Novel Synthesis of 2-Amino[1,4,5]benzoxadiazepine Derivatives *via* a Mild One-Pot Reaction

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Received February 4, 2002

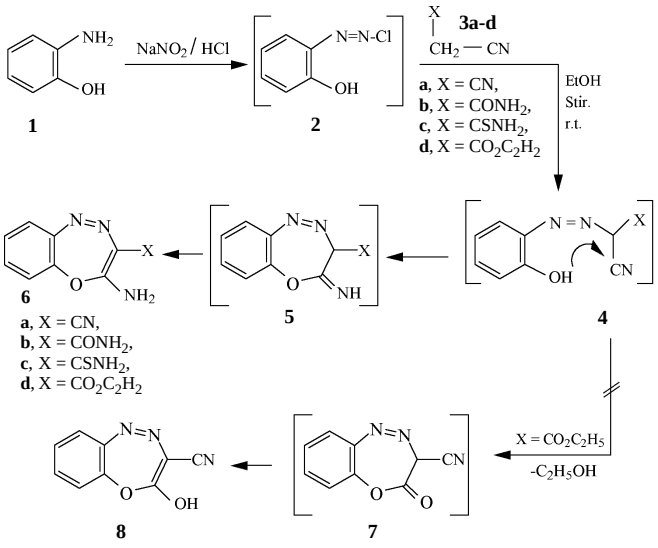
The diazonium salt of 2-aminophenol **2** was coupled *in situ* with malononitrile derivatives **3a-d**, 2-cyanomethylthiazolin-4-one **9**, 2-cyanomethylbenzimidazole **11a,** and 2-cyanomethylbenzothiazole **11b** to give 2-amino[1,4,5]benzoxadiazepine derivatives **6a-d, 10** and **12a,b** *via* a one-pot reaction.

J. Heterocyclic Chem., **39**, 1109 (2002).

In literature, most of the reactions lead to the formation of seven-membered rings based on condensation reactions of 2-aminophenol derivatives followed by cyclisation [1-3]. Herein, and in continuation with our interest to prepare new heterocyclic compounds [4-7], we report a different, mild and an efficient new route to prepare 2-amino[1,4,5]benzoxadiazepine derivatives *via* a one-pot reaction.

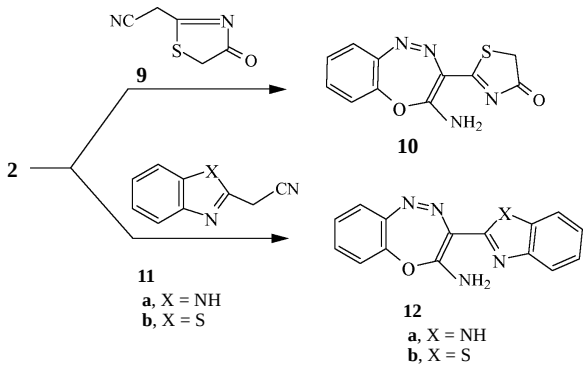
Thus, 2-aminophenol **1** reacted with nitrous acid in the presence of concentrated hydrochloric acid at a temperature of 0 °C to give the corresponding diazonium salt **2**. The diazonium salt **2** was then coupled *in situ* with malononitrile **3a** in ethanol containing sodium acetate to yield 2-amino[1,4,5]benzoxadiazepine-3-carbonitrile **6a** (Scheme 1). The IR spectrum of **6a** (KBr, ν = cm^{-1}) showed characteristic absorption bands at 3445-3380, 2218, 1602 cm^{-1} assigned to NH_2 , CN and C=C groups. The ^{1}H NMR ($CDCl_3$, δ = ppm) spectrum revealed signals at δ 7.1-7.7 ppm due to aromatic and one singlet for the amino protons. The MS of **6a** showed *m/z* at 186 (M^+, 80 %). Similarly, the diazonium salt **2** coupled with cyanoacetamide **3b** and cyanothioacetamide **3c** to give the corresponding 3-substituted of 2-amino[1,4,5]benzoxadiazepine **6b,c** (Scheme 1).

Scheme 1



However, the diazonium salt **2** reacts with ethyl cyanoacetate **3d** under stirring to yield a product where the mass spectrum shows a molecular ion with *m/z* = 234. The IR spectrum (KBr, ν = cm^{-1}) of the product revealed absorption bands at 1602, 1687 and 3445-3430 cm^{-1} assigned to C=C, CO and NH_2 groups with lack of the characteristic absorption band due to the CN group. The ^{1}H NMR spectrum ($CDCl_3$, δ = ppm) of the product **6d** showed a triplet at δ 1.4-1.6, a quartet at 4.3-4.4, a multiplet at 7.0-7.7 and singlet signal at 13.4 ppm assigned to the amino protons. The quite high chemical shifts of the low field signals indicate the presence of intramolecular hydrogen bonding between the amino and the ester functions.

Scheme 2



Therefore, the structure **6d** resulting from the nucleophile attack of the cyano group of ethyl cyanoacetate is highly preferred over the possible structure **8** resulting from nucleophile attack of the ester group of ethyl cyanoacetate followed by elimination of ethanol. The MS of **6d** showed *m/z* at 234 (M+1, 11), 233 (M^+, 85), 160 (M-$CO_2C_2H_5$, 62), 121 (11), 108 (100) and 93 (20 %).

Some laboratory available active methylene heterocyclic compounds were successfully used as couplers with the diazonium salt **2**. Thus, 2-cyanomethylthiazolin-4-one **9** reacts with **2** under the same reaction conditions to afford **10** in 55 % yield. The MS of **10** showed *m/z* at 260 (M^+, 25 %). The IR spectrum (KBr) showed absorption bands at 1610, 1675 and 3425-3225 cm^{-1} due to C=C, CO and NH_2 groups, respectively. Finally, the diazonium salt **2** was coupled with 2-cyanomethylbenzimidazole **11a** and 2-cyanomethylbenzothiazole **11b** to yield [1,4,5]benzoxadiazepine derivatives **12a,b**. The structures of **12a,b** were established based on spectral and elemental analysis.

EXPERIMENTAL

All melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded (potassium bromide, ν = cm^{-1}) on a Shimadzu 408 and a Pye Unicam Spectrophotometer. ^1H NMR spectra (deuterochloroform, δ = ppm) were recorded on a Varian EM 390, 90 MHz spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a mass Spectrometer MS 9 (AET) EI Mode, and all the Microanalysis were carried out at Microanalytical Center, Cairo University, Egypt.

Coupling of Diazonium Salt **2** with Active Methylene Compounds **3a-d, 9** and **11a,b**.

General Procedure.

A solution of the diazonium chloride **2** (prepared from 1 g, 10 mmoles of 2-aminophenol **1** soluble in a mixture of 10 mL of absolute ethanol, 3 mL of concentrated hydrochloric acid, and 5 g of sodium nitrite in 15 mL of cold water was added dropwise during a period of 15 minutes) was added to 10 mL of a well stirred cold ethanol solution of each coupler **3a-d**, **9**, **11a,b** (10 mmoles) in the presence of 3 g of anhydrous sodium acetate. The reaction mixture was left overnight at room temperature. The resulting solid product formed was collected by filtration, washed by water and recrystallized from a proper solvent.

2-Amino[1,4,5]benzoxadiazepine-3-carbonitrile (**6a**).

Compound **6a** was obtained 65 % yield, mp 190 °C; IR (KBr): ν 1602 (C=C), 2218 (CN), 3445-3380 cm^{-1} (NH_2); ^1H-NMR ($CDCl_3$): δ 7.1-7.7 (m, 4H, Ar-H), 7.9 (s, 2H, NH_2); MS, *m/z* 186 (80 %).

Anal. Calcd. for $C_9H_6N_4O$ (186.17): C, 58.06; H, 3.25; N, 3.01. Found: C, 58.09; H, 3.28; N, 3.04.

2-Amino[1,4,5]benzoxadiazepine-3-carboxamide (**6b**).

Compound **6b** was obtained in 55 % yield, mp 220 °C; IR (KBr): ν 1608 (C=C), 1670 (CO), 3350, 3220 cm^{-1} (NH_2); ^1H-NMR ($CDCl_3$): δ 7.3-7.8 (m, 4H, Ar-H), 8.0 (s, 4H, 2 NH_2); MS, *m/z* 204 (50 %).

Anal. Calcd. for $C_9H_8N_4O_2$ (204.19): C, 59.94; H, 3.95; N, 27.44. Found: C, 59.90; H, 4.01; N, 27.55.

2-Amino[1,4,5]benzoxadiazepine-3-carbothioamide (**6c**).

Compound **6c** was obtained in 50 % yield, mp 160 °C; IR (KBr): ν 1610 (C=C), 3400, 3230 cm^{-1} (NH_2); ^1H- NMR ($CDCl_3$): δ 7.1-7.7 (m, 4H, Ar-H), 7.8 (s, 4H, 2 NH_2); MS, *m/z* 220 (35 %).

Anal. Calcd. for $C_9H_8N_4OS$ (220.25): C, 49.08; H, 3.66; N, 25.44. Found: C, 49.20; H, 3.72; N, 25.55.

Ethyl 2-Amino[1,4,5]benzoxadiazepine-3-carboxylate (**6d**).

Compound **6d** was obtained in 60 % yield, mp 210 °C; IR (KBr): ν 1602 (C=C), 1687 (CO), 3445-3430 cm^{-1} (NH_2); ^1H-NMR ($CDCl_3$): δ 1.4-1.6 (t, 3H, CH_3), 4.3-4.4 (q, 2H,CH_2), 7.0-7.7 (m, 4H, Ar-H), 13.4 (s, 2H, NH_2); MS, m/z 233 (M^+, 85 %).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$ (233.23): C, 56.65; H, 4.75; N, 18.02. Found: C, 56.69; H, 4.83; N, 18.10.

2-Amino-3-(4-oxo-2-thiazolinyl)[1,4,5]benzoxadiazepine (**10**).

Compound **10** was obtianed in 55% yield, mp 200 °C ; IR (KBr): ν 1610 (C=C), 1675 (CO), 3425-3225 cm^{-1}(NH_2); ^1H NMR ($CDCl_3$): δ 5.7 (s, 2H, CH_2), 7.1-7.6 (m, 4H, Ar-H), 9.2 (s, 2H, NH_2); MS, *m/z* 260 (25 %).

Anal. Calcd. for $C_{11}H_8N_4O_2S$ (260.27): C, 50.76; H, 3.10; N, 21.53; S, 12.32. Found: C, 50.63; H,3.01; N, 21.37; S, 12.39.

2-Amino-3-(2-benzimidazolyl)[1,4,5]benzoxadiazepine (**12a**).

Compound **12a** was obtained in 57 % yield, mp 170 °C; IR (KBr): ν 1615 (C=C), 3340, 3215 cm^{-1} (NH_2, NH); ^1H-NMR ($CDCl_3$): δ 7.1-7.9 (m, 9H, Ar-H + NH), 9.7 (s, 2H, NH_2); MS, *m/z* 277 (30 %).

Anal. Calcd. for $C_{15}H_{11}N_5O$ (277.28): C, 64.98; H, 4.00; N, 25.26. Found: C, 65.11; H, 4.07; N, 25.38.

2-Amino-3-(2-benzothiazolyl)[1,4,5]benzoxadiazepine (**12b**).

Compound **12b** was obtained in 57 % yield, mp 185-87 °C; IR (KBr): ν 1612 (C=C), 3360 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$): δ 7.0-7.7 (m, 8H, Ar-H), 9.3 (s, 2H, NH_2); MS, *m/z* 294 (35%).

Anal. Calcd. for $C_{15}H_{10}N_4OS$ (294.33): C, 61.21; H, 3.42; N, 19.04. Found: C, 61.24; H, 3.54; N, 19.13.

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