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# SYNTHESIS OF FUSED [1, 4] DIAZEPINES BY BASE CATALYSED CONDENSATION OF 1, 2-DIAMINES WITH CARBONYL COMPOUNDS

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diazepines,
1, 2-diamines,
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## ABSTRACT

Based on the principle of base catalyzed condensation reaction of 1, 2-diamines with carbonyl compounds, an efficient method for the synthesis of fused 1, 4-diazepines was developed. High yields were obtained for both electron-releasing as well as electron-withdrawing substituted 1, 4-diazepine derivatives by the mentioned method.

**INTRODUCTION:** Compounds containing diazepine moieties are of significant interest in medicinal & pharmaceutical research due to their important biological activities [1]. Besides being core unit of commercial drugs such as Diazepam, Oxazepam, Laurazepam, Anthramycin & Mazhethramycin; there are numerous Diazepines that are described with anti-inflammatory, anticancer, anti-HIV, antibacterial, herbicidal and PAF receptor antagonist activities [1, 2, 3]. Investigators are motivated to continuously develop strategies for producing new diazepine-based compounds due to the surprisingly vast biological activities exhibited by diazepines [1].

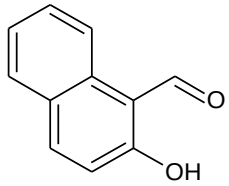
In this context cross-condensation reactions have been of great value as they provide robust route to install desired substitution in diazepines. Recently many cross-condensation reactions have been reported for the synthesis of fused-diazepines. However, a large number of the modified methods reported in the literature, suffer from several drawbacks such as the use of a large amount of catalysts, unsatisfactory product yields and critical product isolation procedures.

The objective of current research article is to develop an efficient & practically useful procedure for the synthesis of fused-diazepines.

The common procedure for the synthesis of these compounds is a one pot condensation between *o*-phenylenediamines and carbonyl compounds.[4] In the present research, base catalysed condensation of 1, 2-diamines with 2-hydroxy-1-naphthaldehyde is attempted to obtain the fused-diazepines with desired substitutions. The different derivatives are shown in **Figure 1**. The Infra-red spectra of 2-hydroxy-1-naphthaldehyde suggests that hydroxyl group at 2-position of carbaldehyde is present as ketone, due to resonance (No broad peak at 3400-3600 $cm^{-1}$).

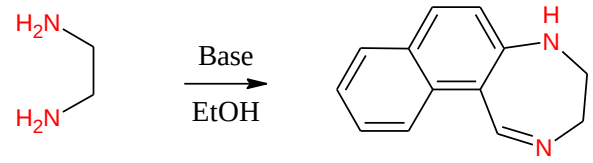
Thus, the hypothesis for the reaction remains same, that is, base catalysed one pot condensation of 1, 2-diamines with carbonyl compounds. The principle of reaction is similar to Friedlaender Synthesis [5], which is utilized with modifications in the reactants. Similarly different derivatives were synthesised using substituted reactants are shown in **Figure 2**.

**FIG. 1**



2-hydroxynaphthalene-1-carbaldehyde

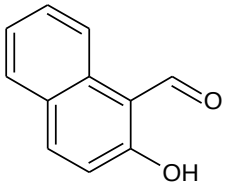
**SCHEME 1**




2-hydroxynaphthalene-1-carbaldehyde 1,2-diamine 4,5-dihydro-3*H*-naphtho[2,1-*e*][1,4]diazepine

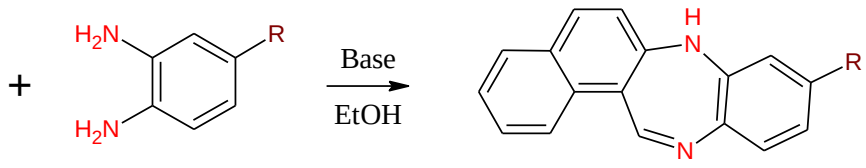
**6a**

**FIG. 2**



2-hydroxynaphthalene-1-carbaldehyde

**SCHEME 2**




2-hydroxynaphthalene-1-carbaldehyde substituted 1,2-phenylenediamine 5H-naptho[2,1-e]benzo[b][1,4]diazepi

**SYNTHETIC ROUTE FOR DERIVATIVES**

Where; R = H (**6b**), $CH_3$ (**6c**), Cl (**6d**), $NO_2$ (**6e**)

## MATERIALS AND METHODS:

**General:** Melting points were determined on a "Veego VMP-I" melting point apparatus and were uncorrected. FTIR spectra were taken on "Jasco FT/IR-410", using KBr pressed pellet technique. The 1H-NMR spectra were run on a Bruker spectrometer in $CDCl_3$ (300 MHz) using tetramethylsilane as internal standard. Chemicals were purchased from Aldrich, Himedia and Fluka. All the reactants were identified by comparison of melting points with those reported in the literature. The year of Experimentation was 2011, at the Appasaheb Birnale College of Pharmacy, Sangli, Maharashtra, India.

**General procedure for the base catalysed condensation of 1, 2-diamines & 2-hydroxy-1-naphthaldehyde**: A mixture of 2-hydroxy-1-naphthaldehyde (1.72gm, 10 mmol), aliphatic or aromatic 1,2-diamine **1–5** (10 mmol) and triethylamine (4.04ml, 40 mmol) in 98 % EtOH (50 mL) was heated on heating mantle under reflux for 3.5 hrs at 78-80°C. Then the reaction mixture was cooled and the formed solid was collected by filtration and dried. The completion of reaction was monitored by TLC using 'Toluene: Acetone" (5: 4) as mobile phase. Then the compounds were filtered and washed twice with ethanol (2 × 10 mL).

**4, 5-dihydro-3H-naphtho [2, 1-e] [1, 4] diazepine** (**6a**): Greenish-yellow solid, m.p. 185°C, $R_f$ 0.53; IR ν: 3371, 3285, 3050, 2933, 1643, 1541, 1490, 1358, 1206, 835, 742 $cm^{-1}$, 1H-NMR (CDCl3, 300 MHz): δ 8.8 (s, 1H, NH), 7.8 (d, 1H), 7.5-7.6 (dd, 1H), 7.36 (t, 1H), 7.26 (s, 1H), 6.84 (d, 1H), 3 (t, 2H, -CH2-), 2.32 (m, 2H, -$CH_2$-) ppm.

**5H-naphtho [2, 1-e] benzo [b] [1, 4] diazepine** (**6b**): Yellow solid, m.p. 170°C, $R_f$ 0.78; IR ν: 347 3, 3374, 3046, 2922, 1611, 1561, 1384, 817,754 $cm^{-1}$, 1H-NMR (CDCl3, 300 MHz): δ 9.44 (s, 1H, NH), 8.18 (d, 1H), 7.86-7.75 (dd, 2H), 7.54 (t, 1H), 7.3-7.4 (m, 2H), 7.26 (s, 1H), 7.1-7.2 (complex, 2H), 6.84 (m, 2H) ppm.

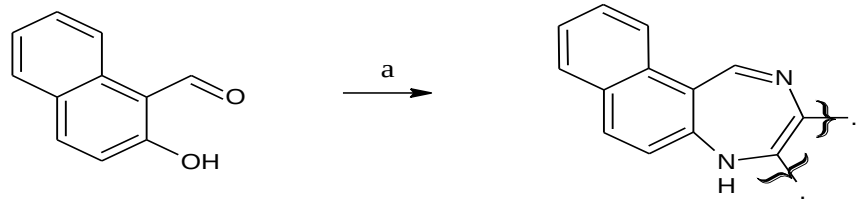
**7-methyl-5H-naphtho[2, 1-e] benzo [b] [1, 4]diazepine** (**6c**): Orange solid, m.p. 160°C, $R_f$ 0.8; IR ν: 3395, 3326, 3223, 3022, 2977, 1615, 1541, 1384, 828,753 $cm^{-1}$, 1H-NMR (CDCl3, 300 MHz): δ 9.42 (s, 1H, NH), 8.2 (d, 1H), 7.75-7.84 (dd, 2H), 7.54 (t, 1H), 7.36 (t, 1H), 7.26 (s, 1H), 7.18 (d, 1H), 7.1 (d, 1H), 6.68 (d, 2H), 2.31 (s, 3H, $CH_3$) ppm.

**7-chloro-5H-naphtho[2, 1-e] benzo [b] [1, 4] diazepine** (**6d**): Brown solid, m.p. 220°C, $R_f$ 0.92; IR ν: 3417, 3055, 2922, 1620, 1309, 818, 735, 417 $cm^{-1}$, 1H-NMR (CDCl3, 300 MHz): δ 9.45 (s, 1H, NH), 8.15 (d, 1H), 7.66 (d, 1H), 7.76 (d, 1H), 7.46 (t, 1H), 7.54 (t, 1H), 7.16-7.3 (complex, 2H), 7.05 (d, 1H), 6.69 (d, 1H) ppm.

**7-nitro-5H-naphtho [2, 1-e] benzo [b] [1, 4] diazepine** (**6e**): Yellowish solid, m.p. 198°C, $R_f$ 0.86; IR ν: 3473, 3346, 2923, 1634, 1582, 1317, 820, 735 $cm^{-1}$, 1H-NMR (CDCl3, 300 MHz): δ 9.37 (s, 1H, NH), 8.29 (d, 1H), 7.65 (d, 1H), 7.73 (d, 1H), 7.53 (t, 1H), 7.44 (t, 1H), 7.26-7.29 (complex, 2H), 7.03 (d, 1H), 6.74 (d, 1H) ppm.

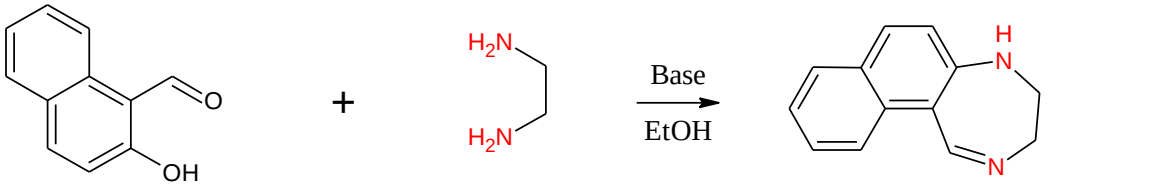
**RESULT AND DISCUSSION:** The synthesis of derivatives **6a-6e** starting from 2-hydroxy-1- naphthaldehyde has been carried out by treating it successively with 1,2-diamines **1-5** under mild basic conditions. The method leads to satisfactory yields of derivatives. Different derivatives are shown in Figure 3.

**FIG. 3: LIST OF COMPOUNDS SYNTHESISED**



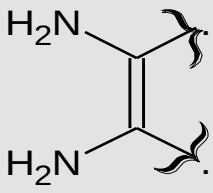
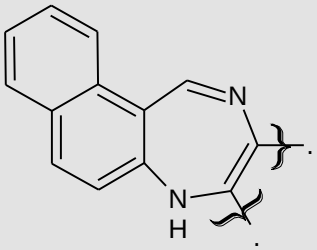
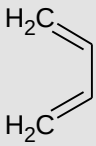
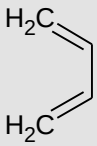
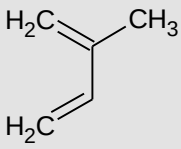
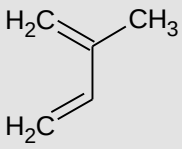
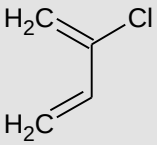
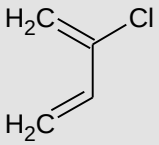
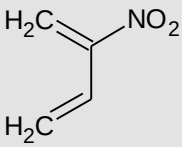
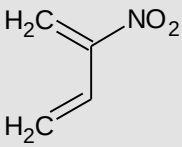

2-hydroxynaphthalene-1-carbaldehyde fused 1,4-diazepines

Scheme 1 [a] 1, 2-Diamine (**1**-**5**), $Et_3N$, EtOH reflux, 3.5hrs 78-80°C




2-hydroxynaphthalene-1-carbaldehyde 1,2-diamine 4,5-dihydro-3*H*-naphtho[2,1-*e*][1,4]diazepine

**1** **6a**

| 1, 2-Diamine | Product |
|---|---|
|  |  |
| **2**  | **6b**  |
| **3**  | **6c**  |
| **4**  | **6d**  |
| **5**  | **6e**  |

TLC was used to monitor the completion of the reaction; the structures of products were assessed by interpretation of IR and NMR spectra obtained. The spectroscopic data of IR and $^{1}$H-NMR are in agreement with the structure of fused 1, 4-diazepine derivatives [3, 4, 6, 7, 8, 9, 10].

**CONCLUSION:** The efficient, one pot synthesis of a new series of 1, 4-diazepine derivatives using triethylamine as catalyst for the condensation of 1, 2-diamines with carbonyl compounds has been achieved in this article. The results have shown that the products were synthesized in high-yields and shorter reaction times for both electron-releasing and electron-withdrawing substituted derivatives (**6c**, **6d** & **6e**); with potentially interesting biological and medicinal properties.

**ACKNOWLEDGEMENTS:** The authors wish to thank Sophisticated Analytical Instrument Facility Division, CDRI, Lucknow; for providing $H^{1}$-NMR spectral data. Authors also wish to extend their gratitude to Principal, Appasaheb Birnale College of Pharmacy, Sangli, for providing necessary facilities.

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