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# A new green approach to 2,3–Dihydro-1H-1,5 –benzodiazepines

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**ABSTRACT**

Reaction of some diamines and ketones in the presence of catalytic amount of dodecylbenzene sulfonic acid leads to the formation of 2,3–dihydro -1H-1,5-benzodiazepines in good yields. It seems that dodecylbenzene sulfonic acid has two roles: first it acts as a surfactant to dissolve starting materials in water, and second it acts as an acidic catalyst to activate carbonyl groups.

**Key words:** benzodiazepine, dodecylbenzene sulfonic acid, imine–enamine cyclization.

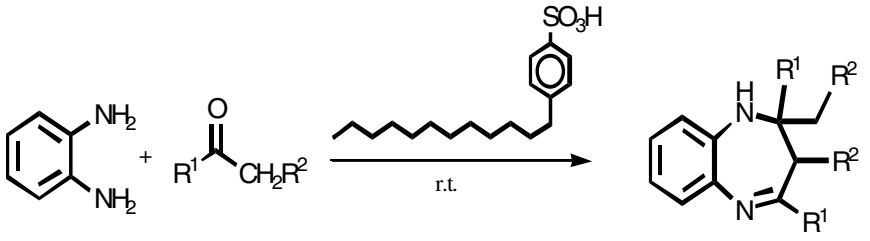
## INTRODUCTION

Benzodiazepines are very important compounds because of their pharmacological properties[1]. Despite their importance from a pharmacological point of view, comparatively few methods for the preparation of 1,5- benzodiazepines have been reported. These include condensation reaction of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds or ketones in the presence of $BF_3$–$OEt_2$, $NaBH_4$, polyphosphoric acid, $SiO_2$, MgO and $POCl_3$.[2-6] Unfortunately, many of these processes suffer from one or other limitations such as drastic reaction conditions, low yields and co-occurrence of several side reactions[7-9].

In this work, we report a facile method for the synthesis of 2,3 – dihydro–1H–1,5–benzodiazepines by the condensation of *o*-phenylenediamine with ketones in the presence of a catalytic amount of dodecylbenzene sulfonic acid in water.

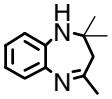
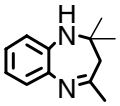
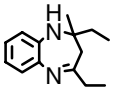
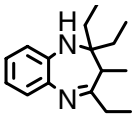
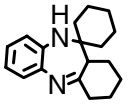
The reactions were carried out in water at room temperature for 12h by taking 1:202 mol ratio mixture of *o*-phenylenediamine and the ketone in the presence of 1 mol % dodecylbenzene sulfonic acid to give the desired products (Scheme 1).

It is noteworthy that starting from unsymmetrical ketone such as 2-butanone (entry



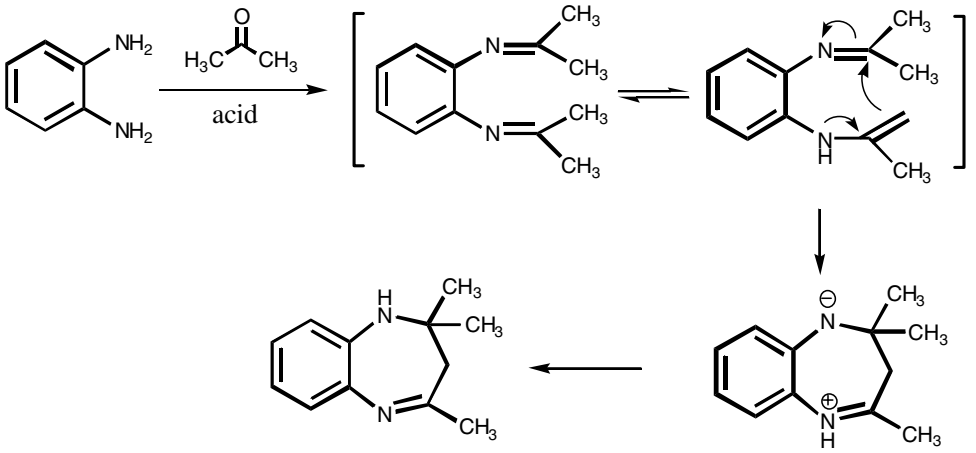

**Scheme 1.**

**Table 1: Dodecylbenzene sulfonic acid catalyzed formation of 2,3 – dihydro-1H-1,5–benzodiazepines**

| Entry | Ketone | Product | Yield (%) |
|---|---|---|---|
| 1 | $CH_3COCH_3$ |  | 82 |
| 2 | $PhCOCH_3$ |  | 80 |
| 3 | $CH_3COCH_2CH_3$ |  | 75 |
| 4 | $CH_3CH_2COCH_2CH_3$ |  | 85 |
| 5. |  |  | 78 |

3), the ring closure occurs selectively only from one side of carbon skeleton yielding a single product. All products were characterized by comparison of their melting point and $^1$H- NMR spectra with those of authentic samples.

For example, in $^1$H–NMR spectrum of 2, 2, 4–trimethyl-2,3–dihydro-1H- benzodiazepine (entry 1) in $CDCl_3$ , the $CH_3$ groups showed two singlet at δ=1.34 (6H) and 2.34 (3H) ppm. The $CH_2$ and NH groups appeared at δ= 2.26 (2H) and 3.46 (1H) ppm, respectively. The aromatic protons appeared at δ=6.61-7.28 (4H) ppm, as expected.




**Scheme 2.**

The mechanism of the reaction 2-6 probably involves an intramolecular imine–enamine cyclization as shown in Scheme 2.

In conclusion, a mild and green method has been developed for the synthesis of 2,3–dihydro -1H -1,5–benzodiazepines.

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