Silica gel / $NaHSO_4$: An Efficient and Recyclable Heterogeneous Catalyst for high yield Synthesis of 1, 5-Benzodiazepine Derivatives under Microwave Irradiation

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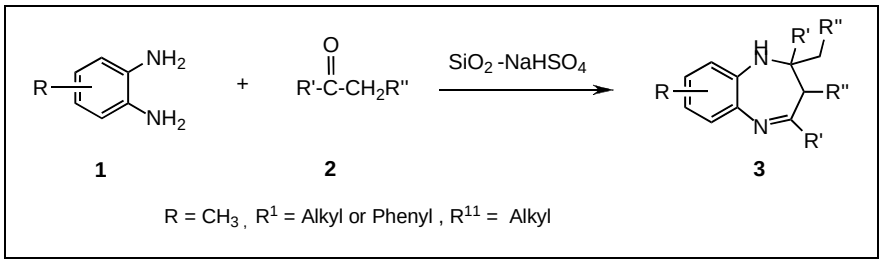
Received June 7, 2006



Silica gel supported sodium hydrogen sulfate catalyzes efficiently the condensation of *o*-phenylene-diamines with ketones under microwaves in solvent free conditions to afford the corresponding 1,5-benzo-diazepine derivatives in high yields. Compared to conventional reaction conditions, this new approach consistently has the advantage of excellent yields (90-98%) and short reaction times of 0.50 – 1.00 min.

J. Heterocyclic Chem., **44**, 929 (2007).

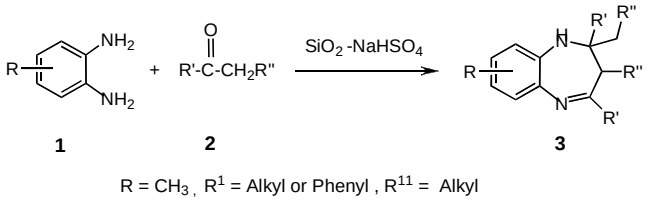
INTRODUCTION

Benzodiazepines and their derivatives are an important class of bioactive molecules and are widely used as anti-convulsant, ant anxiety, analgesic, sedative, anti depressant, anti inflammatory, and hypnotic agents [1-3]. Some of the benzodiazepine derivatives are used as dyes for acrylic fibers [4] in photography. Particularly, 1,5-benzodiazepines are useful precursors for the synthesis of some fused ring benzodiazepine derivatives [5] such as triazolo-, oxadiazolo-, oxazino-, or furanobenzodiazepines. Due to their wide range of applications these compounds have received a great deal of attention in connection with their synthesis. Many reagents have been reported in the literature [6] for this condensation including BF_3-etherate, $NaBH_4$, polyphosphoric acid, $Yb(OTf)_3$ and $MgO/POCl_3$. Recently these condensations have been reported even in an ionic liquid medium [7,8]. However many of these methodologies are associated with several short comings such as long reaction times, expensive reagents, harsh conditions, low product yields, occurance of several side products and difficulty in recovery and reusability of the catalysts. Generally 1,5-benzodiazopines are synthesised by the condensation of *o*-phenylene diamines with α,β-unsaturated carbonyl compounds or with ketones.

Recently, the use of solid supported reagents [9] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, silica gel impregnated with sodium bisulfate has advantages of low cost, ease of preparation, and catalyst recycling. Since the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration.

In view of the recent surge in the use of heterogeneous catalysts [10,11] we wish to report a simple, convenient and efficient method for the preparation of 1,5-benzodiazepine derivatives using a solid supported reagent, SiO_2-$NaHSO_4$, as an inexpensive and eco-friendly catalyst. The catalyst was prepared by using known procedure [12]. This method under Microwave irradiation not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalyst can act as eco-friendly for a variety of organic transformations, non-volatile, recyclable, non-explosive, easy to handle, and thermally robust. In view of the emerging importance of the heterogeneous catalyst, we wish to explore the use of silica gel supported sodium hydrogen sulfate as recyclable catalyst for the synthesis of 1,5-benzodiazepines (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

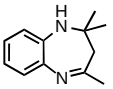
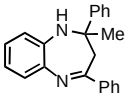
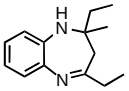
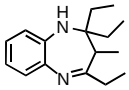
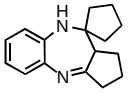
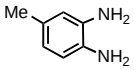
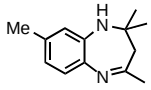
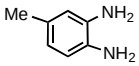
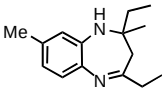
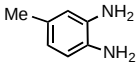
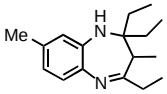
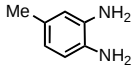
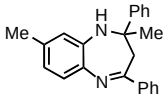
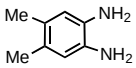
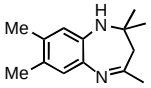
The treatment of *o*-phenylenediamine with acetone in the presence of silicagel supported sodium hydrogen sulfate resulted in the formation of 2,3-dihydro-2,2,4-tri-

methyl-1*H*-1,5-benzo[*b*][1,4]diazepine in 98%, 93%, 87% and 88% yields over four cycles.

In a similar fashion, various ketones reacted smoothly with *o*-phenylenediamines under these reaction conditions to give the corresponding 1,5-benzodiazepine derivatives in 85-98% yield under solvent free conditions. The crude products were purified either by recrystallization from *n*-hexane or by silica gel column chromatography. The reaction of cyclic ketones with *o*-phenylenediamine in the presence of this catalyst afforded fused ring 1,5-benzodiazepine derivatives in good yields. All the products were characterized by IR, ^{1}H NMR, and mass spectral analysis and also by comparison with authentic samples. The reactions of various ketones with *o*-phenylenediamines in the presence of silica gel supported sodium hydrogen sulfate are superior in terms of yields and reaction rates and the results are presented in the Table 1

The rate enhancement under microwave irradiation may be attributed to the effective absorption of microwaves by the polar media. Thus microwaves have been applied to accelerate reaction rates and to improve the yields of the products. The classical synthesis of 1,5-benzodiazepine derivatives [6d] requires long reaction time at reflux temperature to moderate yields. In general microwave assisted reactions are clean, rapid and afford higher yields than those obtained by conventional methods. *o*-phenylenediamine and ketone were mixed with dry catalyst and subjected to microwave irradiation at 450 watts using

Table1: Microwave assisted,SiO_2-$NaHSO_4$ catalysed efficient synthesis of 1,5-benzodiazepines .

Entry	Diamine	Ketone	Product[a]	Conventional		Microwave Irradiation[C]	
				Time(m)	Yield(%)[b]	Time(m)	Yield(%)[b]
a		CH_3COCH_3		30	90	0.50	98
b		$PhCOCH_3$		40	88	0.75	95
c		$CH_3COCH_2CH_3$		40	88	0.75	95
d		$CH_3CH_2COCH_2CH_3$		40	85	0.80	95
e				60	85	1.00	90
f		CH_3COCH_3		30	90	0.75	96
g		$CH_3COCH_2CH_3$		40	87	0.75	92
h		$CH_3CH_2COCH_2CH_3$		40	85	0.70	90
i		$PhCOCH_3$		45	88	1.00	95
j		CH_3COCH_3		50	87	1.00	95

a: All products were characterized by IR,[1] HNMR, and mass spectra
b: Isolated and unoptimized yields
c:Pulsed irradiations (15 sec interval) at 450 watts using BPL-BMO 700T Domestic microwave oven.

BPL, BOM-700T microwave oven for an appropriate time. The advantage of the use of heterogeneous catalyst for this transformation is that ease of catalyst/substrate separation provided by a heterogeneous catalyst. However, the products were obtained of the same purity as in the first run, and the yields were almost consistent for a few cycles. The results of the reactions at microwave irradiation conditions are compared with the reflux conditions and short reaction times were observed, which is more economical in terms of time. Compared to conventional method, enhanced reaction rates, improved yields and high selectivity are the features obtained in microwave irradiation.

CONCLUSION

In summary, we have developed a simple, convenient and effective method for facile synthesis of 2,3-dihydro-1,5-benzodiazepines by the condensation of ketones with *o*-phenylenediamines using $NaHSO_4$-SiO_2 catalyst in solvent free conditions under microwave irradiation. Present methodology offers very attractive features such as reduced reaction times, higher yields and economic viability of the catalyst, when compared with conventional method as well as with other catalysts. The simple procedure combined with easy of recovery and reuse of this catalyst make this method economic, benign chemical process for the synthesis of 1,5-benzodiazepines of biological importance. The operational simplicity of the procedure is also attractive. The catalyst can be prepared from available inexpensive reagents and can be easy recycled, which is heterogeneous and non-hazardous. The reaction progress was monitored by TLC and NMR and MS were used for analysis of the products. NMR spectra were recorded on a 300 MHz and Mass spectra were recorded on a LC-MS.

EXPERIMENTAL

General procedure for the synthesis of 2,3-dihydro-1, 5-benzodiazepines. **(a)** A mixture of *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), and Silicagel supported sodium hydrogen sulfate, (5 mole%) was stirred at reflux temperature for an appropriate time (Table1). (b) A mixture of *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), and Silicagel supported sodium hydrogen sulfate (5mole%) were mixed in a pyrex test tube and subjected to microwave irradiation for an appropriate time (Table 1). After completion of the reaction, 10 ml of CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was concentrated and the products were purified by silicagel column (100-200 mesh) and eluted with ethyl acetate - *n*-hexane (2:8) to afford pure compounds in 90-98% yield. The wet catalyst was recycled and no appreciable change in activity was noticed after a few cycles. Spectral data for compounds **3a-3j** are given in Table 1. For compounds **3a**, **3c** and **3e** the spectroscopic data is in full agreement with the literature data [7].

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3b). Solid, m.p. 150-152 ℃, ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H), 2.95 (d, 1H, *J* = 12.8 Hz), 3.15 (d, 1H, *J* = 12.8 Hz) 3.45 (brs, NH), 6.55-7.0 (m, 3H), 7.15-7.35 (m, 7H), 7.55-7.65 (m, 4H). ^{13}C NMR (Proton decoupled, $CDCl_3$) δ: 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.1, 126.8, 126.9, 127.8, 128.1, 128.5, 129.5, 137.9, 139.5, 139.9, 147.4, 167.3; EIMS: *m/z*: 312 [M^+], 297, 235, 194, 103, 77, 40; IR (KBr): ν 3320, 1631, 1597 cm^{-1}.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine 3d: Solid, m.p. 143-145 ℃, ^{1}H NMR ($CDCl_3$:) δ 0.70-1.0 (m, 10H), 1.20-1.38 (m, 4H), 1.50-1.65 (m, 2H), 2.40-2.60 (m, 2H), 2.87 (q, 1H, *J* = 6.8 Hz), 3.65 (brs, NH), 6.58 (d, 1H, *J* = 8.0 Hz), 6.65 (t, 1H, *J* = 8.0 Hz), 6.90 (t, 1H, *J* = 8.0 Hz), 7.38 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (Proton decoupled, $CDCl_3$) δ: 7.4, 7.8, 11.4, 12.1, 28.0, 28.4, 35.6, 46.2, 68.8, 117.5, 118.0, 126.7, 132.8, 13.9, 142.4, 173.8; EIMS: *m/z*: 244 [M^+], 229, 215, 194, 103, 77, 40; IR (KBr): ν 3320, 1631, 1597cm^{-1}.

2,2,4,8-Tetramethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3f). Solid, m.p. 127-129 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6H), 2.19 (s, 2H), 2.23 (s, 3H), 2.80 (s, 3H), 6.65-6.75 (s, 1H), 6.70-6.80 (1H), 7.05-7.10 (m, 1H); ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 20.9, 29.6, 30.4, 30.8, 45.8, 67.0, 122.6, 126.6, 127.0, 131.8, 136.7, 138.1, 174.3. EIMS: *m/z*(%): 202 (M^+ 40), 187 (100), 146 (70), 77(15), 41 (20). IR (KBr): ν_{max} 3325, 1665, 1600 cm^{-1}.

2-Methyl-2,4-diethyl-8-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3g). Light yellow solid; m.p. 116-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* = 7.0 Hz), 1.15-1.30 (m, 6H), 1.50–1.70 (m, 1H), 2.05-2.10 (d, 1H, *J* = 12.8 Hz), 2.15-2.20 (d, 1H, *J* = 12.8 Hz), 2.30 (s, 3H), 2.50-2.65 (m, 2H), 2.90 (brs, 1H, NH), 6.55-7.00 (m, 3H); EIMS: *m/z* (relative intensity %): 230 (M^+, 15), 201 (20), 172 (40), 132 (100), 90 (50), 56 (25); IR (KBr): ν_{max} 3500, 3220, 1620 cm^{-1}

2,2,4-Triethyl-3,8-dimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3h). Solid, m.p. 153-155 ℃, ^{1}H NMR ($CDCl_3$) δ: 0.71-1.0 (m, 10H), 1.20-1.38 (m, 4H), 1.51-1.65 (m, 2H), 2.25(s,3H), 2.40-2.62 (m, 2H), 2.87 (q, 1H, J = 6.8 Hz), 3.65 (brs, NH), 6.58-7.35 (m,3H).EIMS: m/z: 258 [M^+], 244, 229, 215, 194, 103, 77, 40. IR (KBr) ν: 3320, 1631, 1597cm^{-1}.

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (3i). Yellow color solid; m.p 91-93 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.80 (s, 3H), 2.41 (s, 3H), 2.98 (d, 1H, *J* = 12.7 Hz), 3.15 (d, 1H, *J* = 12.7 Hz), 3.50 (brs, 1H, NH), 6.70-7.69 (m, 13H). ^{13}C NMR (Proton decoupled, 50 MHz, $CDCl_3$): δ 20.6, 28.5, 45.8, 51.2, 113.5, 125.5, 126.4, 127.3, 128.1, 128.3, 128.6, 128.8, 129.1, 130.9, 131.2, 134.0, 136.8, 164.8; EIMS: *m/z*(%): 326 (M^+ 10), 261 (100), 246 (90), 206 (40), 145 (50), 102 (35), 76 (30). IR (KBr): ν_{max} 3315, 1657, 1600 cm^{-1}.

2,2,4,7,8-Pentamethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3j). Yellow solid, m.p. 112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.35 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H) 2.22 (s, 2H), 2.34 (s, 3H), 2.80 (brs, NH, 1H), 6.52 (s, 1H), 6.39 (s, 1H); ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 18.9, 19.1, 29.8, 30.3, 30.4, 45.3, 67.7, 122.8, 127.8, 129.9, 133.6, 135.5, 138.4, 171.3; EIMS: *m/z*(%): 216 (M^+ 20), 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100); IR (KBr): ν_{max} 3290, 1635, 1605 cm^{-1}.

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