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One-Pot Synthesis of Pyrano[2,3-*d*]pyrimidinone Derivatives Catalyzed by *L*-Proline in Aqueous Media

M. Bararjanian, S. Balalaie*, B. Movassagh and A.M. Amani
Peptide Chemistry Research Group, K. N. Toosi University of Technology and P.O. Box 15875-4416, Tehran, Iran

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An efficient protocol has been developed for the synthesis of various pyrano[2,3-*d*]pyrimidinones from condensation of aromatic aldehydes, malononitrile and barbituric-or thiobarbituric acid in aqueous ethanol using *L*-proline as a neutral bifunctional catalyst.

Keywords: Aqueous media, *L*-Proline, Pyrano[2,3-*d*]pyrimidinone, Domino Knoevenagel-cyclocondensation

Dedicated to Prof. Abbas Shafiee on the occasion of his 70th birthday

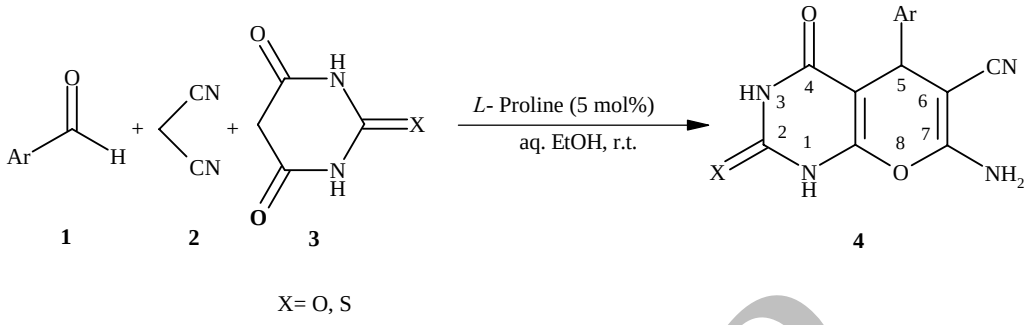
INTRODUCTION

With green chemistry becoming a central issue in both academic and industrial research in the 21st century [1], the development of environmentally benign and clean synthetic procedures have become the goal of present day organic synthesis. Many organic solvents are harmful and their use should therefore be minimized as far as possible or even excluded altogether. Green alternatives under investigation for organic reactions are water [2], supercritical fluids, in-particular CO_2 [3] and solvent-free condition (SFC) [4]. The use of water as the reaction medium exhibits a remarkable benefit because this green solvent is highly polar and therefore immiscible with most organic compounds. Moreover the water-soluble catalyst resides and operates in the aqueous media, and separation of organic compounds is thus easy. Reactions in aqueous media are generally environmentally safe, devoid of any carcinogenic effects, simple work up, comparatively cheaper to operate and especially important in industry [5]. Thus, there is a need for developing multi-component reactions (MCR's) in water and without the use of any harmful organic solvent.

There is a continuous widespread interest in the synthesis of pyrano-pyrimidinones because of the diverse biological properties associated with this system. Compounds with such annulated uracils have antitumor, [6] antibacterial [7], antihypertensive [8], hepatoprotective [8], cardiotonic [8], vasodilator [9], bronchiodilators [9] and antiallergic activities [10]. Some of them exhibit antimalarial [11], antifungal [12], analgesics [13] and herbicidal [14] properties.

There are several reports for the synthesis of 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones in which arylidene malononitrile with barbituric acid have been reacted under either traditional thermal condition [15] or microwave irradiation [16]. Recently, a microwave-assisted three-component cyclocondensation of barbituric acid, benzaldehyde and alkyl nitriles in the absence or presence of triethylamine was reported [17]. There is also a report on a one-pot synthesis of 1,3,5-triaryl-1,2,3,4,-tetrahydro-4-oxo-7-methyl-2-thioxo-5*H*-pyrano[2,3-*d*]pyrimidines by the

*Corresponding author. E-mail: balalaie@kntu.ac.ir



Scheme 1

condensation of various 2-thiobarbituric acids with benzylideneacetones in glacial acetic acid in the presence of phosphorous pentoxide [18]. Each of the above methods has its own merit, with at least one of the limitation of drastic conditions to apply novel conditions, long reaction times and effluent pollution. Thus, new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to those heterocycles and their diverse biological properties. As part of our program for applying novel organocatalysts to multi-component reactions [19], herein we report an efficient one-pot three-component synthesis of various 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*] pyrimidinones and 7-amino-6-cyano-5-aryl-4-oxo-2-thioxo-5*H*-pyrano [2,3-*d*]pyrimidinones catalyzed by *L*-proline in water-based media at room temperature.

In addition to its use in peptide chemistry, the amino acid *L*-proline is often applied as a chiral precursor in the total synthesis of natural products [20]. In the last two decades, *L*-proline has attracted much attention as an efficient organocatalyst for several powerful asymmetric transformations such as the aldol reaction, halolactonization, Michael, and Mannich reactions, reduction of C=O, C=N and C=C bonds, alkylations and allylations and synthesis of optically active phosphorous compounds [20]. *L*-Proline is bifunctional compound, with a carboxylic acid and an amine portion. These two functional groups can both act as acid or base and can also facilitate chemical transformations in concert similar to enzymatic catalysis [21].

In this report we describe a novel and highly efficient three-component one-pot synthesis of well functionalized pyrano[2,3-*d*]pyrimidinones *via* a domino Knoevenagel-cyclocondensation reaction using *L*-proline as catalyst in aqueous medium at room temperature (Scheme 1) [21].

EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. IR spectra were obtained on an ABB FT-IR (FTLA 2000) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE at 300 and 75 MHz instrument using TMS as internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Mass spectra were obtained by using a GC-MS Hewlett Packard (EI, 20 eV) instrument.

General Procedure for the Synthesis of Pyrano[2,3-*d*]pyrimidinones (4a-p)

A solution of an aldehyde **1** (1 mmol), malononitrile (**2**, 1.2 mmol), barbituric or thiobarbituric acid (**3**, 1 mmol) and *L*-proline (5.8 mg, 5 mol%) in H_2O (10 ml) and EtOH (10 ml) was stirred at room temperature for 2 h. After completion of the reaction, the solid product was collected by filtration and recrystallized with ethanol.

Selected Data for Compounds 7-Amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidinone (4a-p)

7-Amino-6-cyano-5-(4-bromophenyl)-5H-pyrano[2,3-d]pyrimidinone (4a). M.p.: 230-231 °C (lit: 227-229 °C) [17]. IR (KBr) (ν_{max}/cm^{-1}): 3329, 3300, 3187, 3073, 2195, 1694, 1672; ^{1}H NMR: (300 MHz, DMSO-d_6) 4.23 (1H, s, H-5), 7.17 (2H, br s, NH_2), 7.18 (2H, d, $^{3}J_{HH}$ = 8.0 Hz, H-Ar), 7.48 (2H, d, $^{3}J_{HH}$ = 8.0 Hz, H-Ar), 11.09 (1H, br s, NH), 12.01 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) 35.3, 58.4, 88.0, 119.0, 119.7, 129.6, 131.1, 143.5, 149.4,

152.3, 157.6, 162.4 ppm.

7-Amino-6-cyano-5-(4-bromophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4b). M.p.: 236 °C (dec.). IR (KBr) (ν_{max}/cm^{-1}): 3370, 3340, 3189, 3080, 2220, 1684, 1567; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.26 (1H, s, H-5), 7.17 (2H, br s, NH$_2$) 7.20 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-Ar), 7.48 (2H, d, $^3J_{HH}$ = 8.2 Hz, H-Ar), 12.45 (1H, br s, NH), 13.66 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.3, 58.5, 82.8, 119.0, 120.0, 129.9, 132.2, 132.7, 143.0, 157.4, 160.3, 174.0 ppm.

7-Amino-6-cyano-5-(3-chlorophenyl)-5H-pyrano[2,3-d] pyrimidinone (4c). M.p.: 240-241 °C. IR (KBr) (ν_{max}/cm^{-1}): 3419, 3324, 3196 3100, 2192, 1690, 1663, ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.25 (1H, s, H-5), 7.18-7.26 (6H, m, H-Ar, NH$_2$), 11.08 (1H, br s, NH), 12.10 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.5, 58.2, 87.8, 119.1, 126.3, 126.8, 127.3, 130.2, 132.9, 146.7, 149.6, 152.5, 157.7, 162.6 ppm.

7-Amino-6-cyano-5-(3-chlorophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4d). M.p.: 237-238 °C. IR (KBr) (ν_{max}/cm^{-1}): 3373, 3330, 3193 , 3161, 2203, 1683, 1569 cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.29 (1H, s, H-5), 7.19 (2H, br s, NH$_2$), 7.21-7.35 (m, 4H, H-Ar), 12.45 (1H, br s, NH), 13.50 (1H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.5, 58.0, 92.8, 119.0, 126.5, 127.5, 128.3, 130.2, 133.0, 146.1, 152.0, 157.6, 160.3, 174.0 ppm; MS: ($C_{14}H_9ClN_4O_2S$) *m*/*z* (%) = 334 (M^{+}+2, 7.2), 332 (M^{+}, 19.6%), 266 (100), 268 (43.3), 231 (55.8), 221 (63.9).

7-Amino-6-cyano-5-(4-cyanophenyl)-5H-pyrano[2,3-d] pyrimidinone (4e). M.p.: 254-256 °C. IR (KBr) (ν_{max}/cm^{-1}): 3383, 3329, 3220, 3187, 2229, 2199, 1674, 1638 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.34 (1H, s, H-5), 7.24 (2H, br s, NH$_2$), 7.44 (2H, d, $^3J_{HH}$ = 7.6 Hz, H-Ar), 7.76 (2H, d, $^3J_{HH}$ = 7.6 Hz, H-Ar), 11.10 (1H, br s, NH), 12.14 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.2, 58.1, 87.9, 110.0, 119.3, 119.4, 129.0, 132.7, 150.0, 150.2), 153.1, 158.2, 163.0 ppm; MS: ($C_{15}H_9N_5O_3$) *m*/*z* (%) = 307 (M^{+}), 249 (100), 240 (62), 205 (21), 197 (39), 179 (35).

7-Amino-6-cyano-5-(2,3-dichlorophenyl)-5H-pyrano[2, 3-d]pyrimidinone (4f). M.p.: 240-242 °C. IR (KBr) (ν_{max}/cm^{-1}): 3442, 3353, 3273, 3164, 2197, 1670, 1620; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.82 (1H, s, H-5), 7.22 (2H, br s, NH$_2$), 7.29 (2H, d, $^3J_{HH}$ = 4.3 Hz, H-Ar), 7.50 (1H, t, $^3J_{HH}$ = 4.3 Hz, H-Ar), 11.09 (1H, br s, NH), 12.14 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 34.0, 57.7, 88.3, 119.5, 129.1, 129.8, 131.2, 132.6, 144.6, 150.4, 153.7, 158.8, 163.2 ppm; MS: ($C_{14}H_8Cl_2N_4O_3$) *m*/*z* (%) = 352 (M^{+}+2), 350 (M^{+}), 354 (M^{+}+ 4, 0.3), 249 (100), 206 (60).

7-Amino-6-cyano-5-(2,3-dichlorophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4g). M.p.: 257- 258 °C. IR (KBr) (ν_{max}/cm^{-1}): 3460, 3316, 3172, 3064, 2190, 1671, 1635; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.85 (1H, s, H-5), 7.28-7.35 (4H, m, H-Ar, NH$_2$), 7.51 (1H, d, $^3J_{HH}$ = 7.4 Hz, H-Ar), 12.46 (1H, br s, NH), 13.70 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 34.0, 57.5, 93.3, 119.4, 129.2, 130.0, 131.3, 132.6, 144.0, 153.1, 158.6, 160.9, 174.9 ppm; MS: ($C_{14}H_8Cl_2N_4O_2S$) *m*/*z* (%) = 370 (M^{+}+4), 368 (M^{+}+2), 366 (M^{+}), 265 (100), 267 (41), 222 (18), 206 (82), 187(23).

7-Amino-6-cyano-5-(2,4-dichlorophenyl)-5H-pyrano[2, 3-d]pyrimidinone (4h). M.p.: 241-242 °C. IR (KBr) (ν_{max}/cm^{-1}): 3387, 3311, 3180, 3023, 2195, 1641, 1630; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.73 (1H, s, H-5), 7.20 (2H, br s, NH$_2$), 7.34 (2H, br s, H-Ar), 7.53 (1H, br s, H-Ar), 11.09 (1H, br s, NH), 12.14 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 32.9, 56.8, 87.2, 118.7, 127.7, 128.8, 132.0, 133.2, 140.1, 149.6, 152.9, 152.9, 157.9, 162.4 ppm; MS: ($C_{14}H_8Cl_2N_4O_3$) *m*/*z* (%) = 354 (M^{+}+ 4), 352 (M^{+}+2), 350 (M^{+}), 249 (100), 206 (92).

7-Amino-6-cyano-5-(2,4-dichlorophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4i). M.p.: 238.5-239.5 °C. IR (KBr) (ν_{max}/cm^{-1}): 3388, 3306, 3198, 2196, 1687, 1647; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.75 (1H, s, H-5), 7.25 (2H, br s, NH$_2$), 7.33 (2H, d, $^3J_{HH}$ = 7.9 Hz, H-Ar), 7.38 (1H, d, $^3J_{HH}$ = 7.9 Hz, H-Ar), 12.54 (1H, br s, NH), 13.64 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 38.7, 57.6, 88.0, 119.4, 128.5, 129.6, 132.8, 134.1, 140.9, 150.4, 153.7, 158.8, 163.2 ppm.

7-Amino-6-cyano-5-(3-hydroxyphenyl)-5H-pyrano[2,3-d]pyrimidinone (4j). M.p.: 158-160 °C. IR (KBr) (ν_{max}/cm^{-1}): 3439, 3337, 3193, 3028, 2206, 1677, 1625; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.10 (1H, s, H-5), 6.56 (2H, br s, NH$_2$), 6.59 (1H, m, H-Ar), 7.04-7.10 (m, 3H, H-Ar), 9.33 (1H, br s, OH), 11.09 (1H, br s, NH), 12.07 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.6, 59.9, 89.5, 114.7, 114.9, 118.8, 120.1, 130.1, 146.5, 150.4, 153.1, 158.1, 158.5, 163.3 ppm; MS: ($C_{14}H_{10}N_4O_4$) *m*/*z* (%) = 298 (M^{+}), 249 (6), 232 (17), 188 (12), 142 (100), 128 (30), 115 (33).

7-Amino-6-cyano-5-(3-nitrophenyl)-5H-pyrano[2,3-d] pyrimidinone (4k). M.p.: 268-270 °C. IR (KBr) (ν_{max}/cm^{-1}): 3415, 3315, 3203, 3020, 2192, 1688, 1659, 1529, 1348; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.47 (1H, s, H-5), 7.28 (2H, br s, NH$_2$), 7.60 (1H, t, $^3J_{HH}$ = 7.8 Hz, H-Ar), 7.74 (1H, d, $^3J_{HH}$ = 7.8 Hz, H-Ar) 8.06-8.10 (2H, m, H-Ar), 11.11 (1H, br s, NH), 12.17 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.5, 58.5, 88.3, 119.8, 122.8, 122.9, 130.7, 135.3, 147.3, 148.6, 150.4, 153.5, 158.7, 163.4 ppm; MS: ($C_{14}H_9N_5O_5$) *m*/*z* (%) = 327 ($M^{+\cdot}$), 261 (50.9), 260 (43.9), 244 (100), 214 (70.48).

7-Amino-6-cyano-5-(3-nitrophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4l). M.p.: 233.5-234 °C. IR (KBr) (ν_{max}/cm^{-1}): 3420, 3311, 3197, 2201, 1682, 1635, 1569, 1327; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.52 (1H, s, H-5), 7.31 (2H, br s, NH$_2$), 7.60 (1H, t, $^3J_{HH}$ = 7.0 Hz, H-Ar), 7.76 (1H, d, $^3J_{HH}$ = 7.0 Hz, H-Ar), 8.10 (2H, d, $^3J_{HH}$ = 1.2 Hz, H-Ar), 12.46 (1H, br s, NH), 13.70 (1H, brs, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.5, 58.3, 93.3, 119.7, 122.9, 123.2, 130.7, 135.5, 146.6, 148.6, 152.9, 158.5, 161.1, 174.9 ppm; MS: ($C_{14}H_9N_5O_4S$) *m*/*z* (%) = 343 ($M^{+\cdot}$), 277 (100), 260 (23), 230 (17), 179 (49).

7-Amino-6-cyano-5-(4-nitrophenyl)-5H-pyrano[2,3-d] pyrimidinone (4m). M.p.: 239-240 °C (Lit: 237-238 °C) [17]. IR (KBr) (ν_{max}/cm^{-1}): 3380, 3321, 3182, 2196, 1696, 1640, 1519, 1348; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.42 (1H, s, H-5), 7.26 (2H, br s, NH$_2$), 7.52 (2H, d, $^3J_{HH}$ = 7.2 Hz, H-Ar), 8.14 (2H, d, $^3J_{HH}$ = 7.2 Hz, H-Ar), 11.12 (1H, br s, NH), 12.17 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.7, 57.5, 87.5, 119.0, 124.3, 130.7, 146.4, 149.6, 151.9, 152.7, 157.8, 162.6 ppm.

7-Amino-6-cyano-5-(4-nitrophenyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4n). M.p.: 235-236 °C. IR (KBr) (ν_{max}/cm^{-1}): 3366, 3320, 3190, 2197, 1687, 1518, 1346; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.46 (1H, s, H-5), 7.31 (2H, br s, NH$_2$), 7.55(2H, d, $^3J_{HH}$ = 8.3 Hz, H-Ar), 8.15 (2H, d, $^3J_{HH}$ = 8.3 Hz, H-Ar), 12.47 (1H, br s, NH), 13.50 (1H, br s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d$_6$) 35.6, 57.3, 92.4, 118.8, 123.6, 129.3, 146.5, 151.2, 152.1, 157.6, 160.3, 174.1 ppm.

7-Amino-6-cyano-5-(4-trifluoromethyl)-5H-pyrano[2,3-d]pyrimidinone (4o). M.p.: 250-251 °C. IR (KBr) (ν_{max}/cm^{-1}): 3419, 3324, 3196, 2192, 1690, 1663; ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.34 (1H, s, H-5), 7.22 (2H, br s, NH$_2$), 7.45 (2H, d, *J* = 7.6 Hz, H-Ar), 7.65 (2H, d, *J* = 7.6 Hz, H-Ar), 11.10 (1 H, br s, NH), 12.14 (1H, br s, NH) ppm.

7-Amino-6-cyano-5-(4-trifluoromethyl)-4-oxo-2-thioxo-5H-pyrano[2,3-d]pyrimidinone (4p). M.p.: 239-240 °C. IR (KBr) (ν_{max}/cm^{-1}): 3383, 3186, 2198, 1671, 1637, ^{1}H NMR (300 MHz, DMSO-d$_6$) 4.35 (1H, s, H-5), 7.26 (2H, br s, NH$_2$), 7.48 (2H, d, *J* = 8.1 Hz, H-Ar), 7.66 (2H, d, *J* = 8.1 Hz, H-Ar), 12.46 (1H, br s, NH), 13.70 (1H, br s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$) 36.0, 58.6, 93.5, 119.7, 126.1, 126.2, 129.3, 131.0, 149.0, 152.8, 158.3, 161.1, 174.9 ppm; MS: ($C_{15}H_9F_3N_4O_2S$) *m*/*z* (%) = 366 ($M^{+\cdot}$, 28%), 300 (100), 231 (43), 221 (75), 202 (57).

RESULTS AND DISCUSSIONS

The experimental procedure is simple. Solutions of equimolar amounts of aromatic aldehyde **1**, malononitrile **2** and barbituric or thiobarbituric acid **3** in H_2O-EtOH (1:1), at room temperature, are mixed thoroughly in the presence of a catalytic amount of *L*-proline (5 mol%) to afford various functionalized pyrano[2,3-*d*]pyrimidinones **4a-p** in good yields.

In order to optimize conditions, we used 3-nitrobenzaldehyde, barbituric acid and malononitrile and tested with various amount of *L*-proline as catalyst. The best result was achieved by using 5 mol% of *L*-proline.

In the absence of *L*-proline, there was not reaction. To show that *L*-proline is an efficient catalyst rather than a mild base, or acid catalyst we tried the reaction in a solution, with the pH of 7, but also there were no reaction.

The work-up of the reaction is accomplished by simple filtration, followed by recrystallization. Table 1 shows the results obtained in the reactions of a series of representative aldehydes with malononitrile and barbituric or thiobarbituric acid. Reactions are very clean so that pyranopyrimidinones **4a-p** were obtained as a sole product during suitable times in good to high yields. As is evident from the results in Table 1, the yields are comparable for various aldehydes and barbituric acids.

Although we have not yet established the mechanism of the one-pot reaction of benzaldehyde derivatives, a possible explanation for reaction of malononitrile and barbituric or thiobarbitoric acid in the presence of *L*-proline is given in

Table 1. *L*-Proline Catalyzed Synthesis of Pyrano-pyrimidinones **4a-p** in Aqueous Media

Product	Ar	X	Time (min)	Yield (%)[a]
4a	4-Br-C_6H_4	O	90	75[17]
4b	4-Br-C_6H_4	S	150	78
4c	3-Cl-C_6H_4	O	40	68
4d	3-Cl-C_6H_4	S	40	70
4e	4-NC-C_6H_4	O	60	83
4f	2,3-Cl_2-C_6H_3	O	60	76
4g	2,3-Cl_2-C6H3	S	105	80
4h	2,4-Cl_2 -C_6H_3	O	35	75
4i	2,4-Cl_2-C_6H_3	S	90	72
4j	3-HO-C_6H_4	O	90	86
4k	3-O_2N-C_6H_4	O	60	75
4l	3-O_2N-C_6H_4	S	120	88
4m	4-O_2N-C_6H_4	O	45	73[17]
4n	4-O_2N-C_6H_4	S	90	76
4o	4-F_3C-C_6H_4	O	30	72
4p	4-F_3C-C_6H_4	S	45	85

[a]Yields refer to those of pure isolated products characterized by mass spectrometry and IR ,^{1}H and ^{13}C NMR spectroscopic data.

Scheme 2. We suggest that, *L*-proline is an effective catalyst for the formation of iminium ion **5** in a reversible reaction with the benzaldehyde. The higher reactivity of the iminium ion compared to the carbonyl group species is utilized to facilitate the Knoevenagel condensation between aryl aldehyde **1** and malononitrile **2**, which proceeds *via* intermediate **6** and, after dehydration, olefin **7** is produced. *L*-Proline also catalyzes the generation of a proposed enamine intermediate **8**, which is formed from barbituric or thiobarbituric acid **3** and *L*-proline. Enamine intermediate **8** is added to olefine **7** to generate the product **4**, after proton transfer, tautomerization and hydrolysis of intermediate **9**.

The structures of the products were confirmed from physical and spectroscopic (IR, ^{1}H and ^{13}C NMR) and mass spectrometry data. The ^{1}H NMR spectra exhibited the absence of the methylene protons of the barbituric or thiobarbituric acid and the presence of a proton (H-5) at 4.3-4.8 ppm as a singlet, and also a distinguished peak at 34-36 ppm for C-5 in ^{13}C NMR spectroscopy. The mass spectra of these compounds displayed molecular ion peaks. Selected spectroscopic data has been given in experimental section.

In summary, this method is attractive, since it offers some advantages over earlier reported protocols. It avoids the use of dry and toxic solvents and multi-step procedures. Some of the advantages of the present method include neutral conditions, good isolated yields of the products, easy work-up and use of aqueous media.

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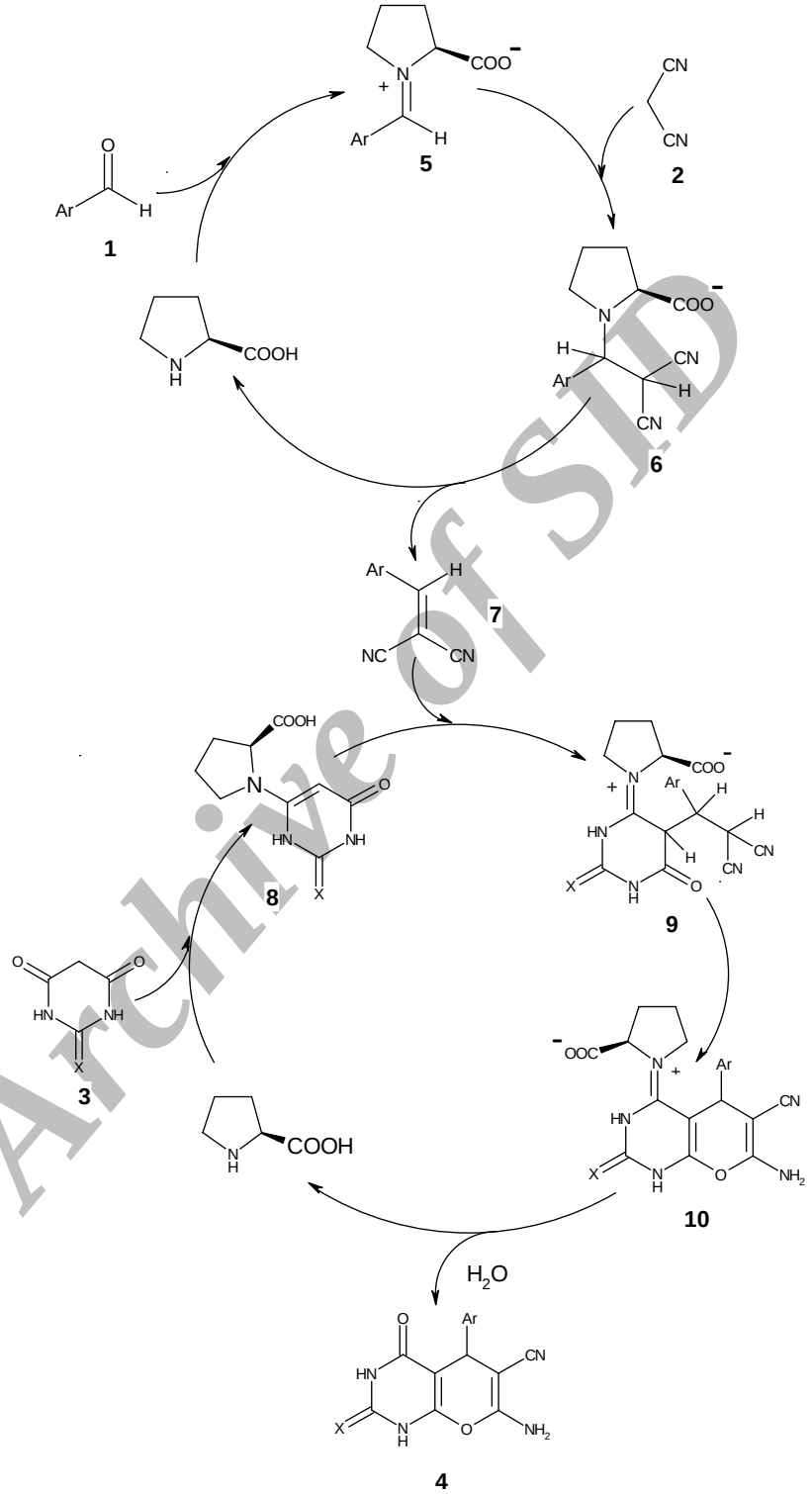

Scheme 2. Proposed mechanism for the one-pot synthesis of pyrano[2,3-*d*]pyrimidinones catalyzed by *L*-proline (5%) in aqueous solution

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