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An Efficient One-Pot Synthesis of 1, 5-Benzodiazepine Derivatives Catalyzed by TBAB under Mild Conditions

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Abstract: 2,3-Dihydro-1*H*-1,5-benzodiazepines were synthesized by reaction of *o*-phenylenediamine with ketones (acyclic / cyclic) under solvent free conditions in the presence of tetra butyl ammonium bromide (TBAB) in short reaction time with excellent yield.

Keywords: Tetra butyl ammonium bromide, 1, 5-Benzodiazepine, *o*-Phenylenediamine, Ketones, Short reaction time

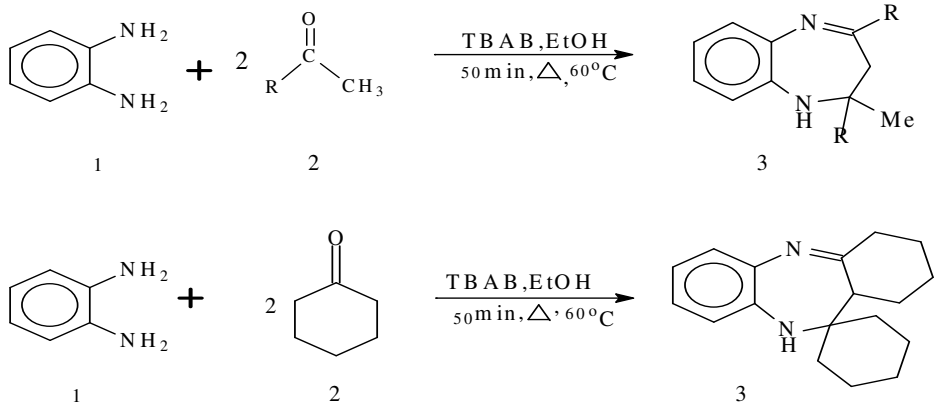
Introduction

Benzodiazepines and their derivatives are important class of nitrogen containing heterocyclic compounds because of their pharmacological properties[1]. So many members of this family are nowadays mostly used as anti-anxiety, anti-inflammatory, tranquilizing, anti-convulsant, anti-depressive, anti-bacterial, analgesic, sedative and hypnotic agents[2]. The first benzodiazepine was introduced as a drug nearly thirty years before[3]. They are also used against viral disease and cardiovascular disorder[4]. Some benzodiazepine derivatives are used in fine chemical industries such as photographical dyes for acrylic fiber[5] they are used as a valuable synthons for the synthesis of fused ring benzodiazepines class of compounds like triazolo, oxadiazolo, oxazino and furano-benzodiazepines[6] due to their wide demand they have received a great attention of different chemist. According to the literature survey several synthetic methodology have been introduced for the synthesis of benzodiazepines, these include condensation of *o*-phenylenediamine with α-β unsaturated carbonyl compounds[7], β haloketones[8] or ketones in the presence various catalyst such as BF_3OEt[9], $NaBH_4$[10], PPA- SiO_2[11], MgO-$POCl_3$[12], $Yb(OTf)_3$[13], amberlyst-15[14], $Ag_3PW_{12}O_{40}$[15], solid

super acid sulphated zirconia[16], acetic acid – under MWI[17], $AgNO_3$[18], zinc montmorilonite as catalyst at r.t[19] and ionic liquid[20,21]. However these methodologies have several disadvantages such as harsh reaction condition, long reaction time, expensive reagents, low yield, tedious workup and formation of side products. Keeping in mind in the present study we have develop a one pot synthesis of 1, 5-benzodiazepines by condensation of *o*-phenylenediamine with ketones under mild conditions catalyzed by tetrabutylammonium bromide (Scheme 1).

Experimental

A mixture of *o*-phenylenediamine (10 mmole), ketones (20 mmole) and phase transfer catalyst TBAB (catalytic amount) was reflux for 50 min in ethyl alcohol (10 mL) at 60 ^oC, after completion of reaction (monitored by TLC) the reaction mixture was cooled and poured on crushed ice, extracted from ethyl acetate (30 mL) and washed with water and brine (20 mL each). The solvent was removed by distillation under reduced pressure. The crude product was purified by column chromatography (eluent, ethyl acetate – pet-ether). The corresponding 1, 5 benzodiazepines and fused ring benzodiazepine derivatives were obtained in 85-95% yield.



Scheme 1

Characterizations

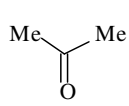
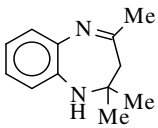
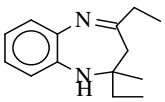
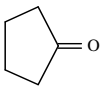
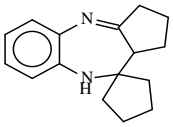
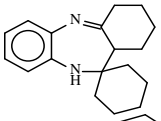
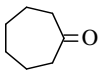
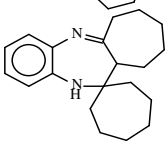
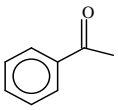
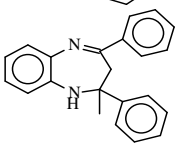
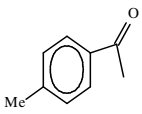
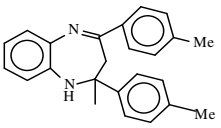
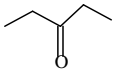
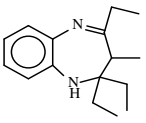
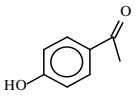
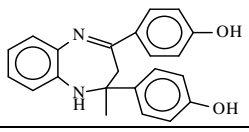
All H^1 NMR spectra were recorded in $CDCl_3$ on a Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetra methyl silane. Infrared spectra were recorded on a PerkinElmer infra red spectrophotometer using KBr discs, TLC was performed on silica gel coated aluminum plates using ethyl acetate and pet ether (3:7 v/v) as eluent, melting points were determined on an electronic melting point apparatus and were uncorrected.

Results and Discussion

Tetrabutylammonium bromide (TBAB) is a cheap and readily available reagent it efficiently catalyze the condensation of ketones with *o*-phenylenediamine at 60 ^oC, under mild conditions, in short reaction time (50 min) with excellent yield of the product. In the present study, *o*-phenylenediamine, cyclic /acyclic ketones and catalytic amount of TBAB were reflux at 60 ^oC in 10 mL ethyl alcohol after completion of the reaction (monitored by TLC) the series of corresponding1,5 benzodiazepines and fused ring benzodiazepine derivatives were

obtained in 85-95% yield. Whereas the yield is comparatively lower in presence of other PTC such as tricaprilmethylammonium chloride (Aliquat-336) and triethylbenzyl-ammonium chloride (TEBA) *etc*. The results are summarized in Table 1. The structures of the synthesized compounds were established by their mp, IR and H^1 NMR spectroscopy. The ^{1}H NMR and IR spectrum of selected compounds (**3a, 3d, 3f, 3g and 3i**) obtained are shown in the Figures 1 -7 respectively.

Table 1. TBAB-catalyzed synthesis of 1, 5-benzodiazepines under mild conditions

Entry	Ketone{2}	Products{3}	Yield, %	mp, ^{0}C
a			85	144 -145
b			86	138 -139
c			88	136 -138
d			85	138 -140
e			85	138 -140
f			95	150 -152
g			88	140 -142
h			92	142 -144
i			88	145 -147

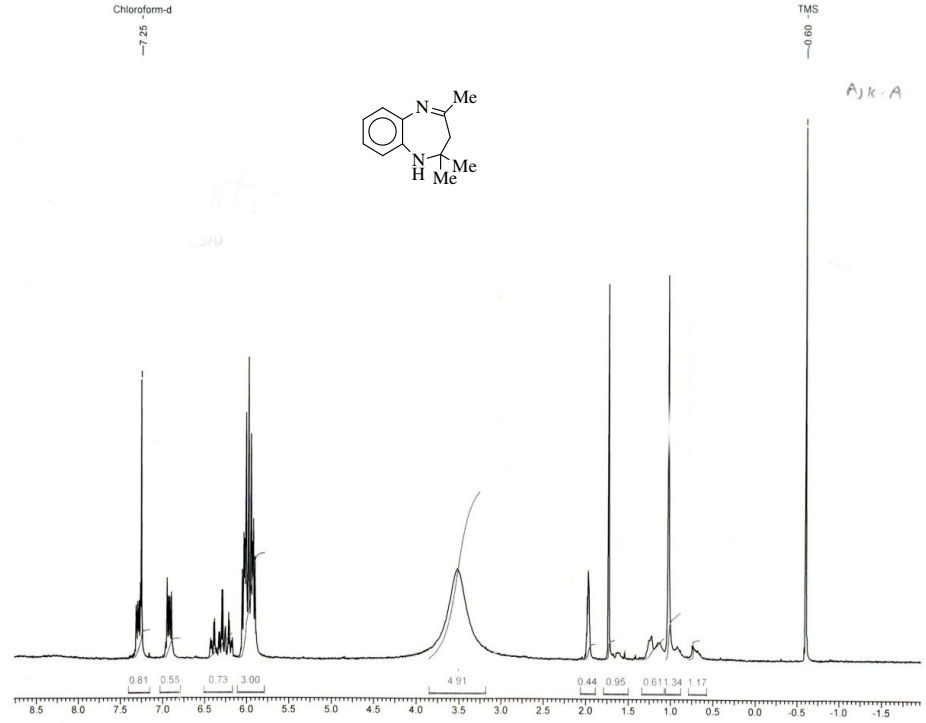


Figure 1. ^{1}H NMR spectra of (**3a**)

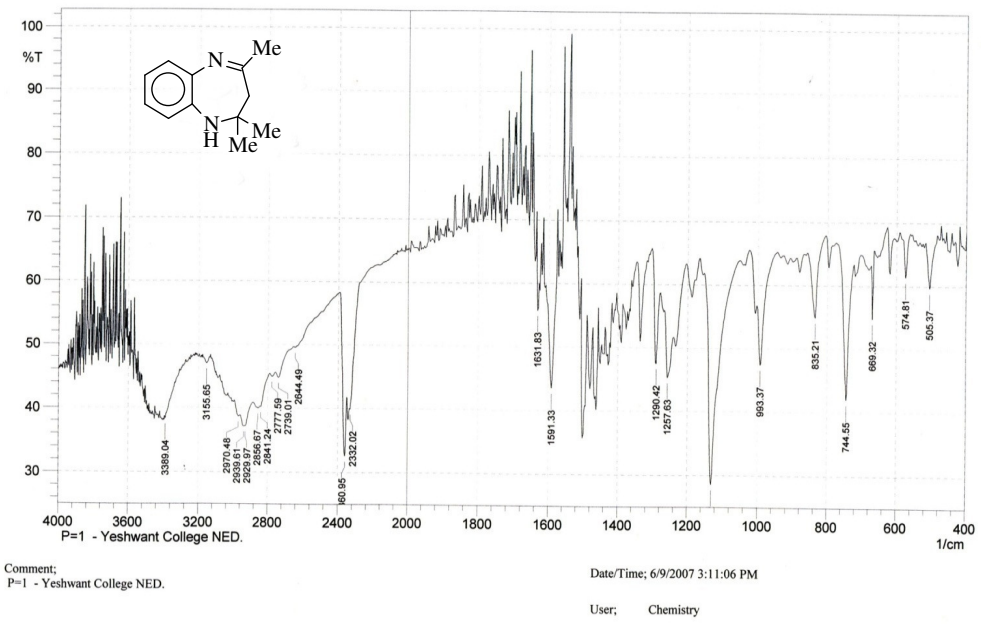


Figure 2. IR spectra of (**3a**)

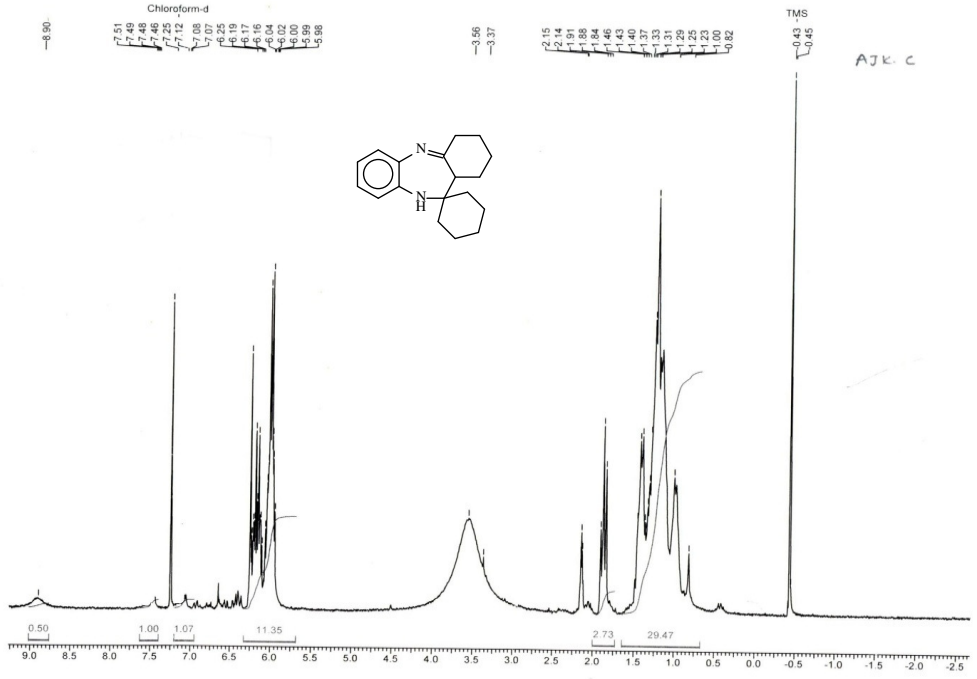


Figure 3. ^{1}H NMR spectra of (**3d**)

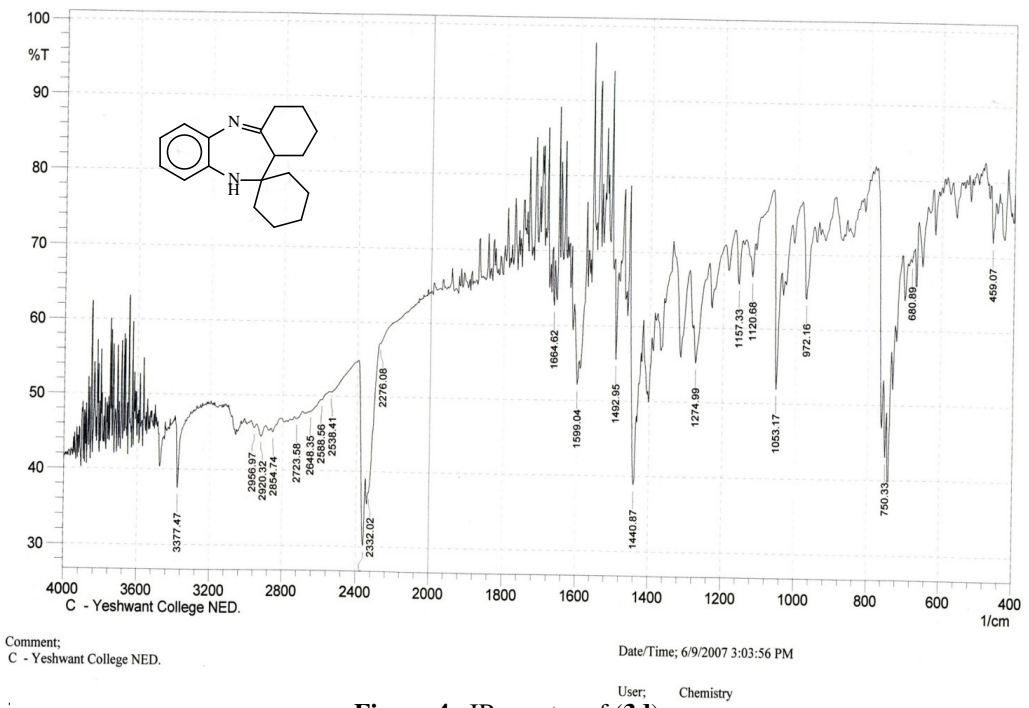


Figure 4. IR spectra of (**3d**)

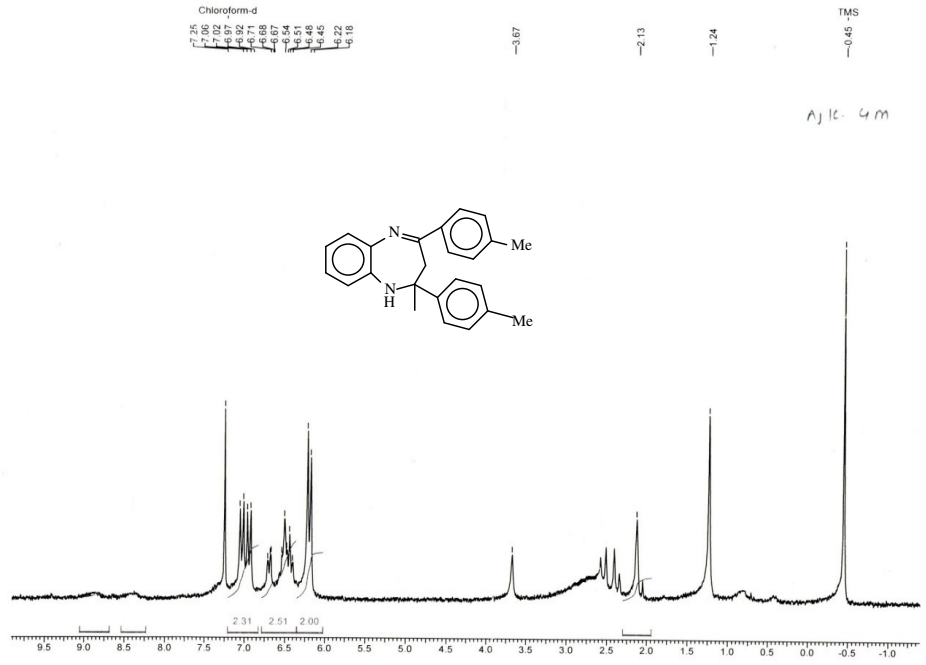


Figure 5. ^{1}H NMR spectra of (**3g**)

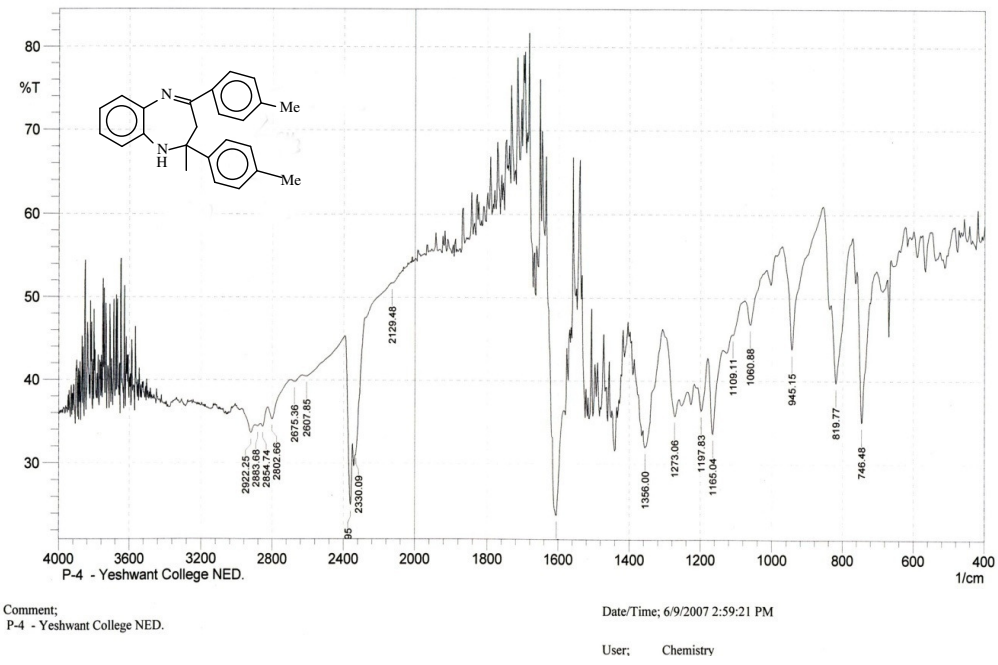


Figure 6. IR spectra of (**3g**)

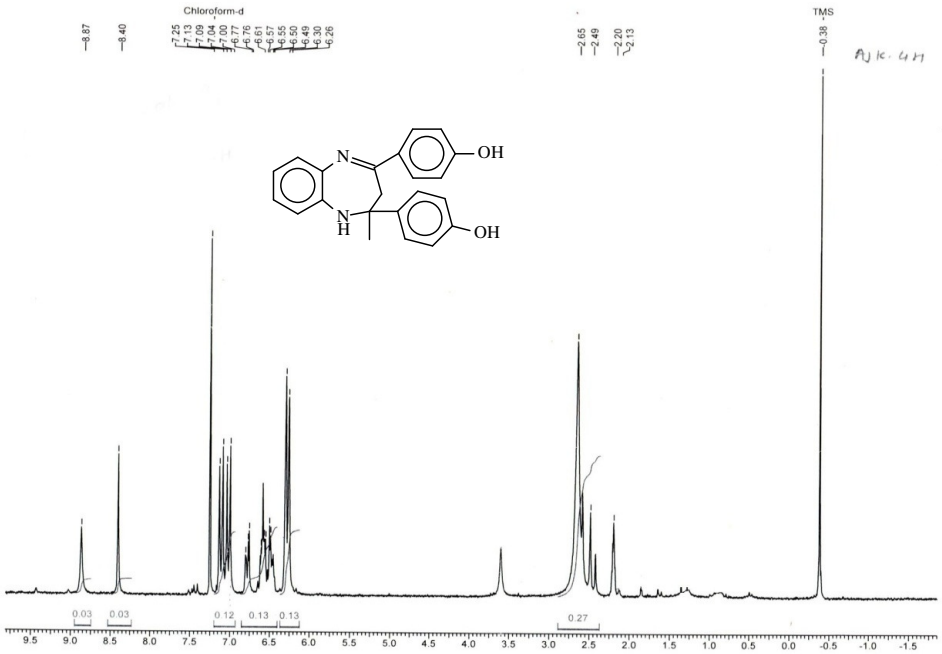


Figure7. ^{1}H NMR spectra of (**3i**)

Spectral data for selected compounds

3a. IR (KBr): 3389, 2970, 1631,1591,1470,1100,744 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 1.1 (s, 6H), 1.4 (s, 2H), 1.90 (s, 3H), 3.6 (brs, 1H), 5.9-7.0 (m, 4H); MS (m/z):188 (M^+) **3d.** IR (KBr): 3377,1664,1599,1440,750 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 0.7-1.5 (m, 16H), 1.7-2.2 (m, 3H), 3.56 (brs, 1H), 6.1-7.0 (m, 4H). **3f.** IR (KBr): 3377, 1631 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 1.34 (s, 3H), 2.2 (d, 1H, J=12.8 Hz), 2.4 (d, 1H, J=12.8Hz), 3.6 (brs, 1H), 7.7 - 7.1 (m, 14H). **3g.** IR (KBr): 2922, 1600, 1356,746 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 2.13 (s, 6H), 1.24 (s, 3H), 2.4 (d, 1H, J=6.9 Hz), 2.5 (d, 1H J= 6.9 Hz), 3.67 (brs, 1H), 6.0-6.66 (m, 4H), 6.72-7.2 (m, 8H); **3i.** IR (KBr): 3377, 1631, 1440 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 1.3 (s, 3H), 2.2 (d, 1H), 2.49 (d, 1H), 3.6 (brs, 1H), 8.4 (s,1H), 8.87 (s,1H), 6.3- 6.7 (m, 4H), 6.8 -7.2 (m, 8H)

Conclusion

We have developed a new, mild and efficient method for the synthesis of 1, 5-benzodiazepines. The workout procedure is easy, environmental friendly and inexpensive catalyst, short reaction time, reaction mild reaction conditions and in excellent yield.

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