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International Letters of Chemistry, Physics and Astronomy

11(2) (2014) 106-115 ISSN 2299-3843

Two step One-Pot Synthesis of Novel 5-(4-Fluorophenyl)-1*H*-Beno[*e*][1,4]Diazepin-2(3*H*)-One and it's Base Catalyzed Transformation to *N*-Alkyl and C-3 Arylidene Derivatives

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ABSTRACT

We have demonstrated two step one-pot synthesis of novel 5-(4-Fluorophenyl)-1*H*-Beno[*e*][1,4]Diazepin-2(3*H*)-one using 2-Amino-4'-fluorobenzophenone as initial stating material. The small library of N-alkylation and C-3 benzylidene derivatives have been synthesized by base catalyzedreaction of 5-(4-fluorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(3)** nucleus with various alkyl halides and aromatic aldehydes respectively.

***Keywords*:** Benzodiazepines; Base catalyzed; Cross-aldol

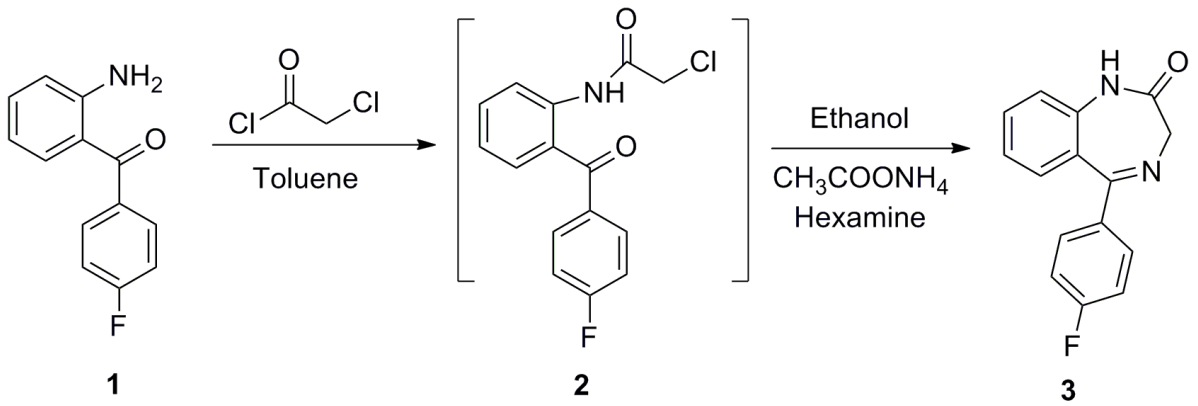
1. INTRODUCTION

In heterocyclic chemistry one of the most prominent class of privileged structure is 1,4-benzodiazepine. This important class of central nervous system (CNS) active agents and its peptidomimetic nature makes them the important target to study in medicinal aspects. Diazepine ring system and its derivatives have shown considerable uses in medicinal drug discovery towards wide range of biological activities[1-4] such as anticonvulsant, antianxiety, analgesic, sedative, anti-depressive and hypnotic agents as well as anti-inflammatory agents[5]. In the last few years, the area of biological importance of 1,4-benzodiazepines have been extended to many diseases such as cancer, viral infection and cardiovascular disorders[6,7]. In addition, 1,4-benzodiazepine derivatives are key intermediates in the synthesis of various fused heterocyclic system[8].

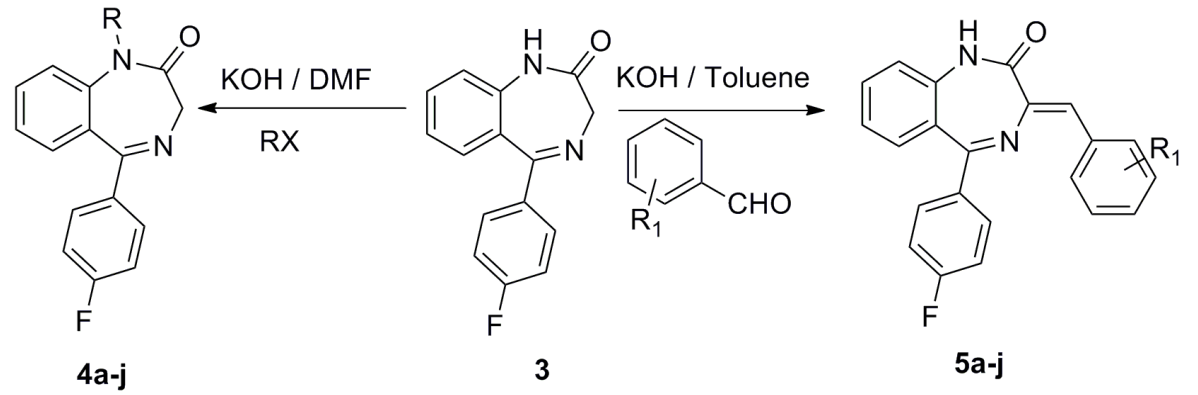
Owing to their versatile applications, various methods for the synthesis of benzodiazepines have been reported in the literature. These include condensation reactions of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds[9] in the presence of various kind of catalysts[10-18]. The most extensively used methods for preparing 1,4-benzodiazepines

begins with an 2-aminobenzophenone. The first method involves the treatment of appropriate2-aminobenzophenone with haloacetyl halide to afford the amide, followed by the addition of ammonia to first displace the chlorine giving the glycinamide. Then cyclization by imine formation will give the 1,4-benzodiazepine with higher yield[18].The other method involves treating the 2-aminobenzophenone with an amino acid ester hydrochloride in pyridine to give 1,4-benzodiazepine in one step, with a variety of substituent.

In our current research work we have demonstrated two step one-pot synthesis of 5-(4-fluorophenyl)-1*H*-beno[*e*][1,4]diazepin-2(3*H*)-one (**3)** by some modification of earlier reported method (Scheme 1). The intermediate **3** is treated with various alkyl halides in presence of KOH as a base and DMF as solvent to yield compounds **4a-j.** In the similar way compounds **5a-j** were synthesized by the cross-aldol reaction of intermediate **3** with various aldehyde by using KOH as base and toluene as solvent (Scheme 2).



Scheme 1. Synthesis scheme of 5-(4-fluorophenyl)-1*H*-beno[*e*][1,4]diazepin-2(3*H*)-one.



Scheme 2. General procedure for the synthesis of 1-substituted-5-(4-fluorophenyl)-1*H*-benzo[*e*] [1,4]diazepin-2(3*H*)-one **(4a-j)** and 3-benzylidene-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one **(5a-j).**

2. RESULT AND DISCUSSION

We have demonstrated two step one-pot synthesis of 5-(4-fluorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(3)** starting from commercially available2-Amino-4'-

fluorobenzophenone and chloroacetyl chloride followed by cyclization using hexamethylenetetramine and ammonium acetate. The synthesized compound 5-(4-fluorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(3)** possess amidic proton indiazepine nucleus which favors any aliphatic alkyl halide to react as a electrophile in presence of base. On the other side the diazepine ring **(3)** with active methylene group adjacent to carbonyl behave as a synthon for cross-aldol reaction with different aldehydes in the presence of base. Initially, to optimize the reaction condition and yield, compound 5-(4-fluorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(3)** was reacted with Methyl iodide in the presence of various base and solvent to generated targeted compound (**4a**).

Similarly, compound **(3)** was reacted with benzaldehyde in the presence of various base and solvent to generated targeted compound (**5a**). As a result, we found that maximum yield and smooth conversion to related product **4a** and **5a** obtained from **(3)** by using KOH. NaOH also gives good result. But in weak inorganic base and organic base, the reaction takes much more time and yields are less (Table 1).

Table 1. Optimization of the synthesis of compounds **4a** and **5a**.

Entry	Solvent	Base	Yield % of 4a	Yield % of 5a
1	Toluene	DBU	20	35
2	Toluene	K_2CO_3	40	48
3	**Toluene**	**KOH**	60	**90**
4	Toluene	NaOH	48	84
5	Ethanol	DBU	33	28
6	Ethanol	K_2CO_3	45	32
7	Ethanol	KOH	71	68
8	Ethanol	NaOH	64	60
9	Acetonitrile	DBU	30	20
10	Acetonitrile	K_2CO_3	52	43
11	Acetonitrile	KOH	68	58
12	Acetonitrile	NaOH	60	55
13	DMF	DBU	34	30
14	DMF	K_2CO_3	70	35
15	**DMF**	**KOH**	**87**	66
16	DMF	NaOH	83	50

Having established the optimal condition, we next examined the scope of the reaction for the construction of small library of N-alkylation and C-3 benzylidine derivatives was synthesized by using various alkyl halides and substituted benzaldehydes respectively. The results were summarized in Table 2.

Table 2. Synthesis of compounds **4a-j** & **5a-j**.

Entry	R	[a]Yield (%)	Time hrs	MP	Entry	R_1	[a]Yield (%)	Time hrs	MP
4a	$-CH_3$	87	2.0	112-114	**5a**	H	90	8.0	192-195
4b	$-CH_2CH_3$	83	2.5	162-164	**5b**	$3\text{-}NO_2$	85	8.5	202-204
4c	$-(CH_2)_2CH_3$	88	3.0	123-125	**5c**	$3,4\text{-di}OCH_3$	83	9.5	189-191
4d	$-CH(CH_3)_2$	84	2.5	98-100	**5d**	$4\text{-}OCH_3$	87	8.5	223-225
4e	$-(CH_2)_3CH_3$	80	3.0	88-90	**5e**	4-Cl	94	8.0	192-194
4f	$-CH_2CH(CH_3)_2$	89	3.5	72-74	**5f**	4-F	90	8.5	167-169
4g	$-(CH_2)_4CH_3$	90	2.5	93-95	**5g**	$4\text{-}NO_2$	92	10.0	219-219
4h	$-(CH_2)_2CH(CH_3)_2$	88	4.0	84-86	**5h**	4-Br	89	8.0	183-185
4i	C_6H_{11}	79	4.5	137-139	**5i**	2-OH	80	8.5	152-154
4j	$-CH_2C_6H_4 4\text{-}NO_2$	90	4.0	157-159	**5j**	$2,5\text{-di}OCH_3$	81	9.0	144-145

a: Isolated yield in %

The characterization of synthesized compounds was carried out by Mass, ^{1}H NMR and IR spectroscopy. In ^{1}H NMR spectrum of compound **3** shows singlet of amidic –NH- at 8.83 δ ppm which is disappered in compound **4a** and the promising peak of methyl substitution is observed at 3.42δ ppm. Further it is confirmed by IR that the absorption band 3282 cm^{-1} of secondary amide in compound **3** is diappeared in compound **4a**. Mass spectra is also supports the molecular weight of **4a**.In ^{1}H NMR spectrumof compound **3** shows methylene proton (-CH_2-) at 4.31δ ppm, which is absent in **5a**. The promising peak of arylidine proton (-CH=) is observed at 6.39 δ ppm. Further mass and IR spectra supports the structure of **5a**.

2. 1. Experimental

For all these conversions, progress of reaction was carried out on TLC plate silica gel GF^{254} and the melting points were recorded by open capillary method. IR spectra were recorded on a Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker AVANCE II 400 MHz and 300 MHzspectrometer. Elemental analysis of the all the synthesized compounds were carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

2. 1. 1. Procedure for the synthesis of 5-(4-fluorophenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (3)

To a solution of 2-Amino-4'-fluorobenzophenone (4.6 mmol) in toluene (10 mL), a solution of chloroacetyl chloride (4.9 mmol) in toluene (2 mL) was added drop wise at 0 °C within 30 min. The reaction mixture was further stirred at room temperature for 5 h. The resulting reaction mixture was evaporated to dryness. The crude product of intermediate compound 2-chloro-*N*-(2-(4-fluorobenzoyl)phenyl)acetamide (**2**) was taken in ethanol (40 mL), hexamethylenetetramine (13.8 mmol) and ammonium acetate (13.8 mmol) were added. The reaction mixture was refluxed for 3 h. Then the reaction mixture was evaporated to dryness. Distilled water (30 mL) was added, and the resulting suspension was stirred at 60 °C for 0.5 h. The suspension was cooled to 20 °C and filtered. The crude product was crystallized from toluene to obtained **3** in 85 % yield.

2. 1. 2. General procedure for the synthesis of 1-substituted-5-(4-fluorophenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (4a-j)

To a solution of 5-(4-fluorophenyl)-1*H*-beno[*e*][1,4]diazepin-2(3*H*)-one (3.9 mmol) in DMF (10 mL), potassium hydroxide (4.6 mmol) and appropriate alkyl halide (3.9 mmol) were added at 0 °C. The reaction mixture was stirred for 3-5 h at this temperature. After completion of reaction, it was poured into cold water. The separated solid was filtered, washed with water and dried. The crude product was crystallized from ethanol to give analytical pure product **4a-j**in 79-90 % yield.

2. 1. 3. General procedure for the synthesis of 3-benzylidene-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one (5a-j)

5-(4-Fluorophenyl)-1*H*-beno[*e*][1,4]diazepin-2(3*H*)-one (3.9 mmol), potassium hydroxide (3.9 mmol) and appropriate aromatic aldehydes (3.9 mmol) were taken in toluene (20 mL). The reaction mixture was heated to reflux for 8-10 hrs. The progress of reaction was monitored by thin layer chromatography. After completion of reaction mixture cooled to room temperature and the separated solid product was filtered, washed with cold toluene and dried. The crude product was recrystallized from ethanol to give corresponding product **5a-j** in 80-94 % yield.

2. 1. 4. Spectroscopic data for the compounds 4a-j and 5a-j

5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (3). White solid, yield 85 %, mp 172-174 °C; R_f 0.42, (8:2 hexane-EtOAc); IR (KBr): 3282, 3120, 3068, 3051, 2955, 1693, 1672, 1504, 1232, 1024, 839, 810, 731, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 4.31 (S, 2H, CH_2), 7.04-7.09 (m, 2H, Ar), 7.15-7.19 (m, 2H, Ar), 7.26-7.33 (m, 1H, Ar), 7.49-7.57 (m, 3H, Ar), 8.83 (s, 1H, NH); MS (m/z): 254 [M^+]; Anal. Calcd for $C_{15}H_{11}FN_2O_2$: C, 70.86; H, 4.36; N, 11.02; Found: C, 70.84; H, 4.34; N, 11.03.

5-(4-Fluorophenyl)-1-methyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. 4a. White solid, yield 87 %, mp 112-114 °C; R_f 0.38 (8:2 hexane-EtOAc); IR (KBr): 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298, 1050, 880, 834, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 3.42 (s, 1H, CH), 3.75-3.79 (d, 1H, CH, J=12Hz), 4.78-4.82 (d, 1H, CH, J = 12 Hz), 7.05-7.10 (m, 2H, Ar), 7.20-7.29 (m, 1H, Ar), 7.32-7.37 (m, 2H, Ar), 7.54-7.65 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 34.23, 56.53, 114.83, 115.05, 121.33, 123.69, 127.67, 129.62, 131.30,

131.39, 131.45, 143.54, 168.13, 169.30; MS (m/z): 268 [M^+]; Anal. Calcd for $C_{16}H_{13}FN_2O$: C, 71.63; H, 4.88; N, 10.44; Found: C, 71.64; H, 4.84; N, 10.42.

1-ethyl-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4b). Yellow solid, yield 82 %, mp 162-164 °C; R_f 0.44 (8:2 hexane-EtOAc); IR (KBr): 3078, 2865, 2821, 1686, 1620, 1462, 1341, 1298, 1054, 834, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.34-1.40 (t, 3H, CH), 3.05-3.12 (m, 2H, CH), 3.68-3.72 (d, 1H, CH, J = 12), 4.73-4.77 (d, 1H, CH, J = 12), 7.03-7.08 (m, 2H, Ar), 7.12-7.20 (m, 1H, Ar), 7.27-7.31 (m, 2H, Ar), 7.44-7.60 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 33.65, 55.12, 60.23, 113.62, 116.02, 120.96, 123.36, 126.88, 129.44, 130.98, 131.25, 134.14, 143.48, 167.74, 170.23; (m/z): 282 [M^+]; Anal. Calcd for $C_{17}H_{15}FN_2O$: C, 72.32; H, 5.36; N, 9.92; Found: C, 72.34; H, 5.38; N, 9.96.

5-(4-fluorophenyl)-1-propyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4c). Yellow solid, yield 90 %, mp 123-125 °C; R_f 0.30 (8:2 hexane-EtOAc); IR (KBr): 3068, 3024, 2958, 2900, 1684, 1495, 1482, 808, 732, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.18-1.25 (t, 3H, CH), 2.18-2.32(m, 2H, CH), 3.17-3.22 (t, 2H, CH), 3.66-3.70 (d, 1H, CH, J = 12), 4.68-4.72 (d, 1H, CH, J = 12), 6.98-7.04 (m, 2H, Ar), 7.10-7.18 (m, 1H, Ar), 7.26-7.28 (m, 2H, Ar), 7.42-7.56 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 15.42, 22.98, 45.36, 59.92, 113.18, 115.66, 120.18, 122.84, 126.78, 129.08, 131.18, 131.36, 131.74, 143.32, 168.16, 169.49; MS (m/z): 296 [M^+]; Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45; Found: C, 72.95; H, 5.78; N, 9.46.

5-(4-fluorophenyl)-1-isopropyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4d). White solid, yield 83 %, mp 98-100 °C; R_f 0.25 (8:2 hexane-EtOAc); IR (KBr): 3118, 3067, 3054, 2958, 2901, 1683, 1582, 1469, 810, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.22-1.24 (d, 3H, CH_3), 1.50-1.60 (d, 3H, CH_3), 3.70-3.74 (d, 1H, CH, J = 12), 4.53-4.57 (m, 1H, CH, J = 12), 4.68-4.71 (d, 1H, CH), 7.05-7.11 (m, 2H, Ar), 7.23-7.26 (m, 1H, Ar), 7.42-7.52 (m, 3H, Ar), 7.61-7.63 (m, 2H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 21.55, 44.32, 59.92, 113.18, 115.66, 120.18, 122.84, 126.78, 129.08, 131.18, 131.36, 132.56, 143.32, 168.16, 169.49; MS (m/z): 296 [M^+]; Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.95; H, 5.78; N, 9.45; Found: C, 72.97; H, 5.79; N, 9.47.

1-butyl-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4e). Yellow solid, yield 80 %, mp 88-90 °C; R_f 0.28 (8:2 hexane-EtOAc); IR (KBr): 3154, 3085, 2968, 2910, 1685, 1564, 1420, 1350, 1232, 854, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.14-1.29 (t, 3H, CH), 2.33-2.48 (m, 2H, CH), 3.68-3.86 (t, 2H, CH), 3.73-3.77 (d, 1H, CH, J = 12), 4.53-4.68 (m, 2H, CH), 4.42-4.46 (d, 1H, CH, J = 12), 7.04-7.12 (m, 2H, Ar), 7.14-7.26 (m, 1H, Ar), 7.08-7.22 (m, 2H, Ar), 7.38-7.50 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 17.68, 28.86, 35.02, 42.26, 58.14, 113.38, 114.25, 121.03, 123.22, 127.18, 128.92, 130.98, 131.11, 131.42, 142.80, 167.79, 169.01; MS (m/z): 310 [M^+]; Anal. Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03; Found: C, 73.57; H, 6.19; N, 9.07.

5-(4-fluorophenyl)-1-isobutyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4f). Yellow solid, yield 87 %, mp 72-74 °C; R_f 0.34 (8:2 hexane-EtOAc); IR (KBr): 3156, 3058, 2968, 2905, 1985, 1564, 1369, 810, 694 cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.20-1.31 (d, 3H, CH_3), 1.42-1.54 (d, 3H, CH_3), 3.68-3.72 (d, 1H, CH, J = 12), 4.40-4.46 (m, 1H, CH), 4.51-4.55 (d, 1H, CH, J = 12), 4.58-4.70 (m, 2H, CH), 7.10-7.17 (m, 2H, Ar), 7.16-7.19 (m, 1H, Ar), 7.98-7.09 (m, 3H, Ar), 7.36-7.39 (m, 2H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 21.92, 28.16, 56.67, 62.28, 112.90, 115.23, 119.68, 123.08, 127.32, 128.88, 130.77, 131.44, 132.18, 143.38, 167.76, 169.09; MS (m/z): 310 [M^+]; Anal. Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03; Found: C, 73.50; H, 6.11; N, 9.10.

5-(4-fluorophenyl)-1-pentyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4g). White solid, yield 79 %, mp 93-95 °C; R_f 0.25 (9:1 Chloroform: Methanol); IR (KBr): 3110, 3056, 2956, 2845, 1345, 1254, 1056, 842, 730, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 1.02-1.16 (t, 3H, CH), 1.28-1.36(m, 2H, CH), 1.45-1.56 (m, 2H, CH), 1.57-1.66 (m, 2H, CH), 3.73-3.77 (d, 1H, CH, J = 12), 4.14-4.28 (m, 2H, CH), 4.30-4.34 (d, 1H, CH, J = 12), 7.12-7.33 (m, 2H, Ar), 7.38-7.49 (m, 1H, Ar), 6.98-7.09 (m, 2H, Ar), 7.52-7.63 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 18.22, 21.56, 28.32, 39.75, 47.27, 55.14, 112.88, 114.58, 120.85, 123.36, 127.02, 129.32, 131.12, 131.45, 132.78, 142.27, 167.82, 169.27; MS (m/z): 324 [M^+]; Anal. Calcd for $C_{20}H_{21}FN_2O$: C, 74.05; H, 6.53; N, 8.64; Found: C, 74.07; H, 6.59; N, 8.67.

5-(4-fluorophenyl)-1-isopentyl-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4h). Yellow solid, yield 85 %, mp 84-86 °C; R_f 0.23 (8:2 hexane-EtOAc); IR (KBr): 3125, 3089, 3021, 2985, 1236, 1056, 854, 795, 830, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 0.64-0.71 (dd, 6H, 2 x CH_3), 1.22-1.33 (m, 1H, CH), 3.51-3.57 (m, 1H, CH), 3.63-3.66 (d, 1H, CH, J = 12), 4.28-4.35 (m, 1H, CH), 4.62-4.65 (d, 1H, CH, J = 12), 5.19 (s, 2H, CH_2), 6.95-7.00 (m. 2H, Ar), 7.10-7.14 (m, 1H, Ar), 7.17-7.19 (m, 1H, Ar), 7.32-7.34 (d, 1H, Ar), 7.45-7.53 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 18.44, 22.54, 36.65, 53.52, 57.14, 115.16, 115.37, 122.17, 124.33, 129.92, 130.13, 131.33, 131.42, 131.48, 142.63, 168.93, 169.36; MS (m/z): 324 [M^+]; Anal. Calcd for $C_{20}H_{21}FN_2O$: C, 74.05; H, 6.53; N, 8.64; Found: C, 74.10; H, 6.65; N, 8.77.

1-cyclohexyl-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4i). Yellow solid, yield 82 %, mp 137-139 °C; R_f 0.35 (8:2 hexane-EtOAc); IR (KBr): 3074, 2856, 2828, 1694, 1635, 1482, 1343, 1298, 1058, 840, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.1-1.9 (m, 10H, CH), 3.63-3.66 (d, 1H, CH, J = 12), 4.38-4.41 (m, 1H, CH, J = 12), 4.56-4.58 (d, 1H, CH), 6.98-7.04 (m. 2H, Ar), 7.24-7.30 (m, 1H, Ar), 7.14-7.20 (m, 1H, Ar), 7.38-7.40 (d, 1H, Ar), 7.51-7.59 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 28.32, 28.78, 30.45, 59.23, 68.69, 116.32, 116.77, 121.87, 124.36, 128.56, 130.03, 131.20, 131.45, 131.61, 142.58, 163.12, 170.31; MS (m/z): 333 [M^+]; Anal. Calcd for $C_{21}H_{21}FN_2O$: C, 74.98; H, 6.29; N, 8.33; Found: C, 74.90; H, 6.25; N, 8.37.

5-(4-fluorophenyl)-1-(4-nitrobenzyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (4j). Yellow solid, yield 92 %, mp 157-159 °C; R_f 0.49 (8:2 hexane-EtOAc); IR (KBr): 3241, 3068, 3015, 2956, 2881, 1330, 1268, 1054, 834, 830,756, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 3.63-3.66 (d, 1H, CH, J = 12), 4.55-4.58 (d, 1H, CH, J = 12), 5.53 (s, 2H, CH), 7.13-7.19 (m. 2H, Ar), 7.22-7.28 (d, 2H, Ar), 7.35-7.41 (m, 1H, Ar), 7.48-7.52 (m, 1H, Ar), 7.53-7.57 (d, 2H, Ar), 8.02-8.08 (d, 2H, Ar), 7.59-7.63 (m, 3H, Ar); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 59.23, 68.69, 116.32, 116.77, 121.87, 124.36, 125.28, 126.82, 130.03, 130.63, 131.20, 131.45, 131.61, 144.18, 144.58, 148.94, 169.08, 170.31; MS (m/z): 389 [M^+]; Anal. Calcd for $C_{21}H_{16}FN_3O_3$: C, 67.86; H, 4.14; N, 10.79; Found: C, 67.90; H, 4.15; N, 10.77.

3-benzylidene-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5a). Yellow solid, yield 90 %, mp 192-195 °C; R_f 0.25 (8:2 hexane-EtOAc); IR (KBr): 3450, 3110, 3054, 2990, 2932, 2854, 1456, 1305, 1250, 1005, 805, 732, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 6.39 (s. 1H, CH), 7.08-7.12 (m, 1H, Ar), 7.21-7.37 (m, 7H, Ar), 7.46-7.53 (m, 3H, Ar), 7.76-7.79 (m, 2H, Ar), 8.15 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): δ 115.25, 115.46, 118.09, 121.39, 122.58, 126.58, 126.74, 127.50, 128.19, 128.92, 129.90, 129.95, 131.89, 134.75, 138.93, 140.5, 164.23, 171.00; MS (m/z): 342 [M^+]; Anal. Calcd for $C_{22}H_{15}FN_2O$: C, 77.18; H, 4.42; N, 8.18; Found: C, 77.20; H, 4.45; N, 8.22.

5-(4-fluorophenyl)-3-(3-nitrobenzylidene)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5b). Yellow solid, yield 83 %, mp 202-204 °C; R_f 0.28 (8:2 hexane-EtOAc); IR (KBr): 3390,

3072, 2856, 2832, 1684, 1635, 1482, 1356, 1298, 830, 750, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ ppm 6.44 (s. 1H, CH), 7.06-7.11 (m, 1H, Ar), 7.24-7.40 (m, 4H, Ar), 7.50-7.67 (m, 3H, Ar), 7.82-7.93 (m, 3H, Ar), 8.08-8.11 (d, 1H, Ar), 8.58 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 120.15, 120.47, 121.01, 126.53, 126.79, 127.80, 129.01, 131.73, 134.32, 135.48, 137.11, 137.15, 137.24, 139.46, 141.68, 143.84, 147.81, 152.92, 165.53, 175.11; MS (m/z): 387 [M^+]; Anal. Calcd for $C_{22}H_{14}FN_3O_3$: C, 68.21; H, 3.64; N, 10.85; Found: C, 68.20; H, 3.67; N, 10.83.

3-(3,4-dimethoxybenzylidene)-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5c). Yellow solid, yield 93 %, mp 189-191 °C; R_f 0.21 (8:2 hexane-EtOAc); IR (KBr): 3232, 2997, 2906, 2833, 1683, 1670, 1506, 1363, 1265, 1026, 848, 802, 761, 731, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 3.19 (s, 1H, Ar), 3.36 (s, 1H, Ar), 6.02 (s. 1H, CH), 6.90 (s, 1H, Ar), 6.94-7.08 (m, 2H, Ar), 7.11-7.17 (m, 4H, Ar), 7.57-7.62 (d, 2H, Ar), 7.68-7.73 (m, 2H, Ar), 7.94 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 53.28, 54.63, 109.68, 112.77, 117.33, 120.68, 121.39, 122.58, 125.89, 126.08, 127.35, 127.96, 128.71, 130.26, 131.22, 133.68, 134.33, 137.86, 138.64, 161.27, 163.56, 168.15; MS (m/z): 402 [M^+]; Anal. Calcd for $C_{24}H_{19}FN_2O_3$: C, 71.63; H, 4.76; N, 6.96; Found: C, 71.67; H,4.71; N, 6.93.

5-(4-fluorophenyl)-3-(4-methoxybenzylidene)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5d). Yellow solid, yield 81 %, mp 223-225 °C; R_f 0.24 (8:2 hexane-EtOAc); IR (KBr): 3442, 3202, 2956, 2916, 2845, 1656, 1504, 1345, 1240, 834, 803, 765, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 3.36(s, 3H, CH), 6.61(s, 1H, =CH), 7.13-7.18 (m, 4H, Ar), 7.34-7.37 (m, 3H, Ar), 7.48-7.54 (m, 3H, Ar), 7.79-7.83 (m, 2H, Ar), 8.30 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 114.34, 114.89, 119.83, 123.12, 124.17, 127.36, 126.89, 128.42, 129.65, 132.74, 133.88, 134.56, 135.08, 138.96, 141.38, 161.68, 164.08, 169.44; MS (m/z): 372 [M^+]; Anal. Calcd for $C_{23}H_{17}FN_2O_2$: C, 74.18; H, 4.60; N, 7.52; Found: C, 74.22; H,4.61; N, 7.57.

3-(4-chlorobenzylidene)-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5e). Yellow solid, yield 87 %, mp 192-194-225 °C; R_f 0.26 (8:2 hexane-EtOAc); IR (KBr): 3076, 2964, 2891, 2837, 1691, 1676, 1483, 1155, 1091, 842, 761, 734, 688 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 6.46(s, 1H, =CH), 7.28-7.32(m, 2H, Ar), 7.36-7.42(m, 3H, Ar), 7.46-7.52(m, 2H, Ar), 7.68-7.74(m, 4H, Ar), 8.52(s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 116.82, 118.24, 121.63, 122.58, 123.26, 124.14, 125.66, 125.89, 126.56, 128.44, 130.38, 132.71, 132.96, 133.01, 135.69, 139.13, 158.73, 167.30; MS (m/z): 376 [M^+]; Anal. Calcd for $C_{22}H_{14}ClFN_2O$: C, 70.12; H, 3.74; N, 7.43; Found: C, 70.14; H, 3.75; N, 7.45.

3-(4-fluorobenzylidene)-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one.(5f). Yellow solid, yield 83 %, mp 167-169 °C; R_f 0.25 (8:2 hexane-EtOAc); IR (KBr): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1298, 784, 746, 698, cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 6.48 (s, 1H, =CH), 7.30-7.34 (m, 3H, Ar), 7.40-7.44 (m, 3H, Ar), 7.61-7.65 (m, 2H, Ar), 7.86-7.92 (m, 4H, Ar), 8.36(s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 118.96, 122.23, 123.48, 124.56, 124.88, 125.64, 127.02, 128.60, 129.36, 132.94, 133.18, 134.11, 136.38, 139.88, 160.49, 162.75, 164.38, 169.26; MS (m/z): 360 [M^+]; Anal. Calcd for $C_{22}H_{14}F_2N_2O$: C, 73.33; H, 3.92; N, 7.77; Found: C, 70.35; H, 3.95; N, 7.72.

5-(4-fluorophenyl)-3-(4-nitrobenzylidene)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one.(5g). Yellow solid, yield 93 %, mp 217-219 °C; R_f 0.23 (8:2 hexane-EtOAc); IR (KBr): 3452, 3154, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298, 784, 765, 702, 684 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 6.84 (s. 1H, CH), 7.28-7.32 (s, 1H, Ar), 7.42-7.48 (m, 3H, Ar), 7.81-7.86 (m, 4H, Ar), 7.95-7.99 (d, 2H, Ar), 8.10-8.14 (m, 2H, Ar), 8.06 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 112.42, 114.56, 119.13, 122.88, 124.92, 125.45, 127.30, 127.98,

128.67, 129.76, 131.48, 133.18, 134.56, 135.80, 138.06, 164.26, 168.38, 171.55; MS (m/z): 387 [M^+]; Anal. Calcd for $C_{22}H_{14}FN_3O_3$: C, 68.21; H, 3.64; N, 10.85; Found: C, 68.23; H, 3.62; N, 10.85.

3-(4-bromobenzylidene)-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5h). Yellow solid, yield 88 %, mp 183-185 °C; R_f 0.29 (8:2 hexane-EtOAc); IR (KBr): 3420, 3074, 2923, 2956, 1695, 1680, 1459, 1154, 1056, 845, 761, 734, 690 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 6.46 (s, 1H, =CH), 7.28-7.32 (m, 2H, Ar), 7.36-7.42 (m, 3H, Ar), 7.46-7.52(m, 2H, Ar), 7.68-7.74 (m, 4H, Ar), 8.52(s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 113.28, 120.42, 124.35, 124.81, 125.46, 126.87, 127.93, 129.06, 129.90, 130.58, 131.18, 132.09, 134.60, 138.73, 156.85, 160.96, 161.41, 166.42; MS (m/z): 420 [M^+]; Anal. Calcd for $C_{22}H_{14}BrFN_2O$: C, 62.72; H, 3.35; N, 6.65; Found: C, 62.75; H, 3.34; N, 6.75.

5-(4-fluorophenyl)-3-(2-hydroxybenzylidene)-1*H*-benzo[e][1,4]diazepin-2(3*H*)-one. (5i). Yellow solid, yield 79 %, mp 152-154 °C; R_f 0.42 (8:2 hexane-EtOAc); IR (KBr): 3485, 3078, 2854, 2831, 2685, 1456, 1256, 854, 705, 684 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 4.90 (s, 1H, OH), 6.10 (s, 1H, =CH), 6.56-6.28 (m, 2H, Ar), 7.12-7.18 (m, 2H, Ar), 7.36-7.42 (m, 3H, Ar), 7.55-7.59 (m, 1H, Ar), 7.78-7.84 (m, 4H, Ar), 8.06 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 114.23, 116.06, 120.72, 121.56, 124.33, 125.74, 126.18, 126.90, 127.29, 127.70, 128.31, 130.63, 132.42, 134.67, 137.16, 138.53, 160.20, 162.58, 163.38, 168.51; MS (m/z): 358 [M^+]; Anal. Calcd for $C_{22}H_{15}FN_2O_2$: C, 73.73; H, 4.22; N, 7.82; Found: C, 73.75; H, 4.24; N, 7.85.

3-(2,5-dimethoxybenzylidene)-5-(4-fluorophenyl)-1*H*-benzo[e][1,4]diazepin-2(3*H*) –one. (5j). Yellow solid, yield 85 %, mp 144-145 °C; R_f 0.25 (8:2 hexane-EtOAc); IR (KBr): 3473, 3078, 3045, 2954, 2895, 2828, 1684, 1645, 1484, 1325, 1250, 854, 735, 697 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 3.15 (s, 1H, Ar), 3.25 (s, 1H, Ar), 6.08 (s. 1H, CH), 6.96 (s, 1H, Ar), 6.90-6.98 (m, 2H, Ar), 7.05-7.12 (m, 4H, Ar), 7.44-7.50 (d, 2H, Ar), 7.58-7.64 (m, 2H, Ar), 7.86 (s, 1H, NH); ^{13}C NMR: (100 MHz, DMSO): *δ* 54.05, 55.63, 107.36, 111.97, 116.83, 119.06, 121.22, 123.18, 124.77, 125.52, 126.78, 126.23, 127.56, 128.57, 128.89, 130.75, 132.38, 132.94, 133.71, 137.06, 162.64, 168.61; MS (m/z): 402 [M^+]; Anal. Calcd for $C_{24}H_{19}FN_2O_3$: C, 71.63; H, 4.76; N, 6.96; Found: C, 71.67; H,4.71; N, 6.93.

3. CONCLUSION

We have extrapolate the reactivity of 5-(4-fluorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one not only on active methylene but also on the secondary amide. Out of various bases it is observed that KOH is the most suitable base to carry out both this reactions. This library of novel synthesized compounds also beneficial to synthesize other novel heterocylic compounds.

ACKNOWLEDGEMENT

We are thankful to Department of Chemistry, Saurashtra University for providing necessary research facilities and SAIF, Punjab University for providing instrumental support.

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(Received 03 March 2014; accepted 09 March 2014)