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Sodium perchlorate catalysed synthesis of 1,5-benzodiazepines in an aqueous media

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ABSTRACT

Sodium perchlorate was found to be an efficient agent for the preparation of 2,3-Dihydro-1H-1,5-benzodiazepine derivatives by the condensation of o-phylenediamine and various ketones in the presence of stoichiometric amount of $NaClO_4$ in an aqueous media.

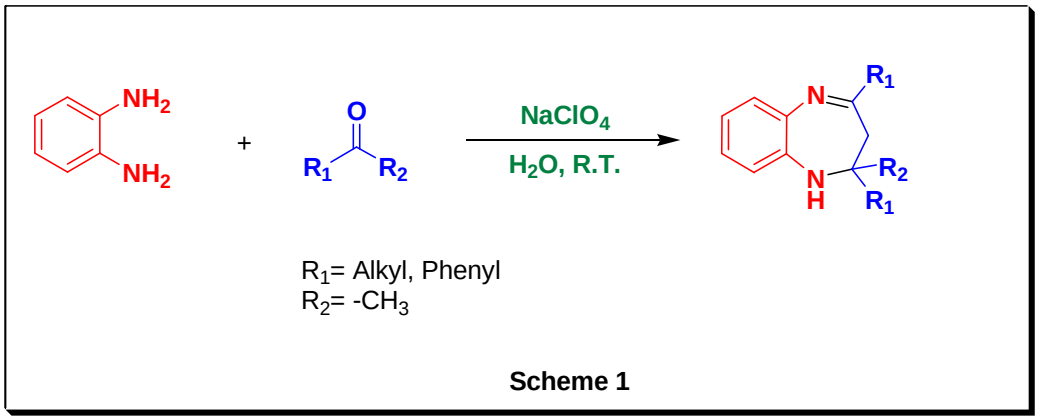
Keywords: Sodium perchlorate, o-phenylenediamine, benzodiazepienes, ketones, aqueous media.

INTRODUCTION

Benzodiazepines and their polycyclic derivatives are important classes of bio-active compounds. They find numerous applications as anti-convulsant, anti-anxiety and hypnotic agent[1,2]. More recently the biological interest of 1,5-benzodiazepines has been extended to various diseases like cancer, viral infection and cardiovascular disorder[3]. Some benzodiazepines derivatives are used as dyes for the acrylic fibres[4] in photography and also as anti-inflammatory agents[5]. Particularly, 1,5-benzodiazepines are useful precursors for synthesis of some fused ring benzodiazepine deriuvatives[6] such as triazolo-, oxadiazolo-, oxazino- or furano benzodiazepines. Due to their broad spectrum of biological activity, these compounds have received a great deal of attention in connection with their synthesis. Generally, benzodiazepines are synthesized by the condensation of o-phylenediamine with α, β-unsaturated carbonyl compounds, β-haloketones or with ketones. A variety of catalysts BF_3-OEt_2[7], Polyphosphoric acid[8], $CeCl_3$-NaI/SiO_2[9], I_2[10], $ZnCl_2$[11], SmI_2[12], $YbCl_3$[13], MgO/$POCl_3$[14], Amberlyst-15[15], $Yb(OTf)_3$[16], $Ga(OTf)_3$[17], Al_2O_3/P_2O_5[18], AcOH/MW[19], Sulfated zirconia[20], NBS[21], CAN[22], montmorrilonite K-10[23], $Ag_3PW_{12}O_{40}$[24], $InBr_3$/$InCl_3$[25] and ionic liquids[26], Silica suphuric acid[27], Camphor sulphonic acid[28], $ZrOCl_2$[29]. However, many of these methodologies are associated with several short commings such as harsh reaction condition, low product yield, use of organic solvent, occurrence of several side products and tedious work up procedures. Some reagents employed are very expensive. Therefore, the development of the new economic, green, method for synthesis of these compounds is desirable.

Recently, organic reactions in water have attracted much attention, because water is a cheap, safe, and environmentally benign solvent[30]. In the course of our investigation to develop green methodologies for the synthesis of heterocyclic compounds in an aqueous media. We report the synthesis of 1,5-benzodiazepines using sodium perchlorate in aqueous media. Sodium perchlopate is readily available reagent and it catalyses many organic

reactions in the organic solvents[31]. However, to the best of our knowledge, there are no earlier reports on the preparation of 1,5-benzodiazepines in aqueous media using sodium perchlorate Scheme 1.



Scheme 1

MATERIALS AND METHODS

General procedure for the synthesis of 1,5-benzodiazepines derivatives:

To the mixture of *o*-phenylenediamine (1 mmol), acetophenone (2 mmol) and sodium perchlorate (2 mmol), in water (5ml) was allowed to stirr vigorously at room temperature for appropriate time reported in **Table1**. Reaction progress was monitored by TLC. After completion of the reaction (TLC) the product was collected by simple filtration, washed with water and dried. This crude product was then recrystalized in n-hexane or by coloumn chromatography by using silica gel EtOAc: n-Hexane 2:8 as eluent where ever necessary.

Characterization data of compounds.

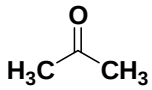
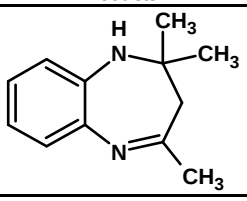
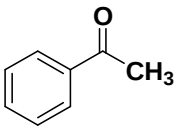
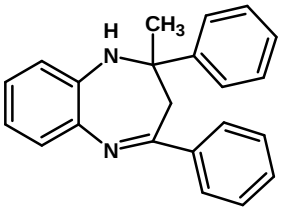
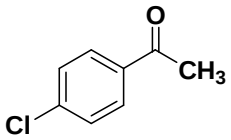
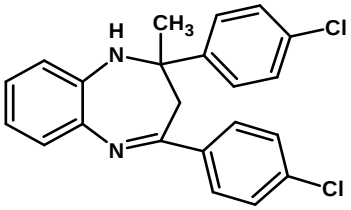
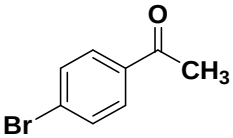
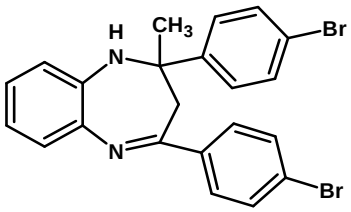
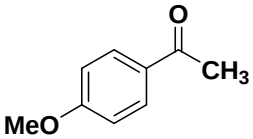
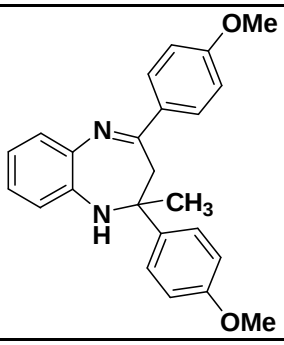
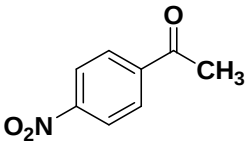
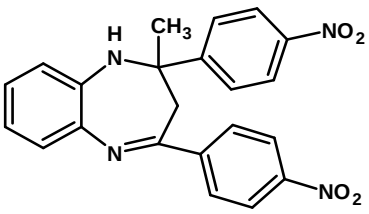
2,3-dihydro-2,2,4-trimethyl-1H-benzo[b][1,4]diazepine(compound 1)
IR (KBr in cm^{-1}3289, 3020, 2915-2880,1597-1450.^{1}HNMR (300 MHz, $CDCl_3$) δ6.60-7.25(m, 4H), 3.45 (Br. s, 1H), 2.33 (s, 3H), 2.25 (s, 2H), 1.35(s, 6H). ^{13}CNMR (300 MHz, $CDCl_3$) δ171.6, 140.5,137.6, 126.5, 125.2,121.9, 121.4, 67.5, 45.0, 30.2, 29.7. MS (EI): m/z 188.

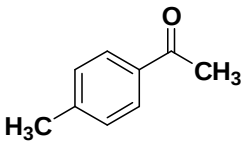
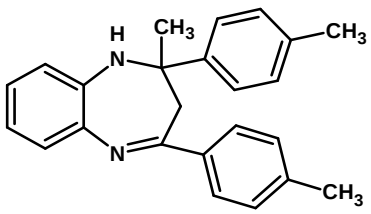
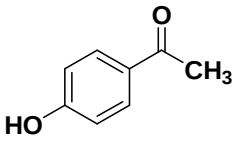
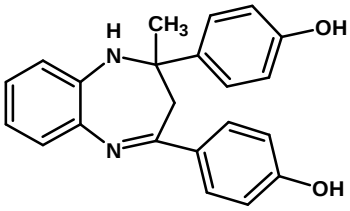
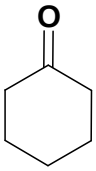
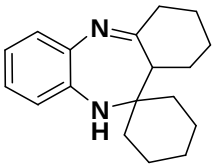
2,3-dihydro-2-methyl-2,4-diphenyl-1H-benzo[b][1,4]diazepine(compound 2)
IR (KBr in cm^{-1}3250, 3030, 2901-2925,1575-1480.^{1}HNMR (300 MHz, $CDCl_3$) δ 7.50-7.60 (m, 4H),7.10-7.30(m, 6H), 6.50-6.95(m, 4H), 3.40 (Br. s, 1H), 3.12(d, J= 12.6 Hz, 1H), 2.92 (d, J= 12.6 Hz 1H) 1.78(s, 3H). ^{13}CNMR (300 MHz, $CDCl_3$) δ 167.3, 146.3, 139.8, 139.2,138.0, 129.6, 128.3, 128.0, 127.8, 126.9, 126.8, 126.1, 125.2, 121.2,120.9, 73.4, 42.9, 29.7 MS (EI): m/z 312.

RESULTS AND DISCUSSION

For the reasons of economy and pollution use of aqueous media in organic synthesis is of great interest in order to modernize classical procedures making them more clean, safe and easy to perform. Therefore, empahsis was given to carry out synthesis of 1,5-benzodiazepines using sodium perchlorate in an aqueous media at room temperature.
In our initial experiments towards the development of efficeint methodology for the synthesis 1,5-benzodiazepines reaction of o-phenylenediamine with acetophenone was performed using stoichiometric amount of sodium perchlorate catalyst in an aqueous media at room temperature **Scheme 1.** To our surprise reaction was proceed to give desired product 2,3-dihydro-2-methyl-2,4-diphenyl-1H-benzo[b][1,4]diazepine with good yield (**Entry 1, yield 85%**). Therefore, considering the effective activity of sodium perchlorate in water, it has been explored as a powerful catalyst in the synthesis of 1, 5-benzodiazepines. The results are summarised in **Table 1.** Acetophenone with substituted -Cl, -Br, $-NO_2$ and -OH gives satisfactory results with good yields (**Entry 3,4, 6,8, yield 75-88%**). Similarly, cyclic ketone such as cyclohexanone also reacted well efficiently to give high yield (**Entry 9, yield 90%).**

Table 1: Synthesis of 1,5-benzodiazepines catalysed by $NaClO_4$ in aqueous media.

Entry.	Ketones	Products	Reaction Time (h)	Yield[a] (%)	M.P.(°C)
1			3	90	146
2			3	85	150
3			4	87	141
4			4	88	145
5			6	85	116
6			3.5	87	157

7			7	80	142
8			3.5	75	220
9			5	90	135

CONCLUSION

In summary this is the first report on the use of $NaClO_4$ in an aqueous media for synthesis of 1,5 benzodiazepines. The use of commercially available sodium perchlorate and green solvent makes this method quite simple, more convenient and economic. Mild reaction conditions, simple work-up process and high yields of products are advantageous features of this method.

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