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A convenient and green synthesis of (Z)-4-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one promoted by L-proline

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ABSTRACT

A convenient and green synthesis of Z-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-1-phenylpyrazolin-5(4H)-one **6(a-h)**, promoted by L-proline is being reported. Two methods **(A & B)** have been established for the preparation of compounds **6(a-h)**. In method A, 1, 3-diphenyl-1H- pyrazole-4-carbaldehyde **4(a-h)** were treated with reactive pyrazolones **5** in the presence of L-proline and ethanol at room temperature under stirring for 15 min to afford **6(a-h)**. In method B, the 1,3-diphenyl-1H-pyrazolin-5-(4H)-4-carbaldehyde **4(a-h)**, pyrazolones **5** and L-proline were ground for 30 min. to afford 6(a-h).

KEYWORDS

1;
3-di-phenyl-1H-pyrazolin-5-(4H)-4-carbaldehyde;
Pyrazolones, Knoevenagel condensation;
L-proline, Ethanol, physical grinding.

INTRODUCTION

Pyrazole and its derivatives occupy an important position in medicinal and pesticide chemistry having a wide range of bioactivities[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]. Recently, various researchers have reported different protocols for the synthesis of these pyrazole derivatives. Some of the recently developed procedures for the synthesis of 4-pyrazolylmethylenepyrazol-5(4H)-ones via Knoevenagel condensation of pyrazolone and pyrazole aldehydes are reported to employ methods like triethylamine in ethanol under reflux[14], ethanol under microwave irradiation[15], sodium acetate and acetic acid under reflux[16], ionic liquids such as ethylammoniumnitrate[17], borate Zirconia as catalysts in water solution[18], sodium acetate/PEG-400[19], silica perchloric acid[20] etc. However, some of the above reported methods required higher temperatures, expensive ionic liquids, or high-catalyst-loading in reactions. Some are even disadvantaged as they seem to occur with not so high yields. Therefore, to overcome these difficulties and also to find better ways of synthesising these products, especially those using green protocols, it was considered worthwhile to study the condensation of pyrazole derivatives with pyrazolones.

EXPERIMENTAL SECTION

All the reagents and chemicals such as acetophenone derivatives, hydrazine hydrates and β-ketoesters were

obtained from commercial sources and used without further purification. Melting points were determined using open capillary tube in sulphuric acid bath, TLC were run on Silica gel-G and visualization was done using Iodine or UV-light, IR spectra were recorded using Perkin-Elmer spectrum version 10.03.02 instrument in KBr Pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ / DMSO using Varian 400-MHz instrument. 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 6(a-h)

A mixture of **4** (10 m.mol), the pyrazolone **5** (10 m.mol), L-proline (40 mol. %) and ethanol (10 ml) was stirred at room temperature for a specified period of time (TABLE 4). After completion (as shown by TLC checking) of reaction, the mixture was poured into ice cold water (20ml). The separated solid was filtered, washed with water (2×15 ml) and dried to obtain a crude product 6. The later was recrystallized from a suitable solvent to afford pure **6**.

Method B: under physical grinding method

A mixture of appropriate **4(a-h)** (10 m.mol), active methylene group containing pyrazolone **5** (10 m.mol), L-Proline (40 mol. %) was thoroughly ground with pestle in an open mortar at room temperature for 20-30 minutes while the reaction was monitored by TLC. The mixture was then treated with cold water (10ml). The separated solid was filtered, washed with water (2×15 ml) and dried to get a crude product **6(a-h)**. Then the crude was recrystallized from a suitable solvent to afford pure **6(a-h)**.

Spectral data for synthesized compounds 6(a-h)

3-methyl-1-phenyl-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)-1H-pyrazol-5(4H)-one(6a): IR (KBr, cm^{-1})

3125.7, 2982, 1675 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): δ= 2.42(s,3H, -CH3), δ= 7.38-7.99 (m,15H aromatic protons and 1H olefinic proton), δ= 10.88 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 169.8, 156.6, 141.8, 141.1, 140.5, 135.8, 133.6, 132.9, 132.3, 130.8,126.8,126.3, 125.5, 125.1, 124.6, 124.2, 123.3, 120.6, 118.2, 20.2. LC-MS: *m/z* 405 Q+1 mode.

(Z)-3-methyl-4-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-1-phenyl-1H-pyrazol-5(4H)-one (6b)

IR (KBr, cm^{-1}): 3539, 312, 3152, 1625, 1590, 778 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): *δ* 2.30 (s, 3H, –CH3), *δ* 7.18–7.96 (m,14H aromatic protons and 1H olefinic proton), δ= 10.60 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 168.6, 156.2, 149.7, 146.2, 142.8,142.1, 140.8,140.3, 132.3, 130.8, 128.7, 128.1, 126.3,125.5, 124.8, 120.7, 120.4, 120.1, 20.8. LC-MS: m/z 450 (Q+1).

(Z)-4-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6c)

IR (KBr, cm^{-1}): 3108, 3072, 2902, 1624, 1573,743 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): *δ* 2.39 (s, 3H, CH3), *δ* 7.20–8.48 (m,14H aromatic protons and 1H olefinic proton), δ= 10.66 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 163.2, 156.8, 151.3, 140.3, 137.5, 135.7, 134.5, 134.1, 133.8, 129.8, 129.5, 129.1, 128.6, 126.5, 124.8, 118.2, 115.2, 99.6, 20.5; LC-MS: m/z 439 (Q+1).

(Z)-4-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6d)

IR (KBr cm^{-1}): 3125.7, 2982, 1675 cm-1; 1H NMR (400 MHz, DMSO-d6/ TMS): δ= 2.34(s,3H, -CH3), δ= 7.18-9.42 (m,14H aromatic protons and 1H olefinic proton), δ= 10.20 (s,1H pyrazole ring proton); 13C NMR (100 MHz, DMSO-d6-TMS): δ: 163.6, 156.2, 153.3, 140.4, 138.1, 137.5, 134.62, 132.1, 129.9, 129.5, 128.7, 128.0, 125.6, 124.6, 120.6, 117.5, 22.8. LC-MS: m/z 483 (Q+1).

(Z)-3-methyl-4-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-1-phenyl-1H-pyrazol-5(4H)-one (6e)

IR (KBr, cm^{-1}): 3539, 312, 3152, 1625, 1590, 778 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): δ= 2.18(s,3H, -CH3), δ= 7.23-7.84 (m,14H aromatic protons and 1H olefinic proton), δ= 10.42 (s,1H

Full Paper

pyrazole ring proton); 13C NMR (100 MHz, DMSO-d6-TMS): δ: 168.6, 156.2, 149.7, 146.2, 142.8,142.1, 140.8,140.3, 132.3, 130.8, 128.7, 128.1, 126.3,125.5, 124.8, 120.7, 120.4, 120.1, 20.8. LC-MS: m/z 450 (Q+1).

(Z)-3-methyl-1-phenyl-4-((1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl) methylene)-1H-pyrazol-5(4H)-one (6f)

IR (KBr, cm^{-1}): 3063, 1790, 1685, 1654, 1460, 680, 2885 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): δ= 2.66(s,3H, -CH3), δ= 3.04(s,3H, -CH3), δ= 7.58-8.60 (m,14H aromatic protons and 1H olefinic proton), δ= 9.96 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 168.5, 157.4, 142.6, 140.1, 132.9, 130.6, 128.7, 128.5, 126.6, 124.2, 120.8, 120.5, 120.1, 20.2. LC-MS: m/z 419 (Q+1).

(Z)-4-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6g)

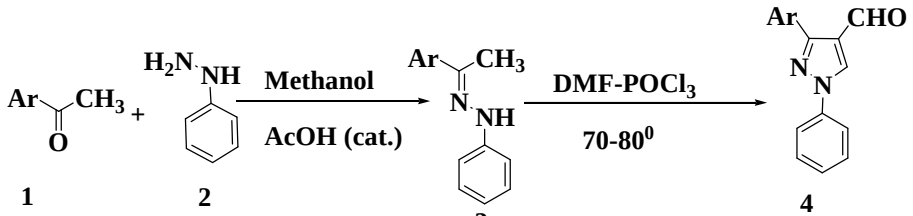
IR (KBr, cm^{-1}): 3325, 3158, 1620, 1574, 1435 cm^{-1}; 1H NMR (400 MHz, DMSO-d6/ TMS): *δ* 2.64 (t, 3H, CH3), *δ* 3.76 (t, 3H, OCH3), δ= 7.38-7.99 (m,14H aromatic protons and 1H olefinic proton), δ= 9.96 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 164.6, 160.8, 157.8, 156.4, 142.3, 142.1,141.5, 141.1, 140.6, 130.7, 130.2, 129.3, 128.9, 128.5, 126.6, 125.2, 124.4, 122.7, 120.3, 119.5, 118.8, 58.6, 20.4.LC-MS: m/z 435 (Q+1).

(Z)-4-((3-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (6h)

IR (KBr cm^{-1}): 3125.7, 2982, 1675 cm-1; 1H NMR (400 MHz, DMSO-d6/ TMS): δ= 2.42(s,3H, -CH3), δ= 7.88-8.26 (m,13H aromatic protons and 1H olefinic proton), δ= 10.70 (s,1H pyrazole ring proton); ^{13}C NMR (100 MHz, DMSO-d_6-TMS): δ: 163.5, 155.5, 154.2, 145.4, 143.1, 140.5, 138.2, 134.4, 130.9, 129.8, 129.2, 128.6, 127.6, 124.6, 122.6, 119.5, 22.6. LC-MS: m/z 473 Q+1 mode.

RESULTS AND DISCUSSION

The starting materials, 1-phenyl-3-aryl-1H-pyrazole-4-carbaldehyde **4(a-h)** were prepared by using Vilsmeier-Haack reaction of acetophenonearylhydrazones **3(a-h)**[21] which in turn were obtained from acetophenones **1(a-h)**, by condensation with phenyl hydrazine **2** in the presence of methanol containing catalytic amount of acetic acid.(Scheme-1)

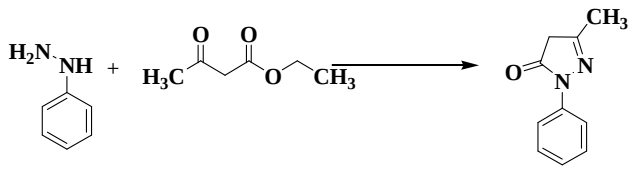


1a=-C_6H_5
1b=-C_6H_5-NO_2 (m)
1c=-C_6H_5-Cl (m)
1d=-C_6H_5-Br (m)
1e=-C_6H_5-NO_2 (p)
1f= C_6H_5-CH_3 (p)
1g= C_6H_5-Ome (p)
1h= C_6H_5-Cl (o,p)

3a=-C_6H_5
3b=-C_6H_5-NO_2 (m)
3c=-C_6H_5-Cl (m)
3d=-C_6H_5-Br (m)
3e=-C_6H_5-NO_2 (p)
3f= C_6H_5-CH_3 (p)
3g= C_6H_5-Ome (p)
3h= C_6H_5-Cl (o,p)

4a=-C_6H_5
4b=-C_6H_5-NO_2 (m)
4c=-C_6H_5-Cl (m)
4d=-C_6H_5-Br (m)
4e=-C_6H_5-NO_2 (p)
4f= C_6H_5-CH_3 (p)
4g= C_6H_5-Ome (p)
4h= C_6H_5-Cl (o,p)

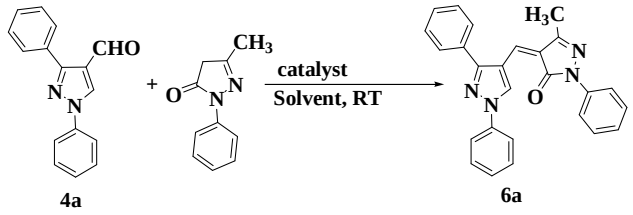
Scheme 1 : Synthesis of 1, 3-di-phenyl-1H-pyrazolin-5-(4H)-4-carbaldehyde 4(a-h)



Scheme 2 : Synthesis of pyrazolone 5.

In another sequence of reactions, 3-substituted -1H or 1- substituted-5(4H)-one **5** was prepared by the condensation of β–ketoesters with hydrazines (Scheme-2)

Treatment of **4a** (i.e.**4**, Ar= Ph) with **5** in ethanol



Scheme 3 : Condensation 4a with 5 in the presence of various catalysts in different solvents at room temperature

TABLE 1: Condensation of 4a (1mmol), with 5(1 mmol), in the presence of various catalysts in different green and non green solvents at room RT

Entry	Catalyst	Solvent	Time (min.)	Yields # (%)
1	Et_3N/ Ethanol	Ethanol	30	70
2	Piperidine	Ethanol	50	72
3	Pyridine	Ethanol	60	68
4	Na_2CO_3	Ethanol	60	Nil
5	K_2CO_3	Ethanol	60	Nil
6	L-Proline	Ethanol	10	96
7	L-Proline	Water	180	Nil
8	L-Proline	Acetonitrile	25	78
9	L-Proline	Tetrahydrofuran	28	76
10	L-Proline	Chloroform	50	75
11	L-Proline	Benzene	180	65
12	L-Proline	Toluene	120	62

 # refers to yields of isolated products only

containing L-proline as catalyst at room temperature for just 10 min. resulted in the formation of the title compound (Z)-4-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**6a**,i.e. **6**, Ar=Ph) in high yield (TABLE 1, entry 6). Compound 6a has been described in literature[14-20]. However, it has also been characterised in our work based on spectral data. (Please see the Experimental Section for details).

In order to optimize the reaction conditions, (TABLE 1) (Scheme-3) condensation of **4a**, with **5** was chosen as a model. For this purpose, representative reactions involving treatment of **4a** (1mmol) with **5** (1mmol) were carried out in the presence of various catalysts in different solvents at room temperature (Scheme 3). Details of these studies are presented in TABLE 1.

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 preformed with 10, 20, 30, 40, 50 mol% L-proline and also without the catalyst. Among them, 40 mol% 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 1 TABLE 2).

To compare the effectiveness of L-proline with other catalysts in the synthesis of 4-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene)-1-phenyl pyrazolin-**5**(4H)-one, results of the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde, 3-methyl-1-phenyl-1H-

TABLE 2 : Effect of catalyst amount on the synthesis of 6a

Entry	Solvent	Amount of catalyst (mol %)	Time (min)	Yield # (%)
1	Ethanol	0	180	NR*
2	Ethanol	10	25	72
3	Ethanol	20	22	75
4	Ethanol	30	18	80
5	Ethanol	40	10	96
6	Ethanol	50	10	90
7	Solvent free	40	21	94

 # refers to yields of isolated products only; * No reaction at room temp.

Full Paper

TABLE 3 : Comparing the result of the reaction of 4a, with 5 using L-proline with the results reported catalysts.

S.No.	Catalyst/ conditions	Time (min)	Yields (%)	Ref.
1	Et_3N/Ethanol/reflux	30	70%	14
2	Ethanol/MWI	25	85%	15
3	AcONa/AcOH/reflux	30	67%	16
4	Ethyl ammonium nitrate/RT	30	84%	17
5	B_2O_3-ZrO_2/H_2O/reflux	30	70%	18
6	AcONa/PEG-400/60^{0}c	70	84%	19
7	SiO_2-$HClO_4$/MeOH/80^{0}C	30	88%	20
8	L-proline/ Ethanol/ RT	10	96%	Present work
9	L-proline/ solvent free	20	94%	Present work

pyrazol-5(4H)-one have tabulated in TABLE 3. With respect to results, compared to the previously reported methods, L-proline was formed to be relatively better in terms of reaction times and yields.

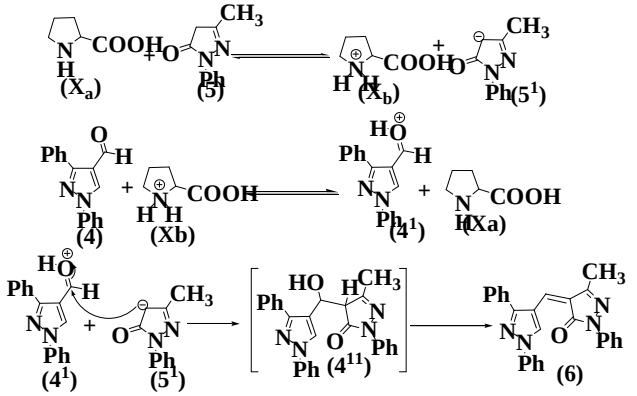
Alternatively, the condensation of **4a** with **5** was also carried out under solvent-free conditions. Here **4a**, **5** and L-proline 40mol% were ground together for 30 min. in a porcelain mortar under solvent-free condition leading to a colored solid mass of the product **6a** in 90-94% yield (TABLE 4) (Scheme-6). Probably, the low yields obtained in the solvent free conditions were due to the low interactions of L-proline with the starting materials.

There are two possible mechanisms for the formation of **6** from **4** and **5** in the presence of L-proline as catalyst as shown in Schemes 4 and 5 respectively.

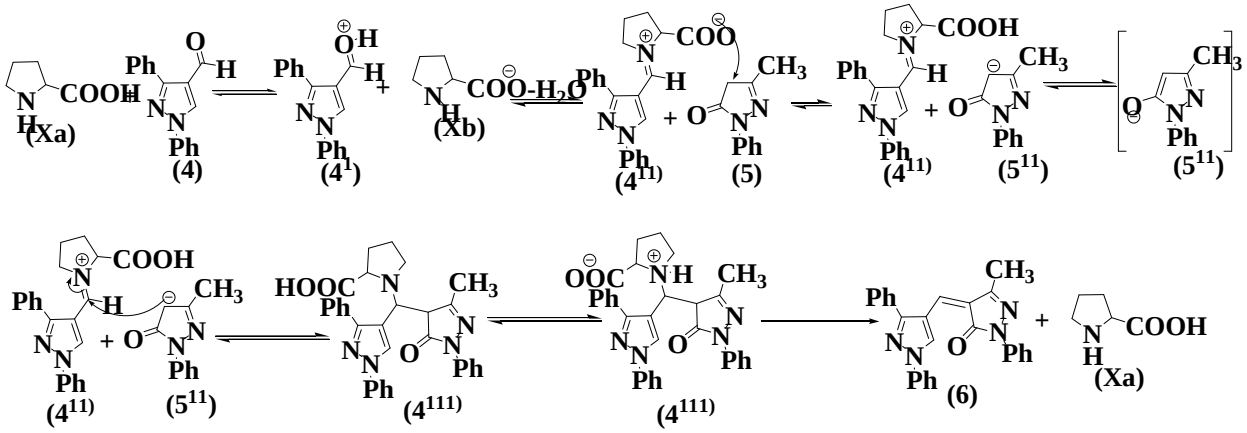
In the first mechanism shown in Scheme-4, L-proline abstracts the proton from pyrazolone (5), forming the carbanion of pyrazolone (5^{I}), which then attacks the protonated pyrazole-4-carboxaldehyde (4^{I}), forming the corresponding intermediate (4^{II}) which loses water to form the end product **6**.

In the second mechanism shown in Scheme-5, L-proline protonates the pyrazole aldehyde to form 4^{1}, which then forms the corresponding iminium intermediate 4^{II}. 4^{II} extracts the proton from 5, forming the carbanion 5^{II}. The latter attacks 4^{II}, forming the intermediate 4^{III}, which eventually loses L-proline with displacement by water to form 4^{III} and the latter loses water to form **6**.

In substance, it can be said that the two mechanisms shown in Schemes 4 and 5 differ from one another in



Scheme 4: Plausible mechanism for the formation 6a in the presence of L-proline

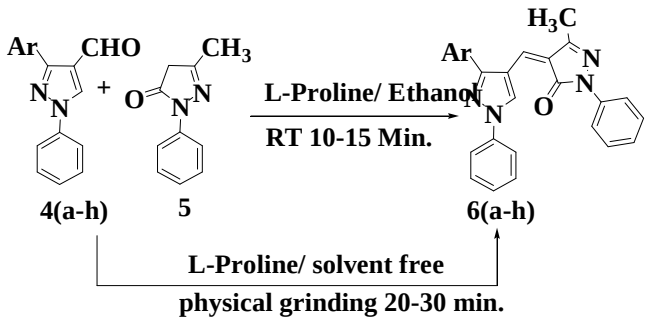


Scheme 5 : Plausible mechanism for the formation 6a in the presence of L-proline

TABLE 4 Preparation of compound 6(a-h)[a]

Entry	Ar	Product	Time (min)		Yield [b] (%)		m.p.(^{0}C)
			Method (A)	Method(B)	Method(A)	Method(B)	
1	$-C_6H_5$	6a	10	21	96	94	214-218 (Lit.m.p.212) [16]
2	$-C_6H_5-NO_2$ (m)	6b	12	25	92	90	220-224
3	$-C_6H_5$-Cl (p)	6c	10	22	95	93	240-242 (Lit.m.p.238)[16]
4	$-C_6H_5$-Br (p)	6d	11	22	95	93	228-230 (Lit.m.p.228)[24]
5	$-C_6H_5-NO_2$ (p)	6e	15	29	94	92	242-246 (Lit.m.p.242)[21]
6	$-C_6H_5-CH_3$ (p)	6f	15	23	96	94	236-238
7	$-C_6H_5$-Ome (p)	6g	15	27	92	91	162-164 (Lit. m.p.167-169) [19]
8	$-C_6H_4-Cl_2$ (o,p)	6h	12	24	93	92	208-210

[a] Reaction conditions: pyrazole-4-carbaxaldehyde (1 m.Mol), pyrazolone (1 m.Mol), L-proline (40mol%) in Ethanol (5 mL) stirring at room temperature / physical grinding under solvent free conditions; [b] Isolated yields



Scheme 6 : Synthesis of compound 6 (a-h) catalysed by L-Proline

that Scheme 4 involves a simple proton-transfer process catalyzed by the L-proline

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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