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An Expeditious Synthesis of 1,5-Benzodiazepine Derivatives Catalysed by *p*-toluenesulfonic Acid

M.A. Pasha and V.P. Jayashankara
Department of Studies in Chemistry,
Central College Campus,
Bangalore University, Bangalore-560 001, India

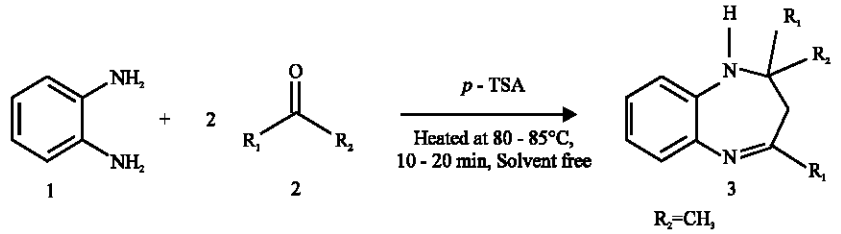
Abstract: 2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized by the condensation of *o*-phenylenediamine (OPDA) with cyclic/acyclic ketones in the presence of *p*-toluenesulfonic acid (*p*-TSA) as catalyst at 80-85 °C temperature, the yields are high and the reactions go to completion within 10-20 min.

Key words: *o*-phenylenediamine, ketones, *p*-toluenesulfonic acid, 1,5-benzodiazepines, Solvent free condition

Introduction

Sternbach *et al*. (1971) first introduced benzodiazepines as drugs. While some are used as anti-convulsant, anti-anxiety, analgesic, sedative, antidepressive and hypnotic agents (Fryer, 1991) some other benzodiazepine derivatives find application in industries, such as in photography and as dyes for acrylic fibers (Haris and Straley, 1970). It is also found that 1,5-benzodiazepines are valuable synthons for the preparation of other fused compounds such as triazolo, oxadiazolo, oxazino and furano-benzodiazepines (Aversa , *et al*., 1986; Chimirri *et al*., 1990; El-Sayed *et al*., 1999).

Expeditious synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines and related derivatives and improvements in the syntheses have been sought continuously. Thus the preparation of this type of heterocyclic nucleus is of much importance, consequently, methods have been reported by using a variety of reagents such as Br_3 (Yadav and Reddy, 2005), $MgO\text{-}POCl_3$ (Balakrishna and Kaboudin, 2001), solid super acid sulfated zirconia (Reddy and Sreekanth, 2003), zirconia solid acid (Benjaram *et al*., 2005), $Yb(OTf)_3$ (Curini *et al*., 2001), $Sc(OTf)_3$, (Surya *et al*., 2005), molecular iodine (Chen and Lu, 2005). Under microwave irradiation using acetic acid (Pozarentzi *et al*., 2002), $Al_2O_3\text{-}P_2O_5$ (Kaboudin and Navaee, 2001) and polymer (PVP) supported ferric chloride (Adharvana and Syamasundar, 2005). Many of the existing methods involve expensive reagents, require strongly



Scheme 1.

Corresponding Author: M.A. Pasha, Department of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore-560 001, India

acidic conditions, longer reaction times, high temperature, give unsatisfactory yields and involve cumbersome product isolation and environmental pollution. Therefore, there is a need for versatile, simple and environmentally friendly processes for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines (Scheme I).

Materials and Methods

Melting points were determined on a Buchi melting point apparatus. IR, ^{1}H NMR, ^{13}C NMR and Mass spectra were recorded on Nicolet 400D FT-IR spectrophotometer, 200 MHZ Brucker spectrometer and Shimadzu GC-MS QP 5050A, respectively. All ketones, *o*-phenylenediamine and *p*-TSA were commercial products and were used without further purification.

General procedure for 1,5-Benzodiazepine: *o*-Phenylenediamine (1.08 g, 10 m mol) and *p*-TSA (0.12 g, 0.6 m mole) were ground well and transferred to a 50 mL round bottomed flask, to this 3-pentanone (1.72 g, 20 mmol) was added and heated at 80-85°C for 10-20 min. After completion of the reaction {monitored on TLC [EtOAc: Cyclohexane (1:6)]}, the reaction mixture was diluted with water and extracted with EtOAc (2×10 mL). The combined organic layer was dried over anhyd. Na_2SO_4, concentrated in vacuo to afford 2,2,4-triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (2.24 g, 92 %) after silica gel chromatography.

Results and Discussion

In continuation with our work on synthesis of medicinally important molecules under environmentally safe conditions (Pasha *et al*., 2005) we have found that, *p*-TSA, which is an inexpensive and common organic chemical, can efficiently catalyze this reaction. Synthesis of 2,3-dihydro-1*H*-1, 5-benzodiazepines using acyclic, cyclic and aromatic ketones (2a) and *o*-phenylenediamine (1, 2:1 equivalents respectively) in the presence of *p*-TSA (catalytic amount) at 80-85°C under solvent free conditions is achieved in good to excellent yields with in 10 min, the results are given in Table 1.

The same process was successfully extended to get other 1, 5-benzodiazepine derivatives, the treatment of *o*-phenylenediamine with acetone (entry 2a, Table 1) in the presence of *p*-TSA at 80-85°C gave 2, 2, 4-trimethyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine in 94% yield. Similarly, 2-butanone, 3-pentanone and *iso*-butylmethylketone (entries 2b-d) reacted smoothly with *o*-phenylenediamine to give the corresponding 1,5-benzodiazepines in 70-92% yields and cyclic ketones like cyclopentanone, cyclohexanone and cycloheptanone also afforded 75-82% product (entries 2e-g). Interestingly acetophenone (entry 2h) also easily reacted with *o*-phenylenediamine within 20 min to yield 2-methyl-2, 4-diphenyl-2, 3-dihydro-1*H*-1, 5-benzodiazepine (92%, entry 3h).

Characterization of the products by Spectral analysis:

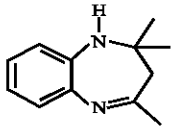
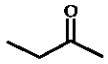
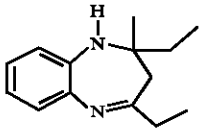
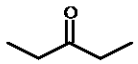
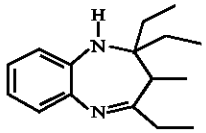
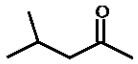
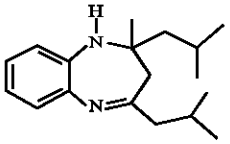
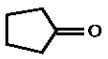
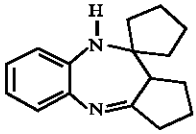
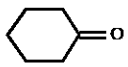
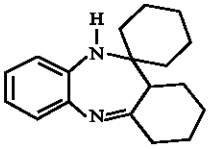
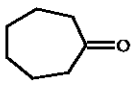
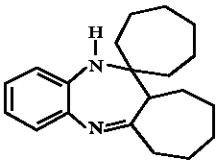
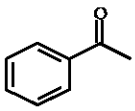
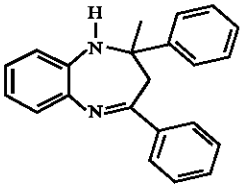
2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (3a)

Yellow crystals; mp-Found, 137-138 °C; Reported:136-138[5]

IR (KBr): 3343, 1657, 1610 cm^{-1}

^{1}H NMR (200 MHZ, $CDCl_3$): δ = 1.34(s, 6H), 2.21(s, 2H), 2.38(s, 3H), 2.93(br s, 1 H, NH), 6.64-7.4 (m, 4H)

Table 1: Condensatio of *o*-phenylenediamine with acyclic, cyclic and aromatic ketones is the presence of cat *p*-TSA

Entry (1)	Ketones (2)	Yield (%)[b]	Product[a] (3a-h)
a		94	
b		80	
c		92	
d		70	
e		80	
f		82	
g		75	
h		92	

[a]All the products are known, characterized by IR, MS, NMR spectral analysis and comparedwith the authentic samples. [b] Isolated yields.

^{13}C NMR (200 MHZ, $CDCl_3$): δ = 29.6, 30.2, 45.1, 67.4, 121.3, 122.1, 125.2, 126.5, 137.7, 140.3,171.7.
MS: *m/z* = 188 (M^+)

2,4-Diethyl-2-methyl-2,3-dihydro-1H-1,5-benzodiazepine (3b)
Yellow solid; mp-Found, 138 °C; Reported: 137-139 °C [5]
IR (KBr): 3335, 1648, 1605 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 0.98(t, 3 H, *J* = 6.9 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 1.71 (q, 2H, *J* = 6.9 Hz), 2.14 (m, 2 H), 2.36(s, 3H), 2.68 (q, 2H, *J*=7.0 Hz), 3.24 (br s, 1H,NH), 6.79–7.36 (m, 4H)
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 8.6, 10.7, 26.6, 35.6, 35.8, 42.3, 70.6, 121.9, 125.5, 126.1, 127.2, 137.9, 140.7,175.7.
MS: *m/z* = 216 (M^+)

2, 2, 4-triethyl-3-methyl-2, 3-dihydro-1H-1, 5-benzodiazepine (3c)
Colorless solid; mp-Found: 142-144 °C; Reported: 143-144°C[11]
IR (KBr): 3325, 1642, 1610 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 0.73-1.05(m, 10 H), 1.20-1.39 (m, 4H), 1.50-1.65(m, 2H) 2.40-2.60 (m, 2 H), 2.88(q, 1H, *J* = 6.9 Hz), 3.77 (br s,1H,NH), 6.58 (d, 1H, *J* = 8.0 Hz), 6.69(t, 1H, *J* = 8.0 Hz), 6.93 (t, 1H, *J* = 8.0Hz),7.37(d,1H, *J* = 8.0 Hz)
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 7.4, 7.9, 11.6, 12.3, 28.0, 28.7, 35.6, 46.3, 68.6, 117.6, 118.0, 126.9, 132.8,139.2,142.4, 173.4.
MS: *m/z* = 244 (M^+)

2-Methyl-2,4-diisobutyl-2,3-dihydro-1H-1,5-benzodiazepine (3d)
Yellow solid; mp-Found: 119 °C; Reported: 118-120 °C[11]
IR (KBr): 3335, 1645, 1600 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 0.98-1.05(m, 12H), 1.33 (s, 3 H), 1.49-1.53 (m, 2H), 1.65-1.78 (m, 1H) 2.08-2.25 (m, 3H), 2.26 (d, 2H, *J* = 12.8 Hz), 6.61-6.65 (m, 1H), 6.86-6.98 (m, 2H), 7.05-7.16(m, 1H)
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 22.6, 22.8, 24.5, 24.9, 25.3, 26.3, 28.4, 43.5, 51.7, 51.9, 70.5, 121.4, 121.5,128.2,127.2, 137.8,142.4, 174.0
MS: *m/z* = 272(M^+)

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[b] cyclopenta[e][1,4]diazepine (3e)
Yellow solid; mp-Found: 136-138 °C; Reported: 137-138 248 °C[5]
IR (KBr): 3335, 1660, 1610 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 1.32-1.91(m, 12H), 2.35-2.60 (m, 3H), 4.52 (br s, NH, 1 H), 6.74-7.39 (m, 4H).
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 23.5, 24.1, 24.3, 28.8, 33.4, 38.5, 39.2, 56.4, 67.3, 118.6, 119.3, 126.9, 133.1,139.2,143.8, 178.2.
MS: *m/z* = 240(M^+)

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1H-dibenzo[b,e] [1,4]diazepine (3f)
Yellow solid; mp-Found: 136-138 °C Reported: 136-137 °C[5]
IR (KBr): 3290, 1646, 1605 cm^{-1}

^{1}H NMR (200 MHZ, $CDCl_3$): δ = 1.24–1.85(m, 16H), 2.30-2.74(m, 3H), 4.48 (br s, NH, 1H), 6.69-7.35 (m, 4H).
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 21.8, 21.7, 23.5, 24.5, 25.3, 33.5, 34.4, 39.3, 40.8, 52.4, 63.1, 121.3, 121.6,126.3,129.7, 138.1,142.6, 178.8.
MS: *m/z* = 268(M^+)

10-Spirocycloheptan-6,7,8, 9,10,10a,11,12-octahydrobenzo[b] cyclohepta[e] [1,4]diazepine (3g)
Yellow solid; mp-Found: 136 °C; Reported: 135-136 °C[5]
IR (KBr): 3235, 3280,1645, 1600 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 0.92-1.95(m, 20H), 2.28-2.96(m, 3H), 3.60 (br s, NH, 1 H), 6.62-7.37 (m, 4H).
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 22.6, 23.2, 26.6, 28.4, 28.8, 29.5, 29.8, 30.1, 38.5, 41.0, 54.3, 72.5, 121.3,121.6,125.5, 127.6,138.1, 139.8, 179.2.
MS: *m/z* = 296 (M^+)

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (3h)
Yellow solid; mp-Found: 150-152 °C; Reported: 151-152 °C[11]
IR (KBr): 3345,1635 cm^{-1}
^{1}H NMR (200 MHZ, $CDCl_3$): δ = 1.82(s, 3H), 2.96(d, 1H, *J* = 12.8 Hz), 3.16 (d, 1H, *J* = 12.8 Hz) 3.45 (br s NH), 6.56-7.0 (m, 3H), 7.15-7.38 (m, 7H), 7.55-7.67 (m, 4H)
^{13}C NMR (200 MHZ, $CDCl_3$): δ = 166.5, 146.5, 140.1, 139.6, 138.1, 129.8, 128.1, 128.4, 121.2, 127.1, 126.5, 125.5, 121.8, 121.5, 73.9, 43.2, 29.8.
MS: *m/z* = 312 (M^+)

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