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Research Article

Synthesis of 1, 5-Benzodiazepine Derivative Incorporated on s-Triazine through Piperidinyl and Amine Linker

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ABSTRACT

Synthesis of 1,5-benzodiazepine derivative bearing piperidinyl linker and using Mannich's reaction to provide the amine group for the incorporation the benzodiazepine nucleus into s-triazine molecular framework through linker has been described. The structures of all the compounds have been established on the basis of their elemental analysis and (IR, ^{1}HNMR and MS) spectral data.

Keywords: 1,5-Benzodiazepine, s-triazine, pharmacophore.

1. INTRODUCTION

1,5-Benzodiazepine and its derivatives have received significant attention due to their wide range of pharmacological and therapeutic properties. They are establish in compounds which are active against peptide hormones,[1] interleukin converting enzymes[2] and potassium blockers.[3] More recently, biological interest of 1,5-benzodiazepines has been broaden to various diseases such as cancer viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase) and cardiovascular disorders.[4-5] The piperidine ring is a pervasive structural moiety present in many alkaloid natural products and also an important synthetic building block in the design of drug candidate. 4-Piperidones were reported to possess analgesic, anti-inflammatory, anticancer, local anaesthetic, CNS, and antimicrobial activity.[6]

s-Triazine derivatives possess biological activities such as anti-plasmodial, antitumor, anticancer, antiviral, anti-inflammatory, antifungal, anti-protozoal, antimalarial, and anti-microbial activities.[7] The exceptional features of 2,4,6-trichloro-1,3,5-triazine derivative (TCT) is to provide a template to hold three biologically active motifs in the same molecular framework, by virtue of allowing its highly active chlorine atoms to be replaced by nucleophiles one after the other, in a sequence depending upon the variation of a temperature based strategy, has caused this molecule to remain in the mainstay as an evergreen pharmacophore in the design and development of novel agents from this nucleus.

Greatly encouraged by the biologically active pharmacophore properties of both 1,5-benzodiazepine and s-triazine molecules we intended to develop the bioactive molecule which could enhances the biological activity in the resulting materials by providing an additive affect on the overall potency. Herein, in this paper we report, the study directed to incorporate the benzodiazepine nucleus into s-triazine molecular framework through linker.

2. MATERIALS AND METHODS

Melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S. ^{1}HNMR spectra were recorded in $CDCl_3$ on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm.

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2.1 Preparation of 2-chloro-4,6-dicyclopropyl-1,3,5-triazine (2)

To a solution of 2,4,6-trichloro-1,3,5-triazine (TCT) (**1**, 1.84g, 0.01mol) in 1,4 dioxan (10ml), cyclopropylamine (**2,** 1ml, 0.0095mol) in 1,4 dioxan (5.0ml) was added at 0-5 °C. Anhydrous K_2CO_3 (1.75g, 0.01mol) was added and the mixture was stirred for 2 h. After completion of reaction, further amount of cyclopropylamine (**2,** 0.54ml, 0.0095mol) in 1,4 dioxan (50ml) and anhydrous K_2CO_3 (1.75g, 0.01mol) was added in above reaction mixture at 35°C and the mixture was stirred for 2h. The mixture was poured on crushed ice and neutralized with dil HCl. The resulting solid mass was filtered and washed with dil ethanol, dried over anhydrous Na_2SO_4 and recrystallized from ethanol:water (1: 9) mixture to give **2** (1.35g, yield 73%, mp-210-12°C). IR (KBr) cm^{-1}, 3255 [N-H str.], 1567 [C=C str.], 1178 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 4.03 [s, 2H, NH], 2.32 [m, 8H, CH_2], 1.41 [m, 2H, CH]; MS: m/z (%): 225.8 (100.0%), 227.2 (38%), Anal. Calcd for $C_9H_{12}N_5Cl$, Calculated: C 47.90, H 5.36, N 31.03; Found: C 47.72, H 5.33, N 30.89.

2.2 Preparation of 4-methyl-2,3-dihydro-1*H*-1, 5-benzodiazepin-2-one (3)

o-Phenylenediamine (1.0g, 0.009mol) and ethyl acetoacetate (1.2ml, 0.009mol) were heated in xylene (10ml) for 1h. The mixture was left overnight to give **3** (1.44g, yield 90%, mp-140-142°C). IR (KBr) cm^{-1}, 3315 [N-H str.], 3140 [NH-CO str.], 3078 [C-H str. ArH], 2910 [C-H str. CH_3], 1680 [C=O str.], 1624 [C=N str.], 1567 [C=C str.], 1178 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 8.02 [s, 1H, NH], 7.01-7.68 [m, 4H, ArH], 4.39 [s, 2H, CH_2], 1.47[s, 3H, CH_3]; MS: [M^+]: 174, Anal. Calcd for $C_{10}H_{10}N_2O$, Calculated: C 68.95, H 5.79, N 16.08; Found: C 68.67, H 5.76, N 16.01.

2.3 Preparation of 4-methyl-2-methylthio-3*H*-1, 5-benzodiazepine (4)

Equimolar quantities of compound **3** (1.74g, 0.01mol) and Lawesson's reagent (3.36g, 0.01mol) was taken in pyridine and the reaction mixture was irradiated in a microwave at 360 W for 6 min. The reaction mixture was cooled, poured on crushed ice and further recrystallization from chloroform. 1.5g (0.01mol) of this compound was taken in 10% sodium hydroxide solution (5.0ml) and methyl iodide (2ml) in methanol (15ml) was irradiated in a to microwave at 360W for 6 min. The solution was concentrated to 10ml, water was then added and the product obtained by extraction with methylene chloride was recrystallized from ethanol-hexane mixture to give **4** (1.06g, yield 66%, mp-184-186°C). IR (KBr) cm^{-1} 3070 [C-H str. ArH], 2910 [C-H str. CH_3], 1640 [C=N str.], 1570 [C=C str. ArH], 1050 [C-N str.], 680 [C-S str]. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12-7.45 [m, 4H, ArH], 1.87 [s, 2H, CH_2], 2.55 [s, 3H, SCH_3], 1.54 [s, 3H, CH_3]; MS: [M^+]: 204, Anal. Calcd for $C_{11}H_{12}N_2S$, Calculated: C 64.67, H 5.92, N 13.71, S 15.70; Found: C 64.78, H 5.96, N 13.77, S 15.78.

2.5 Preparation of 2-(4-oxopiperidinyl)-4-methyl-1, 5-benzodiazepine (6)

The mixture containing compound **4** (1.73g, 0.01mol) and 4-piperidone (**5,** 0.49g, 0.012mol) in ethanol (10ml) and sodium hydroxide (3.5ml, 40% solution) was irradiated in a microwave for 3 min at 360 W. It was then cooled to room temperature and poured into ice cold water and the residue obtained was purified by recrystallization with ethanol to give **6. (**1.43 g Yield 77%, m.pt 194-96°C). IR (KBr) cm^{-1} 3058 [C-H str. ArH], 2968 [C-H str. CH_3], 1675 [C=O str.], 1639 [C=N str.], 1472 [C=C str. ArH], 1253 [C-N str.]. ^{1}H NMR (400 MHz, $CDCl_3$) δppm 7.33-7.88 [m, 4H, ArH], 2.88 [t, 4H, $(CH_2)_2$], 2.24 [t, 4H, $(CH_2)_2$], 1.84 [s, 2H, CH_2], 1.40 [s, 3H, CH_3]; MS: [M+]: 255 Anal. Calcd for $C_{15}H_{17}N_3O$, Calculated: C 70.56, H 6.71, N 16.46; Found: C 70.68, H 6.75, N 16.59.

2.6 Preparation of 3-Aminomethyl-1-(4-methyl-3H-1,5-benzodiazepin-2-yl)-piperidin-4-one (7)

The mixture containing compound **6** (0.61 g, 0.003 mol), bistrimethylsilyamine (0.49, 0.003 mol) and formaldehyde (2.5ml, 37%) in ethanol (10ml) was irradiated in a microwave for 5 min at 360 W. It was then cooled to room temperature and poured into ice cold water and the residue obtained was purified by recrystallization with ethanol to give **7** (0.52 g, yield 78%, mp-198-200 °C). IR (KBr) cm^{-1} 3279 [N-H str.], 3059 [C-H str. ArH], 2859 [C-H str. CH_3], 1684 [C=O str.], 1635 [C=N str.], 1481 [C=C str. ArH], 1242 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$)

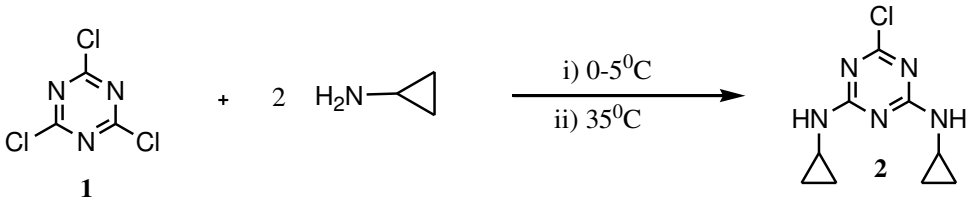
δppm 7.26-7.68 [m, 4H, ArH],], 5.22 [s, 2H, NH_2], 1.88 [s, 2H, CH_2], 3.23 [d, 2H, CH_2], 2.98 [d, 2H, CH_2], 2.82 [m, 1H, CH], 2.32 [t, 4H, $(CH_2)_2$], 1.31 [s, 3H, CH_3]; MS: [M+]: 284 Anal. Calcd for $C_{16}H_{20}N_4O$, Calculated: C 67.58, H 7.09, N 19.70; Found: C 67.44, H 7.04, N 19.62.

2.7 Preparation of N-[2',4',6'-bis-cyclopropylamino-[1,3,5]triazin-2-ylaminomethyl]-1-(4-methyl-3H-1,5-benzodiazepin-2-yl)-piperidin-4-one (8)

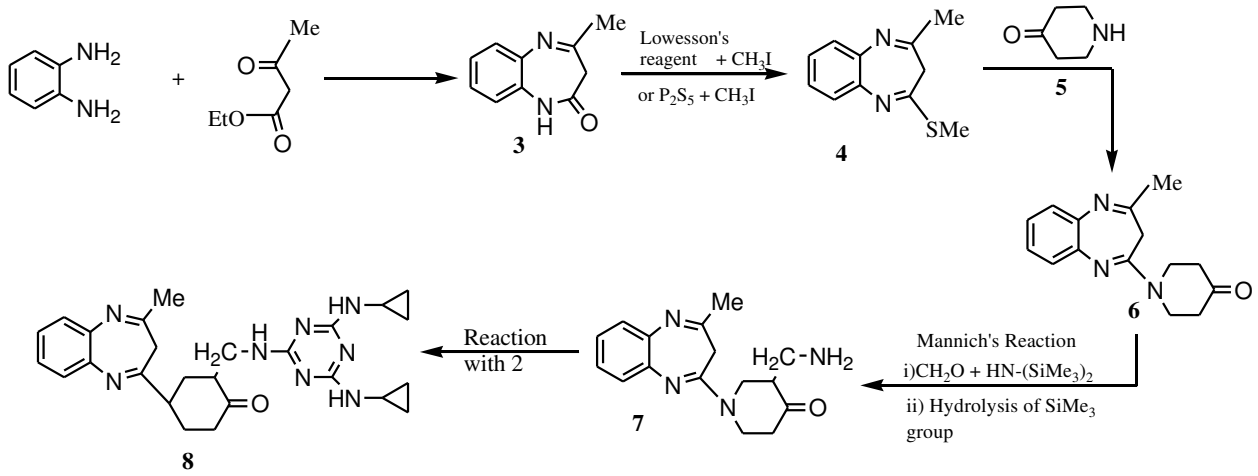
A mixture of compound **2** (0.225g, 0.001mole), K_2CO_3 (0.5g) and compound **7** (0.22g, 0.001mole) in dry THF (10ml) was refluxed for 6h. The reaction mixture was poured into crushed ice and neutralized with dil. HCl. The resulting solid was filtered, washed with water and recrystallized from ethanol: water (9:1) to give **8** (0.97g, yield 68%, mp-306-308^{o}C). IR (KBr) cm^{-1} 3420 [N-H str.], 3033 [C-H str], 2945 [C-H str. ArH], 2756 [C-H str. CH_3], 1634 [C=N str.], 1567 [C=C str. ArH], 1146 [C-N str.]; ^{1}H NMR (400 MHz, CDCl3) δppm 7.24-7.53 [m, 4H, ArH], 4.18 [s, 3H, NH], 3.10 [s, 2H, CH_2], 2.63 [t, 4H, $(CH_2)_2$], 1.94 [s, 2H, CH_2], 2.40 [t, 4H, $(CH_2)_2$], 1.60 [m, 2H, CH],1.47 [m, 8H, $(CH_2)_4$], 1.32 [s, 3H, CH_3]; MS: [M+]: 473 Anal. Calcd for $C_{25}H_{31}N_9O$, Calculated: C 63.40, H 6.60, N 26.62; Found: C 63.29, H 6.56, N 26.49.

3. RESULTS AND DISCUSSION

The strategy outlined in scheme-1 was employed for the preparation of 2 from TCT (1) with 2-moles of cyclopropylamine in a succession (first at 0-5^{o}C and then at 35^{o}C). The aim of the strategy depicted in scheme-2 was to install on 4 positions of the 1,5-benzodiazepine ring, the disubstituted s-triazine nucleus through aminomethyl spacer in 8. Firstly, 4-methyl-1,3-dihydro-1H-(1,5)-benzodiazepin-2-one (3) was synthesized by the reaction of o-phenylenediamine with one mole of acetoacetic ester. Iminothiomethyl ethers derivative of compound 4 was utilized in the present work in its nucleophile displacement with piperidone to give compound 6. Compound 4 in turn was prepared from 3 on its reaction with lowesson's reagent whose subsequent reaction with CH_3I provided compound 4. Further the strategy involved the formation of 8 from 6. In this proposed strategy, the secondary amine function of bis-trimethylsilylamine was used to enter in reaction with formaldehyde which in turn formed the corresponding Mannich base, on their reaction with the substrate 6, (the hydrolysis of the bistrimethylsilyl function of the Mannich's base: not shown) to generate 7, whose primary amine function will be allowed to react with 2 to furnish 8.



Scheme-1



Scheme-2

4. CONCLUSION

In summary, the procedure reported provided an easy access to the incorporation of 4-methyl-1,3-dihydro-1*H*-(1,5)-benzodizepin-2-one **(3)** to the 4,6-dicyclopropylamino-s-triazine framework through amine and piperidinyl linker.

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