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Acetic Acid in PEG-400: An Efficient System for Synthesis of 1-Cinnamoyl-2-Pyrazoline Derivatives

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ABSTRACT

An efficient method for the synthesis of biologically active 3,5-diaryl-1-cinnamyol-2-pyrazolines is reported. A new series of 1-cinnamoyl-2-pyrazoline derivatives were synthesized by the treatment of appropriate chalcones with cinnamoyl hydrazide using acetic acid in polyethylene glycol-400 as reaction solvent under mild reaction condition. Structures of the newly synthesized compounds were confirmed by the spectral analysis. The advantage of this method is simple work up, shorter reaction time and exclusion of expensive catalyst is reported.

1. Introduction

Pyrazolines are heterocyclic compounds of five membered unsaturated ring structure having three carbon atoms and two nitrogen atoms in adjacent positions. Several pyrazoline derivatives possess important pharmacological activities and therefore they are useful materials in drug research. 2-Pyrazolines are biologically active scaffolds with a variety of biological activities like antimicrobial [1], antitubercular [2], anti-inflammatory [3], anticancer [4], antitumor [5], anticonvulsant [6], and anti-HIV [7]. Some of the pyrazoline derivatives are also reported to possess anti-inflammatory [8], antidiabetic [9] and antidepressant properties [10].

On the other hand, cinnamic acid derivatives, especially those combining the cinnamoyl moiety with hydroxyl groups, present strong free radical scavenging properties [11]. Acids, esters, amides, hydrazides and related derivatives of cinnamic acid with such activities are reported in the literature for their health benefits [12-13].

As far as the different pyrazolines are concerned, 2-pyrazoline derivatives became the most frequently studied pyrazolines, various methods are used for the preparations of 2-pyrazolines. The treatment of α, β-unsaturated ketones with hydrazines seems to be the most popular for this purpose. Keeping these biological observations of pyrazolines in mind along with social responsibilities and in continuation of our work on the synthesis of biologically active heterocyclic compounds [14-16], it was planned to synthesize some new series of 2-pyrazoline derivatives containing cinnamoyl moiety under mild condition.

2. Experimental Methods

Melting points were determined by in an open capillary method and are uncorrected. The chemicals and solvents used for laboratory grade and were purified. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded (in DMSO-d_6) on Avance-300 MHz spectrometer using TMS as an internal standard. The mass were recorded on EI-Shimadzu-GC-MS spectrometer.

*2.1 General Experimental Procedure for the Synthesis of Chalcones (**1a-h**)*

An equimolar mixture of substituted acetophenone (1 mmol), and aromatic aldehyde (1 mmol) was mixed in 15 mL polyethylene glycol-400 (PEG-400) taken in 100 mL conical flask. Then 2-3 mL of saturated solution of KOH (aprox 40 %) was added into the flask. The solution becomes reddish brown color. The reaction mixture was kept for overnight at room temperature. On the next day morning, the completion of the reaction was monitored by TLC. After completion of the reaction, then the contents of the flask were poured into 50 mL ice cold water. The corresponding solid was separated then filtered. The crude product was recrystallized from suitable solvent. The yield and M.P. of the product was noted.

Similarly all the compounds were synthesized by the same procedure. The physical and analytical data of the compounds were mentioned in Table 1.

Table 1 The physical and analytical data of synthesized chalcone derivatives

Entry	Substitution					Mol.	Yield	M.P
(1a-h)	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	Formula	(%)	(°C)
a	OH	H	H	Cl	OH	$C_{15}H_{11}O_3Cl$	90	130-132
b	H	H	Cl	H	OH	$C_{15}H_{11}O_2Cl$	85	127-129
c	H	H	Cl	H	Cl	$C_{15}H_{10}OCl_2$	95	134-136
d	H	H	Cl	H	Br	$C_{15}H_{10}OBrCl$	92	116-118
e	OH	H	H	Cl	Br	$C_{15}H_{10}O_2BrCl$	86	96-98
f	OH	H	H	F	OMe	$C_{16}H_{13}O_3F$	85	138-140
g	H	H	CH$_3$	H	OMe	$C_{17}H_{16}O_2$	86	106-108
h	OH	H	H	Cl	Cl	$C_{15}H_{10}O_2Cl_2$	90	126-128

*2.2 General Procedure for the Synthesis of 1-Cinnamoyl-2-Pyrazoline **3(a-h)***

An equimolar mixture of chalcone (**1a**) (1 mmol) and cinaamoyl hydrazide 2 (1 mmol) was mixed in 20 mL poly ethylene glycol-400 (PEG-400) taken in 50 mL round bottom flask. The catalytic amount of glacial acetic acid (1-2 mL) was added into the flask. The reaction mixture was stirred on magnetic stirrer at 50 °C for 1 hr. The completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into cold water. The solid was separated then filtered. The crude product (**3a**) was recrystallized from ethanol solvent. The yield and M.P. of the product was determined.

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Similarly all the compounds were synthesized by the same procedure. The physical and analytical data of the compounds was mentioned in Table 2.

Table 2 The physical and analytical data of synthesized 1-cinnamoyl 2-pyrazolines

Product	Substitution					Mol.	Yield	M.P.
	R_1	R_2	R_3	R_4	R_5	Formula	(%)	(°C)
3a	OH	H	H	Cl	OH	$C_{24}H_{19}N_2O_3Cl$	90	220-222
3b	H	H	Cl	H	OH	$C_{24}H_{19}N_2O_2Cl$	85	180-182
3c	H	H	Cl	H	Cl	$C_{24}H_{18}N_2OCl_2$	92	195-197
3d	H	H	Cl	H	Br	$C_{24}H_{18}N_2OClBr$	80	210-212
3e	OH	H	H	Cl	Br	$C_{24}H_{18}N_2O_2BrCl$	85	205-207
3f	OH	H	H	F	OMe	$C_{25}H_{21}N_2O_3F$	90	178-180
3g	H	H	CH_3	H	OMe	$C_{26}H_{24}N_2O_2$	82	230-232
3h	OH	H	H	Cl	Cl	$C_{24}H_{18}N_2O_2Cl_2$	86	170-172

*2.2.1 1-Cinnamoyl-3-(2-hydroxy-5-chlorophenyl)-5-(4- chlorophenyl)-2-pyrazoline (**3a**)*

IR (KBr, cm^{-1}): 1615, 1645, 3232; ^1H NMR (DMSO-d_6, δ ppm): 3.11 (dd, 1H, H_A), 3.72 (dd, 1H, H_B), 5.31 (dd, 1H, H_X), 6.11 (s, 1H, -OH); 6.71-7.95 (m, 14H, Ar-H+CH=CH), 11.52 (s, 1H, -OH); EIMS (*m/z*): 418 (M^+), 420 (M+2); Anal. Calcd. For $C_{24}H_{19}N_2O_3Cl$: C, 68.82; H, 4.57; N, 6.69 %. Found: C, 68.69; H, 4.42; N, 6.52 %

*2.2.2 1-Cinnamoyl-3-(4-chlorophenyl)-5-(4-hydroxyphenyl)-2-pyrazoline (**3b**)*

IR (KBr, cm^{-1}): 1610, 1648, 3256; ^1H NMR (DMSO-d_6, δ ppm): 3.21 (dd, 1H, H_A), 3.84 (dd, 1H, H_B), 5.26 (dd, 1H, H_X), 6.19 (s, 1H, -OH); 6.78-8.15 (m, 15H, Ar-H+CH=CH); EIMS (*m/z*): 402 (M^+), 404 (M+2); Anal. Calcd. For $C_{24}H_{19}N_2O_2Cl$: C, 71.55; H, 4.75; N, 6.95 %. Found: C, 71.42; H, 4.86; N, 6.88 %

*2.2.3 1-Cinnamoyl-3-(4-chlorophenyl)-5-(4-chlorophenyl)-2-pyrazoline (**3c**)*

IR (KBr, cm^{-1}): 1618, 1646, 3056; ^1H NMR (DMSO-d_6, δ ppm): 3.16 (dd, 1H, H_A), 3.81 (dd, 1H, H_B), 5.34 (dd, 1H, H_X), 6.85-8.35 (m, 16H, Ar-H+CH=CH); EIMS (*m/z*): 420 (M^+); Anal. Calcd. For $C_{24}H_{18}N_2OCl_2$: C, 68.42; H, 4.31; N, 6.65 %. Found: C, 68.36; H, 4.46; N, 6.78 %

*2.2.4 1-Cinnamoyl-3-(4-chlorophenyl)-5-(4-bromophenyl)-2-pyrazoline (**3d**)*

IR (KBr, cm^{-1}): 1610, 1642, 3025; ^1H NMR (DMSO-d_6, δ ppm): 3.08 (dd, 1H, H_A), 3.62 (dd, 1H, H_B), 5.12 (dd, 1H, H_X), 6.81-8.21 (m, 16H, Ar-H+CH=CH); EIMS (*m/z*): 464 (M^+); Anal. Calcd. For $C_{24}H_{18}N_2OClBr$: C, 61.89; H, 3.91; N, 6.01 %. Found: C, 61.76; H, 3.98; N, 5.91 %

*2.2.5 1-Cinnamoyl-3-(2-hydroxy-5-chlorophenyl)-5-(4- bromophenyl)-2-pyrazoline (**3e**)*

IR (KBr, cm^{-1}): 1616, 1645, 3245; ^1H NMR (DMSO-d_6, δ ppm): 3.22 (dd, 1H, H_A), 3.65 (dd, 1H, H_B), 5.28 (dd, 1H, H_X), 6.86-8.28 (m, 14H, Ar-H+CH=CH), 11.28 (s, 1H, -OH); EIMS (*m/z*): 480 (M^+); Anal. Calcd. For $C_{24}H_{18}N_2O_2ClBr$: C, 59.83; H, 3.77; N, 5.81 %. Found: C, 59.92; H, 3.86; N, 5.68 %

*2.2.6 1-Cinnamoyl-3-(2-hydroxy-5-fluorophenyl)-5-(4- methoxyphenyl)-2-pyrazoline (**3f**)*

IR (KBr, cm^{-1}): 1612, 1640, 3256; ^1H NMR (DMSO-d_6, δ ppm): 3.26 (dd, 1H, H_A), 3.38 (s, 3H, $-OCH_3$), 3.72 (dd, 1H, H_B), 5.21 (dd, 1H, H_X), 6.82-8.41 (m, 14H, Ar-H+CH=CH), 11.62 (s, 1H, -OH); EIMS (*m/z*): 416 (M^+); Anal. Calcd. For $C_{25}H_{21}N_2O_2F$: C, 72.11; H, 5.08; N, 6.73 %. Found: C, 72.24; H, 5.19; N, 6.61 %

*2.2.7 1-Cinnamoyl-3-(4-methylphenyl)-5-(4- methoxyphenyl)-2-pyrazoline (**3g**)*

IR (KBr, cm^{-1}): 1618, 1648, 3072; ^1H NMR (DMSO-d_6, δ ppm): 2.32 (s, 3H, $-CH_3$), 3.26 (dd, 1H, H_A), 3.41 (s, 3H, $-OCH_3$), 3.61 (dd, 1H, H_B), 5.28 (dd, 1H, H_X), 6.91-8.52 (m, 15H, Ar-H+CH=CH); EIMS (*m/z*): 396 (M^+); Anal. Calcd. For $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.11; N, 7.07 %. Found: C, 78.64; H, 6.19; N, 7.18 %

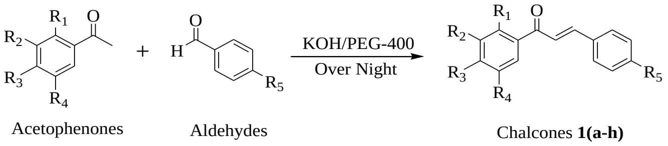
*2.2.8 1-Cinnamoyl-3-(2-hydroxy-5-chlorophenyl)-5-(4- chlorophenyl)-2-pyrazoline (**3h**)*

IR (KBr, cm^{-1}): 1615, 1648, 3281; ^1H NMR (DMSO-d_6, δ ppm): 3.21 (dd, 1H, H_A), 3.71 (dd, 1H, H_B), 5.31 (dd, 1H, H_X), 6.88-8.56 (m, 14H, Ar-H+CH=CH), 11.52 (s, 1H, -OH); EIMS (*m/z*): 436 (M^+); Anal. Calcd. For $C_{24}H_{18}N_2O_2Cl_2$: C, 65.91; H, 4.15; N, 6.41 %. Found: C, 65.82; H, 4.26; N, 6.54 %

3. Results and Discussion

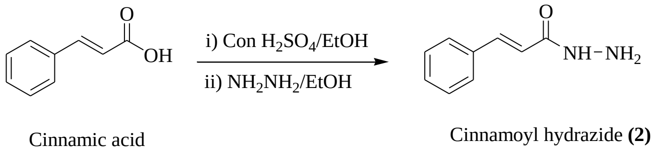
In recent years, polyethylene glycol (PEG-400) prompted reactions [17-20] have attracted the attention of organic chemists due to their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, ease of work-up, eco-friendly nature and economical cost. PEG is non-toxic, non-halogenated, inexpensive potentially recyclable and water soluble which facilitate its removal from reaction product. With our recent success on the development of new selective environmentally friendly methodologies using polyethylene glycol (PEG-400) [21-23] as a solvent for the preparation of biologically active compounds, herein we report the synthesis of some new cinnamoyl 2-pyrazolines derivatives by the cyclization reaction of chalcones with cinnamoyl hydrazide using catalytic amount of acetic acid in PEG-400 as an efficient reaction solvent.

The starting compounds (chalcones) **1(a-h)** were prepared by the Claisen-Schmidt condensation method. The aromatic acetophenones and aldehydes were mixed in PEG-400 taken in a conical flask. The aqueous KOH solution was added to it and kept for overnight. On the next day morning, the progress of the reaction was monitored by the TLC and worked up with water to yielded corresponding chalcones **1(a-h)** (Scheme 1, Table 1). The synthesis of 1-cinnamoyl-2-pyrazoline derivatives **3(a-h)** were prepared by the condensation of chalcones with cinnamoyl hydrazide (2) using catalytic amount of AcOH in PEG-400 as an efficient reaction solvent system.



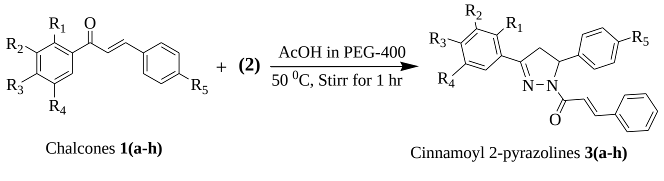
Scheme 1 Synthesis of chalcones using KOH in PEG-400 **1(a-h)**

The cinnamoyl hydrazide was prepared by the classical esterification method. The synthesis of cinnamoyl hydrazide was carried out from the esterification of cinnamic acid with ethanol in conc.H_2SO_4 followed by the treatment with hydrazine hydrate under reflux condition to yielded corresponding cinnamoyl hydrazide (Scheme 2). This formed cinnamoyl hydrazide was used as intermediate for the synthesis of cinnamoyl 2-pyrazolines.



Scheme 2 Synthesis of Cinnamoyl hydrazide

Further, the formed cinnamoyl hydrazide (**2**) intermediate was treated with different chalcone derivatives **1(a-h)** for the period of one hour using catalytic amount of acetic acid in polyethylene glycol-400 as reaction solvent to formed corresponding 1-cinnamoyl 2-pyrazolines (Scheme 3, Table 2). Initially, we carried out the above reaction in different solvents such as ethanol, acetic acid, DMF and polyethylene glycol-400. The reaction time and yield of the product was not significant. The only PEG-400 solvent showed satisfactory shorter reaction time. We turned our attention towards to obtain good to excellent yields of the products. The catalytic amount of acetic acid was used in combination with PEG-400; the reaction was completed very smoothly in high yield. Encouraged by the results, we focused our attention to variety of substituted chalcones. In all cases, the reaction proceeded efficiently in high yields under mild reaction temparature using catalytic amount of acetic acid in PEG-400 as an alternative reaction solvent.



Scheme 3 Synthesis of 1-cinnamyol 2-pyrazolines **3(a-h)**

Structures of all newly synthesized compounds were elucidated by the spectroscopic methods. The IR spectra of the products showed a characteristic band between 1600-1620 cm^{-1} referring to C=N double band between the N-2 and C-3 atoms. The IR spectrum of the products were also showed 1640-1660 cm^{-1} revealed to C=O of cinnamoyl group. In the ^1H NMR spectra of 2-pyrazolines, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system proved the 2-pyrazoline structure. Phenolic proton appeared as a singlet near δ 11.0-13.0 due to the hydrogen bonding, while other aromatic and aliphatic protons were observed at excepted regions. The mass spectra of the 1-cinnamyol 2-pyrazolines derivatives were showed molecular ion peak corresponding to their molecular formula.

4. Conclusion

In this present work, we have developed a simple and efficient system towards the synthesis of substituted 1-cinnamoyl 2-pyrazoline derivatives. The reaction of substituted chalcones with cinnamoyl hydrazide using catalytic amount of glacial acetic acid in polyethylene glycol (PEG-400) as an efficient reaction solvent at mild reaction condition is described. The advantages of the present protocol are the simple work up procedure, high yields of products and shorter reaction time is reported. The avoidance of expensive catalyst is the main advantage of this methodology.

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