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ZOC-Catalyzed an efficient synthesis of 1, 5-Benzodiazepines under mild conditions

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ABSTRACT

2,3-Dihydro-1H-1,5-benzodiazepines are synthesized by reaction of o-phenylenediamine with ketones (acyclic as well as cyclic) under mild and solvent free conditions in the presence of catalytic amount of zirconium oxychloride in short reaction time with excellent yield.

Keywords*:* ZOC, 1, 5-Benzodiazepine, *o*-phenylenediamine, ketones, solvent free reaction.

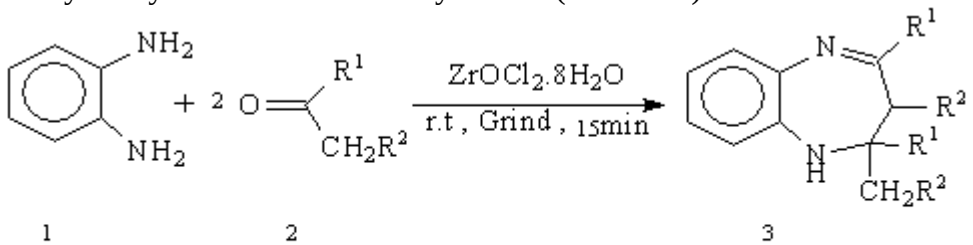
Abbreviation: ZOC(zirconium oxychloride)

INTRODUCTION

Benzodiazepines are widely used class of bioactive compounds due to their remarkable biological and pharmacological properties. [1,2] They are well documented for antianxiety, hypnotic, tranquilizing, anti-inflammatory, anticonvulsant, antifeedant, antibacterial, analgesic, sedative and antidepressive properties. [1] They are valuable synthons for the synthesis of triazolo, oxadiazolo, oxazino and furano-benzodiazepines.[3-6] Some benzodiazepine derivatives are used in fine chemical industries such as photographical dyes for acrylic fibers.[7] In view of their importance, they have received a great deal of interest by different chemist and in the literature different methods for their preparations have been introduced. These include condensation of *o*-phenylenediamine with α-β unsaturated compounds,[8] β- haloketones or ketones.[9] For their condensation purpose, many reagents have been reported such as BF_3OEt_2,[10] $NaBH_4$,[11] PPA-SiO_2,[12] MgO-$POCl_3$,[13] Yb(OTf) $_3$,[14] $AgNO_3$,[15] $Ag_3PW_{12}O_{40}$, [16] solid super acid sulphated zirconia,[17] Zirconia solid acid,[18] acetic acid – under MWI,[19] Amberlyst-15, [20] ionic liquid,[21] $SbCl_3$-Al_2O_3,[22] and Zn[L-Proline]$_2$,[23] but some of these methods are having some drawbacks such as long reaction time, harsh reaction condition expensive reagents, low yield, tedious workup and formation of side products.

Because of their important therapeutic value, better search of regent and routs are continually being developed we herein report a new reagent for the synthesis of 2,3dihydro-1*H*-1,5-

benzodiazepines by condensation of *o*-phenylenediamine with ketones under solvent free conditions catalyzed by a solid zirconium oxychloride(Scheme 1).



1 2 3

R^1, R^2 = H or Alkyl

Scheme 1

MATERIALS AND METHODS

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 Perkin Elmer Infrared 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.

General procedure for the synthesis of 1, 5-benzodiazepines

A mixture of *o*-phenylenediamine (10 mmole), ketones (20 mmole) and ZOC (catalytic amount) were ground well using mortar and pestle for 15 min., after completion of the reaction [monitored on TLC, eluent: ethyl acetate: pet. ether (3:7)], the reaction mixture was diluted with ethyl acetate, filtrate was washed with water. The solvent was removed by distillation under reduced pressure. The crude product was purified by recrystallisation using ethyl alcohol solvent, which were further purified by column chromatography.

Spectral data of the selected products

3a. IR (KBr): 3389, 2970, 1631,1591,1470,1100,744 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 1.1 (s, 6H), 1.8 (s, 2H), 2.0 (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)

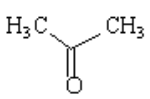
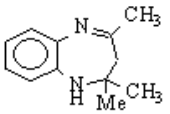
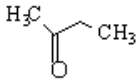
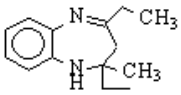
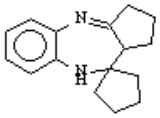
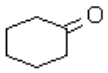
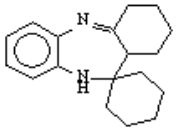
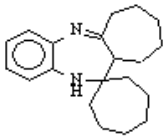
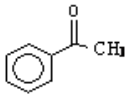
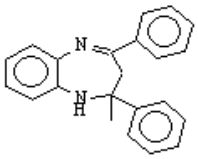
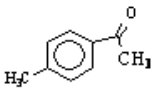
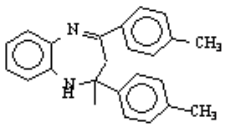
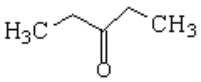
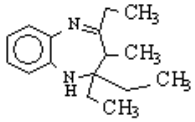
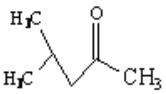
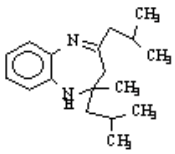
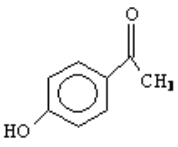
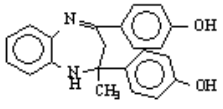
3g. IR (KBr): 2922, 1600, 1356,746 cm^{-1}; H^1 NMR ($CDCl_3$): δ= 2.13 (s, 6H), 1.24 (s, 3H), 2.4 (d, 1H, J=6.9 Hz), 2.5 (d, 1H J= 6.9 Hz), 3.67 (brs, 1H), 6.0-6.66 (m, 4H), 6.72-7.2 (m, 8H);

3j. 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)

RESULTS AND DISCUSSION

Zirconium oxychloride is a cheap and easily available reagent. It efficiently catalyze the condensation of ketones (cyclic and acyclic) with *o*-Phenylenediamine at room temperature, under solvent free conditions, in short reaction time with excellent yield of the product. *o*-Phenylenediamine (OPD), ketones and zirconium oxychloride (catalytic amount) were ground well using mortar and pestle at room temperature, the corresponding 1,5-benzodiazepine and fused ring benzodiazepine derivatives were obtained in 80-85 % yield, whereas ZrO_2 gave very low yield. Completion of the reaction was monitored by TLC.

Table1: Synthesis of 1, 5-Benzodiazepines Catalyzed by Ziconiumoxychloride under solvent- Free Conditions.

Entry	Ketone(2)	Products(3)	Yield(%)	M.P(°C)
a			80	138 -140
b			82	138 -139
c			84	136 -138
d			85	138 -140
e			85	138 -140
f			83	150 -151
g			85	140 -142
h			82	145 -146
i			80	118-119
j			82	150 -151

The results are summarized in Table 1. The structures of the products were confirmed by comparison of their IR, H^1-NMR and Mass spectroscopy data and melting points with those samples reported in the literature.

CONCLUSION

It can be summarized that it is a mild and efficient method for the synthesis of 2, 3-dihydro 1*H*, 1, 5-benzodiazepines. The work out is easy , no solvent is required, reaction time is short, reaction condition are mild and yield are excellent, same method can be applied for the synthesis of wide variety of benzodiazepines.

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