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RESEARCH ARTICLE

Rapid and Efficient Synthesis of 2,3-Dihydro-1*H*-1,5-Benzodiazepines Catalyzed by Chloroacetic Acid Screened among Various Aliphatic Acids under Solvent Free Conditions

AKSHDEEP SANDHAR and RAJESH K. SINGH*

Pharmaceutical Chemistry Division, Shivalik College of Pharmacy
(Under Local Govt Deptt., Punjab) Nangal, Distt.Rupnagar, Punjab-140126, India
rksingh244@gmail.com

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Abstract: A series of 1, 5-benzodiazepines were synthesized by condensation of *o*-phenylenediamine with different ketones and effect of different aliphatic acids used as catalyst was studied. Among the various acids screened, chloroacetic acid came out to be a versatile catalyst and the corresponding products were obtained in good to excellent isolated yields (85-94%) under solvent free conditions.

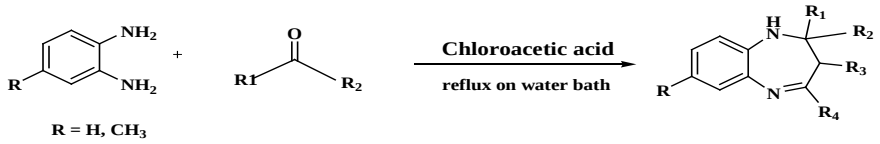
Keywords: 1, 5-Benzodiazepines, *o*-Phenylenediamine, Ketones, Aliphatic acids, Chloroacetic acid, Solvent free conditions

Introduction

The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications. Benzodiazepine moieties are reported to possess anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressant, hypnotic[1], anti-inflammatory[2], anti-viral[3], anti-HIV[4], anti-microbial[5] and anti-tumor[6] activities. They are also valuable synthons for the preparation of fused ring compounds such as triazolo, oxadiazolo, oxazino, furanobenzodiazepines[7]. The wide range of applications of benzodiazepines has attracted many researchers and various methods are known for their synthesis using different catalysts under different conditions. These methods include condensation of *o*-phenylenediamine and ketones in the presence of a variety of catalysts like *p*-toluenesulfonic acid[8], silica sulfuric acid[9], *p*-nitro benzoic acid[10], sodium tetrachloroaurate(III) dehydrate[11], $AlCl_3$[12], polyethylene glycol[13]. But these methods involve many limitations like tedious work up procedure, producing undesired washes, applications of expensive catalyst and reagents, long reaction times, unsatisfactory yield; require separation of the catalyst from the product and formation of side products.

As a part of our continuous efforts towards the exploration of various catalysts for the efficient and green synthesis of biologically active molecules[14,15], we have examined various

readily available acids for their catalytic activity in the synthesis of 1,5-benzodiazepines. In our study various aliphatic acids like malonic acid, trichloroacetic acid, formic acid, succinic acid *etc*. have been used to catalyze the synthesis of 1,5-benzodiazepine by condensation of *o*-phenylenediamine with acetophenone as model reaction, out of which chloroacetic acid came out to be the most effective catalyst for the synthesis of various benzodiazepine derivatives.



Scheme 1. Chemical reaction for the synthesis of 1,5-benzodiazepines using chloroacetic acid

Experimental

o-phenylenediamine (1 mmole), chloroaceticacid (10 mol% or 0.1 mmole) and various ketones (2.25 mmole) were taken in R.B.F and refluxed on water bath for 40-60 min. 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 and basified with ammonia solution, if required. The precipitated solid was separated, washed thoroughly with water and dried. The residue was subjected to column chromatography to get the desired compounds.

2,3- Dihydro-2- methyl- 2,4- diphenyl-1H-1,5- benzodiazepine: (Entry 1)

IR (KBr): 3277 cm^{-1} (Sec N-H), 3061 cm^{-1} (Aromatic C-H), 2972 cm^{-1} (Aliphatic C-H), 1559 cm^{-1} (Aromatic C=C); ^{1}H-NMR ($CDCl_3$):δ 1.8 (s, 3H, $-CH_3$), δ 3.1 (d, 1H, -CH), δ 3.2 (d,1H, -CH), δ 6.8-7.7 (m, 14H, ArH); Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.60; H, 6.42; N, 8.94.

2,2,4- Trimethyl- 2,3-dihydro -1H-1,5-benzodiazepine: (Entry 2)

IR (KBr): 3292 cm^{-1} (NH), 2955 cm^{-1} (Aromatic CH), 1632 cm^{-1} (Alkene C=C), 1474 cm^{-1} (Aromatic C=C); ^{1}H-NMR ($CDCl_3$):δ 1.3 (s, 6H, $-C(CH_3)_2$), δ 2.2 (s, 2H, $-CH_2$), δ 2.4 (s, 3H, $-CH_3$), δ 6.7-7.2 (m, 4H, ArH); Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88; Found: C, 76.51; H, 8.52; N, 14.92.

2,4- Dimethyl-2-ethyl-2,3-dihydro-1H-1,5-benzodiazepine: (Entry 3)

IR (KBr): 3339 cm^{-1} (Sec N-H), 3058 cm^{-1} (Aromatic C-H), 2968 cm^{-1} (Aliphatic C-H), 1639 cm^{-1} (C=N), 1472 cm^{-1} (Aromatic C=C), 1253 cm^{-1} (C-N); ^{1}H-NMR ($CDCl_3$):δ 0.8 (t, 3H, $-CH_3$), δ 1.3 (t, 3H, $-CH_3$), δ 1.3 (s, 3H, $-CH_3$), δ 1.7 (q, 2H, $-CH_2$), δ 2.2 (m, 2H, $-CH_2$), δ 2.6 (q, 2H, $-CH_2$),δ 3.3 (brs, 1H, NH), δ 6.5-7.3 (m, 4H, ArH); Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.88; N, 13.85; Found: C, 77.25; H, 8.88; N, 14.01.

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[b,e][1,4] diazepine (Entry 4)

IR (KBr): 3279 cm^{-1} (Sec. NH), 3059 cm^{-1}(Aromatic CH), 2859 cm^{-1} (Alkane CH), 1635 cm^{-1} (Imine C=N), 1481 cm^{-1} (Aromatic C=C), 751 cm^{-1} (orthosubstitutedoop); ^{1}H-NMR ($CDCl_3$) :δ 1.2-1.9 (m, 16H, $-CH_2$), δ 2.3-2.6 (m, 3H, -CH), δ 4.5 (1H, br, NH), δ 6.8-7.9 (m, 4H, ArH); Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44; Found: C, 80.62; H, 9.05; N, 10.54.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[b]cyclohepta[e][1,4] diazepine (Entry 5)

IR (KBr): 3328 cm^{-1} (Sec. NH), 3060 cm^{-1} (Aromatic CH), 2923 cm^{-1} (Alkene CH), 2852 cm^{-1} (Alkane CH), 1617 cm^{-1} (Imine C=N), 1493 cm^{-1} (Aromatic C=C). ^{1}H-NMR ($CDCl_3$): δ 1.5-2.4 (m, 21H, $-CH_2$, -NH), δ 2.6 (m, 2H, $-CH_2$), δ 2.8 (m, 1H, -CH), δ 6.6-7.4 (m, 4H, ArH); Anal. Calcd. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45; Found: C, 81.15; H, 9.56; N, 9.54.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1H-1,5-benzodiazepine(Entry 6)

IR (KBr): 3454 cm^{-1} (Sec. NH), 2924 cm^{-1} (Aromatic CH), 2854 cm^{-1} (Alkane CH), 1437 cm^{-1} (Aromatic C=C), 1237 cm^{-1} (C-N), 946 (1,2,4-substituted oop); ^{1}H-NMR ($CDCl_3$):δ 1.2 (s, 6H, $-CH_3$), δ 1.35 (s, 3H, $-CH_3$), δ 2.3 (m, 5H,$-CH_3$, -CH, -CH), δ 6.5 (s, 1H, ArH), δ 6.79 (d, 1H, J = 7.4, ArH), δ 7.0 (d, 1H, J = 8.7, ArH); Anal. Calcd. for $C_{18}H_{13}N_2$: C, 77.17; H, 8.97; N, 13.85; Found: C, 77.22; H, 8.91; N, 13.93.

2,3-Dihydro-2,8- dimethyl- 2,4- diphenyl-1H-1,5-benzodiazepine (Entry 7)

IR (KBr): 3335 cm^{-1} (Sec. NH), 3058 cm^{-1} (Aromatic CH), 2970 cm^{-1}(Alkene CH), 2858 cm^{-1} (Alkane CH), 1613 cm^{-1} (Imine C=N), 1493 cm^{-1} (Aromatic C=C), 1328 cm^{-1} (C-N), 759 cm^{-1} (Ortho substituted oop); ^{1}H-NMR($CDCl_3$):δ 1.75 (s, 3H, $-CH_3$), δ 2.6 (br, 4H,$-CH_3$, -NH), δ 2.9 (d, 1H, -CH), δ 3.1 (d, 1H, -CH),δ 7.2-7.9 (m, 14H, ArH); Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58; Found: C, 84.68; H, 6.84; N, 8.45.

11-Spirocyclocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1H-dibenzo[b,e] [1,4]diazepine (Entry 8)

IR (KBr): 3351 cm^{-1} (Sec. NH), 2931 cm^{-1} (Alkene CH), 2857 cm^{-1} (Alkane CH), 1633 cm^{-1} (Imine C=N), 1484 cm^{-1} (Aromatic C=C); ^{1}H-NMR ($CDCl_3$):δ 1.7-2.5 (m, 18H, $-CH_2$), δ 3.0 (s, 3H, $-CH_3$), δ 3 (t, 1H,-CH), δ 7.3-7.9 (m, 3H, ArH); Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92; Found: C, 80.86; H, 9.34; N, 9.98.

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydro-8-methylbenzo[b]cyclohepta [e][1,4]diazepine: (Entry 9)

IR (KBr): 3266 cm^{-1} (NH), 2916 cm^{-1} (Aromatic CH), 1633 cm^{-1} (Imine C=N), 1484 cm^{-1} (Aromatic C=C). ^{1}H-NMR ($CDCl_3$), δ/ ppm: δ 1.6 (m, 22H, $-CH_2$), δ 2.2 (s, 3H, $-CH_3$), δ 3.1 (br, 2H, -NH, -CH), δ 6.5 (s, 1H, -CH), δ 6.76 (d, 1H, J = 7.8, -CH), δ 7.1 (d, 1H, J = 7.9, -CH); Anal. Calcd. for $C_{21}H_{30}N_2$: C, 81.24; H, 9.74; N, 9.02; Found: C, 81.29; H, 9.79; N, 9.15.

Results and Discussion

The catalytic efficiency of malonic acid, cinnamic acid, oxalic acid, succinic acid, formic acid, trichloroacetic acid, tartaric acid, chloroacetic acid were studied and chloroacetic acid gave the best result for the easy, less time taking and high yielding synthesis of 1,5-benzodiazeines derivatives (Table 1).

First of all, we studied the influence of chloroacetic acid for the synthesis of 1,5-benzodiazepine using *o*-phenylenediammine and acetophenone as a model and varying the amount of chloroacetic acid by simple optimization study (Table 2). The catalyst quantity was optimized to 10 mol% of chloroacetic acid and excellent results (94% yields) were achieved.

Table 1. Reaction of *o*-phenylenediamine with acetophenone promoted by aliphatic acids in synthesis of 1,5-benzodiazepines

Entry	Aliphatic Acid	Time, h	Yield, %
1	Malonic Acid	1	80
2	Cinnamic Acid	1	75
3	Oxalic Acid	1	70
4	Succinic Acid	1	72
5	Formic Acid	1	85
6	Trichloroacetic Acid	1	90
7	Tartaric Acid	1	60
8	Chloroacetic Acid	1	94

Table 2. Optimization of concentration of chloroacetic acid for the synthesis of 1,5-benzodiazepines under solvent-free condition

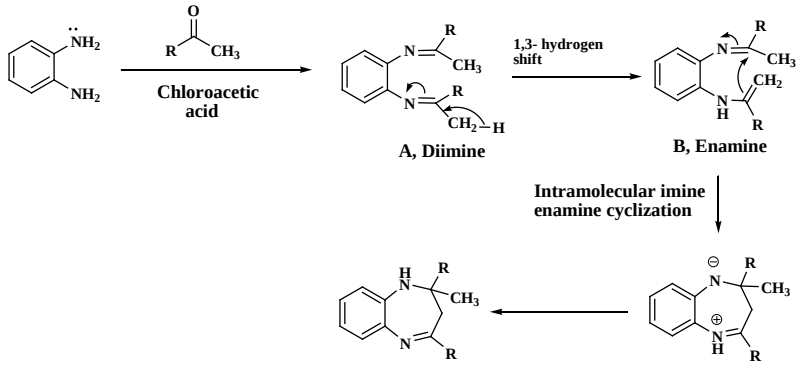
Amount of catalyst mol, %	Time, h	Yield, %
20	1	94
15	1	94
10	1	94
5	1	88

Various 1, 5-benzodiazepine derivatives have been synthesized from *o*-phenylenediamines and ketones using chloroacetic acid in 85-94% yields (Table 3). Diamines with electron releasing group (entry 6-9) also reacted smoothly with ketones to afford products in good yields.

Table 3. Condensation of *o*-phenylenediamine with various ketones catalyzed by chloroacetic acid

Entry	R	R_1	R_2	R_3	R_4	Yield, %	Time, h	M.P.^{0}C	M.P.^{lit}, ^{0}C
1	H	CH_3	C_6H_5	H	C_6H_5	94	60	149-150	151-152[16]
2	H	CH_3	CH_3	H	CH_3	88	50	138-139	137-139[16]
3	H	CH_3	C_2H_5	H	CH_3	85	50	137-139	137-138[16]
4	H	$-(CH_2)_5-$	$-(CH_2)_5-$			87	40	137-138	138-139[9]
5	H	$-(CH_2)_6-$	$-(CH_2)_6-$			90	40	133-134	136-139[9]
6	CH_3	CH_3	CH_3	H	CH_3	89	50	126-128	127-128[9]
7	CH_3	CH_3	C_6H_5	H	C_6H_5	87	60	91-92	92-93[17]
8	CH_3	$-(CH_2)_5-$	$-(CH_2)_5-$			92	60	140-142	142-143[17]
9	CH_3	$-(CH_2)_6-$	$-(CH_2)_6-$			85	60	121-122	124-125[17]

The proposed mechanism of the reaction (Scheme 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 ring.



Scheme 2. Proposed mechanism and possible intermediates

Conclusion

In conclusion, we have studied the catalytic activity of various easily available aliphatic acids and found chloroacetic acid as an efficient, inexpensive, efficient catalyst for the one pot synthesis of 1,5-benzodiazepines under solvent free conditions. The solvent-free procedure as well as high yield and selectivity, makes this protocol an attractive and user friendly alternative for the synthesis of 1,5-benzodiazepines.

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