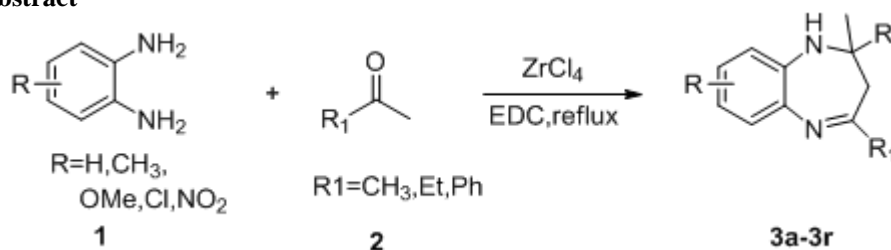


## Synthesis of 1, 5-benzodiazepines catalyzed by Zirconium tetrachloride (ZrCl<sub>4</sub>)

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### Graphical abstract



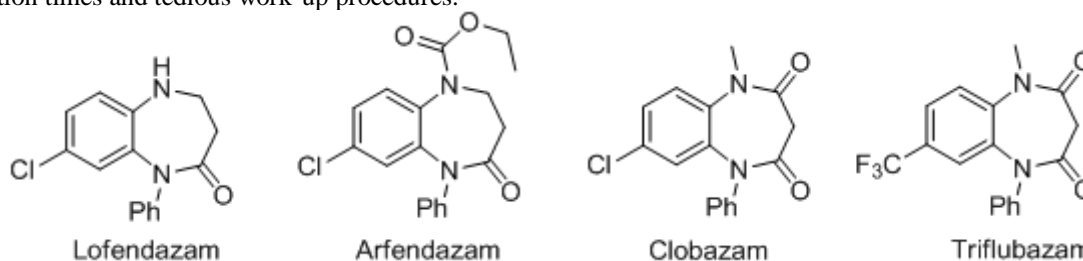
**Abstract:** A simple and efficient method for the synthesis of 2, 3-dihydro-1H-1, 5-benzo diazepines have been developed using zirconium tetrachloride as catalyst. A variety of carbonyl compounds and ortho-phenylenediamines were reacted very well in this condensation reaction. All the reactions were carried out at EDC reflux conditions.

**Keywords:** Carbonyl compounds, OPD, ZrCl<sub>4</sub>, EDC, benzodiazepines,

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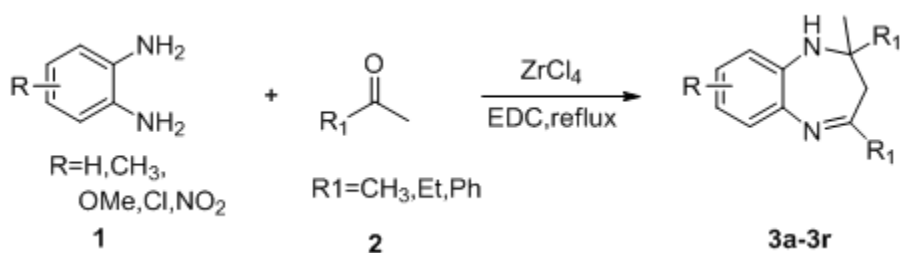
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The condensation reactions are occupying top position in organic and medicinal chemistry for their high degree of atom economy. 2,3-Dihydro-1H-1,5-benzodiazepines are ranked one of the most powerful tools for the synthesis of complex heterocyclic scaffolds drug discovery program.<sup>1</sup> Moreover, benzodiazepines are valuable synthones used for the preparation of various compounds with wide range of applications. Thus, 1,5-benzodiazepines attracts researchers as well as academicians. Hence, several methods have been reported in the literature, for their preparation using various catalysts and protocols.<sup>2-4</sup> Unfortunately, many of the reported methods suffers from drastic reaction conditions, low yields, expensive reagents, several side reactions, long reaction times and tedious work-up procedures.



Figures-1

Hence, there is a need to development, a simple and efficient methodology for synthesis of 1,5-benzodiazepines and it is an active ongoing research area for further improvement towards milder reaction conditions and high yields. Zirconium tetrachloride [ZrCl<sub>4</sub>] is known in the literature as mild and efficient catalyst for various organic transformations.<sup>5</sup> As part of our ongoing program towards developing new synthetic methodologies, herein, we wish to report, our results on the condensation of acetone and acetophenone with and ortho-phenylenediamine and substituted ortho-phenylenediamines to afford, the corresponding 1,5-benzodiazepine derivatives using zirconium tetrachloride in catalytic amount (10 mol%) at ethylene dichloride reflux conditions, as shown in the scheme-1.



Scheme-1

In a typical experiment, ortho-phenylenediamine (OPDA) (1mmol) was treated with an excess amount of acetone (3 mmol) in presence of the catalyst zirconium tetrachloride (10% mol) for a period of 2h at ethylene dichloride reflux to afford the corresponding product, 2,3-dihydro-1H-1,5-benzodiazepines in excellent yields (82%). The reaction was carried out at room temperature but the conversion was very poor by TLC observation, then we opted reflux condition.

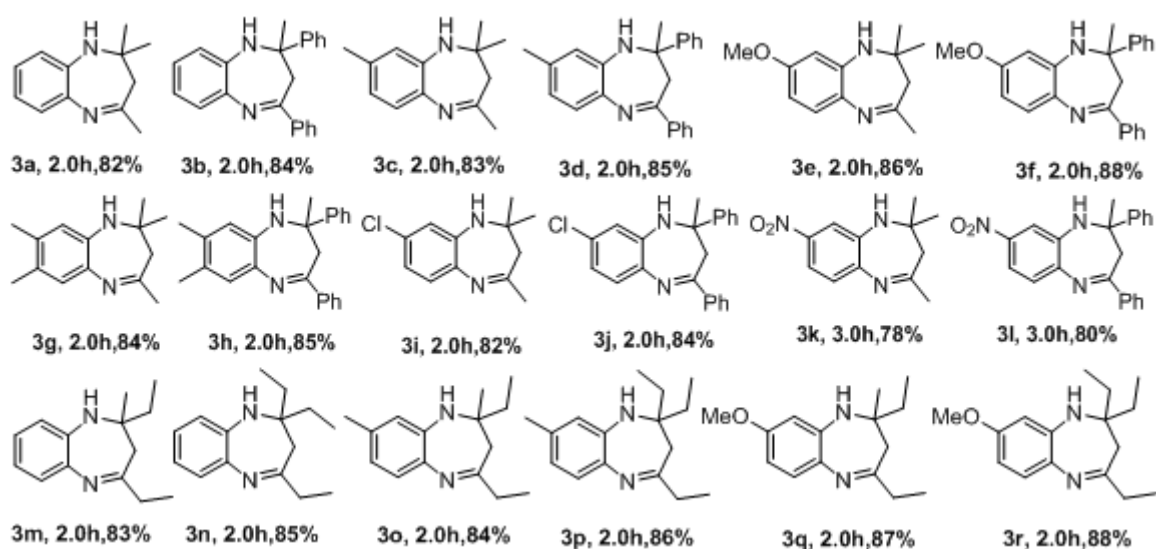


Figure-2

Encouraged by the results obtained with OPD and acetone, we have extended the scope of condensation reaction possibility to substituted ortho-phenylenediamines with 2-butanone, 3-pentanone and acetophenone. All the reactions were completed within 2 hours of reaction time with very good yields, whereas, in the case of nitro-OPD was refluxed for 3 hours. All the products are neat and yields also very good (78-88%) and confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR and mass spectroscopy analysis and compared with literature reports. The complete results are summarized in the figure-2.

In conclusion, we have developed an improved and efficient method for the synthesis of 2,3-dihydro-1H-1,5-benzodiazepines in excellent yields. Zirconium tetrachloride was proved as mild, moisture stable and highly efficient catalyst for this condensation. All the reactions were carried out at room temperature. The simple work-up procedure, mild reaction conditions and the generality of this protocol will be superior over existing methods to cater the needs of academia as well as pharmaceutical industry.

#### Experimental Section:

**General methods:** Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. <sup>1</sup>H NMR spectra were recorded on Gemini-200 spectrometer in CDCl<sub>3</sub> using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

**General procedure;** To a stirred mixture of ortho-phenylenediamine (1 mmol) and ketone compound (3mmol) in ethylenedichloride (10 mL) was added the catalyst zirconium tetrachloride (10% mol). The resulting reaction

mixture was stirred at reflux for appropriate time (mentioned in the table-1). The completion of reaction was confirmed by thin layer chromatography (TLC). The reaction mixture was diluted by adding ethyl acetate (30 mL) and washed with water, brine finally dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The obtained crude products were purified by column chromatography (on silica gel 60-120 mesh), while eluting with ethyl acetate-hexane mixture in 4:6 ratio. The pure products were confirmed by their <sup>1</sup>H NMR, IR and mass spectroscopy analysis.

#### **Acknowledgement:**

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#### **References:**

- [1]. (a) Landquist, J. K.; Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*, Pergamon, Oxford, 1984, 1, 166.; (b) Mazimba, O.; Molefe, C. S. T. *Int. J. Chem. Studies*. **2015**, 3, 3, 46.; (c) Sternbach, L. H. *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 34.
- [2]. (a) Herbert, J. A. L.; Suschitzky, H. *Perkin Trans-1*. **1974**, 2657.; (b) Morales, H. R.; Bulbarello, A.; Contreras, R. *Heterocycles*. **1986**, 24, 135.; (c) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, 42, 3193.
- [3]. (a) Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Thomas, D.; Lahoti, R. J.; K. V. Srinivasn, K. V. *Tetrahedron Lett.* **2003**, 44, 1835.; (c) Chen, W. Y.; J. Lu, J. *Synlett*. **2005**, 8, 1337.
- [4]. (a) Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun.* **1999**, 29, 1941.; (b) Balakrishna, M. S.; B. Kaboudin, B. *Tetrahedron Lett.* **2001**, 42, 1127.; (c) Minothora, P.; Julia, S. S.; Constantinos, A. T. *Tetrahedron Lett.* **2002**, 43, 1755.; (d) Kaboudin, B.; Navae, K. *Heterocycles*. **2001**, 55, 1443.
- [5]. (a) Smitha, G.; Srivari, C.; Reddy, C. S. *Synthesis*. **2008**, 6, 829.; (b) Tinnis, F.; Lundberg, H.; Kivijarvi, T.; Adolfsson, H. *Org. Synth.* **2015**, 92, 227.