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Ultrasound mediated synthesis of some pyrazoline derivatives using biocompatible deep eutectic solvent (DES)

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ABSTRACT

In this report an attempt was made to synthesize some pyrazoline derivatives by benzalkonium chloride and urea based deep eutectic (DES) solvent using thermal(NUS) and ultrasonic (US) methods. Similar reaction was tested by conventional solvent (glacial acetic acid) by thermal method. Result obtained in all of the approaches was calculated and compared with regard to the reaction time, temperature and % yield in both of the methods considering the glacial acetic acid and DES as solvent. Reaction took 15 hr to complete when conventional solvent(glacial acetic acid) were used by thermal method, but same reaction finishes in 4hr in thermal and 1hr in ultrasonic method using DES as solvent. Ultrasound assisted synthesis along with DES works under room temperature (RT) irrespective of thermal method where products are formed at much elevated temperature(<80^{0}C). Similarly, rise in %yield was observed in DES led reaction either in thermal or ultrasonic method. Interestingly, in DES-ultrasound combined reaction the % yield was as much as 88%. Furthermore, cost effective, recyclable, environmental friendly nature of DES together with ultrasound make ideal for the present research.

Keywords: Benzalknium chloride, DES, Pyrazoline, Ultrasound

INTRODUCTION

Scientists around the world racing over each other to the use of less hazardous, cost effective solvents for the synthesis of compounds of pharmaceutical interest. Among, recently used solvents deep eutectic solvents (DES) are widely acceptable for the varieties of organic transformations [1,2], biotransformation [3,4] and bioprocesssing [5]. Owing to difficulties facing with conventional volatile organic solvents, the use of biocompatible and recyclable green solvents will be a hope for the future constructive research. Although DES's can be considered as successor of most commonly used green solvent from decades called ionic liquids(ILs)[6], due to their similar molecular composition and striking solvent properties as general ILs [7]. DES is a combination of two or more compounds that has a melting point lower than each participant [8]. Ionic liquids (ILs) are ionic compounds, however deep eutectic solvents (DES's) are ionic mixtures and former are liquid at or below 100^{o}C [9]. Deep eutectic solvents (DES's) are formed from mixture of organic halide salts (Choline chloride or other quaternary ammonium salts) with the compounds (Urea, Thiourea, Glycerol etc.) capable of donating hydrogen bonds. Thus the capability of hydrogen bonding with the halide salts makes the eutectic mixtures called DES. Hydrogen bonding capacity of one of the component of DES led to the depression in freezing point and melting point to their individuals [1].

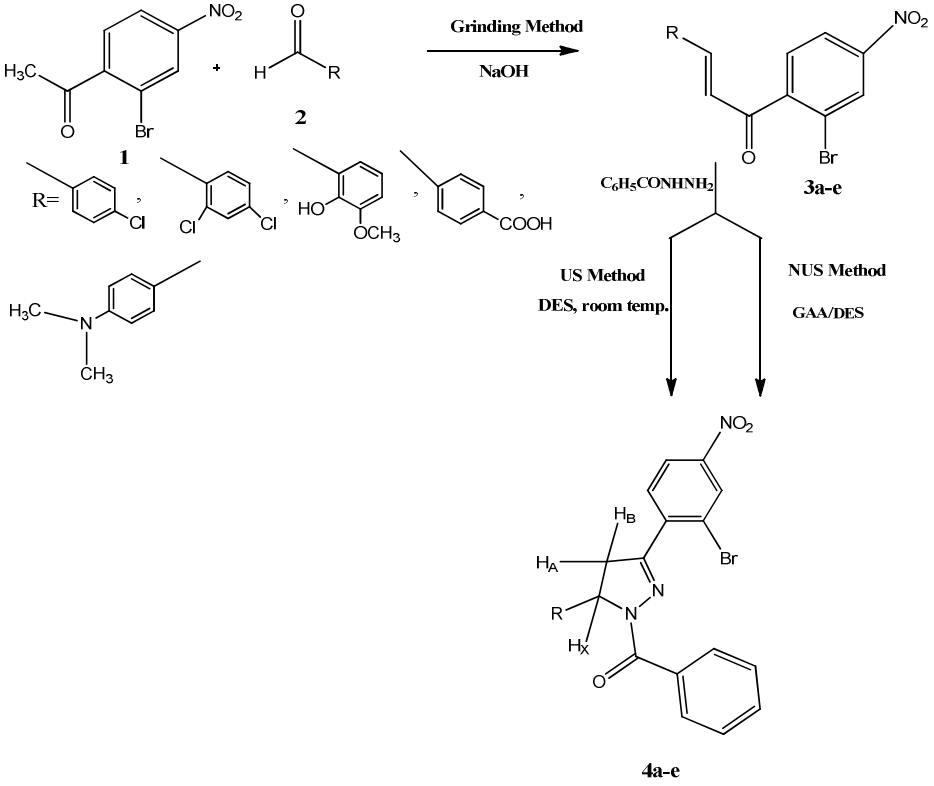
Ultrasound technology creates revolution in the field of organic synthesis, food processing and health care [10-14]. As a general, physical phenomenon called acoustic cavitation played role for organic transformation reactions and these are formed due to sequential formation, growth and collapse of bubbles generated through the chemical reactions [15]. In this research, I report the synthesis of some pyrazoline derivatives with the application of newly prepared benzalkonium chloride and urea based deep eutectic solvent (DES) using ultrasound assisted reactions. Pyrazoline derivatives were also prepared by conventional thermal method using glacial acetic acid for comparison.

MATERIALS AND METHODS

Chemicals used in current research were purchased from Loba Chem (India) and Sigma Aldrich (USA). There is no further purification were carried out for these chemicals.

Ultrasonic instrument were used for ultrasound assisted synthesis at operating frequency of 20 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 elucidating total proton were recorded by NMR instrument, BRUCKER-PLUS (500MHz) using TMS as internal standard. Mass fragmentation was calculated on micromass (LCT Premier, waters). Work described in this research was presented as scheme 1.

Scheme 1



Chemistry

Synthesis of chalcone by manual grinding method (3a-e)

All the chalcones (3a-e) were synthesized from condensation of 2-bromo-4-nitrocetophenone and substituted aldehydes by solvent-less manual grinding method using solid NaOH. An observable color change in 5 min showed chalcone formation, which was further confirmed by TLC and spectroscopic data.

1-(2-bromo-4- nitrophenyl)-3(4-chlorophenyl) prop-2-en-1-one (3a)

IR (KBr, cm^{-1}: υ_{max} 1680(C=O), 1589(CH=CH), ^{1}H NMR (500MHz, DMSO-d6): δ 8.03-8.02(1H, d,=CH-Ar, J= 8.4Hz), δ 7.62-7.58(1H,d, -CO-CH=, J= 8.4Hz), 8.0-7.57 (7H, m, Ar-H)

1-(2-bromo-4- nitrophenyl)-3-(2,4-dichlorophenyl) prop-2-en-1-one (3b)
IR (KBr, cm^{-1}: υ_{max} 1685(C=O), 1591(CH=CH), ^1H NMR (500MHz, DMSO-d6): δ 8.32-8.24(1H, d, =CH-Ar, J= 8.14Hz), δ 8.11-7.98(1H, d, -CO-CH=, J= 8.08Hz), 8.36-7.45 (6H, m, Ar-H)

1-(2-bromo-4- nitrophenyl)-3-(2-hydroxy-3-methoxyphenyl) prop-2-en-1-one (3c)
IR (KBr, cm^{-1}: υ_{max} 1682(C=O), 1605(CH=CH), ^1H NMR (500MHz, DMSO-d6): δ 7.32-7.12(1H, d, =CH-Ar, J= 7.64Hz), δ 7.22-7.16(1H, d, -CO-CH=, J= 8Hz), 84.-7.68 (5H, m, Ar-H)

4-(3-(2-bromo-4- nitrophenyl)-3-oxoprop-1-en-1-yl) benzoic acid) (3d)
IR (KBr, cm^{-1}: υ_{max} 1680(C=O), 1586(CH=CH), ^1H NMR (500MHz, DMSO-d6): δ 7.96-7.85(1H, d, =CH-Ar, J= 8.04Hz), δ 7.67-7.43(1H, d, -CO-CH=, J= 6.88Hz), 8.31-7.89 (7H, m, Ar-H)

5-(2-bromo-4- nitrophenyl)-1-(4-(dimethyl amino) phenyl) pent-1-en-3-one (3e)
IR (KBr, cm^{-1}: υ_{max} 1686(C=O), 1594(CH=CH), ^1H NMR (500MHz, DMSO-d6): δ 7.66-7.59(1H, d, =CH-Ar, J= 7.77Hz), δ 7.51-7.41(1H, d, -CO-CH=, J= 6.58Hz), 8.01-7.92 (7H, m, Ar-H).

Synthesis of pyrazoline derivatives (4a-e)
There are three different approaches were adopted for the synthesis of desired pyrazoline derivatives (4a-e)- (A) Synthesis by thermal method using conventional reaction medium i.e glacial acetic acid , (B) synthesis by thermal method using deep eutectic solvent(DES) and (C) synthesis by DES coupled with ultrasonic method. Newly prepared DES is a mixture of benzalkonium chloride as a salt and urea as a hydrogen bond donor by literature method [1, 8].

Synthesis of pyrazoline derivatives by thermal method using conventional solvent (glacial acetic acid)
In this method pyrazoline derivatives (4a-e) was synthesized by refluxing mixture of prepared chalcone (3a-e) (0.005 molar) and acid hydrazide (0.005 molar) in glacial acetic acid (20mL). At the end of 15 hr, reaction was found to be complete as confirmed by TLC in a solvent system (*n*-hexane: EtOAc, 80: 20 v/v). Resultant reaction mixture was washed with water dried and recrystallized from ethanol.

Synthesis of pyrazolne derivatives by thermal method using DES
In this method above reaction was repeated using DES (8mL) as a solvent. The resultant reaction was extracted by dichloromethane using separating funnel. The dichloromethane layer was separately collected and evaporated to get desired product. DES was reused up to four reaction cycles.

Synthesis of pyrazoline derivatives by ultrasonic method using DES
Pyrazoline derivatives was also prepared by ultrasonic method in a sonicating flask under sonication probe (ACE probe, 20 kHz frequency) at 40% amplitude with a 5s ON and 5s OFF cycle from time t = 0 h. The temperature of the reaction was kept at 30±2°C by using jacketed reactor. Rest of the work up procedure was followed same as discussed in thermal method.

Spectroscopic data of synthesized pyrazoline derivatives (4a-e)
(3-(2-bromo-4-nitrophenyl)5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (4a)
M.F. $C_{22}H_{15}BrClN_3O_3$; Yield (88%); m.p. 153-154 °C. IR (KBr, cm^{-1}: υ_{max} 1682 (C=O), 1562 (C=N), 1379 (C-N), ^1H NMR (500MHz, DMSO-d6): δ 8.49-7.88 (12H, m, Ar), 6.44 (1H, dd, H_x, J = 5.8, 5.8 Hz), 4.54 (1H, dd, H_B, J = 10.2, 10.2 Hz), 3.52 (1H, dd, H_A, J = 5.5, 5.5 Hz), m/z: 485(M^{+1}).

(3-(2-bromo-4-nitrophenyl)5-(2,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (4b)
M.F. $C_{22}H_{14}BrClN_3O_3$; Yield (81%); m.p. 158-164 °C. IR (KBr, cm^{-1}: υ_{max} 1682 (C=O), 1564 (C=N), 1379 (C-N), ^1H NMR (500MHz, DMSO-d6): δ 8.33-8.18 (11H, m, Ar), 6.32 (1H, dd, H_x, J = 6.2, 6.2 Hz), 4.44 (1H, dd, H_B, J = 9.7, 9.7 Hz), 3.65 (1H, dd, H_A, J = 5.7, 5.7 Hz), m/z: 520(M^{+1}).

(3-(2-bromo-4-nitrophenyl)5-(2-hydroxy-3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl) methanone (4c)
M.F. $C_{23}H_{18}BrN_3O_5$; Yield (79%); m.p. 147-149 °C. IR (KBr, cm^{-1}: υ_{max} 1686 (C=O), 1576 (C=N), 1375 (C-N), ^1H NMR (500MHz, DMSO-d6): δ 8.22-8.11 (11H, m, Ar), 6.24 (1H, dd, H_x, J = 6.2, 6.2 Hz), 4.36 (1H, dd, H_B, J = 10.1, 10.1 Hz), 3.32 (1H, dd, H_A, J = 5.4, 5.4 Hz), m/z: 497(M^{+1}).

4-(1-benzoyl-3-(2-bromo-4-nitrophenyl)-4,5-dihydro-1H-pyrazol-5-yl)benzoic acid(4d)
M.F. $C_{23}H_{16}BrN_3O_5$; Yield (75%); m.p. 155-157 °C. IR (KBr, cm^{-1}: υ_{max} 1689 (C=O), 1581 (C=N), 1378 (C-N), ^{1}H NMR (500MHz, DMSO-d6): δ 8.29-8.15 (12H, m, Ar), 6.45 (1H, dd, $H_{x,}$ J = 6.6, 6.6 Hz), 4.48 (1H, dd, $H_{B,}$ J = 10.5, 10.5 Hz), 3.42 (1H, dd, $H_{A,}$ J = 5.8, 5.8 Hz), m/z: 495(M^{+1}).

(3-(2-bromo-4-nitrophenyl)5-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)(phenyl) methanone(4e)
M.F. $C_{24}H_{21}BrN_4O_3$; Yield (89%); m.p. 160-162 °C. IR (KBr, cm^{-1}: υ_{max} 1680 (C=O),1588 (C=N), 1389 (C-N), ^{1}H NMR (500MHz, DMSO-d6): δ 8.39-8.13 (12H, m, Ar), 6.38 (1H, dd, $H_{x,}$ J = 6.4, 6.4 Hz), 4.48 (1H, dd, $H_{B,}$ J = 10.2, 10.2 Hz), 3.33 (1H, dd, $H_{A,}$ J = 5.6, 5.6 Hz), m/z: 494(M^{+1}).

RESULTS AND DISCUSSION

The present series of pyrazoline (4a-e) was outlined as scheme 1. The prepared chalcone was used in the synthesis of pyrazoline derivatives using conventional solvent (glacial acetic acid) and benzalkonium chloride based deep eutectic solvent (DES) adopting thermal method. Same pyrazolines were also synthesized using ultrasonic method in a green solvent system (DES). Both analytical and spectral data (^{1}H-NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. Considering the compound **4a**, the infra red spectra (IR) showed C=N and C-N peak at 1562 and 1379 cm^{-1} respectively. In the ^{1}H-NMR spectra, the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed double doublet as a characteristics pyrazoline pattern at δ 6.44 (H_X), δ 4.54 (H_B), and δ 3.52 (H_A). Spectral values of the rest of the pyrazoline lies in almost similar range as described in experimental section.

Grinding method was used to synthesize starting material i.e. chlacone. This approach is more viable and economical compared to conventional heating.

Target pyrazoline derivatives have been prepared by thermal method (NUS) using conventional solvent (glacial acetic acid) and benzalkonium chloride & urea (BZK: Urea: 1:2) based deep eutectic solvent (DES) as depicted in Table 1. Similar reactions were run by using ultrasonic method (US) in DES medium.

Table: - 1 Effect of DES and conventional solvent in the synthesis of pyrazoline derivatives by NUS and US method

Entry	Reaction medium	Reaction Conditions	Temperature (^{0}C)	Yield (%)
1.	Glacial acetic acid	NUS[a]	172	56
2.	DES (BZK:Urea)[d]	NUS[b]	85	78
3.	DES (BZK:Urea)[d]	US[c]	RT.	88

[a]Reaction conditions: NUS(thermal method): Chalcone (0.005 mole), Acid hydrazide (0.005 mole), Solvent (20 mL), reaction time = 15h.
[b]Reaction conditions: NUS(thermal method): Chalcone (0.005 mole), Acid hydrazide (0.005 mole), Solvent (20 mL), DES (BZK:Urea:1:2), reaction time = 4h.
[c]Reaction conditions: US(ultrasonic method): Chalcone (0.005 mole), Acid hydrazide (0.005 mole), Solvent (20 mL), DES (BZK:Urea:1:2), reaction time = 1h.
[d]DES-deep eutectic solvent; BZK- benzalkonium chloride.

The results received in both methods and influence of reaction medium (glacial acetic acid, DES) was compared. There was better yield obtained using DES(BZK:Urea) as reaction medium as compared to glacial acetic acid in thermal method(NUS) as shown in Table 1. In thermal method using conventional solvent took 15 to complete the reaction as compared to DES mediated reaction which finishes the same work in just 4hr.

When similar reaction was run by ultrasonic method along with DES the time of reaction was reduced to approximately 1hr. The yield % was also several folds higher when DES and ultrasonic method were used together (Table 2). Therefore, mutual effect of ultrasound and DES played a vital role to the accomplishment of desired product with improved yield in a minimum expense of time. In this particular scheme benzalkonium chloride & urea (BZK: Urea: 1:2) based deep eutectic solvent (DES) was reused in the synthesis of each derivatives of pyrazoline. Thus, the effect of DES after each run was evaluated in terms of yield% of desired product and it was found to be good (Table 2).

Table: - 2 Deep eutectic solvent (DES) catalyzed synthesis of pyrazoline derivatives (4a-e) 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)
4a	4	52	78	88
4b	4.5	55	76	86
4c	4	60	75	85
4d	4	53	74	85
4e	4.5	49	69	81

Furthermore, mechanism involved to the formation of pyrazoline was also investigated. There is no any clear cut evidence regarding the actual role of DES [16, 17]. The hydrogen bond donor ability of urea and acidic nature of benzalkonium chloride might be the reason that DES acts as catalyst to make rearrangement and cyclization of reacting species that leads to the target compounds. The role of ultrasound to the synthesis of pyrazolines should not be ignored as well. During sonic reactions, there are tiny bubbles generated as a result of high temperature and pressure inside the reaction medium [18]. Production of the millions bubbles generates high reactive species (molecules) and might be help in rearrangement and cyclization process.

CONCLUSION

Pyrazoline derivatives were successfully synthesized by adopting thermal method (NUS) and ultrasonic method (US) in a two different reaction medium called glacial acetic acid and benzalkonium chloride based deep eutectic solvent. DES was found to be determinant factor in relation to % yield, temperature and time either used in thermal or ultrasonic method for the synthesis of desired compounds. Result was overwhelming, when DES and ultrasonic method used together. Recyclability of DES was also studied and found courageous, when used continuously for the synthesis of five derivatives of pyrazoline. Moreover, benzalkonium chloride and urea based DES is a good alternative to harsh expensive solvent and together with ultrasound technology will be a promising combination to catalyze many of organic reactions.

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