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SYNTHESIS AND CHARACTERIZATION OF NEW DERIVATIVES OF 1H-2, 3-DISUBSTITUTED-[1, 2-e] [1, 3]-BENZODIAZEPINE-4, 7-DIONE

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ABSTRACT

The one-step polar nucleophilic (2+5=7) polar cycloaddition→ reaction of phthalimide with Schiff bases derived from heterocyclic amines and heterocyclic aldehydes or ketones in dry tetrahydrofuran (THF) gave 1H-2,3-disubstituted-[1,2-e][1,3]-benzodiazepine-4,7-dionesin good yields. The products were identified by their melting points, UV, FT-IR and ^{1}HNMR spectra.

KEYWORDS: Benzodiazepine-4, 7-Dione, Phthalimide, Schiff Bases, Synthesis

INTRODUCTION

Diazepines is a class of seven-membered ring heterocyclic compounds consisting of two nitrogen atoms in the position -1, 2 , -1,3 and -1,4 in the cycloheptane ring. Benzodiazepine refers to the structure composed of benzene ring fused to the seven-membered diazepine ring (1). This class of compounds has been thoroughly explored due to the great interest for new central nervous system (CNS) active compounds. Diazepines and benzodiazepines were first introduced for the treatment of anxiety, a large number of these compounds with sedative, hypnotic, anticonvulsant, and muscle relactant properties combind with low toxicity have been synthesized (2,3,4). Benzodiazepines were obtained from the reaction of benzoyl amides and methylamine(5).

Photochemical rearrangement of 4-substituted carbethoxyimiopyridiniumylids produced 1,2-diazepinesingoodyields(6,7).Derivatives of substituted of 5H-pyrazolo[1,5-d][1,4]benzodiazepines were synthesized from the reaction of substituted pyrazolo[1,5-c]quinazoline with sodium methoxide (8). The quite known drugs of 1,4 benzodiazepine derivatives, such as chlorodiazepoxide (Librium), diazepam (Valium), lorazepam, flunitrazepam, and clonazepam were synthesized from 4-chloro-N-methylaniline and substituted benzoyl chlorides in multi steps reactions including intermediate rearrangement (9,10).

Another 5-substituted hexahydro-1H-[1,4]diazepine analogues were synthesized from N,N-dibenzyl-2-ethylinediamine and methyl-2,4-dibromobutyrate through nucleophilic substitution, reduction, chlorination, benzylation, and amidation (11). Dimethyl-2-phenyl-1H-imidazole-4,5-dicarboxylate was reacted with guanidine hydrochloride in absolute ethanol in the presence of sodium methoxide to give 6-amino-2-phenylimidazolo[4,5-e][1,3]diazepine-4,8(1H,5H)-dione (12). New synthetic pathway for the synthesis of 1,3-dioxo-hexahydropyrido[1,2-c][1,3]diazepine carboxylate was developed starting from pyroglutamate ester (13).

Benzofuro[3,2-e]-1,4-diazepines were prepared by chloroacetylation of 2-acyl-3-aminobenzofuran and subsequent treatment withhexamethylenetetramine in ethanol via the complex salts. Similarreaction with ethyl 3-aminobenzofuran-2 carboxylate produced 3H-benzofuro[3,2-e]-1,4-diazepin-2,5(1H,4H)-dione in good yield (14).

EXPERIMENTAL

General: Uncorrected melting points were determined in open capillary on electro-thermal melting points apparatus. UV/Vis. spectra were recorded on UV/Vis. 6405 Jenway spectrophotometer in the range 200 – 800 nm. The IR spectra were recorded on FTIR 8400 s Shimadzu spectrophotometer using KBr disk. And the 1HNMR were recorded on Bruker 400 MHz spectrophotometer using CDCl3 solvent , the chemical shifts are reported as % values (ppm) downfield Me4Si.

Synthetic Procedures

Synthesis of Schiff Bases (3a-h): In a typical experiment the heterocyclic amine (0.02 mol) dissolved in absolute ethanol (10 ml) was mixed with heterocyclic carbonyl compound (0.02 mol) dissolved in the same solvent(30ml) , in around bottom flask equips with condenser. The mixture was refluxed for 1 hour, then left to cool down in an ice bath, where by crystalline solid separated out, filtered out, washed with 5ml 2% HCl solution and then with distilled water, recrystallized from ethanol, and dried. Eight compounds (3a-h) were prepared by this procedure, structural formula, melting points, crystal color, and yield percentages are given in table (1).

Synthesis of 1H-2,3-Disubstituted-[1,2-e][1,3]Benzodiazepine-4,7-Diones (5a -h): In a typical experiment the phthalimide (0.003 mol) dissolved in dry tetrahydrofuran (THF) (10 ml) was added to an equivalent of the Schiff base dissolved in the same solvent , contained in a round bottom flask equipped with condenser. The mixture was refluxed for 2 hours, then cooled down in an ice bath, whereby a crystalline solid separated out, filtered out, recrystallized twice from absolute ethanol, and dried. Eight benzodiazepines (5a -h) were prepared by this procedure, melting points, crystal color, and yield percentages are given in table (2). All synthesized compounds names are listed in table (3).

Table 1: Properties of Synthesized Schiff Bases (3a -h)

Yield %	Color	M.P.(C^0)	Molecular Wt. (g/mole)	Molecular Formula	Code Comp.
89	Orange	160-161	332	$C_{19}H_{16}N_4O_2$	3a
78	Brown	140	294	$C_{17}H_{17}N_4O$	3b
77	Yellow	165-166	292	$C_{17}H_{16}N_4O$	3c
69	Pale yellow	121	183	$C_{11}H_9N_3$	3d
91	Yellow	204-206	281	$C_{16}H_{14}N_3O_2$	3e
87	Orange	178	224	$C_{11}H_8N_4O$	3f
65	Brown	200-201	173	$C_9H_7N_3O$	3g
73	Green-yellow	202-204	184	$C_{10}H_8N_4$	3h

Table 2: Properties of Synthesized 1, 3-Benzodiazepine-4, 7-Diones (4a -h)

Yield %	Color	M.P. (C^0)	Molecular Wt.(g/Mole)	Molecular Formula	Comp. Code
85	Red	185-184	479	$C_{27}H_{21}N_5O_4$	5a
88	Pale-yellow	196	396	$C_{25}H_{22}N_5O_3$	5b
65	Yellow	222-221	439	$C_{25}H_{20}N_5O_3$	5c
78	white	210-208	330	$C_{19}H_{13}N_4O_2$	5d
81	Pale-yellow	176-175	428	$C_{24}H_{19}N_4O_4$	5e
69	deep-yellow	224-222	371	$C_{20}H_{13}N_5O_3$	5f
61	Brown	190-189	320	$C_{17}H_{11}N_4O_3$	5g
59	white	119-118	331	$C_{18}H_{12}N_5O_2$	5h

RESULTS AND DISCUSSIONS

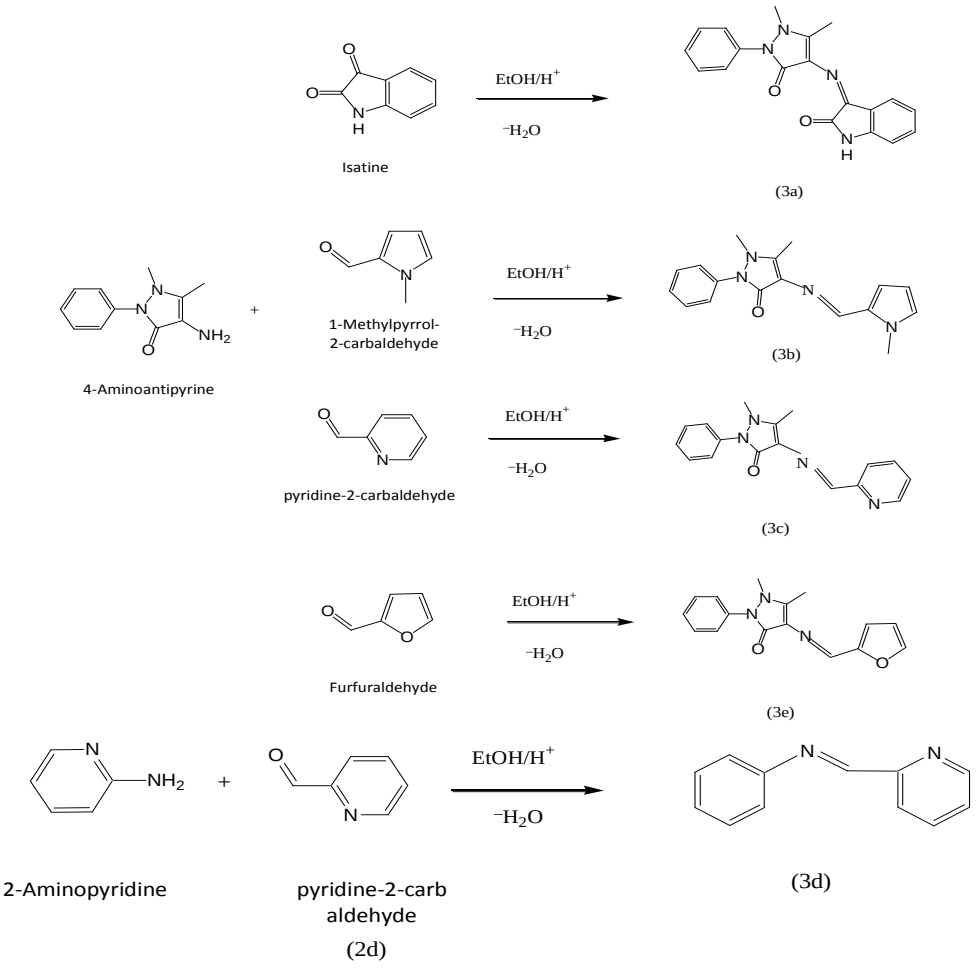
The synthesis of Schiff bases (3a-h) were obtained by the reaction of heterocyclic amines(1) and heterocyclic

aldehydes or ketones(2) in the acidic medium and absolute ethanol, scheme (I).The IR data indicated the formation of compounds(3a-h) by the appearance of the new band at (1566 – 1650cm-1) belonging to the stretching vibration of C═N group, and the new bands at (1643 – 1735 cm-1), (3000-3110 cm-1), and (3409-3490 cm-1) belonging to the stretching vibration of C=O,C═C─Haromatic, and N-H Lactam, respectively. The suggested mechanism for the preparation of compounds (3a-h) is shown in scheme (II).

A one-pot polar (2+5) cycloaddition reactions of Schiff bases and phthalimide (4) in anhydrous tetrahydrofuran under reflux conditions afforded 2,3-disubstituted-[1,2-e][1,3]benzodiazepine-4,7-diones,compounds (5a-h) as shown in scheme (III).

The suggested mechanism for these reactions involve nucleophilic attack by the electron lone-pair of the nitrogen atom in the Schiff base on the carbon atom of the carbonyl group of phthalimide compound (4), scheme (IV). Analytical and spectroscopic data of the products (5a-h) confirmed the success of the cyclization reaction of seven-membered ring system by the disappearance C=N band of (3a-h) compounds at (1566 – 1650cm-1), and the new bands were appeared at (3201 – 3471 cm-1) and (1643 – 1750 cm-1) belonging to the stretching vibration of N-H Lactam and C=O Lactam groups, respectively.

In the 1H NMR spectra, the existence of (5a-h) was revealed by appearance of the (N-CH3) group (3.13ppm) and the appearance of a new peak at (3.98ppm) integrating for (N-N-CH3). The (N-H) groups of the benzodiazepines rings resonate as singlet at (8.65-9.69 ppm), while (CH3) group, was recorded at (2.45 ppm) as a singlet, and aromatic and hetero aromatic protons was observed at (7.43 – 8.23 ppm) as multiplet.



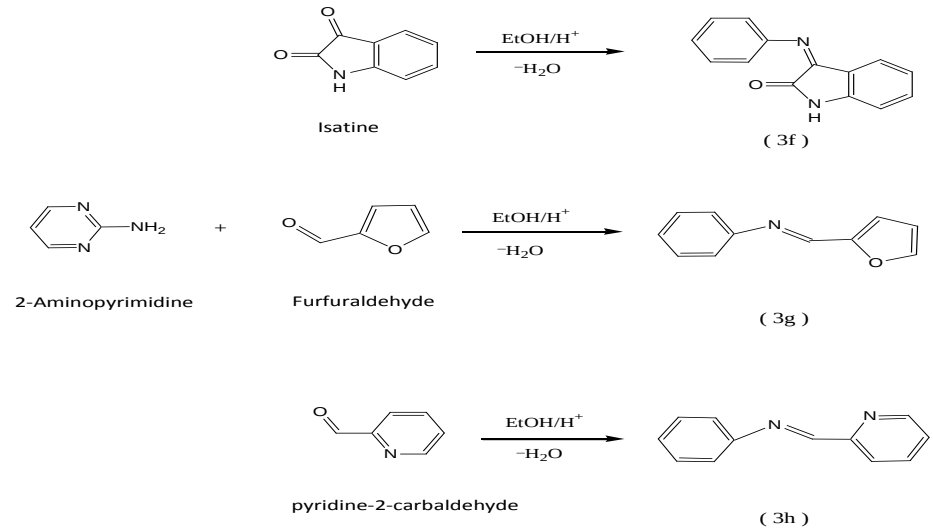


Figure 1: Synthesis of Schiff Bases Compounds (3a-h)

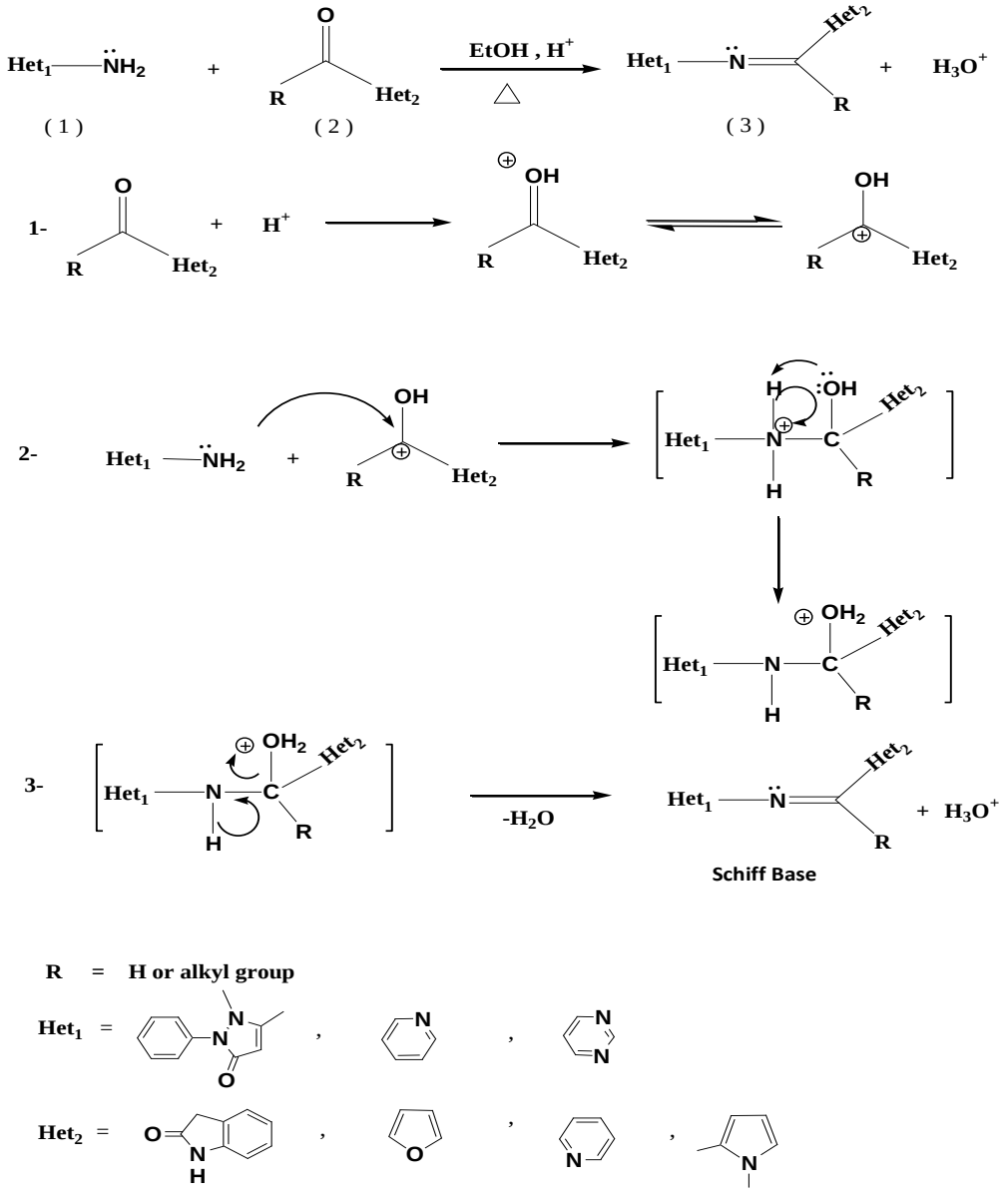


Figure 2: Synthetic Route to Target Compounds (3a–h)

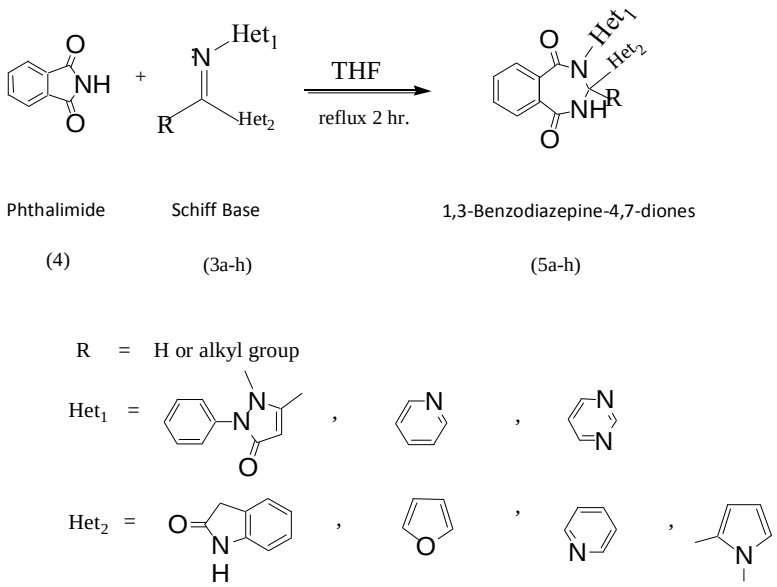


Figure 3: Synthesis of 1, 3-Benzodiazepine-4, 7-Diones, (5a-h)

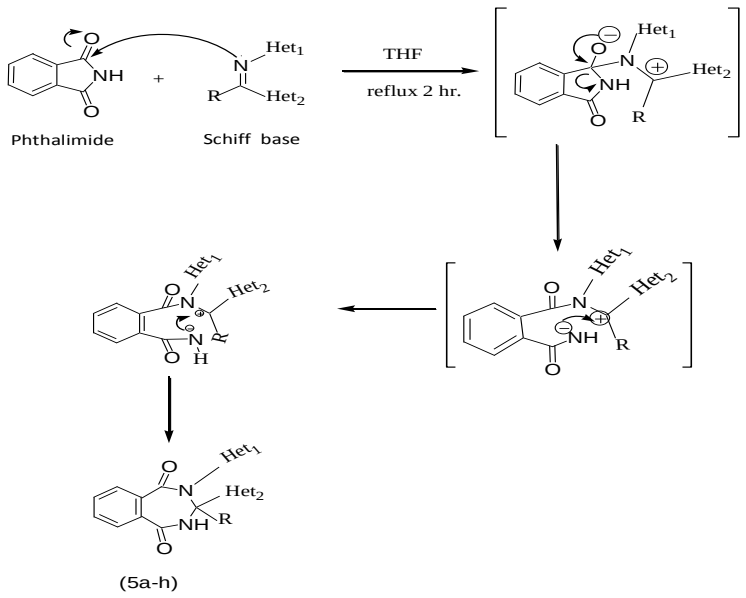


Figure 4: Synthetic Route to Target Compounds (5a–h)

Table 3: IUPAC Names of the Synthesized Schiff bases (3a-h) and 1, 3-Benzodiazepine-4, 7-Diones (5a-h) Compounds

Compound Code	IUPAC Name
3a	N-(2-Oxindolidine)-1-phenyl-2,3-dimethyl-4-pyrazoloneamine
3b	N-(1-Methylpyrrol-2-yl-methylidine)-1-phenyl-2,3-dimethyl-4-pyrazoloneamine
3c	N-(2-Pyrid-2-yl-methylidine)-1-phenyl-2,3-dimethyl-4-pyrazoloneamine
3d	N-(2-Pyrid-2-yl-methylidine)-2-pyridineamine
3e	N-(2-Furfur-2-yl-methylidine)-1-phenyl-2,3- dimethyl-4-Pyrazoloneamine
3f	N-(2-Oxindolidine)-2-pyrimidineamine
3g	N-(2-Furfur-2-yl-methylidine)-2-pyrimidineamine
3h	N-(2-Pyrid-2-yl-methylidine)-2-pyrimidineamine
5a	1H-2-(3.4-Spirooxindole-2-yl)-3-(1-phenyl-2,3-dimethyl pyrazolon-4-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5b	1H-2-(1-Methylpyrrol-2-yl)-3-(1-phenyl-2,3-dimethyl pyrazolon-4-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione

Table 3: Contd.,

5c	1H-2-(Pyrid-2-yl)-3-(1-phenyl-2,3-dimethyl pyrazolon-4-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5d	1H-2,3-(Dipyrid-2-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5e	1H-2-(Furfur-2-yl)-3-(1-phenyl-2,3-dimethyl pyrazolon-4-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5f	1H-2-(3.4-Spirooxindole-2-yl)-3-(pyrimid-2-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5g	1H-2-(Furfur-2-yl)-3-(pyrimid-2-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione
5h	1H-2-(Pyrid-2-yl)-3-(pyrimid-2-yl)-[1,2-e][1,3]-benzodiazepine-4,7-dione

REFERENCES

1. G.W.H. Chesman and S.G Gremberg, Synthesis and characterization of -5,6-dihydro-7h-pyrolo[1,2-d][1,4]benzodiazepine-6-one,J. Heterocyclic Chem.,16 , pp. 241-247,1979.
2. Heather Ashton, The diagnosis and management of benzodiazepine dependence, Current Opinion in Psychiatry, 18, pp. 249-255, 2005.
3. R. C. Oude Voshaar, W. J. Gorgels, A. J. J. Mol,A. J. L. M. Van Balkom, J. Mulder, E. H. Van de Lisdonk,M. H. M. Berteler and F. G. Zitman, Long-term outcome of two forms of randomized benzodiazepine discontinuation, British Journal of Psychiatry, 188 , pp. 188-189, 2006.
4. A. Chirimi, G. De Sarro, S. Quartarone, M. L. Barreca, R. Caruso, L. De Luca, and R. Gitto, Search for competitive 2-Amino-3-(3-hydro-5-methyl-4-isoxazole) propionic acid receptor antagonist, Synthesis, Pharmalogical properties and computational studies,Pure Appt. Chem., vol. 76, No. 5, pp. 931-939, 2004.
5. R. Ian Fryer, J. V. Earley , G. F. Field, W. Zally, and L. H. Sternbach, A synthesis of Amidine from Cyclic Amides, J. Org. Chem., vol. 34, No. 4, pp. 1143-1145,1969.
6. J. Streith, J. P. Luttinger and M. Nastasi, Photochemical Synthesis of 1,2-diazepines , J. Org. Chem., vol. 36, No. 20, pp. 1143-1145,1971.
7. J. Kurtta, K. Iwatw, and T. Tsuchiya, Studies on DiazepinesXXV., Chem. Pharm. Bull.
8. G. F. Field, W. J. Zally, and Leo H. Sternbach, Expansion of Some Chloromethylpyrazolo[1,5-c]quinazolines and 1,2,4-Benzothiazolo-1,1-dioxide, J. Org. Chem., 36 ,20,2968-2971, 1971.
9. W. H. Brown and C. S. Fote, Organic Chemistry,3ed. Brooks / Cole-Thomson Learning, pp. 930-933, 2002.
10. J. McMurry,Organic Chemistry,6ed.,Brooks/Cole-Thomson Learning, 499-532, 2004.
11. J. Shan Shin, Li Jun LEI, Hai Fang Mao, JianFeng LI, Ru Yun JI, Synthesis of 5-Substituted-hexahydro-1H-1,4-diazepine analogues, Chinees Chemical Letters, 12 , 11 , 951-954, 2001.
12. Huan-Ming Chen and R. S. Hosmane, 6-Amino-2-phenylimidazo[4,5-e][1,3]diazepine-4,8(1H,5H)-dione, Molecules, 5 , M164 , 2000.
13. N. Dieltiens, D. D. Claeys, B. Allaert, F. Verpoort, and C. V. Stevens, Synthesis of 1,3-dioxo-hexahydropyrido[1,2-c][1,3]diazepine carboxylates, Chem. Comm., 4477-4478, 2005.
14. K. M. Basavaraja, V.P.Vaidya, and C.Chandrashekhar, Synthesis of Benzofuro[3,2-e]-1,4-diazepinesof Pharmacological Interest, E-Journal of Chemistry, 5 , 3, 567-571, 2008.