ORIGINAL RESEARCH PAPER

Chemistry

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

SYNTHESIS OF NEWER AZEPINE DERIVATIVES VIA CORRESPONDING OXOKETENE DITHIOACETALS

Kasar Madhukar Gangadhar

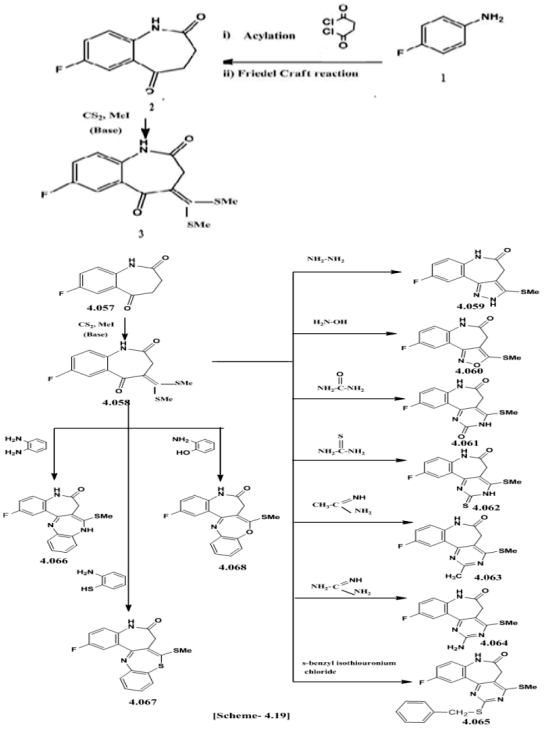
Dept. of Chemistry, SNNC –ASC College , Kusumba , Dhule-MS

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-phenylenediamine6 (ii) o-aminothiophenol7 (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 CS2 + CH3I 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 and were used as obtained, from the suppliers without further purifications. 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 ppm. Mass spectra were recorded on Bosch Tech. X.

Experimental Section

Preparation of 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, washed with cold water, 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 4h (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^{-1} 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.

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^{-1}: 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

Preparation of 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 (C), 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

Preparation of 2-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 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 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$C_{18}H_{13}FN_2$ OS$_2$: C, 60.65/60.52;H, 3.68/3.62;N, 7.86/7.68;S, 17.99/17.78

Preparation of 2-fluoro-8-(methylthio)-5H-benzo-[b]benzo[2,3] azepino[4,5-e] [1,4] oxazepin-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 forC$_{18}$H$_{13}$FN$_2$ O$_2$S :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$_3$I 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 oxoketenedithioaceta ls in synthesis, was exploited to provide an easy access to face 'd' 1,5 (benzodiazepino, benzothiazepinoand 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 university authorities for providing laboratory facilities.

REFERENCES

1) V.N. Pathak, R. Joshi and N.Gupta, Synthesis,spectral studies and antimicrobial activity of 7-chloro-2-alkyl//aryl-4-alkyl/aryl-3-arylidene-3H-1,5-benzodiazepine, Ind.J.Chem.,2006, 46B, 1191-1197.
2) U.C. Pant, H. Chandra and S. Goyal, Synthesiss of 1,5-benzothiazepines: Part XXX- Synthesis and antimicrobial studies of 10-substituted-6a,7-dihydro-6H-7- (4-fluorophenyl)-6-phenyl [1] benzopyrano [3,4-c] [1,5] benzothiazepines, Ind.J.Chem., 2006, 45B, 752-757.
3) S.R. Cherkupally, P.R. Gurrala, N. Adki and S. Avula, Synthesis and biological study of novel methylene-bis-benzofuranyl-[1,5]-benzothiazepines, Org. Commun., 2008, 1(4), 84-94.
4) A. Levai and A. Iss-Szikszai, Synthesis of optically active 1,5-benzothiazepines, Arkivoc, 2008, (i), 65-86.
5) A.R. Katrizky, R. Abonia and B.Yang, Synthesis of 3,4,7,8-Tetrahydro-6H-pyrido 1,2,3-ef-1,5-benzodiazepin-2 (1H) ones via benzotriazole methodology, Synthesis, 1998, 1487-1490.
6) R.M. Claramun, D. Sanz, S. Aggarwal, A. Kumar, S.P. Om Prakash singh and J. Elguero, The reaction of o-phenylenediamine with - -unsaturated carbonyl compounds, Arkivoc (General paper), ISSN 1424-6376, 2006, 14, 35-45.
7) A. Levai and J. Jeko,"Oxazepines and Thiazepines 46". Synthesis of tetracyclic 1,5-benzothiazepines by the reaction of , , , –unsaturated ketones with aminothiophenol, Arkivoc(General paper), 2008, 14, 234-240.