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Synthesis of 1-*H*-1,5-Benzodiazepines Derivatives Using $SiO_2/ZnCl_2$

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ABSTRACT: *A general and easy method for the synthesis of several 1-H-1,5-benzodiazepines using $SiO_2/ZnCl_2$ under solvent-free conditions is described. This efficient and improved method furnishes selectively and in good yields the corresponding 1-H-1,5-benzodiazepines derivatives starting from o-phenylenediamine and cyclic or acyclic ketones. The catalytic system was reused up four times, and the use of focused microwaves accelerates the reaction.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:180–185, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20674

INTRODUCTION

Benzodiazepines and their derivatives represent a significant group of biologically active compounds and exhibit a number of important biological properties, such as anticonvulsant, antianxiety, anti-inflammatory, analgesic, hypnotic, antidepressive, and sedative agents [1]. Their synthesis has been receiving much attention in the field of medicinal and pharmaceutical chemistry [1]. Recently, the use of 1-*H*-1,5-benzodiazepines has been extended to various diseases such as cancer, viral infection, and cardiovascular disorders [2]. In addition, the derivatives of 1-*H*-1,5-benzodiazepines are used as intermediates in the synthesis of fused ring compounds [3] and are also used as dyes for acrylic fibers in photography [4]. Benzodiazepines are commonly synthesized by the condensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds [5], β-haloketones [6], or principally with ketones [7]. In the procedures using ketones, many reagents have been used, including $BF_3{\cdot}OEt_2$ [7a], $NaBH_4$ [7b], $Ga(OTf)_3$ [7c], L-proline [7d], molecular iodine [7e], acetic acid under microwave (MW) irradiation [7f], ionic liquids [7g], among others [7h-o]. Many of these processes have some limitations, such as long reaction times, generation of by-products, harsh reaction conditions, poor yields, and tedious work-up procedures [7]. Therefore, the search for a better catalyst for the synthesis of 1,5-benzadiazepines in terms of mild reaction conditions, operational simplicity, economic viability, and selectivity, continues to attract the interest of synthetic organic chemists.

In this way, the use of heterogeneous catalysts, such as solid-supported ones, has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of the catalysts [8]. Indeed, as the reaction is heterogeneous in nature, the catalytic system can conveniently be separated by simple filtration. Among various solid supports, silica is usually preferred

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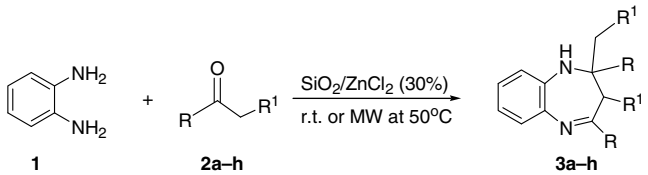


1 **2a–h** **3a–h**

R = alkyl, aryl
R^1 = alkyl

SCHEME 1 General scheme of the reaction.

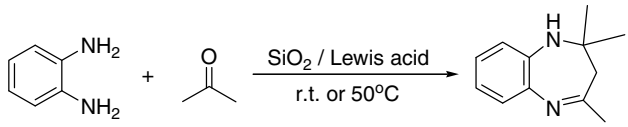
since it displays many advantageous properties: excellent stability (chemical and thermal), high-surface area, good accessibility, and organic groups can be robustly anchored to the surface, to provide catalytic centers [9]. Under this conception, our group developed new protocols using $SiO_2/ZnCl_2$ as a heterogeneous catalyst under solvent-free conditions and MW irradiation for different organic reactions, including the synthesis of 1,2-disubstitued benzimidazoles [10].

Because the interesting application of 1-*H*-1,5-benzodiazepines and in continuation to our studies in the development of new and cleaner methods for classical synthesis [10,11], we report herein the results of the preparation of 1-*H*-1,5-benzodiazepines catalyzed by $SiO_2/ZnCl_2$ under solvent-free conditions at room temperature, or under MW irradiation (Scheme 1).

RESULTS AND DISCUSSION

Our initial studies have focused on the development of an optimum set of reaction conditions. Thus, a mixture of *o*-phenylenediamine **1** (1.0 mmol) and dimethyl ketone **2a** (2.5 equiv) was reacted with different silica-supported catalysts at room temperature, and the results are presented in Table 1. Different silica-supported catalysts (0.06 g) of Zn, Al, Fe, as well as silica alone were tested, displaying a moderated to good catalytic activity. The best result was obtained using the catalytic system $SiO_2/ZnCl_2$ (25%), giving the desired 1,5-benzodiazepine **3a** in 85% yield (Table 1, entry 4). To our satisfaction, the use of a slight larger amount of $ZnCl_2$ (30%) yielded 91% of compound **3a** after 20 min of reaction at room temperature (Table 1, entry 5). Unfortunately, when the $ZnCl_2$ ratio was reduced from 30% to 10% or the reaction temperature was increased to 50°C, a decrease in the yield of product **3a** was observed (Table 1, entries 6 and 7). A reaction using a larger amount of catalytic system (0.120 g) afforded product **3a** in comparable yield (Table 1, entries 5 vs. 8). In a optimized reaction

TABLE 1 Reaction Conditions Optimization



1 **2a** **3a**

Entry	*Supported Lewis Acid*	*Time (min.)*	*Yield (%)*[a,b]
1	None	150	69
2	$FeCl_3$ (25%)	60	74
3	$AlCl_3$ (25%)	40	73
4	$ZnCl_2$ (25%)	20	85
5	$ZnCl_2$ (30%)	20	91
6	$ZnCl_2$ (10%)	80	75
7	$ZnCl_2$ (25%)[c]	11	80
8	$ZnCl_2$ (25%)[d]	20	89

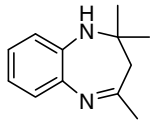
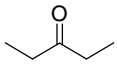
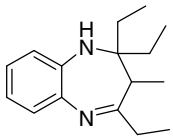
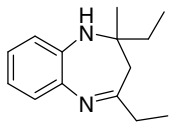
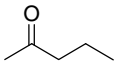
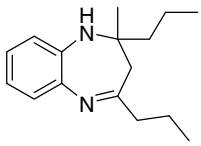
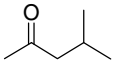
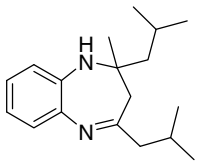
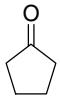
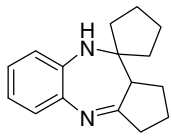
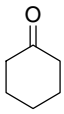
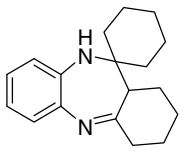
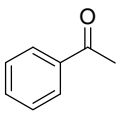
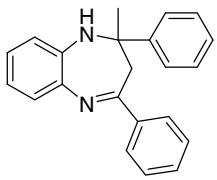
[a]Yields are given for isolated products.
[b]Reactions performed using *o*-phenylenediamine **1** (1.0 mmol), dimethyl ketone **2a** (2.5 equiv), and the catalyst (0.06 g).
[c]Reaction was performed at 50°C.
[d]Reaction using 0.120 g of $SiO_2/ZnCl_2$.

(Method A), *o*-phenylenediamine **1** (1.0 mmol) was reacted with dimethyl ketone **2a** (2.5 equiv) using $SiO_2/ZnCl_2$ (30%) (0.06 g) at room temperature during 20 min, affording 1,5-benzodiazepine **3a** in 91% yield.

To obtain an efficient protocol in terms of energy economy, we realized a study to reduce the reaction time. Thus, the mixture was stirred under different temperatures under MW irradiation. High levels of consumption of the starting materials was observed in these experiments, and the best result was achieved after irradiation at 50°C for 1.0 min, giving the corresponding product **3a** in 89% isolated yield (Table 2, Method B).

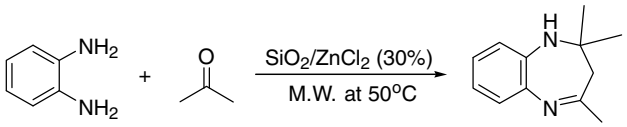
To extend the scope of our methodology, the possibility of performing the reaction with other ketones was investigated under our two methodologies (Table 2). In most cases, the reaction proceeded smoothly to give 1-*H*-1,5-benzodiazepines **3a–h** in good to excellent yields under both methods. Symmetrical alkylketones **2a** and **2b** were suitable substrates for the reaction, and the respective products were obtained in good to excellent yields (Table 2, entries 1–4). It is interesting to note that, when we used unsymmetrical ketones, such as 2-butanone **2c**, 2-pentanone **2d**, or 4-methyl-butan-2-one **2d** as substrates, the ring closure occurs selectively only from one side of the carbon skeleton giving a single product (Table 2, entries 5–10). Cyclic ketones such as cyclopentanone and cyclohexanone reacted to give the corresponding 1-*H*-1,5-benzodiazepines **3f** and **3g** in excellent yields (Table 2, entries 11–14). Reaction of *o*-phenylenediamine **1** with acetophenone **2h**

TABLE 2 Reaction of *o*−Phenylenediamine **1** with Ketones **2a–h** Using $SiO_2/ZnCl_2$ as a Solid-Supported Catalyst

Entry	*Ketone*	Method[a]	*Time (min)*	*Product*	Yield (%)[b]	*mp (°C) [Lit.]*
1		A	20		91	139–140 [12]
2	**2a**	B	1.0	**3a**	89	
3		A	40		80	142–144 [13]
4	**2b**	B	2.0	**3b**	94	
5		A	30		93	138–140 [12]
6	**2c**	B	1.5	**3c**	91	
7		A	40		94	140–142 [14]
8	**2d**	B	2.5	**3d**	93	
9		A	60		60	119–120 [12]
10	**2e**	B	4.0	**3e**	87	
11		A	40		85	138–140 [12]
12	**2f**	B	3.0	**3f**	93	
13		A	40		90	135–137 [15]
14	**2g**	B	3.0	**3g**	96	
15		A	30		97	149–151 [12]
16	**2h**	B	5.0	**3h**	95	

[a]Method A: Reactions are performed in the presence of ketone **2** (2.5 mmol) and *o*-phenylenediamine **1** (1.0 mmol) using 0.060 g of $SiO_2/ZnCl_2$ (30%) at room temperature. Method B: Reactions are performed in the presence of ketone **2** (2.5 mmol) and *o*-phenylenediamine **1** (1.0 mmol) using 0.060 g of $SiO_2/ZnCl_2$ (30%) at 50°C in a MW reactor.
[b]Yields are given for isolated product.

TABLE 3 Reuse of Catalyst in the Synthesis of 1,5-Benzodiazepine **3a**



1 **2a** **3a**

Run	*Reaction Time (h)*	*Yield (%)*[a]
1[b]	1.0	89
2[c]	1.0	88
3[c]	1.0	88
4[c]	1.5	85
5[c]	2.5	79

[a]Yields are given for isolated products.
[b]Reactions performed using *o*-phenylenediamine **1** (1.0 mmol), dimethyl ketone **2a** (2.5 equiv), and $SiO_2/ZnCl_2$ (30%) (0.06 g).
[c]Recovered $SiO_2/ZnCl_2$ was used.

gave excellent yields of product **3h** (Table 2, entries 15 and 16). The results depicted in Table 2 show that the use of MW irradiation (Method B) is better than conventional reaction (Method A), furnishing the corresponding products in comparable yields but in very short reaction time (Table 2, Method A vs. Method B).

A reuse study of the catalyst was carried out for the reaction presented in Table 3, according Method B. After completion of the condensation of dimethylketone with *o*-phenylenediamine, the reaction mixture was diluted with ethyl acetate and the catalyst was recovered by filtration. The solid-supported catalyst was dried in an oven and reused for subsequent experiments under similar reaction conditions. The catalyst maintained its good level of efficiency even after being reused four times (Table 3). The product **3a** was obtained in 89, 88, 88, 85, and 79% yields after successive cycles. The observed fact that yields of the product remained comparable in these experiments, established the recyclability and reusability of the catalyst without significant loss in activity.

CONCLUSION

In conclusion, we have presented here an efficient methodology for the synthesis of 1-*H*-1,5-benzodiazepines in good yields by the condensation of *o*-phenylenediamine with aryl, cyclic, or acyclic ketones using $SiO_2/ZnCl_2$ as a solid-supported catalyst. The catalytic system was reused up four times without lost of activity. This clean protocol minimizes the organic solvent and energy demands, as well as, the reaction time could be reduced to a few minutes using MW irradiation.

EXPERIMENTAL SECTION

General

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 and 300 MHz on a Bruker DPX-200 and 300 NMR spectrometer, respectively. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$, or tetramethylsilane (TMS) as the internal reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in hertz, and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 50 and 75 MHz on a Bruker DPX-200 and 300 NMR spectrometer, respectively. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Column chromatography was performed using Merck Silica Gel (230–400 mesh) following the standard methods. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. The reactions were monitored by TLC for disappearance of starting material.

Preparation of Solid-Supported Catalyst ($SiO_2/ZnCl_2$, 30%)

To a 100-mL beaker, silica gel 60 (7.0 g), $ZnCl_2$ (3.0 g), and water (3.0 mL) were added. The suspension was stirred for 15 min at room temperature, dried in an oven at 50°C for 30 min, at 100°C for additional 30 min, and finally at 150°C for 2 h. After this procedure, the catalyst was cooled in a desiccator.

General Procedure for the Synthesis of 1-H-1,5-Benzodiazepines **2a–h**

Method A: To a mixture of appropriate ketone **2** (2.5 mmol) and *o*-phenylenediamine **1** (1.0 mmol), 0.060 g of $SiO_2/ZnCl_2$ (30%) was added and the whole mixture was stirred at room temperature. The reaction progress was followed by TLC. *Method B*: In a 10-mL glass vial equipped with a small magnetic stirring bar, containing the appropriate ketone **2** (2.5 mmol) and *o*-phenylenediamine (1.0 mmol), 0.060 g of $SiO_2/ZnCl_2$ (30%) was added and the vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated in a focused microwaves reactor (CEM) at 50°C, using an irradiation power of 200 W and pressure of 100 psi. After stirring for the time indicated in Table 2, ethyl acetate (10 mL) was added, and the organic solution

was separated of the $SiO_2/ZnCl_2$ by filtration. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel eluting with hexanes/AcOEt 9:1 mixture, yielding the products.

*2,2,4-Trimethyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3a***).* White solid: mp 139–140°C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.34 (s, 6H), 2.22 (s, 2H), 2.36 (s, 3H), 2.97 (br s, 1H, NH), 6.70–6.72 (m, 1H), 6.95–7.01 (m, 2H), 7.11–7.15 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 29.78, 30.41, 45.02, 68.34, 121.67, 122.02, 125.43, 126.74, 137.84, 140.68, 172.37. IR (KBr) (cm^{-1}): 3288, 1631, 1595. MS (EI): *m/z* (% relative intensity) = 188 (M^+, 37), 173 (100), 133 (64), 77 (6), 65 (11).

*2,2,4-Triethyl-3-methyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3b***).* Yellow solid: mp 142–144°C. ^{1}H NMR (300 MHz, $CDCl_3$): 0.77 (t, 3H, J = 7.4), 0.88 (t, 3H, J = 7.5), 0.93 (d, 3H, J = 7.0), 1.22 (t, 3H, J = 7.4), 1.30–1.38 (q, 2H, J = 7.4), 1.51–1.59 (m, 2H), 2.48–2.56 (m, 2H), 2.78–2.85 (q, 1H, J = 7.0), 3.62 (br s, 1H, NH), 6.59 (d, 1H, J = 8.0), 6.72 (t, 1H, J = 8.0), 6.95 (t, 1H, J = 8.0). 7.32 (d, 1H, J = 8.0). ^{13}C NMR (75 MHz, $CDCl_3$): 7.29, 7.84, 11.56, 12.31, 28.01, 28.38, 35.69, 46.05, 60.31, 117.50, 117.95, 126.68, 132.24, 132.75, 139.03, 173.74. IR (KBr) (cm^{-1}): 3288, 1635, 1600. MS (EI): *m/z* (% relative intensity) = 244 (M^+, 10), 215 (100), 147 (65), 92 (7). 77 (9), 65 (6).

*2,4-Diethyl-2-methyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3c***).* Yellow solid: mp 138–140°C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.96 (t, 3H, J = 7.4), 1.19–1.32 (m, 6H), 1.58–1.71 (m, 2H), 2.21–2.37 (m, 2H), 2.69–2.81 (q, 2H, J = 7.4), 3.76 (br s, 1H, NH), 6.72–6.79 (m, 1H), 6.91–7.08 (m, 2H), 7.32–7.38 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 8.60, 10.70, 26.60, 35.60, 35.80, 42,30, 70.60, 121.90, 125.50, 126.10, 127.20, 137.90, 140.70, 175.70. IR (KBr) (cm^{-1}): 3331, 1637, 1594. MS (EI): *m/z* (% relative intensity) = 216 (M^+, 16), 187 (100), 145 (24), 133 (26), 77 (6), 65 (6).

*2-Methyl-2,4-dipropyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3d***).* Yellow solid: mp 140–142°C. ^{1}H NMR (200 MHz, $CDCl_3$): 0.89–1.05 (m, 6H), 1.25 (s, 3H), 1.32–1.61 (m, 4H), 1.63–1.82 (m, 2H), 2.08–2.24 (m, 2H), 2.47–2.57 (m, 2H), 3.32 (br s, 1H, NH), 6.65–6.74 (m, 1H), 6.91–6.99 (m, 2H), 7.01–7.18 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 13.76, 14.35, 17.26, 19.59, 27.33, 42.16, 44.46, 45.52, 70.52, 121.47, 121.51, 125.18, 126.75, 137.75, 140.39, 174.91. IR (KBr) (cm^{-1}): 3331, 1635, 1597. MS (EI): *m/z* (% relative intensity) =/*m/z*: 244 (M^+, 11), 201 (100), 161 (13), 133 (16), 87 (3), 77 (9), 65 (7).

*2-Methyl-2,4-diisobutyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3e***).* White solid: mp 119–120°C. ^{1}H NMR (300 MHz, $CDCl_3$): 0.91–1.03 (m, 12H), 1.33 (s, 3H), 1.46–1.59 (m, 2H), 1.69–1.81 (m, 1H), 2.11–2.31 (m, 3H), 2.46 (d, 2H, J = 7.5), 6.67–6.72 (m, 1H), 6.94–6.99 (m, 2H), 7.12–7.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.45, 22.72, 24.18, 24.91, 25.06, 26.35, 28.14, 43.25, 51.71, 51.84, 71.10, 121.52, 121.58, 125.32, 127.08, 137.77, 140.50, 174.32. IR (KBr) (cm^{-1}): 3396, 1635, 1597. MS (EI): *m/z* (% relative intensity) = 272 (M^+, 6), 215 (100), 173 (32), 133 (32), 92 (7), 77 (5), 65 (4).

*10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[b]cyclopenta[e][1,4] diazepine (***3f***).* Yellow solid: mp 138–140°C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.26–1.85 (m, 8H), 2.11–2.25 (m, 4H), 2.37–2.49 (m, 2H), 2.78–2.86. (m, 1H), 3.99 (br s, 1H, NH), 6.63 (d, 1H, J = 7.9), 6.79 (t, 1H, J = 8.4), 6.95 (t, 1H, J = 7.9), 7.94 (d, 1H, J = 8.4). ^{13}C NMR (50 MHz, $CDCl_3$): 23.50, 24.10, 24.30, 28.80, 33.40, 38.50, 39.20, 56.40, 67.30, 118.60, 119.30, 126.90, 133.10, 139.20, 143.80, 178.20. IR (KBr) (cm^{-1}): 3338, 1641, 1604. MS (EI): *m/z* (% relative intensity) = 240 (M^+, 36), 211 (100), 183 (24), 145 (54), 132 (55), 91 (25), 77 (21), 65 (27).

*10-Spirocyhexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[b,e][1,4]diazepine (***3g***).* Yellow solid: mp 135–137°C. ^{1}H NMR (200 MHz, $CDCl_3$): 1.16–1.96 (m, 14H), 2.32 (t, 2H, J = 6.2), 2.44–2.66 (m, 1H), 3.87 (br s, 1H, NH), 6.51–6.64 (m, 1H), 6.69–6.75 (m, 2H), 6.89–7.09 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 21.80, 21.70, 23.50, 24.50, 25.30, 33.50, 34.40, 39.30, 40.80, 52.40, 63.10, 121.30, 121.60, 126.30, 129.70, 138.10, 142.60, 178.80. IR (KBr) (cm^{-1}): 3406, 1637, 1595. MS (EI): *m/z* (% relative intensity) = 268 (M^+, 17), 225 (100), 169 (15), 145 (54), 132 (44), 92 (9), 77 (18), 65 (9).

*2-Methyl-2,4-diphenyl-2,3-dihydro-1-H-1,5-benzodiazepine (***3h***).* White solid: mp 149–151°C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.76 (d, 3H, J = 4.3), 2.97 (dd, 1H, J = 13.0, 4.4), 3.14 (dd, 1H, J = 13.0, 4.4), 3.52 (br s, 1H, NH), 6.82–6.86 (m, 1H), 7.03–7.09 (m, 2H), 7.17–7.39 (m, 7H), 7.56–7.62 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 29.85, 43.05, 73.68, 121.39, 121.62, 125.39, 126.30, 127.04, 127.99, 128.27, 128.58, 129.70, 138.03, 139.55, 140.06, 147.57, 167.65. IR (KBr) (cm^{-1}): 3452, 1633, 1597. MS (EI): *m/z* (% relative intensity) = 312 (M^+, 6), 297 (16), 194 (100), 103 (17), 77 (14).

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