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Evaluation of Physicochemical Properties of Glacial Acetic Acid Mediated Solvent Free One Pot Synthesis of 1, 5-Benzodiazepines and Its Chloroacetylated Derivatives

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ABSTRACT

A series of compounds of 1,5-benzodiazepines and its chloroacetylated derivatives have been synthesized and its physicochemical parameters were evaluated in order to determine the potency of the compounds for good CNS activity. This solvent free reaction mediated by glacial acetic acid was found to be very efficient with high yield. The structures were confirmed on the basis of TLC, IR and ^{1}HNMR and CHN elemental studies. The log P values of two of the compounds shows that compounds have the potential to be CNS active and all other parameters like non-value, non-value, n-violations and number of rotatable bonds also lies in the ranges that are required for blood brain barrier penetration. This synthesis provides a new hope that the free chloro group in this structure can be utilized for further substitution of various heterocyclic rings which possess potent CNS activity.

Keywords: Benzodiazepines, Chloroacetylation, *o*-Phenylenediamine, Glacial acetic acid

INTRODUCTION

Benzodiazepines are an important class of heterocyclic scaffold because they possess wide range of therapeutic and pharmacological properties. Benzodiazepines and its derivatives include wide range of pharmacological activities such as anticonvulsant, antianxiety, analgesic, sedative, antidepressive and hypnotic agents [1,2]. In few years, the area of biological interest of 1, 5-benzodiazepines has been extended to several diseases such as cancer, viral infection and cardiovascular disorders [3,4]. In addition, 1, 5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as triazolo, oxadiazolo, oxazino or furano benzodiazepines [5-8]. Besides, benzodiazepine derivatives are also of commercial importance as dyes for acrylic fibers in photography [9]. Despite their importance from pharmacological, industrial and synthetic point of view, comparatively large number of processes for the preparation of 1, 5-benzodiazepines reported in the literature. These include condensation reactions of *o*-phenylenediamine with α, β-unsaturated carbonyl compounds [10], with ketones in the presence of $BF_3{\cdot}Et_2O$, $NaBH_4$, Polyphosphoric acid or SiO_2, $MgO/POCl_3$, Yb $(OTf)_3$, Al_2O_3/P_2O_5 or AcOH under microwave conditions, Amberlyst-15 in the ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br), $CeCl_3{\cdot}7H_2O/NaI$ supported on silica gel, $InBr_3$, Sc $(OTf)_3$, sulfated zirconia, $InCl_3$, CAN, $ZnCl_2$ under thermal conditions, $AgNO_3$ [11-26]. These reactions also occur with various catalysts under solvent free conditions. Nevertheless, many of these methods suffer from disadvantages such as long reaction times, harsh reaction conditions, requirement of anhydrous conditions, elevated temperature, low product yields, occurrence of several side products and difficulties in recovery of the products, high cost. Some of these catalysts may breakdown into more hazardous and non-degradable toxic compounds which can cause harm to human body. Therefore, search for a safe and mild protocol for synthesis of these molecules is a matter for scientist to continued excellent investigation.

In this article we revealed an efficient and green approach for synthesis of 1, 5-benzodizepines. Some of the reagents employed are very expensive. Consequently, the search continues for better catalysts in terms of operational simplicity and economic viability to synthesize 1,5-benzodiazepines. In recent years, it was examined that various readily available acids are gaining considerable attention due to its commercial availability. It was revealed that various aliphatic acids like malonic acid, trichloroacetic acid, formic acid, succinic acid and others have been used to catalyze the synthesis of 1,5-benzodiazepines. But it was found that in all these aliphatic acids glacial acetic acid is the most effective catalyst for the synthesis of various 1,5-benzodiazepines derivatives

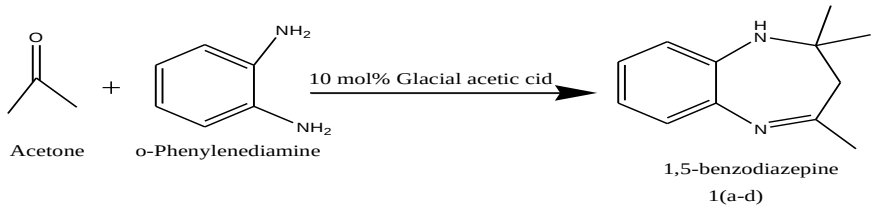
MATERIALS AND METHODS

Experimental section

General procedure for the synthesis of 2, 3-dihydro-1H-1, 5-benzodiazepines

In the first instance, *o*-phenylenediamine (1 equiv.), acetone (2.25 equiv.) and glacial acetic acid (10 mol%) were taken in R.B.F and refluxed on

water bath for atleast 1 h. After the completion of the reaction monitored via TLC using $CHCl_3$ and MeOH (9.5:0.5 ml) as eluent, the reaction mass was poured into crushed ice to get the precipitate. The precipitated solid was separated, washed thoroughly with water and dried. The residue was subjected to column chromatography to get the desired compounds (Tables 1 and 2) Schemes 1 and 2.



Scheme 1: Synthesis of 1,5-benzodiazepines

Table 1: Glacial acetic acid mediated synthesis of 1,5-benzodiazepines

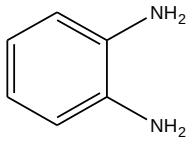
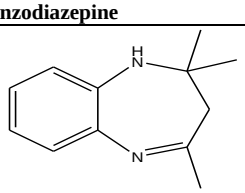
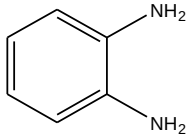
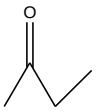
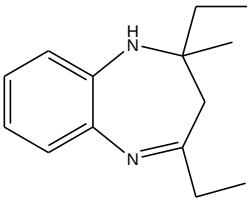
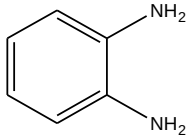
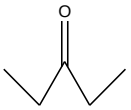
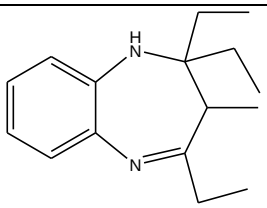
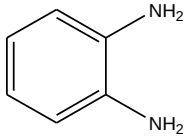
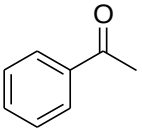
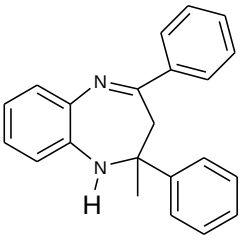
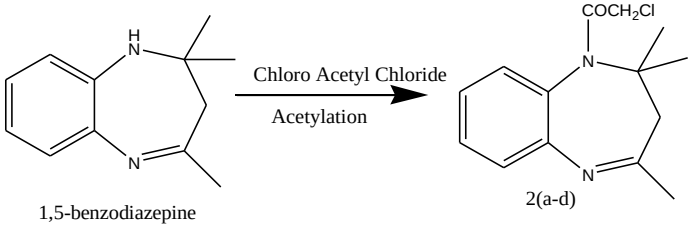
Compounds	Diamine	Ketone	Benzodiazepine	Time (min)	Yields (%)
1a				55	94
1b				60-65	89
1c				60	86
1d				95	82

Table 2: Physical and analytical data of 1,5-benzodiazepines

Compounds	Molecular formula	Molecular weight	Melting point	Elemental analysis		
				C	H	N
1a	$C_{12}H_{16}N_2$	188.13	149-150	76.55	8.57	14.88
1b	$C_{14}H_{20}N_2$	216.16	144-147	77.73	9.32	12.95
1c	$C_{16}H_{24}N_2$	244.38	138-139	78.64	9.90	11.46
1d	$C_{22}H_{20}N_2$	312.14	128-130	84.58	6.45	8.97



Scheme 2: Synthesis of acetyl derivatives of 1, 5-benzodiazepines

General procedure for the synthesis of chloroacetyl derivatives of 1, 5-benzodiazepines 2(a-d)

The benzodiazepines (0.01 mol) were refluxed in chloroacetyl chloride (0.04 mol) for 6-8 h. On cooling crystals separated out which were filtered, washed with little acetic acid and recrystallized from acetic acid (Table 3).

2a. *2-chloro-1-((Z)-2,3-dihydro-2,2,4-trimethylbenzo[b][1,4]diazepin-1-yl)ethanone*

IR=1720 (C=O, str), 1666.38 (C=N, str) 3062.32 (CH-str aromatic) 2857.95 (CH-aliphatic) 1528.22 (C=C, str), 1288.36 (C-N, str) ^{1}HNMR (DMSO-d6): δ7.31-7.12(m, 4H), 4.32 (br s,1H), 2.32(s, 3H), 2.19(s,2H), 1.28(s, 6H).

2b. *2-chloro-1-((Z)-2,4-diethyl-2,3-dihydro-2-methylbenzo[b][1,4]diazepin-1-yl)ethanone*

IR=1620(C=O, str), 1646.28(C=N, str) 3335.31 (CH-str aromatic) 2867.65 (CH-aliphatic) 1530 (C=C, str), 1284.11 (C-N, str) ^{1}HNMR (DMSO-d6): δ 0.97 (t,3H), 1.21 (t,3H), 1.70 (q,2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.42 (s, 3H), 2.71 (q, 2H), 3.25 (br s, 1H, NH) 6.90-7.55 (m, 4H), 4.32 (br s,1H), 2.32(s, 3H), 2.19(s,2H), 1.28(s, 6H).

2c.*2-chloro-1-((Z)-2,2,4-triethyl-2,3-dihydro-3-methylbenzo[b][1,4]diazepin-1-yl)ethanone*

IR=1680 (C=O, str), 1610.28 (C=N, str) 3325.31 (CH-str aromatic) 2789.45 (CH-aliphatic) 1530 (C=C, str), 1284.11 (C-N, str) ^{1}HNMR (DMSO-d6): δ 0.72-1.11 (m,10H), 1.25-1.42 (m,4H), 1.55-1.70 (m,2H), 2.41-2.61 (m, 2H), 2.86 (q, 1H), 3.42 (br s, 1H, NH), 6.80 (d,14H), 7.11 (t,1H), 7.35(t, 1H), 7.80(d, 1H).

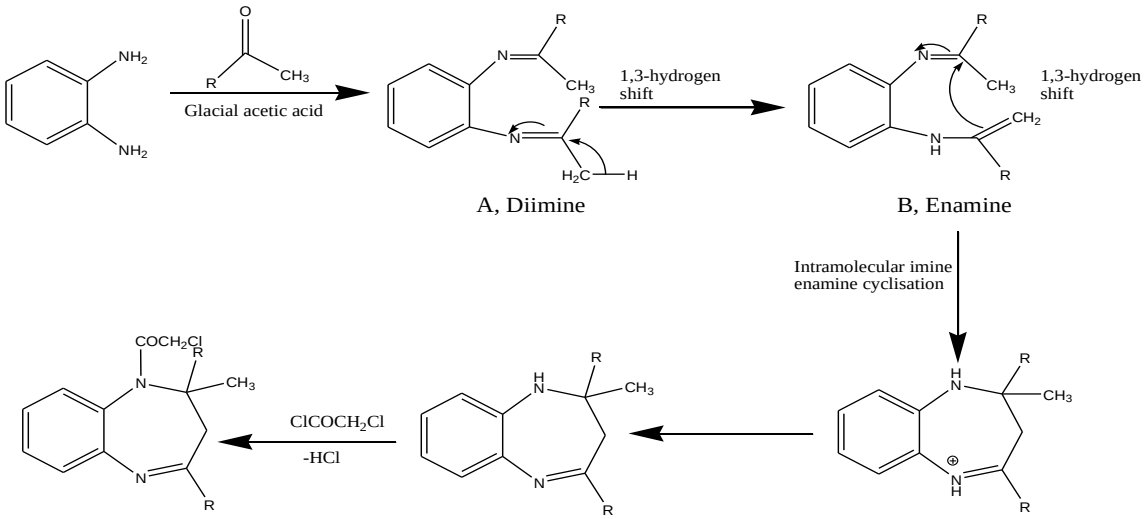
2d. *2-chloro-1-((E)-2,3-dihydro-2-methyl-2,4-diphenylbenzo[b][1,4]diazepin-1-yl)ethanone*

IR=1636 (C=O, str), 1648.38(C=N, str) 3316 (CH-str aromatic) 2962.65 (CH-aliphatic) 1532 (C=C, str), 1289.50 (C-N, str) ^{1}HNMR (DMSO-d6): δ 7.58-7.45 (m,4H), 7.34-7.12 (m,7H), 7.09-6.88 (m,3H), 4.31 (br s, 1H, NH) 3.21(d, 1H), 2.90 (d,1H), 1.78 (s, 3H).

Table 3: Physical and Analytical Data of chloroacetylated derivatives of 1, 5-benzodiazepines

Compounds	Molecular formula	Molecular weight	Melting point	Elemental analysis			
				C	H	N	O
2a	$C_{14}H_{17}ClN_2O$	264.1	180-182	63.51	6.47	10.58	6.04
2b	$C_{16}H_{21}ClN_2O$	292.13	190-194	65.63	7.23	9.57	5.46
2c	$C_{18}H_{25}ClN_2O$	320.17	189-191	67.38	7.85	8.73	4.99
2d	$C_{24}H_{21}ClN_2O$	388.13	199-200	74.12	5.44	7.20	4.11

The proposed mechanism of the reaction (Schemes 1 and 2) involves an intramolecular imine enamine cyclization promoted by chloroacetic acid. Amine of *o*-phenylenediamine attacks carbonyl group of ketone giving the intermediate diimine A. A 1, 3-hydrogen shift of the attached methyl group then occurs to form an isomeric enamine B, which cyclize to afford seven membered rings.



Under the optimized conditions, aliphatic ketones such as acetone reacted with 1, 2 phenylenediamine in presence of CAC to form the corresponding benzodiazepine in excellent yield. This may be due to the steric hindrance of a methyl group in the proximity of the carbonyl carbon. Alicyclic ketones such as cyclopentanone, cyclohexanone and cycloheptanone gave excellent yields of products. With the present methodology, aromatic ketones such as acetophenone and substituted acetophenone with both electron donating and withdrawing groups generally produced the corresponding benzodiazepines in good to excellent yields, with the latter performing somewhat better.

Physicochemical parameters

Evaluation of physicochemical parameters

The drugs were synthesized in such a way that they have the potency to cross the blood brain barrier (BBB) and found to be CNS active. To attain such behavior, Lipophilicity is an important parameter for distribution and active transport of drug in biological system. The partition coefficient is the first most and important parameter which defines the lipophilicity. Partition coefficient can be determined by shake-flask method and by different computational methods. The log P value of all the compounds was determined experimentally and through online softwares (www.molinspiration.com/cgi-bin/properties) and was calculated by Moriguchi method (Moriguchi et al.). Other parameters like molecular weight, n ON value, nOHNH value, n-violations and number of rotatable bonds are determined through online softwares (www.chemsilico.com/cs_product/products.html). Results are shown in Tables 4-6.

Table 4: Experimental log *P* values

S. No.	Compound	Abs.	Conc. (µg/ml)	Drug (mg) in distilled water	Drug (mg) in octanol	Log P=C(org)/C(aq)
1	2a	0.112	8.212	3.11	6.89	2.21
2	2b	0.194	8.129	2.4	7.6	3.16
3	2c	0.21	8.107	1.86	8.14	4.37
4	2d	0.24	8.001	1.79	8.21	4.58

Table 5: Physicochemical parameters values

S. No.	Compound	nON value	nOHNH value	n-Violation	Rotatable bonds
1	2a	3	0	0	1
2	2b	3	0	0	3
3	2c	3	0	1	4
4	2d	3	0	1	3

Table 6: Partition coefficient values experimental vs calculated value

S. No.	Compound	mi Log *P*	C Log *P*	Observed Log *P* (experimental)
1	2a	3.25	3.09	2.32
2	2b	4.25	4.15	3.49
3	2c	5.23	5.19	4.46
4	2d	5.68	6.09	4.89

CONCLUSION

In summary, we have demonstrated a novel, mild, efficient method for the synthesis of 2-chloro-4-methyl-3H-benzo [β] [1,5] diazepine derivatives. Novel 1, 5-benzodiazpine derivatives of the 2-chloro-4-methyl-3H-benzo[β] [1,5] diazepine were studied for their antibacterial and antifungal activity.

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