Asian Journal of Chemistry Vol. 20, No. 6 (2008), 4571-4575

Synthesis and Spectral Studies of Novel Diazepine Derivatives

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Condensation of various 1,3-diketone derivatives (**1a-f**) with ethylene diamine and *o*-phenylene diamine in absolute ethanol led to synthesis of novel 1,4-diazepines and 1,5-benzodiazepine derivatives. Structure of newly synthesized 1,4-diazepine derivative (**2a-f**) and 1,5-benzodiazepine derivatives (**3a-f**) were established on the basis spectral studies *viz.*, IR, ^{1}H NMR, ^{13}C NMR.

Key Words: 1,3-Diketone, Ethylene diamine, *o*-Phenylene diamine, Diazepine, Benzodiazepine.

INTRODUCTION

Diazepines are useful as anticancer[1], antibacterial[2], psychotropic[3], antiemetic[4], anticonvulsant[5] and herbicidal[6], muscle relaxant[7], antihypertensive[8], antidepressant[9] and antiasthamatic[10], antiinflammatory and bronchodilating agents[11]. Substituted 1,4-diazepine and their derivatives possess anti-HIV activity[12] lesser than that of zidovudine (3'-azidthymidine *i.e.* AZT). They also showed platelet-activity factor (PAF) antagonistic[13] and serotoninergic S_3 antagonistic activities[14]. 1,5-Benzodiazepine derivatives show a large number of pharmacological properties such as they acted as sedatives[15], cerebrovasodilators[16], neuroleptics[17], antisphasmadic, anticonvulsants[18] and tranquilizing agents[19]. Realizing the medicinal importance of diazepines derivatives and in continuation of our earlier work[20,21]. In this work, the synthesis of some new 1,4-diazepines and 1,5-benzodiazepine derivatives are reported.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded in KBr disks on Nicolet-mega-FT-IR550 spectrometers. ^{1}H NMR and ^{13}C NMR were recorded on model DRX 300 at 300.13 and 75.48 MHz, respectively in $CDCl_3$/DMSO-d_6 using TMS as internal standard. The purity of newly synthesized compounds were checked by TLC.

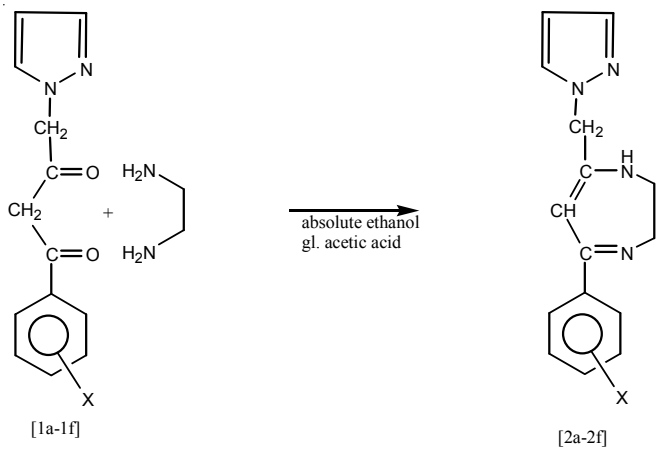
Generalized preparation of diazepine nucleus: A mixture of diketones (**1a-f**, 0.01 M) and ethylenediamine (0.01 M) was refluxed in absolute ethanol (10 mL) by making reaction medium slightly acidic. The

reaction mixture was refluxed for 3 h and then cooled to room temperature. The solid residue was recrystallized from acetone-ethanol mixture yield crystalline product. Purity of compounds were checked by TLC using (benzene:ethanol:ammonia 7:2:1) upper layer as mobile phase.

Generalized preparation of benzodiazepine nucleus: A mixture of diketones (**1a-f**, 0.01 m) and *o*-phenylene diamine (0.01 M) were refluxed in absolute ethanol (10 mL) by making reaction slightly acidic. The reaction mixture was refluxed for 6-8 h and then cooled to room temperature. The solid residue was recrystallized from ethanol yield crystalline product. Purity of compounds were checked by TLC using (benzene:ethanol:ammonia 7:2:1) upper layer as mobile phase.

RESULTS AND DISCUSSION

Condensation of 1-phenyl-4-(pyrazol-1-yl)-butane-1,3-dione (**1a**) and its derivatives (**1b-f**) having various substituents in phenyl ring, with ethylene diamine in absolute ethanol and refluxing the mixture for 3 h results in the formation of 1*H*-1,4-diazepine derivatives (**2a-f**).



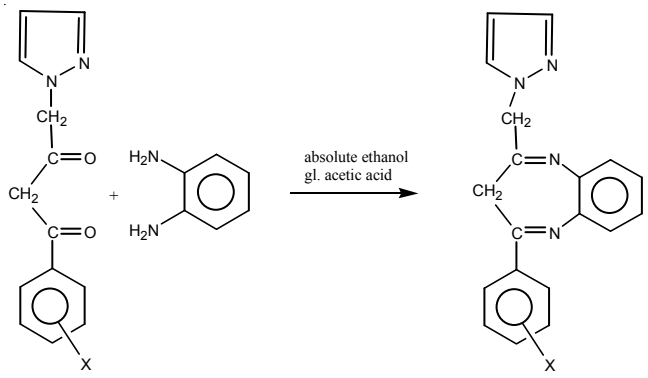
[1a-1f] [2a-2f]

X = H, CH_3, OCH_3, Br, Cl, NO_2

Scheme-I

Similarly condensation of 1-phenyl-4-(pyrazol-1-yl)-butane 1,3-dione (**1a**) its derivative (**1b-f**) having various substituent in phenyl ring, with *o*-phenylene diamine in absolute ethanol and refluxing for 6-8 h results in the formation of 3*H*-1,5-benzodiazepine derivatives (**3a-f**). Elemental analysis and spectral analysis of title compounds are given in Tables 1 and 2, respectively.

Infrared spectra of compound (**2a-f**, **3a-f**) showed a NH stretching vibration around 3320 cm^{-1}, Ar-H stretching vibration around 3040 cm^{-1} and CH stretching vibration around 2940 cm^{-1}.



[1a-1f] [3a-3f]

X = H, CH_3, OCH_3, Br, Cl, NO_2

Scheme-II

TABLE-1
ELEMENTAL ANALYSIS OF TITLE COMPOUNDS

Compd.	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Calcd. (Found)		
				C	H	N
2a	$C_{15}H_{16}N_4$	186	42	71.42 (70.40)	6.34 (6.31)	22.22 (22.25)
2b	$C_{16}H_{18}N_4$	170	38	72.18 (68.10)	6.70 (6.65)	21.05 (21.07)
2c	$C_{15}H_{18}N_4O$	157	44	68.08 (68.00)	6.38 (4.20)	19.85 (19.86)
2d	$C_{15}H_{15}N_4Br$	201	37	54.54 (54.30)	4.54 (4.20)	16.96 (16.94)
2e	$C_{15}H_{15}N_4Cl$	198	30	62.82 (62.37)	5.23 (5.10)	19.54 (19.52)
2f	$C_{15}H_{16}N_5O_2$	193	50	60.60 (60.10)	5.05 (5.00)	23.56 (23.58)
3a	$C_{19}H_{16}N_4$	140	52	76.00 (75.90)	5.33 (5.28)	18.66 (18.70)
3b	$C_{20}H_{18}N_4$	145	46	76.43 (76.20)	5.73 (5.63)	17.83 (17.86)
3c	$C_{20}H_{18}N_4O$	155	53	72.72 (60.12)	5.45 (5.40)	16.96 (17.00)
3d	$C_{19}H_{15}N_4Br$	205	40	60.31 (60.12)	3.96 (3.85)	14.81 (1487)
3e	$C_{19}H_{15}N_4Cl$	146	43	68.16 (68.05)	4.48 (4.50)	16.74 (16.79)
3f	$C_{19}H_{15}N_5O_2$	213	55	66.08 (66.01)	4.34 (4.40)	20.28 (20.30)

The ^{1}H NMR spectra of compounds (**2a-f**, **3a-f**) showed a multiplet in the range of δ 6.75-8.50 ppm due to aromatic protons. A singlet observed at δ 8.75 ppm is due to presence of NH proton and triplet observed around δ 3.15 ppm is due to presence of -NCH_2CH_2N- protons.

^{13}C NMR spectra of compounds (**2a-f**) showed 9 lines between region δ 120-150 ppm due to aromatic carbon. Two carbons of C=N groups are appeared around δ 165 ppm. Two lines for two carbon of CH_2 attached to nitrogen atoms of diazepine ring appeared around δ 47 ppm. Active methylene carbon which appeared in diketones at δ 88.13 ppm undergo slightly upward shift and observed at δ 85 ppm indicating the formation of diazepine ring.

TABLE-2
SPECTRAL ANALYSIS OF TITLED COMPOUNDS

Compd.	IR (KBr, ν_{max}, cm^{-1})	^1H NMR ($CDCl_3$/DMSO-d_6)	^{13}C NMR $CDCl_3$/DMSOd_6) (δ ppm)
2a	3325 (N–H), 3040 (Ar–H) 1580 (C=N), 2920 (C–H)	3.30 (2H, t, CH_2N=), 3.00 (2H, tCH_2NH), 8.75 (1H, s, NHC=C), 7.01 (1H, >CH), 7.15-8.45 (8H, aromatic), 2.10 (2H, s, CH_2-N)	120-150 (nine lines, 9 aromatic carbon, 164-165 (two lines, two C=N), 45 & 47 (two lines, =NCH_2CH_2–NH), 83 (>CH), 35 (CH_2-N)
2b	3320 (N–H), 3050 (Ar–H) 1590 (C=N), 2924 (C–H)	3.39 (2H, t, CH_2N=), 3.15 (2H, tCH_2NH), 8.69 (1H, s, NHC=C), 7.00 (1H, >CH), 7.25-8.54 (7H, aromatic), 2.35 (3H, s, CH_3), 2.08 (2H, s, CH_2-N).	118-152 (nine lines, 9 aromatic carbon, 162 & 164 (two lines, two C=N), 46 & 48 (two lines, =NCH_2CH_2–NH), 84 (>CH), 21 (CH_3)
2c	3322 (N–H), 3060 (Ar–H) 1585 (C=N), 2940 (C–H)	3.20 (2H, t, CH_2N=), 3.00 (2H, tCH_2NH), 8.85 (1H, s, NHC=C), 7.00 (1H, >CH), 7.15-8.55 (7H, aromatic), 3.89 (3H, s, OCH_3), 2.07 (2H, s, CH_2-N).	115-150 (nine lines, 9 aromatic carbon, 164 & 166 (two lines, two C=N), 46 & 47 (two lines, =NCH_2CH_2–NH), 84 (>CH), 56 (OCH_3)
2d	3325 (N–H), 3056 (Ar–H) 1594 (C=N), 2930 (C–H)	3.25 (2H, t, CH_2N=), 3.05 (2H, tCH_2NH), 8.55 (1H, s, NHC=C), 7.00 (1H, >CH), 7.15-8.35 (7H, aromatic), 2.05 (2H, s, CH_2-N).	120-152 (nine lines, 9 aromatic carbon, 163 & 165 (two lines, two C=N), 45 & 46 (two lines, =NCH_2CH_2–NH), 83 (>CH)
2e	3335 (N–H), 3052 (Ar–H) 1584 (C=N), 2910 (C–H)	3.25 (2H, t, CH_2N=), 3.05 (2H, tCH_2NH), 8.55 (1H, s, NHC=C), 7.00 (1H, >CH), 7.15-8.35 (7H, aromatic), 2.03 (2H, s, CH_2-N).	117-156 (nine lines, 9 aromatic carbon, 164 & 165 (two lines, two C=N), 45 & 47 (two lines, =NCH_2CH_2–NH), 84 (>CH)
2f	3325 (N–H), 3030 (Ar–H) 1588 (C=N), 2928 (C–H)	3.33 (2H, t, CH_2N=), 3.08 (2H, tCH_2NH), 8.65 (1H, s, NHC=C), 6.96 (1H, >CH), 7.25-8.40 (7H, aromatic), 2.07 (2H, s, CH_2-N).	118-155 (nine lines, 9 aromatic carbon, 162 & 164 (two lines, two C=N), 43 & 44 (two lines, =NCH_2CH_2–NH), 83 (>CH)
3a	3030 (Ar–H), 1540 (C=N) 2930 (C–H), 3320 (N–H)	8.65 (1H, s, NH), 7.20 (2H, s, >CH), 7.34-8.53 (12H, aromatic), 2.06(2H, s, CH_2-N).	118-153 (fifteen lines, 15 aromatic carbon, 162 & 165 (two lines, two C=N), 45 & 47 (two lines, =NCH_2CH_2–NH), 83 (>CH)
3b	3035 (Ar–H), 1593 (C=N) 2938 (C–H), 3315 (N–H)	8.70 (1H, s, NH), 7.15 (2H, s, >CH), 7.24-8.49 (11H, aromatic), 2.25 (3H, s, CH_3), 2.13 (2H, s, CH_2-N).	119-154 (fifteen lines, 15 aromatic carbon, 162 & 163 (two lines, two C=N), 45 & 46 (two lines, =NCH_2CH_2–NH), 83 (>CH), 22 (CH_3)
3c	3020 (Ar–H), 1605 (C=N) 2940 (C–H), 3324 (N–H) 1090 (O–C)	8.73 (1H, s, NH), 7.2 (1H, s, >CH), 7.34-8.53 (11H, aromatic), 3.79 (3H, s, OCH_3), 2.08 (2H, s, CH_2-N).	120-155 (fifteen lines, 15 aromatic carbon, 163 & 164 (two lines, two C=N), 46 & 47 (two lines, =NCH_2CH_2–NH), 84 (>CH), 52 (OCH_3)
3d	3026 (Ar–H), 1600 (C=N) 2937 (C–H), 3340 (N–H)	8.62 (1H, s, NH), 7.12 (2H, s, >CH), 7.24-8.55 (11H, aromatic), 2.10(2H, s, CH_2-N).	121-153 (fifteen lines, 15 aromatic carbon, 164 & 165 (two lines, two C=N), 44 & 45 (two lines, =NCH_2CH_2–NH), 83 (>CH)
3e	3030 (Ar–H), 1588 (C=N) 2940 (C–H), 3340 (N–H)	8.55 (1H, s, NH), 7.14 (2H, s, >CH), 7.20-8.43 (11H, aromatic), 2.11(2H, s, CH_2-N).	116-151 (fifteen lines, 15 aromatic carbon, 163 & 165 (two lines, two C=N), 45 & 47 (two lines, =NCH_2CH_2–NH), 85 (>CH)
3f	3040 (Ar–H), 1595 (C=N) 2934 (C–H), 3330 (N–H)	8.67 (1H, s, NH), 7.12 (1H, s, >CH), 7.24-8.54 (11H, aromatic), 2.08(2H, s, CH_2-N).	122-156 (fifteen lines, 15 aromatic carbon, 166 & 168 (two lines, two C=N), 47 & 48 (two lines, =NCH_2CH_2–NH), 84 (>CH)

^{13}C NMR spectra of compounds (**3a-f**) showed 15 lines between region δ 115-152 ppm due to aromatic carbon. Two carbon of C=N groups are appeared around δ 162 and 165 ppm. Two lines for two carbons of CH_2 attached to nitrogen atoms of diazepine ring appeared around δ 47 and 44 ppm. Active methylene carbon which appeared in diketones at δ 88.13 ppm undergo slightly upward shift and observed at δ 83 ppm indicating the formation of diazepine nucleus.

ACKNOWLEDGEMENT

One of the authors (UB) is thankful to UGC, New Delhi for the award of Senior Research Fellowship.

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(*Received*: 21 July 2007; *Accepted*: 8 March 2008) AJC-6427