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Note

Synthesis and characterization of a new chromanoisoxazole

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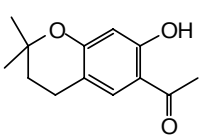
The synthesis of a new chromanoisoxazole **4** has been reported. Acylation of resorcinol using anhyd. $ZnCl_2$ and gl. acetic acid affords resacetophenone, which on nuclear prenylation with isoprene/PPA/xylene gives chroman **2.** Compound **2** on treatment with *p*-chlorobenzaldehyde/ ethanol/KOH 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.

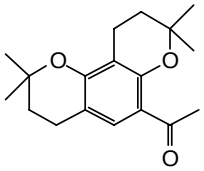
IPC: **Int.Cl.**[7] **C 07 D**

The synthesis of a chromanoisoxazole **4** from chalcone employing the **Scheme I**[1] and its X-ray crystallographic studies is reported.Resorcinol was acylated using anhyd. $ZnCl_2$ 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[2] 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.



1



2

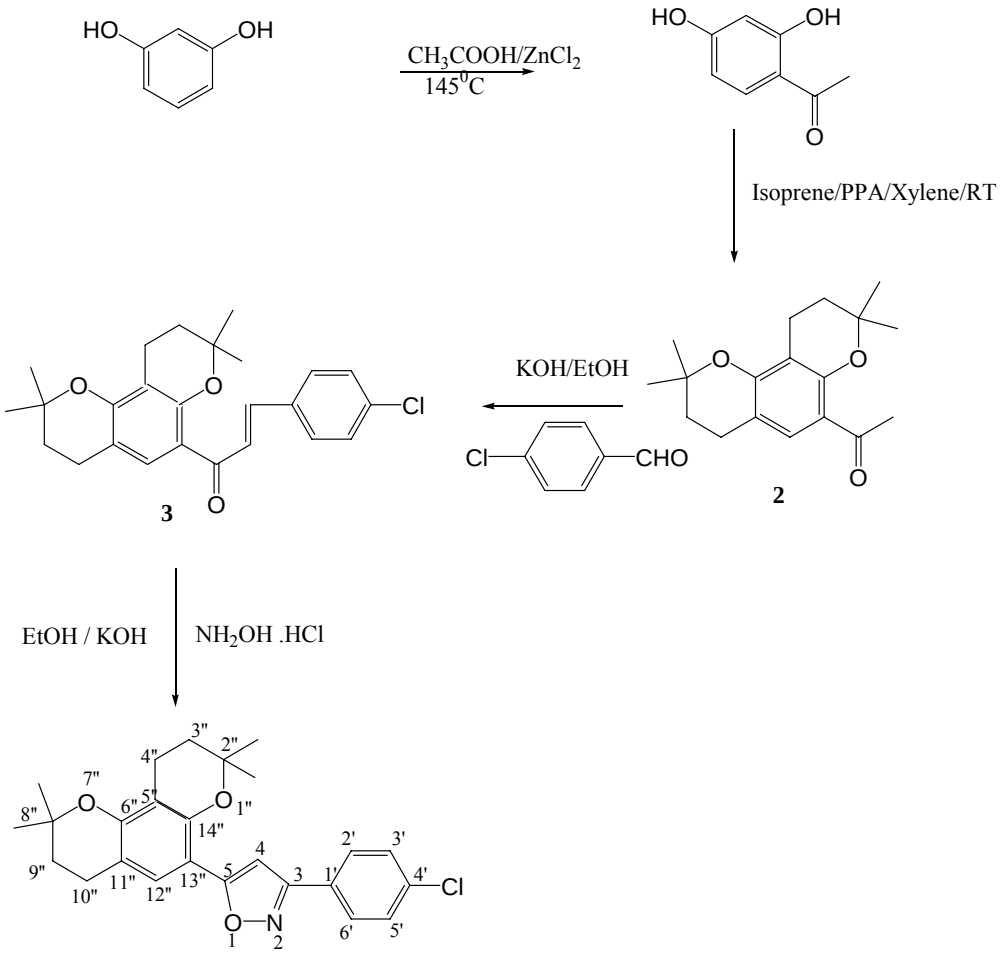
Chroman **2** thus formed was then condensed with *p*-chlorobenzaldehyde in the presence of alcoholic KOH and stirred for 72 hr at room temperature. This after usual work up and purification by column chromatography furnished the pure chalcone **3**. Purity of the chalcone obtained was checked by HPLC,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

The chalcone thus obtained was condensed with hydroxylamine hydrochloride in the presence of KOH/C_2H_5OH. 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 (CH_3CN). Similarly the fluorescence emission maximum was found to be 404 nm in CH_3CN.

Literature search revealed that Battaglia[3] *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 C_4-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 C_4-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 ^{13}C NMR spectrum showed characteristic chemical shifts δ at C_3 at (163.5), C_4 (98.9) and C_5 (164.9) which were in good agreement with the reported values for similar structures[4]. Further confirmation of structure [5-7] 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 [8] of the compound **4** showed characteristic ring stretching vibrations at 1600-1300 cm^{-1} and 1300-1200 cm^{-1}. In the ^1H NMR of isoxazole **4**, the C_4-H appeared at δ 6.92 irrespective of 3-aryl substitution, confirming the structure of the compound **4**.



4

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

Scheme I

X-ray crystallographic studies of the synthesized chromanoisoxazole. The isoxazole ring is planar (maximum deviation of 0.002Å 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 0.2754Å and -0.3105 and 0.3393Å from their least-squares planes. The asymmetric parameters are ΔC_2 [C14, C15] = 1.974 and ΔC_2 [C21, C24] = 7.48 (Duax & Norton 1975)[9]. 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, β=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 I.**

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, spectrofluoro-photometer RF-540.

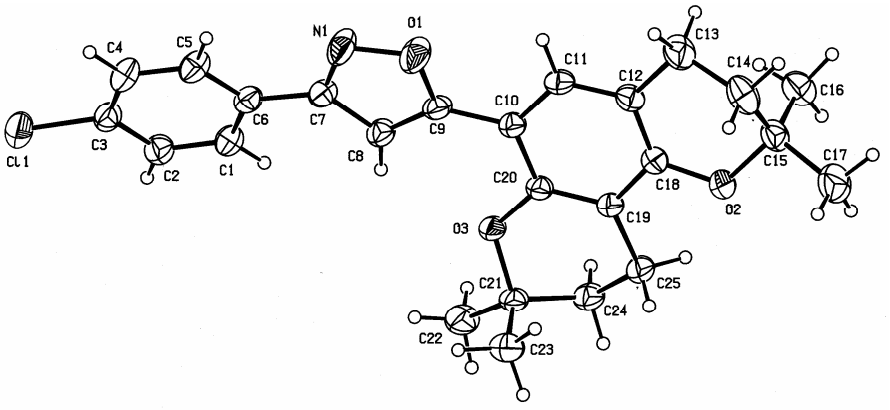


Figure 1 — An ORTEP diagram of Compound **4** withatomic numbering Scheme

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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