$ZnCl_2$ at MMT K-10 Catalysed Synthesis of 1,5-Benzodiazepine-2,4-diones from β-amino carbonyls

Mr. Sagar Narayan Dakhane*
Assistant Professor**,** MES Abasaheb Garware College, Pune-04 Affiliated to Savitribai Phule Pune University Pune Maharashtra, India,, Email:sagarsnd@gmail.com

Abstract:. 1,5-benzodiazepine-2,4-diones are the most studied group of diazepine, which act as inhibitors of HIV-1 capsid assembly and reverse transcriptase. The benzodiazepine-2,4-dinone derivatives were prepared from β-amino carbonyl compounds by greener method using metal catalyst loaded on MMT K-10. The starting materials β-amino carbonyls were synthesized by multicomponent Mannich reaction at room temperature using 20 mol percentage of NH_4Cl. Metal supported Montmorillonite K10-catalyzed reactions of various substituted β-amino carbonyls with OPDAs afforded 1,5-bezodiazapine-2,4-diones. Among the synthesized catalysts, the 10% Zn-K_{10} exhibited high conversion up to 90% and high selectivity up to 100% towards 1,5-bezodiazapine-2,4-diones

Keywords: β-aminocarbonyls, 1,5 –benzodiazepine, MMT-K-10, impregnation method, OPDAs,

1. Introduction:

Nanoclays have been one of the significant industrial minerals and with the recent development of nanoclay technology. Montmorillonite, {[M2(OH)2(Si4O10)]·xH2O}, M = Al and/or Mg is one of the most important nanoclay minerals used in various organic reactions[1] . Montmorillonite has the capability to exchange various metal cations like Al^{3+}, Zn^{2+}, $Mn^{2+,}$ $Fe^{3+,}$$Cu^{2+,}$ $Cr^{3+,}$ Ni^{2+} etc. by the cations present in the interlayer of nanoclay mineral[2]. The catalytic activity of nanoclay mineral has been enhanced by manipulating the pore size, intercalating and replacing interlayer cations and surface area [3]. A number of acid-treated montmorillonite clays and high porosity silicas have previously been shown to be effective supports for $ZnCl_2$ and $FeCl_3$ used in many organic transformations .The catalytic activity of $ZnCl_2$, on these supports is very much higher than that of the unsupported salt, and these catalysts are of some interest as possible replacements for homogeneous catalysts [4-5]. In present work various metal catalysts supported on Montmorillonite clay K-10 were synthesized by scheme 1 and used for synthesis of diazepine derivatives. They showed very good catalytic activity for conversion of β-amino carbonyls to diazepine.

Scheme1:

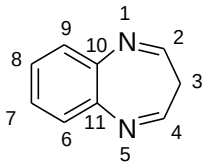
K10 Montmorillonite + MCl_2 ⟶ M-K-10

M= Zn, Fe, Ba

Benzodiazepine and their derivatives are the important class of heterocyclic compounds having important biological activities. Derivatives of benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents [6-8]. In the last decade, the area of biological interest of 1,5-benzodiazepines has been extended to several diseases such as cancer, viral infection and cardiovascular disorders [9-11]. Besides, benzodiazepine derivatives are also of commercial importance as dyes for acrylic fibers in photography [12]. The core structure of 1,5-bezodiazepine is shown in the fig 1. The structure has two

nitrogen atoms at positions 1 and 5 in a seven membered diazepine ring fused to a benzene ring. The ring system occurs in the diimine forms where there is conjugation between the two imino groups and the benzene ring, which bring stability to the system [13].

Fig 1: The core structure of 1,5-benzodiazepine



Benzodiazepines and analogues exhibit muscle relaxant, anti-anxiety, anticonvulsant, anti HIV1, anticoagulant, antiobesity, calcium channel blockers, cholecystokinin antagonists, thrombopoietin receptor agonist, anti-leukemic, anti-epileptic, anti-cancer, antiviral, antifungal, antibacterial, analgesic, anti-inflammatory, anthelmintic, antipyretic and antiulcer properties [14-17]. We explored its antifungal activity by antibiofilm efficacy in this work.

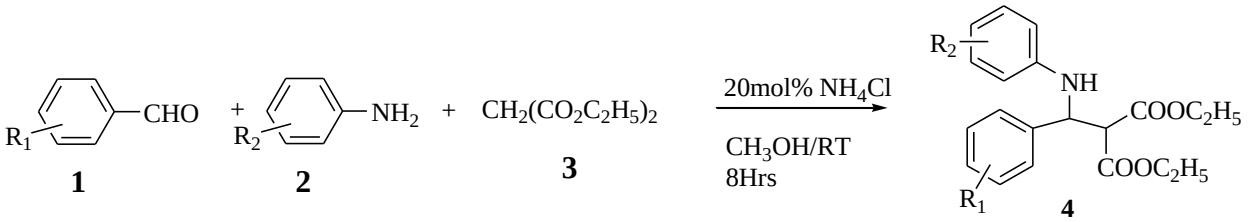
A number of preparations have been known since the late 1800s for the synthesis of benzodiazepine derivatives. Though many of these methods are very effective, they involve the use of various acids or reagents that are not environmentally compatible, produce a large amount of waste and require longer reaction times.[18] Moreover, many of these methods give relatively large amounts of undesirable by-products whose removal is tedious and are also not satisfactory with respect to operational simplicity to isolate the yield. Thus, it has become very important to follow methods which could be considered as better and eco-friendly viable, green synthetic methods. These biologically active derivatives can be easily synthesized from β-amino carbonyl compounds. In this regard we focus on the synthesis of 1,5-benzodiazepine-2,4-diones derivatives from β-amino carbonyl compounds which are very important building blocks for the synthesis of molecules having great potential in pharmaceutical and material science [19-21].

These structural moieties are present in many bioactive natural products as a core structural framework.

Therefore present work is focused on development of such 1,5-benzodiazepine structure based modeling of bioactive molecules [22-23] and to further elucidate the important role of target conformation in molecular docking results, we decided to explore the significance of HIV- 1 PR flexibility through ensemble docking of 1,5-benzodiazepine-2,4-diones into the multiple crystallographic structures of HIV-1 proteases [24-26]. 1,5-benzodiazepine-2,4-diones are potent and selective HIV-1 PR inhibitors with sub-nanomolar HIV-1 PR inhibition activity [27-29] and hence was selected as a model in our studies. The synthetic work in our project is based on Mannich reaction which is a classic protocol for the synthesis of β-amino carbonyl compounds, which are important intermediates for the construction of various nitrogen-containing natural products and pharmaceuticals and it is a reaction with high atom-economy [30-32]. The multicomponent Mannich reaction is a green and classical method for the synthesis of our stating materials. The classical Mannich reaction, a three-component condensation between structurally diverse substrates containing at least one acidic hydrogen atom, an aldehyde component and an amine reagent leads to Mannich bases [33]. Different reaction conditions have been widely described for the multicomponent Mannich reaction in the presence of a variety of catalysts [34]

In present work by considering green chemistry principle we focused our interest on bronsted acid NH_4Cl to catalyze multicomponent Mannich reaction shown in scheme 2. It is water soluble and ecofriendly mild acidic catalyst. The main advantage of this is that β-amino carbonyl compounds do not require further purification.

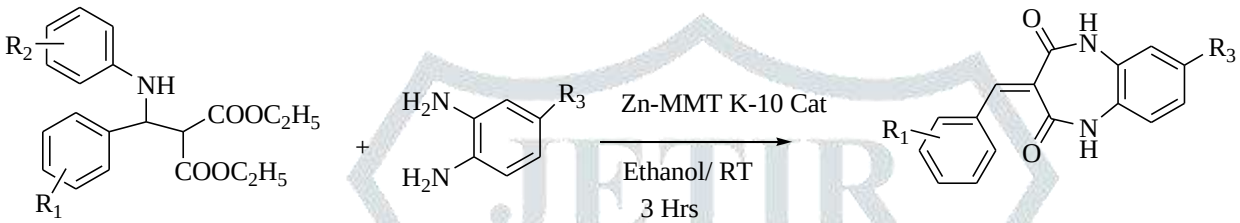
Scheme2:



1 **2** **3** **4**

These compounds are used to synthesize1,5-benzodiazepine-2,4-diones derivatives using Zn-MMTK-10 catalyst in scheme 3 shown below

Scheme 3:



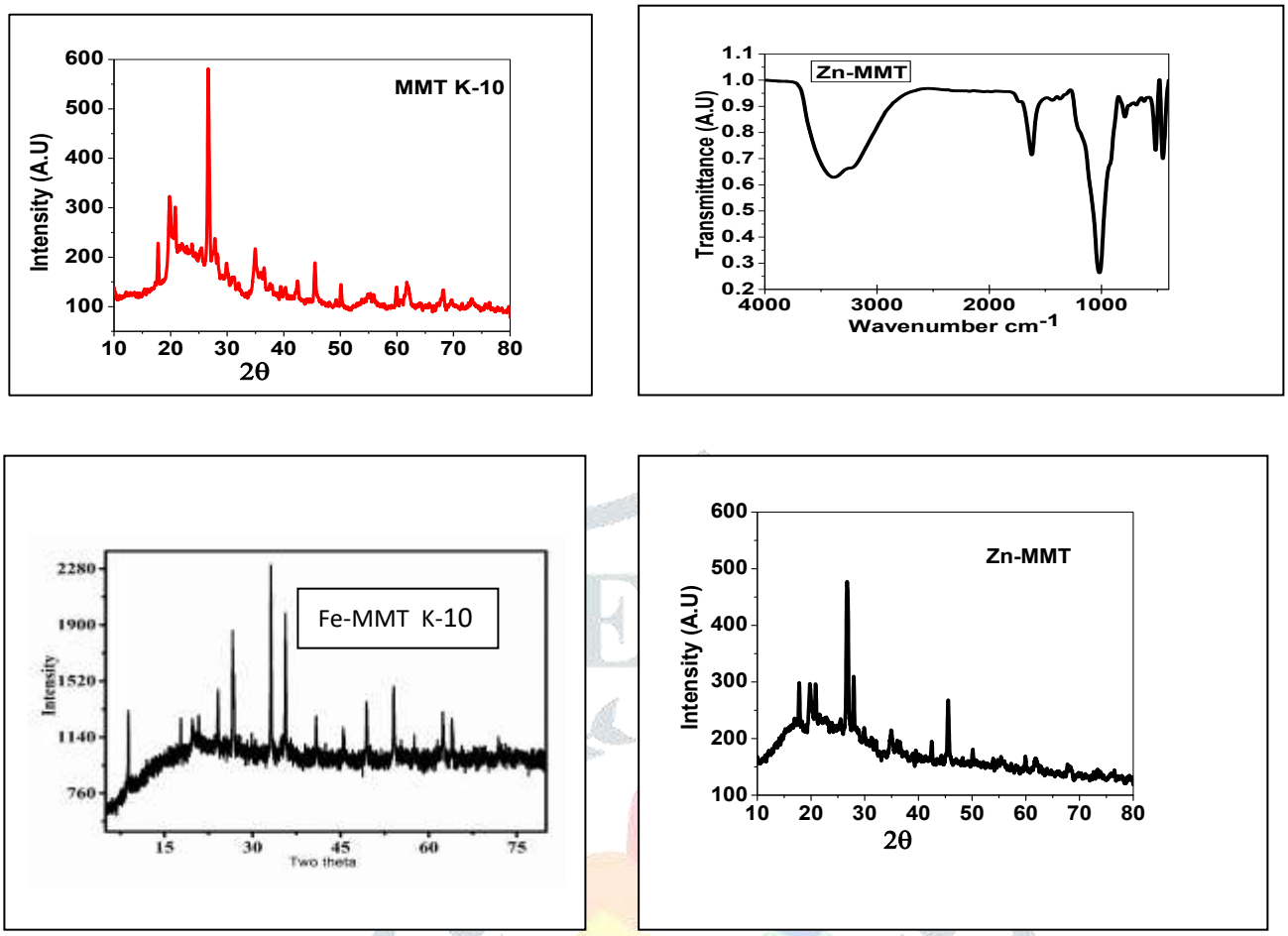
Beside this the use of metal catalyst supported over MMT K-10 explore the synthetic methodologies become more economic under green conditions to yield bioactive 1,5 benzodiazepines.

2. Result and discussion:

(a) Synthesis of catalyst:

Specific surface area of raw montmorillonite nanoclay and amount of Zn was determined by BET methods using a Quantachrome NOVA 1000 surface area analyser at liquid nitrogen temperature. The surface area of the raw montmorillonite nanoclay was found to be 230 m^2 g^{-1} and that of Zn/K-10 was 23 m^2g^{-1} for 0.01 molar concentration of $ZnCl_2$ salt. Pyridine adsorption in situ FT-IR spectroscopy was performed for K-10 and Zn incorporated K-10 catalysts and the spectra recorded after out gassing at 200 °C. Adsorption of pyridine on the parent K-10 clay resulted in absorption bands at 1540 and 1450 cm^{-1}, which can be assigned to pyridine molecules interacting with Bronsted and Lewis acid sites, respectively. The surface study of MMT K-10 and metal loaded MMT K-10 was confirmed by XRD and Bronsted and lewis acidic sites were confirmed by IR bands shown in fig.2 Incorporation of zinc led to an increase in Lewis acidity and there is a decrease in concentration of acid sites with increase in zinc loading in the range of 0.1–0.6 mmol Zn per gram of K-10. It is seen that Zn/K-10 showed the highest activity with 90% conversion of β- amino carbonyls to corresponding 1,5 diazepine derivatives on reaction with o-phenylene diamines. The effect of Zn^{2+} concentration on the catalytic activity of the Zn/K-10 was studied with Zn^{2+} concentrations ranging from 0.01 to 0.50 mmol/g. The Formation of diazepine derivatives increased linearly up to 0.22 mmol/g of zinc and further increase has the marginal effect on the catalytic activity. Zn^{2+} is exchanged with interlayer cations as well as the Bronsted acid sites up to a concentration of 0.22 mmol/g. The higher loading results in incorporation of zinc species as ZnO after calcination, which does not contribute to the catalytic activity. The Zn2+ ion is known as “moderate Lewis acid” cation owing to its moderate hardness, which explains the reason for higher activities of Zn/K-10

Fig. 2 XRD of MMT K-10 clay and metal loaded on MMT K-10



(b)Synthesis of β-amino carbonyls:

Initially, the three-component Mannich reaction of benzaldehyde (3.0 mmol), aniline (3 mmol), and diethyl malonate (3 mmol) was examined (Scheme 2). As a preliminary study, several Lewis acids, bronsted acids and solvents were screened in the model reaction. The results of extensive various acids and solvents screening and optimization are shown in a table 1. The NH_4Cl catalyzed Mannich reactions in organic solvents such as acetonitrile, 1,2-dichloroethane, methanol, ethanol, toluene and mixtures of toluene/water and gave the desired products in low yield with the foramtion of aldol side products. Among the screened solvent systems, methanol was the solvent of choice, since in this solvent the Mannich-type reactions proceeded smoothly and afforded the desired adducts in high yields at room temperature. Consequently, we conclude that the NH_4Cl is more reactive in methanol than in other organic solvents. At room temperature, the Mannich reaction proceeded to completion affording the Mannich adduct in good to excellent yield.

Fig3. X-ray crystal structure of β-amino carbonyl compound (entry 4 in Table 2)

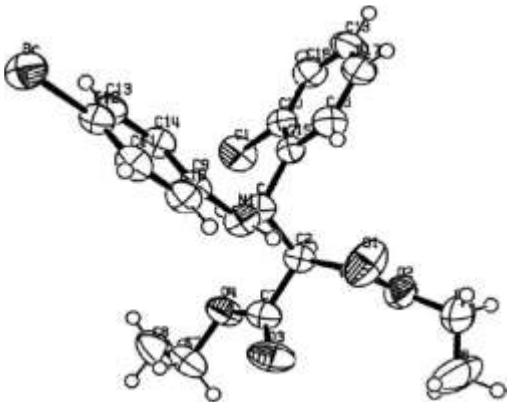


Table 1-Effect of NH_4Cl on Multicomponent Mannich reaction

Entry	NH_4Cl catalyst	Time (hr)	solvent	Product Yield(%)[a]
1	5 mol %	72	Methanol	30
2	10 mol%	48	Methanol	35
3	15 mol %	24	Methanol	60
4	20 mol%	08	Methanol	90
5	25 mol%	72	Methanol	25

[a] Isolated yield of products.

The reaction in methanol without using any catalyst gave a low yield of the product. Furthermore, we were excited to find that only 20 mol % NH_4Cl of the catalyst gave good yields at room temperature. Furthermore, simple workup in water opened the route for an entirely green highly efficient one-pot multicomponent Mannich reaction. Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used various aldehydes and amines and the results shown in table 2 clearly demonstrates that NH_4Cl is an excellent. Thus, a variety of aromatic aldehydes, including electron withdrawing and electron-donating groups, were tested using our new method in methanol in the presence of NH_4Cl. Generally, excellent yields of diethyl malonate were obtained for a variety of aldehydes including those bearing an electron donating groups. Furthermore, several electron withdrawing aromatic aldehydes led to the desired products in good yield. However, under the same reaction conditions aliphatic aldehydes, such as isobutyaldehyde, gave a mixture, due to enamine formation; the desired product was obtained in low yield. The scope of our method was extended to other amines. In the case of amines having an electron-donating group, such as 4-isopropylaniline, the corresponding amino ketones were obtained in good yields. Furthermore, amines with electron-withdrawing groups, such as 4-chloroaniline, 3-chloroaniline and 4-bromoaniline gave the desired product in excellent yields. The structure of β-amino carbonyl was confirmed by X-ray crystal structure analysis for entry 4 in table 2 shown in fig

Table2: Multicomponent Mannich reaction of substituted aldehydes, aniline and diethylmalonate

Entry	R1	R2	Time (hr)	Yield[a](%)	MP(lit)°C	δ(ppm), J(Hz)[b]
1	H	H	8	90	93	5.1(d, J= 4.4)
2	4-Cl	H	6	95	107	5.4(d, J= 4.6)
3	2,4-Cl	3-Cl	6	95	104	5.4(d, J= 4.6)
4	4-Br	4-Br	6	97	108	5.2(d, J= 4.5)
5	2-Br	3-Cl	6	98	102	5.2(d, J= 4.5)
6	4-CH_3	3-Cl	9	80	98	5.5(d, J= 4.6)
7	4-OCH_3	4-Cl	9	75	106	5.5(d, J= 4.6)
8	2-OH	4-Cl	9	70	110	5.1(d, J= 4.4)
9	4-CH_3	4-Cl	8	80	96	5.4(d, J= 4.5)
10	4-OCH_3	3-Cl	8	80	102	5.3(D, J= 4.4)

[a] Isolated yield of products. [b] Products are characterized by spectral analysis

(c) Zn-MMT K-10 catalysed Synthesis of 1,5-bezodiazapine-2,4-diones:

This communication reports on the formation of 1,5 benzodiazepine from the reaction of *o*-phenylenediamine and β-amino carbonyls using Zn-MMT K-10 as a catalyst in ethanol as a solvent. The formation of this product was also confirmed by a reaction of *o*-phenylenediamine with acetone in ethanol under conventional heating conditions in presence of acetic acid to yield benzodiazepine. The initial objective was to form a benzimidazole derivative from the reaction of *o*-phenylenediamine and β-amino carbonyls using $ZnCl_2$ at .MMT K-10 in ethanol as a solvent. It was later observed that the benzimidazole formation *via* a condensation reaction had not taken place. This was attributed to the fact that the activation energy required for the reaction of *o*-phenylenediamine and β-amino carbonyls was not achieved. This phenomenon was further ascertained by performing the reaction of *o*-phenylenediamine and acetone under reflux condition in the absence of ac acid then the product obtained was 2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazopine which confirmed that the cyclization occurred without the involvement of acid. Then, further investigations were undertaken to examine the capability of the catalytic system Zn- MMT K-10 to catalyze the reaction between o-phenylenediamine and various substituted β-amino carbonyls to yield 1,5-bezodiazapine-2,4-diones under the optimized reaction condition in scheme 3. As seen from Table 3 o-phenylenediamines could react with β-amino carbonyls to afford the corresponding 1,5-benzodiazepines in moderate to excellent yields (80−98%, entries 1−10, Table 3). The acidic surface of catalyst removes the aniline fragment with subsequent formation of benzylidene double bond. It was found that electron deficient β-amino carbonyls react with o-phenylenediamines more smoothly to furnish the corresponding products in higher yields (91− 98%, entries 1−4 Table 3) than those electron rich β-amino carbonyls (60−70%, entries 5-9 Table 3). The synthesized compounds were characterized using IR and NMR spectroscopy (1H, 13C), mass spectrometry as well as elemental analysis. All the characterization data were in agreement with the proposed structures of the compounds.

Table3: Synthesis of 1,5-bezodiazapine-2,4-diones using Zn-MMT K-10 catalyst

Entry	R1	R2	R3	Yield[a](%)	MP (°C)
1	H	H	H	91	203
2	4-Cl	H	H	92	156
3	2,4-Cl	3-Cl	H	98	168
4	4-Br	3-Cl	3-CH_3	98	159
5	2-Br	3-Cl	3-CH_3	90	186
5	4-CH_3	3-Cl	3-Cl	70	200
7	4-OCH_3	4-Cl	3Cl	64	196
8	2-OH	4-Cl	3-CH_3	70	188
9	4-CH_3	4-Cl	3-Cl	70	205
10	4-OCH_3	3-Cl	3-CH_3	65	190

[a] Isolated yield of products.

3. Conclusion:

1,5-benzodiazepine-2,4-diones the potent and selective HIV-1 PR inhibitors were synthesized at room temperature from *o*-phenylenediamine and β-amino carbonyls in presence of Zn-MMT K-10 as a catalyst. The spectral characterization confirmed the structure of product. The yield and synthetic methodology is excellent as compared to reported methods in literature.

4. Experimental:

Montmorillonite K-10 was purchased from Fluka AG, Switzerland. Its wt.% composition was SiO2 = 70, Al2O3 = 15, Fe2O3 = 1.5, CaO = 2.5, MgO = 3, Na2O = 0.5, K2O = 1.5, and H2O = 6 and bulk density = 300 ± 30 g/l. Aromatic aldehydes, substituted aniline, diethyl malonate and o-phenylenediamines purchased from S.D. Fine Chem Ltd., Mumbai and used without further purification. The reaction progress was monitored by TLC on silica gel pre-coated F254 Merck plates. Spots were visualized by ultraviolet irradiation. Melting points were determined on a digital Gallen-Kamp MFB-595 instrument using open capillary tubes IR spectra were recorded as potassium bromide discs using Bruker-Vector 22 FTIR spectrophotometer (SPPU, Pune). The NMR spectra were recorded in DMSO-d_6 as the solvent. Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV.

4.1 Preparation of catalyst:

A known amount of K-10 (10 g) was stirred with 0.5M zinc chloride solution prepared in water (50 ml) at 80 ◦C for overnight and then cooled to room temperature and the exchanged

clay was separated by filtration. The above procedure was repeated once to ensure maximum zinc exchange. The residue obtained was filtered and washed twice with 100 ml of distilled

water. This zinc-exchanged K-10 was dried at 120 ◦C for 12 h and then calcinated in muffle furnace at 400 ◦C. The catalysts with varying concentrations of Zn in K-10 were prepared by taking different zinc chloride stock (0.01–0.5 M) solutions, by following the above procedure.

Similarly, Fe/K-10 and Ba/K-10 catalysts were prepared by exchanging with the pre decided stock solutions of the corresponding metal chlorides by following the above procedure. BET surface area of catalysts was determined by surface area analyser. The amount of exchanged metals on supports was determined by atomic absorption spectrophotometer. It was characterized by powder XRD and FT-IR.

4.2 General procedure of preparation of β-amino carbonyls:

In 5 ml methanol 20 mol % NH4Cl was dissolved. In this aldehyde (3 mmol), diethyl malonoate (3 mmol) and aniline (3 mmol) were added at once. This mixture was allowed to stir for 8 Hrs at room temperature. It was monitored by TLC .The white solid product was washed with hexane. It was then filtered off, dried weighed and determined its mp before and after recrystallization in ethanol. The product was characterized by spectral analysis.

4.3 General procedure for the synthesis of 1,5-bezodiazapine-2,4-diones:

In 10 ml ethanol mixture of *o*-phenylenediamine and β-amino carbonyl were added in 1:1 molar ratio and stirred at room temperature for 30 minutes. To this solution 0.5 mmol of Zn-MMT K-10 catalyst was added and reaction mixture was further stirred for 3 hours at room temperature. The progress of reaction was monitored by TLC. After consumption of starting material the reaction was quenched by adding water. The product was extracted by diethyl ether. The solid yellow coloured product was isolated by evaporating the solvent. The product was further purified by column chromatography in hexane:ethyl acetate (70:30) to afford pure product. It was characterised by spectral analysis.

Acknowledgments

Great support from Dr. P.B.Buchade, principal of the Abasaheb Garware College, Pune and Dr. P.D. Lokhande Professor of SPPU, Pune, Maharashtra, India.

References:

[1] D.M. Roundhill, Chem. Rev. 91 (1992) 1.

[2] D.M. Roundhill, Catal. Today 92 (1997) 1.

[3] T.E. M¨uller, M. Beller, Chem. Rev. 98 (1998) 675.

[4] K. Tanabe, W.F. Hoelderich, Appl. Catal. A Gen. 181 (1999) 399.

[5] R.W. Layer, Chem. Rev. 63 (1963) 489.

[6] Aastha P, Navneet K, Anushu A, Pratima S, Dharma K. 1,5- Benzodiazepines: Overview of properties and synthetic aspects. Res J Chem Sci. 2013; 3:90-103.

[7] Eleftheriadis N, Neochoritis CG, Tsoleridis CA,Stephanidou-Stephanatou J, Iakovidou-Kristi Z. One-pot microwave assisted synthesis of new 2-alkoxycarbonylmethylene-4-oxo-1,5-benzo-,naphtha-and pyridodiazepines and assessment of their cytogenic activity. European J Med Chem. 2013; 67:302-309.

[8] Salve PS, Mali DS. 1,5-benzodiazepine: A versatile pharmacophore. Int J Pharma Bio Sci. 2013; 43(11):345-370.

[9] Salve PS, Mali DS. An expenditious and efficient microwave assisted synthesis of 1,5-benzodiazepine derivatives. J Chem Pharma Res. 2013; 5(2):158-161.

[10] Sternbach H, Montclair UNI 1, 4-benzodiazepine-4- oxides. US Patent 2893992, 1959.

[11] Mihic SJ, Harris RA. Hypnotics and sedatives, in: Brunton LL, Chabner BA, Knollmann BC, (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics. McGraw Hill and Company, New York 2011, 457-480.

[12] Bariwal JB, Upadhyay KD, Manvar AT, Trivedi JC, Singh JS, Jain KS *et al*. 1, 5-Benzothiazepine, a versatile pharmacophore: a review. Eur J Med Chem. 2008; 43(11):2279-2290.

[13]Casher MI, Botswick JR, Yasugi S. Benzodiazepines: a versatile clinical tool. Current Psychiatry 2012; 11(4):55- 63.

[14]Brambilla G, Carrozzino R, Martelli A. Genotoxicity and carcinogenicity studies of denzodiazepines. Pharmacoles 2007; 56(6):443-458.

[15] Claramunt RM, Alkorta I, Elgureo J. A theoretical study of the conformation and dynamic properties of 1,5- benzodiazepines and their derivatives. Comput Theor Chem 2013; 1019:108-115.

[16] Kurasawa Y, Okamoto Y, Ogura K, Takada A. Facile synthesis of novel 3-quinoxalinyl-1,5-benzodiazepines *via* ring transformation. Stable tautomers in the 1, 5- benzodiazepin-2-one ring system. J Heterocycl Chem.1995; 22(3):661-664.

[17] Rabahi A, Hamdi SM, Rachedi Y, Hamdi M, Talhi O, Paz FAA, *et al*. X-ray crystallography and theoretical studies of the reaction mechanism for the synthesis of 1,5- benzodiazepines from dehydroacetic acid derivatives and o-phenylenediamine. J Mol Struct. 2014; 1061:97-103.

[18] Steffan RJ, Failli AA. Pyrrolobenzodiazepine carboxyamide vasopressin agonists. European Patent, EP 2000; 1(149):104B1.

[19] Kester M, Karpa DK, Vrana EK. Elsevier's Integrated Review Pharmacology, 2nd ed Elsevier, Amsterdam, 2012.

[20] Pagel JF, Parnes BL. Medications for the treatment of sleep disorders: An overview. J Clin Psychiatry. 2001; 3(3):18-125.

[21] Malcolm, GABA systems, benzodiazepines and substance dependence. J Clin Psychiatry. 2003; 64(3):36-40

[22]Ha, S. K.; Shobha,D.; Moon, E.; Chari, M. A.; Mukkanti, K.; Kim, S.-H.; Ahn, K.-H.; Kim, S. Y. Bioorg. Med. Chem. Lett. 2010, 20, 3969−3971.

[23] Tilton, J. C.; Doms, R. W. Antiviral Res. 2010, 85, 91.

[24] McColl, D. J.; Chen, X. Antiviral Res. 2010, 85, 101.

[25]Titolo, S., Mercier, J.-F.; Wardrop, E.; von Schwedler, U.; Goudreau, N.; Lemke, C.; Faucher, A.-M.; Yoakim, C.; Simoneau, .B.; Sundquist, W. I.; Mason, S.'Discovery of potent HIV-1 capsid assembly inhibitors.' 17th Conference on Retroviruses and Opportunistic Infections 2010. Oral abstract 50.

[26] Adamson, C. S.; Freed, E. O.Antiviral Res. 2010, 119.

[27] Ganser-Pornillos, B. K.; Yeager, M.; Sundquist, W. I. Curr. Opin. Struct. Biol. 2008, 18, 203;

[28] Pornillos, O.; Ganser-Pornillos, B. K.; Kelly, B. N.; Hua, Y.; Whitby, F. G.; Stout, C. D.; Sundquist, W. I.; Hill, C. P.; Yeager, M. Cell 2009, 137,1282.

[29]Sundquist, W. I.; Wang, H.; Hill, C. P.; Stemmler, T. L.; Davis, D. R.; Alam, S. PCT Int. Appl. WO 2003013425, 2003, p 127.

[30] Krautha¨user, S.; Christianson, L. A.; Powell, D. R.; Gellman, S. H. J. Am. Chem. Soc. 1997, 119, 11719–11720.

[31]Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. J. Med. Chem. 1998, 41, 973–980.

[32]Kobayashi, S.; Matsubara, R.; Kitagawa, H. Org. Lett. 2002, 4, 143–145;

[33] Davis, F. A.; Zhang, Y.; Anilkumar, G. J. Org. Chem. 2003, 68, 8061–8064;

[34] Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. Org. Lett. 2003, 5, 3639–3640;