A Fast and Efficient Method for the Synthesis of 1,5-Benzodiazepine Derivatives Under Solvent-Free Conditions

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ABSTRACT: *Silica sulfuric acid is found to catalyze efficiently the condensation of o-phenylenediamines with various linear and cyclic ketones to afford the corresponding 1,5-benzodiazepines in quantitative yields under solvent-free conditions at room temperature.*

KEY WORDS: *1,5-Benzodiazepine, Ortho-phenylenediamine, Solid acid catalyst, Silica sulfuric acid, Synthesis.*

INTRODUCTION

It is known that 1,5-benzodiazepines (BDs) exhibit a wide range of biological activities, they are also commercially employed as dyes for acrylic fibres and as an anti-inflammatory agent [1-4]. Additionally, they are valuable synthons for the synthesis of various fused ring benzodiazepine derivatives [5-7]. Owing to the versatile biological activities, industrial and synthetic applications of these compounds, introduction of an alternative methodology is very important in synthetic organic chemistry.

1,5-Benzodiazepines are generally synthesized by the condensation of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds [8], β-haloketones [9] or ketones in the presence of a protic organic and inorganic acids such as HOAc [10], 1,3,5-tri-carboxylic acid (trimesic acid) [11], polyphosphoric acid (PPA) [12], $HClO_4/SiO_2$ [13], Lewis acids such as BF_3-OEt_2 [14], $Yb(OTf)_3$ [15], $InBr_3$ [16], I_2 [17,18], $FeCl_3$ [19], and $Sc(OTf)_3$ [20], SO_4^{2-}/ZrO_2 [21], ionic liquids such as Amberlyst- 15®/ [bmim]PF_6 [22], [bbim]Br [23], and some others such as $NaBH_4$ [24], $(CH_3)_2S/Br_2$ [25], $MgO/POCl_3$ [26], Zeolite [27], $Ag_3PW_{12}O_{40}$ [28], and ceric ammonium nitrate (CAN) [29]. However, in spite of their utility, many of these methods suffer major or minor limitations like tedious work up procedure, the necessity of neutralization of strong acidic media producing undesired washes, applications of expensive reagents, long reaction times, unsatisfactory yields and require separation of the catalyst from the product. Moreover, the main disadvantage of most of the methods is that the catalysts are destroyed in the work-up procedure and cannot be recycled.

The use of recyclable solid acid catalysts makes the process convenient, economic and environmentally benign. Therefore, the discovery of novel and inexpensive catalyst, which can be easily separated, reused and is not contaminated by the products is very important in synthetic organic chemistry.

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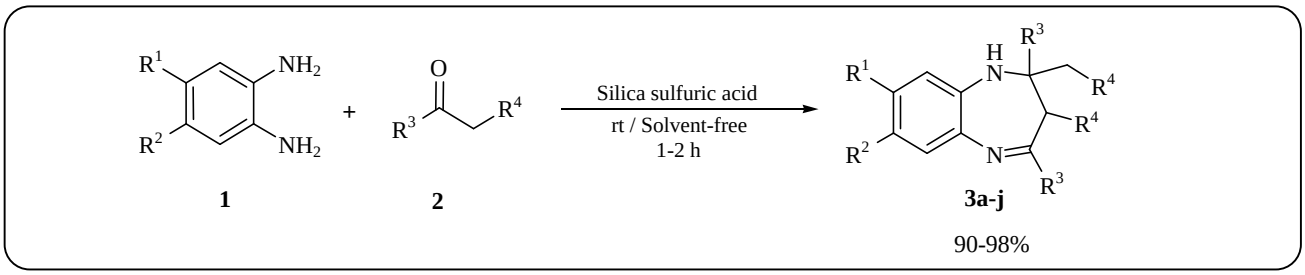


Scheme 1.

In connection with our previous work using silica sulfuric acid [30] and other solid acid catalysts in organic transformations [31-36], we wish to report the results of a study of the preparation of 1,5-benzodiazepines using silica sulfuric acid as an inexpensive and recyclable solid acid catalyst under solvent-free conditions, which is easily separated from reaction mixture (scheme 1).

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. All the products are known compounds, which were identified by comparison of their mp, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data with those of authentic samples.

***General experimental procedure for the synthesis of 2,3-dihydro-2-methyl-2,4-diphenyl-1H-1,5-benzodiazepine* (3b)**

A mixture of *o*-phenylenediamine (0.108 g, 1 mmol) and acetophenone (0.252 g, 2.1 mmol) was stirred at room temperature in the presence of silica sulfuric acid (0.05 g) for 1.2 h. After completion of the reaction (monitored by TLC), 5 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 product was purified on a small silica gel column (60 mesh) being eluted by an ethyl acetate/*n*-hexane (2:8 v/v) mixture to afford 0.290g (93%) pure compound of **3b**: Yellow solid; mp 150-151 °C; IR (KBr), ν_{max}/cm^{-1}: 3332, 1637, 1598, 1426. ^{1}H NMR ($CDCl_3$), δ/ ppm: 1.70 (s, 3H, CH_3), 2.95 (d, 1H, CH_2), 3.15 (d, 1H, CH_2), 3.35 (br s, 1H, NH), 6.65-7.10 (m, 2H, C_6H_4), 7.25-7.48 (m, 10H, C_6H_5), 7.55-7.68 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 29.7, 41.4, 74.3, 121.6, 122.0, 125.4, 126.7, 127.3, 127.4, 128.3, 128.5, 128.8, 129.6, 138.1, 139.2, 140.6, 145.3, 166.3.

Compound **3a:** Yellow solid; mp 135-136 °C; IR (KBr), ν_{max}/cm^{-1}: 3295, 1633, 1593, 1437. ^{1}H NMR ($CDCl_3$), δ/ ppm: 1.35 (s, 6H, $2CH_3$), 2.23 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.98 (br s, 1H, NH), 6.74-7.27 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 29.9, 30.5, 45.1, 68.5, 121.8, 122.1, 125.6, 126.8, 137.9, 140.6, 172.5.

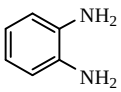
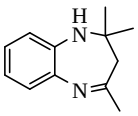
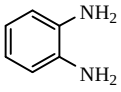
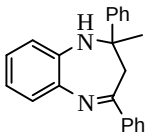
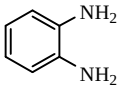
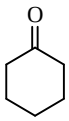
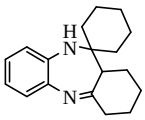
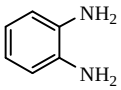
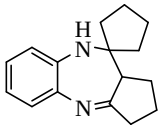
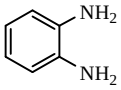
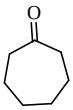
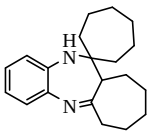
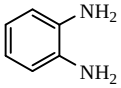
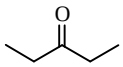
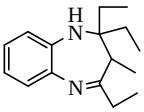
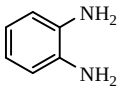
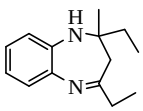
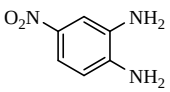
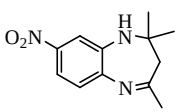
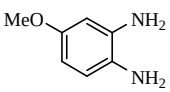
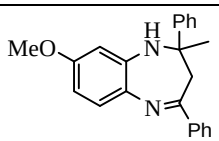
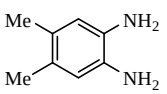
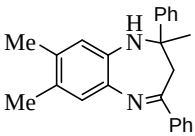
Compound **3c:** Yellow solid; mp 136-137 °C; IR (KBr), ν_{max}/cm^{-1}: 3322, 1626, 1568, 1442, 1365. ^{1}H NMR ($CDCl_3$), δ/ ppm: 0.85-2.36 (m, 19H, $9CH_2$ and CH), 3.48 (br s, 1H, NH), 6.85-7.60 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 21.5, 21.7, 23.4, 23.5, 24.5, 25.1, 33.2, 34.4, 39.3, 40.6, 52.4, 63.1, 121.5, 126.4, 129.6, 138.2, 142.4, 178.5.

Compound **3d:** Yellow solid; mp 137-138 °C; IR (KBr), ν_{max}/cm^{-1}: 3327, 1620, 1568, 1430, 1372. ^{1}H NMR ($CDCl_3$), δ/ ppm: 1.20-2.50 (m, 15H, $7CH_2$ and CH), 3.90 (br s, 1H, NH), 6.55-7.77 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 23.1, 24.3, 24.5, 28.8, 33.5, 38.2, 39.2, 54.2, 67.1, 118.8, 119.2, 126.8, 132.1, 139.3, 143.4, 178.2.

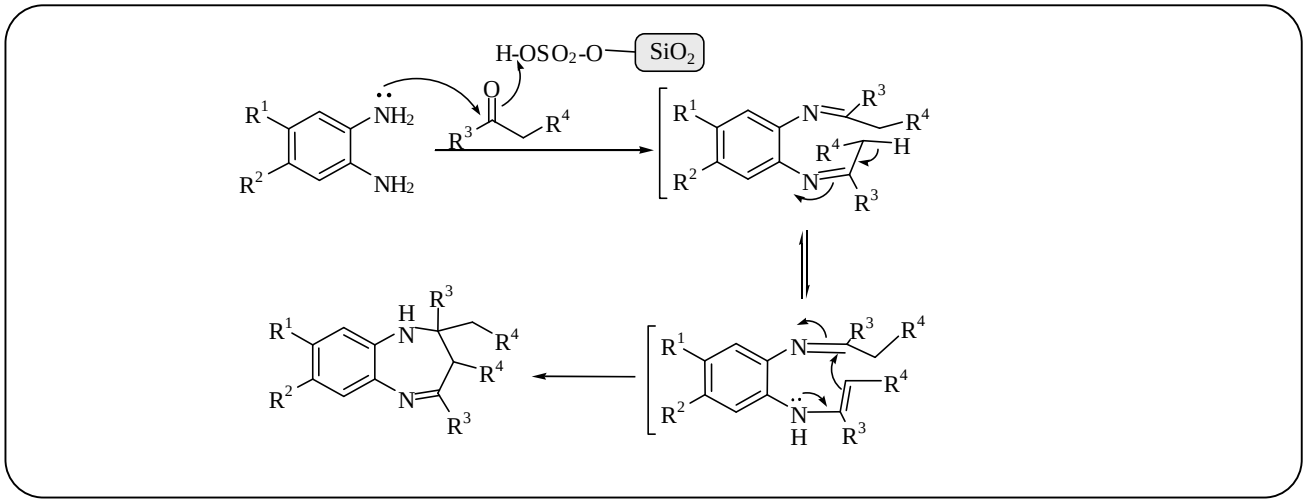
Compound **3e:** Yellow solid; mp 134-136 °C; IR (KBr), ν_{max}/cm^{-1}: 3328, 1623, 1550, 1442, 1360. ^{1}H NMR ($CDCl_3$), δ/ ppm: 1.15-2.45 (m, 19H, $9CH_2$ and CH), 3.95 (br s, 1H, NH), 6.52-7.70 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 22.7, 23.1, 24.3, 24.5, 27.2, 28.1, 33.5, 34.3, 38.2, 39.2, 54.2, 55.4, 67.1, 118.8, 119.2, 126.8, 132.1, 139.3, 143.4, 178.2.

Compound **3f:** Yellow solid; mp 144-145 °C; IR (KBr), ν_{max}/cm^{-1}: 3322, 1630, 1595. ^{1}H NMR ($CDCl_3$), δ/ ppm: 0.73-1.65 (m, 16H, $2CH_2$ and $4CH_3$), 2.35-2.52 (m, 2H, CH_2), 2.85 (q, 1H, CH), 3.78 (br s, 1H, NH), 6.67-7.42 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$), δ/ ppm: 7.5, 7.8, 11.5, 12.2, 28.1, 28.3, 35.5, 46.1, 68.9, 117.7, 118.1, 125.6, 132.7, 140.0, 142.4, 173.6.

Table 1: Synthesis of 1,5-Benzodiazepine Derivatives at Room-Temperature.

Entry	Diamine	Ketone	Product	Time (h)	Yield (%)	Mp (°C)	
						Found	Reported
3[a]				1	98[a]	135-136	137-139[b]
3b				1.2	93	150-151	151-152[b]
3c				1.5	91	136-137	138-139[b]
3d				1	95	137-138	137-139[b]
3e				2	90	134-136	136-137[b]
3f				1.5	96	144-145	144-145[b]
3g				2	92	135-137	137-138[b]
3h				1.5	90	115-116	113-114[c]
3i				1.5	96	123-124	123-124[c]
3j				1.5	95	115-116	114-116[d]

a) The yields were found 96, 93, 90 and 85% with using recovered catalyst after five runs, respectively.
b) Ref. [15], c) Ref. [13] and [28], d) Ref. [10].



Scheme 2.

Compound **3g:** Yellow solid; mp 135-137 °C; IR (KBr), ν_{max}/cm^{-1}: 3327, 1635, 1568, 1442. ^1H NMR ($CDCl_3$), δ/ ppm: 0.95-1.66 (m, 6H, $2CH_3$), 1.71-2.13 (m, 4H, CH_2), 2.37 (s, 3H, CH_3), 2.69 (q, 2H, CH_2), 3.65 (br s, 1H, NH), 6.75-7.57 (m, 3H, C_6H_3). ^{13}C NMR ($CDCl_3$), δ/ ppm: 8.6, 11.2, 26.8, 35.6, 35.7, 42.3, 70.5, 121.8, 125.1, 126.2, 127.1, 137.8, 140.6, 175.6.

Compound **3h:** Yellow solid; mp 115-116 °C; IR (KBr), ν_{max}/cm^{-1}: 3320, 1625, 1590, 1558, 1432, 1362. ^1H NMR ($CDCl_3$), δ/ ppm: 1.36 (s, 6H, $2CH_3$), 2.25 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.99 (br s, 1H, NH), 6.75-7.57 (m, 3H, C_6H_3). ^{13}C NMR ($CDCl_3$), δ/ ppm: 29.9, 30.5, 45.1, 68.5, 111.8, 112.1, 125.6, 140.6, 144.4, 148.2, 172.6.

Compound **3i:** Yellow solid; mp 123-124 °C; IR (KBr), ν_{max}/cm^{-1}: 3340, 1620, 1585, 1436. ^1H NMR ($CDCl_3$), δ/ ppm: 1.76 (s, 3H, CH_3), 2.96 (d, 1H, CH_2), 3.18 (d, 1H, CH_2), 3.45 (br s, 1H, NH), 3.77 (s, 3H, OCH_3), 6.35 (d, 1H, C_6H_3), 6.62 (dd, 1H, C_6H_3), 7.10-7.63 (m, 11H, C_6H_3 and $2C_6H_5$). ^{13}C NMR ($CDCl_3$), δ/ ppm: 29.5, 42.3, 54.4, 74.2, 104.8, 109.4, 123.6, 126.5, 127.2, 127.6, 128.1, 128.5, 128.8, 129.6, 137.3, 145.3, 146.3, 161.2, 165.3.

Compound **3j:** Yellow solid; mp 115-116 °C; IR (KBr), ν_{max}/cm^{-1}: 3290, 1615, 1548, 1442, 1360. ^1H NMR ($CDCl_3$), δ/ ppm: 1.70 (s, 3H, CH_3), 2.24 (s, 6H, $2CH_3$), 2.95 (d, 1H, CH_2), 3.12 (d, 1H, CH_2), 3.38 (br s, 1H, NH), 6.60 (s, 1H, C_6H_2), 7.10 (s, 1H, C_6H_2), 7.15-7.61 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ/ ppm: 18.6, 19.3, 29.6, 43.1, 75.1, 122.3, 125.4, 126.8, 126.9, 127.8, 128.2, 129.5, 129.6, 129.7, 134.8, 135.8, 137.7, 139.8, 147.7, 166.8.

RESULTS AND DISCUSSION

As illustrated in table 1, both of the linear and cyclic ketones react with the diamines containing both electron-donating and electron-withdrawing groups on aromatic rings, without any significant difference, to give the corresponding 1,5-benzodiazepine derivatives in quantitative yields. It is important to note that, starting from unsymmetrical ketones such as 2-butanone, the ring closure occurs selectively only from one side of the carbon skeleton giving a single product. Best results were obtained using 0.05 g of silica sulfuric acid; lower loading resulted in lower yields, while upper loading did not increase reaction yields significantly. The catalyst, recovered by filtration from the reaction media can be reused several times without any loss of activity (table 1, Entry **3a**). All reactions were completed within 1-2 h.

As shown in scheme 2, the proposed mechanism of the reaction [8,10,15] involves an intramolecular imine-enamine cyclization promoted by silica sulfuric acid.

CONCLUSIONS

In summary, we have developed an efficient and simple method for the synthesis of 1,5-benzodiazepine derivatives in the presence of silica sulfuric acid as a very inexpensive and recyclable solid acid catalyst which is found to catalyze efficiently the condensation of *o*-phenylenediamines with various linear and cyclic ketones in excellent yields under solvent-free conditions at room temperature. The easy work-up procedure, recyclable catalyst, short reaction times, selectivity, and very good

yields make this method an attractive and a useful contribution to the existing approaches.

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