

# Deep Eutectic Solvent Catalyzed One-Pot Synthesis of Biologically Significant 1,3,5 trisubstituted Pyrazoline Derivatives

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**Abstract:** Simple, cost-effective method for synthesis of 4,5-dihydro-1H-pyrazole derivatives from 1,3-diphenyl - 2-propen-1-ones and phenyl hydrazine employing “nonconventional” deep eutectic solvent (DES) as “green” reaction media and catalyst, has been completed effectively. We optimize this cyclisation by using different greener solvents and we got surprising results from Choline chloride:glycerol (1:2) as a DES. Hydrogen-bond donating characteristics and high dissolution property increases the yield of pyrazoline derivatives. DES avoids the use of toxic catalyst and volatile solvents. Structures of the synthesized compounds have been elucidated by means of IR, <sup>1</sup>H NMR and mass spectral data. The antibacterial activity of the synthesized compounds was performed by Agar well diffusion method.

**Index Terms:** Deep eutectic solvent, Tri substituted pyrazoline, choline chloride: glycerol.

## INTRODUCTION

Volatile organic solvents (VOCs) are high on the list of environmental pollution. So, replacement of VOCs in favour of safe, bio-renewable reaction media are a great demand. Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) established in 2005 for incorporation of green chemistry and engineering into the pharmaceutical industry (Capua, 2016; Hunang, 2000).

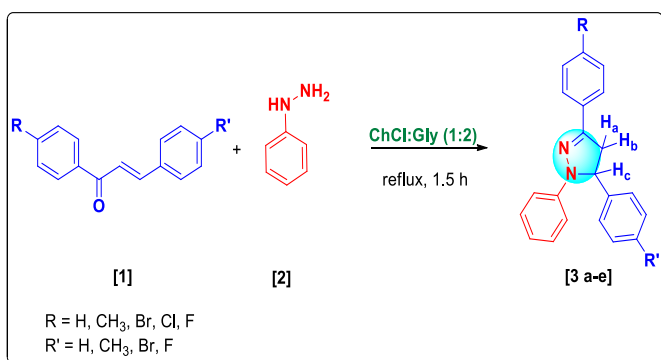
One of the biologically active heterocycle is pyrazoline. Substituted pyrazolines are found as a core structure in a variety of biologically-active compounds. The pyrazoline ring contains N-N bond linkage which is considered to be the basic factor in their biological actions. They exhibit a wide spectrum of biological activities such as antimicrobial (Hassan, 2013),

analgesic, anti-inflammatory (Taylor, 2010), antiepileptic (Anandarajagopal, 2010), antidepressant and antitubercular (Ahmad, 2016). Majority, pyrazoline compounds shows anticancer effects against human cancer cell lines such as A498, A549, A549, HT-29, HCT-15, 502713, HOP-62, A-545, MCF-7, SF-295 (Ahmad, 2016). The reported methods for synthesis of pyrazoline have certain inadequacies, such as tedious work-up procedure and volatile solvents. To avoid this problem greener approach is highly desirable (Joshi, 2012; Huang, 2012).

Deep eutectic solvents (DESs), have been investigated by Abbott et al. (Abbot, 2003; Abbot, 2004). It is a mixture of substituted quaternary ammonium salt with hydrogen-bond-forming compounds. When these compounds mixed at the correct molar ratio, form a homogeneous mixture (Abbot, 2001). Eutectic mixtures having a melting point lower than its individual components (Abbot, 2011). Choline chloride (ChCl), or 2-hydroxy-N,N,N-trimethylethanaminium chloride, has been widely used as an organic salt to produce eutectic mixtures, when blended with cheap and safe hydrogen bond donors like glycerol, the main by-product of biodiesel industry. So, new application of this natural and renewable polyol as a solvent in organic synthesis because of its biodegradable, low toxicity, cheap, and non-flammable characteristics (Yang, 2013). As, per earlier research findings from our work (Bhirud) we synthesized these derivatives by using Sulphamic acid as a catalyst (Bhirud, 2018; Bhirud, 2020; Bhirud 2021). Now, in this attempt we try to avoid catalyst and volatile organic solvents.

## RESULTS AND DISCUSSION

In the present investigation, 1,3,5-triphenyl-2-pyrazoline were synthesized from chalcone and phenyl hydrazine by using greener reaction media. As per the optimization performed, In the first attempt, the cyclization was accomplished in PEG 400, then we used ethylene glycol, but the yield was not satisfactory (38%) even in long reaction time (6 h). By observing the above low yield of product and knowing the importance of DES, we chose ChCl:glycerol (1:2) and interestingly, we obtained a much better result with 87% yield and 1.5h reaction time. Therefore, we decided to use ChCl:glycerol (1:2) as a solvent for the conversion of chalcone and phenyl hydrazine to desired product pyrazoline (3a-e). The structures of all the compounds were confirmed by IR, <sup>1</sup>H NMR and mass spectra.



**Scheme 1:** Synthesis of 5-(substituted phenyl)-1-phenyl-3-(substituted phenyl)-4,5-dihydro-1H-pyrazole [3a-e]

## ANTIMICROBIAL ACTIVITY

In the present investigation, four microorganisms were used to evaluate the antibacterial activity of synthesized products. (Vankatasatyanarayana, G, 2016: Sreedhar, 2010). The utilized test organisms are: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 19429, *Salmonella typhi* ATCC 23564 and *Staphylococcus aureus* ATCC 29737. The zone of inhibition in mm was shown in (Table 1). Substituted pyrazoline [3a] does not shows any activity whereas [3b] having bromine group shows good activity (20 mm) against *Salmonella typhi* comparable to standard drug streptomycin. The pyrazoline [3d] having a Bromo and fluoro substitution showed highest antibacterial activity (23 mm) against *Escherichia coli*. Rest of the compounds showed poor activity against the test organisms.

## EXPERIMENTAL

FT-IR spectra were recorded on Shimadzu IR affinity model

Table 1. Results of *in vitro* antimicrobial screening of compounds [3a-e]

Compounds	Zone of inhibition in mm			
	<i>E. coli</i>	<i>P.aeruginosa</i>	<i>S.aureus</i>	<i>S.typhi</i>
3a	-	-	-	-
3b	13	15	14	20
3c	-	13	-	16
3d	23	14	-	15
3e	17	12	16	21
Streptomycin	28	27	25	26

1 spectrometer using KBr pellets. <sup>1</sup>H NMR spectra was recorded on a Bruker AVANCE-III 500 MHz FTNMR spectrometer in CDCl<sub>3</sub> using TMS as internal standard (IISER, Bhopal). For mass spectra WATERS, Q-TOF MICROMASS spectrometer was used (SAIF, Chandigarh). All chemicals were used without purification.

A. General procedure for the preparation of 5-(substituted phenyl)-1-phenyl-3-(substituted phenyl)-4,5-dihydro-1H-pyrazole [3a-e]

A round-bottom flask equipped with a magnetic stirrer, chalcone (5 mmol), phenyl hydrazine (5 mmol), ChCl:Gly (15 mL) was refluxed for 1.5 h. The progress of the reaction was checked by TLC (Ethyl acetate:Hexane 70:30). After completion, the reaction mixture was poured in ice (50gm). The solid was obtained by simple filtration. Product washed with cold water, and purified by ethanol.

B. Spectral data of 4,5-dihydro-1H-pyrazole derivatives:

- 5-(4-bromophenyl)-1-phenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazole [3a]: White solid; m. p. 211- 213°C; IR (KBr) (cm<sup>-1</sup>): 1590 (C=N), 1546 (C=C), 518 (C-Br); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (δ) 2.40 (s, 3H), 3.24 (dd, C4-Ha, 1H), 3.93 (dd, C4-Hb, 1H), 5.90 (dd, C5-Hc, 1H), 7.29 (ddd, 5H), 7.45 (m, 3H), 7.57 (dd, 2H), 7.73 (d, 2H), 7.90 (d, 1H); LC-MS (m/z): 390 (M)<sup>+</sup>, 392 (M+2H)<sup>+</sup>.
- 3-(4-bromophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole [3b]: Yellowish solid; m. p. 230- 231°C; IR (KBr) (cm<sup>-1</sup>): 1595 (C=N), 1545 (C=C), 526 (C-Br); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (δ) 3.15 (dd, C4-Ha, 1H), 3.98 (dd, C4-Hb, 1H), 5.30 (dd C5-Hc, 1H), 6.86 (t, 1H), 7.13 (d, 2H), 7.31 (m, 7H), 7.60 (dd, 4H); LC-MS (m/z): 376 (M)<sup>+</sup>, 378(M+2H)<sup>+</sup>.

- 3) 3-(4-chlorophenyl)-1-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazole [3c]: White solid; m.p. 218- 220°C; IR (KBr) (cm<sup>-1</sup>): 1604 (C=N), 1518 (C=C), 601 (C-Cl); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (δ) 2.30 (s, Ar-CH<sub>3</sub>, 3H), 3.35 (dd, C4-Ha, 1H), 4.10 (dd, C4-Hb, 1H), 5.30 (dd C5-Hc, 1H), 6.72 (t, 1H), 6.88 (dd, 2H), 7.18 (m, 6H), 7.45 (d, 2H), 7.76 (d, 2H); LC-MS (m/z): 346 (M)<sup>+</sup>, 348(M+2H)<sup>+</sup>.
- 4) 5-(4-bromophenyl)-3-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole[3d]: Yellow White solid; m.p. 200-202°C; IR (KBr) (cm<sup>-1</sup>): 1585 (C=N), 1510 (C=C), 525 (C-Br), 680 (C-F); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (δ) 3.22 (dd, C4-Ha, 1H), 3.80 (dd, C4-Hb, 1H), 5.15 (dd, C5-Hc, 1H), 7.15 (dd, 2H), 7.24 (m, 6H), 7.56 (dd, 3H), 7.60 (dd, 2H) ; LC-MS (m/z): 394 (M)<sup>+</sup>, 396(M+2H)<sup>+</sup>.
- 5) 5-(4-fluorophenyl)-1-phenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazole [3e]: White solid; m. p. 235-238°C; IR (KBr) (cm<sup>-1</sup>): 1609 (C=N), 1520 (C=C), 634 (C-F); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (δ) 2.35 (s, Ar-CH<sub>3</sub> 3H), 3.40 (dd, C4-Ha, 1H), 3.90 (dd, C4-Hb, 1H), 5.27 (dd, C5-Hc, 1H), 6.85 (dd, 2H), 6.84 (d, 1H), 7.20 (m, 6H), 7.39 (d, 2H), 7.82 (d, 2H); LC-MS (m/z): 330 (M)<sup>+</sup>, 332 (M+2H)<sup>+</sup>.

#### CONCLUSION

We developed an effective method for the synthesis of 1,3,5 trisubstituted 2-pyrazoline from the condensation reaction of 1,3-diphenyl propen-1- ones with phenyl hydrazine by using DES. This protocol affords pure products in good yields. The advantages of this procedure include mild reaction conditions, good yields, simple workup process and easy removal of catalyst. The newly synthesized compounds [3d] showed good antibacterial activity (23 mm) against Escherichia coli.

#### COPYRIGHT FORM

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