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Short communication

Catalytic synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by ferric perchlorate

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Abstract

2,3-Dihydro-1*H*-1,5-benzodiazepines are synthesized by the condensation of *o*-phenylendiamine and various ketones in the presence of $Fe(ClO_4)_3$.

Keywords: Ferric perchlorate; 1,5-Benzodiazepines; *o*-Phenylenediamine; Ketones

1. Introduction

Benzodiazepines are interesting compounds because they belong to an important class of the pharmacologically pre-eminent 1,5-benzodiazepines which have been extensively used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, hypnotic and anti-inflammatory agents [1–4]. Additionally, they are useful synthons for the synthesis of various fused-ring compounds such as triazolo-, oxazino-, oxadiazolo- and furano-benzodiazepines [5]. Due to their wide range of pharmacological activity, synthetic and industrial applications, the synthesis of these compounds has recently received a great deal of attention for the discovery of improved protocols towards milder and high yielding approaches. A variety of catalysts such as $BF_3{\cdot}OEt_2$ [6], $NaBH_4$ [7], PPA-SiO_2 [8], MgO–$POCl_3$ [9], $Yb(OTf)_3$ [10], Al_2O_3–P_2O_5 [11], HOAc-microwave [12], SO_4^{-2}–ZrO_2 [13], I_2 [14], $InBr_3$ [15], Ag_3 PW_{12} O_{40} [16], [L-proline]$_2$ Zn [17], solid acid [18] and ionic liquids [19,20] have been employed to affect this transformation.

However, many of these methods are associated with several drawbacks such as applications of expensive reagents, drastic reaction conditions, extended reaction times, occurrence of side products, unsatisfactory yields and complicated experimental procedure. Hence, there is a need to develop a convenient, efficient and practically useful process for the synthesis of 1,5-benzodiazepines. Recently we have used ferric perchlorate as a versatile catalyst in organic synthesis [21–24]. Due to interesting application of 1,5-benzodiazepines and in continuation of our interest in heterocyclization [25] and catalytic reactions [26] in this communication we report our results for the synthesis of 1,5-benzodiazepines using ferric perchlorate as a catalyst.

2. Results and discussion

The scope and generality of the above process is illustrated with respect to the reactions of different *o*-phenylenediamines and a wide range of ketones (Table 1). The reactions were carried out at room temperature for 15–35 min by taking a 1:2.5 mol ratio mixture of *o*-phenylenediamine and the ketone in the presence of 2 mol% $Fe(ClO_4)_3$ in solvent-free condition to give the desired products (Scheme 1) in excellent yields. Both aromatic and aliphatic ketones equally underwent the conversion well. However, the ketones should contain at least α-hydrogen. Cyclic ketones such as cyclohexanone afforded fused-ring 1,5-benzodiazepines (entries: 3, 9). It is noteworthy to mention that by starting from an unsymmetrical ketone such as 2-butanone (entries 2, 3), the ring closure occurs selectively only from one side of carbonyl group yielding a single product. The diamines carrying electron-donating as well as electron-withdrawing groups on the aromatic rings worked

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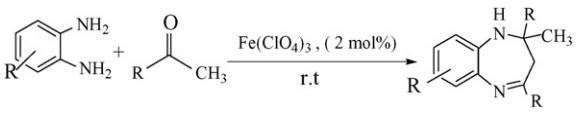


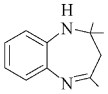
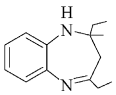
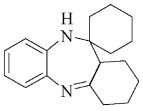
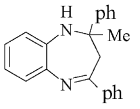
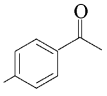
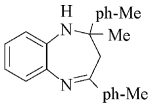
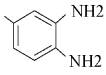
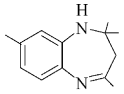
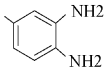
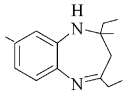
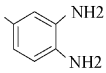
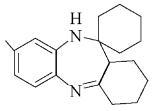
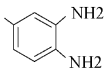
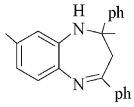
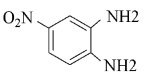
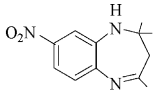
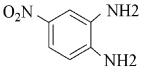
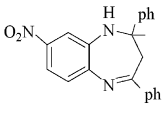
Scheme 1.

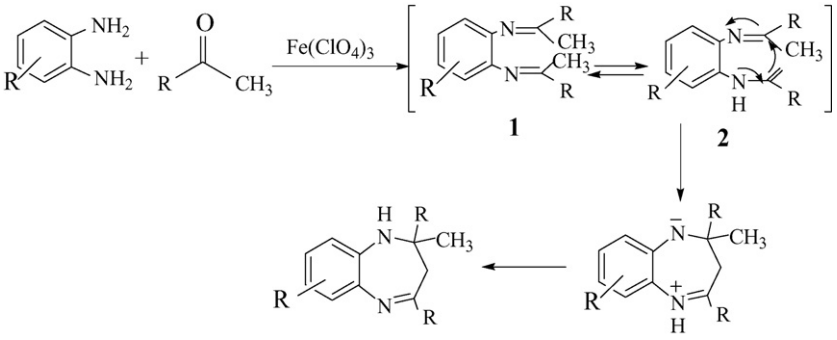
equally well. No solvent used in this reaction. The work up procedure is simple and the products were obtained in high yields.

The mechanism of the reaction [27] probably involves an intramolecular imine–enamine cyclization promoted by $Fe(ClO_4)_3$ as shown in Scheme 2. Amino groups of *o*-phenylenediamine attack carbonyl group of ketone giving the intermediate diimine **1**. 1,3-Hydrogen shift attached to methyl group then occurs to form an isomeric enamine **2**, which cyclizes to afford seven-member ring.

The alternative mechanism involving, the aldol condensation of ketones to give α,β-unsaturated carbonyl compound which can subsequently undergoes 1,4-addition is ruled out, because such an aldol condensation did not happen in ketones with α-hydrogen in the presence of ferric perchlorate.

Table 1
$Fe(ClO_4)_3$-catalyzed synthesis of 1,5-benzdiazepines under solvent-free conditions

Entry	Diamine	Ketone	Product	Time (min)	mp (°C)		Yield (%)
					Observed	Founded	
1				15	137–139	136–138 [28]	85
2				17	136–139	137–139 [28]	90
3				30	137–139	136–137 [28]	87
4				25	149–152	150–152 [28]	84
5				25	143–144	143 [29]	89
6				15	126–129	127–129 [28]	82
7				20	115–119	116–118 [28]	93
8				35	138–139	138 [29]	86
9				27	90–92	91–93 [28]	87
10				25	112–114	113–114 [28]	88
11				35	136–138	136–138 [28]	87



Scheme 2.

3. Conclusion

In conclusion, we have demonstrated a novel, efficient and solvent-free process for the synthesis of 1,5-benzodiazepines using ferric perchlorate as a catalyst. The simple experimental procedure, mild reaction conditions, short reaction time and high yields are the advantages of the present protocol.

4. Experimental

4.1. Synthesis 2,3-dihydro-1,5-benzodiazepines: general procedure

A mixture of appropriate *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), and $Fe(ClO_4)_3$ (0.02 mmol, 0.01 g) were mixed in a one neck flask at room temperature for 15–35 min (Table 1). The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL), and CH_2Cl_2 (10 mL) was added to the reaction mixture. The organic layer was concentrated and the product was purified by silica gel column chromatography (100–200 mesh) with ethyl acetate–*n*-hexane (2:8) as eluent to afford pure compound.

*4.2. Selected spectroscopic data for (**8**, **9**)*

8. mp 138–139C IR (cm^{-1}) 3260 (NH), 1665 (C–N); ^1H NMR (200 MHz, $CDCl_3$)—1.96–2.75 (m, 19H, 8× CH_2 and Ar–CH_3), 2.95–3.29 (m, 3H, N–C– and N–C–CH_2), 4.99 (br s, 1H, NH), 7.00–7.50 (m, 3H, Ar–H).

9. mp 90–92 °C IR (cm^{-1}) 3275 (NH), 1659 (C–N); ^1H NMR (200 MHz, $CDCl_3$)—1.8 (s, 3H, CH_3), 2.41 (s, 3H, Ar–CH_3), 2.98–3.03 (d, 1H, $J = 13$, CH_2 a), 3.13–3.17 (d, 1H, $J = 13$, CH_2 b), 3.5 (br s, 1H, NH), 6.70–7.69 (m, 13H, Ar–H).

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