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A One-Pot, Three-Component Efficient New Synthesis of Pyrrolo-[3,2-*D*] Isoxazole Derivatives Catalyzed by *L*-Proline in Acetic Acid Media[1]

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Abstract

A one-pot, three-component reaction of 4-hydroxy coumarin, arylglyoxals, and 5-amino-3-methylisoxazole in the presence of *L*-proline as an organocatalyst in acetic acid under reflux conditions provides a series of new pyrrolo [3,2-*d*] isoxazole derivatives **(4a-l)** in excellent yields.

Keywords: *One-pot synthesis; L-proline catalyst; Arylglyoxals; Efficient new synthesis; Pyrrolo[3,2-d]isoxazoles.*

Introduction

Multi-component reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion. Designing such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis. As such processes avoid time consuming, and costly purification processes, as well as protection-deprotection steps, they provide a powerful tool towards the one-pot synthesis of diverse and complex compounds as well small, and drug-like heterocycles [1]. Multi-component reactions play an important role in modern synthetic organic chemistry, as they generally occur in a single pot, and exhibit a high atom-economy, selectively and potentially reduces the development costs and complexity in the process [2].

Fused isoxazoles have been reported with diverse structural features and versatile biological properties such as antitumor [3], analgesic [4], antimicrobial [5], and treatment of hyper cholestremia and hyperlipidemia [6], and as chemotherapeutic agents [7].Similarly, Fused pyrroles are found to possess diverse pharmacological properties, such as antileukemic [8], potent DHFR inhibitor TNP – 351 activity [9, 10], antiviral [11], antiasthamatic [12], and anti-HIV agnets [13].

L-proline is a bi-functional chiral organo-catalyst which is inexpensive, efficient, readily available and facilitates chemical transformations in concert similar to enzymatic catalysis by acting as an acid or base [14]. It has been extensively used in the synthesis of variety of heterocycles [15], and also in aldol, Mannich and Michael reactions [16, 17].

Pyrrolo[3,2-*d*]pyrimidine derivatives was reported by Bharti and Pravin [18], which involves a one-pot three-component reaction of 4-hydroxy coumarin, an aldehyde, and 1,3-dimethyl-6-aminouracil. Later in the above reaction, an aldehyde was replaced by arylglyoxal by Choudhury and co-

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workers [19]. Arylglyoxals are efficiently synthesized in the form of hydrates by the oxidation of acetophenones with selenium dioxide in ethanol under refluxing conditions [20]. In this paper, now, we replace the 1,3-dimethyl-6-amino uracil, by 5-amino-3-methylisoxazole in order to synthesize new pyrrolo[3,2-*d*]isoxazoles, which are scanty in the literature.

Scanning the literature on fused pyrroles has revealed that different methods have been adopted for their synthesis, and some of them find application in pharmaceutical field. Through, there are more reports are available in the literature for the synthesis of fused pyrroles, there is only two reports are available on the synthesis of pyrrolo-isoxazoles [21, 22].

In view of the emerging importance of environmental awareness, the development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic synthesis [23-25]. This prompted us to develop a simple, convenient, efficient, economical, and environmentally benign approach for the one-pot synthesis of title compounds. In the quest for developing a less-toxic, potentially green catalyst, we thought of using *L*-proline for this reaction. As a sequel to our work on the synthesis of fused isoxazoles, we, herein, report the synthesis of pyrrolo[3,2-*d*]isoxazoles by a multi-component one-pot condensation of 4-hydroxy coumarin **(1)**, arylglyoxal **(2)**,and 5-amino-3-methylisoxazole **(3)** in the presence of *L*-proline catalyst. However, there is no report available all the use of *L*-proline as catalyst in the synthesis of pyrrolo-isoxazoles.

Results and Discussion

The reaction of 4-hydroxy coumarin **(1)**, phenylglyoxal **(2)**, and 5-amino-3-methylisoxazole **(3)**was chosen as the model reaction. In the absence of *L*-proline, no product was observed at room temperature even after 24h (Entry 1). Refluxing the reaction mixture in acetic acid without the catalyst for 6 h gave the desired product **(4)** only in 10% yield (Entry 2). Later, this reaction was attempted in the presence of other catalysts, such as K_2CO_3, $ZrOCl_2$, and *p*-TSA using acetic acid as solvent. The reaction produced 20%, 30%, and 35% yields respectively (Entry 3, 4 and 5). The reaction was further explored in the presence of pyrrolidine, triethylene diamine and tetra-*n*-butyl ammonium bromide in acetic acid media, which resulted 40%, 45%, and 50% yields respectively (Entry 6, 7 and 8).The model reaction was then conducted with *L*-proline catalyst (10 mol%) in acetic acid under refluxing condition for 6h. To our surprise, the reaction afforded 90% yield (Entry 9) of the product, *viz.,* 4-hydroxy-3-(3-methyl-5-phenyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl-2*H*-chromen-2-one**(4a)**. The model reaction in the presence of *L*-proline was also conducted in organic solvents such as ethanol, acetonitrile, dichloromethane, and tetrahydrofuran. All these reactions produced less amounts of (50% - 60%) of the product (Entry 10, 11, 12 and 13). As can be seen, the use of *L*-proline proved to be best and necessary in term of yields and efficiency of the reaction. Among all the reactions tested, maximum yield 90% was obtained in the presence of *L*-proline catalyst (10 mol%) in acetic acid solvent by refluxing at 80ºC for 6 h. **(Scheme-1)**.

Having established the optimized reaction conditions, the reaction was further studied by increasing the catalyst loading to 20 mol%. No improvement in the yield of **4a** was observed (Entry 14). The reaction was also explored with a decreased catalyst loading of 5 mol%., which did not result satisfactory yields (60%) (Entry 15). The effect of temperature on this reaction was also examined. Neither increasing nor decreasing the temperature for 80ºC afforded better yields (Entry 16, 17).

To investigate the scope of this reaction under the optimal conditions, various arylglyoxals were exposed in a three-component one-pot condensation with 4-hydroxy coumarin **(1)** and 5-amino-3-methylisoxazole **(3)** in the presence of 10mol% *L*-proline at 80ºC for 6h in acetic acid. As expected, all these reactions afforded the corresponding products *i.e.,* 4-hydroxy-3-(3-methyl-5-aryl-6*H*-pyroolo[3,2-*d*]-isoxazol-4-yl-2*H*-chromen-2-ones**4b-4l** in 80-90% yields. All the products **4b-4l** were isolated in pure form by simple recrystallization without the need for tedious chromatography. No side products were detected. The method proved to be efficient and compatible with electron-releasing and electro-withdrawing groups on arylglyoxals, demonstrating its general applicability. Based on these observations, it was concluded that the optimal conditions for major conversion of the reactants in to products are a) temperature of 80ºC, b) a reaction time of 6h, and c) the use of 10 mol%. *L*-proline in acetic acid.**(Scheme-2).**

All the newly synthesized compounds **4a-4l** were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. Elemental analysis data were also consistent with the proposed structures.

The plausible mechanism for the formation of pyrrolo[3,2-*d*]isoxazoles **4** shown in **Figure. 1.** Knoevenagel condensation of arylglyoxal **2** with the 4-hydroxy coumarin catalysed by *L*-proline may result in the intermediate product **A**. The Michael addition of 5-amino-3-methylisoxazole **3** to the compound **A**, probably gives another intermediate **C**, which ultimately undergoes intramolecular heterocyclization to produce the product **4**.

Conclusions

Pyrrolo[3,2-*d*]isoxazole derivatives **4a-4l** were synthesized by the one-pot, three-component reaction by using *L*-proline as an organocatalyst in acetic acid media. This reaction involves a new protocol, and rare synthesis of pyrrolo[3,2-*d*]isoxazoles, which are scanty in the literature. The reaction is efficient involving excellent yields, and benefits from a simple method of purification, which does not require chromatography. This ease of purification compliments the one-pot synthesis, making the technology practical, easy to perform, and facile.

Experimental

All the melting points were determined on a Fisher-Johns melting point apparatus, and are uncorrected. Analytical TLC was performed on Merck precoated 60 F25M silica gel plates. Visualization was carried out by exposure to iodine vapour. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. 1H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. 13C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in *δ*ppm with tetramethyl silane as an internal standard. ESI mass spectra were recorded on a Agilent LC-MSD mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for the synthesis of 4-hydroxy-3-(3-methyl-5-phenyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-ones (4a-l)

A mixture of 4-hydroxy coumarin **(1)** (1 mmol), arylglyoxal hydrate **(2)** (1 mmol), 5-amino-3-methylisoxazole **3** (1 mmol) and *L*-proline (10 mol%) in acetic acid (10 mL) was heated under reflux for 6h. The progress of the reaction was monitored by TLC. After the completion of the reaction, as indicated by TLC, the contents are cooled. The precipitated compound was filtered, washed with cold water, and dried. Recrystalization of the product was affected from benzene.

4-Hydroxy-3-(3-methyl-5-phenyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one (4a) Yield 70%; Pale Yellow solid; mp 150-152^{o}C; IR: ν_{max} 3410 (OH), 3362 (NH),1700 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ2.26 (s, 3H, isoxazole CH_3), 6.87-7.76 (m, 9H, Ar-H), 10.96 (bs, 1H, NH, D_2O exchangeable), 11.45 (bs, 1H, OH, D_2O exchangeable); ^{13}C NMR (75MHz, $CDCl_3$):δ12.85, 101.51, 103.75, 107.87, 116.58, 117.32, 120.12, 123.14, 124.58, 125.36, 126.58, 127.63, 128.69, 129.32, 130.25, 131.85, 151.25, 153.24, 161.68, 165.24, 167.69. MS:*m/z* 359 $(M+H)^{+}$. Anal calcd for $C_{21}H_{14}N_2O_4$: C, 70.36; H, 3.93; N, 7.85. Found: C, 70.39; H, 3.91; N, 7.82.

4-Hydroxy-3-(3-methyl-5-(*p*-tolyl)-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one(4b)Yield75%;Pale Yellow solid; mp 145-147^{o}C;IR: ν_{max} 3414 (OH), 3365 (NH), 1685 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 2.50 (s, 3H, Ar-CH_3), 6.85-7.79 (m, 8H, Ar-H), 10.98 (bs, 1H, NH, D_2O exchangeable), 11.48 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.80, 24.56, 102.11, 104.35, 106.97, 115.88, 118.02, 121.02, 123.65, 124.75, 125.69, 126.89, 127.36, 128.21, 129.69, 130.55, 131.85, 150.85, 152.24, 160.98, 164.34, 166.79. MS: *m/z* 373 $(M + H)^{+}$. Anal calcd for $C_{22}H_{16}N_2O_4$: C, 70.94; H, 4.33; N, 7.55.Found: C, 70.96; H, 4.31; N, 7.54.

4-Hydroxy-3-(5-(4-methoxyphenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one(4c)Yield72%;Pale Yellow solid; mp 160-162^{o}C;IR: ν_{max} 3418 (OH), 3368 (NH), 1690 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, isoxazole CH_3), 3.68 (s, 3H, Ar-OCH_3), 6.80-7.81 (m, 8H, Ar-H), 10.90 (bs, 1H, NH, D_2O exchangeable), 11.51 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.83, 58.68, 101.81, 105.05, 107.17, 116.28, 119.12, 120.02, 121.85, 123.85, 124.66, 125.29, 126.98, 127.51, 128.69, 129.75, 130.75, 151.75, 153.24, 161.78, 163.30, 167.29. MS:

m/z 389 (M+ H)$^+$. Anal calcd for $C_{22}H_{16}N_2O_5$: 68.02; H, 4.14; N, 7.24.Found: C, 68.04; H, 4.13; N, 7.22.

3-(5-(4-Chlorophenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one(4d)Yield70%;Pale Yellow solid; mp 170-172°C. IR: ν_{max} 3416 (OH), 3368 (NH), 1700 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 6.80-7.72 (m, 8H, Ar-H), 10.92 (bs, 1H, NH, D_2O exchangeable), 11.41 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.80, 100.21, 102.65, 105.97, 114.88, 116.52, 119.82, 121.10, 122.78, 124.96, 125.58, 127.96, 128.75, 129.66, 130.65, 131.92, 150.05, 154.20, 162.28, 164.24, 168.09. MS: *m/z* 393 (M+ H)$^+$. Anal calcd for$C_{21}H_{13}ClN_2O_4$: C, 64.25; H, 3.34; N, 7.12.Found: C, 64.28; H, 3.32; N, 7.14.

4-Hydroxy-3-(3-methyl-5-(4-nitrophenyl)-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one(4e)Yield65%;Pale Yellow solid; mp 175-177°C;IR: ν_{max} 3418 (OH), 3370 (NH), 1685 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, isoxazole CH_3),6.82-7.75 (m, 8H, Ar-H), 10.95 (bs, 1H, NH, D_2O exchangeable), 11.45 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.21, 101.31, 103.25, 104.55, 113.38, 117.02, 118.95, 120.60, 121.88, 122.97, 124.66, 126.76, 127.88, 129.89, 131.60, 132.12, 151.25, 155.21, 161.28, 165.30, 167.39. MS: *m/z* 404 (M+ H)$^+$. Anal calcd for $C_{21}H_{13}N_3O_6$: C, 62.51; H, 3.25; N, 10.45.Found: C, 62.53; H, 3.23; N, 10.44.

3-(5-(4-Fluorophenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one(4f)Yield68%;Pale Yellow solid; mp 182-184°C;IR: ν_{max} 3420 (OH), 3370 (NH), 1710 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, isoxazole CH_3), 6.88-7.79 (m, 8H, Ar-H), 10.97 (bs, 1H, NH, D_2O exchangeable), 11.48 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.86, 101.61, 103.85, 106.90, 115.18, 117.32, 120.02, 121.26, 123.18, 124.69, 125.89, 127.69, 128.98, 129.67, 131.98, 132.32, 151.21, 155.30, 163.38, 164.20, 169.19. MS:*m/z* 377 (M+ H)$^+$. Anal calcd for $C_{21}H_{13}FN_2O_4$: C, 67.05; H, 3.47; N, 7.41.Found: C, 67.02; H, 3.45; N, 7.40.

3-(5-(3,4-Dimethoxyphenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (4g)Yield72%;Pale Yellow solid; mp 191-193°C;IR: ν_{max} 3419 (OH), 3370 (NH), 1695 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ2.28 (s, 3H, isoxazole CH3), 3.78 (s, 3H, Ar-OCH3), 3.89 (s, 3H, Ar-OCH3), 6.88-7.85 (m, 7H, Ar-H), 10.95 (bs, 1H, NH, D2O exchangeable), 11.53 (bs, 1H, OH, D2O exchangeable), ^{13}C NMR (75MHz, $CDCl_3$):δ 12.85, 58.68, 59.36, 102.21, 106.15, 107.44, 115.68, 118.62, 120.32, 122.65, 123.85, 124.88, 125.69, 127.18, 127.69, 129.09, 130.21, 131.25, 150.35, 154.14, 162.08, 164.20, 168.19. MS: *m/z* 419 (M+ H)$^+$. Anal calcd for $C_{23}H_{18}N_2O_6$: C, 66.05; H, 4.33; N, 6.67.Found: C, 66.02; H, 4.30; N, 6.69.

4-Hydroxy-3-(3-methyl-5-(*o*-tolyl)-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one (4h)Yield70%;Pale Yellow solid; mp 155-157°C;IR: ν_{max} 3412 (OH), 3363 (NH), 1680 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, isoxazole CH_3),6.82-7.75 (m, 8H, Ar-H), 10.96 (bs, 1H, NH, D_2O exchangeable), 11.45 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.78, 24.71, 101.31, 103.55, 107.17, 114.68, 117.82, 120.36, 122.77, 123.82, 124.60, 125.39, 126.86, 127.61, 128.79, 131.05, 132.65, 151.25, 153.35, 161.36, 163.64, 165.89. MS: *m/z* 373 (M+ H)$^+$. Anal calcd for $C_{22}H_{16}N_2O_4$: C, 70.98; H, 4.31; N, 7.50.Found: C, 70.96; H, 4.30; N, 7.52.

4-Hydroxy-3-(5-(2-methoxyphenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one (4i)Yield72%;Pale Yellow solid; mp 165-167°C;IR: ν_{max} 3419 (OH), 3364 (NH), 1700 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, isoxazole CH_3),3.68 (s, 3H, Ar-OCH_3), 6.82-7.85 (m, 8H, Ar-H), 10.92 (bs, 1H, NH, D_2O exchangeable), 11.53 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.80, 58.67, 100.85, 104.35, 106.87, 115.26, 118.22, 121.00, 121.91, 122.95, 123.86, 125.31, 126.90, 127.55, 128.88, 129.73, 131.25, 150.35, 154.24, 162.18, 164.40, 168.89. MS: *m/z* 389 (M+ H)$^+$. Anal calcd for$C_{22}H_{16}N_2O_5$: C, 68.07; H, 4.10; N, 7.23.Found: C, 68.04; H, 4.11; N, 7.22.

3-(5-(4-Bromophenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (4j)Yield70%;Brown solid; mp 190-192°C;IR: ν_{max} 3415 (OH), 3363 (NH), 1686 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, isoxazole CH_3), 6.78-7.70 (m, 8H, Ar-H), 10.92 (bs, 1H, NH, D_2O exchangeable), 11.40 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.81, 100.68, 102.35, 105.80, 116.28, 116.32, 121.12, 122.06, 123.66, 124.87, 126.29, 127.69, 129.08,

130.17, 132.22, 133.58, 152.01, 154.22, 164.31, 165.00, 168.11.MS: *m/z* 437 $(M+H)^+$. Anal calcd for $C_{21}H_{13}BrN_2O_4$: C, 57.77; H, 2.95; N, 6.45.Found: C, 57.76; H, 2.94; N, 6.44.

3-(5-(2,4-Dichlorophenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (4k)Yield65%;Pale Yellow solid; mp 198-200°C;IR: ν_{max} 3419 (OH), 3370 (NH), 1690 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, isoxazole CH_3), 6.83-7.75 (m, 7H, Ar-H), 10.95 (bs, 1H, NH, D_2O exchangeable), 11.45 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.98, 101.01, 103.25, 106.22, 113.98, 115.32, 118.92, 120.12, 123.18, 123.96, 124.68, 125.96, 126.75, 130.06, 131.15, 132.22, 151.01, 153.85, 163.22, 165.04, 167.39. MS: *m/z* 427 $(M+H)^+$. Anal calcd for $C_{21}H_{12}Cl_2N_2O_4$: C, 59.12; H, 2.84; N, 6.55.Found: C, 59.14; H, 2.83; N, 6.57.

3-(5-(2,4-Dibromophenyl)-3-methyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (4l)Yield68%;Brown solid; mp 220-222°C;IR: ν_{max} 3418 (OH), 3364 (NH), 1701 (C=O) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, isoxazole CH_3),6.78-7.70 (m, 7H, Ar-H),. 10.95 (bs, 1H, NH, D_2O exchangeable), 11.42 (bs, 1H, OH, D_2O exchangeable);^{13}C NMR (75MHz, $CDCl_3$):δ 12.80, 101.18, 103.65, 106.32, 117.08, 118.02, 120.22, 121.66, 122.86, 123.97, 125.39, 128.29, 129.23, 131.27, 132.68, 134.58, 153.21, 154.35, 165.31, 166.02, 167.61. MS: *m/z* 517 $(M+H)^+$. Anal calcd for $C_{21}H_{12}Br_2N_2O_4$: C, 48.85; H, 2.34 N, 5.45.Found: C, 48.83; H, 2.34; N, 5.44.

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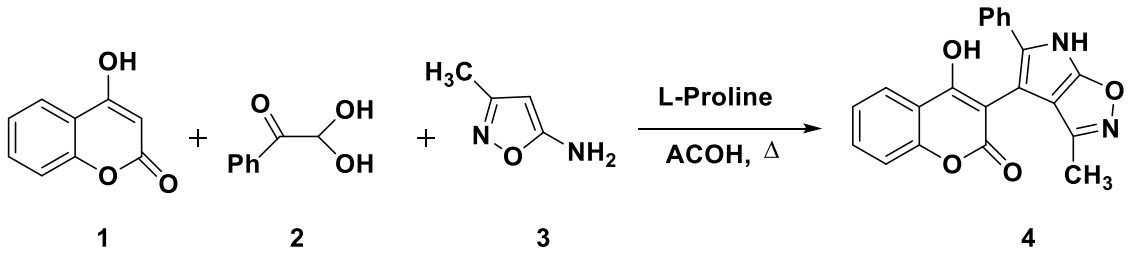
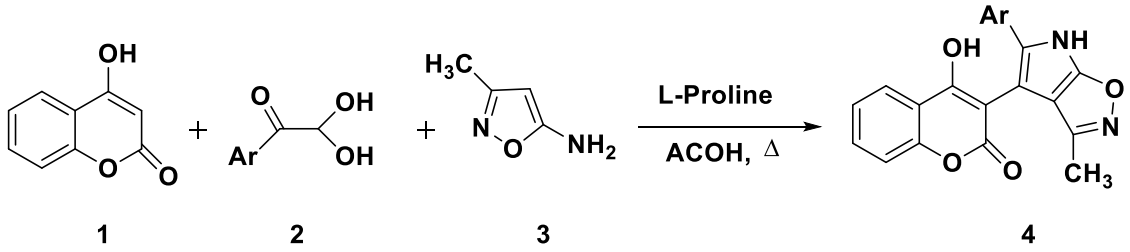
Table 1. Optimization of the reaction conditions[a]

Entry	Catalyst	Solvent	Reaction time (min)	Temperature (°C)	Yield (%)
1	-	-	24h	25	-
2	-	Acetic acid	6h	80	10
3	K_2CO_3	Acetic acid	6h	80	20
4	$ZrOCl_2$	Acetic acid	6h	80	30
5	*p*-TSA	Acetic acid	6h	80	35
6	Pyrrolidine	Acetic acid	6h	80	40
7	Tri ethyl diamine	Acetic acid	6 h	80	45
8	*n*-tetra-butyl bromide	Acetic acid	6h	80	50
9	*L*-Proline (10%)	Acetic acid	6h	80	90
10	*L*-Proline (10%)	Ethanol	6 h	80	50
11	*L*-Proline (10%)	Acetonitrile	6 h	80	55
12	*L*-Proline (10%)	Dichloro methane	6 h	80	60
13	*L*-Proline (10%)	Tetrahydrofuran	6 h	80	55
14	*L*-Proline (20%)	Acetic acid	6h	80	90
15	*L*-Proline (5%)	Acetic acid	6h	80	60
16	*L*-Proline (10%)	Acetic acid	6h	100	50
17	*L*-Proline (10%)	Acetic acid	6h	40	45

[a]**Reaction conditions:1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), *L*-proline (10 mol%), acetic acid, 80°C, 6h.



Scheme1 Trail reaction for the synthesis of 4-hydroxy-3-(3-methyl-5-phenyl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-one**(4a).**



4a: Ar = Cs_6H_5 **4b:** Ar = 4-$CH_3C_6H_4$
4c: Ar = 4-$OCH_3C_6H_4$ **4d:** Ar = 4-ClC_6H_4
4e: Ar = 4-$NO_2C_6H_4$ **4f:** Ar = 4-FC_6H_4
4g: Ar=3,4-$(CH_3O)_2C_6H_3$ **4h:** Ar = 2-$CH_3C_6H_5$
4i: Ar = 2-$OCH_3C_6H_4$ **4j:** Ar = 4-BrC_6H_4
4k: Ar = 2,4-$Cl_2C_6H_3$ **4l:** Ar = 2,4-$Br_2C_6H_3$

Scheme 2: Synthesis of 4-hydroxy-3-(3-methyl-5-aryl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-ones**(4a-4l)**

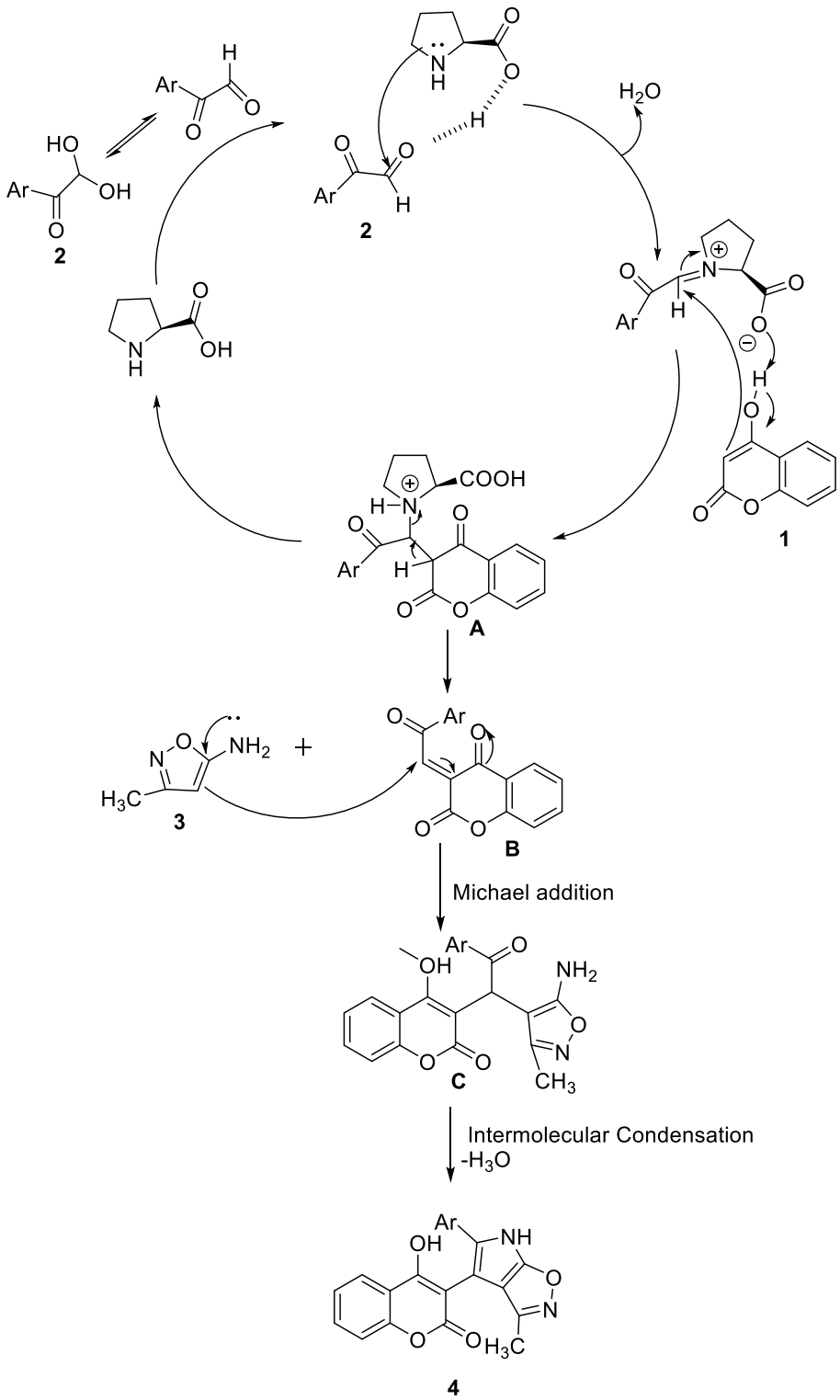


Figure 1: Plausible mechanism forthe formation of 4-hydroxy-3-(3-methyl-5-aryl-6*H*-pyrrolo[3,2-*d*]isoxazol-4-yl)-2*H*-chromen-2-ones**(4a-4l)**