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

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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

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 (phosphorous 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). IR spectra were recorded by KBr discs using FT/IR - 4100 JASKO model in the ratio of 1:100. 1H-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 synthesised 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-hydroxy phenyl) propenone (IIIa)
IR(KBr, cm-1): max 1686 (C=O), 1576(CH=CH), 1H-NMR(500MHz,DMSO-d6):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-nitrophenyl)-3-(4-methoxy phenyl) propenone (IIIb)
IR(KBr, cm-1): max 1682 (C=O), 1579(CH=CH), 1H-NMR(500MHz,DMSO-d6):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-nitrophenyl)-3-(4-methoxy phenyl) propenone (IIIc)
IR(KBr, cm-1): max 1680 (C=O), 1581(CH=CH), 1H-NMR(500MHz,DMSO-d6):δ 8.04-8.02(1H, d=CH-Ar, J=8.3Hz), 7.82-7.68(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): max 1686 (C=O), 1572(CH=CH), 1H-NMR(500MHz,DMSO-d6):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 (POCl₃) with heating. Reaction was repeated using deep eutectic solvent (DES) with conventional heating and without heating under ultrasound irradiation. DES was prepared by benzoalkonium chloride and urea by given literature [12].

Synthesis of oxadiazole derivatives using conventional solvent (phosphorus oxychloride) guided by thermal/non-ultrasonic (NUS) method
Equal quantity (0.001 moles) of chalcones(IIIa-d)and acyldiazidein 5 ml of phosphorus oxychloride (POCl₃) 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 get the desired product. DES was again used in next reaction cycles at least 3-4 times.

**Synthesis of oxadiazole derivatives using DES guided by 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 5 s ON and 5 s 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. C₂₂H₁₂Br₂N₂O₄; Yield (92%); m.p. 157-158°C, IR(KBr, cm⁻¹):υmax 1654 (C=C), 1559 (C=N), 1166 (C-O-C).¹HNMR(500MHz,DMSO-d₆): 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⁺).

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

M.F. C₂₃H₁₃BrNO₃; Yield (95%); m.p. 162-164°C, IR(KBr, cm⁻¹):υmax 1656(C=C), 1561 (C=N), 1168 (C-O-C).¹HNMR(500MHz,DMSO-d₆): 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⁺).

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

M.F. C₂₃H₁₃BrNO₃; Yield (88%); m.p. 1554(C=C), 1166 (C-O-C).¹HNMR(500MHz,DMSO-d₆): 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⁺).

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

M.F. C₂₂H₁₂BrNO₃; Yield (90%); m.p. 1554(C=C), 1166 (C-O-C).¹HNMR(500MHz,DMSO-d₆): 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⁺).

**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 ultrasonic method with DES for comparison. Spectral data were carried out of synthesized oxadiazole compounds using conventional solvent under thermal method, but reaction was completed in around 3 h using DES. In an ultrasonic irradiation with DES same reaction was completed in just 1 h. Percentage yield was also found better using DES and ultrasonic together (Table 1, 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 act as catalyst and together with ultrasonic effects leads to cyclization.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction medium</th>
<th>Reaction conditions</th>
<th>Temperature(°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phosphorous oxychloride</td>
<td>NUS</td>
<td>155</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>DES(BZK:Urea)³</td>
<td>NUS⁴</td>
<td>92</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>DES(BZK:Urea)³</td>
<td>US⁵</td>
<td>RT</td>
<td>89</td>
</tr>
</tbody>
</table>
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*aReaction conditions: NUS(thermal method): Chalcone (0.001 mole), Acid hydrazide (0.001 mole), Solvent (5 mL), reaction time = 20 h.*

*bReaction conditions: NUS(thermal method): Chalcone (0.001 mole), Acid hydrazide (0.001 mole), Solvent (5 mL), DES (BZK:Urea:1:2), reaction time = 3 h.*

*cReaction conditions: US(ultrasonic method): Chalcone (0.001 mole), Acid hydrazide (0.001 mole), Solvent (8 mL), DES (BZK:Urea:1:2), reaction time = 1 h.*

**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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thermal Method (US)</td>
<td>Ultrasonic Method (US)</td>
</tr>
<tr>
<td>VIa</td>
<td>3 h</td>
<td>60</td>
</tr>
<tr>
<td>VIb</td>
<td>3 h</td>
<td>55</td>
</tr>
<tr>
<td>Vlc</td>
<td>3 h</td>
<td>52</td>
</tr>
<tr>
<td>VId</td>
<td>3.5 h</td>
<td>58</td>
</tr>
</tbody>
</table>

**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.

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**REFERENCES**


