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Sustainable efficient synthesis and antibacterial studies of dibenzo (b, e) (1, 4) diazepine derivatives based on Cu-bronze catalyst

Asgar Jafar Khan[1]*, Mohammad A.Baseer[2]

[1]Laboratory of Organic Synthesis, Milliya College, Beed-431122, (INDIA)

[2]Organic Chemistry Research Laboratory, Yeshwant Mahavidyalaya, Nanded-431602, (INDIA)

E - mail : khan_asgar@yahoo.com

ABSTRACT

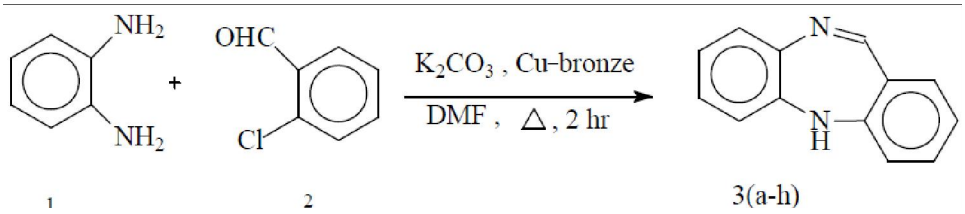
This study represent mild and a sustainable efficient rout for the synthesis of dibenzo (b, e) (1, 4) diazepine derivatives using Cu-bronze as a novel catalyst by condensation of *o*-phenylenediamine with aromatic aldehydes. This method is advantageous because of high yield of product easy workup procedure. The synthesized compounds were characterized by ^{1}HNMR, Mass and IR spectral analysis and screened for their potential as antibacterial.

KEYWORDS

Cu-bronze, Dibenzo (b, e) (1, 4) diazepine derivatives; *o*-phenylenediamine; Substituted aromatic aldehydes.

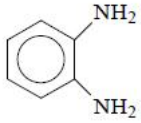
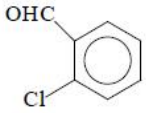
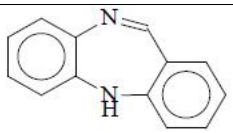
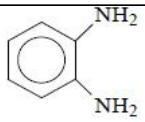
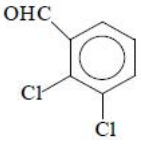
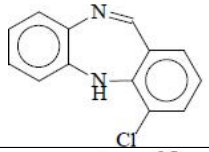
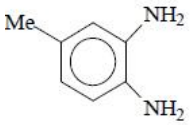
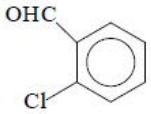
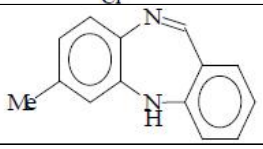
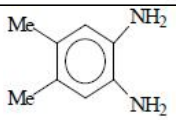
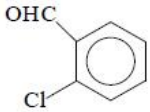
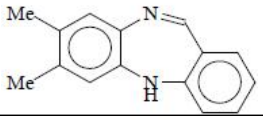
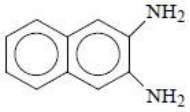
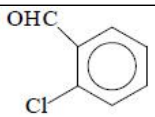
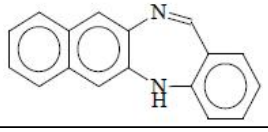
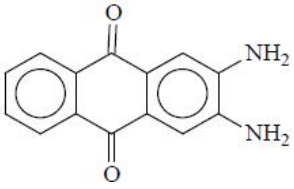
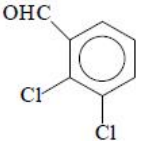
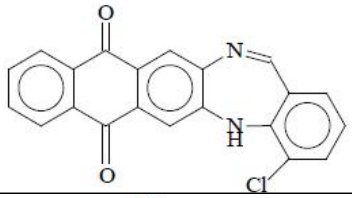
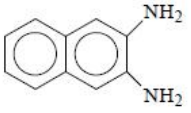
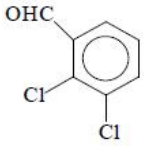
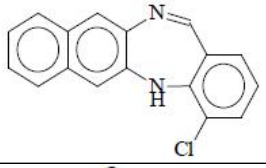
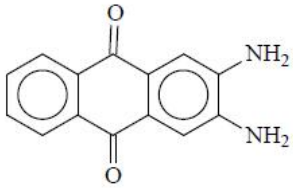
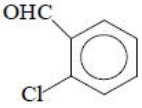
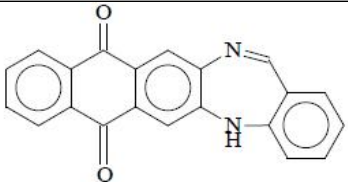
INTRODUCTION

In the field of organic chemistry an important largest area of research have been occupied by heterocyclic compounds. Synthesis of N containing heterocyclic compounds especially several type of benzodiazepine derivatives have been provoked much interest due to reported broad spectrum of biological activities such as anti-convulsant, anti-depressive, anti-bacterial, anti-anxiety, anti-inflammatory, tranquilizing, analgesic, hypnotic and sedative agents[1,2]. Benzodiazepines play a leading role in the treatment of cardiovascular disorder[3]. Additionally they have application in fine chemical industries such as photographical dyes for acrylic fiber[4]. Also have been reported to be used as a valuable synthons for the synthesis of fused ring benzodiazepines class of compounds like triazolo, oxadiazolo, oxazino and furano-benzodiazepines[5]. Keeping in view this broad spectrum of biological activity associated with these compounds various synthetic route have been reported in the literature, these include condensation of *o*-Phenylenediamine with á-â unsaturated carbonyl compounds[6], â haloketones[7] or Ketones in the presence various catalyst such as BF_3OEt[8], $NaBH_4$[9], PPA- SiO_2[10], TBAB[11], MgO-$POCl_3$[12], Yb $(OTf)_3$[13], Citric Acid[14], Amberlyst-15[15], sodium dodecyl sulfate[16], $Ag_3PW_{12}O_{40}$[17], solid super acid sulfated zirconia[18], acetic acid – under MWI[19], $AgNO_3$[20], zinc montmorilonite as catalyst at r.t[21], ionic liquid[22, 23], CAN[24], $ZnCl_2$[25] and $Hg(OTf)_2$[26]. However, despite the potential utility of these catalysts, a limitation with the majority of benzodiazepine derivatives syntheses is that of tedious workup procedure, formation of side products, involve long reaction time, give low yield of products and use expensive reagents. Furthermore, very few polycyclic bioactive benzodiazepines are reported in the literature. On the basis of these findings, we became interested in synthesis and



Scheme 1

TABLE 1 : Cu-bronze catalyzed synthesis of dibenzo (b, e) (1, 4) diazepine derivatives 3(a-h)

Entry	Phenylenediamine	Aldehydes	Products	Yields (%)	M.P.
a				80	94-96
b				85	98-99
c				82	92-93
d				84	112-113
e				82	198-199
f				82	268-269
g				85	190-191
h				82	272-274

antibacterial evaluation of novel dibenzo (b, e) (1, 4) diazepine derivatives. Herein, we described the synthesis of a dibenzo (b, e) (1, 4) diazepine derivatives (Scheme 1) and all compounds were evalu-

ated for their potential as antibacterial.

The Copper-bronze catalyzed condensation and intramolecular cyclisation was initially attempted and Buchwald's condition[27] for intramolecular N-arylation reactions were investigated. No reaction was observed without use of catalyst.

EXPERIMENTAL

All ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetra methyl silane. Infrared spectra were recorded on a Perkin Elmer infra red spectrophotometer using KBr discs and Mass spectra were taken on ESI –Esquire 3000 Brukers Daltonics instrument, TLC was performed on silica gel coated aluminum plates using ethyl acetate and pet ether (3:7 v/v) as eluent, melting points were determined on an electronic melting point apparatus and were uncorrected.

General procedures for the synthesis of Dibenzo (b, e) (1, 4) diazepine derivatives 3(a-h)

A mixture of *o*-phenylenediamine (10 mmole), substituted benzaldehydes (10 mmole), Cu-bronze (10 mol %) and Potassium carbonate (2 equiv), refluxed for 2 hrs in 20ml dimethyl formamide, the completion of reaction was monitored by TLC. After completion of reaction the reaction mixture was cooled and poured on crushed ice, extracted from ethyl acetate (20ml) and washed with water and brine. The solvent was removed by distillation under reduced pressure. The crude product was purified by column chromatography over slica-gel (60-120 mesh) using (eluent, ethyl acetate – pet-ether). The corresponding dibenzo (b, e) (1, 4) diazepine derivatives were obtained in 80-85 % yield.

RESULTS AND DISCUSSION

In the current strategy, the synthesis of Dibenzo (b, e) (1, 4) diazepine derivatives from *o*-phenylenediamine has been carried out successfully with substituted benzaldehydes in the presence of Copper-bronze and potassium Carbonate, cleaner transformation obtained, the progress of the reaction was monitored by TLC. The substrate and catalyst is not reported earlier in the literature to the best of our knowledge.. The products were obtained in excellent yield, the characterization of the synthesized compounds has been carried out by IR, ^{1}H-NMR and Mass spectroscopy data, all the synthesized compounds were screened for their potential as antibacterial, the results are summarized in TABLE 1 and TABLE 2.

ANTIBACTERIAL ACTIVITY

All the compounds were screened for their antibacterial activity against bacterial strains such as Bacillus subtilis, Pseudomonas aeruginosa Staphylococcus Aureus, Escherichia coli using penicillin as standard drugs. The activity was determined using cup plate agar diffusion method by measuring the inhibition zone in millimeter. Nutrient agar was used as a culture medium. A 1mg/ml solution in dimethyl formamide was used. The agar medium was incubated with bacterial culture tested. After 24hrs of incubation at 37^{0}C, the diameter of inhibition zone (in millimeters) was measured. The results of the antibacterial activity are given in TABLE 2.

Among the compounds screened 3f, 3g and 3h showed good activity against all bacteria. The remaining compounds 3a-3e were found to be moderately active against all bacteria.

Spectral data of the selected products

3a

IR (KBr): 3389, 2970, 1631,1591,1470,1100,744 cm^{-1};

^{1}HNMR ($CDCl_3$): δ= 3.4 (brs, 1H), 6.1-7.1 (m, 9H); MS (m/z):194 (M^+)

3b

IR (KBr): 3390, 2950, 1650,1590,1470,1100,744 cm^{-1};

^{1}HNMR ($CDCl_3$): δ=3.5 (brs, 1H), 6.0-6.9 (m, 8H); MS (m/z): 228 (M^+)

3c

IR (KBr): 3389, 2922, 1600, 1356,746 cm^{-1};

^{1}HNMR ($CDCl_3$): δ= 2.5 (s, 3H) 3.6 (brs, 1H), 6.0-7.5 (m, 8H); MS (m/z): 208 (M^+)

3d

IR (KBr): 3377, 1664, 1599, 1440,750 cm^{-1};

TABLE 2 : Antibacterial activity of dibenzo (b, e) (1, 4) diazepine derivatives 3(a-h)

Compound	Bacteria [Zone of Inhibition in mm]			
	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Staphylococcus Aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*
3a	10	18	11	20
3b	11	19	12	19
3c	11	23	15	21
3d	12	14	10	18
3e	11	14	12	16
3f	17	25	16	22
3g	16	21	14	17
3h	18	27	15	26
Penicillin	18	33	20	28

^{1}HNMR ($CDCl_3$): δ= 2.2 (s, 6H), 3.4 (brs, 1H), 6.1-7.3(m, 7H); MS (m/z):222 (M^+).

3h

IR (KBr): 3389, 2970, 1731,1581,1460,1100,744 cm^{-1};

^{1}HNMR ($CDCl_3$): δ= 3.5 (brs, 1H), 6.5-7.0 (m, 11H); MS (m/z):324 (M^+)

CONCLUSION

In conclusion, we have developed a Cu-bronze catalyzed condensation and intramolecular cyclization reaction which provide a dibenzo (b, e) (1, 4) diazepine derivatives as antibacterial agents with excellent to good yield. The route is flexible and allows for the preparation of series of compounds 3(a-h). The catalyst is novel, inexpensive and readily available.

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REFERENCES

[1] **(a)** H.Schutz; Benzodiazepines, Springer Heidelberg, **2**, 240 **(1982)**; **(b)** R.K.Smalley; In Comprehensive Organic Chemistry, D.Barton, W.D.Ollis (Eds); Pergamon, Oxford, **4**, 600 **(1979)**; **(c)** J.K.Landquist; In Comprehensive Hetero-cyclic Chemistry, A.R.Katritzky, C.W.Rees (Eds); Pergamon: Oxford, **1**,166 **(1984)**.

[2] L.O.Randall, B.Kappel; In Benzodiazepines, S.Garattini, E.Mussini, L.O.Randall (Eds); Raven Press: New York, and references cited therein **27,(**1973**); (b)** C.W.Kuo, C.Wang, V.Kaval, C.F.Yao; Molecules, **13,** 2313 **(2008)**.

[3] **(a)**K.S.Atwal, J.L.Begye, A.Hedberg, S.Moreland; J.Med.Chem, **30,** 635 **(1987)**; **(b)** M.D.Braccio, G.Grassi, G.Roma, L.Vergin, M.Mura, M.Marongiu; Eur.J.Med.Chem., **36**, 935 **(2001)**; **(c)** H.Benedikta, D.Pudziunaite, R.Janciene, L.kosychora; Arkivoc, **4**, 512 **(2000)**.

[4] R.C.Harris, J.M.Straley; US Patent 1,537, 753,757, 1968., Chem. Abstr., **73**, 100,054W **(1970)**.

[5] **(a)** M.Essaber, A.Baouid, A.Hasnaoui, A.Benharref, J.P.Lavergne; Synth. Commun., **28**, 4097 **(1998)**;

(b) A.M.El-Sayed, Abdel, H.Ghany, A.M.El-Saghier; Synth.Commun., **29**, 3561 **(1999)**; **(c)** X.J.Xu, H.T.Wu, S.Jin; Chin.J.Chem., **17,** 84 **(1999)**; **(d)** X.Y.Zhang, J.X.Xu, S.Jin; Chin.J. Chem., **17**, 404 **(1999)**; **(e)** K.V.Reddy, P.S.Rao, D.Ashok; Synth.Commun., **30**, 1825 **(2000)**.

[6] P.Stahlofen, W.Ried; Chem. Ber., **90**, 815 **(1957)**.

[7] W.Ried, E.Torinus; Chem. Ber., **92**, 2902 **(1959)**.

[8] J.A.Herbert, H.Suschitzky; J.Chem.Soc.Perkin-Trans., **1**, 2657 **(1974)**.

[9] H.R.Morales, A.Bulbarela, R.Contreras; Heterocycles, **24**, 135 **(1986)**.

[10] D.I.Jung, T.W.Choi, Y.Kim, I.S.Kim, Y.M.Park, Y.G.Lee, D.H.Jung; Synth.Commun, **29**, 1941 **(1999)**.

[11] M.A.Baseer, A.J.Khan; E- Journal of Chemistry, **9(1)**, 407-417 **(2012)**.

[12] M.S.Balakrishna, B.Kaboudin; Tetrahedron..Lett., **42**, 1127 **(2001)**.

[13] M.Curini, F.Epifano, M.C.Marcotullio, O.Rosati; Tetrahedron. Lett., **42**, 3193 **(2001)**.

[14] M.A.Baseer, A.J.Khan, Rec. Res. Sci. Tec., **3**, 101 **(2011)**.

[15] J.S.Yadav, B.V.S.Reddy, B.Eshwaraian, K.Anuradha; Green.Chem., **4**, 592 **(2002)**.

[16] G.Sharma, R.Kumar, A.K.Chakraborti; Tett. Lett., **49**, 4269 **(2008)**.

[17] J.S.Yadav, B.V.S.Reddy, S.PraveenKumar, K.Nagaiah, N.Lingaiah, P.S.Saiprasad, Synthesis., **6**, 901 **(2004)**.

[18] B.M.Reddy, P.M.Sreekanth; Tetrahedron.Lett., **44**, 4447 **(2003)**.

[19] M.Pozarentzi, J.S.Stephanatou, C.A.Tsoleridis; Tetrahedron, Lett., **43**, 1755 **(2002)**.

[20] R.Kumar, P.Chaudhary, S.Nimesh, A.K.Varma, R.Chandra; Green. Chem.**, 8,** 519 **(2006)**.

[21] R.Varala, E.Ramu, S.R.Adapa; Arkivoc, references cited therein, **171 (2006)**.

[22] D.V.Jarikote, S.A.Siddiqui, R.Rajagopal, T.Daniel, R.J.Lahoti, K.V.Srinivasan; Tetrahedron Lett., **44**, 1835 **(2003)**.

[23] Du.Yuying, T.Fuli, Z.Wenzhi; Synthetic.Commun., **36**, 1661 **(2006)**.

[24] R.Varala, R.Enugala, S.Nuvala, S.R.Adapa; Synlett., 1009 **(2006)**.

[25] M.Pasha; V.P.A ans Jayashankara, Hetercycles, **68**, 1017 **(2006)**.

[26] M.Gourhari, K.Utpal, K.Rajiv, N.B.Rudraksha; Tetrahedron.Lett., **53**, 1460 **(2013)**.

[27] Review: B.H.Yang, S.L.Buchwald; J.Organomet. Chem., **576**,125-146 **(1999)**.