

CITRIC ACID-CATALYZED SOLVENT FREE, AN EFFICIENT ONE-POT SYNTHESIS OF 2, 3-DIHYDRO-1H-1, 5-BENZODIAZEPINE DERIVATIVES

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Abstract

2,3-Dihydro-1H-1,5-benzodiazepines are synthesized by reaction of *o*-Phenylenediamine with ketones (acyclic / cyclic) under solvent free conditions in the presence of citric acid in short reaction time with excellent yield.

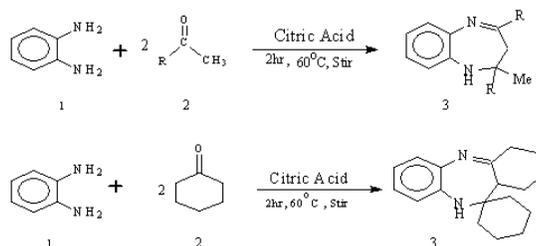
Keywords: 2, 3-Dihydro-1, 5-benzodiazepines, *o*-Phenylenediamine, ketones, Citric acid, Solvent free conditions

Introduction

Benzodiazepines and their derivatives are potentially important class of medicinally active compounds and have been widely used as anti-anxiety, tranquilizing, anti-inflammatory, anti-convulsant, anti-bacterial, analgesic, sedative, anti-depressive and hypnotic agents [1, 5]. The Benzodiazepine nucleosides have been used against viral disease, e.g., AIDS [6], cardiovascular disorder [7-9]. Some benzodiazepine derivatives are used in fine chemical industries such as photographic dyes for acrylic fiber[10], they are also utilized in the synthesis of fused ring benzodiazepines class of compounds like triazolo,oxadiazolo,oxazino and furano-benzodiazepines[11-14] and hence they have received a great deal of interest by different chemist. As per literature survey the several synthetic

methodology have been introduced, these include condensation of *o*-Phenylenediamine with α - β unsaturated carbonyl compounds[15], β haloketones [16], or Ketones in the presence of BF₃OEt [17], NaBH₄[18], PPA-SiO₂[19], MgO-POCl₃[20], Yb(OTf)₃[21], Amberlyst-15[22] and Ag₃PW₁₂O₄₀[23], solid super acid sulphated zirconia[24], acetic acid – under MWI[25], AgNO₃[26], ionic liquid[27,28] and zinc montmorillonite as catalyst at RT[29]. However some of 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 we herein develop a one pot synthesis of 1, 5-benzodiazepines by condensation of *o*-Phenylenediamine with ketones under solvent free conditions catalyzed by citric acid. (Scheme-1).

Scheme-1



Results and Discussion

Citric acid is a cheap and readily available reagent it efficiently catalyze the condensation of ketones with *o*-Phenylenediamine at 60°C, under solvent free conditions, in short reaction time (2hr) with excellent yield of the product. In the current strategy, *o*-Phenylenediamine, cyclic /acyclic ketones and catalytic amount of Citric acid were stir well, extracted with ethyl

acetate and then washed with water, the desired product of 1, 5 benzodiazepines and fused ring benzodiazepine derivatives were obtained in 75-85% yield. Completion of the reaction was monitored by TLC. The results are summarized in Table-1. The structures of the products were confirmed by their M.P, IR, Mass and H¹NMR spectroscopy data and found to

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be in agreement with the values reported in the literatures .

Conclusions

In conclusion, it can be summarized that we have develop a new, mild and efficient method for the synthesis of 1,5-benzodiazepines.The workout is easy, inexpensive catalyst, no solvent is required ,reaction conditions are mild and yield are excellent.

Experimental

All H¹ NMR spectra were recorded in CDCl₃ on a Bruker AC 200 and Bruker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetramethyl 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(uncorrected) were determined on an electronic melting point apparatus.

Table 1.Characterization data of Compounds 3a-h synthesized by Citric Acid-Catalyzed Condensation of *o*-Phenylenediamine with various Ketones under solvent free conditions

Entry	Ketone(2)	Products(3)	Yield(%)	M.P(°C)
1			75	138-139
2			80	144-145
3			82	134-138
4			85	138-140
5			75	138-140
6			78	150-152
7			80	140-142
8			82	145-144

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Typical Procedure for the synthesis of 2, 3-Dihydro-1, 5-benzodiazepines

A mixture of *o*-phenylenediamine (10 mmole), ketones (20 mmole) and Citric acid (catalytic amount) was heated to 60°C and stirred for

another 2hrs, completion of the reaction monitored on TLC.The reaction mixture was then quenched with water, extracted with ethyl acetate (2×10), the organic phase was collected, dried over Magnesium Sulfate and evaporated under reduced pressure. Column chromatography of the crude products provided the desired product 2, 3-dihydro-1, 5-benzodiazepines (3a-g) as solid substances in 75-85% yields (Scheme-1, Table-1).

Spectral data of the selected products:

3a. IR (KBr): 3389, 2970, 1631,1591,1470,1100,744 cm^{-1} ;

^1H 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} ;

^1H 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} ;

^1H 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} ;

^1H 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);

3h. IR (KBr): 3377, 1631, 1440 cm^{-1} ;

^1H 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)