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SYNTHESIS OF BENZIMIDAZOLES, BENZOXAZOLES AND BENZOTHIAZOLE BY THE REACTION OF 2-AMINO-4,5-DIHYDRO-3-FURANCARBONITRILE AND *o*-SUBSTITUTED ANILINES IN THE CATALYSIS OF TRIMETYLAMINE HYDROCHLORIDE

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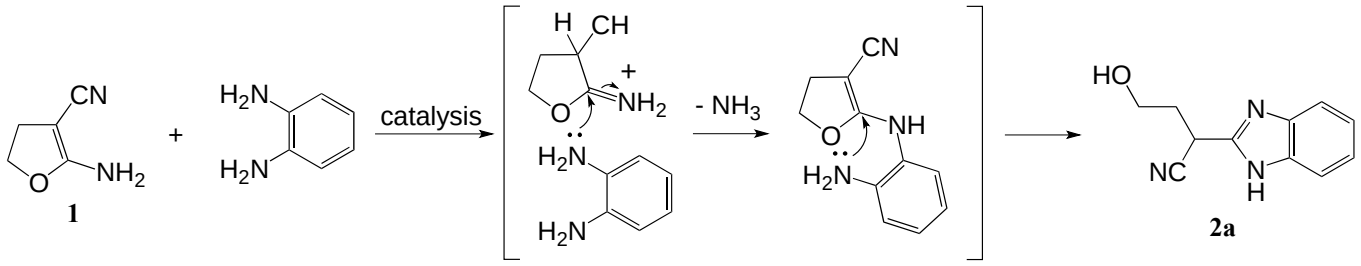
Abstract – Efficient synthesis of benzimidazoles, benzoxazoles and benzothiazole from the reaction of 2-amino-4,5-dihydro-3-furancarbonitrile with *o*-substituted anilines in the catalysis of trimethylamine hydrochloride was achieved. The structures of the obtained products were established by spectroscopic data.

Heterocyclic compounds such as benzimidazole, benzoxazole, and benzothiazole are useful structures that provide many biological effects such as anti-microbial,[1] anti-viral,[2] anti-inflammatory,[3] anti-hypertensive,[4] anti-cancer,[5] antioxidant,[6] and anti-diabetic[7] effects. Therefore, efficient synthetic methods for these heterocyclic compounds are needed. In the synthetic methods reported so far, aldehydes,[8] orthoesters,[9] acyl chlorides,[10] carboxylic acids,[11] amides,[12] carbon dioxide,[13] and alkenes[14] are often used as carbon sources for reaction with *o*-substituted anilines. The cyclic compounds 3-aminorodanine[15] and D-glucose[16] are also sometimes used as carbon sources. In this study, we investigated an efficient method for the synthesis of benzimidazoles, benzoxazoles, and benzothiazole by using the cyclic compound 2-amino-4,5-dihydro-3-furancarbonitrile (**1**),[17] which has been studied in our laboratory for many years, as a carbon source and reacting it with *o*-substituted anilines.

The reaction of 2-amino-4,5-dihydro-3-furancarbonitrile (**1**) and 1,2-phenylenediamine as *o*-substituted anilines was investigated. The reaction was carried out using triethylamine, triethylamine hydrochloride, trimethylamine hydrochloride, ammonium chloride,[18] ammonium acetate,[19] acetic acid,[20] and hydrochloric acid[21] as catalysts, and various solvents such as THF, ethanol, 1,4-dioxane and DMSO. As a result, refluxing compound **1** and 1,2-phenylenediamine in 1,4-dioxane for 3 hours with trimethylamine hydrochloride catalyst afforded benzimidazole **2a** in a good yield of 77%. In this reaction, the β carbon of

the enamine moiety of **1** is protonated by a catalyst to produce an iminium ion. 1,2-Phenylenediamine is added to the iminium ion, and ammonia is eliminated. After that, the intramolecular nucleophilic addition of the intermediate forms an imidazole ring and cleaves the furan ring to give **2a**. The IR spectrum of **2a** displays bands at 3289 cm^{-1} due to an amino group and a hydroxy group and at 2259 cm^{-1} due to a non-conjugated cyano group. The ^{1}H NMR spectrum of **2a** shows a signal of δ 2.16-2.23 due to methylene proton at the 2-postion of α-hydroxyethyl, a signal of δ 3.50-3.58 due to methylene proton at the 3-postion of α-hydroxyethyl, a signal at δ 4.56-4.58 due to methine proton at the α-position of α-hydroxyethyl. The ^{13}C NMR spectrum of **2a** exhibits signals at δ 28.8, δ 35.5 and δ 58.1 corresponding to C-α, C-2 and C-1 of α-hydroxyethyl carbons, respectively.

Table 1. Optimization of the reaction conditions



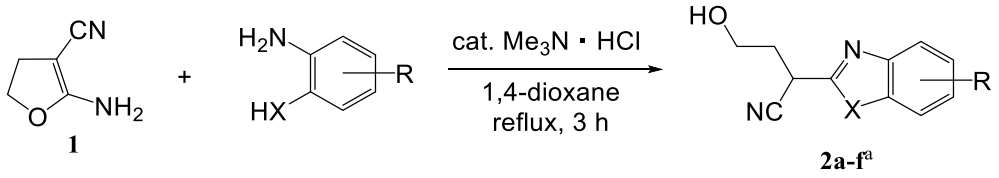
Entry	Catalysis (0.1 equiv.)	Solvent	Temp	Time	**2a** (Yield /%)[a]
1	Et_3N	THF	reflux	3 h	-
2	Et_3N·HCl	THF	reflux	3 h	70
3	Me_3N·HCl	THF	reflux	3 h	72
4	NH_4Cl	THF	reflux	3 h	71
5	$AcONH_4$	THF	reflux	3 h	66
6	AcOH	THF	reflux	3 h	67
7	HCl aq.	THF	reflux	3 h	63
8	Me_3N·HCl	EtOH	reflux	3 h	59
9	Me_3N·HCl	1,4-dioxane	reflux	3 h	77
10	Me_3N·HCl	DMSO	100 °C	3 h	44

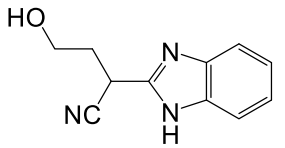
[a] Isolated yields.

In addition, the reactions of **1** and *o*-substituted anilines, including 4,5-dichloro-1,2-phenylenediamine, 4,5-dibromo-1,2-phenylenediamine, 4,5-dimethy-1,2-phenylenediamine and 1,2-naphthalenediamine, gave the corresponding benzimidazole derivatives **2b-e** in yields of 73-81%.

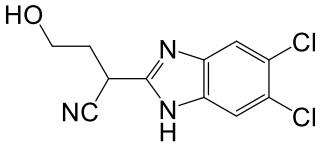
Furthermore, reactions using 2-aminophenol, 2-aminonaphthol, and 2-aminobenzenethiol as *o*-substituted anilines similarly gave benzoxazole **2f**, naphthoxazole **2g**, and benzothiazole **2h** in 87%, 80% and 77% yields, respectively.

Table 2. Synthesis of benzimidazoles, benzoxazoles and benzothiazole

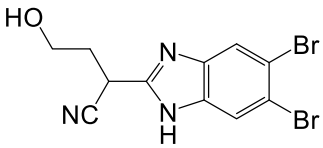




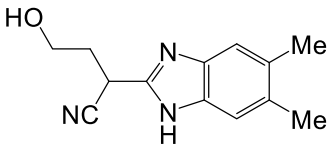
2a (77%)



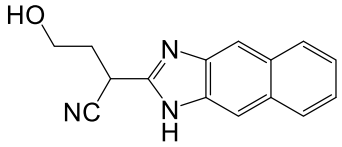
2b (76%)



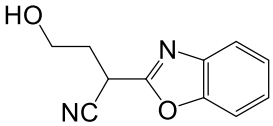
2c (73%)



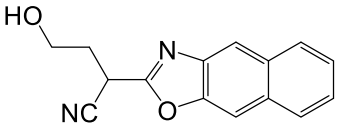
2d (80%)



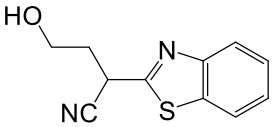
2e (81%)



2f (87%)



2g (80%)



2h (77%)

[a] Isolated yields.

In conclusion, we have developed a method for the synthesis of benzimidazoles, benzoxazoles and benzothiazole using 2-amino-4,5-dihydro-3-furancarbonitrile (**1**) and *o*-substituted anilines in the catalysis of trimethylamine hydrochloride. It was clarified that this method enables easy synthesis of benzimidazole, benzoxazoles and benzothiazole by using a catalytic amount of trimethylamine hydrochloride. Benzimidazoles, benzoxazoles and benzothiazole can be used as bioactive substances as important synthetic intermediates.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Thermo Fisher Scientific Nicolet IS5 FT-IR spectrometer equipped with an iD7 diamond ATR accessory. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-ECZ600R spectrometer at 600.17 and 150.91 MHz, respectively. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to TMS as an internal standard. Positive FAB MS spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on a YANACO MT-6 CHN analyzer. The starting compound **1** was prepared in our laboratory according to the procedure reported in the literature.[17]

General procedure for the preparation of benzimidazoles 2a-e, benzoxazoles 2f,g and benzothiazole 2h from 1 and *o*-substituted anilines. A solution of **1** (0.55 g, 5 mmol), 1,2-phenylenediamine (0.54 g, 5 mmol), 4,5-dichloro-1,2-phenylenediamine (0.89 g, 5 mmol), 4,5-dibromo-1,2-phenylenediamine (1.33 g, 5 mmol), 4,5-dimethyl-1,2-phenylenediamine (0.68 g, 5 mmol), 1,2-diaminonaphthalene (0.79 g, 5 mmol), 2-aminophenol (0.55 g, 5 mmol), 3-amino-2-naphthol (0.80 g, 5 mmol) and/or 2-aminobenzenethiol (0.63 g, 5 mmol) in the presence of catalysis of trimethylamine hydrochloride (0.05 g, 0.5 mmol) in 1,4-dioxane (5 mL) was refluxed for 3 h. After removal of the solvent under reduced pressure, water (saline in the case of **2a**,**f**) was added to the residue. The obtained solid was isolated by filtration, washed with water (saline in the case of **2a**,**f**), dried, and recrystallized from an appropriate solvent to give **2a-h**.

α-(2-Hydroxyethyl)-1*H*-benzimidazole-2-acetonitrile (2a): pale yellow prisms; (0.77 g, 77%), mp 146-147 °C (acetone); IR (ATR): ν 3289 (NH, OH), 2259 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.16-2.23 (m, 2H, α-hydroxyethyl 2-H), 3.50-3.58 (m, 2H, α-hydroxyethyl 1-H), 4.56-4.58 (m, 1H, α-H), 5.01 (br s, 1H, OH), 7.15-7.18 (m, 2H, aryl H), 7.52-7.53 (m, 2H, aryl H), 12.5 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 28.8 (C-α), 35.2 (α-hydroxyethyl C-2), 58.1 (α-hydroxyethyl C-1), 115.1, 115.9 (C aryl), 119.4 (CN), 122.7, 137.9, 139.2 (C aryl), 149.0 (C-2); MS: *m/z* 202 [M+H]$^{+}$. Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.57; H, 5.59; N, 20.84.

5,6-Dichloro-α-(2-hydroxyethyl)-1*H*-benzimidazole-2-acetonitrile (2b): colorless prisms; (1.03 g, 76%), mp 190-192 °C (acetone); IR (ATR): ν 3111 (NH, OH), 2253 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.13-2.22 (m, 2H, α-hydroxyethyl 2-H), 3.50-3.60 (m, 2H, α-hydroxyethyl 1-H), 4.61-4.64 (m, 1H, α-H), 4.90 (br s, 1H, OH), 7.82 (s, 2H, aryl H), 13.0 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 28.9 (C-α), 35.0 (α-hydroxyethyl C-2), 58.0 (α-hydroxyethyl C-1), 116.1, 118.1 (C aryl), 119.0 (CN), 125.2, 138.7 (C aryl), 152.0 (C-2); MS: *m/z* 271 [M+H]$^{+}$. Anal. Calcd for $C_{11}H_9N_3OCl_2$: C, 48.91; H, 3.36; N, 15.56. Found: C, 48.86; H, 3.31; N, 15.54.

5,6-Dibromo-α-(2-hydroxyethyl)-1*H*-benzimidazole-2-acetonitrile (2c): colorless needles; (1.30 g, 73%), mp 203-204 °C (acetone); IR (ATR): ν 3109 (NH, OH), 2253 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ

2.14-2.20 (m, 2H, α-hydroxyethyl 2-H), 3.50-3.53 (m, 2H, α-hydroxyethyl 1-H), 4.60-4.62 (m, 1H, α-H), 5.06 (br s, 1H, OH), 7.96 (s, 2H, aryl H), 12.8 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 28.9 (C-α), 35.1 (C-3), 58.0 (α-hydroxyethyl C-1), 116.9 (C aryl), 119.0 (CN), 120.4, 120.6, 139.8 (C aryl), 152.0 (C-2'); MS: *m/z* 360 $[M+H]^+$. Anal. Calcd for $C_{11}H_9N_3OBr_2$: C, 36.80; H, 2.53; N, 11.70. Found: C, 36.77; H, 2.48; N, 11.73.

α-(2-Hydroxyethyl)-5,6-dimethyl-1*H*-benzimidazole-2-acetonitrile (2d): colorless prisms; (0.91 g, 80%), mp 194-195 °C (acetone); IR (ATR): ν 3128 (NH, OH), 2249 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.12-2.22 (m, 2H, α-hydroxyethyl 2-H), 2.25 (s, 6H, $2CH_3$), 3.49-3.57 (m, 2H, α-hydroxyethyl 1-H), 4.50-4.53 (m, 1H, α-H), 4.88 (br s, 1H, OH), 7.28 (br s, 2H, aryl H), 12.4 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.4 (CH_3), 28.7 (C-α), 35.2 (α-hydroxyethyl C-2), 58.1 (α-hydroxyethyl C-1), 112.7, 118.7 (C aryl), 119.5 (CN), 131.1, 131.2, 141.4 (C aryl), 147.9 (C-2); MS: *m/z* 230 $[M+H]^+$. Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.11; H, 6.66; N, 18.39.

α-(2-Hydroxyethyl)-1*H*-naphth[2,3-*d*]imidazole-2-acetonitrile (2e): pale yellow prisms; (1.02 g, 81%), mp 194-195 °C (acetone); IR (ATR): ν 3126 (NH, OH), 2251 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.22-2.32 (m, 2H, α-hydroxyethyl 2-H), 3.56-3.63 (m, 2H, α-hydroxyethyl 1-H), 4.68-4.71 (m, 1H, α-H), 4.93 (br s, 1H, OH), 7.34-7.35 (m, 2H, aryl H), 7.96-7.98 (m, 3H, aryl H), 8.06 (br s, 1H, aryl H), 12.7 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 29.3 (C-α), 35.0 (α-hydroxyethyl C-2), 58.1 (α-hydroxyethyl C-1), 107.6, 116.0 (C aryl), 119.2 (CN), 124.3, 128.5, 130.4, 135.7, 143.9 (C aryl), 153.7 (C-2); MS: *m/z* 252 $[M+H]^+$. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.70; H, 5.18; N, 16.58.

α-(2-Hydroxyethyl)-2-benzoxazoleacetonitrile (2f): colorless prisms; (0.88 g, 87%), dec. 57-58 °C (Et_2O); IR (ATR): ν 3385 (OH), 2256 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.18-2.29 (m, 2H, α-hydroxyethyl 2-H), 3.56-3.63 (m, 2H, α-hydroxyethyl 1-H), 4.86 (t, *J* = 5.1 Hz, 1H, OH), 4.89 (dd, *J* = 6.0, 8.4 Hz, 1H, α-H), 7.36-7.42 (m, 2H, aryl H), 7.72-7.75 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 29.1 (C-α), 34.1 (α-hydroxyethyl C-2), 57.9 (α-hydroxyethyl C-1), 111.6 (C aryl), 117.8 (CN), 120.4, 125.5, 126.3, 140.8, 151.0 (C aryl), 161.1 (C-2); MS: *m/z* 203 $[M+H]^+$. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.31; H, 4.95; N, 13.83.

α-(2-Hydroxyethyl)-naphth[2,3-*d*]oxazole-2-acetonitrile (2g): colorless needles; (1.01 g, 80%), dec. 131-132 °C (Et_2O); IR (ATR): ν 3483 (OH), 2250 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.23-2.36 (m, 2H, α-hydroxyethyl 2-H), 3.60-3.68 (m, 2H, α-hydroxyethyl 1-H), 4.89 (t, *J* = 4.8 Hz, 1H, OH), 4.97 (dd, *J* = 5.4, 8.4 Hz, 1H, α-H), 7.48-7.53 (m, 2H, aryl H), 8.02-8.07 (m, 2H, aryl H), 8.21 (s, 1H, aryl H), 8.29 (s, 1H, aryl H); ^{13}C NMR (DMSO-d_6): δ 29.4 (C-α), 34.0 (α-hydroxyethyl C-2), 58.0 (α-hydroxyethyl C-1), 107.3 (C aryl), 117.7 (CN), 117.9, 125.5, 126.4, 128.5, 129.0, 131.5, 131.8, 140.7, 149.7 (C aryl), 163.6

(C-2); MS: *m/z* 253 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.29; H, 4.79; N, 10.97.

α-(2-Hydroxyethyl)-2-benzothiazoleacetonitrile (2h): pale yellow columns; (0.84 g, 77%), dec. 84-85 °C (Et_2O); IR (ATR): ν 3288 (OH), 2258 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20-2.25 (m, 2H, α-hydroxyethyl 2-H), 3.57-3.58 (m, 2H, α-hydroxyethyl 1-H), 4.87-4.89 (m, 1H, OH), 4.95-4.98 (m, 1H, α-H), 7.46-7.47 (m, 1H, aryl H), 7.51-7.53 (m, 1H, aryl H), 8.01 (d, *J* = 7.5 Hz, aryl H), 8.11 (d, *J* = 7.5 Hz, 1H, aryl H); ^{13}C NMR (DMSO-d_6): δ 32.9 (C-α), 36.7 (α-hydroxyethyl C-2), 58.0 (α-hydroxyethyl C-1), 119.3 (CN), 123.0, 123.4, 126.3, 127.2, 135.3, 152.7 (C aryl), 165.7 (C-2); MS: *m/z* 219 $[M+H]^+$. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.51; H, 4.65; N, 12.77.

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