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

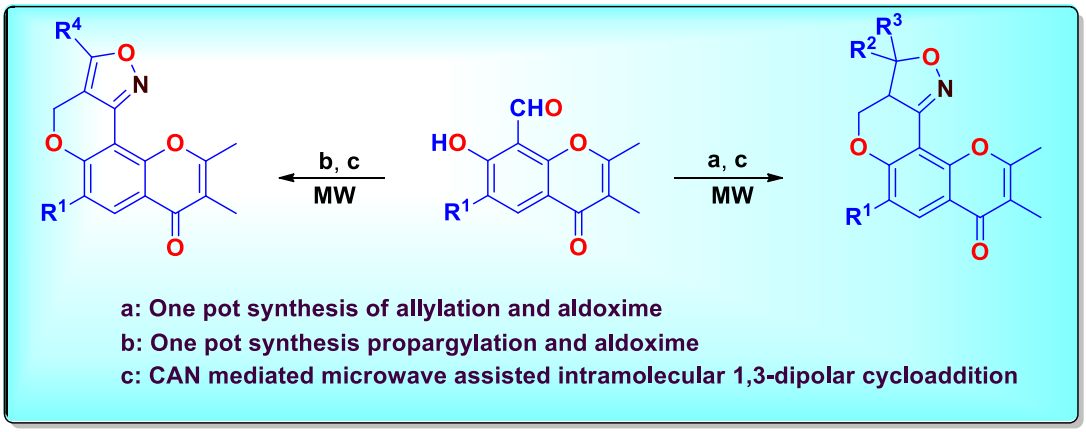
Jayaprakash Rao Yerrabelly,[*a] Shyam Prasad Nuligonda,[a] Sudhakar Mokenapelli,[a] and Prasad Rao Chitneni[a]

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

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy
Dates to be inserted by editorial office

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

Introduction

Chromone heterocyclic frameworks are privileged scaffolds widely occur in the natural products especially in plant kingdom.[1,2] Chromone derivatives extensively showed diverse biological activities[3-8] 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[9] 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[10] 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,[11] inhibitors of human rhinovirus-2-replication,[12] insect anti-feedant,[13] anti-tubulin,[14] selective agonists of dopamine D4 receptors,[15] GABA antagonist,[16] COX-2 inhibitory[17,18] and anti-cancer agents.[19-21] Isoxazoline and Isoxazole were also applied as dyes, electric insulating oils and high temperature lubricants[22, 23] and also as synthetic precursor of bioactive natural products[24](Figure 1).

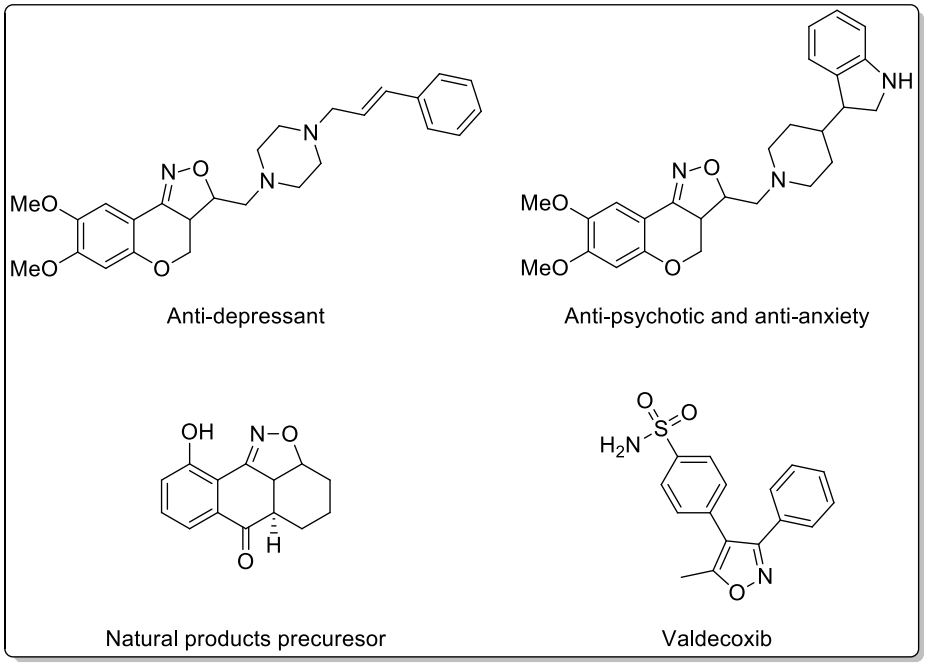


Figure 1. Biologically active isoxazoline/ isoxazole derivatives

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.[25-29] 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 nitrileoxides. 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.[30]

Results and Discussion

7-hydroxy-8-formyl-2,3-dimethylchromones **1a-b** were synthesized using our earlier reported procedure.[31] 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 ^{o}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 hydrochloride 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 (^{o}C)	Time (h)	Yield[c] (%)
1	NaOCl / Et_3N (0.002mol)	CH_2Cl_2	rt	24	50
2	NaOCl / Et_3N (0.002mol)	CH_2Cl_2	40	12	55
3	I_2 (10mol %)	CH_2Cl_2	rt	10	50
4	I_2 (10mol %)	THF	60	10	54
5	BF_3-Et_2O (10mol %)	CH_3CN	80	10	55
6	**CAN (**0.002mol**)**	CH_3CN	**40**	**6**	**60**
7	$Sc(OTf)_3$(10mol%)	CH_3CN	80	10	52
8	No catalyst	THF	60	10	10
9	No catalyst	THF	80	10	12
10	No catalyst	CH_3CN	80	10	14

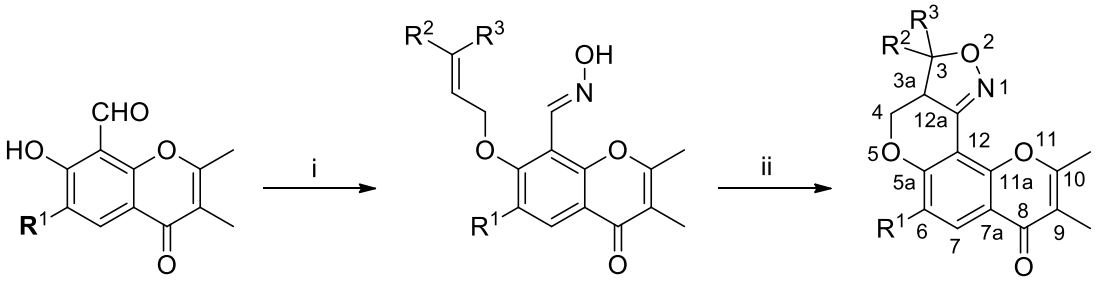
[a]catalyst, [b]solvent used in the reaction and [c]isolated yields of **3a**.

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.

	Conventional				Microwave			
Entry	**Solvent**	**Temp (^{o}C)**	**Time(h)**	**Yield (%)**	**Solvent**	**Temp (^{o}C)**	**Time(m)**	**Yield (%)**
1	CH_2Cl_2	40	6	50	CH_2Cl_2	40	10	70
2	THF	60	6	54	THF	60	10	74
3	CH_3CN	40	**6**	60	**CH_3CN**	**40**	**10**	**90**
4	DMF	80	6	56	DMF	60	10	78
5	H_2O	80	6	20	H_2O	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 aireal 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 ^{1}H NMR(400MHz, $CDCl_3$) 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 ^{13}C NMR(100MHz, $CDCl_3$) signals resonated at δ: 154.2(C-12a), 70.5(C-4), 69.2(C-3), 46.8(C-3a).



1(**a-b**) **2**(**a-h**) **3**(**a-h**)

1a; R^1 = H
2b; R^1 = Cl

2a; **3a**; R^1 = H, R^2 = H, R^3 = H
2b; **3b**; R^1 = H, R^2 = CH_3, R^3 = H
2c; **3c**; R^1 = H, R^2 = CH_3, R^3 = CH_3
2d; **3d**; R^1 = H, R^2 = Ph, R^3 = H

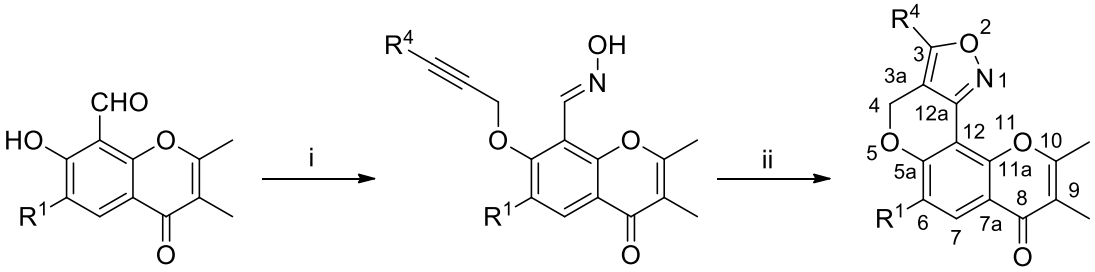
2e; **3e**; R^1 = Cl, R^2 = H, R^3 =H
2f; **3f**; R^1 = Cl, R^2 = CH_3, R^3 =H
2g; **3g**; R^1 = Cl, R^2 = CH_3, R^3 =CH_3
2h; **3h**; R^1 = Cl, R^2 = Ph, R^3 =H

Scheme1. Synthesis of pyrano[4,3-*c*]isaxazoline annulated chromone derivatives (**3a-h**). Reagents and conditions: (i) (a) Substituted allyl bromides, K_2CO_3, DMF, 70 ^{o}C, 2 h; (b) CH_3COONa, $NH_2OH.HCl$, rt, 1 h; (ii) CAN (20 mol%), CH_3CN, 40 ^{o}C, MW, 10 min.

Table 3. Substrate scope and yields of compounds **3a-h** using CAN (0.002 mol) in acetonitrile at 40 ^{o}C under conventional and microwave conditions

		Conventional		Microwave	
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 ^{1}H NMR(400MHz, $CDCl_3$) of compound **5a** newly formed dihydropyrano isoxazole signals appeared at δ: 8.30 (s, 1H, H-3) 5.40 (s, 2H, H-4), and ^{13}C NMR (100MHz, $CDCl_3$) signals resonated at δ: 153.6(C-12a), 110.2(C-3), 103.9(C-3a), 62.3(C-4).



1(**a-b**) **4**(**a-f**) **5**(**a-f**)

1a; R^1 = H
2b; R^1 = Cl

4a; **5a**; R^1 = H, R^4 = H
4b; **5b**; R^1 = H, R^4 = CH_3
4c; **5c**; R^1 = H, R^4 = C_2H_5

4d; **5d**; R^1 = Cl, R^4 = H
4e; **5e**; R^1 = Cl, R^4 = CH_3
4f; **5f**; R^1 = Cl, R^4 = C_2H_5

Scheme 2. Synthesis of pyrano [4,3-*c*] isoxazole annulated chromone derivatives (**5a-f**). Reagents and conditions: i) (a) Substituted propargyl bromides, K_2CO_3, DMF, 70 ^{o}C, 2 h; (b) CH_3COONa, $NH_2OH.HCl$, rt, 1 h; ii) CAN (20 mol%), CH_3CN, 40 ^{o}C, MW, 15 min.

Table 4. Substrate scope and yields of compounds **5a-f** using CAN (0.002 mol) in acetonitrile at 40 ^{o}C under conventional and microwave heating

		Conventional		Microwave	
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 ^{o}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 ^{o}C to afford **2a-h** as white solids with good yields (70-90%).

7-(allyloxy)-2,3-dimethyl-4-oxo-4*H*-chromene-8-carbaldehyde oxime (2a) mp 202-205 ^{o}C, Yield 85%. IR vmax, cm^{-1}: 1650 (C=N), 1685(CO, ketone). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C 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 $C_{15}H_{15}NO_4$ 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(3*H*)-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 ^{o}C then the reaction mixture was stirred for 6 h at 40 ^{o}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 ^{o}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 ºC, after completion of the reaction(monitored by TLC), 50 mL of cold water mixture 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-dihydropyran[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3a) mp 219-222 ^{o}C, Yield 89%. IR spectrum, ν, cm^{-1}: 1630 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{13}NO_4$. 272.0923 $[M+H]^+$, found 272.0914.

3,9,10-Trimethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3b) mp 231-233 ^{o}C, Yield 94%. IR spectrum, ν, cm^{-1}: 1632 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{15}NO_4$ 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(3*H*)-one (3c) mp 213-216 ^{o}C, Yield 92%. IR spectrum, ν, cm^{-1}: 1630 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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, 8.5Hz, 1H), 2.50 (s, 3H), 2.05 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{17}NO_4$ 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(3*H*)-one (3d) mp 218-221 ^{o}C, Yield 88%. IR spectrum, ν, cm^{-1}: 1626 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{17}NO_4$ 348.1236 $[M+H]^+$, found 348.1235.

6-Chloro-9,10-dimethyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3e) mp 236-239 ^{o}C, Yield 88%. IR spectrum, ν, cm^{-1}: 1621 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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-dihydropyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3f) mp 240-242 ^{o}C, Yield 90%. IR spectrum, ν, cm^{-1}: 1629 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.1, 163.8, 160.5, 156.1, 155.3, 131.3, 125.6, 122.5, 115.8, 108.4, 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-dihydropyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3g) mp 231-233 ^{o}C, Yield 90%. IR spectrum, ν, cm^{-1}: 1626 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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), 1.65 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.6, 163.7, 161.1, 156.3, 129.4, 126.3, 125.5, 118.6, 114.1, 110.0, 84.3, 70.4, 40.3, 25.5, 25.1, 18.8, 10.2. $C_{17}H_{16}ClNO_4$. ESI-HRMS m/z calcd for 333.0846 $[M+H]^+$,found 333.0760.

6-Chloro-9,10-dimethyl-3-phenyl-3a,4-dihydropyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(3*H*)-one (3h) mp 218-221 ^{o}C, Yield 87%. IR spectrum, ν, cm^{-1}: 1635 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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, 120.4, 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 ^{o}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 ^{o}C to afford **4a-f** as white solids with good yields (75-91%).

2,3-Dimethyl-4-oxo-7-(prop-2-yl-1-yloxy)-4*H*-chromene-8-carbaldehyde oxime (4a) mp 206-210 ^{o}C, Yield 85%. IR spectrum, ν, cm^{-1}: 1655 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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-HRMS m/z calcd for $C_{15}H_{13}NO_4$ 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(4*H*)-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 ^{o}C then the reaction mixture was stirred for 6 h at 40 ^{o}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 afforded final product **5a-f** as white solid with good yields.

Microwave. To the stirred solution of compounds **4a-f** (1.0 mmol) in acetonitrile (10 mL) was added ceric ammonium nitrate (CAN) (2 mmol) at 0 ^{o}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 **5 a-f** (white solids).

9,10-Dimethylpyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(4*H*)-one (5a) mp 229-231 ^{o}C, Yield 86%. IR spectrum, ν, cm^{-1}: 1636 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{15}H_{11}NO_4$ 270.0766 $[M+H]^+$, found 270.0757.

3,9,10-Trimethylpyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(4*H*)-one (5b) mp 238-235 ^{o}C, Yield 88%. IR spectrum, ν, cm^{-1}: 1626 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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(4*H*)-one (5c) mp 209-212 ^{o}C, Yield 91%. IR spectrum, ν, cm^{-1}: 1622 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{17}H_{15}NO_4$ 298.1079 $[M+H]^+$, found 298.1070

6-chloro-9,10-dimethylpyrano[2',3':5,6]chromeno[4,3-*c*]isoxazol-8(4*H*)-one (5d) mp 249-251 ^{o}C, Yield 90% . IR spectrum, ν, cm^{-1}: 1630 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 8.20 (s, 1H), 5.40 (s, 2H), 2.55 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 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(4*H*)-one (5e) mp 248-249 ^{o}C, Yield 86%. IR spectrum, ν, cm^{-1}: 1628 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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(4*H*)-one (5f) mp 220-221 ^{o}C, Yield 84%. IR spectrum, ν, cm^{-1}: 1626 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $[M+H]^+$.

Acknowledgements

SPN thanks to University Grants Commission (UGC), New Delhi, India for provided senior research fellowship and authors are thankful to Department of Chemistry, Central Facilities for Research and Development (CFRD), Osmania University, Hyderabad, India for providing Laboratory and analysis facilities.

Supplementary Material

The experimental procedures and IR, ^{1}H NMR and ^{13}C NMR spectra associated with this article are available as supplementary data.

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