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Der Pharma Chemica, 2011, 3(2): 273-276
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

One pot method for green synthesis of 1,5-benzodiazepines

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ABSTRACT

Malonic acid has been found to be an efficient catalyst for the synthesis of 2,3-dihydro-1 H -1,5-benzodiazepines from o-phenylenediamine and ketones. This method is simple, cheap, and environmentally-friendly and gives the benzodiazepines in excellent yield.

Keywords. 1,5-benzodiazepines; boric acid; solvent free condition.

INTRODUCTION

Benzadiazepines and their derivatives are very important class of bioactive compounds because of their diverse pharmacological properties [1, 2]. They are widely used as antidepressants, anti-convulsant, analgesic, hypnotic and sedative [1, 2]. Benzadiazepines are important intermediates for the synthesis of fused ring compounds such as triazolo [3], oxadiazolo and furano-benzadiazepines [4-6]. Due to such wide biological significance, the synthesis of these compounds has received a great deal of attention. Some benzodiazepine derivatives are also reported as anti-inflammatory agents [7]. Benzadiazepines have been synthesized by the condensation of o-phenylenediamines with α , β unsaturated carbonyl compounds, β-haloketones or with ketones. This condensation has been carried out using different reagents including BF_3-etherate [8], polyphosphoricacid [9], $NaBH_4$ [10], SiO2 [10], $MgO/POCl_3$ [11], $Yb(OTf)_3$ [12], lead nitrate[13], L-Proline[14], acetic acid under microwave conditions [15] and in ionic liquids [16]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedures. Therefore, the search continues for a better catalyst for the synthesis of 1,5-benzadiazepines in terms of mild reaction conditions, operational simplicity, economic viability and selectivity.

We report a simple and efficient method for the synthesis of 1,5-benzodiazepines using 10 mol % Cesium chloride as a catalyst. (Scheme I).

Cesium chloride is reported as catalyst in variety of transformation.In the present work, we have used Cesium chloride (10 mol%) as a catalyst for synthesis of array of substituted 1,5-benzadiazepines under solvent free conditions.

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on a 300 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. Mass spectra were taken with Micromass - QUATTRO-II of WATER mass spectrometer.

General procedure for preparation of 2,3-dihydro-1,5-benzodiazepines

A mixture of o-phenylenediamine (0.001mol), acetone (0.002mol) and Cesium chloride(0.0001mol) was stirred at 50°c temperature. After completion of the reaction, as indicated by TLC the reaction mixture was poured in water which on filtration gave the crude compound. The crude compounds were purified to afford the desired compound in pure form.

Spectral data of compound 3a: Yellowish solid, mp 136-137°C ^{1}HNMR (CDCl3): 1.35 (S,6H), 2.25 (S,2H), 2.40 (S,3H), 2.96 (br s, 1H,NH), 6.67-7.20 (M.4H.arom); MS: 189 (M-H), 190,

All the synthesized compounds were characterized using mass, and ^{1}H NMR. Also the melting points of synthesized compounds were compared with the corresponding reported melting points in literature [10,17,18].

Scheme 1

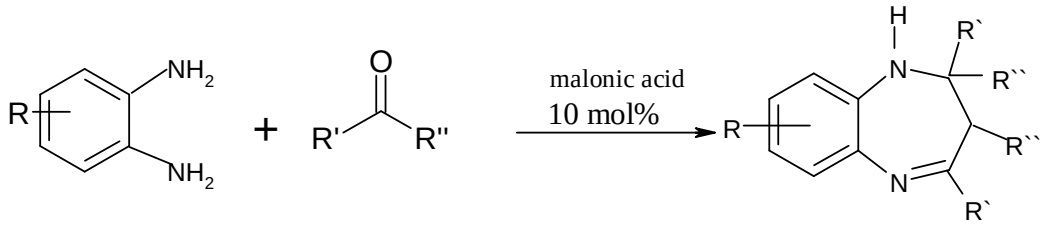
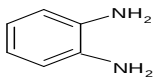
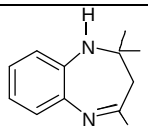
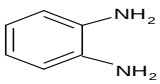
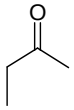
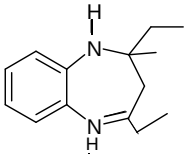
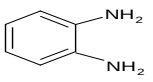
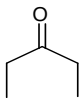
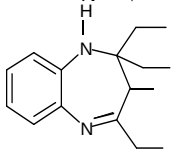
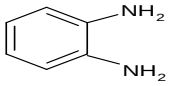
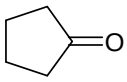
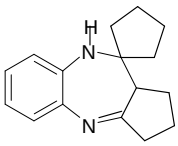
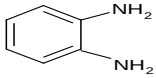
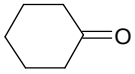
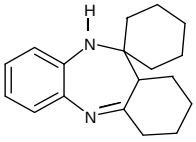
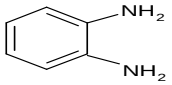
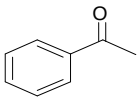
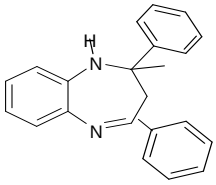
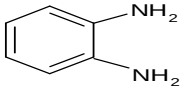
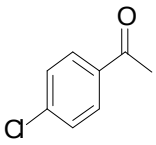
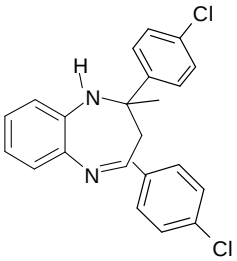
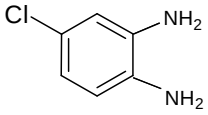
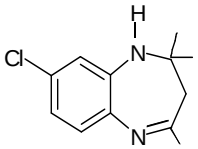
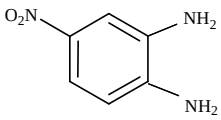
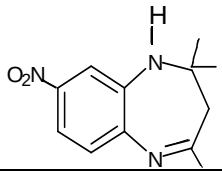


Table 1. Cesium chloride Catalyzed synthesis of 2,3-dihydro-1 H -1,5-benzodiazepines

Entry	Diamine	Ketone	Product	Time	M.P.^{oC} Found	M.P. ^{oC} Reported [Ref]	Yield %
3a				20	135	136-138 [21]	98
3b				25	137	137-139 [22]	98
3c				25	145	43-144 [10]	95

3d				20	135	137-138 [21]	95
3e				20	138	136-137 [22]	95
3f				35	154	150-152 [21]	92
3g				35	159	160-163 [10]	92
3h				30	92	90-92 [22]	98
3i				35	112	113-114 [22]	95

RESULTS AND DISCUSSION

Use of 10 mol% Cesium chloridegave the better yield (98%) for synthesis of 3a. We investigated the reaction of a series of symmetrical and unsymmetrical ketones with a o-phenylenediamine to get the corresponding 2,3-dihydro-1 H -1,5-benzodiazepines. (Table 1). All synthesized derivatives were characterized using mass and ^{1}H NMR. The easy work-up of the reaction was also the advantageous aspect of this method with better yield.

In conclusion, we have developed an efficient and simple alternative for the preparation of substituted 2,3-dihydro-1 H -1,5-benzodiazepines via solvent-free condensation of o-phenylenediamine and the ketone using Cesium chlorideas catalyst. Simple handling, short reaction time, easily and cheaply available Cesium chlorideas catalyst and excellent yield are the advantages of the proposed method.

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