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AN EFFICIENT ECO-FRIENDLY SYNTHESIS OF PYRAZOLE ACRYLOYL ANALOGUES BY AMINO ACID CATALYSIS

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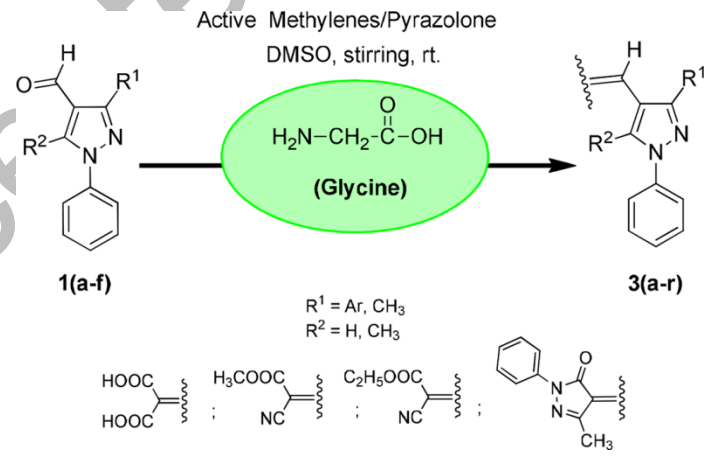
Abstract

An easy and effective green approach of Knoevenagel condensation and arylidene formation with the substrates; pyrazole-3-carbaldehydes and active methylenes under catalytic action of glycine (the simplest amino acid) in DMSO. These reactions were successfully carried out at room temperature.



KEYWORDS: Active methylenes; Arylidenes; Glycine; Knoevenagel condensation; Pyrazole-3-carbaldehyde

INTRODUCTION

One of the acknowledged pathways to develop a new C-C bond through exploitation of an aldehydic or ketonic functionality and an active methylene group is Knoevenagel condensation. Traditionally, these reactions were carried out in organic solvents with basic catalysts and sometimes under acidic conditions also.[1,2] In recent times, various modern homogeneous and heterogeneous catalysts have also been introduced for this purpose, such as guanidine,[3] sodium benzoate,[4] I_2-K_2CO_3,[5] $ZnCl_2$,[6] phosphane,[7] borate zirconia,[8] different ionic liquids,[9] Al_2O_3,[10] silica supported catalysts,[11] zeolites,[12] calcite and fluorite.[13] But even though, expensive reagents, harmful reaction conditions, undesired side products, tedious workups, prolonged reaction times and poor yields are still existed limitations of these methodologies. To deal with these tangible obstacles, more efficient yet facile reaction conditions are being sought.

Although some amino acids were used for condensation reactions [14-16] and there are reports of green Knoevenagel reaction protocols,[17] to the best of our knowledge; this amino acid catalysis was not explored to synthesize pyrazolyl acryloyl analogues or for the condensation of arylaldehydes with pyrazolones. We had earlier explored this possibility in some limited reactions.[18] With the benefit of foresight, we aimed to extend this catalytic potentials of amino acids for synthesizing targeted molecules **3(a-r)**. The present communication deals with the comparative studies of amino acids where glycine found as the most influential catalyst.

RESULTS AND DISCUSSION

To evaluate the efficacy of easily accessible amino acids for condensations, Scheme 1 was designed to monitor their catalytic effect. Malonic acid, methyl or ethyl cyanoacetate and a pyrazolone were used as active methylenes along with aryl/hetarylpyrazole aldehydes. DMSO was used as a solvent to avoid any solubility problems. The reactions were carried out at room temperature and glycine was the preferred amino acid catalyst. The stirring of reaction mixture at room temperature afforded the required products **3(a-r)** within 3-15 hours, the catalytic effect of glycine augmenting the product yield. This eco-friendly reaction conditions were employed throughout this project.

For the syntheses of precursors **1(a-f)**, previously reported procedures were followed.[19] A typical synthetic pathway of cinnamic acids has involved condensation of aldehdyes with malonic acids. It is to be noted that the usual Knoevenagel condensations with malonic acid **2a** produced often accompanied with decarboxylation and lead to acrylic acids.[20] We had earlier reported that performing this reaction with pyridine/piperidine with ethanol as a solvent prevented decarboxylation.[21] Here again mild reaction conditions helped in retaining both carboxyl groups successfully in compounds **3(a-f)** and no decarboxylation was observed. Among all the absorption bands in IR spectrum, the most convincing were of two carbonyl absorption bands which was the first indication of the existence of dicarboxyl groups. Perhaps, one of the carbonyl group is involved in strong intramolecular hydrogen bonding, hence appeared at low frequency. Some of the derivatives were insoluble in common NMR solvents however MS results confirmed their formation.

With methyl or ethyl cyanoacetate **2(b,c)**, the products **3(g-l)** were isolated. As far as stereochemical aspects are concerned, only a single isomer was obtained in all these cases. Keeping in view the least steric hindrance, presumably, the *trans* configuration was the most stable one in which smaller cyano group is on the same side to pyrazole nucleus. In the IR spectrum the carbonyl stretching band of ester group above 1700 cm^{-1} and ^{1}H NMR signals along with MS molecular ion peaks verified the targeted molecules.

The miscellaneous Knoevenagel reactions involved a pyrazolone **2d** as a condensation partner. Different arylidenes **3(m-r)** were prepared and confirmed by the physical and spectroscopic analyses. The details are given in the Table 1.

The model precursors; compound **1a** and malonic acid were used for the initial studies. The comparative studies (Table 2) were furnished between percentage yields of the product **3a** which indicated the catalytic efficiency of each amino acid (20 mol%). It seemed that the bifunctional (basic and acidic) nature of amino acid has facilitated this condensation reaction.

The pH is found to be the critical controlling factor of this reaction as also documented in condensation reaction of furfural and malonic acid by using glycine as a catalyst.[22] In all cases, good to excellent yields were obtained whereas nearly no condensation occured in the absence of an amino acid. The basic amino acids (lysine and histidine) have resulted in good yields however with an acidic glutamic acid, the product was obtained in 48%

yield. Surprisingly, the best results were achieved with glycine. Possibly due to smaller size, glycine could easily participate in reaction mechanism. Therefore, glycine was used as a catalyst of choice for the remaining reactions. Similarly, to see the effects of different solvents, this model reaction was also carried out at room temperature in different solvents (Table 3).

Among these, DMSO stands out as the best solvent and gave excellent yields. To optimize the catalyst quantity, different catalytic amounts (10, 20 and 30 mol%) of glycine were also used. 20 and 30 mol% of glycine gave the best result (Table 4). Consequently, the optimium condition was equivalent amounts of substrates in DMSO, add 20 mol% of glycine and stir at room temperature for the required timings.

Two general mechanistic pathways; Path A (Scheme 2) and Path B (Scheme 3) are possible. Path A first involves the generation of carbanion from an active methylene by glycine.

Whereas in Path B, with glycine and aldehyde, first of all an iminium ion is formed which afterwards reacts with malonic acid.

CONCLUSION

The amino acid glycine was successfully employed as a progressive catalyst for the Knoevenagel condensation of pyrazole-4-carbaldehydes **1(a-f)** with active methylenes and pyrazolone to give pyrazole acryloyl analogues **3(a-r)** efficiently. These valuable

green reactions resulted in excellent yields of products in DMSO solvent at room temperature.

EXPERIMENTAL

Some reagents and chemicals were purchased from the Sigma-Aldrich, Merck and used without purification. The TLC was performed over DC-Alufolien Silica Gel 60 F_{254} Merck to monitor the reaction progress. The melting points were uncorrected. Agilent Technologies Cary 630 FTIR was used for taking FTIR spectra. The ^{1}H NMR spectra were recorded on Bruker DPX-400 MHz Spectrometer in $CDCl_3$. The MAT312 or JEOL MS Route was used for MS spectra. The elemental analyses were determined on Perkin-Elmer 2400 Series II CHN/S Analyzer.

General Procedure For The Synthesis Of Products 3(A-R)

To a mixture of an aldehyde **1(a-f)** (2.0 mmol) and an active methylene **2(a-d)** (2.0 mmol) dissolved in 5 mL of DMSO, 0.022 g of glycine (0.40 mmol, 20 mol%, 0.20 equiv) was added. The stirring was continued at room temperature for 3-15 hrs and then quenched with ice water to obtain neat precipitates of pyrazole acryloyl compound **3(a-r)** which were further purified by recrystallization with ethanol.

(*E*)-Methyl 2-(Cyanocarbonyl)-3-(1,3-Diphenyl-1*H*-Pyrazol-4-Yl)Acrylate (3g)

From **1a** (0.50 g), **3g** was obtained as a white solid; mp 136-138 ºC; Yield: 0.54 g; 82%; IR (ν_{max}-cm^{-1}; neat): 3143-2952 (C-H), 2215 (C≡N), 1726 (C=O), 1605 (C=N), 1591 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.88 (s, 1H; -OCH_3), 7.39 (t, 1H, *J* = 8.0 Hz; Ar-

1H), 7.48-7.53 (m, 5H; Ar-2H & Ar^1-3H), 7.60 (dd, 2H, *J* = 8.0, 1.2 Hz; Ar^1-2H), 7.82 (d, 2H, *J* = 8.0 Hz; Ar-2H), 8.29 (s, 1H; =CH), 9.13 (s, 1H; H-5 Pyr); MS (EI+): m/z (%) 329.0 (M^+, 20.7); Anal. Calcd. For $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76%. Found: C, 73.03; H, 4.65; N, 12.84%.

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SUPPLEMENTAL MATERIAL

The experimental details, characterization data and spectral data for this article can be accessed on the publisher's website.

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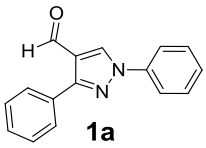
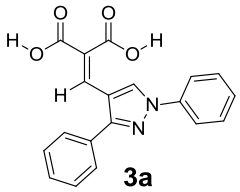
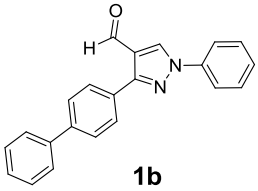
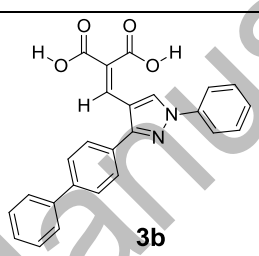
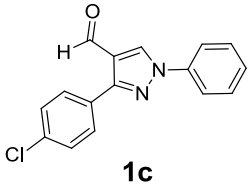
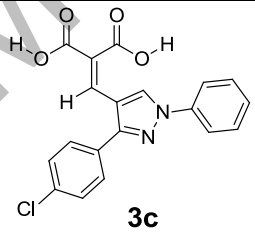
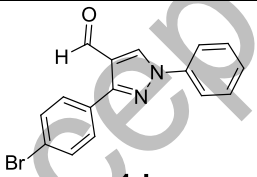
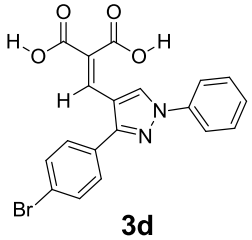
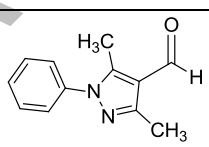
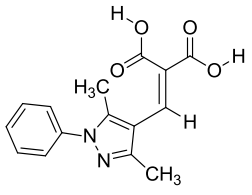
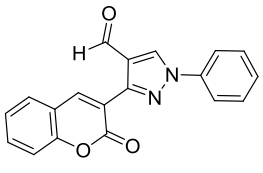
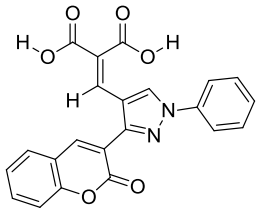
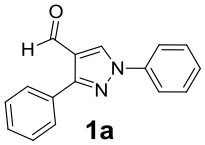
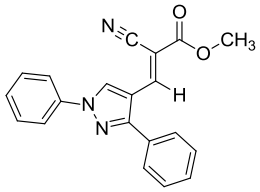
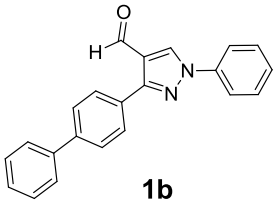
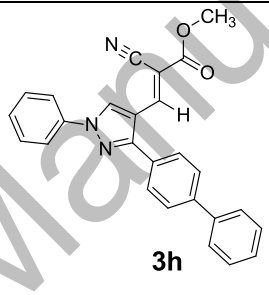
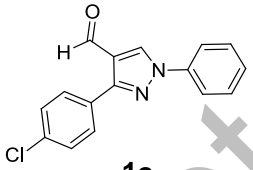
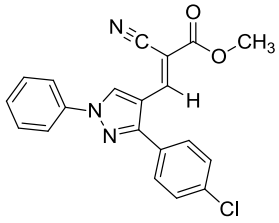
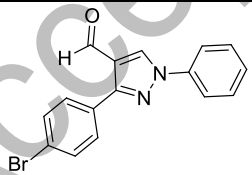
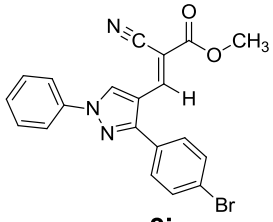
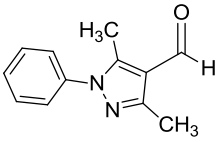
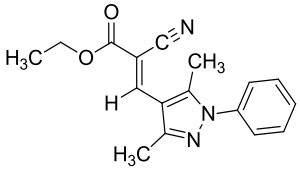
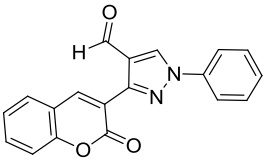
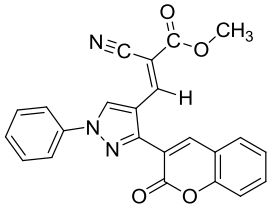
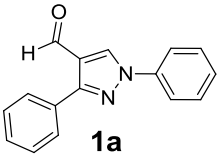
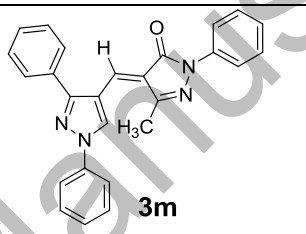
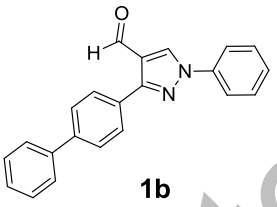
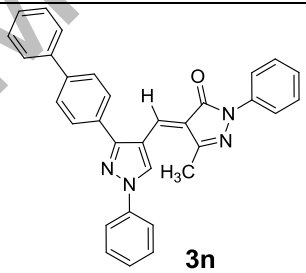
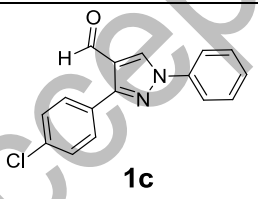
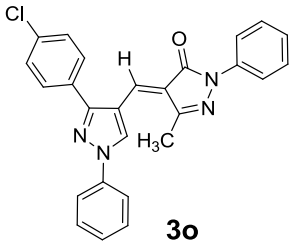
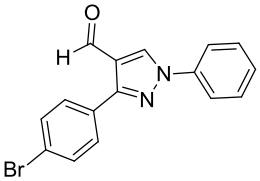
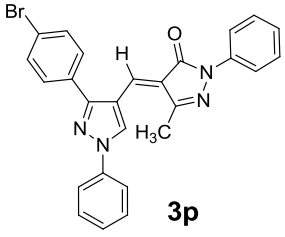
Table 1. Glycine catalysed Knoevenagel condensation for the synthesis of pyrazole acryloyl derivatives **3(a-r)** in DMSO at room temperature

Entry	Carbaldehyde	Active Methylene	Product	Time (h)	Yield (%)
1	 **1a**	**2a**	 **3a**	3	93
2	 **1b**	**2a**	 **3b**	4	84
3	 **1c**	**2a**	 **3c**	3	86
4	 **1d**	**2a**	 **3d**	3.5	82
5	 **1e**	**2a**	 **3e**	4.5	81

6	 **1f**	**2a**	 **3f**	3.5	79
7	 **1a**	**2b**	 **3g**	5.5	89
8	 **1b**	**2b**	 **3h**	6	84
9	 **1c**	**2b**	 **3i**	5	91
10	 **1d**	**2b**	 **3j**	4.5	89

11	 **1e**	**2c**	 **3k**	6	84
12	 **1f**	**2b**	 **3l**	5	81
13	 **1a**	**2d**	 **3m**	12	85
14	 **1b**	**2d**	 **3n**	13	78
15	 **1c**	**2d**	 **3o**	11.5	87
16	 **1d**	**2d**	 **3p**	12	84

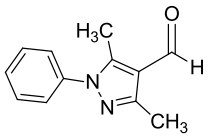
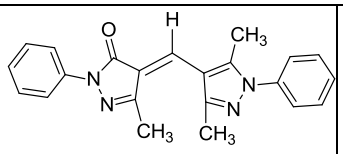
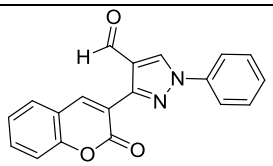
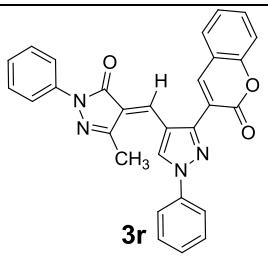
17	 **1e**	**2d**	 **3q**	15	74
18	 **1f**	**2d**	 **3r**	14	78

Table 2. Preliminary screening of different amino acids as catalysts

Entry	Catalyst	Yield (%)
1	Without Catalyst	11
2	**Glycine**	**93**
3	Glutamic Acid	48
4	Asparagine	70
5	Lysine	83
6	Leucine	63
7	Tyrosine	72
8	Tryptophan	69
9	Methionine	66
10	Valine	68
11	Histidine	85

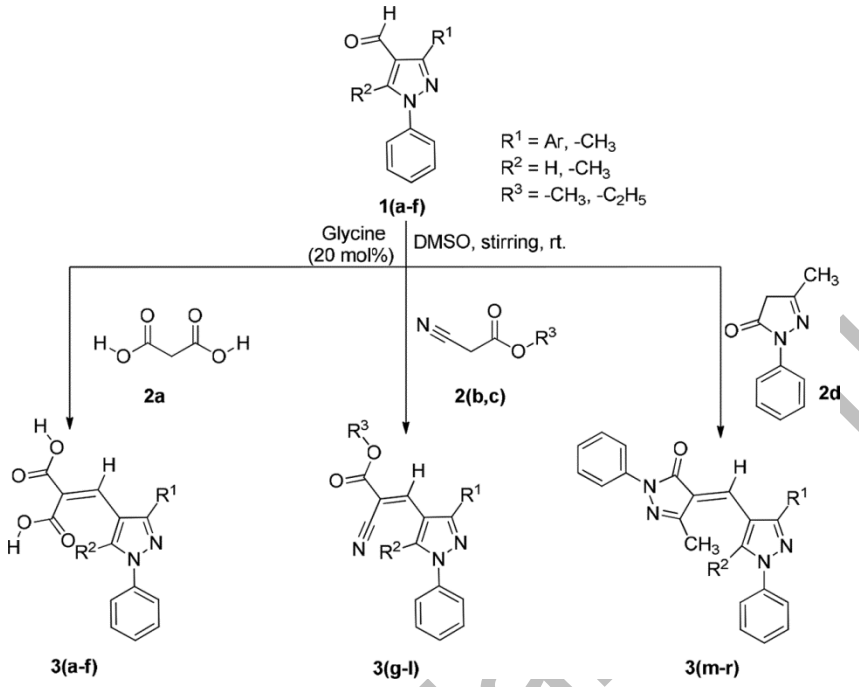
Table 3. Knoevenagel condensation of **1a** and malonic acid with 20 mol% of glycine in different solvents

Entry	Solvent	Yield (%)
1	THF	29
2	CH_2Cl_2	35
3	CH_3CN	56
4	H_2O	22
5	DMF	72
6	**DMSO**	**93**
7	Solvent-free	34

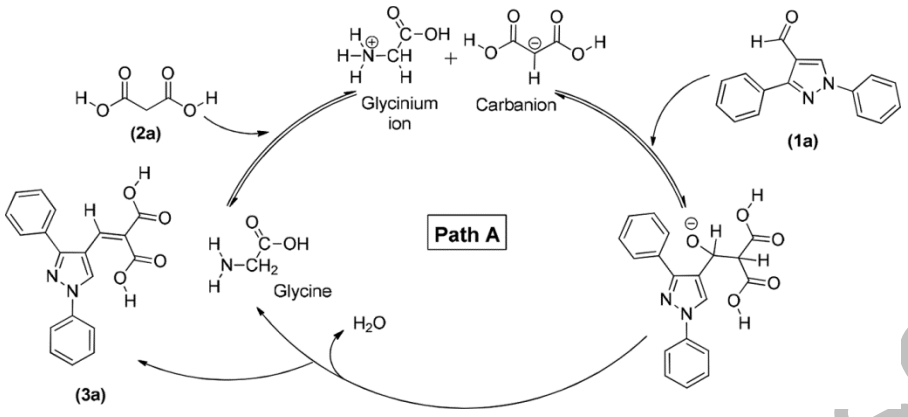
Table 4. Knoevenagel condensation of **1a** and malonic acid in DMSO with different catalytic amounts (mol%) of glycine

Entry	Glycine (mol%)	Yield (%)
1	10	72
2	**20**	**93**
3	30	91

Scheme 1. Synthesis of pyrazole acryloyl analogues **3(a-r)**.



Scheme 2. Plausible Path A for the synthesis of 2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)malonic acid **3a**.



Scheme 3. Plausible Path B for the synthesis of 2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)malonic acid **3a**.