Asian Journal of Chemistry; Vol. 32, No. 5 (2020), 1165-1168

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22574

One-Pot, Water-Mediated, H_2O_2-HCl Catalyzed Synthesis of Benzazepines

NIDHI SINGH and JAYA PANDEY*

Amity School of Applied Sciences, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226028, India

*Corresponding author: E-mail: jpandey@lko.amity.edu

Received: 6 December 2019; *Accepted*: 24 January 2020; *Published online*: 29 April 2020; AJC-19851

One-pot, multicomponent H_2O_2-HCl catalyzed system was employed for the synthesis of a series of benzazepine compounds. The implemented procedure oxidized the carbon-nitrogen bonds and produced benzazepines, while integrating diamines and substituted ketone. The advantage of the exercised synthetic route was that the reaction was water mediated and the completion time was quite reduced compared to the time required by conventional methods.

Keywords: One-pot, Multicomponent reaction, Benzazepine, Diamines, Ketone, Water, H_2O_2-HCl system.

INTRODUCTION

Benzazepines are chemical compounds comprising of a seven membered nitrogen heterocyclic ring fused to a six membered benzene ring [1]. It is an important class of drug compounds. The therapeutic value of benzazepine has been explored through a number of current existing drugs, like benazepril [2] used as oral medication in high blood pressure, heart failure [3] and diabetic renal failure, fenoldopam [4] functioning as antihypertensive agent [5], GSK-189,254 used as H_3 histamine receptor [6] inverse agonist in Alzheimer's disease, ivabradine used as antianginal agent or cardiotonic agent [7,8], lorcaserin used as appetite controlling agent for weight loss in obese patients [9], varenicline used for treating narcotic addicted patients [10], mozavaptan used for treating hyponatremia *via* vasopressin V_2 receptor antagonistic action [11,12]. The multiple therapeutic potential of benzazepines is the reason for its exploration as important drug candidate.

Various synthetic routes have been suggested for benzazepine synthesis. The multipotent compound has been synthesized *via* catalyzation by copper [13,14], lanthanide trichloride [15], ytterbium trichloride [16], iron [17], rhodium [18] and palladium [19,20]. Novel strategy of one-pot synthesis [21] has also been applied to benzazepines. One-pot synthesis are always considered to be better than multistep synthetic routes as the yields are quite high and time consumption is low. It is a greener and efficient approach in chemistry. With this viewpoint, we have advanced to develop a greener, solventless, one-pot synthetic route for benzazepine, catalyzed *via* H_2O_2-HCl system. The idea for this synthesis was derived and inspired from Bahrami's work [22] on benzimidazole.

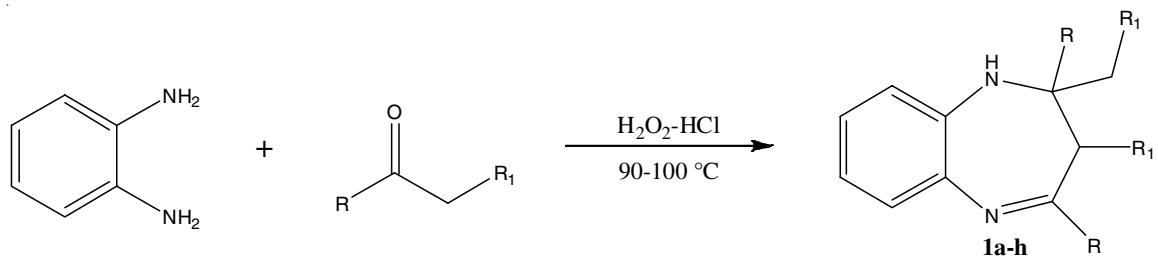
This work focuses on greener, high-yielding options for benzazepine synthesis. *o*-Phenylenediamine and carbonyl compound were used in the ratio of 1:2 and H_2O_2:HCl was used in the ratio of 2:1 for this synthesis. Water has been used as solvent providing a greener approach to this reaction. The novelty of work lies in the catalytic system combined with aqueous solvent system. The synthesized products (**1a-h**) have been outlined in **Scheme-I**.

EXPERIMENTAL

The reagents used were of the make Sigma and Avra and used without any further purification. The instrument used for NMR analysis was JNM-ECZ500R. IR analysis was performed on Perkin Elmer spectrum version 10.03.06. The synthesized compounds were characterized by spectral analysis and yields refer to the isolated products. The melting points were recorded on automatic melting/boiling point apparatus Therm °Cal0. The reactions were monitored *via* TLC and the developed spots were observed under ultraviolet light in UV cabinet.

General procedure: In a round bottom flask, *o*-phenylenediamine (1 mmol) and ketone (2 mmol) were taken. A magnetic stirrer was placed in the same flask. To this flask, a solution of

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.



Compound	1a	1b	1c	1d	1e	1f	1g	1h
R	CH_3	C_2H_5	C_2H_5	C_6H_5	4-OMe-C_6H_4	4-Me-C_6H_4	4-Cl-C_6H_4	4-NO_2-C_6H_4
R_1	H	H	CH_3	H	H	H	H	H

Scheme-I: Synthesis of Benzazepine analogues (**1a-h**) catalyzed by H_2O_2-HCl (2:1) system

30% hydrogen peroxide (6 mmol) and 37% hydrochloric acid (3 mmol) was added. The mixture was continuously stirred at 90-100 °C for 90-180 min (Table-1). The completion of reaction was monitored by TLC (hexane:ethyl acetate 6:4) and observed in UV cabinet. The reaction mixture was extracted with ethyl acetate. The extract was dried over sodium sulphate and the filtrate was concentrated under vacuum and the crude product was collected. The crude product was purified *via* column chromatography in hexane-ethyl acetate system to gain products in 82-95% yields.

Spectral analysis and physical properties of selected compounds

2,2,4-Trimethyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (1a): Dark yellow solid; m.p.: 135-138 °C; yield: 95%; IR (KBr, ν_{max}, cm^{-1}): 3290 (-NH- *str.*), 1580 (-NH- bend.), 3050 (aromatic -C-H- *str.*), 1665 (-C-C- *str.*), 1490 (-C-C- *str.*), 1060 (in plane –C-H bend.), 770 (-C-H- bend.); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 6.6-7.0 (m, 4H), 4.2 (s, 1H), 1.56 (m, 2H), 1.28 (t, 6H), 0.9 (t, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 164.6, 137.0, 132.4, 127.6, 122.8, 118.2, 113.7, 46.1, 44.3, 28.8, 27.6, 18.4; MS (*m/z*): 188 (M^+), 189 (M+1); Elemental anal. calcd. (%) for $C_{12}H_{16}N_2$: C, 76.55, H, 8.57, N, 14.88. Found (%) for $C_{12}H_{16}N_2$: C, 76.35, H, 8.77, N, 14.88.

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (1b): Pale yellow solid; m.p.: 140-143 °C; yield: 92%; IR (KBr, ν_{max}, cm^{-1}): 3285(-NH- *str.*), 1570 (-NH- bend.), 3035 (aromatic -C-H- *str.*), 1660 (-C-C- *str.*), 1490 (-C-C- *str.*), 1060 (in plane –C-H bend.), 760 (-C-H- bend.); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 6.5-7.1 (m, 4H), 4.0 (s, 1H), 1.56 (m, 2H), 1.48 (q, 2H), 1.40 (q, 2H), 1.33 (t, 3H), 1.10 (t, 3H), 0.9 (t, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 164.4, 137.1, 133.2, 127.8, 122.4, 117.8, 112.9, 47.6, 41.1, 35.3, 26.3, 26.1, 8.2, 6.4; MS (*m/z*): 216 (M^+), 217 (M+1); Elemental anal. calcd. (%) for $C_{14}H_{20}N_2$: C, 77.73, H, 9.32, N, 12.95. Found (%) for $C_{14}H_{20}N_2$: C, 77.53, H, 9.42, N, 13.05.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (1c): Yellow solid; m.p.: 143-147 °C; yield: 92%; IR (KBr, ν_{max}, cm^{-1}): 3280 (-NH- *str.*), 1575 (-NH- bend.), 3030 (aromatic -C-H- *str.*), 1650 (-C-C- *str.*), 1480 (-C-C- *str.*), 1060 (in plane –C-H bend.), 765 (-C-H- bend.); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 6.4-7.0 (m, 4H), 4.1 (s, 1H), 1.80 (q, 1H), 1.48 (q, 4H), 1.38 (q, 2H), 1.07 (d, 3H), 0.97 (t, 6H), 0.9 (t, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 165.4, 138.2, 133.9, 128.2, 123.1, 118.2, 113.6, 57.9, 37.7, 30.3, 23.6, 8.7, 7.1; MS (*m/z*): 244 (M^+), 245 (M+1); Elemental anal. calcd. (%) for $C_{16}H_{24}N_2$: C, 78.64, H, 9.90, N, 11.46. Found (%) for $C_{16}H_{24}N_2$: C, 78.52, H, 9.96, N, 11.52.

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (1d): Golden yellow solid; m.p.: 150-154 °C; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3290 (-NH- *str.*), 1580 (-NH- bend.), 3035 (aromatic -C-H- *str.*), 1665 (-C-C- *str.*), 1490 (-C-C- *str.*), 1070 (in plane –C-H bend.), 765 (-C-H- bend.), 680 (-C-H-*str.*); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 7.13-7.18 (m, 5H), 7.29-7.52 (m, 5H), 6.40-7.10 (m, 4H), 4.3 (s, 1H), 1.80 (q, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 165.1, 148.7, 137.0, 131.2, 130.8, 129.0, 128.6, 128.2, 127.8, 126.3, 125.7, 122.7, 118.7, 112.8, 51.0, 45.9, 28.7; MS (*m/z*): 312 (M^+), 313 (M+1); Elemental anal. calcd. (%) for $C_{22}H_{20}N_2$: C, 84.58, H, 6.45, N, 8.97. Found (%) for $C_{22}H_{20}N_2$: C, 84.48, H, 6.55, N, 8.97.

2,4-*Bis*-(4-methoxy-phenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (1e): Yellow solid; m.p.: 152-157 °C; yield: 89%; IR (KBr, ν_{max}, cm^{-1}): 3250 (-NH- *str.*), 1555 (-NH-bend.), 3020 (aromatic -C-H- *str.*), 1640 (-C-C- *str.*), 1465 (-C-C-*str.*), 1270 (-C-O- *str.*), 1055 (in plane –C-H bend.), 765 (-C-H-bend.), 680 (-C-H-*str.*); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 7.61 (d, 2H), 7.02 (d, 2H), 6.80 (d, 2H), 6.69 (d, 2H), 6.6-7.0 (m, 4H), 4.3 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 1.92 (s, 2H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 164.6, 164.3, 159.2, 141.2, 137.0, 130.0, 127.9, 127.1, 123.2, 121.3, 118.2, 114.1, 113.6, 56.3, 51.0, 45.9, 28.7; MS (*m/z*): 372 (M^+), 373 (M+1); Elemental anal. calcd. (%) for $C_{24}H_{24}N_2O_2$: C, 77.39, H, 6.49, N, 7.52, O, 8.59. Found (%) for $C_{24}H_{24}N_2O_2$: C, 77.27, H, 6.55, N, 7.55, O, 8.62.

2-Methyl-2,4-di-*p*-tolyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine (1f): Yellow coloured solid; m.p.: 150-155 °C; yield: 88%; IR (KBr, ν_{max}, cm^{-1}): 3268 (-NH- *str.*), 1568 (-NH- bend.), 3056 (aromatic -C-H- *str.*), 1668 (-C-C- *str.*), 1472 (-C-C- *str.*), 1280 (-C-O- *str.*), 1060 (in plane –C-H bend.), 755 (-C-H-bend.), 670 (-C-H-*str.*); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 7.50 (d, 2H), 7.09 (d, 2H), 7.01 (d, 2H), 6.98 (d, 2H), 6.6-7.0 (m, 4H), 4.0 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H), 1.80 (s, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 164.9, 145.7, 140.0, 138.1, 134.9, 129.3, 128.9, 127.8, 126.2, 122.6, 118.4, 113.8, 51.2, 45.9, 20.9; MS (*m/z*): 340 (M^+), 341 (M+1); Elemental anal. calcd. (%) for $C_{24}H_{24}N_2$: C, 84.67, H, 7.11, N, 8.23. Found (%) for $C_{24}H_{24}N_2$: C, 84.47, H, 7.21, N, 8.33.

2,4-*Bis*-(4-chloro-phenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (1g): Lemon yellow solid; m.p.: 159-162 °C; yield: 89%; IR (KBr, ν_{max}, cm^{-1}): 3272(-NH- *str.*), 1575 (-NH- bend.), 3062 (aromatic -C-H- *str.*), 1673 (-C-C- *str.*), 1478 (-C-C- *str.*), 1288 (-C-O- *str.*), 1058 (in plane –C-H bend.), 755 (-C-H- bend.), 720 (-C-Cl-*str.*), 672 (-C-H-*str.*); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 7.57 (d, 2H), 7.30 (d, 2H), 7.19 (d, 2H), 7.07 (d, 2H), 6.5-7.1 (m, 4H), 1.80 (s, 2H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 165.1, 146.8, 137.4, 136.1, 131.4, 130.7, 129.6, 129.0, 128.6, 127.8, 127.1, 122.8, 118.2, 113.6, 51.8, 45.5, 28.7; MS (*m/z*): 380 (M^+), 381 (M+1); Elemental anal. calcd. (%) for $C_{22}H_{18}N_2Cl_2$: C, 69.30, H, 4.76, N, 7.35, Cl, 18.60. Found (%) for $C_{22}H_{18}N_2Cl_2$: C, 69.40, H, 4.70, N, 7.31, Cl, 18.60.

2-Methyl-2,4-*bis*-(4-nitro-phenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (1h): Corn yellow solid; m.p.: 159-162 °C; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3280 (-NH- *str.*), 1582 (-NH- bend.), 3075 (aromatic -C-H- *str.*), 1685 (-C-C- *str.*), 1482 (-C-C- *str.*), 1290 (-C-O- *str.*), 1130 (-C-N-*str.*), 1058 (in plane –C-H bend.), 780 (-C-H- bend.), 690 (-C-H-*str.*); ^{1}H NMR ($CDCl_3$, 500 MHz, δ ppm): 8.22 (d, 2H), 8.11 (d, 2H), 7.88 (d, 2H), 7.39 (d, 2H), 6.4-7.2 (m, 4H), 4.1 (s, 1H), 1.82 (s, 2H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, δ ppm): 165.1, 146.8, 137.4, 136.1, 131.4, 130.7, 129.6, 129.0, 128.6, 127.8, 127.1, 122.8, 118.2, 113.6, 51.8, 45.5, 28.7; MS (*m/z*): 380 (M^+), 381 (M+1); Elemental anal. calcd. (%) for $C_{22}H_{18}N_4O_4$: C, 65.66, H, 4.51, N, 13.92, O, 15.90. Found (%) for $C_{22}H_{18}N_4O_4$: C, 65.65, H, 4.52, N, 13.84, O, 15.98.

RESULTS AND DISCUSSION

In the presented work, we have used a synthetic green route for benzazepine analogue synthesis, in aqueous medium. The method used is a one-pot synthetic route and a multicomponent reaction, involving *o*-phenylenediamine and carbonyl compound catalyzed by H_2O_2-HCl system. The reaction yields are quite high as the reaction proceeds *via* one-pot synthetic route, thereby minimizing the probability of side products and isolation at each step of a multistep reaction. The yields for the synthesized compounds are summarized in Table-1.

TABLE-1
REACTION BETWEEN *o*-PHENYLENEDIAMINE AND VARIOUS KETONES

Compound	R	R_1	Time (min)	Yield (%)
1a	CH_3	H	90	95
1b	C_2H_5	H	100	92
1c	C_2H_5	CH_3	110	92
1d	C_6H_5	H	130	90
1e	4-OMe-C_6H_4	H	95	89
1f	4-Me-C_6H_4	H	120	88
1g	4-Cl-C_6H_4	H	150	89
1h	4-NO_2-C_6H_4	H	180	90

The probable mechanistic route involves formation of hypochlorous acid (HOCl) by reaction of hydrogen peroxide and hydrochloric acid (H_2O_2:HCl 2:1), which further interacts with *o*-phenylenediamine and 2 mol of carbonyl compound for cyclizing the benzazepine product, followed by elimination of HCl. This oxidative mechanism is responsible for one-pot synthesis of benzazepine analogues.

To conclude, we have devised a new and efficient synthetic route for synthesis of substituted benzazepines. Usage of water as solvent, simple work-up and isolation, one-pot synthesis and high yields, make this method a preferred synthetic route for synthesis of benzazepines.

ACKNOWLEDGEMENTS

The authors are thankful to Amity University Uttar Pradesh, Lucknow campus for providing laboratory facilities for completion of this work. The authors are also thankful to Council of Science and Technology, U.P. (UPCST) (Grant registration #CST/D-2282/2016) and DST (Grant registration #CS-176/2013) for their financial support in completion of this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. T.J. Dodds, *Prim. Care Companion CNS Disord.*, **19**, 16r02037 (2017); https://doi.org/10.4088/PCC.16r02037
2. M.R. O'grady, M.L. O'sullivan, S.L. Minors and R. Horne, *J. Vet. Intern. Med.*, **23**, 977 (2009); https://doi.org/10.1111/j.1939-1676.2009.0346.x
3. J.N. King, C. Christinaz, G. Strehlau and J. Hornfeld, *J. Vet. Pharmacol. Ther.*, **41**, 485 (2018); https://doi.org/10.1111/jvp.12475
4. W.C. Oliver Jr., G.A. Nuttall, K.J. Cherry, P.A. Decker, T. Bower and M.H. Ereth, *Anesth. Analg.*, **103**, 833 (2006); https://doi.org/10.1213/01.ane.0000237273.79553.9e
5. S.W. Martin and K.J. Broadley, *Br. J. Pharmacol.*, **115**, 349 (1995); https://doi.org/10.1111/j.1476-5381.1995.tb15884.x
6. A.D. Medhurst, A.R. Atkins, I.J. Beresford, K. Brackenborough, M.A. Briggs, A.R. Calver, J. Cilia, J.E. Cluderay, B. Crook, J.B. Davis, R.K. Davis, R.P. Davis, L.A. Dawson, A.G. Foley, J. Gartlon, M.I. Gonzalez, T. Heslop, W.D. Hirst, C. Jennings, D.N.C. Jones, L.P. Lacroix, A. Martyn, S. Ociepka, A. Ray, C.M. Regan, J.C. Roberts, J. Schogger, E. Southam, T.O. Stean, B.K. Trail, N. Upton, G. Wadsworth, J.A. Wald, T. White, J. Witherington, M.L. Woolley, A. Worby and D.M. Wilson, *J. Pharmacol. Exp. Ther.*, **321**, 1032 (2007); https://doi.org/10.1124/jpet.107.120311
7. J.C. Kaski, S. Gloekler, R. Ferrari, K. Fox, B.I. Lévy, M. Komajda, P. Vardas and P.G. Camici, *Open Heart*, **5**, e000725 (2018); https://doi.org/10.1136/openhrt-2017-000725
8. M. Volterrani and F. Iellamo, *Card. Fail. Rev.*, **2**, 63 (2016); https://doi.org/10.15420/cfr.2015:26:1
9. D.B. Brashier, A.K. Sharma, N. Dahiya, S.K. Singh and A. Khadka, *J. Pharmacol. Pharmacother.*,**5**, 175 (2014); https://doi.org/10.4103/0976-500X.130158
10. K. Fagerström and J. Hughes, *Neuropsychiatr. Dis. Treat.*, **4**, 353 (2008); https://doi.org/10.2147/NDT.S927
11. K. Yamaguchi, N. Shijubo, T. Kodama, K. Mori, T. Sugiura, T. Kuriyama, M. Kawahara, T. Shinkai, H. Iguchi and M. Sakurai, *Jpn. J. Clin. Oncol.*, **41**, 148 (2010); https://doi.org/10.1093/jjco/hyq170
12. T. Tamura and K. Takeuchi, *BMJ Case Rep.*, **2013** bcr2013010039 (2013); https://doi.org/10.1136/bcr-2013-010039
13. R. Wang, R.X. Jin, Z.Y. Qin, K.J. Bian and X.S. Wang, *Chem. Commun.*, **53**, 12229 (2017); https://doi.org/10.1039/C7CC07027F

14. D. Li, Y. Park, W. Yoon, H. Yun and J. Yun, *Organic Lett.*, 21, 9699 (2019); https://doi.org/10.1021/acs.orglett.9b03853
15. S.E. Feng, F. Xu and Q. Shen, *Chin. J. Chem.*, **26**, 1163 (2008); https://doi.org/10.1002/cjoc.200890213
16. J. Wu, F. Xu, Z. Zhou and Q. Shen, *Synth. Commun.*, **36**, 457 (2006); https://doi.org/10.1080/00397910500383527
17. L.Z. Yu, Q. Xu, X.Y. Tang and M. Shi, *ACS Catal.*, **6**, 526 (2016); https://doi.org/10.1021/acscatal.5b02400
18. A.K. Pandey, S.H. Han, N.K. Mishra, D. Kang, S.H. Lee, R. Chun, S. Hong, J.S. Park and I.S. Kim, *ACS Catal.*, **8**, 742 (2018); https://doi.org/10.1021/acscatal.7b03812
19. P.A. Donets and E.V. Van der Eycken, *Org. Lett.*, **9**, 3017 (2007); https://doi.org/10.1021/ol071079g
20. N. Bozinovic, I. Opsenica and B.A. Solaja, *Synlett*, **24**, 49 (2013); https://doi.org/10.1055/s-0032-1317667
21. T.O. Vieira and H. Alper, *Org. Lett.*, **10**, 485 (2008); https://doi.org/10.1021/ol702933g
22. K. Bahrami, M.M. Khodaei and I. Kavianinia, *J. Chem. Res.*, **2006**, 783 (2006); https://doi.org/10.3184/030823406780199730