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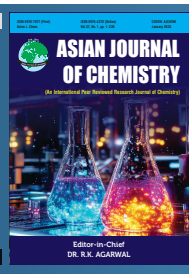

Synthesis of Chromeno/Pyrano-quinolines *via* Tandem Approach involving Michael Addition-Cyclization Catalyzed by *L*-Proline/Cu(II)

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In this study, the reaction of β-nitrovinylquinolines with 1,3-dicarbonyl compounds to furnish chromeno-quinolines under *L*-proline/Cu(II) catalysis was described. The nitro methyl derivatives of chromeno-quinolines were obtained *via* the Michael addition followed by the cyclization reaction of cyclic 1,3-dicarbonyl compounds with β-nitrovinylquinolines in a tandem approach. The reaction with open-chain 1,3-dicarbonyl compounds furnished the corresponding aci form of pyranoquinolines.

Keywords: Chromeno-quinolines, Pyrano-quinolines, β-Nitrovinylquinolines Tandem approach, *L*-Proline/Cu(II), Solvent water.

INTRODUCTION

Quinolines represent one of the important classes of N-heterocycles [1,2] by virtue of their diverse biological activities coupled with the applications in agrochemicals, materials and dyes. Fused heterocycles [3-5] constitute a privileged class due to their extensive presence in natural and synthetic molecules with considerable applications. Amongst fused heterocycles, quinoline-fused ones [6,7] attract much attention owing to their extensive biological and synthetic applications. Especially fused quinoline tetracycles [8] form a significant class due to their wide spread biological activities. They are reported to possess antibacterial, anti-inflammatory, antifungal, antiparasitic, anti-plasmodial, antiproliferative, anti-inflammatory, antitumour activities and also as potent topoisomerase I and II inhibitors. For instance, mappicine ketone [9], a fused quinoline derivative is active against HSV-1, HSV-2 and HCMV viruses, and deaza-flavins [10] (Fig. 1) inhibit tyrosyl-DNA phosphodiesterase II in cancer therapy. Besides quinoline, chromene [11-13] is another significant heterocycle present in plant products like fruits, vegetables and also in natural products that are used as pigments and biodegradable agrochemicals, *etc*.

On the other hand, when quinoline and chromene are present in a single molecular framework result in the chromeno-quinoline [14], yet another prominent bioactive fused heterocycle. Few promising biological agents like anti-inflammatory, anti-tumour, β-selective estrogen ligands have chromeno-quinoline scaffold in them, one of those, 6*H*-chromeno[4,3-*b*]quinoline-6-ones [15] (Fig. 1c) displayed remarkable cytotoxic activity against various cancer cell lines. Thus, the construction of chromenoquinolines by simple synthetic strategies is much needed. In continuation of our work [16-19] on the synthesis of quinoline containing bioactive molecules, here in, we disclose a simple protocol involving tandem approach for the synthesis of chromeno[2,3-*b*]quinolines from β-nitrovinylquinolines, 1,3-dicarbonyl compounds under *L*-proline/Cu(II) catalyst and water as solvent.

EXPERIMENTAL

All reagents were purchased from SD Fine, Spectrochem or AVRA and used without further purification unless otherwise stated. Silicon oil baths on stirrer hotplates were employed with temperature control *via* thermometer. Reaction progress was monitored by thin layer chromatography (TLC) using TLC silica gel 60 F_{254}. Melting points were measured in open capillaries using melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian 400 MHz spectrometer at 300 K. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (*J*) are quoted in Hz to one decimal place. All NMR spectra were measured using

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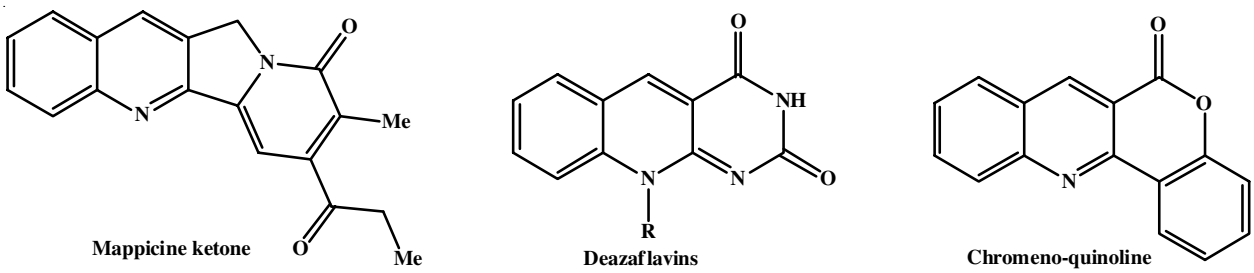


Fig. 1. Biologically active fused quinolines

MestReNova version 6.0.2 (ν). ESI mass spectra were recorded on Micro mass Quattro LC using ESI^+ software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector.

General procedure for the synthesis of β-nitrovinylquinolines (2a,b): 2-Chloroquinoline-3-carbaldehydes (9.83 mmol) and 0.5 mL of nitromethane were mixed in a round-bottom flask and then added 7 mL of MeOH. The reaction mixture was cooled in ice to 5 ºC and then 1 mL of chilled NaOH solution (420 mg of NaOH) was added dropwise with constant swirling and maintaining the reaction mixture temperature between 5-10 ºC. After the completion of addition, stirring continued for the next 30 min and then 5 mL of cold water was added. The reaction mixture was then added slowly to the 24 mL of chilled dil. HCl solution (4 mL conc. HCl in 20 mL water) dropwise with constant stirring. The precipitate separated was filtered, washed with cold water and dried. Finally, it was recrystallized from ethyl acetate to get a pure product.

2-Chloro-3-(2-nitro)vinylquinoline (2a): Yield: 70%; m.p.: 203-205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.44 (d, 1H, *J* = 13.6 Hz, vinyl-H), 8.40 (s, 1H, pyridine-H), 8.05 (d, 1H, *J* = 8.8 Hz, Ar-H), 7.90 (d, 1H, *J* = 8 Hz, Ar-H), 7.85 (t, 1H, Ar-H), 7.71 (d, 1H, *J* = 13.6 Hz, vinyl H), 7.66 (t, 1H, Ar-H); MS: *m/z* 235 (M+1).

General procedure for the synthesis of chromeno-quinolines (4a-k) and (5a,b)

Procedure 1: β-Nitrovinylquinolines (**2**, 0.5 mmol), 1,3-dicarbonyl compound (**3**, 0.5 mmol) and *L*-proline (5.8 mg, 0.05 mmol) were taken in a 25 mL round-bottom flask and DMSO (4 mL) was added. The reaction mixture was stirred at room temperature for 2-4 h. The reaction progress was monitored by thin layer chromatography. After completion of the reaction, the mixture was added slowly to a beaker containing ice with constant stirring. The separated solid was filtered, dried and washed with hexane followed by methanol.

Procedure 2: A 50 mL round-bottom flask was charged with *L*-proline (5.8 mg, 0.05 mmol), $CuCl_2$ (8.6 mg, 0.05 mmol) and water (10 mL), then the mixture was stirred vigorously for 5 min to obtain a clear blue *L*-proline/copper water phase. The reactants β-nitrovinylquinolines (**2**, 0.5 mmol), 1,3-dicarbonyl compound (**3**, 0.5 mmol) and base cesium carbonate (162 mg, 0.5 mmol) were added to the *L*-proline/Cu catalyst. The reaction mixture was refluxed for 2-4 h (monitored by TLC). After the completion of reaction, the contents of the flask were cooled and extracted with ethyl acetate. The organic layers were combined, washed with brine, then dried over anhydrous sodium sulphate and concentrated under reduced pressure. Washing of the obtained crude product with *n*-hexane afforded pure product.

3,3-Dimethyl-12-(nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-1-one (4a): Yield: 94%; m.p.: 133-135 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.11 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.56-7.45 (m, 1H), 4.79 (d, *J* = 2.3 Hz, 1H), 4.77-4.66 (m, 2H), 2.64 (s, 2H), 2.39 (s, 2H), 1.16 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 197.0, 168.5, 154.7, 146.0, 138.4, 131.2, 128.3, 127.6, 127.4, 126.6, 116.0, 108.2, 79.1, 50.7, 41.7, 32.5, 32.4, 29.4, 27.4; MS: *m/z* 339 (M+1).

3-Methyl-12-(nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-1-one (4b): Yield: 93%; m.p.: 135-137 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.54 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 4.96 (dd, *J* = 16.7, 7.5 Hz, 1H), 4.84 (dd, *J* = 12.7, 4.8 Hz, 1H), 4.72 (s, 1H), 2.83-2.65 (m, 1H), 2.45-2.09 (m, 4H), 1.09 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 196.4, 168.8, 167.9, 145.1, 139.2, 130.8, 127.7, 127.4, 126.9, 126.2, 116.9, 108.5 80.2, 44.4, 35.1, 31.8, 27.8, 20.4; MS: *m/z* 325 (M+1).

12-(Nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno-[2,3-*b*]quinolin-1-one (4c): Yield: 93%; m.p.: 135-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-d_6) δ ppm: 8.12 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.76-7.70 (m, 1H), 7.53 (dd, *J* = 11.1, 4.0 Hz, 1H), 4.83 (t, *J* = 5.2 Hz, 1H), 4.71 (s, 1H), 4.70 (s, 1H), 2.90-2.74 (m, 2H), 2.65-2.55 (m, 1H), 2.53-2.42 (m, 1H), 2.19-2.11 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 196.5, 169.2, 154.6, 145.1, 139.2, 130.8, 127.7, 127.4, 126.9, 126.2, 116.9, 108.9, 80.1, 36.3, 31.8, 27.3, 20.1; MS: *m/z* 311 (M+1).

3,3,7-Trimethyl-12-(nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-1-one (4d): Yield: 94%; m.p.: 120-122 ºC; H NMR (400 MHz, $CDCl_3$-d_6) δ ppm: 8.25 (s, 1H), 7.70 (d, *J* = 6.8 Hz, 1H), 7.64 (d, *J* = 6.5 Hz, 1H), 7.48 (s, 1H), 4.80-4.74 (m, 2H), 4. 56 (s, 1H), 2.84 (s, 3H), 2.74 (s, 2H), 2.41 (s, 2H), 1.16 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$-d_6) δ ppm: 196.9, 168.0, 154.3, 142.2, 141.9, 134.7, 133.1, 127.2(2), 126.0, 116.1, 108.5, 79.0, 50.7, 41.5, 32.4, 32.2, 29.3, 27.4, 18.83; MS: 353 (M+1).

3,7-Dimethyl-12-(nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-1-one (4e): Yield: 81%; m.p.: 134-136 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.50 (d, *J* = 3.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 6.8 Hz,

1H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.99-4.80 (m, 2H), 4.70 (s, 1H), 2.78 (ddd, *J* = 20.3, 17.6, 3.5 Hz, 1H), 2.62 (s, 3H), 2.54 (s, 2H), 2.45 (d, *J* = 12.4 Hz, 1H), 2.23 (d, *J* = 9.6 Hz, 1H), 1.09 (d, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 196.4, 168.9, 153.8, 144.1, 139.5, 139.4, 135.2, 130.6, 126.9, 125.5, 116.4, 108.4, 80.2, 44.4, 35.1, 31.8, 27.8, 20.4, 17.5; MS: *m/z* 339 (M+1).

7-Methyl-12-(nitromethyl)-2,3,4,12-tetrahydro-1*H*-chromeno[2,3-*b*]quinolin-1-one (4f): Yield: 86%; m.p.: 131-133 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-d_6) δ ppm: 8.08 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.45-7.37 (m, 1H), 4.81 (t, *J* = 4.9 Hz, 1H), 4.70 (d, *J* = 5.2 Hz, 2H), 2.92-2.79 (m, 2H), 2.74 (s, 3H), 2.59 (dt, *J* = 16.7, 5.3 Hz, 1H), 2.53-2.43 (m, 1H), 2.18-2.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$-d_6) δ ppm: 170.2, 153.8, 145.1, 139.1, 136.2, 131.2, 127.4, 126.3, 125.5, 115.5, 109.3, 79.4, 36.8, 32.4, 28.2, 20.5, 18.1; MS: *m/z* 325 (M+1).

11-(Nitromethyl)-3,11-dihydrocyclopenta[5,6]pyrano-[2,3-*b*]quinolin-1(2*H*)-one (4g): Yield: 90%; m.p.: 141-143 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.63 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 5.20 (dd, *J* = 13.3, 3.3 Hz, 1H), 5.09 (dd, *J* = 13.3, 3.6 Hz, 1H), 4.71 (s, 1H), 2.95-2.80 (m, 2H), 2.67-2.60 (m, = 29.4 Hz, 1H) ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 201.8, 180.4, 154.9, 144.9, 139.7, 130.9, 127.7, 127.4, 126.8, 126.5, 116.0, 112.4, 77.74, 33.2, 31.4, 25.3; MS: *m/z* 297 (M+1).

6-Methyl-11-(nitromethyl)-3,11-dihydrocyclopenta-[5,6]pyrano[2,3-*b*]quinolin-1(2*H*)-one (4h): Yield: 87%; m.p.: 145-147 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.59 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 5.19 (dd, *J* = 13.3, 3.9 Hz, 1H), 5.08 (dd, *J* = 13.4, 4.0 Hz, 1H), 4.69 (s, 1H), 2.88 (d, *J* = 2.7 Hz, 2H), 2.63 (s, 3H), 2.53 (d, *J* = 4.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 201.9, 180.5, 154.2, 144.0, 140.0, 135.3, 130.8, 126.8, 126.2, 125.5, 115.6, 112.3, 77.8, 33.2, 31.4, 25.4, 17.8; MS: *m/z* 311 (M+1).

12-(Nitromethyl)indeno[2′,1′:5,6]pyrano[2,3-*b*]-quinolin-13(12*H*)-one (4i): Yield: 86%; m.p.: 153-155 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-d_6) δ ppm: 8.19 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.81-7.73 (m, 1H), 7.60-7.44 (m, 4H), 7.40 (td, *J* = 7.5, 1.2 Hz, 1H), 4.98 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.93-4.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$-d_6) δ ppm: 191.8, 171.3, 154.6, 145.9, 139.7, 136.3, 133.2, 131.9, 131.6, 131.3, 128.3, 127.7, 127.4, 127.2, 122.5, 119.7, 115.6, 104.1, 78.2, 32.0; MS: *m/z* 345 (M+1).

7-Methyl-12-(nitromethyl)indeno[2′,1′:5,6]pyrano-[2,3-*b*]quinolin-13(12*H*)-one (4j): Yield: 80%; m.p.: 164-166 ºC; ^{1}H NMR (400 MHz, $CDCl_3$-d_6) δ ppm: 8.15 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.59-7.54 (m, 1H), 7.50-7.44 (m, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 4.96 (dd, *J* = 11.7, 2.8 Hz, 1H), 4.92-4.84 (m, 2H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 191.0, 169.9, 153.8, 144.0, 140.5, 135.8, 135.4, 133.4, 131.2, 131.1, 131.0, 127.0, 126.5 125.6, 121.9, 119.1, 115.8, 105.1, 78.8, 31.4, 17.5; MS: *m/z* 359 (M+1).

5-(Nitromethyl)indeno[2′,1′:5,6]pyrano[2,3-*b*]pyridin-6(5*H*)-one (4k): Yield: 80%; m.p.: 128-130 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.33 (d, *J* = 3.5 Hz, 1H), 8.12 (d, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.51-7.42 (m, 4H), 5.14 (dd, *J* = 12.8, 3.9 Hz, 1H), 5.01 (dd, *J* = 12.7, 3.9 Hz, 1H), 4.72 (s, 1H); ^{3}C NMR (101 MHz, DMSO-d_6) δ ppm: 191.0, 169.7, 156.4, 147.7, 140.1, 135.7, 133.3, 131.1, 131.1, 122.7, 121.8, 118.9, 115.8, 104.9, 78.5, 31.3; MS: *m/z* 295 (M+1).

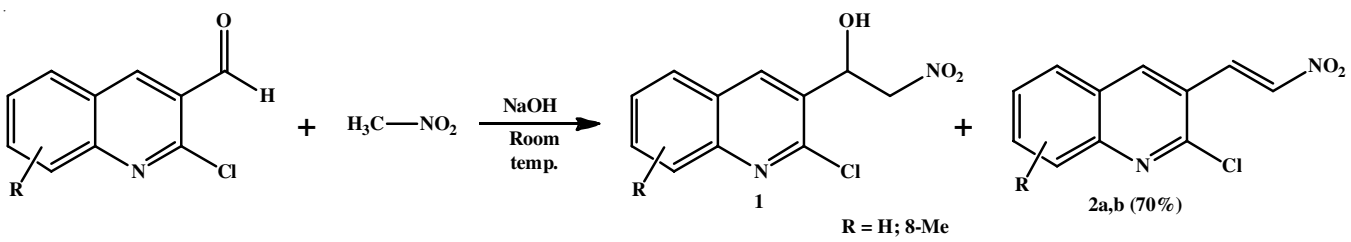
Ethyl 2-methyl-4-(nitromethyl)-4*H*-pyrano[2,3-*b*]-quinoline-3-carboxylate (5a): Yield: 81%; m.p.: 118-121 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.77 (s, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 5.62 (s, 1H), 4.94 (s, 1H), 3.89 (q, *J* = 6.7, 2H), 2.34 (s, 3H), 0.92 (t, *J* = 6.5 Hz, 3H); MS: *m/z* 329 (M+1).

3-Acetoxy- 2-methyl-4-(nitromethyl)-4*H*-pyrano[2,3-*b*]-quinoline (5b): Yield: 78%; m.p.: 122-124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.78 (s, 1H), 8.06 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 5.51 (s, 1H), 4.96 (s, 1H), 2.41 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 192.1, 169.3, 150.4, 145.9(2), 134.2, 130.5, 127.8, 127.4, 127.3(2), 127.2, 114.9, 101.0, 29.2, 15.4; MS: *m/z* 299 (M+1).

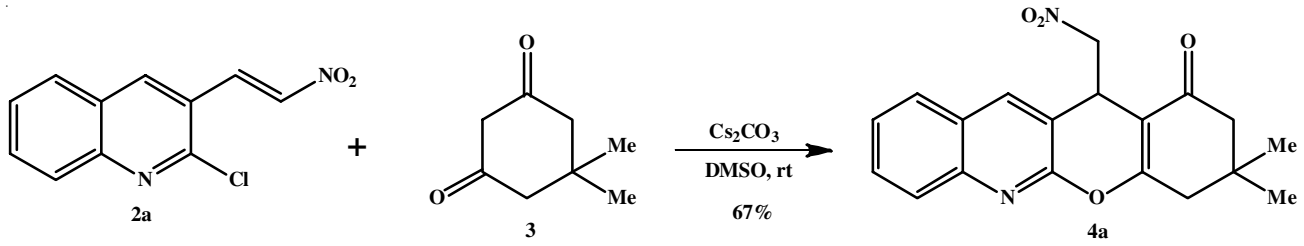
RESULTS AND DISCUSSION

β-Nitrovinylquinolines (2) are the aza-analogues of nitrostyrenes and serve as precursors for the synthesis of chromeno-quinolines, obtained by the reaction of 2-chloro-3-formylquinolines (**Scheme-I**). Reaction of 2-chloro-3-formylquinolines and nitromethane in presence of piperidine or pyrrolidine gave Henry product (**1**) as major. However, the reaction when carried out with NaOH afforded the desired vinylquinoline (**2**) as a major product.

We envisioned that the chromeno-quinolines could be obtained from β-nitrovinylquinolines (**2**) *via* a tandem sequence of Michael addition with 1,3-dicarbonyl compounds and cyclization by intramolecular nucleophilic substitution. In the first attempt, we proceeded with the reaction of 2-chloro-3-(2′-nitro)vinylquinoline (**2**) and dimedone (**3**) in the presence of cesium carbonate at room temperature in DMSO as solvent



Scheme-I: Synthesis of β-nitrovinylquinolines



Scheme-II: Synthesis of chromeno-quinoline **4a**

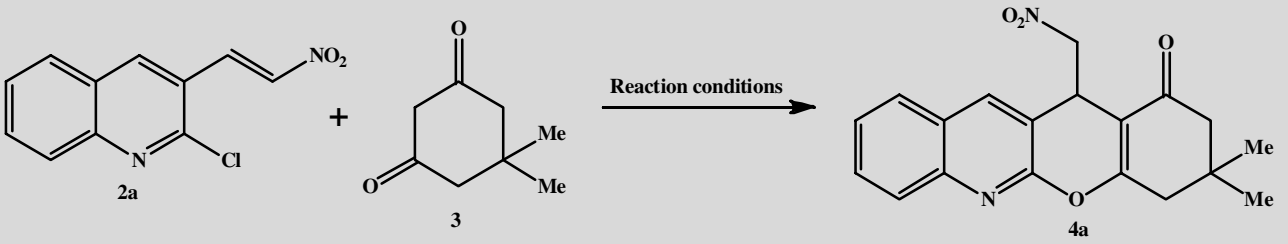
(**Scheme-II**). After 48 h the reaction resulted in 67% conversion to the desired product **4a**. The product was isolated, purified and confirmed by the disappearance of two olefinic protons of vinyl-quinoline (**2**) at δ 8.44, 7.71 and presence of multiplet at δ 4.75 for three protons of -CH_2-NO_2 and C_{12}-H in the ^{1}H NMR spectrum of **4a** and also M+ 1 peak at *m/z* 339 in MS/ESI spectrum.

After establishing the structure of product **4a**, the subsequent emphasize was on the optimization of the reaction conditions for its synthesis. The reaction conditions tried for which, are presented in Table-1. Reaction outcome was almost similar when Cs_2CO_3 (entry 1) was replaced by Na_2CO_3 (entry 2) in subsequent attempt. When the reaction was carried out with NaOMe (entry 3), the reaction time significantly reduced with increase in the yield of product. In the next effort, inorganic bases were replaced by organic, *i.e.* the reaction was performed with DBU (entry 4), the results were much as entry 3. The entry reaction was then explored with *L*-proline since a chiral centre is generated during the reaction, and moreover, small chiral amines [20,21] have gained popularity recently as effective and appealing catalysts for reactions that create C-C bonds. Interestingly the reaction with *L*-proline (entry 5) was found to be quite efficient and resulted in 93% conversion in 2 h but enantioselectivity was not observed. The focus was then shifted towards changing DMSO to a green solvent [22] and the reaction with *L*-proline in water at room temperature and under reflux (entry 6,7), *L*-proline/H_2O in combination with Na_2CO_3, Cs_2CO_3 (entry 8,9) did not take place at all. However, the reaction with addition of $CuCl_2$ to *L*-proline/H_2O in Cs_2CO_3 (entry 10) found to be highly efficient with 94% conversion.

With the optimized conditions established, substrate scope of the reaction was then investigated with various substrates and the results are presented in Table-2. Initially, the synthesis was tried with cyclic 1,3-diones and the reaction proceeded smoo-thly and found to be highly efficient with cyclohexane-1,3-dione derivatives (**3a-c**) and also with pentane-1,3-dione (**3d**), but yields were slightly less with indane-1,3-dione (**3e**). In next variation reaction was attempted with acyclic diones, ethyl acetoacetate and acetylacetone (**3f,g**) which also afforded the corresponding product pyrano-quinolines (**5a,b**). With respect to quinoline part, the reaction progressed well with methyl substituted formyl quinolines and even with pyridine-2-chloro-3-formyl derivative.

Mechanism: The suggested mechanism for the synthesis of chromeno-quinolines (**4**) is presented in **Scheme-III**. Initially *L*-proline forms a complex (**A**) with copper chloride. Complex **A** reacts with dimedone to give intermediate **B**, which then undergoes Michael addition with **2a** followed by intramolecular cyclization with the elimination of HCl giving rise to final product **4a** and regeneration of catalytic complex.

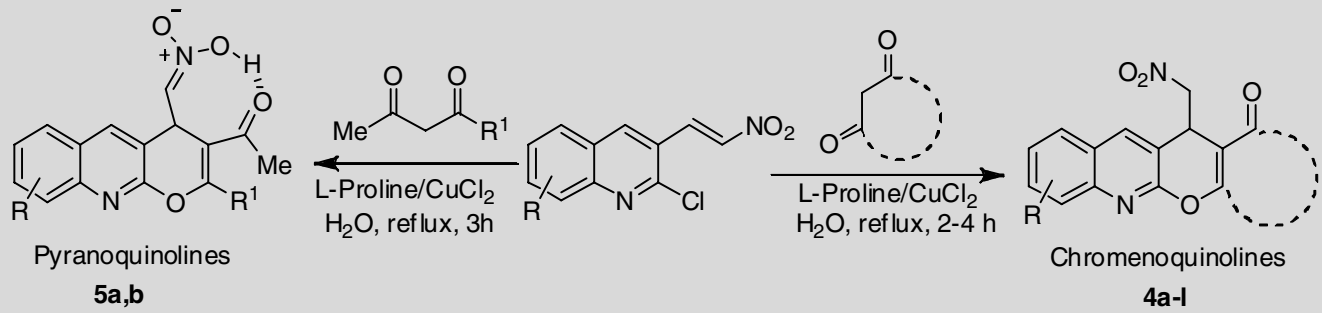
TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF CHROMENO-QUINOLINE (**4a**)

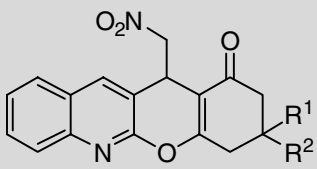


Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	Cs_2CO_3	DMSO	Room temp.	36	67
2	Na_2CO_3	DMSO	Room temp.	36	63
3	NaOMe	DMSO	Room temp.	24	72
4	DBU	DMSO	Room temp.	24	69
5	*L*-Proline	DMSO	Room temp.	2	93
6	*L*-Proline	H_2O	Room temp.	24	NR
7	*L*-Proline	H_2O	Reflux	10	NR
8	*L*-Proline + Na_2CO_3	H_2O	Reflux	10	NR
9	*L*-Proline + Cs_2CO_3	H_2O	Reflux	10	NR
10	*L*-Proline + Cs_2CO_3 + $CuCl_2$	H_2O	Reflux	2	94

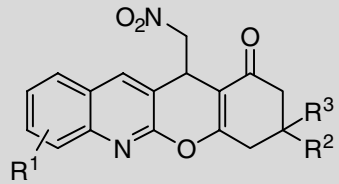
All reactions were performed on 0.5 mmol in 10 mL of solvent and isolated yields are after purification.

TABLE-2
L-PROLINE CATALYZED SYNTHESIS OF CHROMENO-QUINOLINES (**4a-l, 5a,b**) *via* TANDEM APPROACH[a,b]

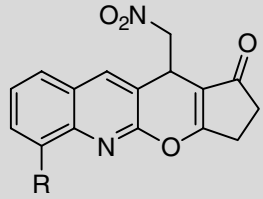




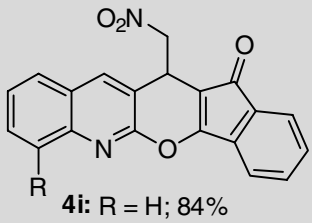
4a: R^1= R^2 = Me; 94%
4b: R^1= H; R^2 = Me; 92%
4c: R^1= R^2 = H; 90%



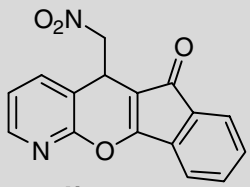
4d: R^1 =8-Me; R^2 = R^3 = Me; 94%
4e: R^1 = 8-Me; R^2= H; R^3 = Me; 93%
4f: R^1 = 8-Me; R^2= R^3 = H; 89%



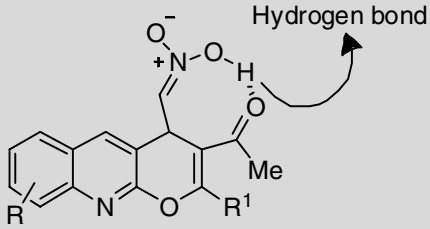
4g: R = H; 90%
4h: R = Me; 86%



4i: R = H; 84%
4j: R = Me: 80%



4k: 80%



5a: R=H; R^1 = OEt; 80%
5b: R=H; R^1 = Me; 78%

Reaction conditions: [a]All reactions were carried out for 2 (0.5 mmol), L-proline (10 mol%), Cu_2Cl_2 (10 mol%), Cs_2CO_3 (1 eq.), H_2O (10 mL). [b]Isolated yields are after purification.

Conclusion

Tandem approach to chromeno/pyrano-quinoline synthesis comprising *L*-proline/Cu(II) catalyzed Michael-addition of acyclic/cyclic1,3-dicarbonyl compounds to β-nitrovinyl-quinolines and intramolecular cyclization is presented. This simple and efficient protocol provides a facile approach for the construction of quinoline containing fused tetra/tricyclic system, an important class of bioactive organic molecules. The significant features of the reaction is that it takes place in aqueous medium, products are obtained in high yields and column chromatography is not required for purification.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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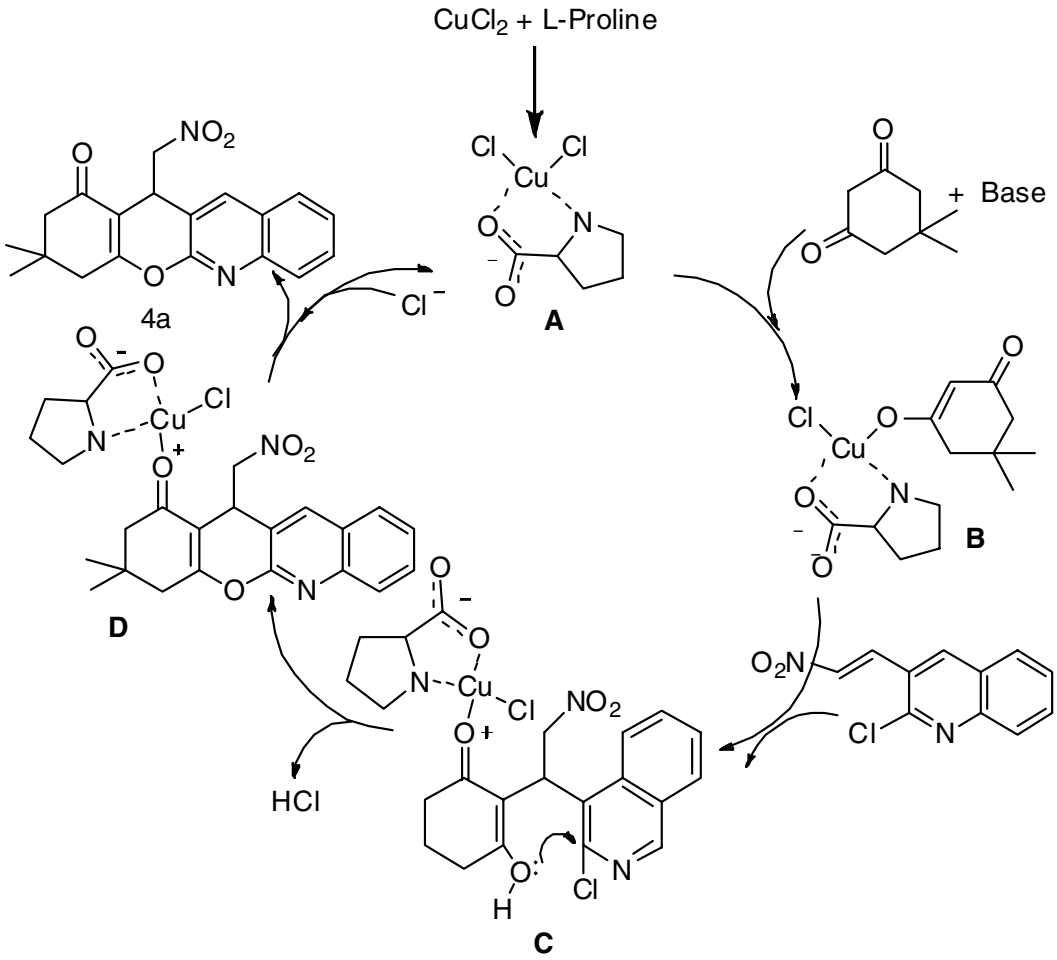

Scheme-III: Plausible reaction mechanism

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