

One-Pot, Water-Mediated, H₂O₂-HCl Catalyzed Synthesis of Benzazepines

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One-pot, multicomponent H₂O₂-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, H₂O₂-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 H₃ 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 V₂ 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

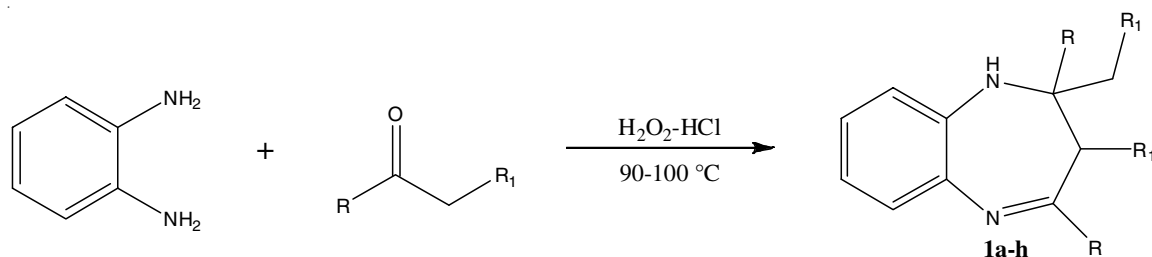
viewpoint, we have advanced to develop a greener, solventless, one-pot synthetic route for benzazepine, catalyzed *via* H₂O₂-HCl system. The idea for this synthesis was derived and inspired from Bahrami's work [22] on benzimidazole.

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 H₂O₂: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



Compound	1a	1b	1c	1d	1e	1f	1g	1h
R	CH ₃	C ₂ H ₅	C ₂ H ₅	C ₆ H ₅	4-OMe-C ₆ H ₄	4-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	4-NO ₂ -C ₆ H ₄
R ₁	H	H	CH ₃	H	H	H	H	H

Scheme-I: Synthesis of Benzazepine analogues (**1a-h**) catalyzed by H₂O₂-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-1H-benzo[*b*][1,4]diazepine (1a): Dark yellow solid; m.p.: 135-138 °C; yield: 95%; IR (KBr, $\nu_{\max}$, 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.); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₂H₁₆N₂: C, 76.55, H, 8.57, N, 14.88. Found (%) for C₁₂H₁₆N₂: C, 76.35, H, 8.77, N, 14.88.

2,4-Diethyl-2-methyl-2,3-dihydro-1H-benzo[*b*][1,4]diazepine (1b): Pale yellow solid; m.p.: 140-143 °C; yield: 92%; IR (KBr, $\nu_{\max}$, 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.); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₄H₂₀N₂: C, 77.73, H, 9.32, N, 12.95. Found (%) for C₁₄H₂₀N₂: C, 77.53, H, 9.42, N, 13.05.

2,2,4-Triethyl-3-methyl-2,3-dihydro-1H-benzo[*b*][1,4]diazepine (1c): Yellow solid; m.p.: 143-147 °C; yield: 92%; IR (KBr, $\nu_{\max}$, 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.); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₆H₂₄N₂: C, 78.64, H, 9.90, N, 11.46. Found (%) for C₁₆H₂₄N₂: C, 78.52, H, 9.96, N, 11.52.

2-Methyl-2,4-diphenyl-2,3-dihydro-1H-benzo[*b*][1,4]diazepine (1d): Golden yellow solid; m.p.: 150-154 °C; yield: 90%; IR (KBr, $\nu_{\max}$, 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.*); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₂H₂₀N₂: C, 84.58, H, 6.45, N, 8.97. Found (%) for C₂₂H₂₀N₂: C, 84.48, H, 6.55, N, 8.97.

2,4-Bis-(4-methoxy-phenyl)-2-methyl-2,3-dihydro-1H-benzo[*b*][1,4]diazepine (1e): Yellow solid; m.p.: 152-157 °C; yield: 89%; IR (KBr, $\nu_{\max}$, 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.*); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₄H₂₄N₂O₂: C, 77.39, H, 6.49, N, 7.52, O, 8.59. Found (%) for C₂₄H₂₄N₂O₂: C, 77.27, H, 6.55, N, 7.55, O, 8.62.

2-Methyl-2,4-di-*p*-tolyl-2,3-dihydro-1H-benzo[*b*][1,4]diazepine (1f): Yellow coloured solid; m.p.: 150-155 °C; yield: 88%; IR (KBr, $\nu_{\max}$, 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.*); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₄H₂₄N₂: C, 84.67, H, 7.11, N, 8.23. Found (%) for C₂₄H₂₄N₂: C, 84.47, H, 7.21, N, 8.33.

2,4-Bis-(4-chloro-phenyl)-2-methyl-2,3-dihydro-1H-benzo[b][1,4]diazepine (1g): Lemon yellow solid; m.p.: 159–162 °C; yield: 89%; IR (KBr, $\nu_{\max}$, 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.*); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₂H₁₈N₂Cl₂: C, 69.30, H, 4.76, N, 7.35, Cl, 18.60. Found (%) for C₂₂H₁₈N₂Cl₂: C, 69.40, H, 4.70, N, 7.31, Cl, 18.60.

2-Methyl-2,4-bis-(4-nitro-phenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine (1h): Corn yellow solid; m.p.: 159–162 °C; yield: 90%; IR (KBr, $\nu_{\max}$, 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.*); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₂H₁₈N₄O₄: C, 65.66, H, 4.51, N, 13.92, O, 15.90. Found (%) for C₂₂H₁₈N₄O₄: 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 H₂O₂-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 ₂ H ₅	H	100	92
1c	C ₂ H ₅	CH ₃	110	92
1d	C ₆ H ₅	H	130	90
1e	4-OMe-C ₆ H ₄	H	95	89
1f	4-Me-C ₆ H ₄	H	120	88
1g	4-Cl-C ₆ H ₄	H	150	89
1h	4-NO ₂ -C ₆ H ₄	H	180	90

The probable mechanistic route involves formation of hypochlorous acid (HOCl) by reaction of hydrogen peroxide and hydrochloric acid (H₂O₂: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.

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CONFLICT OF INTEREST

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

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