Synthesis and characterization of a new chromanoisoxazole

Y L N Murthy¹*, Rani Nanda¹, K Ravi Kumar² & G Y S K Swamy²

¹Dept of Organic Chemistry, Andhra University, Visakhapatnam
²Crystallography Division, Indian Institute of Chemical Technology, Hyderabad 500 007

E-mail- murthyyln@yahoo.co.in

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The synthesis of a new chromanoisoxazole 4 has been reported. Acylation of resorcinol using anhyd. ZnCl₂ and gl. acetic acid affords resacetophenone, which on nuclear prenylation with isoprene/PPA/xylene gives chroman 2. Compound 2 on treatment with p-chlorobenzaldehyde/ethanol/KOH yields a chalcone 3. The product 3 on further treatment with hydroxylamine hydrochloride results in the formation of the chromanoisoxazole 4. The structure of 4 has been characterized by spectroscopic and crystallographic techniques.

Keywords: Chromanoisoxazoles, X-ray crystallographic studies.

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The synthesis of a chromanoisoxazole 4 from chalcone employing the Scheme I and its X-ray crystallographic studies is reported. Resorcinol was acylated using anhyd. ZnCl₂ and gla. acetic acid to give resacetophenone. Resacetophenone was subjected to nuclear prenylation to give chroman 2. To a mixture of resacetophenone, xylene and PPA, isoprene in xylene was added dropwise with stirring for 8 hr. The mixture was stirred for a further 48 hr at room temperature, which after usual work-up and purification using column chromatography furnished pure chroman 2.

It was reported earlier that only one chroman ring was formed. In this paper we report the formation of double chroman 2 in which isoprenylation occurs on both the -OH groups of resacetophenone.

Chroman 2 thus formed was then condensed with p-chlorobenzaldehyde in the presence of alcoholic KOH and stirred for 72 hr at room temperature. This after usual work up and purification by column chromatography furnished the pure chalcone 3. Purity of the chalcone obtained was checked by HPLC, and found to be above 99%.

The chalcone thus obtained was condensed with hydroxylamine hydrochloride in the presence of KOH/C₂H₅OH. After usual work up and purification by column chromatography, the title compound, 4 was isolated. It was further crystallized from methanol, which furnished crystalline product. The compound showed purity of 100% as evidenced by HPLC data. The IUPAC nomenclature of the compound 4 is 3-(4'-chlorophenyl)-5-(3'',4'',9'',10''-tetrahydro-2'',2'',8'',8''-tetramethyl-2''H,8''H-dipyranyl benzo [1,2-b:3,4-b'] ) isoxazole.

The title compound showed absorption spectrum at 324.4 nm (CH₃CN). Similarly the fluorescence emission maximum was found to be 404 nm in CH₃CN.

Literature search revealed that Battaglia et al. had reported the ¹H NMR spectral data of 3, 5-disubstituted isoxazoles where in it was reported that the chemical shifts of the C₄-H were unaffected by the presence of substituted phenyl group at position C-3. On the other hand if the substitution on the phenyl is at C-5 position the chemical shift of C-4 H was observed at δ 6.7-7.05. In the ¹H NMR it was reported that the C₄-H, that appeared at δ 6.92 irrespective of aryl substitution. The gem dimethyls appeared at δ 1.3 and 1.4. The structure was also confirmed by elemental analysis. The ¹³C NMR spectrum showed characteristic chemical shifts δ at C₃ at (163.5), C₄ (98.9) and C₅ (164.9) which were in good agreement with the reported values for similar structures. Further confirmation of structure was done using mass spectral data which showed the molecular ion (m/z) at 423 (5%) and the other fragments as expected.

The IR spectra of isoxazoles of the compound showed characteristic ring stretching vibrations at 1600-1300 cm⁻¹ and 1300-1200 cm⁻¹. In the ¹H NMR of isoxazole 4, the C₄-H appeared at δ 6.92 irrespective of 3-aryl substitution, confirming the structure of the compound 4.
**X-ray crystallographic studies of the synthesized chromanoisoxazole.** The isoxazole ring is planar (maximum deviation of 0.002 Å from the least-squares plane). The two dimethyl-pyrano rings acquired half-chair conformation with their atoms C14 and C15 and C21 and C24 deviate -0.3691 and 0.2754 Å and -0.3105 and 0.3393 Å from their least-squares planes. The asymmetric parameters are $\Delta C_2$ [C14, C15] = 1.974 and $\Delta C_2$ [C21, C24] = 7.48 (Duax & Norton 1975). The crystal is stabilized by C-H…O hydrogen bonding interactions.

An ORTEP diagram of 4 with atomic numbering scheme is presented in Figure 1.

**Crystal data:** C$_{25}$ H$_{26}$ Cl N O$_3$, Mr = 423.92, Monoclinic, Space group $P2_1/c$, $a$=9.0053(8), $b$=14.4702(13), $c$=17.5304(15) Å, $\beta$=101.22(2), $T$=293K, $Z$=4, reflections measured = 13674, unique = 4967. F (000) =896, R=0.0625. Refinement method was full-matrix least-squares on $F^2$, S=1.041. CCDC-247787 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving. html. The X-ray crystal data parameters are presented in Table 1.

**Procedure.** Melting points are uncorrected. IR spectra were recorded on Perkin-Elmer 841 Infra Red spectrometer and Thermo Nicolet FT IR spectrometer. $^1$H NMR spectra were taken on a Perkin-Elmer R-32, 90 MHz or JEOL-JNM Ex-90, 90 MHz using TMS as internal reference. All the solvents were of analytical grade and were distilled before use. The HPLC was recorded using Shimadzu LC 6A with Shimpack silica gel column. Mobile phase used was HPLC grade acetonitrile and flow rate was 1.0 mL/min. The UV absorption maximum was recorded on a Unichem-540 UV-Visible spectrometer and the fluorescence studies were carried out on a Shimadzu, spectrofluorophotometer RF-540.
General synthesis of chromanoisoxazole. A mixture of chalcone (1 mmole), hydroxylamine hydrochloride (600 mg, 1 mmole), and KOH (800 mg) in ethanol was refluxed for 3-5 hr. The reaction mixture was then neutralized with acetic acid and the whole contents were poured into ice cold water (30 mL), where upon a pale brown precipitate slowly separated out. The precipitate was filtered and recrystallized from methanol as needles. The compound 4, thus synthesized, was characterized by the physical and spectral data. The compound 4: m.p 235°C, mol. formula: C_{25}H_{26}O_3NCl; Yield: 56%; R_f Value: 0.9 (Hexane: Ethyl acetate); HPLC purity: 100%; solvent: Acetonitrile; R_t: 3.93 min; (Calcd for C_{25}H_{26}O_3NCl: C, 70.76; H, 6.13; N, 3.30; Cl, 8.37%; Found: C, 70.08; H, 6.06; N, 3.24; Cl, 8.26%); ^1H NMR (CDCl_3, TMS): δ 1.3 (s, 2a'', 8a''- 6H), 1.4 (2b'', 8b''- 6H), 1.8 (t, 3'', 9'' - 4H), s 2.6 (t, 4'', 10'', 4H), 6.9 (s, 1H, C-4), aromatic protons 7.7-7.8 (m, 4H).

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References