

Heterocycles of biological importance: Part 8.¹

Formation of pyrimido[1,2-*a*]benzimidazoles and oxazolo[3,2-*a*]benzimidazoles by conjugate addition of 2-aminobenzimidazoles to 4-hydroxy-2-alkynenitriles

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Abstract

2-Aminobenzimidazole (**1a**) and its 5,6-dimethyl derivative **1b** react with 4-hydroxy-2-alkynenitriles **2a-d** in ethanol under reflux to give 2-amino-4-(1'-hydroxyalkyl)pyrimido[1,2-*a*]benzimidazoles **5a-e** and in dimethylformamide at 155°C to give (2,2-dialkyl-2,3-dihydro-oxazolo[3,2-*a*]benzimidazolylidene)ethanenitriles **7a-e**.

Keywords: Fused imidazoles, fused pyrimidines, fused oxazoles, pharmaceuticals

Introduction

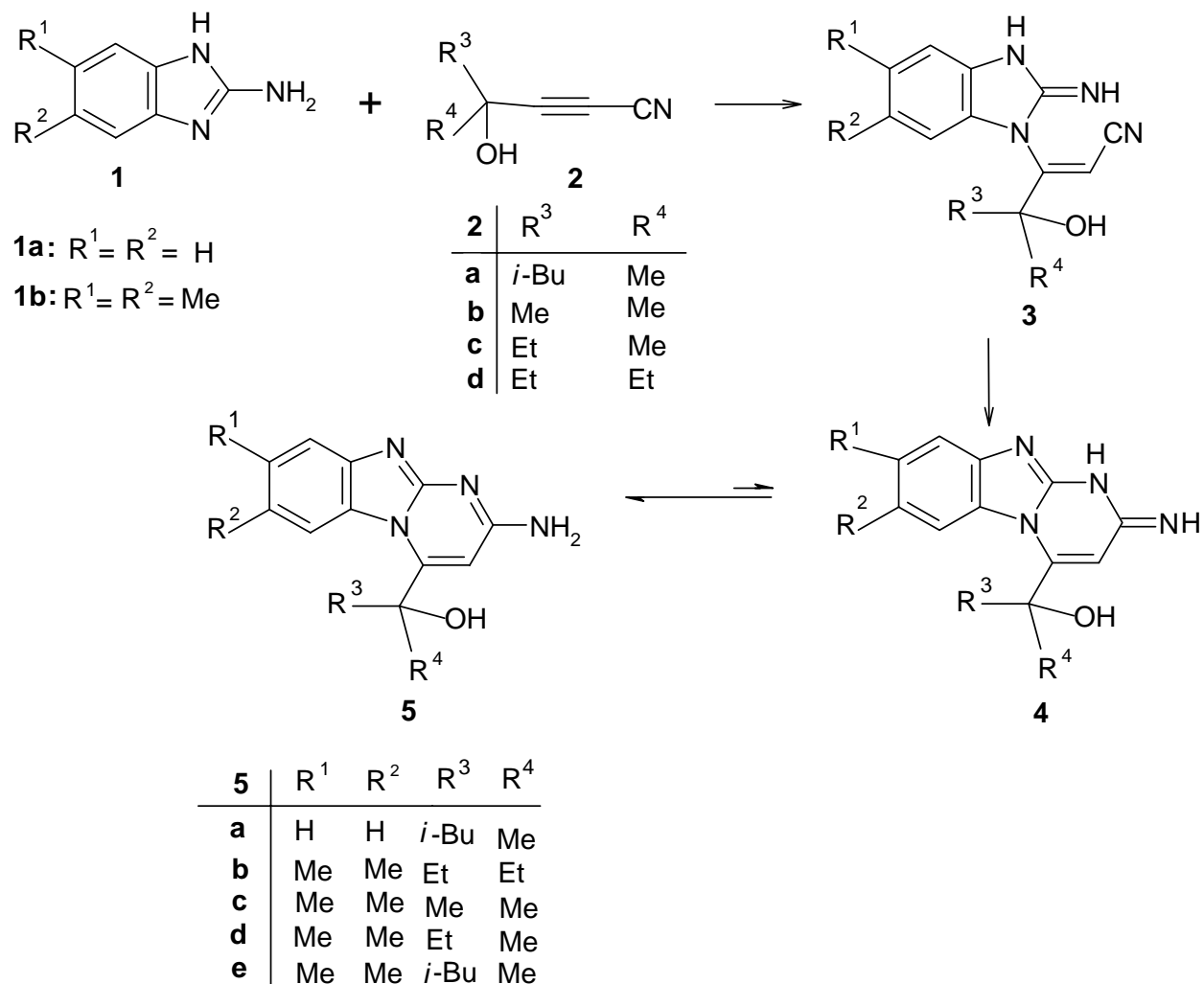
Pyrimidobenzimidazoles have been found to be of pharmacological interest. For example pyrimido[1,2-*a*]benzimidazoles have been described as antihypertensives,^{2,3} antidiabetics,³ antiinflammatory agents,⁴ antirheumatics⁴ and as antibiotics against staphylococcus and mycobacterium ranae.⁵ They have antiarrhythmic effects⁵, herbicidal activity⁶ antidepressant effects,⁷ microfilaricidal and macrofilaricidal effects,⁸ they act as bactericides,⁹ fungicides,⁹ virucides⁹ and as diuretics.¹⁰

These findings prompted us to design compounds with near structural relationship to pyrimido[1,2-*a*]benzimidazoles for further pharmacological tests. We now report the formation of pyrimido[1,2-*a*]benzimidazoles and oxazolo[3,2-*a*]benzimidazoles by addition of 2-aminobenzimidazole (**1a**) and its 5,6-dimethyl derivative **1b** to 4-hydroxy-2-alkynenitriles **2a-d**.

Results and Discussion

We found that the reaction of 2-aminobenzimidazole (**1a**) and its 5,6-dimethyl derivative **1b** with hydroxyacetylenic nitriles **2a-d** proceeds by two possible pathways depending on the reaction solvent.

When nitriles **2a-d** are heated under reflux with 2-aminobenzimidazole (**1a**) or 2-amino-5,6-dimethylbenzimidazole (**1b**) in ethanolic solution for 6–90 hours, 2-amino-4-(hydroxyalkyl)pyrimido[1,2-*a*]benzimidazoles **5a-e** are formed in good yield. The reaction proceeds by the initial attack of the imino ring nitrogen of the benzimidazole to the acetylenic β -carbon, followed by cyclisation to give compounds **5** (Scheme 1).

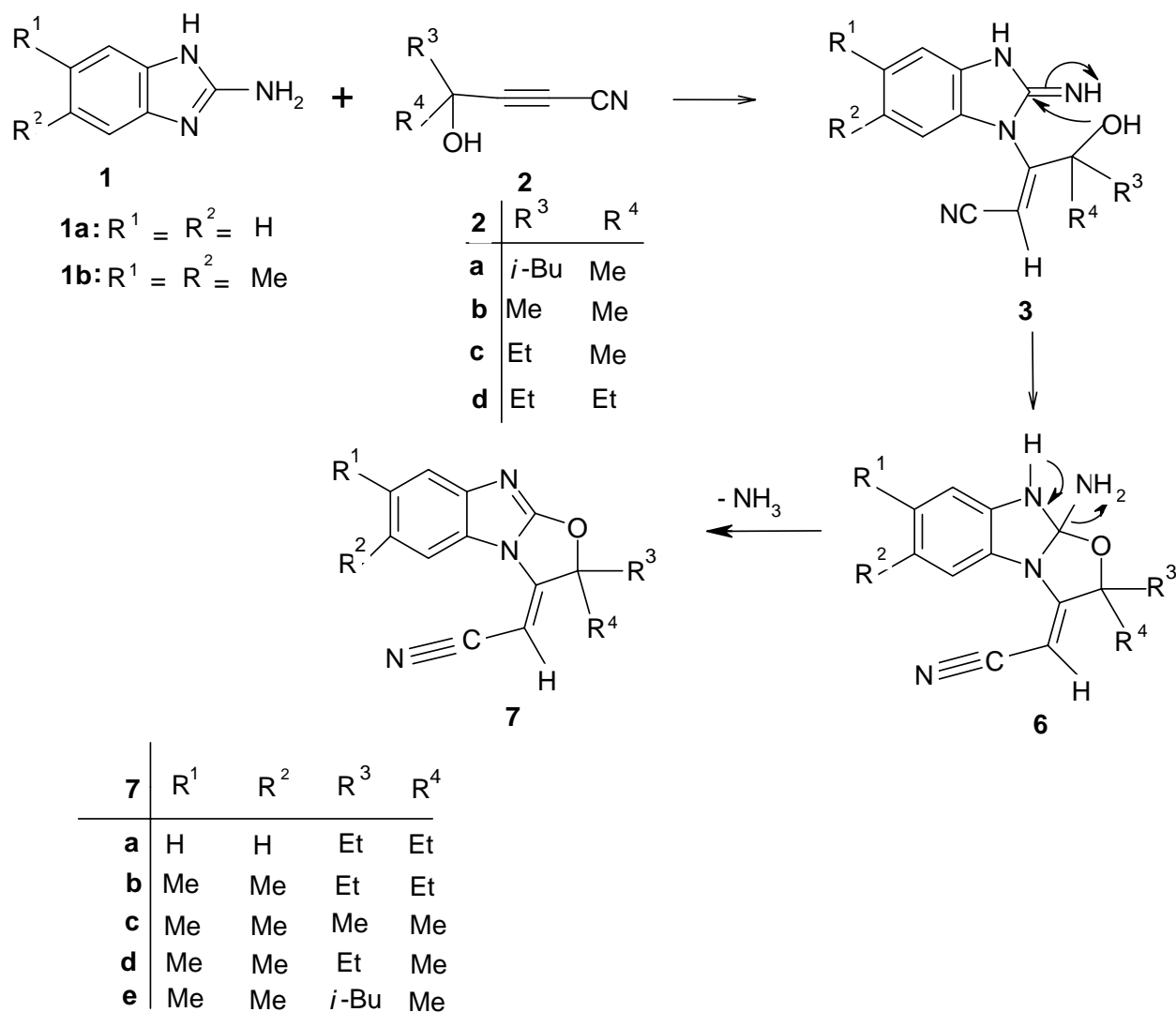


Scheme 1

The results obtained from elemental microanalysis and the IR, 1H NMR, and ^{13}C NMR data as well as the mass spectra are in agreement with the assigned structures **5**. These compounds

showed twin stretching bands in the IR spectra at 3483-3467 and 3389-3375 cm^{-1} for NH_2 as well as intense stretching bands for $\text{C}=\text{N}$ between 1712 and 1644 cm^{-1} and $\text{C}=\text{C}$ between 1655 and 1532 cm^{-1} , further stretching bands for OH (weakly intermolecularly hydrogen bonded) at 3325-3134 cm^{-1} and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900 cm^{-1} . The $^1\text{H-NMR}$ spectra showed signals for the vinylic protons between δ 6.24 and 6.38 ppm, for NH_2 between δ 7.11 and 7.48 ppm and for OH between δ 5.72 and 5.98 ppm. The mass spectra showed peaks for the calculated molecular ions M^+ as the parent ions.

When, however, 4,4-dialkyl-4-hydroxyacetylenic nitriles **2** were heated under reflux with 2-aminobenzimidazole (**1a**) or its 5,6-dimethyl derivative **1b** in *N,N*-dimethylformamide (DMF) it was found that (2,2-dialkyl-2,3-dihydrooxazolo[3,2-*a*]benzimidazolylidene)ethanenitriles of general structure **7** were formed (Scheme 2).



Scheme 2

The elemental analyses of **7a-e** and the mass spectra demonstrate that **5a-e** are 1:1 adducts but compounds **7a-e** are formed *via* an 1:1 addition followed by a condensation (liberation of ammonia). Ammonia may be liberated from the imidazole C-2 when another heteroatom attacks C-2. The only group intramolecularly available is the tertiary hydroxy group in intermediate **3**. Further structure proof for **7a-e** is seen in the presence of intense C≡N stretching bands between 2200-2220 cm⁻¹ demonstrating that in the formation of **7** the nitrile groups are not converted by nucleophilic attack. IR bands between 1640 and 1680 cm⁻¹ are assigned to C=N and between 1660-1620 cm⁻¹ to C=C stretching vibrations. On the other hand, no OH stretching vibrations are seen in the IR spectra of **7a-e**. The ¹H-NMR spectra showed signals for the vinylic protons between δ 4.55 – 5.20 ppm. The low yield of compounds **7** formed in these reactions might be due to losses during purification by column chromatography on alumina.

At this point, the reason for the difference in results of the interaction of **1** and **2** under the two reaction conditions used needs to be tackled. The interaction of **1b** and **2c** was used as a test system. Since these substances, when warmed in DMF to 78°C for five days, did not give compound **5c** in any more than trace quantities, a protic solvent obviously is required for pyrimidobenzimidazole formation. On the other hand, when **5c** was kept in DMF at reflux temperature (155°C), decomposition of **5c** to a plethora of products was observed and no **7d** had been formed even after 8 days. This means that **5** is not in equilibrium with intermediate **3** and the formation of **7** from **3** would be independent and requires a higher energy of activation than that for the formation of **5**.

Experimental Section

General Procedures. Melting points were determined with a Reichert Thermovar microscope and are uncorrected. The IR spectra (KBr) were measured with a Varian Cary 2290 and a Bruker Vector 22 spectrophotometer. The 300 MHz ¹H and 75 MHz ¹³C-NMR spectra were performed on a Bruker WM 300 instrument with tetramethylsilane as internal standard. Mass spectra were obtained with a AMD 605 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 100 g of neutral alumina which had been preheated for 4 hours at 120 °C. Combustion analyses were performed with a CHN elemental analyzer “Carlo Erba” Model 1106. 4-Hydroxy-2-alkynenitriles (**2**) were prepared as previously reported.¹¹

General procedure of synthesis of pyrimido[1,2-*a*]benzimidazoles **5a-e**

Solutions of 0.01 mol each of reactants **1** and **2** in 25 ml of ethanol were kept at reflux for the times specified. The residue obtained upon concentration (in case of **5a**) or the precipitate formed upon cooling were crystallized from DMF. The following products were obtained:

2-Amino-4-(1',3'-dimethyl-1'-hydroxybutyl)pyrimido[1,2-*a*]benzimidazole (5a**).** From 1.33 g of 2-aminobenzimidazole (**1a**) and 1.51 g of 4-hydroxy-4,6-dimethylhept-2-ynenitrile (**2a**) after 43 hrs. 1.48 g (52 %) as colourless crystals, mp 262-264°C; ir: ν/cm⁻¹: 3483, 3315 (NH₂), 1643

(C=N), 1532 (C=C), OH stretch (weakly intermolecularly bonded) at 3134 and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900. NMR data: δ_{H} (DMSO- d_6) 0.66 (3H, d, 4'-H), 0.99 (3H, d, 3'-CH₃), 1.70 (3H, s, 1'-CH₃), 1.87-1.95 (1H, m, 3'-H), 1.98 (2H, d, 2'-H), 5.91 (1H, s, OH), 6.38 (1H, s, 3-H), 7.08 (1H, dd, 8-H), 7.25 (1H, dd, 7-H), 7.48 (2H, s, NH₂), 7.50 (1H, d, H-9), 8.68 (1H, d, 6-H). δ_{C} (DMSO- d_6) 23.9 (4'-CH₃), 24.0 (3'-CH₃), 24.7 (1'-CH₃), 26.9 (C-3'), 46.0 (C-2'), 72.6 (C-1'), 96.4 (C-3), 116.9 (C-9), 118.3 (C-6), 118.7 (C-8), 123.5 (C-7), 128.2 (C-2), 144.6 (C-4), 154.4 (C-5a), 154.6 (C-9a), 160.2 (C-10a). MS: m/z 284 (C₁₆H₂₀N₄O requires 284.4). Anal. Calcd. for C₁₆H₂₀N₄O: C, 67.61; H, 7.04; N, 19.72. Found C, 67.44; H, 7.08; N, 19.69.

2-Amino-7,8-dimethyl-4-(1'-ethyl-1'-hydroxypropyl)pyrimido[1,2-*a*]benzimidazole (5b). From 1.61 g of 2-amino-5,6-dimethylbenzimidazole (**1b**) and 1.37 g of 4-ethyl-4-hydroxyhex-2-ynenitrile (**2d**) after 14.5 hrs. 1.40 g (47 %) of yellowish crystals, no melt below 300°C; ir: ν/cm^{-1} 3474, 3389 (NH₂), 1652 (C=N), 1549 (C=C), OH stretch (weakly intermolecularly bonded) at 3305 and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900. NMR data: δ_{H} (DMSO- d_6) 0.83 (6H, t, 2CH₃), 1.85 (2H, q, CH₂), 2.10 (2H, q, CH₂), 2.88 (3H, s, 8-CH₃), 2.30 (3H, s, 7-CH₃), 5.72 (1H, s, OH), 6.24 (1H, s, 3-H), 7.11 (2H, s, NH₂), 7.2 (1H, s, 9-H), 8.45 (1H, s, 6-H). δ_{C} (DMSO- d_6) 18.05 (2CH₃), 20.0 (8-CH₃), 20.6 (7-CH₃), 27.9 (2CH₂), 75.0 (C-1'), 97.3 (C-3), 117.4 (C-9), 119.2 (C-6), 126.3 (C-8), 126.9 (C-7), 131.9 (C-2), 143.2 (C-4), 152.7 (C-5a), 154.3 (C-9a), 159.8 (C-10a). MS: m/z 298 (C₁₇H₂₂N₄O requires 298.4). Anal. Calcd. for C₁₇H₂₂N₄O: C, 68.46; H, 7.38; N, 18.79. Found C, 68.04; H, 7.49; N, 18.70.

2-Amino-7,8-dimethyl-4-(1'-methyl-1'-hydroxyethyl)pyrimido[1,2-*a*]benzimidazole (5c). From 1.61 g of **1b** and 1.09 g of 4-hydroxy-4-methylpent-2-ynenitrile (**2b**) after 18 hrs., 1.08 g (40 %) of colourless crystals, no melt below 300°C; ir: ν/cm^{-1} 3472, 3387 (NH₂), 1656 (C=N), 1552 (C=C), OH stretch (weakly intermolecularly bonded) at 3316 and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900. NMR data: δ_{H} (DMSO- d_6) 1.66 (6H, s, 2 CH₃), 2.25 (3H, s, 8-CH₃), 2.29 (3H, s, 7-CH₃), 5.98 (1H, s, OH), 6.34 (1H, s, 3-H), 7.16 (2H, s, NH₂), 7.25 (1H, s, 9-H), 8.37 (1H, s, 6-H). δ_{C} (DMSO- d_6) 28.4 (2CH₃), 20.0 (8-CH₃), 20.7 (7-CH₃), 70.0 (C-1'), 95.3 (C-3), 117.4 (C-9), 118.8 (C-6), 126.5 (C-8), 126.7 (C-7), 131.9 (C-2), 143.8 (C-4), 154.1 (C-5a), 154.3 (C-9a), 160.1 (C-10a). MS: m/z 270 (C₁₅H₁₈N₄O requires 270.3). Anal. Calcd. for C₁₅H₁₈N₄O: C, 66.67; H, 6.67; N, 20.74. Found C, 66.58; H, 6.73; N, 20.74.

2-Amino-7,8-dimethyl-4-(1'-methyl-1'-hydroxypropyl)pyrimido[1,2-*a*]benzimidazole (5d). From 1.61 g of **1b** and 1.23 g of 4-hydroxy-4-methylhex-2-ynenitrile (**2c**) after 90 hrs. 1.70 g; (60 %) of orange crystals, no melt below 300°C; ir: ν/cm^{-1} 3469, 3385 (NH₂), 1657 (C=N), 1635 (C=C), OH stretch (weakly intermolecularly bonded) at 3313 and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900. NMR data: δ_{H} (DMSO- d_6) 0.90 (3H, t, 3'-H), 1.60 (3H, s, 1'-CH₃), 1.96-2.10 (2H, m, 2'-H), 2.27 (3H, s, 8-CH₃), 2.30 (3H, s, 7-CH₃), 5.95 (1H, s, OH), 6.33 (1H, s, 3-H), 7.20 (2H, s, NH₂), 7.24 (1H, s, H-9), 8.37 (1H, s, 6-H). δ_{C} (DMSO- d_6) 18.3 (3'-CH₃), 20.0 (8-CH₃), 20.7 (7-CH₃), 25.7 (1'-CH₃), 30.7 (2'-CH₃), 72.6 (C-1'), 96.2 (C-3), 117.5 (C-9), 118.8 (C-6), 126.5 (C-8), 126.8 (C-7), 132.0 (C-2), 143.2 (C-4), 154.2 (C-5a),

154.5 (C-9a), 160.0 (C-10a). MS: m/z 284 ($C_{16}H_{20}N_4O$ requires 284.4). Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.60; H, 7.04; N, 19.72. Found C, 67.57; H, 7.09; N, 19.57.

2-Amino-7,8-dimethyl-4-(1',3'-dimethyl-1'-hydroxybutyl)pyrimido[1,2-*a*]benzimidazole

(5e). From 1.61 g of **1b** and 1.51 g of 4-hydroxy-4,6-dimethylhept-2-ynenitrile (**2a**) after 6.5 hrs: 1.70 g (54 %) of orange crystals, no melt below 300°C; ir: ν/cm^{-1} 3468, 3320 (NH₂), 1643 (C=N), 1552 (C=C), OH stretch (weakly intermolecularly bonded) at 3325 and (strongly hydrogen bonded) as a broad absorption between 3500 and 2900. NMR data: δ_H (DMSO-*d*₆) 0.69 (3H, d, 3'-CH₃), 1.03 (3H, d, 4'-H), 1.69 (3H, s, 1'-CH₃), 1.75-1.91 (1H, m, 3'-H), 2.01 (2H, d, 2'-H), 2.30 (3H, s, 8-CH₃), 2.31 (3H, s, 7-CH₃), 5.90 (1H, s, OH), 6.33 (1H, s, 3-H), 7.14 (2H, s, NH₂), 7.26 (1H, s, 9-H), 8.49 (1H, s, 6-H). δ_C (DMSO-*d*₆) 19.8 (4'-CH₃), 20.3 (3'-CH₃), 23.8 (8-CH₃), 24.3 (7-CH₃), 24.6 (1'-CH₃), 27.0 (C-3'), 45.7 (C-2'), 72.7 (C-1'), 95.8 (C-3), 117.2 (C-9), 119.0 (C-6), 126.2 (C-8), 126.6 (C-7), 131.7 (C-2), 143.0 (C-4), 154.0 (C-5a), 154.5 (C-9a), 159.8 (C-10a). MS: m/z 312 ($C_{18}H_{24}N_4O$ requires 312.4). Anal. Calcd. for $C_{18}H_{24}N_4O$: C, 69.23; H, 7.69; N, 17.95. Found C, 69.40; H, 7.72; N, 17.83.

General procedure of synthesis of 2,3-dihydrooxazolo[3,2-*a*]benzimidazoles 7a-e

Equimolar solutions of the reactants in 50 ml of DMF were heated to reflux for the times specified and concentrated to give crude brown oils. Column chromatography on neutral alumina (activity 5, 300g in case of **7a,b**, 200g in case of **7c-e**) using hexane/ethyl acetate (8:2) or (for **7e**) cyclohexane/ethyl acetate (8:2) gave crystalline products, which were recrystallized from ethyl acetate/hexane (for **7a-c**) or chloroform/hexane (for **7d-e**) The following products were obtained in this way:

(2,2-Diethyl-2,3-dihydrooxazolo[3,2-*a*]benzimidazol-3-ylidene)ethanenitrile (7a). From 2.75 g of **1a** and 2.70 g of **2d** (0.02 mol each) after 7 days: 2.30 g (46 %) of colourless crystals, mp 112°C; ir: ν/cm^{-1} 2220 (C≡N), 1680 (C=N), 1640 (C=C). NMR data: δ_H (DMSO-*d*₆) 0.92 (6H, t, C(CH₂CH₃)₂), 2.15 (2H, q, C(CH₂CH₃)), 2.20 (2H, q, C(CH₂CH₃)), 5.22 (1H, s, =CHCN), 7.20 (1H, dd, 6-H), 7.40 (1H, dd, 7-H), 7.50 (1H, d, 8-H), 8.45 (1H, d, 5-H). MS: m/z 253 ($C_{15}H_{15}N_3O$ requires 253.3). Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.15; H, 5.93; N, 16.60. Found C, 71.15; H, 5.90; N, 16.54.

(2,2-Diethyl-2,3-dihydro-6,7-dimethyloxazolo[3,2-*a*]benzimidazol-3-ylidene)ethanenitrile (7b). From 1.61 g of **1b** and 1.37 g of **2d** (0.01 mol each) after 8 days: 1.13 g (38%) of colourless crystals, mp 95°C; ir: ν/cm^{-1} 2200 (C≡N), 1640 (C=N), 1600 (C=C). NMR data: δ_H (DMSO-*d*₆) 0.93 (6H, t, C(CH₂CH₃)₂), 2.05 (2H, q, C(CH₂CH₃)), 2.18 (2H, q, C(CH₂CH₃)), 2.30 (6H, s, 6-CH₃ and 7-CH₃), 5.20 (1H, s, =CHCN), 7.20 (1H, s, 8-H), 8.20 (1H, s, 5-H). MS: m/z 281 ($C_{17}H_{19}N_3O$ requires 281.4). Anal. Calcd. for $C_{17}H_{19}N_3O$: C, 72.60; H, 6.76; N, 14.95. Found C, 72.66; H, 6.70; N, 14.75.

(2,3-Dihydro-2,2,6,7-tetramethyloxazolo[3,2-*a*]benzimidazol-3-ylidene)ethanenitrile (7c). From 0.81 g of **1b** and 0.55 g of **2b** (5 mmol each) after 7 days; 0.45 g (33 %) of colourless crystals, mp 260°C; ir: ν/cm^{-1} 2220 (C≡N), 1650 (C=N), 1620 (C=C). NMR data: δ_H (DMSO-*d*₆) 1.70 (6H, s, (CH₃)₂), 2.30 (6H, s, 6-CH₃ and 7-CH₃), 4.55 (1H, s, =CHCN), 7.30 (1H, s, 8-H),

8.18 (1H, s, 5-H). MS: m/z 253 ($C_{15}H_{15}N_3O$ requires 253.3). Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.15; H, 5.93; N, 16.60. Found C, 71.20; H, 5.85; N, 16.60.

(2,3-Dihydro-6,7-dimethyl-2-ethyl-2-methyloxazolo[3,2-*a*]benzimidazol-3-ylidene)ethanenitrile (7d). From 3.20 g of **1b** and 2.46 g of **2c** (0.02 mol each) after 7 days: 2.38 g (42 %) of colourless crystals, mp 159 °C; ir: ν/cm^{-1} 2200 (C≡N), 1640 (C=N), 1600 (C=C). NMR data: δ_H (DMSO- d_6) 0.90 (3H, t, $CH_3CCH_2CH_3$), 1.80 (3H, s, $CH_3CCH_2CH_3$), 2.08 (2H, q, $CH_3CCH_2CH_3$), 2.33 (6H, s, 6- CH_3 and 7- CH_3), 5.22 (1H, s, =CHCN), 7.22 (1H, s, 8-H), 8.20 (1H, s, 5-H). MS: m/z 267 ($C_{16}H_{17}N_3O$ requires 267.3). Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.91; H, 6.37; N, 15.73. Found C, 71.91; H, 6.48; N, 15.88.

(2,3-Dihydro-2-isobutyl-2,6,7-trimethyloxazolo[3,2-*a*]benzimidazol-3-ylidene)ethanenitrile (7e). From 1.61 g of **1b** and 1.51 g of **2a** (0.01 mol each) after 3 days: 1.75 g (56 %) of colourless crystals, no melt below 300°C; ir: ν/cm^{-1} 2212 (C≡N), 1648 (C=N) 1605 (C=C). NMR data: δ_H (DMSO- d_6) 0.86 (6H, d, $(CH_3)_2CH$) 1.64-1.68 (1H, m, $(CH_3)_2CHCH_2$), 1.71 (3H, s, $(CH_3)_2CHCH_2CCH_3$), 1.87-2.02 (2H, m, $(CH_3)_2CHCH_2CCH_3$), 2.28 (6H, s, 6- CH_3 and 7- CH_3), 5.55 (1H, s, =CHCN), 7.27 (1H, s, 8-H), 8.08 (1H, s, 5-H). MS: m/z 295 ($C_{18}H_{21}N_3O$ requires 295.4). Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.22; H, 7.12; N, 14.24. Found C, 73.20; H, 7.08; N, 14.48.

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