

Article

Organocatalysis in Synthesis: L-Proline as an Enantioselective Catalyst in the Synthesis of Pyrans and Thiopyrans

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Abstract: The multicomponent reaction (MCR) of aromatic aldehydes **1** and malononitrile (**2**) with active methylenes **5a–h** in the presence of L-proline produced pyrans and thiopyrans **6a–h** stereospecifically and in good yields. Moreover a novel MCR of ethyl propiolate (**8**) with **1** and **2** in the presence of L-proline to afford (*R*)-polysubstituted pyran is also reported. X-ray structures, e.e. and optical activity of the synthesized compounds indicated that L-proline as a catalyst is responsible for the observed enantioselectivity in the studied reactions.

Keywords: L-proline; pyran; assymetric synthesis; enantioselectivity; ethyl propiolate; optical activity

1. Introduction

Polyfunctionally substituted pyrans are no doubt an important class of heterocycles due to their great biological and pharmacological importance [1–6]. The addition of active methylene reagents to arylidenemalononitrile in the presence of homogeneous basic catalysts has been extensively used in the past for the synthesis of these compounds [7–12]. Interest in these reactions has recently been revived [13,14] with the aim of developing green laboratory reaction conditions [15,16], such as replacing homogeneous catalysis with heterogeneous ones [17–20], to synthesize enantiomerically pure pyrans for which diverse biological applications were noticed [21–23] and patented [24–26]. Many of these new approaches use multicomponent reactions and either an organocatalyst [27,28] or

sometimes metal or nanoparticulated catalysts [29–31]. Although in plenty of these reactions a chiral center is being created only a few published works have discussed the exact stereochemistry of the synthesized compounds.

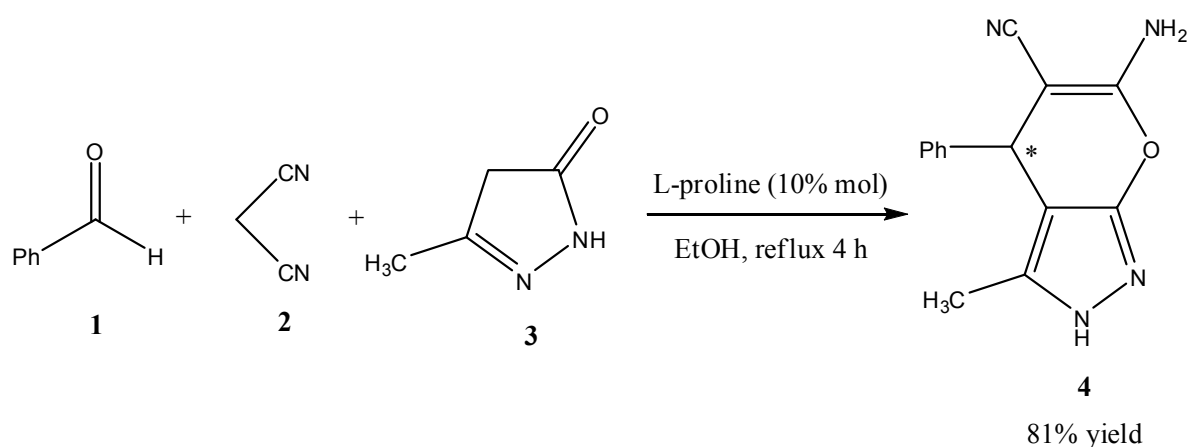
Since L-proline is a readily obtainable naturally occurring amino acid and is easy to obtain in high enantiomeric purity it has been reported as an eco-friendly catalyst for the synthesis of several heterocycles [32–37]. Recently Muramulla *et al.* reported the use of modularly designed organocatalysts (MDO) of L-proline in dichloromethane as a solvent for the synthesis of chiral pyranopyrazoles in moderate e.e. [38]. Gou *et al.* have also reacted aromatic aldehydes, malononitrile, and dimedone, in the presence of D,L-proline as a catalyst in the absence of solvent to obtain 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[b]pyran [27].

It seemed thus of value to see if the use of L-proline as a catalyst in the reaction of active methylene ketones with α,β -unsaturated nitriles in MCRs can be used to induce enantioselectivity of the synthesized pyrans. In this article the syntheses of pyrans, condensed pyrans and thiopyrans are reported. Moreover a novel pyran was prepared via the MCR of ethyl propiolate (**8**) with aldehydes and malononitrile in the presence of L-proline as a catalyst.

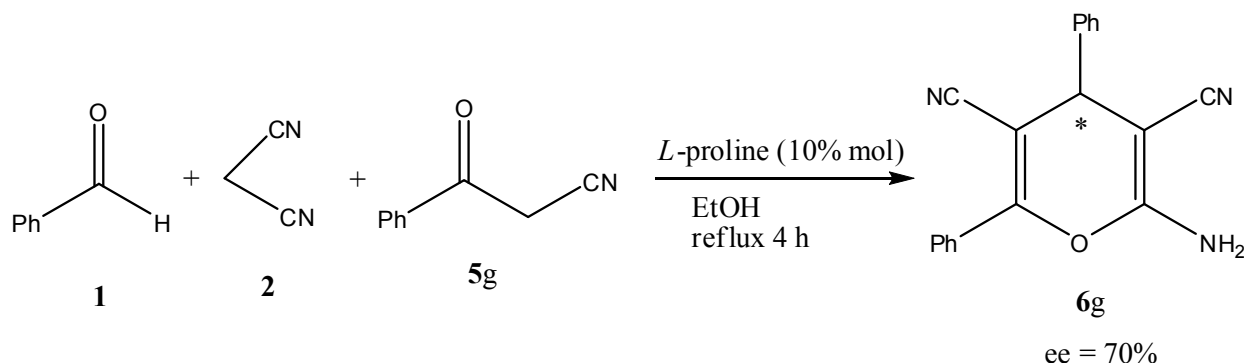
2. Results and Discussion

First in an attempt to synthesize the chiral pyranopyrazoles **4**, we have reacted benzaldehyde (**1**), malononitrile (**2**) and pyrazolon-5-one (**3**) with 10% mol L-proline as the only catalyst. In contrast to Muramulla *et al.*'s findings that for the same reaction using L-proline alone as a catalyst under the reported reaction conditions no product was obtained, in our case after the reaction mixture was refluxed in ethanol for 4 h, the pyranopyrazole **4** was isolated in 81% yield (Scheme 1). To initially test if L-proline has induced any enantioselectivity in this reaction, compound **4** was tested for optical activity and found to be optically active with a specific rotation of +247.02 ($[\alpha]_D$, 25 °C, c = 1, DMF).

Scheme 1. Synthesis of 6-amino-3,4-dimethyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4**).

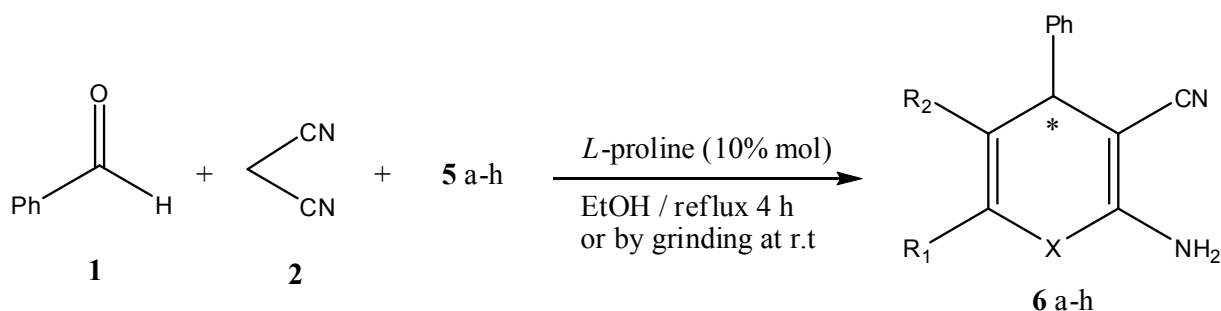


Next reacting benzaldehyde (**1**), malononitrile (**2**) and 3-oxo-3-phenylpropanenitrile (**5g**) in the presence of 10% L-proline as a catalyst afforded 2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile (**6g**) in 83% yield and 70% e.e. (Scheme 2).

Scheme 2. Synthesis of 2-amino-4,6-diphenyl-4*H*-pyran-3,5-dicarbonitrile (**6g**).

The 4*H*-pyran **6g** was found to have 70% e.e. Confirmation that the 4*H*-pyran **6g** indeed displayed an enantiomeric excess was obtained by performing ¹H-NMR experiments with **6g** in the presence of a chiral shift reagent (europium tris[3-heptafluoropropylhydroxymethylene]-(+)-camphorate). After making successive additions of this chiral shift reagent to a CDCl₃ solution of **6g**, the 4*H*-proton at δ_H 4.7 ppm appeared to resolve into two components (most obviously after the addition of 6 mg of the chiral shift reagent), and by calculation of the area under the chosen peak from the ¹H-NMR that showed the maximum separation of the two components, **6g** was found to be in 70% e.e. However at this stage, we cannot judge the predominance of the *R* or *S* enantiomers for this compound.

The above reported results encouraged us to prepare a series of polysubstituted 4*H*-pyrans. Pyrans **6a–h** were all synthesized by the addition of benzaldehyde (**1**) and malononitrile (**2**) to active methylenes **5a–h** using L-proline (10% mol) as a catalyst in a MCR to afford chiral pyrans **6a–h** (Scheme 3). Active methylenes used are listed in Table 1. Structures and yields of the products **6a–h**, as well as the reaction conditions are listed in Table 2.

Scheme 3. Synthesis of enantioselective pyrans, benzopyrans, and thiopyrans **6a–h** in a multicomponent reaction using L-proline as a catalyst.**Table 1.** Compounds **5a–h**.

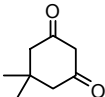
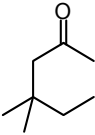
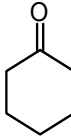
5a	CH ₃ COCH ₂ COOEt	5e	EtCOOCH ₂ COPh
5b	CH ₃ COCH ₂ COCH ₃	5f	PhCH ₂ COOCH ₂ COCH ₃
5c	NCCH ₂ CSNH ₂	5g	PhCOCH ₂ CN
5d		5h	

Table 2. Compounds **6a–h** and their yields.

Compound ^a	X	R ₁	R ₂	Yield (%)
6a	O	CH ₃	COOEt	72
6b	O	CH ₃	COCH ₃	60
6c	S	NH ₂	CN	92
6d *	O			90
6e	O	Ph	COOEt	87
6f	O	CH ₃	COOCH ₂ Ph	65
6g	O	Ph	CN	83
6h *	O			78

^a Compounds were characterized by their spectral data (IR, ¹³C-NMR, ¹H-NMR). * These compounds could be prepared without a solvent at r.t. using grinding for 5 min. Compounds **6a**, **b**, **c**, **e**, **f**, **g** were prepared using EtOH as a solvent and refluxing for 4 h.

Specific rotation measurements for some selected synthesized compounds revealed that these compounds are optically active, which supports the assumption that L-proline when used as a catalyst brings about enantioselectivity in such reactions. The specific rotation of some selected compounds is listed in Table 3.

Table 3. Specific rotation for some of the synthesized compounds.

Entry	Specific rotation [α] _D 25 °C, <i>c</i> = 1, DMF
6a	+318.20
6e	+198.81
6h	+198.20
4	+247.02
13	+272.0

Structures proposed of the products **6a**, **b**, **d**, **e**, **h** were well documented by X-ray crystallography as shown in Figures 1–6 [39]. It is worth mentioning that the ¹H-NMR of the compound **6a** has revealed the formation of two products in 2:1 ratio that could be separated by column chromatography. The first product could be shown by X-ray crystal structure (Figure 1) to be the 4*H*-pyran derivative (*S*)-ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (**6a**), while the other product with molecular formula C₂₂H₂₂N₂O₄ and *m/z* = 378.2 is believed to be diethyl 5,5-dicyano-4,6-dimethyl-2-phenylcyclohexa-3,6-diene-1,3-dicarboxylate (**7**) as was proven by its spectroscopic data (Scheme 4).

Figure 1. X-ray crystal structure of (*S*)-ethyl 5-cyano-2,6-dimethyl-4-phenyl-4*H*-pyran-3-carboxylate (**6a**).

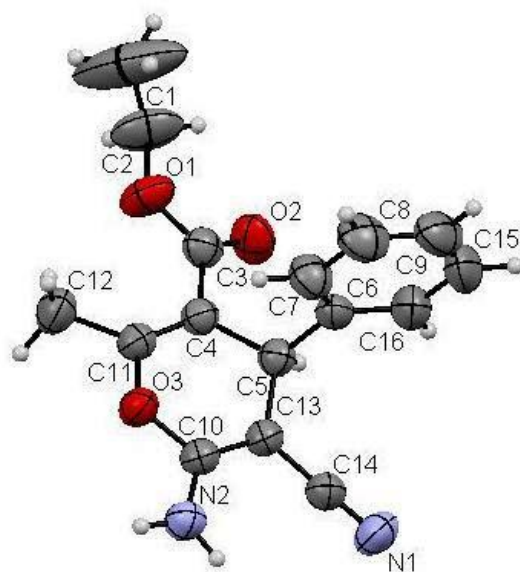


Figure 2. X-ray crystal structure of (*R*)-5-acetyl-2-amino-6-methyl-4-phenyl-4*H*-pyran-3-carbonitrile (**6b**).

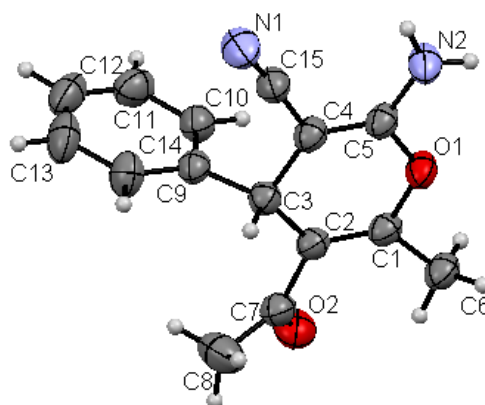


Figure 3. X-ray crystal structure of (*S*)-2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile(**6d**).

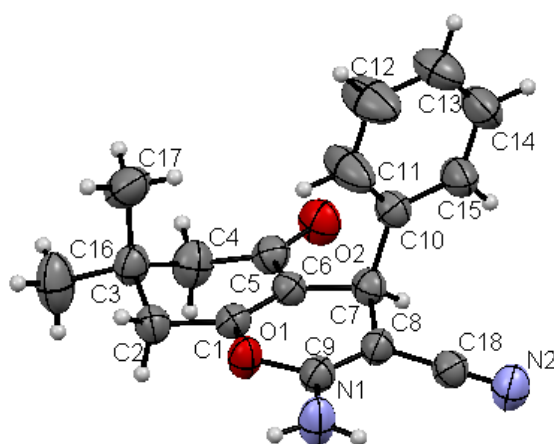


Figure 4. X-ray crystal structure of (*S*)-ethyl 6-amino-5-cyano-2,4-diphenyl-4*H*-pyran-3-carboxylate (**6e**).

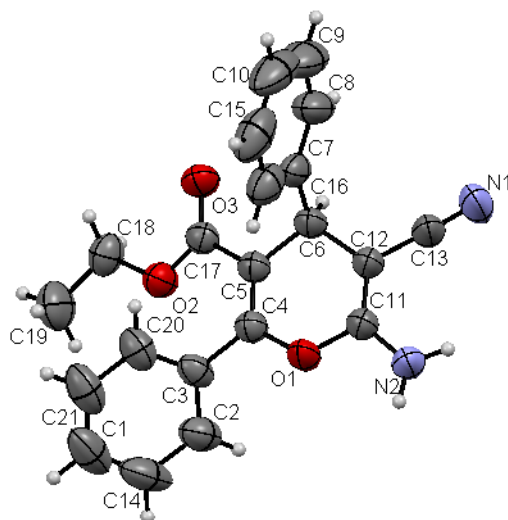


Figure 5. X-ray crystal structure of (*R*)-2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**6h**).

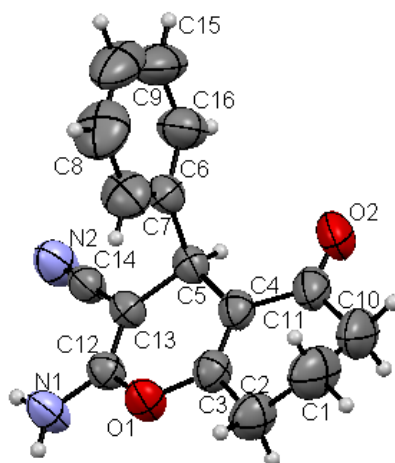
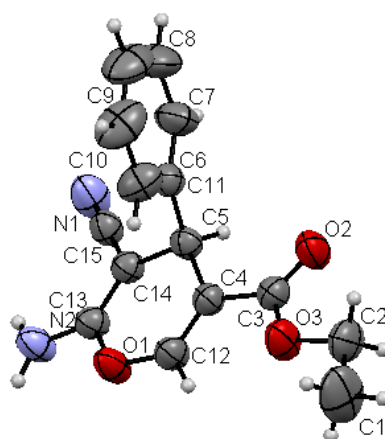
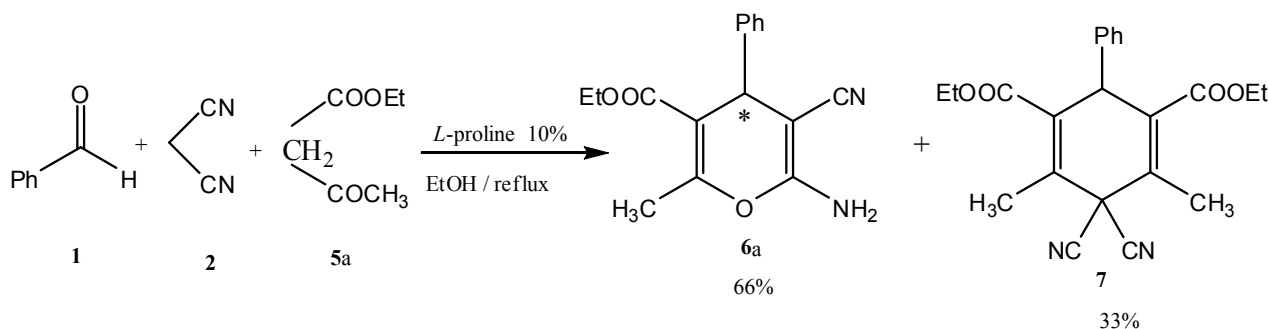


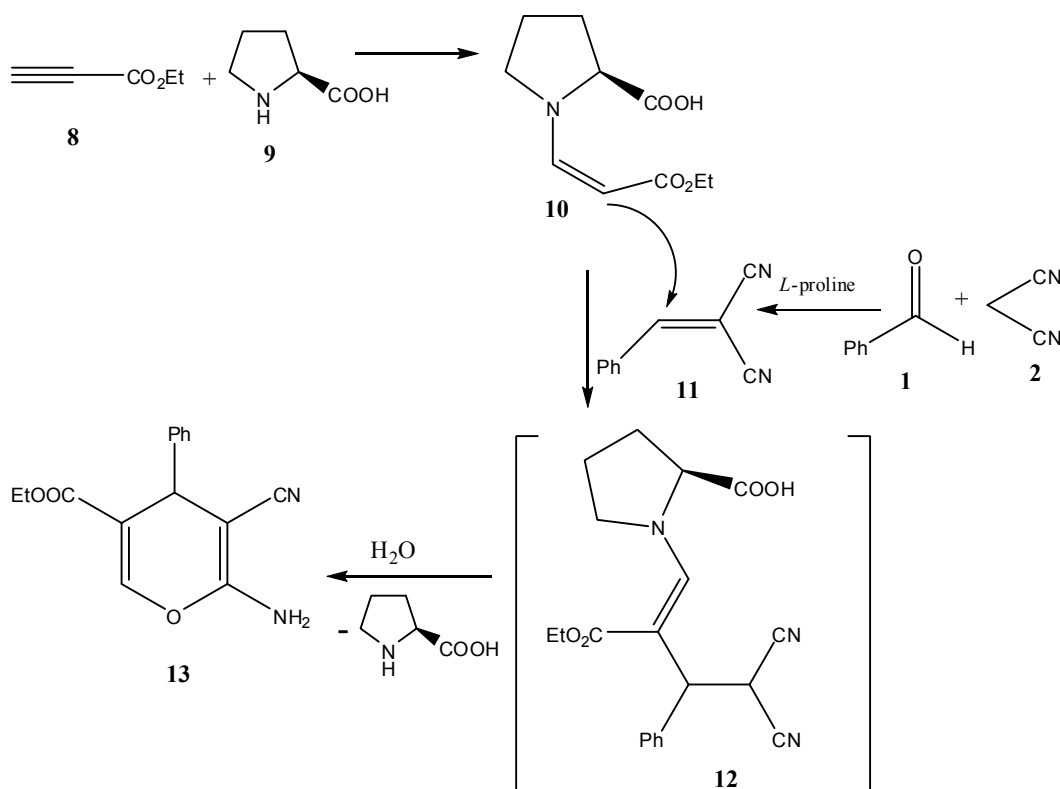
Figure 6. X-ray crystal structure of (*R*)-ethyl-6-amino-5-cyano-4-phenyl-4*H*-pyran-3-carboxylate **13**.



Scheme 4. Synthesis of the two products **6a** and **7** in a 2:1 ratio.

In addition a novel synthesis of pyran **13** could be achieved by mixing benzaldehyde (**1**), and malononitrile (**2**) with ethyl propiolate (**8**) in ethanol and 10% L-proline as a catalyst. It is believed that initially L-proline (**9**) adds to ethyl propiolate (**8**) affording the enamine ester **10**, while benzaldehyde (**1**) condenses with malononitrile (**2**) affording 2-benzylidenemalononitrile (**11**). This was followed by the addition of the electron rich β -carbon in the enamine ester to the electron poor π system in the benzylidine-malononitrile **11**, affording an adduct. This adduct **12** is then hydrolyzed by H_2O and cyclizes into **13** (Scheme 5). Compound **13** was also tested for optical activity and found to be optically active with a specific rotation of $+272.0$ ($[\alpha]_{\text{D}}^{25} \text{ } ^\circ\text{C}$, $c = 1$, DMF). The structure of **13** has been confirmed with certainty via X-ray crystal structure determination (Figure 6).

As shown in the X-ray structures (Figures 1–6), we have obtained the *R*-enantiomer in the case of compounds **9a**, **h**, and **14**, and the *S*-enantiomer in the cases of **9a**, **d**, and **e**, but both enantiomers exist of course in the original product as a mixture.

Scheme 5. Synthesis of (*R*)-ethyl-6-amino-5-cyano-4-phenyl-4*H*-pyran-3-carboxylate (**13**).

3. Experimental

3.1. General

The ^1H -NMR and ^{13}C -NMR spectra were determined by using a Bruker DPX instrument at 400 MHz for ^1H -NMR and 100 MHz for ^{13}C -NMR. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) or DMSO- D_6 ($\delta = 2.5$) for ^1H -NMR and relative to the central CDCl_3 resonance ($\delta = 77.0$) or DMSO- D_6 ($\delta = 40.0$) for ^{13}C -NMR. The coupling constants J are given in Hz. Mass spectra were measured using a high resolution GC-MS (DFS) Thermo spectrometer with EI (70 EV). Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). IR spectra were recorded using KBr disks on a Perkin-Elmer System 2000 FT-IR spectrophotometer. Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. Optical rotations were measured on an Autopol IV (Rudolph Instruments) automatic polarimeter at 25 °C in DMF at concentration 1 mol. X-ray crystal structures were determined using a Single Crystal X-ray Crystallography-Rigaku Rapid II system and all the X-ray samples were prepared by recrystallization from hot ethanol. All melting points were recorded on a Griffin melting point apparatus and are reported uncorrected.

3.2. General Experimental Procedure for the Synthesis of Pyrans **6a–h** and Compound **7**

A mixture of benzaldehyde (**1**, 0.01 mol), malononitrile (**2**, 0.01 mol) and 10% mol L-proline was stirred at r.t. for 2 min. then active methylenes **5a–h** (0.01 mol) were added. The mixture was refluxed in ethanol (10 mL) for 4–6 h followed by TLC. The crude compounds formed were recrystallized from ethanol and further purified using column chromatography using 2:1 petroleum ether/ethyl acetate as an eluent.

Ethyl-5-cyano-2,6-dimethyl-4-phenyl-4H-pyran-3-carboxylate (6a). White crystalline solid, Mp 189–190 °C; yield 72%, ^1H -NMR [DMSO- d_6], δ : ppm = 7.31 (t, 1H, Ar), 7.23 (m, 1H, Ar), 7.15 (d, $J = 7.6$ Hz, 1H, Ar), 6.94 (s, 2H, NH_2), 4.29 (s, 1H), 3.94 (m, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.03 (t, 3H, CH_3); ^{13}C -NMR: δ : ppm = 166 (O=C), 158.8 (C), 156.6 (C), 144.8 (CH), 128.5 (2C), 127.0 (2C), 126.9 (2C), 119.5 (CN), 107.0 (C), 60.0 (CH_2), 58.8 (C), 19.6 (CH_3), 17.0 (CH_3); MS: m/z % 284.1 (M+100); Anal. calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$ (284.30): C, 67.59; H, 5.67; N, 9.85; O, 16.882. Found: C, 67.63; H, 5.66; N, 9.71%.

5-Acetyl-2-amino-6-methyl-4-phenyl-4H-pyran-3-carbonitrile (6b). White crystalline solid, Mp 185–186 °C; yield 72%, ^1H -NMR [DMSO- d_6] δ 7.34 (m, 2H, Ar), 7.23 (m, 1H, Ar), 7.18 (m, 2H, Ar), 6.87 (s, 2H, NH_2), 4.46 (s, 1H), 2.25 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 198 (O=C), 158.2 (C), 154.8 (C), 144.5 (CH), 128.7 (2C), 127.1 (2C), 126.9 (2C), 119.8 (CN), 114.9 (C), 57.7 (C), 29.8 (CH_3), 18.4 (CH_3); MS: m/z % 254.1 (M+100); Anal. calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$ (254.1): C, 70.85; H, 5.55; N, 11.02; O, 12.58. Found: C, 71.40; H, 5.34; N, 10.98; O, 12.28%.

2,6-Diamino-4-phenyl-4H-thiopyran-3,5-dicarbonitrile (6c). Yellow crystalline solid, Mp 192–193 °C; yield 92%, ^1H -NMR [DMSO- d_6], δ : ppm = 7.35 (m, 2H, Ar), 7.26 (m, 3H, Ar), 6.93 (s, 4H, 2 NH_2), 4.26 (s, 1H); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 151.2 (2C), 143.5 (C), 128.7 (2C), 127.1 (C),

126.6 (2C), 118.8 (2C, CN), 71.9 (2C), 43.3 (C); MS: m/z % 254.1 (M+100); Anal. calcd for $C_{13}H_{10}N_4S$ (255.31): C, 61.15; H, 4.34; N, 21.94; S, 12.55. Found: C, 61.14; H, 4.02; N, 21.50; S, 12.51%.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6d). Faint yellow crystalline solid, Mp 228–230 °C; yield 90%, 1H -NMR [DMSO- d_6], δ : ppm = 7.30 (m, 2H, Ar), 7.18 (m, 3H, Ar), 7.02 (s, 2H, NH_2), 4.20 (s, 1H), 2.62 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 1.91 (m, 2H, CH_2); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 197.6 (C=O), 174.2 (C), 163.8 (C), 144.9 (C), 128.2 (2CH), 127.3 (2CH), 126.5 (CH), 119.4 (CN), 113.6 (C), 58.7 (C), 38.4 (CH_2), 36.3 (C), 35.4 (CH_2), 32.4 (C), 25.5 (2 CH_3); MS: m/z % 294.1 (M+100); Anal. calcd for $C_{18}H_{18}N_2O_2$ (294.3): C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.67; H, 6.25; N, 9.34; O, 10.70%.

Ethyl 6-amino-5-cyano-2,4-diphenyl-4H-pyran-3-carboxylate (6e). Yellow crystalline solid, Mp 191–192 °C; yield 87%, 1H -NMR [DMSO- d_6], δ 7.45 (m, 5H, Ar), 7.36 (m, 2H, Ar), 7.26 (m, 3H, Ar), 7.04 (s, 2H, NH_2), 4.26 (s, 1H), 3.75 (q, 2H, CH_2), 0.73 (t, 3H, CH_3); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 156.5 (C=O), 159.1 (C), 154.2 (C), 144.1 (C), 133.1 (C), 129.9 (CH), 128.6 (2CH), 128.4 (2CH), 128.0 (2CH), 127.3 (2CH), 127.1 (CH), 119.7 (CN), 108.9 (C), 60.19 (CH_2), 56.9 (C), 40.1 (CH), 13.2 (CH_3); MS: m/z % 346.1 (M+100); Anal. calcd for $C_{21}H_{18}N_2O_3$ (346.3): C, 72.82; H, 5.24; N, 8.09; O, 13.86. Found: C, 72.90; H, 5.28; N, 8.06; O, 13.76%.

Benzyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (6f). White crystalline solid, Mp 199–200 °C; yield 65%, 1H -NMR [DMSO- d_6], δ 7.26 (m, 6H, Ar), 7.13 (m, 2H, Ar), 7.08 (m, 2H, Ar), 6.95 (s, 2H, NH_2), 5.02 (q, 2H, CH_2), 4.34 (s, 1H), 2.34 (s, 3H, CH_3); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 156.3 (C=O), 158.3 (C), 157.4 (C), 144.8 (C), 135.7 (C), 128.5 (2CH), 128.2 (2CH), 127.8 (CH), 127.5 (2CH), 127.1 (2CH), 126.8 (CH), 119.7 (CN), 106.8 (C), 65.7 (CH_2), 57.3 (C), 18.3 (CH_3); MS: m/z % 346.2 (M+100); Anal. calcd for $C_{21}H_{18}N_2O_3$ (346.3): C, 72.82; H, 5.24; N, 8.09; O, 13.86. Found: C, 72.75; H, 5.13; N, 8.09; O, 14.03%.

2-Amino-4,6-diphenyl-4H-pyran-3,5-dicarbonitrile (6g). Yellow crystalline solid, Mp 162–163 °C; yield 83%, 1H -NMR [DMSO- d_6], δ 7.80 (m, 2H, Ar), 7.57 (m, 3H, Ar), 7.45 (m, 2H, Ar), 7.37 (m, 2H, Ar), 7.32 (s, 2H, NH_2), 3.44 (s, 1H); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 158.5 (C), 157.6 (C), 142.2 (C), 131.7 (C), 130.0 (CH), 128.9 (2CH), 128.7 (2CH), 127.9 (CH), 127.8 (2CH), 127.7 (2CH), 118.9 (CN), 117.3 (CN), 55.6 (C); MS: m/z % 299.6 (M+100); Anal. calcd for $C_{19}H_{13}N_3O$ (299.3): C, 76.24; H, 4.38; N, 14.04; O, 5.35. Found: C, 76.84; H, 4.42; N, 14.01; O, 4.69%.

2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6h). Yellow crystalline solid, Mp 172–173 °C; yield 78%, 1H -NMR [DMSO- d_6], δ : ppm = 7.30 (m, 2H, Ar), 7.18 (m, 3H, Ar), 7.02 (s, 2H, NH_2), 4.20 (s, 1H), 2.62 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 1.91 (m, 2H, CH_2); ^{13}C -NMR: [DMSO- d_6], δ : ppm = 198.8 (C=O), 174.4 (C), 164.4 (C), 144.8 (C), 128.3 (2CH), 127.1 (2CH), 126.5 (CH), 119.7 (CN), 113.8 (C), 58.2 (C), 36.3 (C), 35.4 (CH_2), 26.4 (CH_2), 19.8 (CH_2); MS: m/z % 266.1 (M+100); Anal. calcd for $C_{16}H_{14}N_2O_2$ (266.2): C, 72.16; H, 5.30; N, 10.52; O, 12.02. Found: C, 72.04; H, 5.54; N, 10.41; O, 11.98%.

Diethyl 5,5-dicyano-4,6-dimethyl-2-phenylcyclohexa-3,6-diene-1,3-dicarboxylate (7). Pale yellow crystalline solid, Mp 210 °C; yield 25%, ¹H-NMR [DMSO-d₆], δ: ppm = 7.60–7.42 (m, 5H, Ar), 7.02 (s, 2H, NH₂), 3.95 (s, 1H), 3.93 (m, 4H, 2CH₂), 2.5 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 1.04 (m, 6H, 2CH₃); ¹³C-NMR: [DMSO-d₆], δ: ppm = 167.5 (2C=O), 137 (C), 136 (C), 129 (2C), 128 (C), 127 (C), 125 (C), 123 (2C), 117 (C), 116 (C), 61 (2C), 45 (C), 30 (C), 25 (2C), 15 (2C); MS: *m/z* % 378.4 (M+100); Anal. calcd for C₂₂H₂₂N₂O₄ (378.16): C, 69.83; H, 5.86; N, 7.40; O, 16.91. Found: C, 71.2; H, 5.80; N, 7.5; O, 16.31%.

3.3. Experimental Procedure for the Synthesis of **4**

A mixture of benzaldehyde (**1**, 0.01 mol), malononitrile (**2**, 0.01 mol) and 10% mol L-proline, then pyrazolon-5-one (**3**, 0.01 mol) was added. The mixture was refluxed in ethanol (15 mL) for 4 h and followed by TLC. The crude compound formed was recrystallized from ethanol and further purified using column chromatography using ethyl acetate as eluent.

*6-Amino-3,4-dimethyl-4-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (4)*. Yellow crystalline solid, Mp 225–226 °C; yield 81%, ¹H-NMR [DMSO-d₆], δ 12.1 (s, 1H, NH); 7.30 (m, 2H, Ar), 7.26 (m, 2H, Ar), 7.18 (d, *J* = 7.2 Hz, 1H, Ar), 6.78 (s, 2H, NH₂), 1.79 (s, 3H, CH₃), 1.76 (t, 3H, CH₃); ¹³C-NMR: [DMSO-d₆], δ: ppm = 159.9, 153.9, 147.3, 134.9, 128.0, 126.3, 126.0, 119.9, 116.3, 63.6, 30.1, 24.6, 13.6; MS: *m/z* % 266.1 (M+100); Anal. calcd for C₁₅H₁₄N₄O (266.3): C, 67.65; H, 5.30; N, 21.04; O, 6.01. Found: C, 67.66; H, 5.01; N, 20.98, O, 6.33%.

3.4. Experimental Procedure for the Synthesis of **13**

A mixture of benzaldehyde (**1**, 0.01 mol), malononitrile (**2**, 0.01 mol), ethyl propiolate (**8**, 0.01 mol), pyrazolon-5-one (**3**, 0.01 mol) and L-proline (**9**, 10% mol) was added together. The mixture was refluxed in ethanol (15 mL) for 4 h, followed by TLC. The crude compound formed was recrystallized from ethanol and further purified using column chromatography using ethyl acetate as eluent.

Ethyl-6-amino-5-cyano-4-phenyl-4H-pyran-3-carboxylate (13). White crystalline solid, Mp 227–230 °C; yield 65%, ¹H-NMR [DMSO-d₆], δ 7.71 (s, 1H), 7.32 (m, 2H, Ar), 7.24 (m, 1H, Ar), 7.22 (m, 2H, Ar), 7.02 (s, 2H, NH₂), 4.23 (s, 2H, NH₂), 4.01 (m, 2H, CH₂), 1.07 (t, 3H, CH₃); ¹³C-NMR: [DMSO-d₆], δ: ppm = 164.5 (CH-pyran), 164.1 (C=O), 158.6 (C), 133.3 (CH), 130.5 (2CH), 128.4 (CH), 126.5 (CH), 119.6 (CN), 11.3 (C), 61.7 (CH₂), 57.3 (C), 30.7 (CH), 14.1 (CH₃); MS: *m/z* % 270.1 (M+100); Anal. calcd for C₁₅H₁₄N₂O₃ (270.28): C, 66.66; H, 5.22; N, 10.36; O, 17.76. Found: C, 66.73; H, 5.34; N, 10.35, O, 17.64%.

4. Conclusions

L-Proline could be used as a catalyst in the reaction of active methylene ketones with α,β-unsaturated nitriles in a multicomponent reaction that leads to creation of a chiral center, and bringing about enantioselectivity for the preparation of the produced pyrans and thiopyrans in good yields.

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39. CCDC 850090–850094 and 851560 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via “http://www.ccdc.cam.ac.uk/data_request/cif”.

Sample Availability: Samples of the compounds **6a–h**, **4** and **13** are available from the authors.