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A Facile and green synthesis of (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-one promoted by L-proline

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Abstract: *A facile and green synthesis of (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-one* ***5(a-i)****, promoted by L-proline is being reported. Two methods* ***(A & B)*** *have been established for the preparation of compounds* ***5(a-i)****. In method A, 1H-indole-carbaldehyde* ***4(a-i)*** *were treated with reactive pyrazolones* ***3*** *in the presence of L-proline and ethanol at room temperature under stirring a for 20 min to afford* ***5(a-i)****. In method B, the 1H-indole-carbaldehyde* ***4(a-i)****, pyrazolones 3 and L-proline were ground for 40 min. to afford* ***5(a-i).***

Keywords: *L-Proline, Ethanol, knoevenagel condensation, 1H-indole-carbaldehyde, pyrazolone, (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-one, physical grinding.*

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I. Introduction:

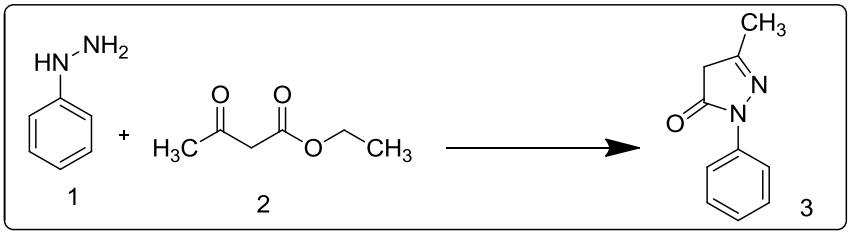
Pyrazole and its derivatives occupy an important position in medicinal and pesticide chemistry having a wide range of bio activities [1-7]. Pyrazolones, which are close structural analogues of pyrazoles, are also associated with broad spectrum of biological activities [8-12].The synthesis of olefins by condensation of active methylene compounds with aldehydes & ketones is known as the Knoevenagel condensation[13]. The synthesis and reactivity of indole derivatives have been a topic of research interest for well over a century. Bulk of literature evidence revealed wide spectrum of biological activities of indole and its analogs as anti-inflammatory, [14-18] anticonvulsant, [19] antitumour, [20] antimicrobial, [21] antibacterial,[22-23] antifungal, [24] Likewise thiadiazole,[25-26] pyrazole [27-30] and pyrazoline [31-32] congeners have also been found to exhibit various biological properties. Indrasena, A. et al. reported the synthesis of (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-ones in the presences of water under reflux conditions [33]. Keeping in view these results, herein we report the synthesis of (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-ones in ethanol and L-proline as a catalyst in room temperature.

The choice of L-proline as the catalyst was based on the fact that it is an eco-friendly and abundantly available bifunctional organo catalyst Capable of playing multiple catalytic roles as an acid, base, or Nucleophile, forming enamine and iminium cations. Being Amphoteric and soluble in water, it also facilitates chemical Transformations in concert, similar to enzymatic catalysis, and In fact L-proline has been described as the smallest Enzyme [34]. The versatile catalytic ability of L-proline is reflected in its applications in diverse organic transformations Such as aldol [35] and Knoevenagel [36] condensations, Michael Addition, [37] and some multicomponent reactions [38], among others.

II. Results And Discussion:

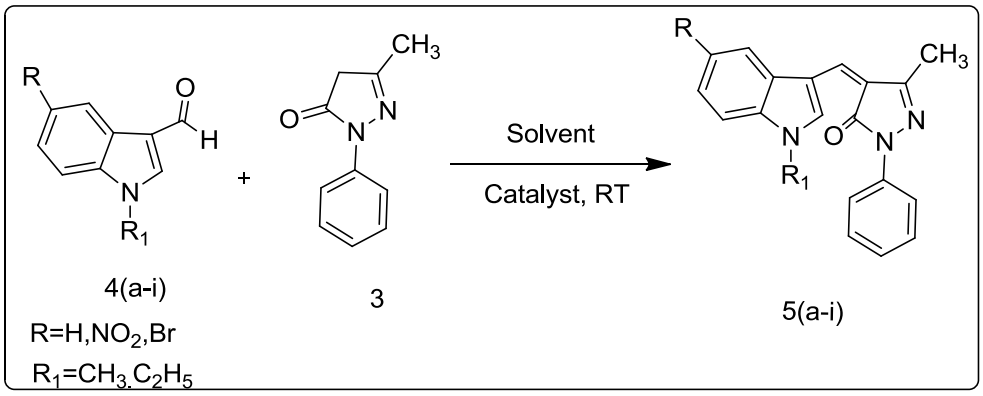
The starting material 3-substituted-1H **or** 1H-substituted-5(4H)-one **2** was prepared by the condensation of β-ketoesters with hydrazines.

Scheme-1



Scheme-1: synthesis of pyrazolone 3.

Scheme-2



Scheme-2: synthesis of compound 5(a-i).

Treatment of **4a** (i.e.**4**, R= H, NO_2, Br) with **3** in ethanol was chosen as a model. For this purpose, representative reactions involving treatment of **4a** (1mmol) with **3** (1mmol) were carried out in the presence of various catalysts in different solvents at room temperature (Scheme 2). Details of these studies are presented in TABLE 1.

TABLE 1: Condensation of 4a (1mmol), with 3(1mmol), in the presence of various catalysts in different green and non green solvents at room RT

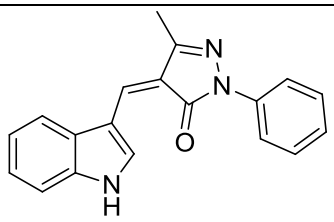
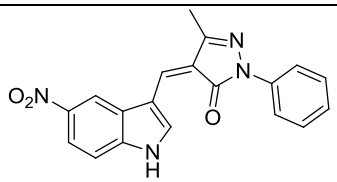
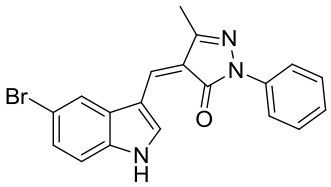
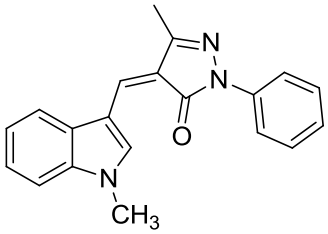
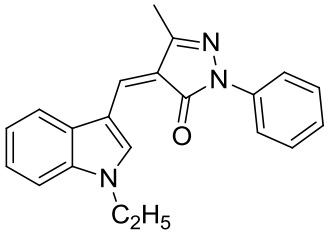
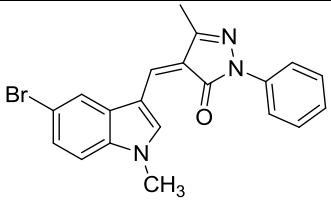
S.No.	catalyst	solvent	Time (min.)	Yields (%)
1	piperdine	Ethanol	80	60
2	pyridine	Ethanol	70	67
3	Na_2CO_3	Ethanol	120	50
4	Et_3N	Ethanol	90	60
5	K_2CO_3	Ethanol	65	50
6	L-Proline	acetonitrile	70	60
7	**L-Proline**	**Ethanol**	**20**	**92**
8	L-Proline	Water	55	45
9	L-Proline	Benzene	40	Nil
10	L-Proline	Chloroform	180	55
11	L-Proline	Toulene	150	65
12	L-Proline	Tetrahydrofuran	130	Nil

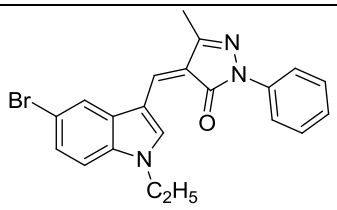
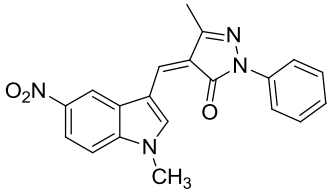
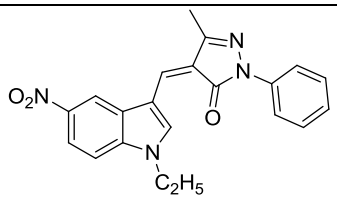
As it is clear from TABLE 1, the best results were obtained in the presence of L-proline in ethanol as solvent. The use of various organic solvents had no noticeable effect on the efficiency of the reaction. Probably the low yields obtained in organic non polar solvents are due to a low solubility of L-proline in these solvents.
Finally, a study was done to determine the effect optimal amount of L-proline. Various trial reactions were preformedwith10, 20, 30, 40, 50 mol% L-proline and also without the catalyst. Among them, 40mol%of L-proline provided the best results for the formation of Product at room temperature (TABLE- 2). Note that, increasing the amount of catalyst did not result in an increased yield of product and or decreased reaction time (entry 6 TABLE 2), also observed that, in the absence of L-proline, no product was detected even for a long time (entry-1TABLE 2).

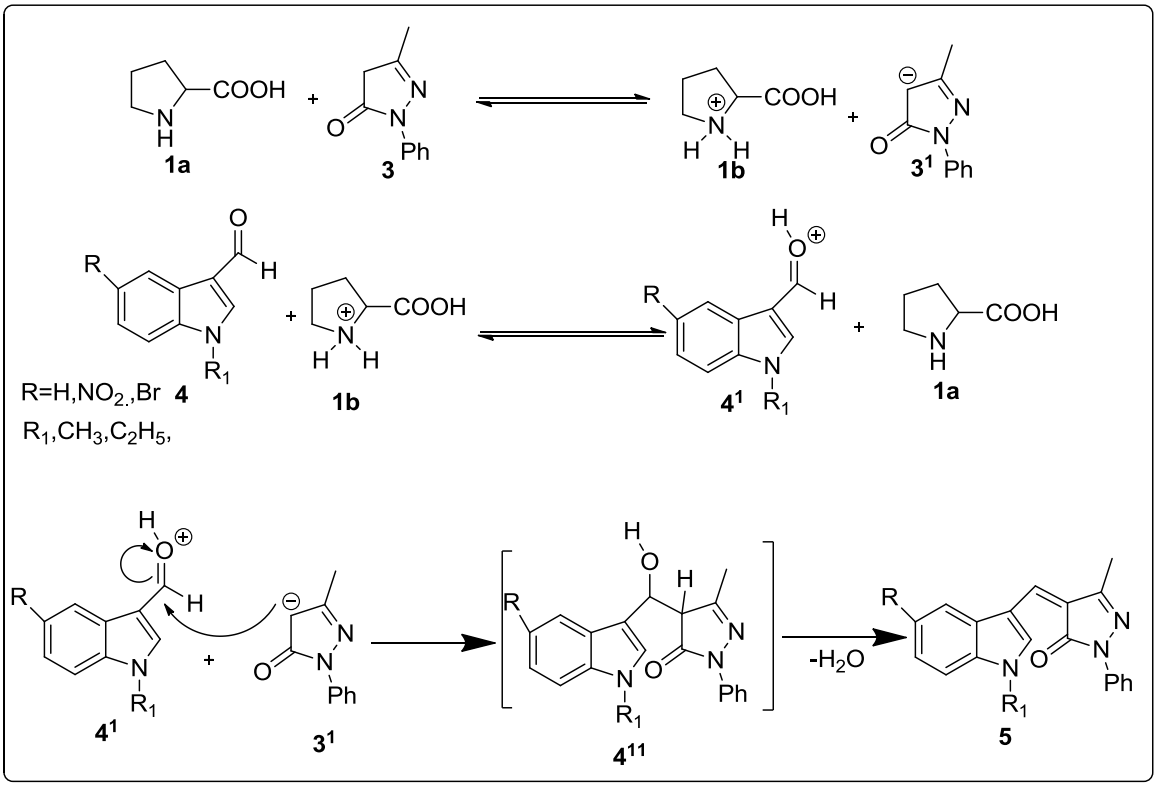
TABLE-2: Effect of catalyst amount on the synthesis of 4a

Entry	solvent	Amount of catalyst (mol %)	Time (Min)	Yields (%)
1	Ethanol	0	180	NR
2	Ethanol	10	35	72
3	Ethanol	20	32	75
4	Ethanol	30	28	80
5	Ethanol	40	20	92
6	Ethanol	50	20	88
7	Solvent-free	40	35	90

TABLE-3: synthesis of various derivatives of of (Z)-4-((1H-indol-3-yl) methylene)-3-methyl-1-phenyl-1H-pyrazole-5(4H)-one:

S.No.	Products	Time (min)		Yield (%)		M.P. (ºC)
		Method-A	Method- B	Method-A	Method- B	
5a		20	35	92	90	238-240^{0}C(lit)[33] 236-238^{0}C
5b		25	32	86	82	>250^{0}C(lit)[33] >250^{0}C
5c		28	38	88	82	>250^{0}C(lit)[33] >250^{0}C
5d		24	36	78	76	238^{0}C(lit)[33] 240-242^{0}C
5e		28	32	82	80	130^{0}C(lit)[33] 127-129^{0}C
5f		22	34	85	83	200-202^{0}C(lit)[33] 196-198^{0}C

5g		25	33	88	86	196-198^{0}C(lit)[33] 200-202^{0}C
5h		25	36	90	88	240^{0}C(lit)[33] 242-244^{0}C
5i		23	35	79	77	>250^{0}C(lit)[33] >250^{0}C

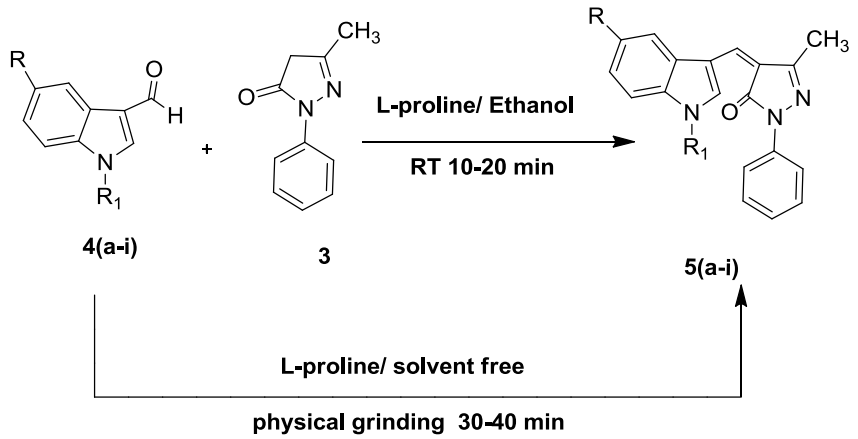


Scheme-3: plausible mechanism for the formation of 5 in the presence of L-Proline

In the mechanism shown in **Scheme-3**, L-proline abstracts the proton from pyrazolone (3), forming the carbanion of pyrazolone (3^1), which then attacks the protonated indol-3-carboxaldehyde(4^1) forming the corresponding intermediate (4^{11}) which lose water molecule to form the product **5.**

Alternatively, the condensation of **4** with **3** was also carried out under solvent-free conditions. Here **4**, **3** and L-proline 40mol%were ground together for 40min. in a porcela in mortar under solvent-free condition leading to a colored solid mass of the product **5** in 76-90%yield (TABLE 3) (Scheme-5). Probably, the low yields obtained in the solvent free conditions were due to the low interactions of L-proline with the starting materials.

Scheme-4:



Experimental Section:

All chemicals were purchased from Aldrich or fluka and used without further purification. Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. All reactions were monitored by Thin-layer chromatography (TLC). ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker Avanc 400MHZ in DMSO-d_6 with TMS as an internal standard. Mass spectra were recorded on an agilent LC-MS instrument giving only M^+ values in Q+1 mode.

Method A: General procedure for synthesis of 5(a-i)

A mixture of **4(a-i)** (10m.mol), the pyrazolone **3** (10m.mol),L-proline (40mol.%) and ethanol (10ml)was stirred at room temperature for a specified period of time (TABLE-3).After completion (as shown by TLC checking) of reaction, the mixture was poured into ice cold water (30ml). The separated solid was filtered, washed with water (2x15ml) and dried to obtain a crude product **5(a-i)**. The later was recrystallized from a suitable solvent to afford pure **5(a-i)**

Method B: under physical grinding method

A mixture of appropriate **4(a-i)** (10m.mol), active methylene group containing pyrazolone **3**(10m.mol), L-Proline(40mol.%) was thoroughly ground with pestle in an open mortar at room temperature for 30-40 minutes while the reaction was monitored by TLC. The mixture was then treated with coldwater (10ml). The separated solid was filtered, washed with water (2x15ml) and dried to get a crude product **5(a-i)**. Then the crude was recrystallized from a suitable solvent to afford pure **5(a-i)**.

III. Conclusion:

This procedure offers several advantages including increasing variation of product yields, mild reaction conditions, and operational simplicity, inexpensive and readily available catalyst all of which make it a useful and attractive strategy for the Knoevenagel condensation.

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