World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 3.347

SYNTHESIS OF 2,3-DIPHENYL QUINOXALINE USING BIOCOMPATIBLE DEEP EUTECTIC SOLVENT.

Santosh Bansilal Katariya*

Department of Chemistry, SIES College, Sion, Mumbai 400 022, India.

Article Received on 11/05/2016 **Article Revised on 31/05/2016** **Article Accepted on 21/06/2016**

***Corresponding Author**
Santosh Bansilal Katariya
Department of Chemistry, SIES College, Sion, Mumbai 400 022, India.

ABSTRACT

An efficient protocol for the synthesis of 2, 3-diphenyl quinoxaline in deep eutectic solvents under solvent-free conditions is reported here. Quinoxaline derivatives are well known in the pharmaceutical industry for their broad-spectrum of biological activities. The reaction is remarkably facile because of the air and water stability of the catalyst, and needs no special precautions. The reaction was completed within 25 minutes with excellent yield. The product formed was sufficiently pure, and can be easily recovered. The use of deep eutectic solvent choline chloride/urea in solid phase offered several significant advantages such as low cost, greater selectivity and easy isolation of products.

KEYWORDS: Green chemistry, deep eutectic solvent (DES), Ultrasonic irradiation.

1. INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen containing benzo heterocyclic compounds containing a ring complex made up of a benzene ring and a pyrazine ring.[1] Quinoxalines derivatives are important biological agents and therefore a significant development of research has been directed towards the synthesis of this class of compounds.[2] In particular, they are used as antibacterial,[3] anti-tumor,[4] antiviral,[5] anti-inflammatory,[6] antifungal,[7] anti-tubercular,[8] antimalarial,[9] antileishanial,[10] and anticonvulsant.[11] They are also used in the agricultural field as insecticides fungicides and herbicides, pesticides as well as their application in dyes, chemical controllable switches, efficient electroluminescent materials and organic semiconductors.[12-14]

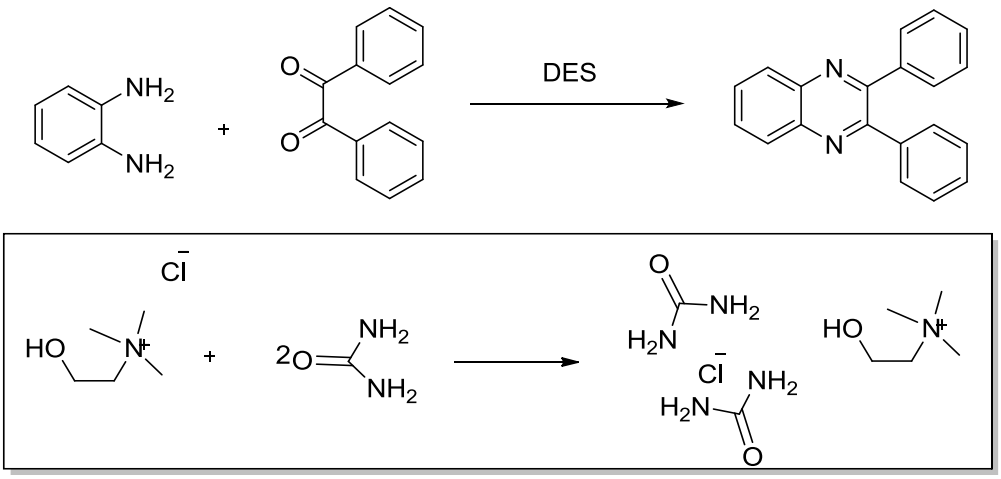
Heterocycles are used in many various industries. However most of these compounds aren't extracted from natural source, but are synthesized to complete the demand. Consequently, many methods have been developed for the synthesis of quinoxaline, despite the progress, the synthesis of these compounds remains some modification less than ideal. Thus, the development of environmentally friendly benign (Green Chemistry), high-yield and clean approaches for the yield of quinoxaline derivatives still remains a highly desired goal in organic synthesis. Performing organic reactions in water has attracted much attention over the past decades due to its numerous advantages such as being considerably safe, nontoxic, environmentally friendly, and cheap. In addition, reactions in water can facilitate access to different reactivity and selectivity patterns compared with those observed in common organic solvents.[15] Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1, 2-diamines with α-diketones,[16] condensation of o-phenylenediamines with 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation.[17]

Recently Feng J., *et al* used o-phenylenediamines and α-hydroxy ketones as reactants in the synthesis of quinoxaline derivatives.[18] Different reaction media were used to perform this synthesis such as the use of acetonitrile or DMSO as solvents,[19, 20] or even cleaner ways as the solvent-free reaction, with various ways to give energy to the substrate, such as microwave radiation,[21] ultrasound[22] or even room temperature.[23] Recently development of a mild and eco-friendly protocol for these highly significant classes of compounds was investigated by Mahadik and coworkers,[24] Where they used ultrasonic radiations to complete the reaction; ethanol employed as a solvent was not only inexpensive but also environmentally benign.

Many of these processes suffer from one or more limitations such as drastic reaction conditions, relatively expensive reagents, low yields, the use of toxic metal salts as catalysts and tedious work-up procedures.

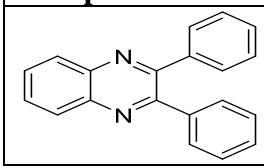
In view of the disadvantages, there remains a scope for the development of facile and green method for the synthesis of the quinoxaline derivatives. Here we use deep eutectic solvent choline chloride/urea in solid phase offered several significant advantages such as low cost, greater selectivity and easy isolation of products.

Scheme



Choline chloride (2-hydroxyethyltrimeethylammoniumchloride) reacts with urea to produce DES.

Table 1: Comparison between traditional synthesis and green techniques.

Compound	Parameter	Traditional method	Green Techniques			
			A	B	C	D
	Time Required	1 hr	08 min	10 min	20 min	25 min
	% Yield	75	97	95	94	93
	Melting point ^{0}C	125-127	126	125	127	126

2. MATERIALS AND METHODS

All common reagents and solvents were used as obtained from commercial supplires without further purification. All chemicals were from S.D Fine chemicals India. Melting points were reported are uncorrected. IR spectra recorded on a FTIR-4100 spectrometer and The ^{1}H NMR spectra were recorded on a Bruker (400 MHz) spectrometer using TMS as internal standard. Chemical shifts were given in ppm relative to internal reference for DMSO and $CDCl_3$.

Representative procedure for the preparation of deep eutectic solvent

Choline chloride (2.8 g, 20 mmol) and urea (2.4 g, 40 mmol) were placed in a round bottomed flask and heated to 70˚C to 80˚C, until homogenous colourless liquid was formed which was used directly for the reactions.

Method A: O-phenylenediamine (0.108 gm, 0.001 mol) and Ben zil (0.210 gm, 0.001 mol) were taken in f at bottom flask, dissolved in ethanol (5 ml) and then p-TSA (0.034g, 0.002 mol) was added to this mixture. The mixture was sonicated for 8 minutes. After completion

of reaction, reaction ass was poured on crushed ice. It was stirred for 10 minutes. The solid separated was filtered, washed with water, dried in oven and crystallized in ethanol.[24]

Method B: O-phenylenediamine (0.18 gm, 0.001 mol), Benzil (0.210 gm, 0.001 mol) and p-TSA ((0.034g, 0.002mol) were taken in flat bottom flask, dissolved in ethanol (5 ml). The mixture was stirred for 10 minutes. After completion of reaction, reaction mass was poured on crushed ice. It was stirred again for 10 minute. The solid separated was filtered, washed with water, dried in oven and crystallised in ethanol.[24]

Method C: O-phenylenediamine (0.18 gm, 0.001 mol), Benzil (0.210 gm, 0.001 mol) and p-TSA (0.034g, 0.002mol) were taken in flat bottom flask, dissolved in water (10 ml). The mixture was stirred for 20 minutes. After completion of reaction, solid separated was filtered, washed with water, dried in oven and crystallized in ethanol.[24]

Method D: O-phenylenediamine (0.18 gm, 0.001 mol), Benzil (0.210 gm, 0.001 mol) and 1 ml deep eutectic solvent were added, then the reaction was stirred for 25 min and a solid product gradually formed. After the completion of reaction as indicated by thin layer chromatography (TLC), water was added, the reaction mass was stirred and the mixture was filtered. The crude product obtained was purified by recrystallization using absolute alcohol.

3. RESU LTS

IR: Characterization

1665.50, 1585.40, 1446.20, 1317.38, 1210.32, 1167.95, 1069.75, 995.33, 873.20, 786.55, 716.78, 639.86(cm^{-1}). The absorption bands at 1665 cm^{-1} and 1585.40 cm^{-1} are due to C-C stretching of aromatic ring at 1210.32 cm^{-1} due to plain bending of C-H in aromatic phenyl ring, weak absorption band at 3061 cm^{-1} due to aromatic -C-H stretching, strong absorption band at 716.78 cm^{-1} and 786.55 cm^{-1} indicate mono substituted benzene ring. The weak absorption band at 1446 cm^{-1} is due to –C=N stretching.

^{1}H-NMR: (400MHz, CDCl3), δ p pm.

7.3 (m, 6H), 7.52 (d, 4H), 7.76 (dd, 2H,), 8.19 (dd, 2H,) ppm.

4. DISCUSSION

Compared with traditional method, and methods reported in literature our method is more convenient. Reactions can be carried out at milder conditions, in shorter time with higher yield and without generation of pollution from these features present method can be

correlated for safer and efficient synthesis of other products. This new strategy has several advantages, such as short reaction time, simple experimental as well as isolation procedures, excellent yield, low cost, and finally, it is in agreement with the green chemistry protocols.

5. CONCLUSION

DES technique is advantageous over conventional methods due to shorter reaction time, avoiding the use of harmful solvents, cleaner reactions, easy work up, and minimization of waste products for synthesis of 2,3-diphenyl quinoxaline. Compared with traditional methods, the applied methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution. It can be concluded that the DES method is an efficient, fast, simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition there is an increase in the yield. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals.

REFERENCES

1 Ghadage R.V. and Shirote P.J., Bangladesh J Pharmacol., 2011; 6: 92-99.
2 Dailey, J. W.; Feast, R. J.; Peace, I. C.; Sage, S.; Till, E. L.; Wood, P. J. Mater. Chem., 2001; 11: 2238.
3 John, P. D.; Leonard, J. C.; Beryl, W. D.; Richard, B. J.; Richard, M. P.; Joseph, E., P.; Wendell, W. W. J. Med. Chem., 1979; 22: 1118.
4 Weng, Q.; Wang, D.; Guo, P.; Fang, L.; Hu, Y.; He, Q.; Yang, B. Eur. J. Pharmacol., 2008; 581: 262.
5 Wilhelmsson, L. M.; Kingi, N.; Bergman., J. J. Med. Chem., 2008; 51: 7744.
6 Wagle, S.; Adhikari, A. V.; Kumari, N. S. Indian J. Chem., 2008; 47: 439.
7 Xu, H.; Fan, L. L. Eur. J. Med. Chem., 2011; 46: 1919.
8 Rao, G. K.; Kotnal, R. B.; Pai, T. J. Chem. Pharm. Res., 2010; 2: 368.
9 Guillon, J.; Moreau, S.; Mouray, E.; Sinou, V.; Forfar, I.; Fabre, S. B.; Desplat, V.; Millet, P.; Parzy, D.; Jarry, C.; Grellier, P. Bioorg. Med. Chem., 2008; 16: 9133.
10 Guillon, J.; Forfar, I.; Mamani-Matsuda, M.; Desplat, V.; Saliege, M.; Thiolat, D.; Massip, S.; Tabourier, A.; Leger, J.; Dufaure, B.; Haumont, G.; Jarry, C.; Mossalayi, D. Bioorg. Med. Chem., 2007; 15: 194.
11 Wagle, S.; Adhikari, A. V.; Kumari, N. S. Eur. J. Med. Chem., 2009; 44: 1135.
12 Mohammad R. I. and Hassani Z., ARKIVOC (xv)., 2008; 280-287.

13 Khaksar S. and Rostamnezhad F., Bull. Korean Chem. Soc, 2012; 33(8): 2581.
14 Singh S., Mishra P., Srivastava M., SingShyam B., Singh J., Tiwari K. P., Green
15 Chemistry Letters and Reviews, 2012; 5(4): 587-593.
16 Kolvari E., Mohammad Ali Z., Marjan P.,Green Chemistry Letters and Reviews, 2012; 5(2): 155-159.
17 Kim S. Y., Park K. H., Chung Y. K., Chem. Commun., 2005; 1321-1323.
18 Zhao Z., Wisnoski D. D., Wolkenberg S. E., Leister W. H., Wang Y., Lindsley C. W., Tetrahedron Lett., 2004; 45(25): 4873-4876.
19 Feng J., Liu Y., Meng Q., Liu B., Synth. Communication, 1998; 28: 193.
20 More S.V., Sastry M.N.V., Wang C.C., Ching-Fa Y., Tetrahedron Lett., 2005; 46: 6345-6348.
21 Rajesh S.B., Swapnil R.S., Suresh S.A., Wamanrao N.J., Sudhakar R.B., Rajendra P.P., Tetrahedron Lett., 2005; 46: 7183-7186.
22 Jafarpour M., Rezaeifard A., Danehchin M., Appl. Catal. A., 2011; 394: 48–51.
23 Sadjadi S., Sadjadi S., Hekmatshoar R.,Sonochem., 2010; 17: 764–767.
24 Krishnakumar B., Velmurugan R., Jothivel S., Swaminathan M., Catal. Commun., 2010; 11: 997–1002.
25 Pranita Mahadik1, Rupen Joshi International Journal of Innovative Science, Engineering & Technology, 2014; 1(6): 482-490.