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Note

A novel approach to the synthesis of 4*H*-tetrazolo[1,5-*a*] [1,4]benzodiazepin-6-ones from 1,2,3-benzotriazin-4-(3*H*)-ones

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Two novel routes have been developed for the synthesis of 4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones **6a-b** from 3-substituted 1,2,3-benzotriazin-4-(3*H*)-ones **2a-b** and **9**.

Keywords: 4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones, 1,2,3-benzotriazin-4-(3*H*) ones, di-*n*-butyl tin oxide, trimethylsilylazide, 2- azidobenzoic acid

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The discovery[1] that the fusion of a third ring on face 'a' of 1,4-benzodiazepine nucleus produced compounds which showed novel psycho-pharmacological activity has triggered an intense interest in the chemistry of other tricyclic hetero ring fused 1,4-benzodiazepines.

A survey of the literature showed that the tetrazolo[1,4]benzodiazepines have received only scant attention though the compounds of this class have been claimed to exhibit sedative, tranquilizing and muscle relaxant effects[2-6]. It is recently shown[7] that 1,2,3-benzotriazin-4-3*H*-one can be used as novel synthans in the synthesis of 1,4-benzodiazepin diones. In continuation of our interest in the synthesis of annelated 1,4-benzodiazepines[8], we sought to explore the possibility of employing the 1,2,3-benzotriazin-4-3H-one in the synthesis of tetrazolo-1,4-benzodiazepines. Two novel routes for the preparation of 4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones **6a-b** from 3-substituted 1,2,3-benzotriazin-4-(3*H*)-ones **2a-b** and **9** (**Schemes I** and **II**) are developed.

An attractive feature of the first route (**Scheme I**) is that the cleavage of the triazine ring of **2a-b** generated the azide and carboxylic acid functions at the required positions in the aromatic ring for their potential reaction with bifunctional molecules like chloro-acetonitrile to give after cyclisation, the desired tetrazolo fused 1,4–benzodiazepine ring in essentially only three synthetic operations overall.

In an alternate process, both the rings (tetrazole and 1,4-benzodiazepine) of **6a** were formed simultaneously in one step, on heating **9** with acid followed by reaction with Me_3SiN_3 in presence of di-*n*-butyl tin oxide[9].

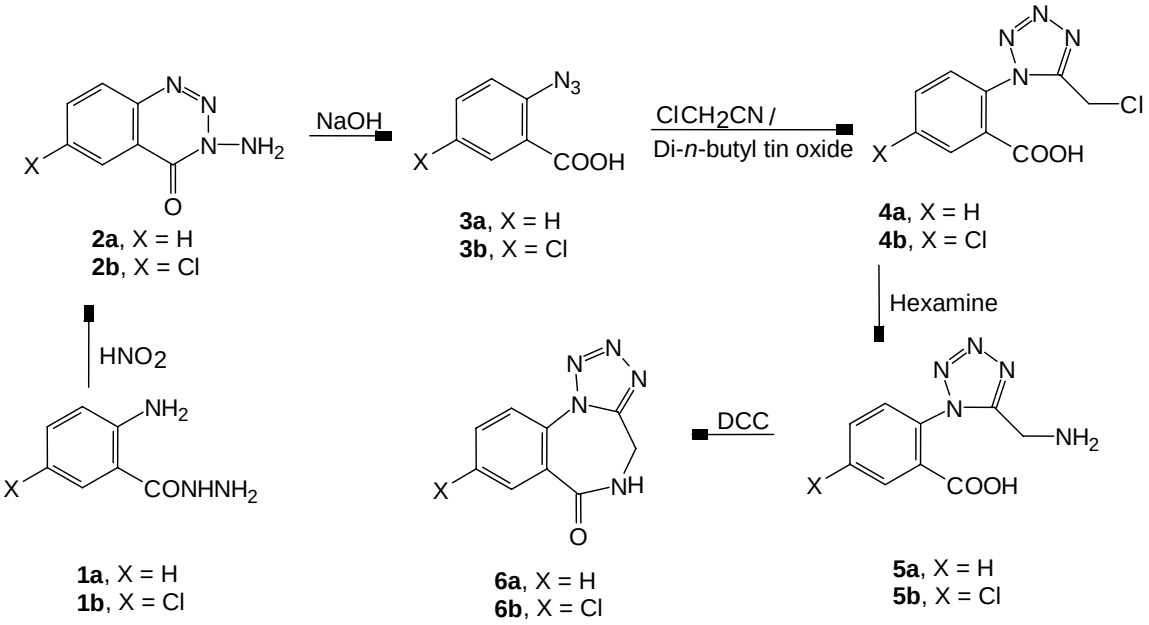
Results and Discussion

2-Azidobenzoic acid **3a** was obtained from 3-amino-1,2,3-benzotriazin–4-(3*H*)-one **2a**[10] following the procedure developed by Heller *et al.*[11] **3a** underwent 1,3-dipolar cycloaddition reaction with chloroacetonitrile in presence of di-*n*-butyl tin oxide[9] to give **4a**. Treatment of **4a** with hexamine afforded **5a**, cyclisation of which in a subsequent step under the influence of DCC[12] yielded **6a** in moderate to good yield (**Scheme I)**.

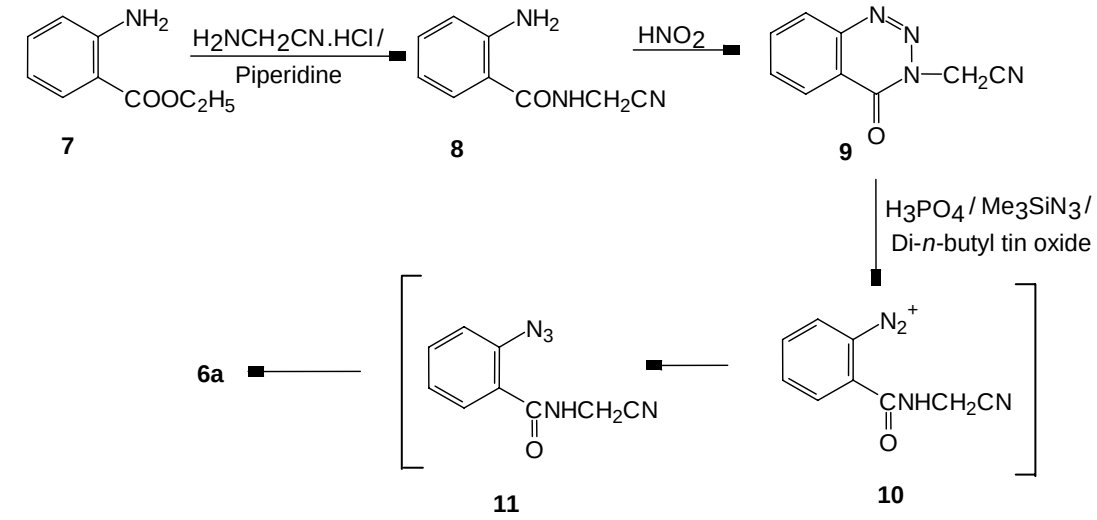
In an alternative route **6a** was produced in one step from **9** (**Scheme II**). The compound **9** was treated with phosphoric acid[13] and trimethylsilylazide in presence of di-*n*-butyl tin oxide[9] to give **6a** probably through the intermediates **10** and **11**. Although we have not attempted to rigorously establish the mechanistic details, it is likely that intramolecular cycloaddition of the nitrile of **11** with azide function of the same yielded the desired compound **6a**. The structures of all the compounds **2-9** were established on the basis of elemental and spectral analysis.

The IR spectrum of compounds **4a** and **5a** displayed a broad band at 3300-2500 and a strong band at 1715 cm^{-1} for the OH and C=O stretching vibrations respectively indicating the presence of carboxylic acid group in these molecules. The formation of the tetrazole ring in **4a** was indicated by the disappereance of the azide peak of **3a** in its IR spectrum. The conversion of the chloromethyl group of **4a** to corresponding amine **5a** was evident by the appearance of twin peak for NH_2 group in the region of 3360-3290 cm^{-1}.

The IR spectra of compounds **8** and **6a** showed characteristic absorptions for the presence of C=O and NH groups in the region of 1630-1690 cm^{-1} and 3250 cm^{-1} respectively. A clue to the formation of tetrazole ring and 1,4-benzodiazepine ring in **6a** was obtained



Scheme I



Scheme II

by the disappearance of the nitrile peak of **9** and appearance of peak for NH group in its IR spectrum.

One of the noteworthy feature of the ^{1}H NMR spectra of compounds **6a-b** was that the enantiotropic C_3 methylene protons of these compounds showed an AB quartet at around 4.03 (with coupling constant J_{AB} = 14Hz) which is in accord to a similar pattern observed for [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines, apparently due to their magnetic nonequivalence character arising from C=N anisotropy in a preferred conformation of the molecule[14,15]. The other IR and ^{1}H NMR data of the compounds **2-9** were found to be in agreement to the structures proposed for these molecules.

Experimental Section

All the melting points are uncorrected. The purity of all the compounds was checked by TLC using the

solvent systems (chloroform : methanol, 9 : 1 v/v) and silica gel G as adsorbent. IR spectra were recorded on a FTIR-8400S CE (Shimadzu) spectrophotometer on KBr pellets. ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were recorded on a Jeol FX 90Q Spectrometer at 89.55 and 22.49 MHz respectively using TMS as internal reference for ^{1}H NMR. Mass spectra were recorded on a Jeol D-300 spectrometer at an ionisation potential of 70ev.

Preparation of 2-(5-chloromethyl-1-tetrazolyl)-benzoic acid 4a-b. To a solution of 2-azido benzoic acid **3a-b** (ref.11, 0.06 mole) and chloroacetonitrile (2.26 g, 0.03 mole) in DMF (30 mL) was added di-*n*-butyl tin oxide (0.003 mole) and the mixture was heated for 12 hr until the chloroacetonitrile was consumed (TLC analysis). DMF was removed under reduced pressure and the residue obtained was dissolved in methanol and reconcentrated. The residue was partitioned between ethylacetate (25 mL) and 10% sodium bicarbonate solution (25 mL). The organic phase was extracted with an additional portion of 10% sodium bicarbonate solution (25 mL). The combined aqueous extracts were acidified to *p*H 2 with 10% hydrochloric acid solution and then extracted with ethylacetate (2 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The product was recrystallized from chloroform and petroleum ether mixture. **4a**: yield 56%; m.p. 170-71^{o}C. Anal. Found: C, 45.61; H, 2.48; N, 23.72. Calcd for $C_9H_7N_4O_2Cl$ (238.5): C, 45.28; H, 2.93; N, 23.52%. IR: 3300-2500 (OH), 1715 (C=O), 1410 (CH_2) cm^{-1}; ^{1}H NMR: δ 7.38-7.65 (m,4H,ArH), 12.32 (s, 1H, COOH), 4.82 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 34.5 (CH_2Cl)**,** 128.7-134 (aromatic carbons),169.4 (COOH). **4b**: yield 58%; m.p.178-79 ^{o}C. Anal. Found: C, 40.21; H, 3.02; N, 20.78. Calcd for $C_9H_6N_4O_2Cl_2$ (273.0): C, 39.56; H, 2.19; N, 20.51%. IR: 3200-2400 (OH), 1710 (C=O), 1400 (CH_2) cm^{-1}; ^{1}H NMR: δ 7.48-7.72 (m,3H,ArH), 12.48 (s, 1H, COOH), 4.88 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 34.6 (CH_2Cl)**,** 128-135 (aromatic carbons),169.6 (COOH).

Preparation of 2-(5-aminomethyl-1-tetrazolyl)-benzoic acid 5a-b A mixture of 2-(5-chloromethyl-1-tetrazolyl)-benzoic acid **4a-b** (0.02 mole) and hexamine (2.8 g, 0.02 mole) in ethanol (25 mL) was heated for 8 hr. The mixture was poured over crushed ice, filtered and washed with water. The product was recrystallized from chloroform.

5a: Yield 52%; m.p. 180-82^{o}C. Anal. Found: C, 48.48; H, 4.48; N, 31.64. Calcd for $C_9H_9N_5O_2$ (219.0): C, 49.31; H, 4.10; N, 31.96%. IR: 3250-2500 (OH), 3360 and 3260 (NH_2), 1710 (C=O), 1380 (CH_2) cm^{-1}; ^{1}H NMR: δ 7.45-7.66 (m, 4H, ArH), 11.82 (s,1H, COOH), 4.33(s, 2H, NH_2), 3.68 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 35.4 (CH_2NH_2)**,** 128.5-134 (aromatic carbons),169.3 (COOH). **5b**: Yield 56%; m.p. 172-73^{o}C. Anal. Found: C, 43.43; H, 2.99; N, 27.47. Calcd for $C_9H_8N_5O_2Cl$ (253.5): C, 42.60; H, 3.15; N, 27.61%. IR: 3260-2400 (OH), 3365 and 3280 (NH_2), 1720 (C=O), 1390 (CH_2) cm^{-1}; ^{1}H NMR: δ 7.48-7.72 (m,3H,ArH), 11.66 (s, 1H, COOH), 3.76 (s, 2H, CH_2), 4.33 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 35.5 (CH_2NH_2)**,** 128.2-136 (aromatic carbons),169.5 (COOH).

Preparation of 4*H*-tetrazolo[1,5-*a*][1,4]benzodi-azepin-6-one 6a-b. 2-(5-Aminomethyl-1-tetrazolyl)-benzoic acid **5a-b** (0.01 mole) was taken in THF (10 mL) and was stirred at room temperature for 0.5 hr. Dicyclohexyl carbodiimide (2.06 g, 0.01 mole) was added and the mixture was refluxed for 5 hr. Mixture was cooled and the residue was removed by filtration. The filterate was poured into ice-cold water and the solid obtained was washed with water. The product was recrystallized from benzene. **6a**: Yield 59%; m.p. 258-60^{o}C. Anal. Found: C, 52.22; H, 3.20; N, 34.58. Calcd for $C_9H_7N_5O$ (201.0): C, 53.73; H, 3.48; N, 34.82%. IR: 3250 (NH), 1690 (C=O), 1520 (C=N) cm^{-1}; ^{1}H NMR: δ 7.52-7.76 (m,4H,ArH), 9.76 (s, br, 1H, NH), 4.03 (q, *J*=14Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 36.8 (CH_2)**,** 127-136 (aromatic carbons),171.4 (CONH); MS: m/z 201(M^+) (100%). **6b**: yield 53%; m.p. 236-37^{o}C. Anal. Found: C, 44.85; H, 3.11; N, 29.85. Calcd for $C_9H_6N_5OCl$ (235.5): C, 45.85; H, 2.54; N, 29.72%. IR: 3240 (NH), 1680 (C=O), 1520 (C=N) cm^{-1}; ^{1}H NMR: δ 7.55-7.78 (m,3H,ArH), 9.78 (s, br, 1H, NH), 4.32 (q, *J*=14Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 37 (CH_2)**,** 125-135.4 (aromatic carbons),171.5 (CONH); MS: m/z 235.5(M^+) (100%), 237.5(M^++2) (32%).

Preparation of 2-amino-*N*-cyanomethyl benza-mide 8. A mixture of ethyl anthranilate **7** (4.95 g, 0.03 mole), aminoacetonitrile hydrochloride (2.79 g, 0.03 mole) and piperidine (2.55 mL, 0.03 mole) in ethanol (25 mL) was refluxed for 12 hr. Mixture was concentrated under reduced pressure and the solid obtained was chromatographed over alumina (neutral) in $CHCl_3$: MeOH (9.5 : 0.5). The product was recrystallized from chloroform to give 2.6 g of **8**. Yield 50%; m.p. 171-72^{o}C. Anal. Found: C, 60.88; H, 4.98; N, 24.22. Calcd for $C_9H_9N_3O$ (175.0): C, 61.71;

H, 5.14; N, 24.00%. IR: 3290 and 3260 (NH_2), 3230 (NH), 1660 (C=O), 2240 (CN) cm^{-1}; ^1H NMR: δ 7.22-8.20 (m,4H,ArH), 8.14 (s, br, 1H, NH), 5.86 (s, 2H, CH_2), 4.33 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): δ 31.6 (CH_2)**,** 114.2 (CN), 116-148 (aromatic carbons), 167.9 (CONH).

Preparation of 3-cyanomethyl-1,2,3-benzotriazin-4-(3*H*)-one 9. 2-Amino-*N*-cyano methyl benzamide **8** (1.75 g, 0.01 mole) was dissolved in 25% HCl (15 mL) and was diazotized with sodium nitrite (1.38 g, 0.02 mole) at 0-5°C. After 1 hr, 5*N* NaOH (15 mL) was added and the mixture was stirred for 10 min. It was then acidified with conc. HCl and the solid obtained was washed with sodium bicarbonate and water. The product obtained was recrystallized from ethanol:water mixture to give 1.41 g of **9**. Yield 75%; m.p. 220-21°C. Anal. Found: C, 58.00; H, 3.62; N, 30.34. Calcd for $C_9H_6N_4O$ (186.0): C, 58.06; H, 3.22; N, 30.10%. IR: 1667 (C=O), 2235 (CN) cm^{-1}; ^1H NMR: δ 7.28-8.42 (m,4H,ArH), 5.98 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 35.3 (CH_2), 114.5 (CN), 119.2-149 (aromatic carbons), 158.7 (CON-).

Alternative route for the preparation of 4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepin-6-one 6a. 3-Cyanomethyl-1,2,3-benzotriazin-4-(3*H*)-one **9** (0.75 g, 0.004 mole) was heated with phosphoric acid(ref. 13, 5 mL) on water-bath for 0.5 hr. To this, a solution of trimethylsilyl azide (0.92 g, 0.008 mole) in toluene (25 mL) and dibutyltin oxide (0.1 g, 0.0004 mole) were added and the mixture was refluxed for 48 hr until the nitrile was consumed (TLC analysis). The reaction mixture was concentrated *in vacuo*.The residue was dissolved in methanol and reconcentrated. It was partitioned between ethylacetate (25 mL) and CH_2Cl_2 (25 mL). The organic phase was extracted with an additional portion of CH_2Cl_2 (25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The product was recrystallized from benzene to give 0.52 g of **6a**.Yield 65%.

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