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Sulfamic Acid Catalyzed One-Pot Synthesis of Biologically Relevant 4,5-dihydro-1H-pyrazole Derivatives

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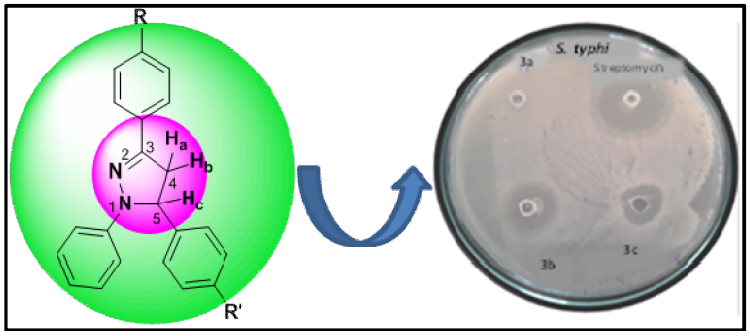
ABSTRACT

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 a catalytic amount of sulfamic acid at reflux temperature is reported. The key features of the protocol include rapid reactions with good yields, simple workup procedure, and easy isolation of products. Structures of the synthesized compounds have been elucidated by means of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The antibacterial activity of the synthesized compounds was performed by Agar well diffusion method.

Graphical Abstract



Keywords: Pyrazoline, Chalcone, Sulfamic acid, catalyst.

INTRODUCTION

Heterocyclic compounds have been synthesized mainly due to the wide range of biological activities. Much attention has been paid to the synthesis of nitrogen containing heterocyclic compounds, like pyrazoline due to its higher pharmacological activity. Pyrazole and its derivatives are the key structural motifs in heterocyclic chemistry and occupy important position in medicinal chemistry [**1**]. Pyrazoline is a π-excessive heterocycle and contains two nitrogen atoms, pyrrole type and pyridine type, at positions one and two. Pyrazole exists in three partially reduced forms, 1-pyrazoline, 2-pyrazoline and 3-pyrazoline [**2**].

Pyrazoline derivatives are the electron rich nitrogen heterocycles. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Considerable attention has been focused on the pyrazoline and substituted pyrazoline due to their interesting biological activities. These compounds have been found to possess anti-microbial, analgesic [**3**] anti-depressant, anticonvulsant [**4**], anti-inflammatory [**5**] and anti-tumour [**6**] properties. In addition, these compounds have been utilized as fluorescence probes in some elaborate chemosensors [**7**]. Recently very important reviews have been published upon the studies of pyrazoline compounds [**8, 9**].

Chalcones are the subject of continuous experimental and theoretical investigations. These flexible molecules appear in various conformations, and their properties depend on ring substitution. The parent (*E*)-chalcone was not found as a natural product but some simple derivatives such as 4-hydroxy and 4-methoxychalcones have been found in plants of the genus *Citrus* and *Flemingia* respectively. Natural derivatives of chalcones were present with aromatic rings, containing hydroxyl, methoxy, methyl and isopentenyl substituents. Chalcones constitute an important class of naturally occurring flavonoid compounds and are well-known intermediates for the synthesis of various heterocycles. Chalcones are useful synthons in the synthesis of a large number of bioactive molecules, such as pyrazolines that are well-known nitrogen-containing heterocyclic compounds [**10**].

The development of a clean procedure for the preparation of heterocyclic compounds is a major challenge in modern heterocyclic chemistry, in view of the environmental, practical and economic issues [**11**]. We have developed efficient method for synthesis of trisubstituted pyrazoline by using sulfamic acid, as a catalyst.

MATERIALS AND METHODS

Melting points was taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates in n-hexane: ethyl acetate system (2:8). The spot was visualized by exposing dry plate in UV chamber. IR spectra were recorded on Schimadzue I R affinity model 1 spectrometer using KBr pellets. ^{1}H NMR spectra was recorded on a Bruker AVANCE-III 500 MHz FTNMR spectrometer in $CDCl_3$ using TMS as internal standard. ^{13}C NMR was recorded on Bruker AVANCE-III 100 MHz in $CDCl_3$ (IISER, Bhopal). Mass spectra were recorded under ESI mode on WATERS, Q-TOF MICROMASS mass spectrometer (SAIF, Panjab University, Chandigarh).

General procedure of preparation of 5-(substituted phenyl)-1-phenyl-3-(substituted phenyl)-4,5-dihydro-1H-pyrazole [3a-e]: A round-bottom flask containing chalcone (5 mmol), phenyl hydrazine (5 mmol), few drops of glacial acetic acid, 20 mol % sulfamic acid in ethanol (15 mL) was refluxed for 2 h. The progress of the reaction was checked by TLC (Ethyl acetate:hexane 80:20). After completion, the reaction mixture was poured in ice-cold water and the precipitate was filtered off, recrystallized from ethanol.

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. 210-212°C;IR (KBr) (cm^{-1}): 1593 (C=N), 1543 (C=C), 516 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$): (δ) 2.38 (s, 3H), 3.28 (dd, C_4-H_a, 1H), 3.95 (dd, C_4-H_b, 1H), 5.86 (dd, C_5-H_c, 1H), 7.28 (ddd, 5H), 7.51 (m, 4H), 7.65 (dd, 1H), 7.77 (d, 2H), 7.97 (d, 1H);^{13}C NMR (100 MHz, $CDCl_3$): (δ)21.8, 50.4, 62.7, 115.4, 117.5, 119.6, 122.5, 124.6, 126.8, 128.5, 128.9, 129.4, 129.7, 131.6, 132.6, 142.3, 142.6,. 145.7; LC-MS (m/z): 390 $(M)^+$, 392 $(M+2H)^+$.

3-(4-bromophenyl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole [3b]: Yellowish solid; m. p. 230-231°C;IR (KBr) (cm^{-1}): 1591 (C=N), 1530 (C=C), 518 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$): (δ) 3.12

(dd, C_4-H_a, 1H), 3.81 (dd, C_4-H_b, 1H), 5.30 (dd C_5-H_c, 1H), 6.86 (t, 1H), 7.13 (d, 2H), 7.32 (m, 7H), 7.58 (dd, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): (δ) 43.3, 64.6, 113.5, 119.4, 122.5, 125.8, 127.2, 127.7, 129.0, 129.2, 131.7, 142.3, 142.6, 148.5; LC-MS (m/z): 376 $(M)^+$, 378$(M+2H)^+$.

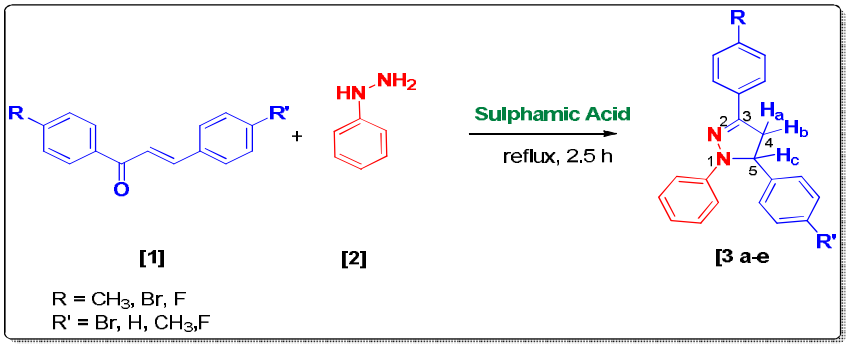
3-(4-chlorophenyl)-1-phenyl-5-(*p*-tolyl)-4,5-dihydro-1H-pyrazole [3c]: White solid; m. p. 220-221°C;IR (KBr) (cm^{-1}): 1598 (C=N), 1512 (C=C), 608 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$): (δ) 2.35 (s, Ar-CH_3, 3H), 3.30 (dd, C_4-H_a, 1H), 3.94 (dd, C_4-H_b, 1H), 5.28 (dd C_5-H_c, 1H), 6.75 (t, 1H), 6.88 (dd, 2H), 7.20 (m, 6H), 7.60 (d, 2H), 7.92 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): (δ) 21.6, 42.3, 63.5, 115.6, 122.3, 128.3, 128.9, 129.7, 134.5, 136.6, 136.9, 140.3, 144.2, 149.6; LC-MS (m/z): 346 $(M)^+$, 348$(M+2H)^+$.

5-(4-bromophenyl)-3-(4-fluorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole[3d]: Yellow White solid; m.p. 199-200°C;IR (KBr) (cm^{-1}): 1589 (C=N), 1508 (C=C), 520 (C-Br), 680 (C-F); ^{1}H NMR (400 MHz, CDCl3): (δ) 3.26 (dd, C_4-H_a, 1H), 3.78 (dd, C_4-H_b, 1H), 5.22 (dd, C_5-H_c, 1H), 6.98 (dd, 2H), 7.24 (m, 6H), 7.56 (dd, 3H), 7.65 (dd, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): 49.5, 63.7, 114.6, 116.5, 120.7, 123.0, 126.4, 126.9, 127.3, 128.7, 129.6, 129.9, 130.6, 141.7, 143.6, 144.4; LC-MS (m/z): 394 $(M)^+$, 396$(M+2H)^+$.

5-(4-fluorophenyl)-1-phenyl-3-(*p*-tolyl)-4,5-dihydro-1H-pyrazole [3e]: White solid; m. p. 232-233°C;IR (KBr) (cm^{-1}): 1601 (C=N), 1522 (C=C), 634 (C-F); ^{1}H NMR (400 MHz, CDCl3): (δ) 2.32 (s, Ar-CH_3 3H), 3.32 (dd, C_4-H_a, 1H), 3.90 (dd, C_4-H_b, 1H), 5.20 (dd, C_5-H_c, 1H), 6.85 (dd, 2H), 6.79 (d, 1H), 7.20 (m, 6H), 7.32 (d, 2H), 7.82 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): (δ)21.4, 41.2, 60.5, 116.2, 118.4, 120.9, 127.5, 128.4, 129.2, 129.8, 133.6, 139.6, 145.2, 151.0; LC-MS (m/z): 330 $(M)^+$, 332 $(M+2H)^+$.

RESULTS AND DISCUSSION

In the present investigation, 1,3,5-triphenyl-2-pyrazoline were synthesized from phenyl hydrazine and 1,3-diphenyl-2-propen-1-ones i.e. chalcones. Chalcone was synthesized according to known procedure [**12**]. For the synthesis of pyrazoline we try green reaction approach by using catalysts. For the optimization studies, we have taken (2.5 mmol) chalcone**1a**, (2.5 mmol) phenyl hydrazine and 20mol% of catalyst, such as montmorillonite K10, Fuller's Earth, Fe^{3+} montmorillonite and sulfamic acid but the best results obtained in presences of sulfamic acid (82% yield). By using this optimized condition we synthesized five different pyrazoline derivatives (Scheme 1, Table 1).



Scheme 1. Synthesis of 5-(substituted phenyl)-1-phenyl-3-(substituted phenyl) -4,5-dihydro-1H-pyrazole **3a-e** using sulfamic acid.

The structures of all compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectra. FT-IR spectra of the compounds showed C=N and C=C (aromatic) stretching bands at 1589-1601 and 1512-1589 cm^{-1} respectively. The ^{1}H NMR spectra of 2-pyrazoline shows, doublets of doublets at δ

3.12-3.32 and 3.78-3.95 *ppm* due to C_4-H_a and C_4-H_b of pyrazoline ring, indicates proton of same carbon atom shows different chemical shift. C_5-H_c of pyrazoline ring also shows doublets of doublets at δ 5.20-5.86 *ppm*. Protons of all three aromatic rings, substituted on 1,3,5 position of pyrazoline shows absorption frequencies between δ 6-8 *ppm*.^{13}C NMR spectra shows band at δ 41-50 and 60-64 *ppm* indicates two sp^3 hybridized carbon atom of pyrazoline ring.

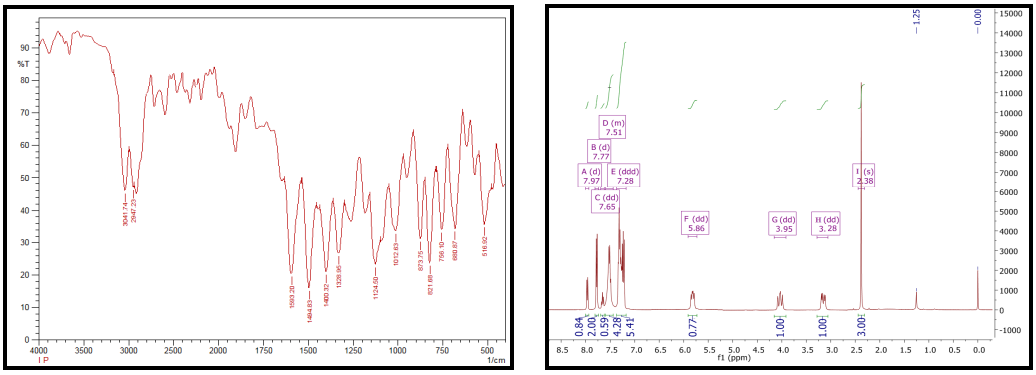


Figure 1. FTIR and ^{1}H NMR spectrum of compound **3a**

Table 1. Expeditious synthesis of 5-(substituted phenyl)-1-phenyl-3-(substituted phenyl) -4,5-dihydro-1H-pyrazole **3a-e** under reflux condition[a]

Entry	R	R'	Time (h)	Yield[b] (%)
3a	CH_3	Br	2	82
3b	Br	H	2	78
3c	Cl	CH_3	2	80
3d	F	Br	2	81
3e	CH_3	F	2	76

[a]Reaction conditions: (5 mmol) Chalcone, (5 mmol) Phenyl hydrazine, few drops Glacial acetic acid and 20 mol% sulfamic acid, [b]Isolated yield

Antimicrobial Activity: The new target synthesized compounds were tested for their *in vitro* antibacterial activity against bacterial strains such as *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* by using agar well diffusion method. Standard drug Streptomycin was used for comparison purpose (Table 2). 15 mL of Muller Hinton agar medium was poured into previously sterilized and labelled petri plates. 100 µL inocula of each test bacterium were sprayed on these petriplates followed by pre incubation at 4°C for 10-15 min for absorption. (6 mm) wells were bored into seeded agar plates and these were loaded with a 100 µL volume with concentration of 100µg mL^{-1} of each compound and standard drug constituted in dimethylsulphoxide (DMSO). The plates were incubated for 24 h at 37°C under aerobic conditions.

Table 2. Results of *in vitro* antimicrobial screening of compounds **3a-e**

Compounds	Zone of inhibition in mm			
	E. coli	*P.aeruginosa*	*S.aureus*	*S.typhi*
3a	-	-	-	-
3b	12	14	15	**19**
3c	-	12	-	17
3d	**22**	14	-	16
3e	18	12	17	**21**
Streptomycin	28	27	25	26

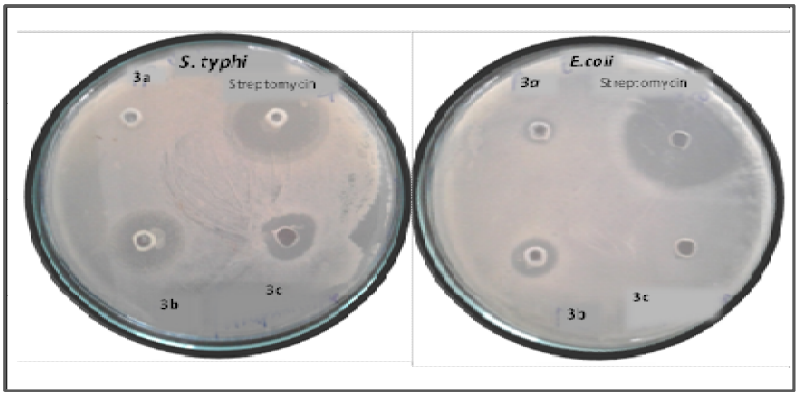


Figure 2. Antimicrobial activity of compounds **[3a-e]**against *E. coli* and *S.typhi*

APPLICATION

This protocol investigates eco-friendly synthesis of pyrazoline derivatives by using sulfamic acid as a catalyst. The research work presented is a significant contribution to the investigation in catalysis as well as medicinal Chemistry.

CONCLUSIONS

We have developed an efficient protocol for the synthesis of 1,3,5 trisubstituted 2-pyrazoline from chalcone and phenyl hydrazine by using sulfamic acid, a water soluble catalyst. We optimized this reaction condition by using different catalysts. Short reaction time, easy removal of catalyst and improvement in the yield of synthesized products are the main achievements of this green protocol. The results revealed that the compound **3d** and **3e** having fluorine substituent on pyrazoline moiety showed significant antibacterial activity.

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