HETEROCYCLES, Vol. 68, No. 5, 2006, pp. 1017 - 1023. © The Japan Institute of Heterocyclic Chemistry
Received, 12th December, 2005, Accepted, 28th March, 2006, Published online, 31st March, 2006. COM-05-10647

SYNTHESIS OF 1,5-BENZODIAZEPINE DERIVATIVES CATALYSED BY ZINC CHLORIDE

Mohamed Afzal Pasha* and Vaderapura Puttaramegowda Jayashankara
Department of Studies in Chemistry, Central College Campus, Bangalore University, Bangalore-560 001, India
E-mail: m_af_pasha@yahoo.co.in

Abstract– 2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized by the condensation of *o*-phenylenediamine (OPDA) with cyclic or acyclic ketones in the presence of zinc chloride as catalyst at 80–85 ºC. The yields are high and the reactions go to completion within 10–20 min.

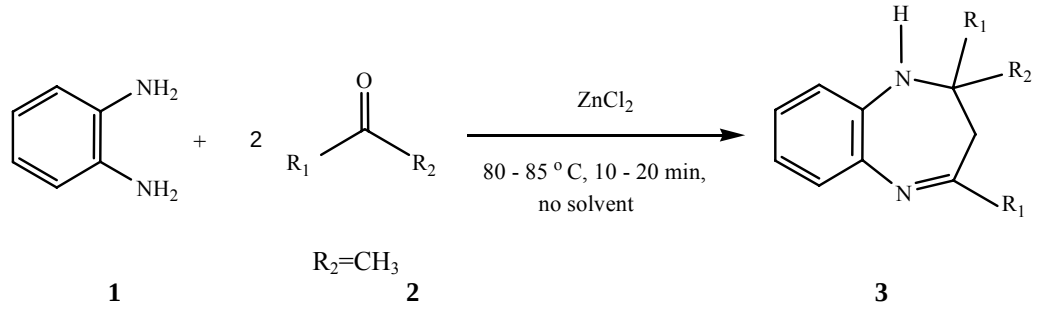
INTRODUCTION

In 1971, Sternbach *et al.* first introduced benzodiazepines as drugs.[1] 2,3-Dihydro-1*H*-1,5-benzodiazepine and its derivatives exhibit biological activity and are widely used in pharmacological studies.[2] Some benzodiazepine derivatives are also used in industries such as photography,[3a] as dyes for acrylic fibers and are used as anti-convulsant, anti-anxiety, analgesic, sedative, anti-depressive and as hypnotic agents.[3b] It is also found that 1,5-benzodiazepines are valuable synthons for the preparation of other fused compounds such as triazolo,[4a] oxadiazolo,[4b] oxazino[4c] or furobenzodiazepines.[4d]

Due to pharmacological importance, synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives has gained acceptance and popularity among the synthetic chemist community and a few methods have been reported for their synthesis from *o*-phenylenediamine (OPDA) and ketones with reagents such as $InBr_3$,[5] $BF_3{\cdot}OEt_2$,[6] MgO-$POCl_3$,[7] polyphosphoric acid-SiO_2,[8] solid superacid sulfated zirconia,[9a] $Ag_3PW_{12}O_{14}$,[9b] zirconia solid acid,[10] $Yb(OTf)_3$,[11] $Sc(OTf)_3$,[12] ionic liquids,[13] molecular iodine[14] and under microwave irradiation using acetic acid,[15] Al_2O_3-P_2O_5,[16] and polymer (PVP) supported ferric chloride.[17] Many of the existing methods involve expensive reagents, strongly acidic conditions, require longer reaction duration, high temperatures, incompatible with other functional groups, and cumbersome product isolation steps to give often unsatisfactory yields. Therefore, there is a need for simple and efficient processes for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines.

RESULTS AND DISCUSSION

Recently, we have reported the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidin-2(1*H*)-thiones from araldehydes, ß-keto esters, urea or thiourea and catalytic amounts of $ZnCl_2$ [18] and $SnCl_2$[19] *via* Biginelli reaction under microwave irradiation. $ZnCl_2$ has now been found to catalyze the reaction of OPDA with ketones to give 2,3-dihydro-1*H*-1,5-benzodiazepines in high yields under solvent free condition as shown in **Scheme 1**.



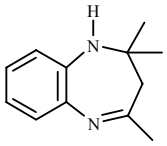
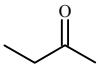
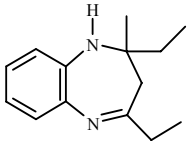
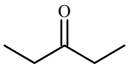
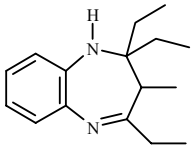
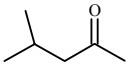
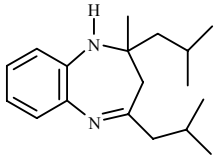
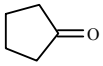
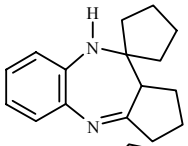
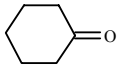
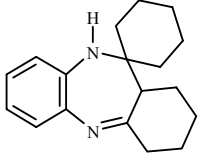
R_2=CH_3

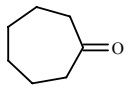
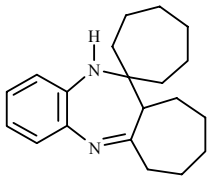
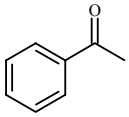
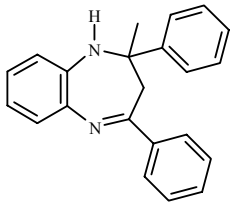
1 **2** **3**

Scheme 1

In a typical experiment, the ketone, OPDA (2:1 equivalents respectively) and $ZnCl_2$ (cat.) were ground well and transferred to a 50 mL round bottomed flask and heated at 80–85 ºC for 10–20 min without solvent to get the product in good to excellent yields. The procedure was successfully extended to the synthesis of other 1,5-benzodiazepine derivatives and the results are summarized in Table 1.

Table 1. Condensation of OPDA (**1**) with acyclic, cyclic and aromatic ketones (**2**) in the presence of $ZnCl_2$.

Entry	Ketones	Yield (%)	Product (**3**)[a]
a		94	
b		80	
c		92	
d		70	
e		80	
f		82	

g		75	
h		92	

a) All the products are known in the literatures (**3a**,[5] **b**,[5] **c**,[11] **d**,[11] **e**,[9b] **f**,[9b] **g**,[9b] **h**[10]) characterized by IR, NMR spectral analysis and compared with the authentic samples.

Comparison of the reported results of the reaction between OPDA and 3-pentanone in the presence of different catalysts with that of the present method involving use of catalytic amounts of different metal chlorides under solvent free condition is given in Table 2.

Table 2. Comparison of the reported methods for the condensation of OPDA with 3-pentanone in the presence of different catalysts.

Entry	Catalyst	Time	Temp. ºC	Yield (%) [b]
1	$InBr_3$[5]	2 h	25	94
2	$InCl_3$[5]	5.5 h	25	90
3	$Yb(OTf)_3$[11]	4 h	25	95
4	Sulfated zirconia [9]	2–3 h	25	84
5	CH_3COOH[14]	2 min	MW	90
6	$ZnCl_2$ [a]	10–20 min	80–85	92
7	$CuCl_2$ [a]	50 min	80–85	70
8	$NiCl_2$ [a]	60 min	80–85	67
9	$CoCl_2$ [a]	60 min	80–85	63
10	$FeCl_3$ [a]	60 min	80–85	58

a) Present method: Reaction condition: 3-pentanone (1.72 g, 20 mmol), OPDA (1.08 g, 10 mmol) and mentioned catalytic amount of metal chloride. b) Isolated yields.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus. IR spectra were recorded on Nicolet 400D FT-IR spectrophotometer, ^{1}H NMR, ^{13}C NMR were recorded on 200 MHz Bruker spectrometer, GC-MS using Shimadzu GC-MS QP 5050A spectrometer, and elemental analysis was performed on

Themo Finnigan FLASH EA 1112 CHNS analyzer. All ketones, OPDA and Lewis acids were commercial products and were used without further purification.

General procedure for 1,5-Benzodiazepines: 3-Pentanone (1.72 g, 20 mmol), OPDA (1.08 g, 10 mmol) and $ZnCl_2$ (0.35 g, ~2.5 mmol) were ground well and transferred to a 50 mL round bottomed flask and heated at 80–85 ºC for 10–20 min. After the completion of the reaction [monitored on TLC {eluant; EtOAc: pet.ether (1:6)}], the reaction mixture was diluted with water and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was directly charged on a silica gel column (EtOAc: pet.ether) to afford 2,2,4-triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazipine (2.24 g, 92 %).

All the products were characterized by comparison of their IR and NMR spectra with those of authentic samples.

2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3a**): Yellow crystals; mp 137–138 ºC (lit.[5] 136–138 ºC); IR (KBr): 3343, 1657, 1610 cm^{-1}; ^1H 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); ^{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; *Anal*. Calcd for $C_{12}H_{15}N_2$: C, 76.66; H, 8.04; N, 14.90. Found: C, 76.60; H, 8.10; N, 14.92; MS: *m/z* = 188 (M^+).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3b**): Yellow solid; mp 138 ºC (lit.[5] 137–139 ºC); IR (KBr): 3335, 1648, 1605 cm^{-1} ; ^1H 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; *Anal.* Calcd for $C_{14}H_{20}N_2$: C, 77.80; H, 9.33; N, 12.90. Found: C, 77.77; H, 9.30; N, 12.89; MS: *m/z* = 216 (M^+).

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3c**): Colorless solid; mp 142–144 ºC (lit.[11] 143–144 ºC); IR (KBr): 3325, 1642, 1610 cm^{-1}; ^1H 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* = 8.0 Hz), 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; *Anal.* Calcd for $C_{16}H_{24}N_2$: C, 78.76; H, 9.91; N, 11.48. Found: C, 78.70;H,

10.00; N, 11.03; MS: *m/z* = 244 (M^+).

2-Methyl-2,4-diisobutyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3d**): Yellow solid; mp 119 ºC (lit.[11] 118–120 ºC); IR (KBr): 3335, 1645, 1600 cm^{-1}; ^1H 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* = 12.8Hz), 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; *Anal.* Calcd for $C_{18}H_{28}N_2$: C, 79.48; H, 10.37; N, 10.29. Found: C, 79.52; H, 10.21; N, 10.20; MS: *m/z* =272 (M^+).

10-Spirocyclopentane-1,2,3,9,10,10a-hexahydrobenzo[*b*]cyclopenta[*e*][1,4]diazepine (**3e**): Yellow solid; mp 136–138 ºC (lit.[5] 137–138 ºC); IR (KBr): 3335, 1660, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32–1.91 (m, 12 H), 2.35–2.60 (m, 3 H), 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; *Anal.* Calcd for $C_{16}H_{20}N_2$: C, 80.07; H, 8.39; N, 11.67. Found: C, 80.11; H, 8.03; N, 11.53; MS: *m/z* = 240 (M^+).

10-Spirocyclohexane-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepine (**3f**): Yellow solid; mp 136–138 ºC (lit.[5] 136 – 137 ºC); IR (KBr): 3290, 1646, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24–1.85 (m, 16 H), 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; *Anal.* Calcd for $C_{18}H_{24}N_2$: C, 80.54; H, 9.01; N, 10.43. Found: C, 80.51; H, 9.04; N, 10.39; 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 136 ºC (lit.[5] 135–136 ºC); IR (KBr): 3235, 3280, 1645, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.92–1.95 (m, 20 H), 2.28–2.96 (m, 3 H), 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; *Anal.* Calcd for $C_{20}H_{28}N_2$: C, 81.15; H, 9.53; N, 9.46. Found: C, 81.03;

H, 9.48; N, 9.29; MS: *m/z* = 296 (M^+).

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3h**): Yellow solid; mp: 150–152 ºC (lit.[11] 151–152 ºC); IR (KBr): 3345, 1635 cm^{-1}; ^1H 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; *Anal.* Calcd for $C_{22}H_{20}N_2$: C, 84.69; H, 6.46; N, 8.96. Found: C, 84.58; H, 6.38; N, 8.93; MS: *m/z* = 312 (M^+).

ACKNOWLEDGEMENTS

One of the authors Jayashankara V P wishes to thank Mrs. Faheemunnisa, Assistant Mistress, Government Model Higher Primary School, Aswathnagar, Bangalore-560094, Karnataka, India for the encouragement. SIF and Deptt. of Organic Chemistry, Indian Institute of Science, Bangalore for recording NMR spectra.

REFERENCES

1. L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.,* 1971, **10**, 34.
2. R. I. Fryer, Bicyclic Diazapines, In “Chemistry of Heterocyclic Compounds”, Vol. 50, ed. by E. C. Taylor, Wiley, New York, **1991**, Chap. II.
3. (a) R. C. Haris and J. M. Straley, US Patent 1537757, **1968** (*Chem. Abstr*., 1970, **73**, 100054w). (b) L. O. Randall, B. Kappel, S. Garattini, and E. Mussini, “Benzodiazepines”, Raven Press: New York, **1973**, 27.
4. (a) M. C. Aversa, A. Ferlazzo, P. Giannetto, and F. H. Kohnke, *Synthesis*, 1986, 230; (b) A. Chimirri, S. Grasso, R. Ottana, G. Romeo, and M. Zappala, *J. Heterocycl. Chem.*, 1991, **27**, 371; (c) A. M. El-Sayed, H. Abdel-Ghany, and A. M. M. El-Saghier, *Synth. Commun.*, 1999, **29**, 3561; (d) K. V. V. Reddy, P. S. Rao, and D. Ashok, *Synth. Commun.*, 2000, **30**, 1825.
5. J. S. Yadav, B. V. S. Reddy, S. Praveenkumar, and K. Nagaiah, *Synthesis,* 2005, 480.
6. J. A. L. Herbert and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1,* 1974, 2657.

7. M. S. Balakrishna and B. Kaboudin, *Tetrahedron Lett.*, 2001, **42**, 1127.

8. D. L. Jung, T. W. Choi, Y. Y. Kim, I. S. Kim, Y. M. Park, Y. G. Lee, and Y. G Yung, *Synth. Commun.*, 1999, 194.

9. (a) B. M. Reddy and P. M. Sreekanth, *Tetrahedron Lett.*, 2003, **44**, 4447; (b) J. S. Yadav, B. V. S. Reddy, S. Praveenkumar, K. Nagaiah, N. Lingaiah, and P. S. Saiprasad, *Synthesis*, 2004, 901.

10. M. R. Benjaram, P. M. Sreekanth, and R. R. Vangala, *J. Molec. Catal. A: Chemical,* 2005, **225**, 71.

11. M. Curini, F. Epifano, M. C. Marcotullio, and O. Rosati, *Tetrahedron Lett.*, 2001, **42**, 3193.

12. K. D. Surya, A. Richard, and Gibbs, *Tetrahedron Lett.,* 2005, **45**, 1811.

13. D. V. Jarikote, S. A. Siddiqui, R. Rajagopal, T. Daniel, R. J. Lahoti, and K. V. Srinivasan, *Tetrahedron Lett.*, 2003, **44**, 1835.

14. W. Y. Chen and J. Lu, *Synlett*, 2005, 1337.

15. M. Pozarentzi, J. S. Stephanatou, and C. A. Tsoleridis, *Tetrahedron Lett.*, 2002, **43**, 1755.

16. B. Kaboudin and K. Navaee, *Heterocycles,* 2001, **55**, 1443.

17. M. Adharvana and C. K. Syamasundar, *Catal. Commun.*, 2005, **6**, 67.

18. M. A. Pasha, N. R. Swamy, and V. P. Jayashankara, *Indian J. Chem.*, 2005, **44B**, 823.

19. M. A. Pasha and V. P. Jayashankara, *Indian J. Heterocycl. Chem.,* 2005, **14**, 261.