Microwave induced synthesis of a new class of pyrano isoxazoline and isoxazole annulated chromones - an intramolecular nitrile oxide cycloaddition with tethered olefins and alkynes

Jayaprakash Rao Yerrabelli, Shyam Prasad Nuligonda, Sudhakar Mokenapelli, and Prasad Rao Chitneni

Natural Products Laboratory, Department of Chemistry, Osmania University, Hyderabad-500007, Telangana, India
Email: yjpr_19@yahoo.com

Abstract

A variety of new highly substituted 6-6-6-5-membered tetracyclic pyrano isoxazoline/isoxazole annulated chromone derivatives have been synthesized via eco-friendly microwave assisted/ ceric ammonium nitrate (CAN) as an oxidant, intramolecular 1,3-dipolar cycloaddition with in situ generated nitrile oxides from aldoximes of alkene/alkyne tethered chromones. This protocol is practically simple and efficient to construct diverse range of substituted pyrano isoxazoline/isoxazole annulated chromone derivatives and gave higher yields of products in microwave irradiation compared to conventional heating. The structures of all the synthesized compounds were established by IR, NMR and MASS spectral analysis.

Keywords: Chromone aldoximes, nitrile oxides, 1,3-dipolar cycloaddition, pyrano isoxazoline/isoxazole

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Introduction

Chromone heterocyclic frameworks are privileged scaffolds widely occur in the natural products especially in plant kingdom. Chromone derivatives extensively showed diverse biological activities such as anti-inflammatory, anti-viral, antioxidant, anti-tumor, anti-hypertensive and also proved as Tyrosine kinase protein inhibitors. Isoxazolines are found to present in wide range of biologically active compounds. Mainly, chromeno[4,3-c]isoxazolines exhibits anti-psychotic, anti-depressant and anti-anxiety activities. Because of labile N-O group of isoxazoline are the rich source of desired bi-functional groups like 1,3-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles, unsaturated oximes and also versatile intermediates. Additionally, isoxazoles are the five membered nitrogen, oxygen heterocyclics act as lysophosphatidic acid (LPA) antagonists, inhibitors of human rhinovirus-2-replication, insect anti-feedant, anti-tubulin, selective agonists of dopamine D4 receptors, GABA antagonist, COX-2 inhibitory and anti-cancer agents. Isoxazoline and Isoxazole were also applied as dyes, electric insulating oils and high temperature lubricants and also as synthetic precursor of bioactive natural products (Figure 1).

![Biologically active isoxazoline/ isoxazole derivatives.](image)

The intramolecular nitrile oxide 1,3-dipolar cycloaddition is the dominant methodology to construct complex polycyclic rings in a single step reaction with an excellent regio/stereo selectivity. In view of the wide biological activities exhibited by the chromones/isoxazolines/isoxazoles and our interest in developing biologically active heterocyclic ring fused chromone derivatives, we planned for the design and synthesis of novel tetracyclic pyrano isoxazoline/isoxazole annulated chromone derivatives using intramolecular [1,3] dipolar cycloaddition of nitrile oxides. Usually, alkenes and alkynes are the good dipolarophiles for the 1,3-dipolar cycloaddition with nitrile oxides to produce directly bicyclic pyrano isoxazoline/isoxazoles. Herein, we report the synthesis of tetracyclic 6-6-6-5-membered pyrano isoxazoline/isoxazole annulated chromones by tandem intramolecular 1,3-dipolar cycloaddition of in situ generated nitrile oxides from alkene/alkyne tethered chromone aldoximes using conventional as well as microwave induced methods. Microwave induced
organic synthesis is emerged as powerful eco-friendly method in developing diverse range of biologically potential heterocyclic compounds in drug discovery program, because of its significant role in improved yields of products, short reaction time, minimum wastage, maximum atom economy and method to approach green synthesis.  

Results and Discussion

7-hydroxy-8-formyl-2,3-dimethylchromones 1a-b were synthesized using our earlier reported procedure. The key intermediates, alkene appended chromone-8-aldoxime derivatives 2a-h were prepared in one pot by treating the bifunctional hydroxy aldehydes 1a-b with substituted allyl bromides, hydroxylamine hydrochloride, in the presence of sodium acetate in DMF at 70 °C. The allylation and hydroxylamine hydrochloride condensation with aldehyde at one time in a single step smoothly proceeded to furnish products 2a-h in good yields. By the routine method these are prepared in two separate steps, initially allylation at phenolic function followed by condensation of hydroxylamine with aldehyde. A number of oxidants and Lewis catalysts were evaluated using suitable solvents for the in situ generation of nitrile oxide from the aldoxime intermediate 2a (Table-1) followed by dipolar cycloaddition at alkene to afford pyrano isoxazoline annulated chromones 3a. Among the oxidants and catalysts employed, we found to furnish CAN (0.002 mol) mediated intramolecular nitrile oxide addition product 3a in a little higher yield (60%) compared to all other variants. Under these optimized conditions the derivatives 3b-h were prepared from their corresponding substrates (Scheme-1).

Table 1. Optimization reaction conditions for the synthesis of compound 3a using various catalysts/oxidants

| Entry | Catalysts/Oxidants a | Solvent b | Temp (°C) | Time (h) | Yield c (%) |
|-------|----------------------|-----------|-----------|----------|-------------|
| 1     | NaOCl / Et3N (0.002mol) | CH2Cl2   | rt        | 24       | 50          |
| 2     | NaOCl / Et3N (0.002mol) | CH2Cl2   | 40        | 12       | 55          |
| 3     | I2 (10mol %)         | CH2Cl2   | rt        | 10       | 50          |
| 4     | I2 (10mol %)         | THF      | 60        | 10       | 54          |
| 5     | BF3-Et2O (10mol %)   | CH3CN    | 80        | 10       | 55          |
| 6     | CAN (0.002mol)       | CH3CN    | 40        | 6        | 60          |
| 7     | Sc(OTf)3(10mol%)     | CH3CN    | 80        | 10       | 52          |
| 8     | No catalyst          | THF      | 60        | 10       | 10          |
| 9     | No catalyst          | THF      | 80        | 10       | 12          |
| 10    | No catalyst          | CH3CN    | 80        | 10       | 14          |

a catalyst, b solvent used in the reaction and c isolated yields of 3a.

With a view to increase the yields of products 3a-h and to reduce reaction time compare to conventional method, we have performed intramolecular cycloaddition using CAN (0.002 mol) as an oxidizing agent under microwave irradiation by taking substrate 2a as model compound and screened with various solvents. Interestingly in the microwave medium, afforded product 3a in higher yields (90%) in short reaction time in acetonitrile solvent compared to conventional heating (Table-2).
Table 2. Optimization reactions for synthesis compound 3a using CAN (0.002 mol) in conventional and microwave conditions

| Entry | Solvent | Temp (°C) | Time (h) | Yield (%) | Solvent | Temp (°C) | Time (m) | Yield (%) |
|-------|---------|-----------|----------|-----------|---------|-----------|----------|-----------|
| 1     | CH₂Cl₂  | 40        | 6        | 50        | CH₂Cl₂  | 40        | 10       | 70        |
| 2     | THF     | 60        | 6        | 54        | THF     | 60        | 10       | 74        |
| 3     | CH₃CN   | 40        | 6        | 60        | CH₃CN   | 40        | 10       | 90        |
| 4     | DMF     | 80        | 6        | 56        | DMF     | 60        | 10       | 78        |
| 5     | H₂O     | 80        | 6        | 20        | H₂O     | 60        | 10       | 40        |

The increase in temperature and higher oxidant loading did not improve the yield of product 3a. The reaction furnished very low yields of the product 3a under the oxidant free conditions. The formation of low yields of products probably due to aerial oxidation. After the optimization of microwave assisted reaction conditions, several pyrano isoxazoline chromone derivatives 3a-h prepared in higher yields in short time compare to conventional method. (Table 3) All the synthesized compounds structures were established by spectral analysis. In the ¹H NMR(400MHz, CDCl₃) of compound 3a newly formed dihydropyranoisoxazoline signals appeared at δ: 4.75 (m, 2H, H-4), 4.2 (m, 1H, H-3a), 3.9 - 4.1 (m, 2H, H-3) and ¹³C NMR(100MHz, CDCl₃) signals resonated at δ: 154.2(C-12a), 70.5(C-4), 69.2(C-3), 46.8(C-3a).

Scheme 1. Synthesis of pyrano[4,3-c]isoxazoline annulated chromone derivatives (3a-h). Reagents and conditions: (i) (a) Substituted allyl bromides, K₂CO₃, DMF, 70 °C, 2 h; (b) CH₃COONa, NH₂OH.HCl, rt, 1 h; (ii) CAN (20 mol%), CH₃CN, 40 °C, MW, 10 min.
Table 3. Substrate scope and yields of compounds 3a-h using CAN (0.002 mol) in acetonitrile at 40 °C under conventional and microwave conditions

| Entry | Product | Time (h) | Yield (%) | Time (m) | Yield (%) |
|-------|---------|----------|-----------|----------|-----------|
| 1     | 3a      | 6        | 60        | 10       | 89        |
| 2     | 3b      | 6        | 52        | 10       | 94        |
| 3     | 3c      | 6        | 50        | 10       | 92        |
| 4     | 3d      | 6        | 48        | 10       | 88        |
| 5     | 3e      | 6        | 48        | 10       | 88        |
| 6     | 3f      | 6        | 52        | 10       | 90        |
| 7     | 3g      | 6        | 50        | 10       | 90        |
| 8     | 3h      | 6        | 48        | 10       | 87        |

Encouraged by these results, we next planned for the synthesis of diverse bicyclic pyrano isoxazole annulated chromones having high substitution. Similar to the preparation of compounds 2a-h as discussed above, 7-propargyloxychromone-8-aldoximes 4a-f were prepared in one pot by coupling 7-hydroxy-8-formylchromone with propargyl bromide and hydroxyl amine hydrochloride in alkaline sodium acetate in DMF. The intermediates 4a-f were subjected to in situ generated nitrile oxide 1,3-dipolar cycloaddition at alkyne under conventional as well as microwave conditions using optimized CAN (0.002 mol) as oxidant in acetonitrile solvent to afford pyrano isoxazole fused chromone derivatives. The microwave irradiation furnished the products 5a-f in good yields (84-91%) compare to conventional method (Scheme-2). The reaction conditions and yields of products summarized in Table-4. The structures of all the compounds 5a-f confirmed by spectral analysis. The 1H NMR(400MHz, CDCl3) of compound 5a newly formed dihydropyrano isoxazole signals appeared at δ: 8.30 (s, 1H, H-3) 5.40 (s, 2H, H-4), and 13C NMR (100MHz, CDCl3) signals resonated at δ: 153.6(C-12a), 110.2(C-3), 103.9(C-3a), 62.3(C-4).

Scheme 2. Synthesis of pyrano [4,3-c] isoxazole annulated chromone derivatives (5a-f). Reagents and conditions: i) (a) Substituted propargyl bromides, K2CO3, DMF, 70 °C, 2 h; (b) CH3COONa, NH2OH.HCl, rt, 1 h; ii) CAN (20 mol%), CH3CN, 40 °C, MW, 15 min.
Table 4. Substrate scope and yields of compounds 5a-f using CAN (0.002 mol) in acetonitrile at 40 °C under conventional and microwave heating

| Entry | Product | Time (h) | Yield (%) | Time (m) | Yield (%) |
|-------|---------|----------|-----------|----------|-----------|
| 1     | 5a      | 6        | 62        | 15       | 86        |
| 2     | 5b      | 6        | 64        | 15       | 88        |
| 3     | 5c      | 6        | 65        | 15       | 91        |
| 4     | 5d      | 6        | 62        | 15       | 90        |
| 5     | 5e      | 6        | 60        | 15       | 86        |
| 6     | 5f      | 6        | 62        | 15       | 84        |

Conclusions

In conclusion, we developed a simple and efficient protocol for the synthesis of highly substituted 6-6-6-5-membered tetracyclic pyrano isoxazoline/isoxazole annulated chromone derivatives 3a-h and 5a-f from allyloxy and propargyloxy appended chromone aldoxime derivatives 2a-h and 4a-f using ceric ammonium nitrate (CAN) under conventional and microwave assisted, regioselective intramolecular 1,3-dipolar cycloaddition. The key step of synthetic route is the one pot generation of 7-alkyloxy-8-aldoxime chromones. We obtained higher yields of products 3a-h and 5a-f in eco-friendly microwave irradiation compared to conventional heating. We believe that these newly developed chromone based isoxazoline/isoxazole scaffolds will find diverse applications in chemical biology and medicinal chemistry.

Experimental Section

General. Silica gel (60–120 mesh) for column chromatography was purchased from M/s Acme Synthetic Chemicals (Mumbai, India) and pre-coated TLC plates (Silica gel 60F254) were purchased from Merck (Darmstadt, Germany). All the chemicals, reagents and solvents were purchased from M/s SD Fine Chemicals (Mumbai, India) with highest grade of purity. Microwave reactions were performed in a Multi synth series microwave system (Milestone). The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz and TMS used as an internal standard. Chemical shifts relative to TMS as internal standards were given as δ values in ppm. Mass spectra were recorded using electron spray ionization on Waters e2695 Separators module (Waters, Milford, MA, USA) mass spectrometer. IR spectra were recorded on a Fourier transform (FT-IR), USA (Perkin-Elmer model 337) instrument. The melting points were determined on a Barnstead Electro Thermal 9200 Instrument.

General procedure for the synthesis of 2,3-dimethyl-7-O-allylated-8-aldoxime chromones (2a-h)

To the stirred solution of compounds 1a-b (1.0 mmol) and potassium carbonate (0.2 mmol) in DMF (10 mL) allyl bromides (1.2 mmol) were added and the reaction mixture was stirred at 70 °C for 2 h, then reaction mixture was cooled to rt and added sodium acetate (3.63 mmol), Hydroxylamine hydrochloride (1.0 mmol) to the mixture and stirred for 1 h. After completion of reaction pale yellow colour solids appeared which were...
poured in water (20 mL) the solid precipitate was collected by filtration, washed with water and dried at 50 °C to afford 2a-h as white solids with good yields (70-90%)

7-(allyloxy)-2,3-dimethyl-4-oxo-4H-chromene-8-carbaldehyde oxime (2a) mp 202-205 °C, Yield 85%. IR vmax, cm⁻¹: 1650 (C=O), 1685(CO, ketone). ¹H NMR (400 MHz, CDCl₃) δ: 8.30 (s, 1H), 7.72 (d, J 8.8 Hz, 1H), 6.95 (d, J 8.8 Hz, 1H), 6.01 (m, 1H), 5.41 (m, 1H), 5.25 (m, 1H), 4.50-4.80 (m, 2H), 2.43 (s, 3H), 2.21 (s, 3H). ¹³C NMR (100 MHz) δ: 183.0, 158.5, 156.1, 142.2, 133.2, 130.1, 118.0, 116.9, 116.1, 113.5, 112.2, 107.5, 70.2, 14.2, 9.0. ESI-HRMS m/z calcd for C₁₅H₁₅NO₄ 274.1079 [M+H]^+, found 274.1034.

General procedure for the synthesis of 9,10-dimethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-ones 3(a-h)

Conventional. To the stirred solution of compound 2a-h (1.0 mmol) in acetonitrile (10 mL) was added ceric ammonium nitrate (CAN) (2 mmol) at 0 °C then the reaction mixture was stirred for 6 h at 40 °C. The reaction progress was monitored by TLC, after completion of the reaction, 20 mL of water was added and extracted with chloroform and washed with brine solution. The crude material was purified by column chromatography in chloroform/methanol (9:1) to give products 3a-h.

Microwave. To the stirred solution of compounds 2a-h (1.0 mmol) in acetonitrile (10 mL) was added ceric ammonium nitrate (CAN) (2 mmol) at 0 °C then the reaction mixture was placed in a quartz tube inserted into a screw capped Teflon vial and subjected to microwave irradiation (200 W) for 10 min, at 40 °C after completion of the reaction (monitored by TLC), 50 mL of cold water was added to reaction mixture and extracted with chloroform, washed with brine solution. The crude sample purified by column chromatography eluting with chloroform/methanol (9:1) in excellent yields.

9,10-Dimethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3a) mp 219-222 °C, Yield 89%. IR spectrum, ν, cm⁻¹: 1630 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, J 8.65 Hz, 1H), 6.95 (d, J 8.8 Hz, 1H), 4.75 (m, 2H), 4.20 (m, 1H), 3.90 - 4.10 (m, 2H), 2.45 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 176.9, 162.3, 159.5, 154.2, 149.8, 129.5, 118.4, 117.4, 114.5, 102.3, 70.5, 69.2, 46.8, 18.3, 10.1. ESI-HRMS m/z calcd for C₁₃H₁₃NO₄ 272.0923 [M+H]^+, found 272.0914.

3,9,10-Trimethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3b) mp 231-233 °C, Yield 94%. IR spectrum, ν, cm⁻¹: 1632 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, J 8.5 Hz, 1H), 6.95 (d, J 8.8 Hz, 1H), 4.40 (m, 1H), 4.70 (m, 1H), 4.20 (m, 1H), 3.60 (m, 1H), 2.45 (s, 3H), 2.05 (s, 3H), 1.60 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 181.0, 161.6, 160.2, 155.6, 153.1, 130.9, 126.2, 118.5, 115.0, 108.5, 73.0, 70.6, 44.2, 21.5, 18.3, 10.2. ESI-HRMS m/z calcd for C₁₆H₁₅NO₄ 286.1079 [M+H]^+, found 286.1070.

3,3,9,10-Tetramethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3c) mp 213-216 °C, Yield 92%. IR spectrum, ν, cm⁻¹: 1630 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, J 8.5 Hz, 1H), 6.95 (d, J 8.5 Hz, 1H), 4.60 (dd, J 1.0, 8.5 Hz, 1H), 4.15 (dd, J 1.0, 8.5 Hz, 1H), 3.50 (dd, J 1.0, 8.5 Hz, 1H), 2.50 (s, 3H), 2.05 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 180.0, 164.8, 162.6, 155.1, 130.8, 125.8, 120.4, 119.5, 115.6, 111.2, 71.0, 41.3, 25.5, 25.1, 18.6, 10.0, 8.0. ESI-HRMS m/z calcd for C₁₆H₁₅NO₄ 300.1236 [M+H]^+, found 300.1230.

9,10-Dimethyl-3-phenyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3d) mp 218-221 °C, Yield 88%. IR spectrum, ν, cm⁻¹: 1626 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (d, J 8.8 Hz, 1H), 7.40-7.60 (m, 6H), 6.95 (d, J 8.6 Hz, 1H), 5.30 (d, J 8.8 Hz, 1H), 4.85 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 2.50 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.1, 165.6, 163.2, 160.8, 156.3, 155.0, 140.1, 132.5, 130.4, 129.1, 128.5, 127.8, 126.6, 125.8, 120.4, 119.6, 113.8, 85.6, 72.1, 41.6, 18.3, 10.2. ESI-HRMS m/z calcd for C₂₁H₁₇NO₄ 348.1236 [M+H]^+, found 348.1235.
6-Chloro-9,10-dimethyl-3a,4-dihydropyran[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3e) mp 236-239 °C, Yield 88%. IR spectrum, ν, cm⁻¹: 1621 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 2.05 (s, 3H), 2.45 (s, 3H), 3.90 - 4.10 (m, 2H), 4.25 (m, 1H), 4.75 (m, 1H), 4.95 (m, 1H), 8.25 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 10.2, 18.0, 46.6, 69.5, 70.4, 102.8, 117.6, 118.4, 122.5, 125.3, 149.3, 154.2, 159.8, 162.4, 176.8. ESI-MS: m/z 306 [M+H]+.

6-Chloro-3,9,10-trimethyl-3a,4-dihydropyran[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3f) mp 240-242 °C, Yield 90%. IR spectrum, ν, cm⁻¹: 1629 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.25 (s, 1H), 4.70 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.60 (m, 1H), 2.45 (s, 3H), 2.05 (s, 3H), 1.60 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 180.1, 163.8, 160.5, 156.1, 155.3, 131.3, 125.6, 122.5, 115.8, 73.6, 70.8, 44.6, 21.2, 18.9, 10.9. ESI-MS: m/z 320 [M+H]+.

6-Chloro-3,3,9,10-tetramethyl-3a,4-dihydropyran[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3g) mp 231-233 °C, Yield 90%. IR spectrum, ν, cm⁻¹: 1626 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.25 (s, 1H), 4.60 (dd, J 1.5, 8.5 Hz, 1H), 4.15 (dd, J 1.0, 8.5 Hz, 1H), 3.50 (dd, J 1.0, 8.5 Hz, 1H), 2.50 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.6, 163.7, 161.1, 156.3, 129.4, 129.1, 125.5, 118.6, 114.1, 110.0, 84.3, 70.4, 40.3, 25.5, 25.1, 18.8, 10.2. C₁₇H₁₆ClNO₄. ESI-HRMS m/z calcd for 333.0846 [M+H]+, found 333.0760.

6-Chloro-9,10-dimethyl-3-phenyl-3a,4-dihydropyran[2',3':5,6]chromeno[4,3-c]isoxazol-8(3H)-one (3h) mp 218-221 °C, Yield 87%. IR spectrum, ν, cm⁻¹: 1635 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.25 (s, 1H), 7.40 -7.60 (m, 5H), 4.85 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 2.50 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 180.0, 164.6, 163.7, 162.3, 158.2, 157.2, 142.1, 137.8, 134.5, 132.6, 130.8, 128.4, 125.8, 124.3, 124.0, 122.6, 112.1, 87.3, 70.8, 40.2, 18.5, 10.6. ESI-MS: m/z 382 [M+H]+.

General procedure for the synthesis 9,10-dimethyl-7-O-propargylated-8-aldoxime chromones (4a-f)
Propargyl bromides (1.2 mmol) were added to the stirred solution of compound 1a-b (1.0 mmol) and potassium carbonate (0.2 mmol) in DMF (10 mL) and the reaction mixture was stirred at 70 °C for 2 h, after completion of the reaction indicated by TLC, the reaction mixture was cooled to RT then Sodium acetate (1.0 mmol) and Hydroxylamine hydrochloride (1.0 mmol) was added to the reaction mixture and stirred for 1 h. After completion of reaction pale yellow colour solid was appeared which was poured in water (20 mL), the solid precipitate was collected by filtration, washed with water and dried at 50 °C to afford 4a-f as white solids with good yields (75-91%).

2,3-Dimethyl-4-oxo-7-(prop-2-yl-1-oxo)-4H-chromene-8-carbaldehyde oxime (4a) mp 206-210 °C, Yield 85%. IR spectrum, ν, cm⁻¹: 1655 (C=N). ¹H NMR (400 MHz, CDCl₃) δ: 8.31 (s, 1H), 7.75 (d, J 8.7 Hz, 1H), 6.80 (d, J 8.7 Hz, 1H), 4.68 (s, 1H), 3.32 (s, 1H), 2.42 (s, 3H), 2.20 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 182.5, 166.5, 158.5, 156.3, 142.5, 130.1, 116.5, 113.8, 112.4, 107.5, 78.9, 76.2, 56.5, 14.5, 8.9. ESI-MS HRMS m/z calcd for C₁₅H₁₃NO₄ 272.0923 [M+H]+, found 272.0878.

General procedure for the Synthesis of 9,10-dimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-ones 5(a-f)

Conventional. To the stirred solution of compound 4a-f (1 mmol) in acetonitrile (10 mL) was added ceric ammonium nitrate (CAN) (2 mmol) at 0 °C then the reaction mixture was stirred for 6 h at 40 °C. The reaction progress was monitored by TLC, after completion of the reaction; 20 mL of water was added to reaction mixture to get solid precipitate it was collected by filtration, washed with water and dried at 50 °C to afford final product 5a-f as white solid with good yields.

Microwave. To the stirred solutions of compounds 4a-f (1.0 mmol) in acetonitrile (10 mL) was added ceric ammonium nitrate (CAN) (2 mmol) at 0 °C then the reaction mixture was placed in a quartz tube inserted into a screw capped Teflon vial and subjected to microwave irradiation (200 W) for 15 min the progress of reaction
monitored by TLC, after completion of the reaction, 50 mL of cold water mixture was added to reaction mixture. The crude sample purified through column chromatography (hexane/ethyl acetate 4:1) to yield products 5a-f (white solids).

9,10-Dimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5a) mp 229-231 °C, Yield 86%. IR spectrum, ν, cm⁻¹: 1636 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.30 (s, 1H), 8.20 (d, J 8.8 Hz, 1H), 7.00 (d, J 8.8 Hz, 1H), 5.40 (s, 2H), 2.55 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 176.9, 162.5, 159.6, 153.6, 151.8, 150.2, 129.6, 118.8, 117.6, 115.4, 110.2, 103.9, 62.3, 18.5, 10.4. ESI-HRMS m/z calcld for C₁₅H₁₅NO₄ 270.0766 [M+H]+, found 270.0757.

3,9,10-Trimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5b) mp 238-235 °C, Yield 88%. IR spectrum, ν, cm⁻¹: 1626 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.20 (d, J 8.8 Hz, 1H), 7.00 (d, J 8.8 Hz, 1H), 5.40 (s, 2H), 2.75 (s, 3H), 2.55 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 178.8, 162.6, 160.2, 155.6, 153.7, 152.9, 130.5, 120.3, 117.8, 116.5, 111.4, 102.6, 61.2, 18.5, 14.3, 10.6. ESI-MS: m/z 284 [M+H]+

3-Ethyl-9,10-dimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5c) mp 209-212 °C, Yield 91%. IR spectrum, ν, cm⁻¹: 1622 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 1.12 (t, J 7.5 Hz, 3H), 2.05 (s, 3H), 2.25 (q, J 7.5 Hz, 2H), 2.55 (s, 3H), 4.90 (s, 2H), 7.20 (d, J 8.8 Hz, 1H), 8.41 (d, J 8.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 180.1, 175.4, 160.5, 158.2, 156.8, 155.2, 132.6, 130.3, 129.6, 120.6, 118.6, 114.5, 65.6, 23.5, 20.3, 18.8, 10.2. ESI-HRMS m/z calcld for C₁₇H₁₇NO₄ 298.1079 [M+H]+, found 298.1070

6-chloro-9,10-dimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5d) mp 249-251 °C, Yield 90%. IR spectrum, ν, cm⁻¹: 1630 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.30 (s, 1H), 8.20 (s, 1H), 5.40 (s, 2H), 2.55 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 179.1, 162.8, 160.6, 155.8, 152.6, 151.2, 130.9, 125.4, 120.8, 117.6, 111.2, 100.8, 62.3, 18.2, 9.9. ESI-MS: m/z 304 [M+H]+

6-chloro-3,9,10-trimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5e) mp 248-249 °C, Yield 86%. IR spectrum, ν, cm⁻¹: 1628 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.20 (s, 1H), 7.00 (d, J 8.5 Hz, 1H), 5.40 (s, 2H), 2.75 (s, 3H), 2.55 (s, 3H), 2.05 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 176.8, 162.5, 159.2, 153.6, 151.2, 150.3, 129.4, 118.6, 117.2, 115.0, 110.1, 103.9, 62.3, 18.4, 14.3, 10.9. ESI-MS: m/z 318 [M+H]+

6-chloro-3-ethyl-9,10-dimethylpyrano[2',3':5,6]chromeno[4,3-c]isoxazol-8(4H)-one (5f) mp 220-221 °C, Yield 84%. IR spectrum, ν, cm⁻¹: 1626 (C=O). ¹H NMR (400 MHz, CDCl₃) δ: 8.24 (s, 1H), 7.20 (d, J 7.8 Hz, 1H), 4.90 (s, 2H), 2.55 (s, 3H), 2.25 (q, J 7.2 Hz, 2H), 2.05 (s, 3H), 1.12 (t, J 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ: 10.0, 18.2, 20.1, 25.3, 65.8, 120.0, 122.3, 125.4, 130.2, 132.5, 135.4, 154.1, 155.6, 158.6, 165.1, 170.1, 180.4. ESI-MS: m/z 332 [M+H]+

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Supplementary Material

The experimental procedures and IR, ¹H NMR and ¹³C NMR spectra for compounds 3a-d, 3g, 5a and 5c associated with this article are available as supplementary data in the online version of the text.
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