SYNTHESIS OF 1,5-BENZODIAZEPINES USING SILICA PERCHLORIC ACID: AN EFFECTIVE REUSABLE HETEROGENEOUS CATALYST UNDER MILD CONDITION.

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ABSTRACT

The synthesis of 1, 5-benzodizepines using highly inexpensive easily to prepare and reusable silica percloric acid ($HClO_4$-SiO_2) as an effective reusable heterogeneous catalyst. The method offers several advantages including mild reaction conditions, elevated product yields, short reaction time and simple workup procedure, which makes it a useful process for the synthesis of desired products.

Keywords: *1, 5-benzodiazepines, perchloric acid ($HClO_4$-SiO_2), reusability studyheterogeneous catalyst.*

INTRODUCTION

Benzodiazepines are pharmacologically very important compounds and widely used as anticonvulsant, antianexiety, analgesic, sedatives, antidepressive and hypnotic activities[1-3]. In addition, 1,5-benzodizepines are used as starting materials for the preparations of fused ring compounds such as triazoles[4], oxadiazoles[5], oxazines[6] and furano-benzo-dizepines[7]. The 1,5-benzodizepines also posses the similar activities as that of 1,4-benzodizepines[2]. Although the first benzodiazepine was introduced as a 30 years ago[8], the research in this area is challenging and hence researchers were attracted towards the synthesis of compounds possessing remarkable biological activitity.Next, now a day's benzodiazepine chemistry is tremendously growing due to its applications in photography[9] and anti-inflammatory activities[10].

Literature survey reveled that there is considerable growth in the synthesis of these compounds. Many of these methods includes the condensation of o-phenylenediamines (OPD) with α, β-unsaturated compounds[11], α-haloketones or with ketones[12] catalyzed by $BF_3.OEt_2$[13], $NaBH_4$[14], Polyphosphoric acid on SiO_2[15], MgO-$POCl_3$[16], Yb(OTf)$_3$, ionic liquids[17] and acetic acid-MWI[18]. However, despite their potential utility, many of these methods suffer from drawbacks such as relatively low yield, formation of by products, use of expensive reagents, incompatibility with other functional groups and relatively harsch reaction conditions. Therefore, the development of mild, efficient and metal free reaction conditions would extend the scope of this conversion. Use of a catatalytic quantity of cheap solid supported acid, which could be removed from the reaction mixture by simple filtration avoiding expensive and toxic regents, could be useful for this purpose.

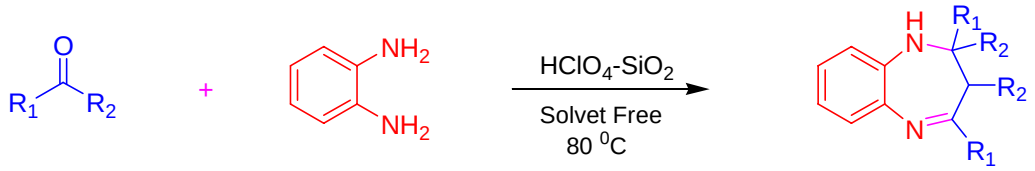
Some of the above methods were associated with tedious reaction workup, hazardous Bronsted acids (HCl and H_2SO_4) and Lewis acids which also difficult to remove from the reaction mixture.

In addition, Lewis acids are also deactivated by nitrogen containing substrates which may decomposes the indole and other functionalities present in the substrates[19].

RESULT AND DISCUSSION

The leading contender for an environmentally acceptable alternative to the synthesis of 1,5-benzodezepines is the use of supported reagents. The activity and selectivity of the reagent disperses on the surface of support is improved as a effective surface area of the reagent can be increase up tone hundred times The fact that supported reagents have good thermal and mechanical stabilities and can be easily handled as they are invariably low toxic, noncorrisive free flowing powers and are easily separated from reaction mixture for reusability.

In recent years, carrying out a reaction with out solvent is a important in order to make the synthesis more environment friendly and ecofriendly. These observations lead us to search the methods improving yield and purity of desired products. The present method describes a clean solvent free synthesis of 2,3-dihydro(1H)-1,5-benzodizepines by condensation of ketones possessing at least one a-hydrogen with o-phenylenediamine (OPD) (Scheme:1) at 80 ^{0}C temperature catalyzed by silica supported perchloric acid ($HClO_4$-SiO_2). Results were summarized in Table: 1.1



1 **2** **3(a-b)**

It has been observed that the nature of substrate and substituents present on substrate does not show any significant effect on the formation of 1,5-benzodizepine product. Hence methodology presented here is found to be general for verities of ketones possessing α-hydrogen.

EXPERIMENTAL

All chemicals were used are of AR grade. Melting points were recorded on Buchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR-240C spectrophotometer on KBr disc.1H NMR spectra were recorded on 300 MHz spectrometer $CDCl_3$ using TMS as an internal standard. Purity of the compounds was checked by TLC, ^{1}H NMR, ^{13}C NMR, spectra and by comparison with authentic samples.

Preparation of $HClO_4$-SiO_2 Catalyst:

$HClO_4$ (1.25 gms. 12.5 mmole, as a70% aqueous solution) was added to the suspension of silica gel (23.75 gms.230-400 mesh) in diethyl ether (75 ml). The mixture was concentrated and

residue dried under vacuum at 100^0C for 72 hrs. to afford $HClO_4$-SiO_2 (0.5 mmolegm^{-1}) as a free flowing powder.

A general procedure for the synthesis of 1, 5-benzodizepines at 80 ^{0}C:

The mixture of ketone (5 mmole), o-phenylene diamine (2.5 mmole) and $HClO_4$-SiO_2 (0.05mmole) is mixed and stirred and heated 80^0C for 5-10 min.. After completion of reaction (TLC), the reaction mixture was diluted with hot methanol, evaporation of solvent afford 1, 5-benzodizepine product. Further product was purified by column chromatography (Petroleum ethers: Ethyl acetate=6:1)

Reusability of $HClO_4$-SiO_2:

Herein also we have investigated the reusability and recycling of $HClO_4$-SiO_2 for the Synthesis of 1, 5-benzodizepines was studied and it is observed that the activity of the catalyst is satisfactory even after five turns (Table: 1.2)

Table: 1.2: Recyclizing ability study of 0.05 mmole $HClO_4$-SiO_2 at 80 ^{0}C:

Entry	Time(min.)	Yield(%)
0	15	93
1	20	93
2	25	90
3	35	88
4	50	87

In conclusion, we have developed a simple and general method for the synthesis of 1,5-benzodizepines using highly inexpensive easily to prepear and reusable silica percloric acid($HClO_4$-SiO_2) as an effective reusable heterogeneous catalyst. The method offers several advantages including mild reaction conditions, elevated product yields, enhanced reaction time and simple workup procedure, which makes it a useful process for the synthesis of desired products.

ACKNOWLEDGEMENT

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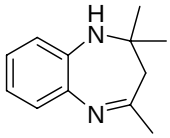
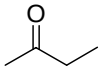
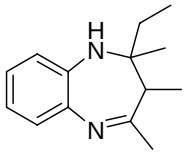
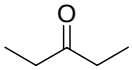
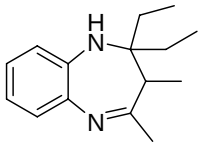
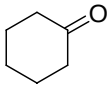
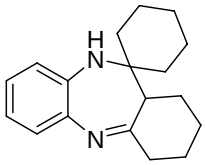
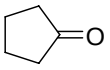
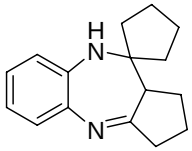
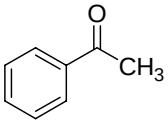
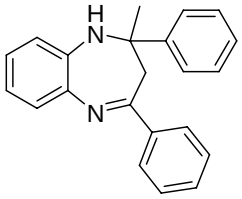
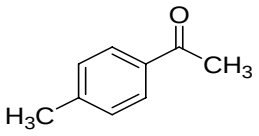
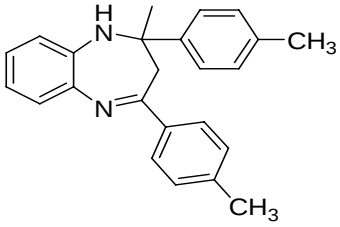
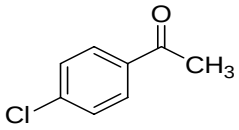
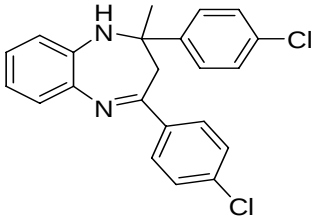
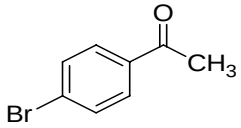
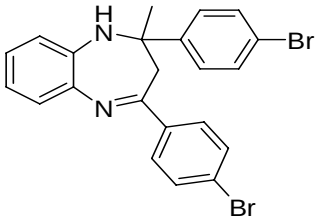
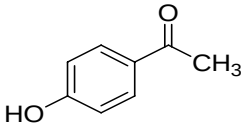
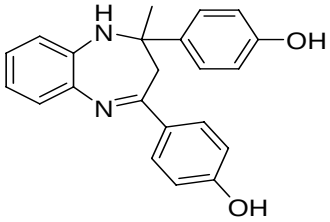
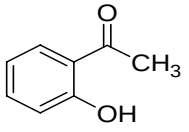
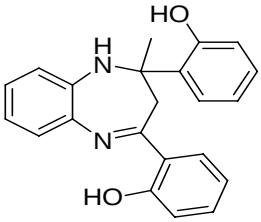
Table: Synthesis of 1,5-Benzodizepines using silica perchloric acid ($HClO_4$-SiO_2) at 80 ^{0}C:

Entry	Substrate	Product	Time(min.)	Yield(%) [a, b]
3a			10	89
3b			10	75
3c			10	82
3d			5	93
3e			5	90
3f			7	92

Contd.

Entry	Substrate	Product	Time(min.)	Yield(%) [a, b]
3g			15	80
3h			15	65
3i			15	79
3i			20	65
3j			20	58

a. Isolated yields of the desired 1,5-benzodizepines.
b. Product were characterized by IR, NMR and by comparison with authentic samples.

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"The human story does not always unfold like a mathematical calculation on the principle that two and two make four. Sometimes in life they make five or minus three; and sometimes the blackboard topples down in the middle of the sum and leaves the class in disorder and the pedagogue with a black eye."

-Winston Churchill