

# BORIC ACID CATALYZED CONVENIENT SYNTHESIS OF 2,3-DIHYDRO-1H-1,5-BENZODIAZEPINES IN WATER UNDER MILD CONDITIONS

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## ABSTRACT

A convenient method for the 2,3-dihydro-1H-1,5-benzodiazepines from cyclocondensation of o-phenylenediamine (OPD) and enolizable ketones using boric acid as a green catalyst in water is described. The corresponding 2,3-dihydro-1H-1,5-benzodiazepines were obtained in excellent yield at room temperature (25 °C). Short reaction time, ecofriendly and environmentfriendly catalytic system are the most acceptable features of the present method.

**Key words:** 2,3-dihydro-1H-1,5-benzodiazepines, Boric acid, o-phenylenediamines, cyclocondensation, enolizable ketones, aqueous medium.

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## INTRODUCTION

Benzodiazepines are pharmacologically very important compounds and widely used as anticonvulsant, antianxiety, analgesic, sedatives, antidepressive and hypnotic activities<sup>1-5</sup>. In addition, 1,5-benzodiazepines are used as starting materials for the synthesis of various heterocyclic ring compounds.<sup>6-9</sup> Due to the widespread applications of benzodiazepines, the synthesis involving inexpensive and environmentally safe catalytic systems is the great challenge.

Several methods were documented for the synthesis of 1,5-benzodiazepines which include the condensation of o-phenylenediamines (OPD) with  $\alpha$ ,  $\beta$ -unsaturated compounds<sup>10</sup>,  $\alpha$ -haloketones or with ketones<sup>11</sup> catalyzed by  $\text{BF}_3 \cdot \text{OEt}_2$ <sup>12</sup>,  $\text{NaBH}_4$ <sup>13</sup>, Polyphosphoric acid on  $\text{SiO}_2$ <sup>14</sup>,  $\text{MgO-POCl}_3$ <sup>15</sup>,  $\text{Yb}(\text{OTf})_3$ <sup>16</sup>,  $\text{Sc}(\text{OTf})_3$ <sup>17</sup> ionic liquids,<sup>18</sup> acetic acid-MWI,<sup>19</sup> NBS,<sup>20</sup>  $\text{Ga}(\text{OTf})_3$ ,<sup>21</sup> and  $\text{ZrCl}_4$ .<sup>22</sup>

However, despite their potential utility, many of these methods suffer from drawbacks such as relatively low yield,<sup>12,13</sup> high reaction temperature,<sup>14</sup> use of expensive reagents,<sup>16,17,23</sup> and long reaction time<sup>24</sup>. Therefore, the development of mild and efficient would extend the scope of this conversion. Use of a catalytic quantity of green solid acids which could be removed from the reaction mixture easily, avoiding expensive and toxic reagents, could be useful for this purpose.

Boric acid is a safe chemical and catalyzes the various synthetically valuable transformations including conjugate addition of aliphatic thiols, dithiols and aromatic thiols to electron deficient olefins,<sup>24</sup> synthesis of amides from carboxylic acid<sup>25</sup> and chemoselective esterification of alpha-hydroxy carboxylic acid.<sup>26</sup>

In addition, reactions in water have received considerable attention due to environmental safety reasons. Water is cheapest, non-toxic and abundant chemical in nature. It has high cohesive energy density (CED) and dielectric constant as compared to organic solvents. It has been utilized for large number of organic reactions.<sup>27,28,29</sup>

## 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. <sup>1</sup>H NMR spectra were recorded on 300 MHz spectrometer  $\text{CDCl}_3$  using TMS as an internal standard.

Purity of the compounds was checked by TLC,  $^1\text{H}$  NMR, spectra and by comparison with authentic samples.<sup>13-17</sup>

#### A general procedure for the synthesis of 2,3-dihydro-1*H*-1, 5-benzodiazepines:

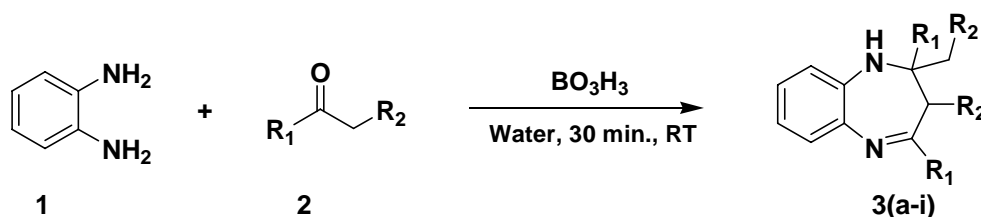
The mixture of enolizable ketone (5 mmole), *o*-phenylene diamine (2.5 mmole) and  $\text{B}(\text{OH})_3$  (10 mole%) in water (3ml) was stirred at room temperature for 30 mins. Completion of reaction was confirmed by using TLC technique. After completion of the reaction, reaction mixture was filtered. The solid obtained was purified by recrystallization in methanol.

In conclusion, we have developed green protocol for synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by cyclocondensation of OPD and enolizable ketones using boric acid. The procedure presented here is simple, general and environmentfriendly for various enolizable ketones involving water as a green solvent.

### RESULT AND DISCUSSION

Herein, we wish to report a simple, environmentally benign and efficient method for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from the cyclocondensation of *o*-phenylenediamine (OPD) and enolizable ketones using boric acid as a 'green' acid catalyst in water at room temperature ( $25^\circ\text{C}$ ).

When attempts were made to carry out the model cyclocondensation of *o*-phenylenediamine(OPD) and acetophenone in presence of boric acid under solvent free condition, formation of 2,3-dihydro-1*H*-1,5-benzodiazepines '3e' was observed with low yield (35%) after 2 hr. stirring at room temperature. The TLC of the reaction mixture (solvent system: pet. Ether/ethyl acetate = 4.5:0.5) indicated the presence of starting materials. However reaction in water shows excellent product yield (99%). This clearly indicated the role of water in the present reaction. Thus we have used the optimized reaction conditions to examine the generality of the reaction. Various aliphatic and aromatic enolizable ketones underwent smooth cyclocondensation with OPD. The nature of the substituents on the aromatic ketones did not show any effect on the rate of the reaction and yield of the 2,3-dihydro-1*H*-1,5-benzodiazepines products (Figure 1). All products were known compounds and can be confirmed by comparing physical constants, spectral data with those of reported in literature.<sup>6-10</sup>



**Figure 1:** **3a:**  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{H}$ ; Yield = 91% (5.0 hrs., 77%<sup>21</sup>); **3b:**  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{CH}_3$ ; Yield = 98% (8.5 hrs., 78%<sup>21</sup>); **3c:**  $\text{R}_1\text{R}_2 = \text{Cyclohexyl}$ ; Yield = 85%; **3d:**  $\text{R}_1\text{R}_2 = \text{Cyclopentyl}$ ; Yield = 90% (14.0 hrs., 68%<sup>21</sup>); **3e:**  $\text{R}_1 = \text{C}_6\text{H}_5$ ;  $\text{R}_2 = \text{H}$ ; Yield = 99% (12.0 hrs., 81%<sup>21</sup>); **3f:**  $\text{R}_1 = 4\text{-ClC}_6\text{H}_4$ ;  $\text{R}_2 = \text{H}$ ; Yield = 89% (10.0 hrs., 90%<sup>21</sup>); **3g:**  $\text{R}_1 = 4\text{-BrC}_6\text{H}_4$ ;  $\text{R}_2 = \text{H}$ ; Yield = 74% (16.0 hrs., 76%<sup>21</sup>); **3h:**  $\text{R}_1 = 4\text{-OHC}_6\text{H}_4$ ;  $\text{R}_2 = \text{H}$ ; Yield = 80%; **3i:**  $\text{R}_1 = 4\text{-IC}_6\text{H}_4$ ;  $\text{R}_2 = \text{H}$ ; Yield = 82% (12.0 hrs., 55%<sup>21</sup>).

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I would feel more optimistic about a bright future for man if he spent less time proving that he can outwit Nature and more time tasting her sweetness and respecting her seniority.

—Elwyn Brooks White, *Essays of E.B. White*, 1977