$InCl_3$-Catalyzed stereoselective synthesis of 1,5-benzodiazepines

J.S. Yadav,* B.V.S. Reddy, G. Satheesh G. Srinivasulu, and A. C. Kunwar

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
E-mail: yadav@iict.res.in

Dedicated to Dr. A. V. Rama Rao on his 70th birthday

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Abstract

o-Phenylenediamines (OPDA) undergo smooth condensation with 4,6-di-*O*-benzyl- or 4,6-di-*O*-acetyl- or 4,6-di-*O*-ethyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose derived from D-glucal in the presence of 2 mol% of $InCl_3$ under mild conditions to afford a new class of 1,5-benzodiazepines in good yields.

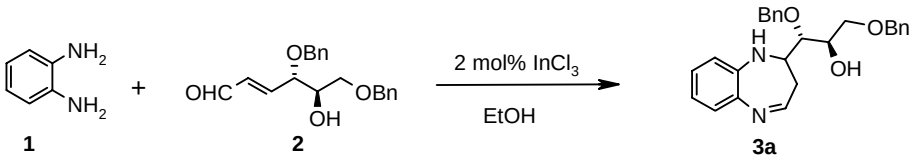
Keywords: *vic*-Diamines, α,β-unsaturated-δ-hydroxyaldehyde, diazepines

Introduction

Benzodiazepines have recently received great importance because of their wide range of therapeutic and pharmacological properties. Many members of diazepine family are nowadays widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents.[1,2] Benzodiazepine derivatives also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[5] As a result, various methods have been developed for the synthesis of 1,5-benzodiazepines.[6,7] Due to their wide range of biological, industrial and synthetic applications, the development of mild and efficient protocols continues to be a challenging endeavor in synthetic organic chemistry. In recent years, indium chloride has evolved as mild and water-tolerant Lewis acid imparting high regio-, stereo- and chemoselectivity in various organic transformations.[8] Compared to conventional Lewis acids, indium trichloride in particular has advantages of low catalyst loading, moisture stability and catalyst recycling. However, there have been no reports on the synthesis of diazepines from α,β-unsaturated sugar aldehyde and *o*-phenylenediamines.

Results and Discussion

In this article, we describe a novel and rapid approach for the synthesis of 1,5-benzodiazepines from *o*-phenylenediamines and 4,6-di-*O*-substituted-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose[9] using indium(III)chloride as a catalyst. Accordingly, treatment of *o*-phenylenediamine **1** with 4,6-di-*O*-benzyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose **2** in the presence of 2 mol% of $InCl_3$ in ethanol at room temperature afforded 1,5-benzodiazepine **3a** in 85% yield (Scheme 1).



Scheme 1

The structure of the product **3a** was established by using various solution NMR experiments like DQFCOSY, NOESY and HSQC. The HSQC spectrum showed that the presence of four CH_2 and eight CH's in the product **3a**.

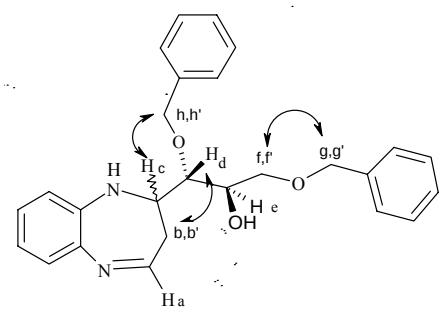
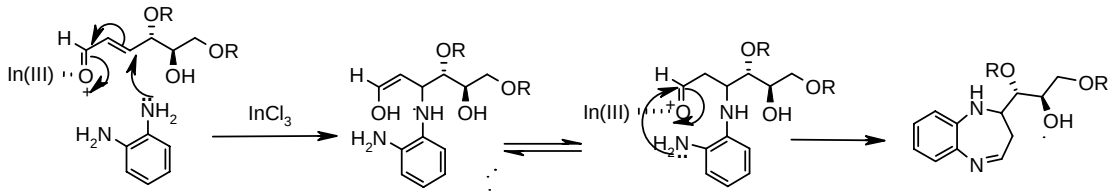


Figure 1. Schematic diagram with long range nOes of **3a**.

In a similar manner, various substituted *o*-phenylenediamines such as 4-methyl-, 4,5-dimethyl-, reacted rapidly with 4,6-di-*O*-benzyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose to give the corresponding benzodiazepine derivatives (entries **1a-c** Table 1). Other substrates such as 4,6-di-*O*-ethyl- and 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose gave the respective substituted 1,5-benzodiazepines in good yields under similar conditions (entries **d-g**, Table 1). All the products were characterized by ^1H, ^{13}C NMR, IR, and mass spectral analysis. The probable mechanism seems to be addition of amine to the unsaturated position of conjugated aldehyde, which is activated by indium trichloride. Thus the

initially formed Michael adduct may undergo cyclization with another amino group leading to the formation of diazepine (Scheme 2).



Scheme 2

Among various acid catalysts such as $CeCl_3.7H_2O$, $YbCl_3$, YCl_3, and $BiCl_3$ tested, indium trichloride was found to give the best results in terms of reaction rates and conversion. Further, we have carried out the experiments using various solvents such as water, ethanol, ionic liquid [bmim]BF_4, acetonitrile and tetrahydrofuran. As a solvent, ethanol appeared to give the best results. The scope and generality of this process was illustrated with respect to various substituted diamines and unsaturated sugar aldehydes and the results are summarized in Table 1.

Conclusions

In summary, we have developed a mild, rapid and efficient method for the synthesis pure 1,5-benzodiazepines through the condensation of sugar derived α,β-unsaturated-δ-hydroxyaldehydes with *o*-phenylenediamines using indium trichloride as the catalyst. The use of commercially available indium trichloride makes this method quite simple, more convenient and practical. It is entirely a novel protocol for the preparation of benzodiazepines in a single-step operation.

Experimental Section

General Procedures. IR spectra were recorded with a Perkin Elmer FTIR spectrophotometer. ^1H NMR spectra were carried out using a Bruker Avance 300, Varian Unity 400 and Varian Unity 500MHz spectrophotometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG Autospec M for FABMS mass spectrometers. Melting points for all the compounds were recorded on Electrothermal-9100 instrument. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel $60F_{254}$ to a thickness of 0.25mm (Merck). Column chromatography was conducted by elution of columns with silica gel 60-120 mesh using ethyl acetate and hexane as eluents.

General synthetic procedure

A mixture of *o*-phenylenediamine (1 mmol), α,β-unsaturated-δ-hydroxyaldehyde (1 mmol) and indium trichloride (0.02 mmol) in ethanol (10 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted by ethyl acetate (3x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate-hexane (1:9) to afford benzodiazepine. Spectral data for selected products.

1,3-Di(benzyloxy)-1-(2,3-dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-(1*S*,2*R*)-propan-2-ol (3a). Pale yellow crystalline solid, m.p. 95-97 ^oC; IR (KBr): 3354, 2921, 1507, 1304, 1101, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.07 (dt, $J_{Ha\text{-}Hb'}$=5.0 Hz, $J_{Hb\text{-}Hb'}$=14.3 Hz, $J_{Hb'\text{-}Hc}$=9.1 Hz, 1H, Hb'), 2.33 (dd, $J_{Hb\text{-}Hc}$=3.6 Hz, $J_{Hb\text{-}Hb'}$=14.3 Hz, 1H, Hb), 3.56 (dd, $J_{Hc\text{-}Hd}$=3.1 Hz, $J_{Hd\text{-}He}$=9.8 Hz, 1H, Hd), 3.67 (dd, $J_{He\text{-}Hf}$=2.1 Hz, $J_{Hf\text{-}Hf'}$=10.5 Hz, 1H, Hf), 3.78 (dd, $J_{He\text{-}Hf'}$=4.0 Hz, $J_{Hf\text{-}Hf'}$=10.5 Hz, 1H, Hf'), 3.80 (m, 1H, Hc), 4.16 (brs, 1H, NH), 4.56 (ABq, *J*=11.2 Hz, 2H, Hh and Hh'), 4.59 (ABq, *J*=11.2 Hz, 2H, Hg and Hg'), 5.03 (ddd, $J_{He\text{-}Hf}$=2.1 Hz, $J_{He\text{-}Hf'}$=4.0 Hz, $J_{Hd\text{-}He}$=9.8 Hz, 1H, He), 5.08 (d, $J_{Ha\text{-}Hb'}$=5.0 Hz, 1H, Ha), 7.5-6.5 (m, 14H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 138.8, 138.5, 137.1, 135.9, 128.2, 128.1, 127.5, 127.2, 119.5, 118.6, 118.4, 117.5, 77.2, 76.2, 72.2, 70.1, 69.4, 66.2, 47.1, 31.6; FABMS: m/z 415 ($M^{+\cdot}$) 367, 293, 277, 247, 173, 136, 115, 91, 81, 69, 55; HRMS calcd for $C_{26}H_{27}N_2O_3$: 415.2021 found: 415.2015.

1,3-Di(benzyloxy)-1-(7-methyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-(1*S*,2*R*)-propan-2-ol (3b). Pale yellow crystalline solid, m.p. 62-64 ^oC; IR (KBr): 3356, 2917, 1597, 1495, 1306, 1102, 807, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (m, 1H), 2.16 (s, 3H), 2.31 (dd, $J_{Hb\text{-}Hf}$ =3.71 Hz, $J_{Hb\text{-}Hb'}$=14.8 Hz, 1H, Hb), 3.55 (dd, $J_{He\text{-}Hf}$=2.9 Hz, $J_{Hf\text{-}Hf'}$=9.6 Hz, 1H, Hf), 3.66 (dd, $J_{He\text{-}Hf'}$=2.2 Hz, $J_{Hf\text{-}Hf'}$=9.6 Hz, 1H, Hf'), 3.75-3.80 (m, 2H, Hd and Hc), 4.1 (brs, 1H, NH), 4.56 (ABq, *J*=11.8 Hz, 2H, Hh and Hh'), 4.58 (ABq, *J*=11.8 Hz, 2H, Hg and Hg'), 5-5.05 (m, 1H, He), 5.06-5.1 (d, $J_{Ha\text{-}Hb}$=3.71 Hz, 1H, Ha), 6.36-6.56 (m, 3H, Ar-H), 7.24-7.38 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.3, 136.1, 135.5, 133.6, 133.0, 130.1, 130.7, 128.4, 128.2, 127.9, 127.6, 127.5, 121.8, 121.0, 120.1, 119.2, 118.3, 78.5, 73.4, 71.5, 69.7, 66.0, 49.4, 49.2, 30.5, 20.4; FABMS: m/z 430 ($M^{+\cdot}$) 201, 189, 175, 133, 109, 91, 79, 69, 55**;** HRMS calcd for $C_{27}H_{30}N_2O_3$: 430.2256 found: 430.2243.

1,3-Di(benzyloxy)-1-(7,8-dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-(1*S*,2*R*)-propan-2-ol (3c). Pale yellow crystalline solid, m.p. 60-61 ^oC; IR (KBr): 3374, 3028, 2919, 2862, 1618, 1512, 1454, 1360, 1091, 1026, 866, 742, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (m, 1H), 2.16 (s, 6H), 2.31 (dd, $J_{Hb\text{-}Hc}$=3.71 Hz, $J_{Hb\text{-}Hb'}$=14.8 Hz, 1H, Hb), 3.55 (dd, $J_{He\text{-}Hf}$=2.9 Hz, $_{Hf\text{-}Hf'}$=9.6 Hz, 1H, Hf), 3.65 (dd, $J_{He\text{-}Hf'}$=2.2 Hz, $J_{Hf\text{-}Hf'}$=9.6 Hz, 1H, Hf'), 3.74-3.79 (m, 2H, Hd and Hc), 4.1 (d, *J*=5.9 Hz, 1H, NH), 4.55 (ABq, *J*=11.8 Hz, 2H, Hh and Hh'), 4.59 (ABq, *J*=11.8 Hz, 2H, Hg and Hg'), 5.01 (ddd, $J_{He\text{-}Hf}$=1.48 Hz, $J_{He\text{-}Hf'}$=3.7 Hz, and $J_{Hd\text{-}He}$=9.6 Hz, 1H, He), 5.06 (t, $J_{Ha\text{-}Hb'}$=5.2 Hz, 1H, Ha), 6.33 (s, 1H, Ar-H), 6.37 (s, 1H, Ar-H), 7.23-7.39 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.3, 133.7, 133.1, 128.8, 128.3, 127.8, 127.6,

127.5, 127.4, 127.2, 120.9, 119.8, 78.5, 76.8, 73.4, 71.4, 69.7, 66.1, 49.0, 30.6, 18.6; FABMS: m/z 444 ($M^{+\cdot}$) 430, 203, 189, 173, 160, 154, 147, 136, 123, 109, 91, 79, 69; HRMS calcd for $C_{28}H_{32}N_2O_3$: 444.2412 found: 444.2403.

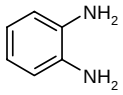
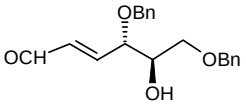
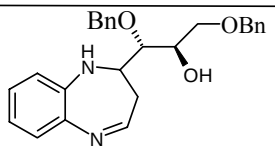
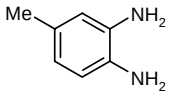
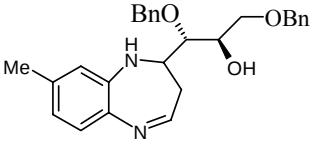
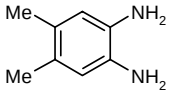
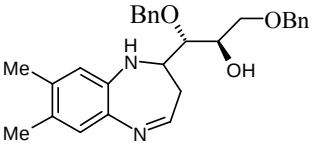
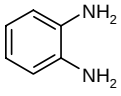
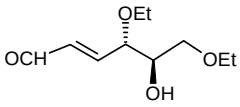
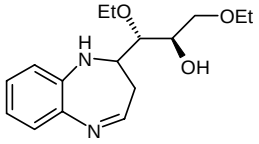
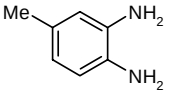
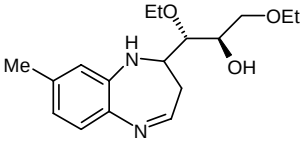
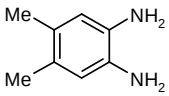
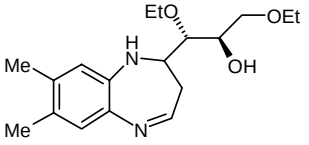
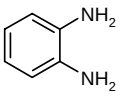
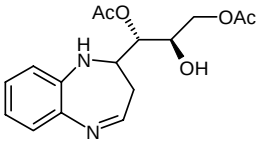
1-(2,3-Dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-1,3-diethoxy-(1*S*,2*R*)-propan-2-ol (3d). Brown crystalline solid, m.p.73-74 °C; IR (KBr): 3356, 2924, 2856, 1597, 1504, 1375, 1304, 1103, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.20-1.35 (m, 6H), 2.05 (dt, *J*=5.0, 14.3 and 9.1 Hz, 1H), 2.38 (dd, *J*=3.6 and 14.3 Hz, 1H), 3.30-3.78 (m, 8H), 3.80 (m, 1H), 4.15 (brs, 1H, NH), 4.98 (ddd, *J*=2.1, 4.0 and 9.8 Hz, 1H), 5.07 (d, *J*=5.0 Hz, 1H), 6.58-6.80 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4, 135.6, 121.3, 120.5, 119.5, 118.4, 78.5, 69.9, 66.7, 65.9, 49.4, 30.5, 29.6, 15.6, 15.0; FABMS: m/z 292 ($M^{+\cdot}$) 176, 146, 120, 91, 71, 57; HRMS calcd for $C_{16}H_{24}N_2O_3$: 292.1786 found: 292.1775.

1,3-Diethoxy-1-(7-methyl-2,3-dihydro-1*H*-benzo[b][1,4]-diazepin-3-yl)-(1*S*,2*R*)-propan-2-ol (3e). Brown crystalline solid, m.p.68-69 °C; IR (KBr): 3356, 2924, 2856, 1597, 1504, 1375, 1304, 1103, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.20-1.27 (m, 6H), 2.05 (dt, *J*=5.0, 14.3 and 9.1 Hz, 1H), 2.17 (s, 3H), 2.35 (dd, *J*=3.6 and 9.8 Hz, 1H), 3.35-3.75 (m, 8H), 3.85 (m, 1H), 4.10 (brs, 1H, NH), 4.95 (ddd, *J*=2.1, 4.0 and 9.8 Hz, 1H), 5.07 (d, *J*=4.5 Hz, 1H), 6.36-6.54 (m, 3H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 133.8, 130.0, 121.7, 119.5, 119.2, 78.5, 76.5, 69.9, 66.7, 65.9, 64.8, 49.2, 30.5, 20.4, 15.6, 15.0; FABMS: m/z 306 ($M^{+\cdot}$) 217, 203, 185, 175, 165, 159, 133, 121, 107, 95, 69, 55; HRMS calcd for $C_{17}H_{26}N_2O_3$: 306.1943 found: 306.1932.

1-(7,8-Dimethyl-2,3-dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-1,3-diethoxy-(1*S*,2*R*)-propan-2-ol (3f). Brown crystalline solid, m.p. 56-58 °C; IR (KBr): 3354, 2972, 2922, 2865, 2361, 1615, 1517, 1448, 1304, 1117, 1023, 869, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (m, 6H), 2.06 (dt, *J*=5.2, 14.2 and 8.9 Hz, 1H), 2.09 (d, *J*=2.4 Hz, 6H), 3.42-3.75 (m, 8H), 3.84 (m, 1H), 4.08 (d, *J*=6.5 Hz, 1H), 4.12 (brs, 1H, NH), 4.95 (ddd, *J*=2.4, 4.2 and 6.5 Hz, 1H), 5.08 (d, *J*=4.9 Hz, 1H), 6.33 (s, 1H, Ar-H), 6.41 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.9, 133.4, 128.6, 128.1, 121.0, 119.8, 78.7, 76.5, 70.1, 67.2, 65.3, 64.5, 49.5, 30.4, 29.1, 18.5, 15.3, 14.6; FABMS: m/z 320 ($M^{+\cdot}$) 173, 147, 119, 109, 95, 81, 69, 55; HRMS calcd for $C_{18}H_{28}N_2O_3$: 320.2099 found: 320.2087.

1-(2,3-Dihydro-1*H*-benzo[b][1,4]diazepin-3-yl)-2-hydroxy-3-methyl carboxyloxy-(1*S*,2*R*) -propyl acetate (3g). Pale yellow crystalline solid, m.p. 89-90 °C; IR (KBr): 3376, 2924, 1736, 1598, 1508, 1370, 1305, 1243, 1106, 1044, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.1-2.2 (m, 1H), 2.13 (s, 3H), 2.39 (dd, *J*=3.2 and 14.7 Hz, 1H), 3.5 (brs, 1H, NH), 3.9 (bd, *J*=3.2 Hz, 1H), 4.10-4.20 (m, 2H), 4.37 (dd, *J*=4.1 and 12.3 Hz, 1H), 4.82 (dd, *J*=3.2 and 9.8 Hz, 1H), 5.15 (t, *J*=4.9 Hz, 1H), 5.31 (ddd, *J*=2.4, 4.9 and 6.5 Hz, 1H), 6.56-6.8 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 170.1, 135.9, 135.3, 121.9, 121.3, 119.5, 118.8, 78.7, 70.8, 63.5, 63.2, 49.7, 29.9, 21.0, 20.8; FABMS: m/z 320 ($M^{+\cdot}$) 219, 191, 154, 136, 91, 69, 57; HRMS calcd for $C_{16}H_{20}N_2O_5$: 320.1372 found: 320.1356.

Table 1. Synthesis of 1,5-diazepines from *o*-phenyldiamines and α,β-unsaturated aldehyde

Entry	Diamine	Aldehyde	Product[a]	Reaction time (min)	Yield(%)[b]
1a				15 min	85
1b		"		12 min	80
1c		"		10 min	78
1d				10 min	85
1e		"		12 min	79
1f		"		15 min	75
1g		"		10 min	86

[a] Products were characterized by 1H NMR, 13C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

References and Notes

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