, m, C_4H_9-*CH*$_2$), 6.98 (1H, m, 3-H), 7.43 (1H, m, 7-H), 7.58 (1H, m, 8-H), 7.89 (1H, m, 9-H), 8.16 (1H, m, 6-H), 8.72 (1H, m, 2-H). δ_C (DMSO-d_6): δ 14.0 (C-5'), 22.1 (C-4'), 25.2 (C-3'), 30.7 (C-2'), 32.2 (C-1'), 106.2 (C-3), 116.3 (C-6), 119.5 (C-9), 121.6 (C-7), 125.8 (C-8), 127.2 (C-5a), 144.3 (C-9a), 151.4 (C-10a), 153.5 (C-4), 155.7 (C-2). MS: *m*/*z* (%) = 239 (M^+, 100), 196 (20), 194 (10), 184 (14), 183 (97), 182 (20), 156 (9), 155 (15), 102 (8), 90 (9). Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found C, 75.10; H, 7.20; N, 17.50.

7,8-Dimethyl-4-pentylpyrimido[1,2-*a*]benzimidazole (13d). 2-Amino-5,6-dimethylbenzimidazole (**1a**, 3.23g, 20 mmol) was refluxed with oct-2-ynal (**9b**, 2.48g, 20 mmol) in ethanol (50 mL) for 3 days. Removal of solvent gave a dark brown oil. Purification of this crude product by column chromatography on neutral alumina (activity 5) eluting with hexane/ethyl acetate (1:9) gave a crude solid. Crystallization from hexane/ethyl acetate gave 3.68g (68%) of colorless crystals, mp 133–135°C; ir: ν /cm^{-1}: 3075 (aryl C-H), 2957 (aliph.C-H), 1627 (C=N), 1603

(C=C). NMR data: δ_H (DMSO-d_6): 0.97 (3H, m, *CH*$_3$-C_4H_8), 1.39 – 1.61 (4H, m, CH_3-*C_2H_4*-C_2H_4), 1.92 (2H, m, C_3H_9-*CH*$_2$-CH_2), 2.43 (3H, s, 8-CH_3), 2.45 (3H, s, 7- CH_3), 3.24 (2H, m, C_4H_9-*CH*$_2$), 6.60 (1H, m, 3-H), 7.64 (1H, s, 9-H), 7.76 (1H, s, 6-H), 8.56 (1H, m, 2-H). δ_C (DMSO-d_6): 4.1 (C-5'), 20.3 (7- CH_3), 20.5 (8- CH_3), 22.1 (C-4'), 25.3 (C-3'), 30.8 (C-2'), 32.1 (C-1'), 105.9 (C-3), 115.8 (C-6), 119.3 (C-9), 125.6 (C-5a), 130.6 (C-7), 135.1 (C-8), 143.0 (C-9a), 151.0 (C-10a), 152.9 (C-4), 154.7 (C-2). MS: *m*/*z* (%) = 267 (M^+, 100), 224 (16), 221 (56), 210 (28), 208 (12), 196 (12), 195 (14), 91 (34), 57 (25), 56 (16), 44 (16), 43 (21), 42 (11), 41 (38), 39 (22). Anal. Calcd. for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found C, 76.40; H, 7.94; N, 15.72.

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