

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-benzodiazepines using highly inexpensive easily to prepare and reusable silica perchloric acid (HClO₄-SiO₂) 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 (HClO₄-SiO₂), reusability study heterogeneous catalyst.

INTRODUCTION

Benzodiazepines are pharmacologically very important compounds and widely used as anticonvulsant, antianxiety, analgesic, sedatives, antidepressive and hypnotic activities¹⁻³. In addition, 1,5-benzodiazepines are used as starting materials for the preparations of fused ring compounds such as triazoles⁴, oxadiazoles⁵, oxazines⁶ and furano-benzo-diazepines⁷. The 1,5-benzodiazepines also possess the similar activities as that of 1,4-benzodiazepines². Although the first benzodiazepine was introduced as a 30 years ago⁸, the research in this area is challenging and hence researchers were attracted towards the synthesis of compounds possessing remarkable biological activity. Next, now a day's benzodiazepine chemistry is tremendously growing due to its applications in photography⁹ and anti-inflammatory activities¹⁰.

Literature survey revealed 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 compounds¹¹, α -haloketones or with ketones¹² catalyzed by BF₃.OEt₂¹³, NaBH₄¹⁴, Polyphosphoric acid on SiO₂¹⁵, MgO-POCl₃¹⁶, Yb(OTf)₃, ionic liquids¹⁷ and acetic acid-MWI¹⁸. 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 harsh reaction conditions. Therefore, the development of mild, efficient and metal free reaction conditions would extend the scope of this conversion. Use of a catalytic quantity of cheap solid supported acid, which could be removed from the reaction mixture by simple filtration avoiding expensive and toxic reagents, could be useful for this purpose.

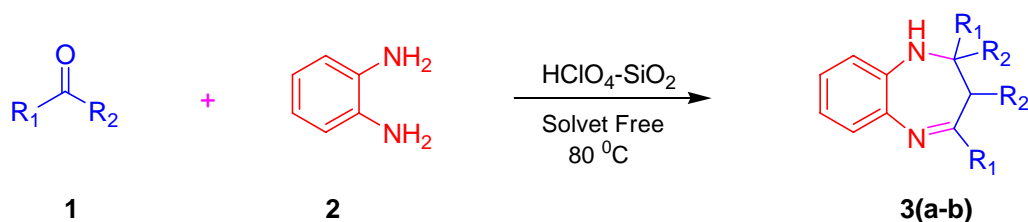
Some of the above methods were associated with tedious reaction workup, hazardous Bronsted acids (HCl and H₂SO₄) and Lewis acids which also difficult to remove from the reaction mixture.

In addition, Lewis acids are also deactivated by nitrogen containing substrates which may decomposes the indole and other functionalities present in the substrates¹⁹.

RESULT AND DISCUSSION

The leading contender for an environmentally acceptable alternative to the synthesis of 1,5-benzodiazepines 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, noncorrosive 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-benzodiazepines by condensation of ketones possessing at least one α -hydrogen with o-phenylenediamine (OPD) (Scheme:1) at 80 °C temperature catalyzed by silica supported perchloric acid ($\text{HClO}_4\text{-SiO}_2$). Results were summarized in Table: 1.1



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-benzodiazepine 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, ¹H NMR, ¹³C NMR, spectra and by comparison with authentic samples.

Preparation of $\text{HClO}_4\text{-SiO}_2$ Catalyst:

HClO_4 (1.25 gms. 12.5 mmole, as a 70% 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°C for 72 hrs. to afford HClO₄-SiO₂ (0.5 mmoleg⁻¹) as a free flowing powder.

A general procedure for the synthesis of 1, 5-benzodizepines at 80 °C:

The mixture of ketone (5 mmole), o-phenylene diamine (2.5 mmole) and HClO₄-SiO₂ (0.05mmole) is mixed and stirred and heated 80°C 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 HClO₄-SiO₂:

Herein also we have investigated the reusability and recycling of HClO₄-SiO₂ 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: Recycling ability study of 0.05 mmole HClO₄-SiO₂ at 80 °C:


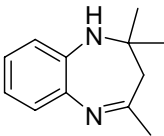
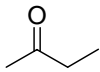
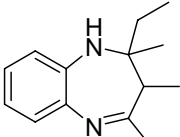
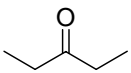
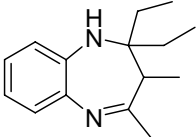
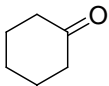
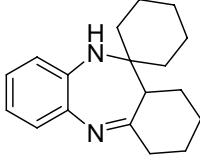
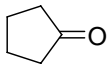
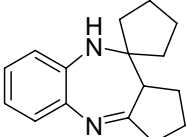
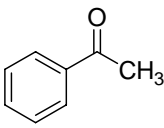
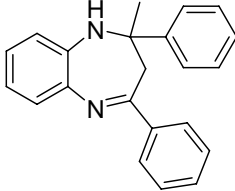
| Entry | Time(min.) | Yield(%) |
|-------|------------|----------|
| 0 | 15 | 93 |
| 1 | 20 | 93 |
| 2 | 25 | 90 |
| 3 | 35 | 88 |
| 4 | 50 | 87 |

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(HClO₄-SiO₂) 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

The authors are thankful to Principal of Padmashri Vikhe Patil College, Pravaranagar (M.S.) for providing necessary laboratory facilities and Dr. J. N. Nigal for constant encouragement.

Table: Synthesis of 1,5-Benzodiazepines using silica perchloric acid (HClO₄-SiO₂) at 80 °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-benzodiazepines.
 b. Product were characterized by IR, NMR and by comparison with authentic samples.

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(Received: 9 April 2008

Accepted: 25 April 2008

RJC-171)

“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