ORIGINAL RESEARCH PAPER

Chemistry

SYNTHESIS AND CHARACTERISATION OF SOME NOVEL HETEROCYCLIC DERIVATIVES OF PHARMACEUTICAL INTEREST

KEY WORDS: *Benzazepinone-2,5-dione, oxoketene dithioacetal, Friedel-Craft cyclocondensation with PPA*

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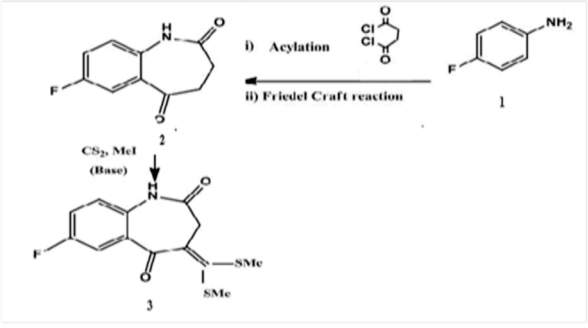
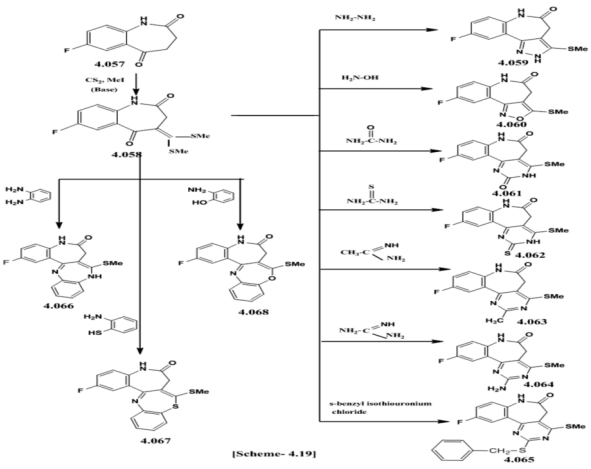
ABSTRACT

Benzo fused derivatives of azepines and their analogues have attracted attention of chemist in the field of drugs and pharmaceuticals1-3.These compounds are widely used as anticonvulsant, antianxiety, analgesic and sedative. Their haemodynamic effects 4 and spasmolytic activities have also been reported5. Encouraged by their impressive pharmacological properties, we thought it worthwhile in this communication to focus research on the synthesis of newer series of benzo-1,5-substituted azepine derivatives fused to benzazepinone moiety to form the part of the same molecular framework.

INTRODUCTION

A highly facile single step approach to the annulation of face 'd' of benzazepinone nucleus with benzodiazepine, benzothiazepine and benzoxazepine ring has been described. The annulation proceeded smoothly on the reaction of oxoketenedithioacetal derivative **3** with (i) o-phenylenediamine[6] (ii) o-aminothiophenol[7] (iii) o-aminophenol[7] in boiling ethanol to afford the corresponding 1,5-benzodiazepines **4,** 1,5-benzothiazepines **5** and 1,5-benzoxazepines **6 (Scheme-1)** respectively in acceptable yields. The 4-ketene dithioacetal analogue of 7-fluorobenzo[b] azepin 2, 5-dione **3** was in turn obtained from the reaction of 7-fluoro-3,4-dihydro-1H-benzo[b] azepine-2,5-dione **2** (with CS_2 + CH_3I in presence of t-BuOK). 7-Fluoro-3,4-di hydro-1H-benzo[b]azepine-2,5-dione **2** resulted from the acylation of p-fluoro aniline with succinyl chloride followed by cyclocondensation of the later with PPA.





[Scheme- 4.19]

MATERIALS AND METHOD

p-Fluoroaniline and succinyl chloride were obtained from commercial sources . All the reagents were used of AR Grade. Melting points were determined in open glass capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel (G) plates.IR spectra were recorded on CE (Schimatzu) FTIR-9050 S.^{1}H- NMR spectra and ^{13}C NMR spectra were recorded on Sea 400 (Bruker) using $CDCl_3$ as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm. Mass spectra were recorded on Bosch Tech.

Experimental

(i)Preparationof 7-fluoro-3,4-dihydro-1H-benzo[b] azepine-2,5-dione (2)

p-Fluoroaniline **(1)** (3.60ml,0.03 mol) was mixed with succinyl chloride (4.92g, 0.03 mol) in dry pyridine (20.0 ml) and the mixture was refluxed for 15 min. Cold reaction mixture was poured slowly with stirring to 150-200ml ice cold water. The solid which settled was filtered, and washed with cold water,further it was recrystallized from methanol and water. PPA (25g) was mixed to 3.21 g (0.01 mol) of it and heated at 150-160°C for 4hr. (the progress of the reaction was monitored by TLC).The reaction mixture was cooled to 20°C and a concentrated aqueous solution of Na_2CO_3 was added to make it alkaline. The product was extracted with ethyl acetate (3x10 ml).The extract was dried over anhydrous Na_2SO_4 and concentrated in vaccum. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **2** (2.85g, yield :79%); m.p.: 158-160 °C; IR (KBr) cm^-: 3240(N-H str.), 2990 (C-H str.), 2900, 1400 (-CH_2 next to C=O), 1712, 1704 (C=O), 1535 (C=Cstr.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 (1H, s, NH), 7.26-7.78 (3H, m, Ar-H), 3.49 (4H, s, $(CH_2)_2$); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C [157.55 (CF), 120.24 (CH), 113.54 (CH), 112.44 (CH)], Ar-C [134.44 (C), 115.25 (C), azepinone], 27.6, 34.4 [$(CH_2)_2$ azepinone)], 176.75 (C of amide), 183.49 (C of carbonyl); MS: m/z 193.17(M^+); Anal. calcd. / found for $C_{10}H_8FNO_2$: C, 62.18 / 62.35; H, 4.17/4.11; N, 7.25/7.48.

(ii) Preparation of 4-(bis (methylthio) methylene)- 7-fluoro-3, 4-dihydro-1H-benzo [b]azepine-2, 5-dione (3)

A mixture of 7-fluoro-3,4-dihydro-1H-benzo[b]azepine-2,5-dione **(2)** (2.82g, 0.01 mol) and CS_2 (1.6 ml,0.01mol) was added to a well stirred and cold suspension of t-BuOK (2.23g,0.02 mol) in dry benzene (7.0ml) and DMF (3.0ml) and the reaction mixture was allowed to stand for 4h. Methyl iodide (3.3ml, 0.02mol) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 h. at room temperature with occasional shaking and then refluxed on a water bath for 3 h. The mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extracts were washed with water, dried over anhydrous sodium sulphate and the solvent was removed by distillation. The product thus obtained was purified by crystallization with ethanol to give **3** (1.7g, yield: 60%); m.p.:155-157°C ; IR (KBr) cm^-: 3240 (N-H str.), 3000 (C-H str.), 2900, 1400 (-CH_2 next to C=O), 1640, 1685 (C=O), 1620 (C=C of α, β–unsaturated ketone), 1535 (C=C str.), 680 (C-S str.); ^{1}H- NMR (400 MHz, $CDCl_3$) δ ppm: 8.0(1H, s, NH), 7.45-7.98 (3H, m, Ar-H), 3.53 (2H, s, CH_2), 2.80 (6H, s, $(CH_3)_2$ of $(SMe)_2$);

^{13}C-NMR (400MHz, $CDCl_3$) δ ppm : Ar-C [164.5 (CF), 121.5 (CH), 113.1 (CH), 112.6 (CH)] , Ar-C [136.8 (C), 136.0 (C), 108.7 (C), azepinone] ,28.60 (CH_2 azepinone), 168.7 (C of amide), 187.0 (C of carbonyl),155.3 [-C-$(SMe)_2$] , 18.0 [2C of $(CH_3)_2$]; MS: m/z 297.37 (M^+); Anal. calcd. /found for $C_{13}H_{12}FNO_2S_2$: C, 52.51/ 52.32; H, 4.07/4.01; N, 14.71/14.48; S, 21.57/ 21.38

(iii)Preparationof 2-fluoro-8-(methylthio)-7,9-dihydrobenzo-[b]benzo[2,3]azepino[4,5-e] [1,4] diazepin-6(5H)-one (4)

A mixture of o-phenylenediamine (0.54g,0.005mol), and 4-bis (methylthio) methylene)-7-fluoro-3,4-dihydro-1H-benzo[b]azepin-2,5-dione **(3)** (1.48g, 0.005 mol) and ethanol (30ml) was refluxed for 5 h.The solvent was distilled over reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform , washed with water and dried over anhydrous sodium sulphate to give **4 (**0.92g, yield: 62%); m.p.:148-150°C ; IR (KBr) cm^-: 3370 (N-H str.), 2980(C-H str.), 2980, 1400 (-CH_2 next to C=O), 1680 (C=O), 1585(C=N), 1525(C=C str.), 697 (C-S str.); ^{1}H- NMR (400 MHz, $CDCl_3$) δ ppm: 8.14(1H, s, NH), 7.44-8.45 (3H, m, Ar-H), 7.12-7.38(4H,m,Ar-H), 4.02(1H,br s, NH),3.24 (2H, s, CH_2), 2.95 (3H, s, Ch_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm :Ar -C[164. 47(.65(CF),124.23(CH),114.54 (CH),114CH)], Ar-C[144.56(C), 137.64(C),128.7(C),120.40©, azepinone], 53.54(CH_2 azepinone),170.72(C ofamide), 150.4(-CSMe),15.74(C of Ch_3), Ar-C[141.6(C),138.1(C), diazepine], Ar C[126.5(CH),124.1(CH),123.5(CH),113.5(CH); MS, m/z: 339.09(100.0%),299.04(100.0%),230.29 (19.7%), 130.89(4.7%);Anal.calcd./found for $C_{18}H_{14}FN_3OS$: C, 63.70/63.84; H,4.16/4.11; N,12.38/12.16; S,9.45/9.22

(iv)Preparationof2-fluoro-8-(methylthio)-5H-benzo[2,3]azepino[4,5-e] [1,4]thiazepin-6 (7H)-one (5)

A mixture of o-aminothiophenol (0.64g), and 4-bis (methylthio) methylene)-7-fluoro-3,4-dihydro-1H-benzo[b]azepin-2,5-dione **(3)** (1.48g, 0.005 mol) and ethanol (30ml) was refluxed for 5 hr.The solvent was distilled over reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform , washed with water and dried over anhydrous sodium sulphate to give **5**, (0.92g, yield: 62%); m.p.:155-157°C ; IR (KBr) cm^-:3300 (N-H str.), 3010 (C-H str.), 2975, 1400 (-CH_2 next to C=O), 1600 (C=O), 1589(C=N), 1568(C=C str.), 710 (C-S-C), 688 (C-S str.); ^{1}H- NMR (400 MHz, $CDCl_3$) δ ppm: 8.14(1H, s, NH), 7.44-8.44 (3H, m, Ar-H), 7.09-7.33 (4H,m,Ar-H), 3.22 (2H, s, CH_2), 2.97 (3H, s, CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm :Ar-C[163.88(CF),123.22(CH), 114.55 (CH), 114.46 (CH)], Ar-C[143.33(C),130.68(C),128.58(C), 120.41 (C) ,azepinone],172.73(C of amide),52.45(CH_2 azepinone), 154.61(-CSMe), 15.71(C of Ch_3), Ar-C[141.66, 138.22 (C), thiazepine ring], Ar-[126.24(CH), 124.14(CH), 123.31(CH), 113.01(CH)]; MS,m/z: 356.44(M+60.0%), 301.04(100%), 289.25(32.9%), 240.25(40%), 178.02(35%), 139.8(45.0%); Anal.calcd./foundfor$C_{18}H_{13}FN_2OS_2$: C, 60.65/60.52; H, 3.68/3.62; N,7.86/7.68; S,17.99/17.78

(v)Preparation of 2-fluoro-8-(methylthio)-5H-benzo-[b]benzo[2,3] aze pino[4,5-e] [1,4] oxaze pin-6(7H)-one (6)

A mixture of o-aminophenol (0.54g), and 4-bis (methylthio) methylene)-7-fluoro-3,4-dihydro-1H-benzo[b]azepin-2,5-dione **(4)** (1.48g) and ethanol (30ml) was refluxed for 5 h.The solvent was distilled over reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform , washed with water and dried over anhydrous sodium sulphate to give **6 (**0.92g, yield: 62%); m.p.:138-140°C ; IR (KBr) cm^-: 3370 (N-H str.),2975 (C-H str.), 2990, 1400 (-CH_2 next to C=O), 1680 (C=O), 1579 (C=N), 1565 (C=C str.), 1096 (C-O-C), 691(C-S str.); ^{1}H- NMR (400 MHz, $CDCl_3$) δ ppm: 8.14 (1H, s, NH), 7.05-7.28 (3H, m, Ar-H), 7.34-8.34 (3H,m,Ar-H), 3.20 (2H, s, CH_2), 2.90 (3H, s, CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm : Ar-C [163.75(CF),123.11(CH),114.62(CH),114.53 (CH)],Ar-C[143.64(C),135.46(C),128.7(C), 120.42 (C), azepinone],170.75(C of amide), 51.54(CH_2 azepinone),161.0(-CSMe),15.4(C of CH_3) ,Ar-C[142.5(C), 138.2(C), oxazepine], Ar-C[127.9 (CH),124.2(CH),120.1 (CH),114.8 (CH)]; MS,m/z:340.07 (M+70%), 301.07 (21.2%), 240.25(100.0%),139.89(2.5%); Anal. calcd./found for$C_{18}H_{13}FN_2O_2S$:C, 63.52/63.38; H, 3.85/3.80; N, 8.23/8.42; S, 9.42/9.29

RESULTS AND DISCUSSION

The synthetic importance of oxoketenedithioacetals, specially the dimethyl thioacetal in the construction of a variety of novel fused heterocyclic systems encouraged us to explore its potential in the annulation of face 'd' of 7-fluoro-benzazepin-2,5-dione **(2)** with such pharmacophoric scaffolds as benzodiazepine,benzothiazepine and benzoxazepine which have been accredited in the literature with a proven record of their bioactive profiles. In consideration of the easy accessibility of the correseponding ketene dimethyl acetals from the base catalysed reaction of CS_2 and CH_3I with compounds containing an active methylene group, we applied this strategy on **2** to append this functionality on to its 4-position to form **3**.The versatility of **3** in allowing a facile annulation of its face 'd' with the above bioactive pharmacophores was exploited in its reaction with (i) o-phenylenediamine (ii) o-aminothiophenol (iii) o-aminophenol to generate **4-6** respectively in acceptable yields.[Scheme-1]

CONCLUSION

In summary, the unprecedented potential of oxoketenedithioacetals in synthesis, was exploited to provide an easy access to face 'd' 1,5 (benzodiazepino, benzothiazepino and benzoxazepino) annulated analogues of benzazepinone **4-6** respectively, from 4- ketene dimethyl thioacetal substituted derivative of 7-fluoro-benz-(b)-azepin-2,5-dione **(3)**.The process is characterized by mild reaction condition and easy work-up procedure.

Acknowledgement:

Authors are thankful to the Banasthali university and SJJT university authorities for providing laboratory And Instrumention facilities.

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