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A Simple And New Method For The Synthesis Of 1,5-Benzodiazepine Derivatives Catalyzed By Boron Sulfonic Acid In Solvent H_2O/EtOH

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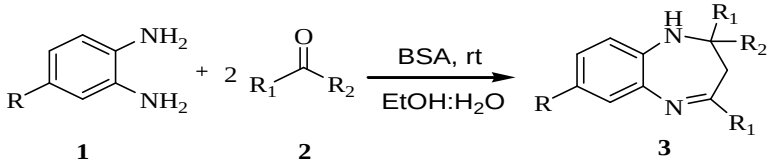
Abstract: An efficient synthesis of 1,5-benzodiazepines from *o*-phenylenediamine (OPD) and 1,2-diketones under solvent H_2O/EtOH conditions in the presence of $B(HSO_4)_3$ as a new catalyst at room temperature. This method is a very easy, rapid, and high yielding reaction for the synthesis of 1,5-benzodiazepine derivatives.
Keywords: Diazepine, boron sulfonic acid, BSA, *o*-phenylenediamine, 1,2-diketone, synthesis.

Introduction:

Benzodiazepines are interesting compounds because of their therapeutic properties[1]. Many members of this family are, in fact, nowadays widely used as tranquilizing and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 30 years ago[2], the research in this area is still very active and is directed towards the synthesis of compounds of enhanced pharmacological activity. These properties make benzodiazepines useful in treating anxiety, anti-convulsant, sedative, anti-depressant[3],platelet-activating factor antagonists, HIV trans-activator Tat antagonists[4], HIV reverse transcriptase inhibitors[5], insomnia, agitation, seizures, muscle relaxant properties, effect of the neurotransmitter, alcohol withdrawal, gamma-aminobutyric acid (GABA-A)[6] and anti tumor[7]. Benzodiazepines are categorized as either short-, intermediate- or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety. 1,5-Benzodiazepines are also used as starting materials for the preparation of some fused ring benzodiazepine derivatives, such as triaxol[8], and oxadiazol[9]. Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of 1,5-benzodiazepines has received little Attention. The literature methods for the synthesis of 1,5-benzodiazepines many of which have been reported recently, include condensation reactions of *o*-phenylenediamines with ,unsaturated carbonyl compounds[10], haloketones[11], or with ketones in the presence of catalysts like BF_3–etherate[12], $NaBH_4$[13], polyphosphoric acid or SiO_2[14], polyethylene glycol[15], and ionic Liquid[16].

We report a facile method relevant 1,5-benzodiazepines were prepared by using this procedure. To establish the generality of this protocol, various *o*-phenylenediamines are reacted with a wide range of ketones and the results are presented in Table 1. As a part of our efforts to explore the utility of surface-mediated reactions, we report here a new method for the preparation of 1,5-benzodiazepine derivatives by condensation of *o*-phenylenediamines with 1,2-diketones. It was found that a mixture of boron solfunic acid[17-23] under solvent conditions was capable of producing high yields of 2-methyl-2,4-di(4-methyl-3-pentenyl)-2,3-dihydro-1H-1,5-

benzodiazepine (Entry k) by condensation of *o*-phenylenediamines with 6-methyl-5-hepten-2-one under mild reaction conditions in 99% yield.



Scheme 1. 1,5-Benzodiazepines synthesis by using boron sulfonic acid

Experimental

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on 200 MHz using TMS as internal standard. IR spectra were recorded on Bomen MB 104 IR spectrometer. Column Chromatography was performed using Silica gel (100–200 mesh). Chemical shifts are given in ppm with respect to internal TMS, and J values are quoted in Hz. Mass spectra were recorded at 70 eV.

General procedure for the preparation of compounds A and L:

A mixture of *o*-phenylenediamines (1mmol) and various ketones (3mmol) was stirred at room temperature in the presence of $B(HSO_4)_3$ (10%, 0.1 gr) catalyst, in solvent ETOH/H_2O; after the completion of the reaction monitored via (TLC) using Ether and ethylacetate (9:1) as eluent; Ethanol (10 ml) was added to crystallize, the catalyst was removed under reduced pressure and the residue was purified by silica gel column chromatography using CH_2Cl_2:MeOH 95:5 as eluent. to afford pure product in 96% yield and structure was confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass.

2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine [A]: Yellow solid crystals: mp 138 ^{0}C; IR (KBr): 3292, 2955, 1632, 1474 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 6H, -C(CH_3)2), 2.2 (s, 2H, -CH_2), 2.4 (s, 3H, -CH_3), 6.7-7.2 (m, 4H, ArH). ^{13}C NMR: (50 MHz, $CDCl_3$) δ 29.7, 30.4, 46, 67.8, 121.8, 122.5, 125.6, 126.4, 137.9, 140.9, 171.5; CHN Analyses: Anal. Calc. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88%. Found: C, 76.51; H, 8.52; N, 14.92%; GC/MS: M^{+} =188.

10-Spirocyclohexan-2,3,4,10,11,11a hexahydro-1*H*-dibenzo[b,e][1,4]diazepine [B]: Yellow solid 137-138 ^{0}C; IR (KBr): 3328, 3060, 2923, 2852, 1617, 1493 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23-1.85 (m, 16H), 2.30-2.70 (m, 3H), 4.50 (br s, 1H), 6.65-7.4 (m, 4H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 21.8, 23.7, 24.5, 25.7, 33.8, 34.7, 39.3, 40.6, 52.4, 63.1, 121.3, 121.7, 126.7, 129.8, 138.1, 142.6, 178.9; CHN Analyses: Anal. Calc. for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45%. Found: C, 81.15; H, 9.56; N, 9.54%; GC/MS: M^{+} =268.

10-Spirocyclocyclopentan-1,2,3,9,10,10a-hexahydrobenzo[b]-cyclopenta[*e*][1,4] diazepine [C]: Yellow solid 139-140 ^{0}C. IR (KBr): 3279, 3059, 2859, 1635, 1481, 751 cm^{-1} . ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30-1.90 (m, 12H), 2.30-2.60 (m, 3H), 4.5 (br s, 1H), 6.8-7.9 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4, 24.0, 24.2, 28.9, 33.3, 38.3, 39.2, 54.3, 67.2, 118.6, 119.3, 126.9, 132.0, 139.1, 143.4, 178.1; CHN Analyses: Anal. Calc. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44%. Found: C, 80.62; H, 9.05; N, 10.54%; GC/MS: M^{+} =240.

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*- 1,5-benzodiazepine [D]: Yellow solid; mp 137-139 ^{0}C. IR (KBr): 3339, 3058, 2968, 1639, 1472, 1253 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8 (t, 3H, Me), 1.30 (t, 3H, Me), 1.31 (s, 3H, Me), 1.7 (q, 2H, CH_2), 2.2 (m, 2H, CH_2), 2.26 (q, 2H, CH_2), 3.3 (br s, 1H), 6.5–7.3 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.7, 10.8, 26.9, 35.5, 35.7, 42.1, 70.5, 121.8, 125.4, 126.2, 127.0, 137.9, 140.8, 175.6; CHN Analyses: Anal. Calc. for $C_{14}H_{20}N_2$: C, 77.33; H, 9.31; N, 12.94%. Found: C, 77.45; H, 9.40; N, 12.82%; GC/MS: M^{+} =216.

11-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-8-methyl-1*H*-dibenzo[b,e][1,4]-diazepine [E]: Yellow liquid; IR (KBr): 3305, 1660, 1597 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.80 (m, 16H), 2.25 (s, 3H), 2.30–2.70 (m, 3H), 4.50 (br s, 1H), 6.40 (s, 1H), 6.70 (d, 1H, J = 8.1 Hz), 7.20 (d, 1H, J = 8.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.2, 20.8, 23.6, 26.5, 27.5, 33.2, 34.8, 43.9, 47.6, 113.4, 123.6, 127.5, 128.6, 132.8, 134.1, 164.8; CHN Analyses: Anal. Calc. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.27; N, 9.91%. Found: C, 80.68; H, 9.40; N, 9.78%.

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5- benzodiazepine [F]: Yellow solid; mp 128–129 ^{0}C; IR (KBr): 3325, 1665, 1600 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6H), 2.19 (s, 2H), 2.23 (s, 3H), 2.80 (s, 3H), 6.68 (s, 1H), 6.70–6.80 (m, 1H), 7.05–7.10 (m, 1H); ^{13}C NMR (50 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; CHN Analyses: Anal. Calc. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.96; N, 13.84%. Found: C, 77.25; H, 8.82; N, 13.72%.

2,2,4-Trimethyl-2,3-dihydro-8-nitro-1*H*-1,5- benzodiazepine [G]: Yellow solid; mp 114–115 ^{0}C; IR (KBr): 3280, 1645, 1600 cm^{-1}. ^{1}HNMR(200 MHz,$CDCl_3$): δ 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.18 (s, 1H), 8.0–8.15 (m, 1H), 8.75–8.80 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.9, 30.0, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7; CHN Analyses: Anal. Calc. for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.01%. Found: C, 61.90; H, 6.58; N, 18.20%.

2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5- benzodiazepine [H]: Yellow solid; mp 113–114 ^{0}C; IR (KBr): 3290, 1635, 1597 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H), 2.22 (s, 2H), 2.34 (s, 3H), 2.80 (br s, 1H), 6.39 (s, 1H), 6.52 (s, 1H). ^{13}C NMR (50 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; CHN Analyses: Anal. Calc. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.31; N, 12.94%. Found: C, 77.85; H, 9.40; N, 12.82%.

2-Methyl--2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine [I]: Yellow solid; mp 151–152 ^{0}C; IR (KBr): 3335, 3058, 2970, 2858, 1613, 1493, 1328, 759 cm^{-1}. ^{1}H NMR(200 MHz,$CDCl_3$): δ 1.75 (s, 3H), 2.6 (br, 4H), 2.9 (d, 1H), 3.1 (d, 1H), 7.2-7.9 (m, 14H, ArH); CHN Analyses: Anal. Calc. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58%. Found: C, 84.68; H, 6.84; N, 8.45%; GC/MS: M^+ =312.

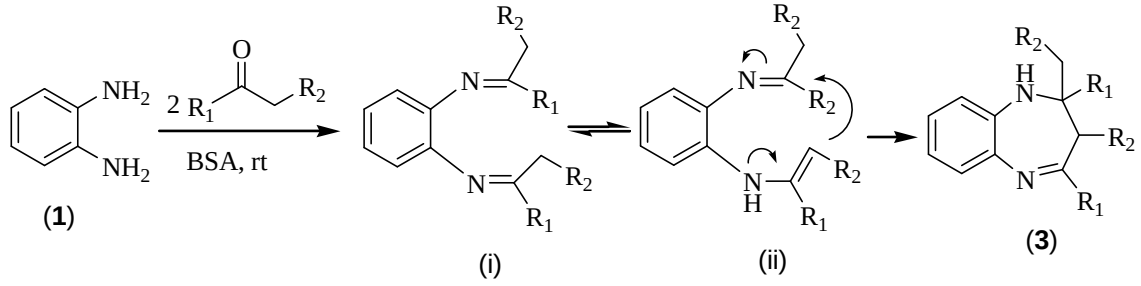
2,4-diisopropyl-2-methyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine [J]: Mp 119 °C; IR (KBr): 3268, 1665 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94 (d, 6H, CH (CH_3)$_2$), 1.12 (s, 3H, CH_3), 1.42 (d, 6H, N_C-CH (CH_3)$_2$), 1.85 (m, 1H, C*H* (CH_3)$_2$), 2.1 (m, 1H, C*H* (CH_3)$_2$), 2.47–2.55 (d, 1H, CH_2 a), 2.57–2.64 (d, 1H, CH_2, b), 3.67 (br s, 1H, NH), 6.64–7.35 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.6, 137.0, 132.8, 127.8, 122.8, 118.2, 113.6, 40.4, 36.1, 29.2, 23.8, 16.5, 14.7; CHN Analyses: Anal. Calc. for $C_{16}H_{24}N_2$: C, 78.64, H, 9.90; N, 11.46%. Found C, 78.54; H, 9.95; N 11.51%.

2-Methyl-2,4-di(4-methyl-3-pentenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine [K]: Yellow solid; mp 158–160 °C; IR (KBr): 3330, 1638 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 1.74 (s, 3H), 2.01–2.70 (m, 10H), 3.15 (s br, 1H), 5.03–5.24 (m, 2H), 6.67–7.19 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.7, 140.6, 137.9, 132.2, 131.9, 127.0, 125.48, 123.8, 123.4, 121.8, 121.7, 70.6, 43.0, 42.9, 42.7, 27.5, 25.7, 25.7, 25.1, 23.0, 17.7, 17.7.

2-Methyl-2,4-ditoluyl-2,3-dihydro-1*H*-1,5- benzodiazepine [L]: Yellow solid; mp 141–143 °C; IR (KBr): 3270, 1644, 1602 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11 (s, 9H), 3.05 (d, 1H, J = 13.6 Hz), 3.17 (d, 1H, J = 13.6 Hz), 3.60 (br s, 1H), 7.12–7.61 (m, 11H); ^{13}C NMR(50 MHz, $CDCl_3$): δ 21.3, 24.4, 28.4, 29.0, 46.4, 52.5, 114.7, 122.2, 126.2, 127.1, 128.6, 132.7, 133.1, 133.6, 135.5, 136.1, 164.9; CHN Analyses: Anal. Calc. for $C_{24}H_{24}N_2$: C, 84.66; H, 7.10; N, 8.22%. Found: C, 84.78; H, 7.22; N, 8.28%.

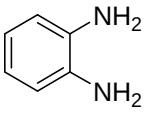
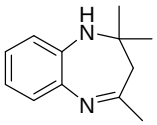
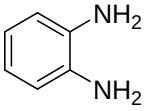
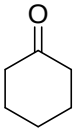
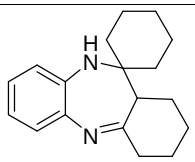
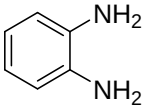
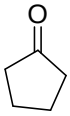
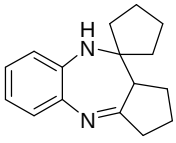
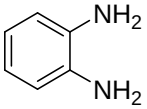
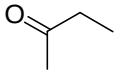
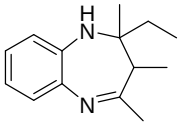
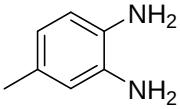
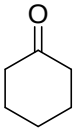
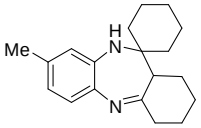
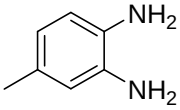
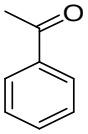
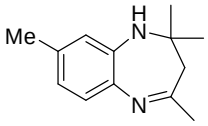
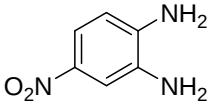
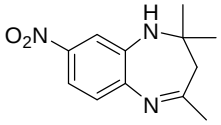
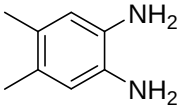
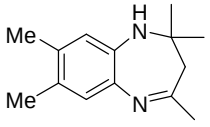
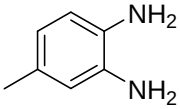
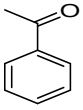
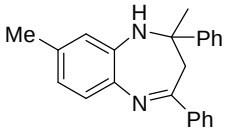
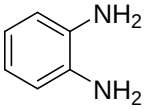
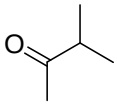
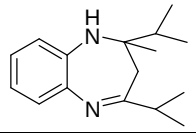
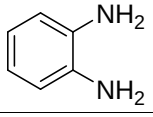
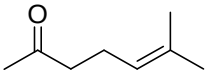
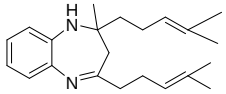
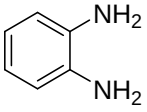
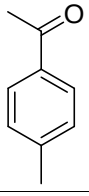
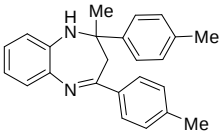
Structure assignments of new compounds:

The mechanism of the reaction probably involves an intramolecular imine–enamine cyclization promoted by $B(HSO_4)_3$ as shown in Scheme 2. *o*-Phenylenediamine attacks to carbonyl group of ketone giving the intermediate diimine (i). A 1,3-shift of the hydrogen attached methyl group then occurs to form an isomeric enamine, which cyclizes to afford seven-membered ring.



Scheme 2. Plausible mechanism of the diazepine synthesis

Table 1: Condensation of *o*-phenylenediamine with various ketones catalyzed by Boron Sulfonic Acid

Entry	Diamine (1)	Diketones (2)	Product (3)	Time (min)	Yield %
A				30	97
B				30	92
C				35	94
D				40	90
E				35	88
F				40	95
G				40	85
H				35	89
I				30	95
J				30	96
K				30	99
L				30	95

Conclusion:

In summary, we report, mild reaction, very good yields highly efficient for the synthesis of 1,5-benzodiazepines in solvent conditions. The use of inexpensive and easily available catalyst, experimental simplicity, simple work-up procedure, high yields with selectivity, recovery and relatively short reaction time and potentially useful for industrial applications are the attractive features of this method.

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