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An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by a solid superacid sulfated zirconia

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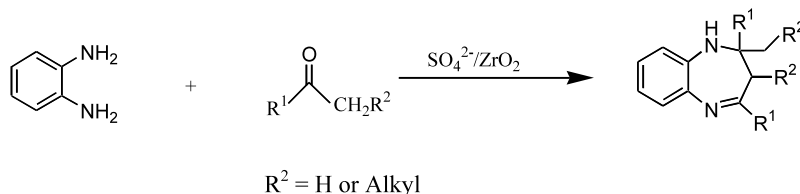
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Abstract—2,3-Dihydro-1*H*-1,5-benzodiazepines are synthesized by the condensation of *o*-phenylenediamine and various ketones in the presence of a versatile solid superacid catalyst ‘sulfated zirconia’ under solvent free conditions. © 2003 Elsevier Science Ltd. All rights reserved.

Benzodiazepines and their polycyclic derivatives are a very important class of bioactive compounds. They are finding numerous new applications and are widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative, and antidepressive agents.^{1,2} Benzodiazepines are also valuable intermediates for the synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furano-benzodiazepines.^{3–5} Due to their broad spectrum of biological activity, these compounds have received a great deal of attention in connection with their synthesis. Generally, benzodiazepines are synthesized by the condensation of *o*-phenylenediamines with α,β -unsaturated carbonyl compounds, β -haloketones or with ketones. Many reagents have been reported in the literature for this condensation including BF_3 -etherate,⁶ polyphosphoric acid,⁷ NaBH_4 ,⁸ SiO_2 , MgO/POCl_3 ,⁹ $\text{Yb}(\text{OTf})_3$,¹⁰ and acetic acid under microwave conditions.¹¹ Recently, these condensations have been reported even in an ionic liquid medium.^{12,13} However, many of these methodologies are associated with several shortcomings such as long reaction times, harsh reaction condi-

tions, low product yields, occurrence of several side products, and difficulty in recovery and reusability of the catalysts. Moreover, some of the reagents employed are very expensive.

Recently considerable attention has been devoted to heterogeneous organic transformations utilizing inorganic solid acids.¹⁴ Generally, heterogeneous catalysts offer several advantages such as mild reaction conditions, high selectivity, high throughput and ease of work-up procedures. Among the various solid acid catalysts investigated, sulfated zirconia has attracted much attention recently because of its super-acidity, non-toxicity and low cost.^{15–21} Sulfated zirconia catalyzes many reactions under very mild conditions in the vapor phase as well as in the liquid phase. It is finding applications in the preparation of large volume chemicals, especially in the petrochemical industry for light alkane isomerization and alkylation reactions. Excellent articles can be found in the literature on the industrial applications of zirconia solid superacid catalysts.^{15,18,21}



Scheme 1.

Keywords: *o*-phenylenediamine; benzodiazepines; superacid; sulfated zirconia.

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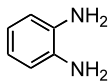
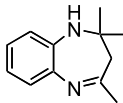
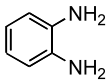
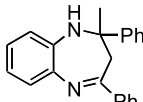
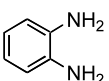
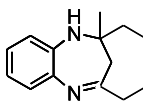
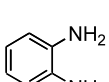
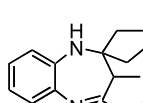
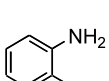

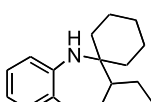
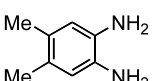
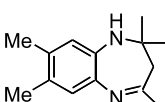
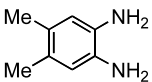
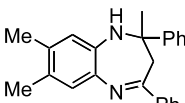
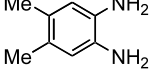
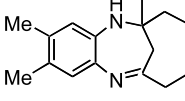
In this communication we report a facile method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by the condensation of *o*-phenylenediamine with ketones under solvent free conditions catalyzed by a solid superacid catalyst (Scheme 1).

The reactions were carried out by taking a 1:2.5 mole ratio mixture of *o*-phenylenediamine and the ketone along with a catalytic amount of sulfated zirconia in a round bottom flask with stirring at ambient conditions for the appropriate time. The reaction proceeds efficiently under ambient conditions giving good to excellent yields of 1,5-benzodiazepines. Cyclic ketones such as cyclohexanone also reacted effectively to produce the corresponding fused ring benzodiazepines. The results are summarized in Table 1. Completion of the reaction was monitored by TLC; NMR and GC–MS were used for analysis of the products. After completion of the reaction, 10 ml of CH₂Cl₂ was added to the reaction mixture and the catalyst was recovered by

filtration. The organic layer was concentrated and the product was purified by silica gel chromatography (60–120 mesh) being eluted by an ethyl acetate and *n*-hexane (2:8 v/v) mixture. The wet catalyst was recycled and no appreciable change in activity was noticed after a few cycles. As is evident from Table 1, the sulfated zirconia catalyzed condensation reactions give rise to excellent yields under ambient conditions in relatively short reaction times (2–3 h). We also tested the title reaction with the acidic zeolite H-ZSM-5. Although this catalyst was active for the condensation reactions, the yields were insignificant when compared to those with the sulfated zirconia catalyst, especially in the case of cyclic ketones.

In conclusion, the use of SO₄²⁻/ZrO₂ solid superacid catalyst for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamine and ketones is an environmentally benign and atom economic process. The easy work-up procedure and recyclable catalyst

Table 1. Condensation of *o*-phenylenediamine with various ketones under solvent free conditions catalyzed by sulfated zirconia. All the reactions were completed in 2–3 h

Entry	Diamine	Ketone	Product	Yield (%)
1		CH ₃ COCH ₃		94
2		CH ₃ COPh		96
3		CH ₃ COCH ₂ CH ₃		91
4		CH ₃ CH ₂ COCH ₂ CH ₃		84
5				80
6		CH ₃ COCH ₃		94
7		CH ₃ COPh		93
8		CH ₃ COCH ₂ CH ₃		91

makes this methodology attractive for large-scale operations.

Preparation of the catalyst. Zirconium hydroxide was prepared from an aqueous solution of zirconium oxychloride by the addition of dilute NH_4OH . About 25 g of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (Aldrich, GR Grade) was dissolved in doubly distilled water; the pH of the resulting solution was 2. To this solution, dilute aqueous ammonia was added drop-wise from a burette with vigorous stirring until the pH of the solution reached 8. The precipitate obtained was washed with distilled water several times until free from chloride ions and then dried at 393 K for 24 h. The sample thus obtained was ground to a fine powder and immersed in an 0.5 M H_2SO_4 solution (30 ml) for 30 min. Excess water was evaporated on a water bath and the resulting sample was oven dried at 393 K for 12 h and calcined at 873 K for 4 h. The X-ray powder diffraction analysis of the sample revealed the presence of tetragonal zirconia and XPS measurements confirmed a highly stabilized zirconia sulfate species.^{22,23}

Acknowledgements

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