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Solvent-Free One Pot Synthesis of Benzo-[b]-1,4-diazepines Using Reusable Sulfamic Acid Catalyst

S.R. Sarda[a], W.N. Jadhav[b], N.B. Kolhe[b], M.G. Landge[c] and R.P. Pawar[d,]*

[a]*Department of Chemistry, J. E. S. College, Jalna-431203, India*

[b]*Organic Chemistry Synthesis Laboratory, Dnyanopasak College, Parbhani-431401, India*

[c]*Department of Chemistry, Vidyanath College, Parli-vaijnath-431515, India*

[d]*Deogiri College, Station Road, Aurangabad-431005, India*

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α-β-Unsaturated carbonyl compounds on condensation with *o*-phenylenediamine in the presence of catalyst sulfamic acid under solvent free conditions, resulted in the formation of corresponding benzo-[b]-1,4-diazepines in excellent yields.

Keywords: Benzodiazepines, α-β-Unsaturated carbonyl compounds, *o*-Phenylene-diamine, Sulfamic acid

INTRODUCTION

Benzodiazepines are an important class of pharmacologically active organic compounds. Considerable interest has been focused on the synthesis of benzodiazepines because of their wide range of biological activities [1] and therapeutics [2]. They also show anxiolytic, ant-inflammatory, anticonvulsant, anti-ischemic, sedative, hypnotic, muscle-relaxant and Anti-HIV activities. Benzodiazepines fused with other heterocyclic systems are reported to possess tranquilizing, antispasmodic and prenasrcotic properties [3]. They are well-known CNS depressant, and are also used as antitumor [4] and antibiotics [5].

Therapeutic values of benzodiazepines have contributed to the development of an efficient and convenient method for their preparation. Conversely, the commonly employed methods involve the cyclocondensation of 1,2-diamines with ketones [6], enones [7], β-haloketones [8], using Ytterbium triflate [9], BF_3-etherate [10], polyphosphoric acid [11], MgO and $POCl_3$ [6], ionic liquids [12], under microwave irradiation [13], $SbCl_3$-Al_2O_3 [14] and zinc montmorillonite heterogeneous catalyst [15], sulfated zirconia [16], $Ag_3PW_{12}O_{40}$ [17], CH_3COOH [18], MCM-41 zeolite [19], Piperidine-AcOH [20], *etc*. These known methods of benzodiazepine synthesis suffered from limitations such as harsh reaction conditions, expensive reagents, low yields, relatively long reaction time and formation of side products. The main disadvantage of the existing methods is that the catalysts are destroyed in work-up procedure and cannot be recovered or re-used. The search is still being continued for a better methodology for the synthesis of benzodiazepines whereby simplicity, reusability, ecofriendly and economic viabilitycould be achieved.

In recent years, sulfamic acid has been used as a powerful catalyst in organic synthesis [21]. It is non-corrosive and nontoxic with an outstanding physical property and stability. Sulfamic acid is a mild and non-volatile inorganic acid, insoluble in common organic solvent. The distinctive catalytic features and intrinsic zwitter ionic property of sulfamic acid are different from those of the conventional acidic catalysts. It has been used as an efficient heterogeneous catalyst for acid catalyzed reaction [22] *via*. acetylation, esterification, nitrile

*Crresponding author. E-mail: rppawar@yahoo.com

formation and transesterification of β-ketoesters. Moreover, some other organic transformations have also been carried out using sulfamic acid catalyst including Biginelli reaction, Beckmann condensation, Pechmann condensations, as well as Friedlander quinoline synthesis [23]. Herein, we wish to report an efficient protocol for the synthesis of benzodiazepines using sulfamic acid as a catalyst under solvent free conditions. Excellent yields of the products were obtained, and sulfamic acid catalyst was recycled and reused for several times.

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. ^{1}H NMR spectra were recorded on at 200 MHz in $CDCl_3$ using TMS as internal standard.

Synthesis of 2,4-Diphenyl-2,3-dihydro-1*H*-benzo-[b]-[1,4]-diazepine (3a)

A mixture of α,β-unsaturated carbonyl compound **1a** (10 mmol), *o*-phenylenediamine **2a** (10 mmol), and sulfamic acid (10 mol%) was heated at 80 °C without any organic solvent for the appropriate time (Table 1). After completion of reaction as indicated by TLC, the reaction mixture was cooled at room temperature and extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed and the residue was column chromatographed using petroleum ether:ethyl acetate (2:3) as the eluent, to obtain pure compound **3a**. The recovered sulfamic acid catalyst was washed with diethyl ether, activated at 70 °C temperature, and reused. Similarly the other derivatives were also synthesized (**3b-m**).

Spectral Data

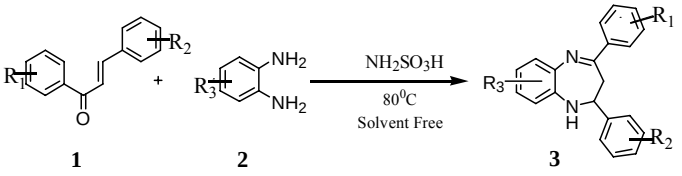
2,4-Diphenyl-2,3-dihydro-1H-benzo-[b]-[1,4]-diazepine (3a). IR (ν, cm^{-1}): 3440, 3350, 3067, 2890, 1604, 1508, 1466, 1210, 834, 770; ^{1}H NMR ($CDCl_3$) δ: 6.8-7.8 (m, 14H, Ar-H), 5.1 (dd, 1H, *J* = 4 and 8 Hz), 3.9 (brs, NH, D_2O exchangeable), 3.1 (dd, 1H, J = 4 and 10 Hz), 3.0 (dd, 1H, J = 8 and 10 Hz).

2-(4-Chloro phenyl)-4-phenyl-2,3-dihydro-1H-benzo [b]-[1,4]-diazepine (3b). IR (ν, cm^{-1}): 3455, 3367, 3045, 2900, 1604, 1516, 1470, 1204, 840, 777. ^{1}H NMR ($CDCl_3$) δ: 6.75-7.9 (m, 13H, Ar-H), 5.2 (dd, 1H, *J* = 4.5 and 9 Hz), 3.6 (brs, NH, D_2O exchangeable), 3.2 (dd, 1H, J = 4.5 and 11 Hz), 3.1 (dd, 1H, *J* = 9 and 11 Hz).

RESULTS AND DISCUSSION

In a typical condensation reaction, α,β-unsaturated carbonyl compound **1a** (10 mmol), *O*-phenylenediamine **2a** (10 mmol), and sulfamic acid (10 mol%) were thoroughly ground in a mortar pestle and the mixture was transferred to a round-bottom flask. The mixture was heated at 80 °C temperature without any organic solvent for the appropriate time as mentioned in Table 1. After completion of the reaction as indicated by TLC, the reaction was worked-up and afforded pure compound **3**. The recovered sulfamic acid catalyst was washed with diethyl ether and activated at 70 °C temperature and reused (Scheme 1).

In this method, reactions were carried out without using any hazardous organic solvent, which reduces both the cost of product and environmental pollution; thus, considered as a green chemistry. α-β-Unsaturated carbonyl compounds were prepared by the well-known Claisen-Schmidt condensation process [24]. Synthesis of benzodiazepines using sulfamic acid catalyst was completed in 2 to 3 h giving 90 to 95% of the desired product (Table 1). The results showed that the efficiency and yield of the reaction was high as compared with other conventional methods. Recovery of catalyst was very easy so that the sulfamic acid was recovered and reused for consecutive reactions without any significant loss of catalyst efficiency (Table 3). The use of 10-mol% of the catalyst was quite sufficient to promote the reaction; higher amount of the catalyst did not improve the yield. The reaction proceeded cleanly at 80 °C without any undesirable side-product being observed. The yield of all isolated products after purification was found to be excellent. However, in the absence of sulfamic acid, the reaction did not proceed following long



1 **2** **3**

Scheme 1

Table 1. Synthesis of Benzo-[b]-1,4-diazepines Using Sulfamic Acid as a Catalyst

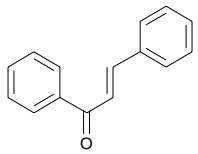
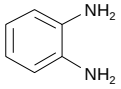
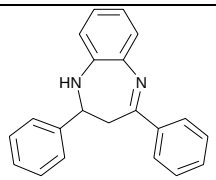
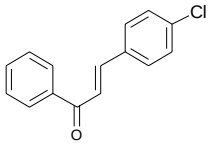
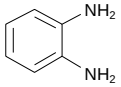
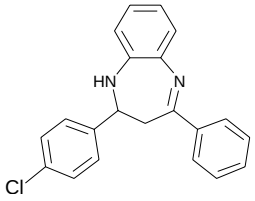
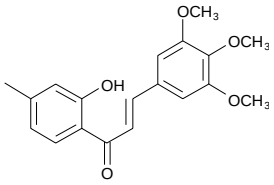
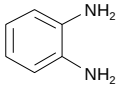
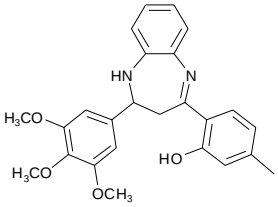
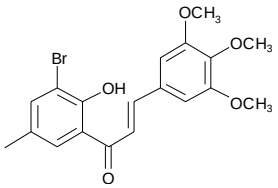
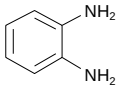
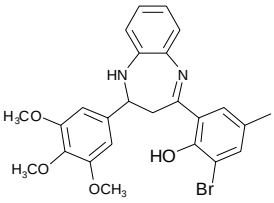
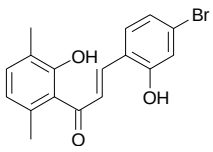
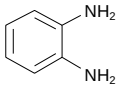
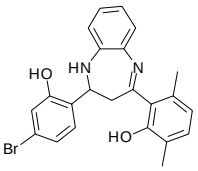
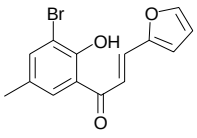
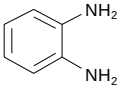
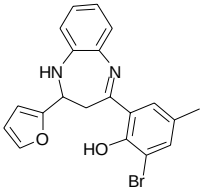
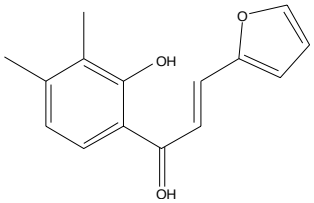
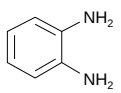
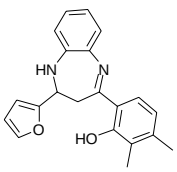
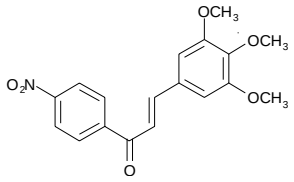
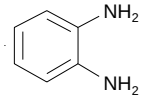
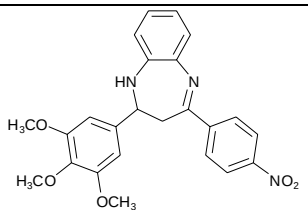
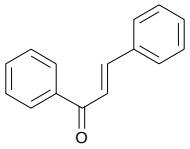
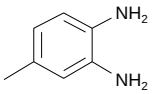
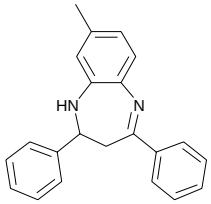
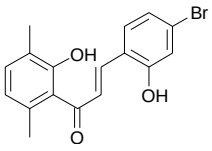
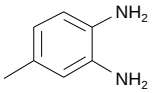
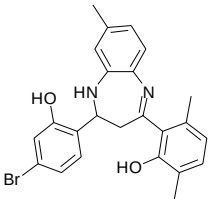
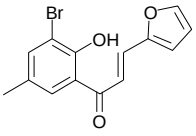
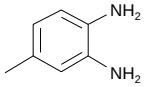
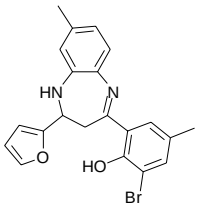
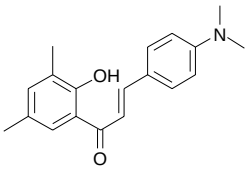
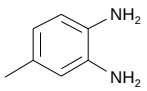
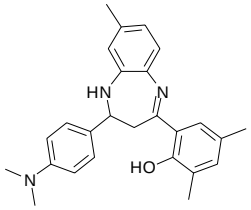
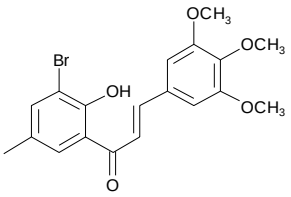
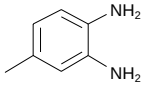
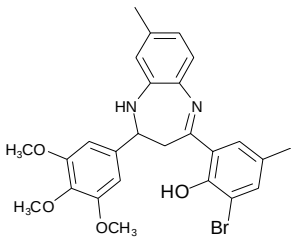
Entry	Chalcone	OPD	Product 3(a-m)	Time (min)	Melting point (°C)	Yield (%)[a]
a				90	132	92
b				100	111	90
c				95	98	85
d				110	110	80
e				110	165	80
f				90	90	85
g				90	107	90

Table 1. Continued

h				120	140	85
i				90	140	85
j				100	95	90
k				95	98	85
l				100	120	90
m				120	145	95

[a]Isolated and unoptimized yield.

Table 2. Synthesis of Benzodiazepines Using Different Catalysts

Catalyst	Solvent[b]	Reaction time	Yield (%)
[CH_3COOH]	Ethanol [18]	10 h	60-70
[MCM-41 zeolite]	Ethanol [19]	8 h	50-60
[Piperidine-AcOH]	Ethanol [20]	6-8 h	80
[$Yb(Otf)_3$]	CH_2Cl_2 [9]	4 h	88
[$SbCl_3$-Al_2O_3]	Solvent free [14]	3-4 h	83-90
[Zn/K-10]	Solvent free [15]	12-18 h	60-80
[$Ag_3PW_{12}O_{40}$]	Solvent free [17]	3-7 h	72-90
[Sulfamic acid]	Solvent free	1.5-2 h	85-92

[b]Literature methods.

Table 3. Recovery of Sulfamic Acid Catalyst in the Synthesis of Benzodiazepines

Entry	α-β-Unsaturated ketone (**1**)	Benzodiazepines (**3**)	Yield (%)		
			Cycle-1	Recycle-2	Recycle-3
a	**1a**	**3a**	94	91	88
b	**2b**	**3b**	93	90	88

reaction times (15-20 h.). The reaction did not proceed with aliphatic diamines, even after heating at higher temperatures for a long time. Compared with the previously reported methods (Table 2), this method offers several advantages in terms of simple procedure and workup, cheap and reusable catalyst, short reaction time, mild reaction conditions, and excellent yield without using any hazardous organic solvent. One more advantage of this process is the possibility of formation of hetero disubstituted benzodiazepines ring.

CONCLUSIONS

In summary, we have demonstrated an efficient and mild protocol for the synthesis of benzo-[b]-1,4-diazepines using sulfamic acid as a recyclable heterogeneous catalyst. Excellent yields of the products were obtained and the catalyst was recycled and reused for several times. The procedure offers several advantages including easy workup, operational simplicity and high product yields. Consequently, our method can be used as a viable alternative to the presently existing procedures.

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