Advances in Bioresearch
Adv. Biores., Vol 7 (4) July 2016: 64-68
©2016 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
ICV Value 8.21 [2014]

Advances
in
Bioresearch

ORIGINAL ARTICLE

Synthesis of some Oxadiazole derivatives using Conventional Solvent and Deep Eutectic Solvent (DES) under Ultrasonic irradiation: A Comparative study

*** [1]Mohammed Afroz Bakht**
*[1]Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam bin Abdulaziz University, P.O. Box- 173, Al-Kharj 11942, Saudi Arabia.
Email: m_afroz007@yahoo.com

ABSTRACT

In continuation of my previous work, here going to report synthesis of some oxadiazole derivatives using benzalkonium chloride and urea mediated deep eutectic solvent (DES) guided by thermal(NUS) and ultrasonic(US) methods. Reaction was also performed using conventional solvent (phosphorous oxychloride) under thermal method. Results was calculated and compared in terms of yield, temperature and time. Interestingly, combined effect DES and ultrasound produces better results compared to other two approaches. Moreover, DES is a non –hazardous recyclable catalyst and together with ultrasound found excellent for organic reactions.

Keywords: *Oxadiazole, Deep eutectic solvent, ultrasound*

Received 12/02/2016 Accepted 10/06/2016

How to cite this article:
Mohammed Afroz Bakht. Synthesis of some Oxadiazole derivatives using Conventional Solvent and Deep Eutectic Solvent (DES) under Ultrasonic irradiation: A Comparative study. Adv. Biores. Vol 7 [4] July 2016: 64-68. DOI: 10.15515/abr.0976-4585.7.4.64-68

INTRODUCTION

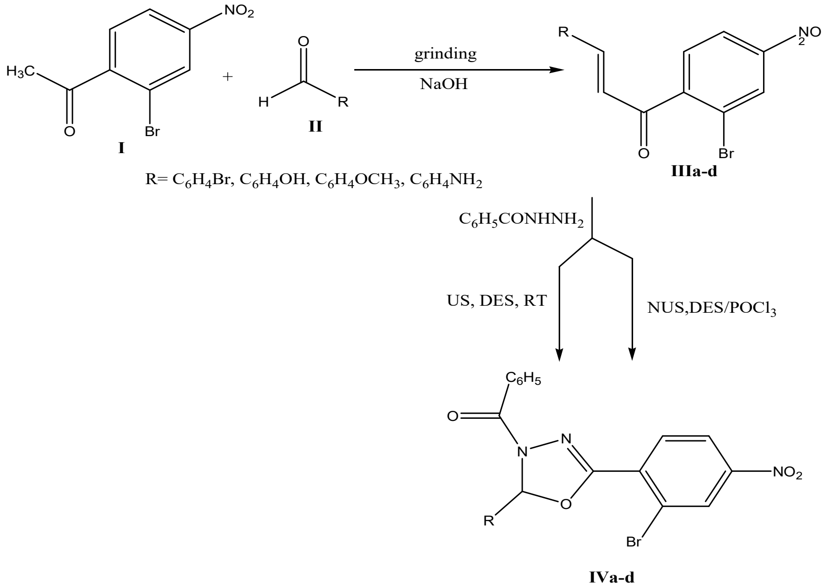
Application of safer solvents, chemicals and technology for the synthesis of organic molecules are prime importance towards discovery and developments of desired drugs. There is great need of cost effective, efficient, on-polluted solvents for the synthesis of compound of pharmacological interest. Therefore, design and development of new methods to reduce waste by the use of safer solvents is the matter of discussion under the light of green chemistry [1]. Around two decades ionic liquids (ILs) preferably used as a green solvent prepared by organic cations and anions [2]. Ionic liquids (ILs) proved as sustainable catalyst due to its good solubility, low volatility and perfect recyclability nature[3]. Many research reports present some limitations and found poor biodegradability and toxicity [4, 5]. Alternative to Ionic liquids (ILs) is deep eutectic solvents (DES's) prepared by mixing quaternary ammonium salts (choline chloride) and compounds having hydrogen bond donor's atoms(Urea, Glycerol etc.) [6,7]. Main advantage of DES to be an ideal benign solvent is its-biodegradable, non-toxic, stable, non-reactive with water, non-inflammability and easy to prepare [8,9]. A team of scientists headed by Abott, discovered first DES(prepared by choline chloride and urea), since then numerous such mixtures has been identified and their wide range of applications reported so far[10-12].

Ultrasound technology was explored in recent times in many areas of science and technology including organic and material synthesis [13-16]. Ultrasound works on the phenomena of acoustic cavitation due to growth and collapse of bubbles during organic transformations [17-19]. Present work described here is extension of our previous affords [20]. Prepared deep eutectic solvent (DES) from benzalkonium chloride and urea based deep eutectic solvent were again used for the synthesis of selected oxadiazole derivatives(IVa-d) under ultrasonic irradiation. Reaction was repeated using conventional solvent (phosphorus oxychloride) guided by thermal method. A result received by both methods was compared in terms of yield, temperature and time.

MATERIALS AND METHODS

In present research chemical were purchased from sigma Aldrich(USA) and no further purification was carried out. Ultrasonic instrument were used for ultrasound assisted synthesis at operating frequency of 24 kHz. Purity of all the compounds was checked by thin layer chromatography in a solvent system (*n*-hexane: EtOAc, 80: 20 v/v). I R spectra were recorded by KBr discs using FT/IR - 4100 JASKO model in the ratio of 1:100. ^{1}H-NMR for total proton calculation determined by NMR instrument, BRUCKER-PLUS (500MHz) using TMS as internal standard. Mass fragmentation was obtained on micromass (LCT Premier, waters). A general scheme1 presented as below.

Scheme 1



Synthesis of Chalcone by manual grinding method (IIIa-d)

All the chalcones (IIIa-d) were synthesized from condensation of 2-bromo-4-nitrocetophenone and substituted aldehydes by solvent-free grinding method using NaOH. A clear color change in 5 min showed chalcone formation, which was confirmed by TLC and spectroscopic data.

1-(2-Bromo-4-nitro phenyl)-3-(4-bromo phenyl) propenone (IIIa)

IR(KBr,cm^{-1}:υmax 1686 (C=O), 1576(CH=CH), ^{1}HNMR(500MHz,DMSO-d$_6$):δ 8.05-8.03(1H, d=CH-Ar, J=8.5Hz), 7.86-7.52(1H, d,-CO-CH=, J= 8.5), 8.01-7.56(7H, m, Ar-H).

1-(2-Bromo-4-nitro phenyl)-3-(4-hydroxy phenyl) propenone (IIIb)

IR(KBr,cm^{-1}:υmax 1682 (C=O), 1579(CH=CH), ^{1}HNMR(500MHz,DMSO-d$_6$):δ 8.02-8.01(1H, d=CH-Ar, J=8.5Hz), 7.86-7.83(1H, d,-CO-CH=, J= 8.5), 7.81-7.79(7H, m, Ar-H).

1-(2-Bromo-4-nitro phenyl)-3-(4-methoxy phenyl) propenone (IIIc)

IR(KBr,cm^{-1}:υmax 1680 (C=O), 1581(CH=CH), ^{1}HNMR(500MHz,DMSO-d$_6$):δ 8.04-8.02(1H, d=CH-Ar, J=8.3Hz), 7.82-7.682(1H, d,-CO-CH=, J= 8.4), 8.01-7.59(7H, m, Ar-H).

3-(4-Amino phenyl)-1-(2-bromo 4-nitro phenyl) propenone (IIId)

IR(KBr,cm^{-1}:υmax 1686 (C=O), 1572(CH=CH), ^{1}HNMR(500MHz,DMSO-d$_6$):δ 8.05-8.02(1H, d=CH-Ar, J=8.4Hz), 7.88-7.65(1H, d,-CO-CH=, J= 8.3), 8.01-7.57(7H, m, Ar-H).

Synthesis of oxadiazole (IVa-d)

Targeted oxadiazole derivatives were synthesized by different approaches discussed here- Primarily synthesized by using conventional solvent (POCl$_3$) with heating. Reaction was repeated using deep eutectic solvent (DES) with conventional heating and without heating under ultrasound irradiation. DES was prepared by benzalkonium chloride and urea by given literature [12].

Synthesis of oxadizole derivatives using conventional solvent (phosphorus oxychloride) guided by thermal/non-ultrasonic(NUS) method

Equal quantity (0.001 moles) of chalcones(IIIa-d)and acidhydrazidein 5 ml of phosphorus oxychloride (POCl$_3$) was refluxed for 18-20 hour. Just after completion of reaction crushed ice (added and neutralized with aqueous sodium hydroxide solution. The product (IVa-d)so obtained was filtered, washed several times with water and recrystallized from methanol.

Synthesis of oxadiazole derivatives using DES guided by thermal /non ultrasonic (NUS) method

Above reaction was run again using DES (8mL) as a solvent. Reaction was extracted by dichloromethane using separating funnel. The dichloromethane layer was separately collected and evaporated to getdesired product. DES was again used in next reaction cycles at-least 3-4 times.

Synthesis of oxadiazole derivatives using DES guidedby ultrasonic(US) method

In an ultrasonic method desired oxadiazole derivatives were prepared in a sonicating flask under sonicating probe(ACE probe, 24 kHz frequency) at 40% amplitude with a 5s ON and 5s OFF cycle from time t = 0 h. Reaction temperature was throughout maintained at 30±2°C using jacketed glass. Remaining procedure of purification and identification was same as discussed in thermal method.

Spectroscopic data of synthesized oxadiazole derivatives (IVa-d)

5-(2-Bromo-4-nitrophenyl)-2-phenyl-1,3,4-oxadiazol-3-yl-(4-bromophenyl)methanone (IVa)

M.F. $C_{21}H_{13}Br_2N_3O_4$; Yield (92%); m.p. 157-158°C.IR(KBr,cm^{-1}:υmax 1654(C=C), 1559(C=N), 1166(C-O-C).^{1}HNMR(500MHz,DMSO-d$_6$)δ: 7.12-8.32 (12H, m,Ar-H), 6.8(1H, d, J= 8.3 Hz), 6.6 (1H,d, J= 13.8 Hz), m/z: 532(M^{+1}).

5-(2-Bromo-4-nitrophenyl)-2-phenyl-1,3,4-oxadiazol-3-yl-(4-hydroxyphenyl)methanone (IVb)

M.F. $C_{21}H_{14}BrN_3O_5$; Yield (95%); m.p. 162-164°C.IR(KBr,cm^{-1}:υmax 1656(C=C), 1561 (C=N), 1168(C-O-C).^{1}HNMR(500MHz,DMSO-d$_6$)δ: 7.10-8.28 (12H, m,Ar-H), 6.9(1H, d, J= 8.7 Hz), 6.6 (1H,d, J= 14.2 Hz), m/z: 469(M^{+1}).

5-(2-Bromo-4-nitrophenyl)-2-phenyl-1,3,4-oxadiazol-3-yl-(4-methoxyphenyl)methanone (IVc)

M.F. $C_{22}H_{16}BrN_3O_5$; Yield (88%); m.p. 165-167°C.IR(KBr,cm^{-1}:υmax 1659(C=C), 1554 (C=N), 1166(C-O-C).^{1}HNMR(500MHz,DMSO-d$_6$)δ: 7.13-8.33 (12H, m,Ar-H), 6.7(1H, d, J= 8.5 Hz), 6.5 (1H,d, J= 13.7 Hz), m/z: 483(M^{+1}).

(4-Aminophenyl)-5-(2-bromo-4-nitrophenyl)2-phenyl-1,3,4-oxadiazole-3-yl-methanone (IVd)

M.F. $C_{21}H_{15}BrN_4O_5$; Yield (90%); m.p. 171-172°C.IR(KBr,cm^{-1}:υmax 1666(C=C), 1554 (C=N), 1166(C-O-C).^{1}HNMR(500MHz,DMSO-d$_6$)δ: 7.14-8.36 (12H, m,Ar-H), 6.9(1H, d, J= 8.4 Hz), 6.7 (1H,d, J= 14.2 Hz), m/z: 468(M^{+1}).

RESULTS AND DISCUSSION

Series under investigation (IVa-d) was presented as scheme 1. Oxadiazole derivatives were synthesized from chalcone using conventional solvent(phosphorous oxychloride) and deep eutectic solvent(DES) prepared by mixing a 1:2 molar ratio of benzalkonium chloride and urea by thermal method (NUS). Each reaction was repeated using ultrasonicmethod with DES for comparison. Spectral data were carried out of all the synthesized compoundsand foundsatisfactory with proposed molecules. Considering compound IVa, IR spectra showed C=N and C-O-C peak at 1559 and 1166 respectively. In NMR, number and types of proton was evaluated on the basis ofchemical shifts and coupling constants. Formation of oxadiazole was confirmed by characteristics peak appeared at δ 6.8 and 6.6 with coupling constant value of 8.3 and 13.8 Hz respectively. All other spectral values also justified to the formation of oxadiazole.

Chalcone derivatives were synthesized by grinding methods without use of heating in order to make eco-friendly and viable reaction system. Selected oxadiazoles was synthesized using conventional solvent with heating referred as thermal or non-ultrasonic (NUS) method. A biocompatible solvent called deep eutectic solvent (DES) was prepared by proper mixing of benzalkonium chloride and urea (1:2). This DES was used as recyclable solvent to synthesized same oxadiazole derivatives to compare the reaction time, temperature, and % yield from conventional solvent ($POCl_3$) as presented in Table 1. The results clearly showed the effect of two solvents ($POCl_3$, DES). It was found good results in terms of yield when DES (BZK:Urea) was used as reaction solvent in thermal(NUS) and ultrasonic(US) method. Maximum 20 hrspent to form oxadiazole compounds using conventional solvent under thermal method,but reaction was completed in around 3h using DES. In an ultrasonic irradiation with DES same reaction was completed in just 1h. Percentage yield was also found better using DES and ultrasound together (Table1, Table 2). Moreover, combined effect of ultrasound and DES has profound effect on the product formation and improvement of necessary parameters. DES was reused in the synthesis of each compound and evaluated for %yield and found satisfactory. Mechanism towards the formation of desired compounds is not clearly understood. DES may acts as catalyst and together with ultrasonic effects leads to cyaclization.

Table: - 1 Effect of DES and conventional solvent in the synthesis of oxadiazole derivatives by thermal (NUS) and ultrasonic (US) method

Entry	Reaction medium	Reaction conditions	Temperature(°C)	Yield (%)
1	Phosphorous oxychloride	NUS[a]	155	48
2	DES(BZK:Urea)[d]	NUS[b]	92	72
3	DES(BZK:Urea)[d]	US[c]	RT	89

[a] *Reaction conditions: NUS(thermal method): Chalcone (0.001 mole), Acid hydrazide (0.001mole), Solvent (5 mL), reaction time = 20h.*
[b] *Reaction conditions: NUS(thermal method): Chalcone (0.001 mole), Acid hydrazide (0.001 mole), Solvent (5 mL), DES (BZK:Urea:1:2),reaction time = 3h.*
[c] *Reaction conditions: US(ultrasonic method): Chalcone (0.001mole), Acid hydrazide (0.001 mole), Solvent (8 mL), DES (BZK:Urea:1:2),reaction time = 1h.*
[d] *DES- Deep eutectic solvent; BZK- Benzalkonium chloride.*

Table: - 2 Deep eutectic solvent (DES) catalyzed synthesis of oxadiazole derivatives (VIa-d) under thermal (NUS) and ultrasonic (US) methods

Entry	Reaction time		Yield(%)	
	Thermal Method (NUS) (h)	Ultrasonic Method(US) (min)	Thermal Method(NUS)	Ultrasonic Method (US)
VIa	3	60	70	87
VIb	3	55	68	88
VIc	3	52	72	89
VId	3.5	58	72	89

CONCLUSION

In conclusion, we have obtained oxadiazole derivatives guided by thermal and ultrasonic method in phosphorous oxychloride (conventional solvent) and deep eutectic solvent (DES). Use of DES in either method increased the yield and reduces the temperature and time. Together with ultrasound produced excellent results. Recyclability studies were also performed and found good. Furthermore, this DES is a good alternative to many hazardous conventional solvents and will be hope for various organic reactions as a catalyst and solvent.

ACKNOWLEDGMENTS

Author is thankful to the Prince Sattam bin Abdulaziz University for providing necessary facilities for the present research.

REFERENCES

1. Azizi. N & Alipour.M(2015), Eco-efficiency and Scalable synthesis of bisamides in deep eutectic solvent, j. mol. liq, 206, 268-271.
2. Zhang.Q, Vigier.K. De. O, Royer.S&Jerome.F(2012), Deep eutectic solvents: Synthesis, properties and applications, Chem. Soc. Rev, 41, 7108-7146.
3. Hu.H, Qiu. F,Ying. A, Yang.J&Meng.H(2014), An environmentally benign Protocol for Aqeous Synthesis of Tetrahydrobenzo [b] Pyrans Catalyzed by cost-Effective Ionic Liquid, Int. J. Mol. Sci, 15, 6897- 6909.
4. Abhilash. S, Suresh.S&Nagarkar.J. M(2014) Choline chloride based deep eutectic solvent as an efficient solvent for the benzylation of Phenols, Tetraheddron Letters, 55, 7243-7246.
5. Romero.A, Santos.A, Tojo.J& Rodriguez. A (2008), Toxicity and biodegradability of imidazolium ionic liquids, J. Hazard. mat, 151, 268-273.
6. Abbott.A. P,Cappar.G, Davies.D. L,Raheed,R. K&Tambyrajah.V(2003), Novel solvent properties of choline cholire/urea mixtures, Chem. Commu, 7, 70-71.
7. Yilmaz.E&Soylak.M (2015), Ultrasound assisted-deep eutectic solvent extraction of iron from sheep, bovine and chicken liver samples, Talanta, 136, 170-173.
8. Chen.Z, Zhou.B, Cai.H, Zhu.W&Zou.X (2009),Simple and efficient methods for selective preparation of α.α – dichloro ketones and β-ketones and β-ketoesters
9. Green. Chem. 11, 275-278.
10. Yu.Y,Lu.X, Zhou.Q, Dong.K, Yao.H&Zhang.S (2008),Biodegradable Napthalene Acid Ionic Liquids: Synthesis, Characterization, and Quantitative Structure-Biodegradation Relationship, Chem. Eur.J, 14, 11174-11182.
11. Kleiner.B&Schorken.K(2014), Native lipase dissolved in hydrophilic green solvents: A versatile 2-phase reaction system for high yield ester synthesis,*Eur j lipid Sci tech*, 117, 167-177.
12. Gorke.G.T, Srienc.F&Kazlauskas.R.J(2010), Towards Advanced Ionic Liquids, Polar, Enzyme-friendly solvents for Biocatalysis, *Biotech Bioprocess Eng*, 15, 40-53.
13. Maugeri.Z, Leitner.W&de María.P .D(2012), Practical separation of alcohol–ester mixtures using Deep-Eutectic-Solvents,Tetrahederon. Letters, 53, 6968-6971.
14. Zeng.H,Li.H & Shao.H(2009), One-pot three-component Mannich-type reactions using Sulfamic acid catalyst under ultrasound irradiation *Ultrason Sonochem*, 16, 758-762.
15. Bennici.S, Lazzarin. G.M & Ragaini.V(2005),CuO based catalysts on modified acidic silica supports tested in the de-NOx reduction,*Ultrson. Sonochem*, 12, 307-312.

16. Wang. S.Y, Ji. S.J &Su. X.M (2008), A Meldrum's acid catalyzed synthesis of bis (indolyl) methanes in water under ultrasonic condition, Chin. J. Chem. 26, 22-24.
17. Zang.H, Zhang.Y&Zang, B.W (2010), Cheng, An efficient ultrasound-promoted method for the one-pot synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives, Ultrason. Sonochem. 17, 495–499.
18. Gao. D.M, Ma. W.L, Li. T.R, Huang. L.Z &Du.Z.T (2012), An Improved Synthesis of 1, 2-Diarylethanols under Conventional Heating and Ultrasound Irradiation, Molecules, 17, 10708-10715.
19. Yadav. J.S, Reddy.B.V.S & Reddy.K.S(2003), Ultrasound-accelerated synthesis of chiral allylic alcohols promoted by indium metal, Tetrahedron, 59, 5333–5336.
20. Handy. S &Lavender. K(2013), Organic synthesis in deep eutectic solvents: Paal-knorr reactions, Tetrahedron Letters, 54, 4377-4379.
21. Bakht M.A (2015), Ultrasound mediated synthesis of some pyrazoline derivatives using biocompatible deep eutectic solvent (DES), Der. Pharma. Chemica, 9, 274-278.