Crystal Structure Analysis of Methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate

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Abstract

The crystal structure of the potential active methyl-3-phenyl-3H-chromeno[4,3-c]isoxazole-3a(4H)-carboxylate (C18H15NO4) has been determined from single crystal X-ray diffraction data. In the title compound crystallizes in the orthorhombic space group P212121 with unit cell dimension a=9.8320 (17) Å, b=9.9890 (18) Å and c= 15.588 (3) Å [α=90°, β= 90° and γ= 90°]. In the structure chromene, isoxazole and carboxylate are almost coplanar each other. All geometrical parameters revealed that chromene ring of pyran ring adopt sofa conformation. The crystal packing is stabilized by intermolecular C-H...O and C-H...N hydrogen bond interaction.

Keywords: Chromene, Pyran, Single Crystal Structure, X-ray diffraction

1. Introduction

Chromenes constitute one of the main class of naturally occurring oxygen heterocycles, which possess several biological and pharmacological properties such as anti-coagulant, anti-sterility, anti-viral, anti-fungal, anti-inflammatory, cardiotonic, anti-diabetic, spasmylytic, diuretic, anti-anaphylactic, anti-cancer activities[1-10] and also useful in treatment of Schizophrenia and Alzheimer’s diseases[11,12]. Recently, the structural modification of chromene scaffold with the addition of heterocyclic substituents at either the second or third position has attracted extensive interest in the field of structure based drug designing (SBDD).

2. Material and Methods

The title compound is crystallized by simple solvent slow evaporation method. Three rounds of crystallization trials to obtained a qualified crystals were achieved. The diffraction quality crystals after screening its size and stability, X-ray diffraction data collection was done at IIT-Madras. The data was reduced with appropriate corrections at the facility and the error free data was taken for structure determination. Using WinGx suite, structure determination was done using SHELXS97 with Direct Methods protocols. After manual inspections and corrections, isotropic refinements followed by anisotropic refinements were carried out. With the satisfied model (agreeable R factor, Goodness of Fit and other) hydrogen atoms were geometrically fixed and after the final refinement the R factor is 4.0%.

3. Experimental Section

3.1. Synthesis of the Title Compound

To a solution of aldoxime 4a (0.63 g, 2 mmol) in 10
mL CCl₄ at 0-10°C was added NCS (0.54 g, 4 mmol, pinch wise) over 3 h. After this period Et₃N (0.57 mL, 4 mmol) was added to the reaction mixture and stirred well at room temperature for 2 h. After completion of the reaction, reaction mixture was evaporated under reduced pressure and the resulting crude mass was diluted with water (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with brine (2×10 mL) and dried over anhydrous Na₂SO₄. The organic layer was evaporated and the crude mass was purified by column chromatography (silica gel 60-120 mesh 5% EtOAc in hexanes) to provide the desired pure product 5a (0.43 g, 70%) as a colorless solid; mp: 130-132°C. Since the compound has not yield the diffraction quality crystals initially, the compound has been recrystallized with ethyl acetate by slow evaporation method to get better quality single crystals.

3.2. X-Ray Crystallography

For the crystal structure determination, the single crystal of the compound C₁₈H₁₅NO₄ was used for data collection on a Bruker Kappa APEXII CCD diffractometer[13]. The MoKα radiation of wavelength (λ = 0.71073 Å) and multi-scan technique for absorption correction were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F²>2σ(F²). The

| Parameters                          | Compound              |
|------------------------------------|-----------------------|
| Empirical formula                  | C₁₈H₁₅NO₄             |
| Formula weight                     | 309.31                |
| Temperature                        | 293(2) K              |
| Wavelength                         | 0.71073 Å             |
| Crystal system, space group        | Orthorhombic, P2₁2₁2₁ |
| Unit cell dimensions               | a = 9.832 (17) Å, b = 9.989 (18) Å, c = 15.588 (3) Å, α = β = γ = 90° |
| Volume                             | 1530.9 (5) Å³         |
| Z, Calculated density              | 4, 1.342 Mg/m³        |
| Absorption coefficient             | 0.104 mm⁻¹            |
| F(000)                             | 684                   |
| Crystal size (mm)                  | 0.25×0.20×0.20        |
| θ range for data collection        | 2.42 to 28.3°         |
| Limiting indices                   | -9 ≤ h ≤ 13, -12 ≤ k ≤ 13, -20 ≤ l ≤ 16 |
| Reflections collected/unique       | 8382/3761             |
| Complement to theta                 | 100%                  |
| Refinement method                  | Full-matrix least-squares on F² |
| Data/restraints/parameters          | 3761/0/209            |
| Goodness-of-fit on F²              | 1.03                  |
| Final R indices [I=2σ(I)]          | R1 = 0.0414, wR2 = 0.1054 |
| R indices (all data)               | R1 = 0.0499, wR2 = 0.1117 |
| Largest diff. peak and hole         | 0.138 and -0.217 e.Å³ |

Fig. 2. Displacement ellipsoids are drawn at the 30% probability level.

Fig. 3. Crystal packing of the title compound, dashed line indicate the inter molecular interaction in the unit cell.
structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97[14,15]. H atoms were positioned geometrically and refined using a riding model, fixing the aromatic C-H distances at 0.93 Å [Uiso(H) = 1.2 Ueq (C)]. The softwares used for Molecular graphics are ORTEP-3 for Windows [16] and PLATON[17]. The software used to prepare material for publication is WinGX publication routines [18]. Experimental data are listed in Table 1. Fig. 1 shows schematic

|     | x   | y   | z   | Ueq*/*Ueq |
|-----|-----|-----|-----|------------|
| C15 | 0.7170 (3) | 0.3871 (2) | 0.02410 (18) | 0.0885 (8) |
| H15 | 0.6326 | 0.3608 | 0.0031 | 0.106* |
| O3  | 1.11601 (12) | 0.80271 (12) | 0.18420 (9) | 0.0550 (3) |
| O1  | 0.80063 (12) | 0.80751 (12) | 0.27848 (7) | 0.0494 (3) |
| C10 | 1.01274 (15) | 0.87692 (15) | 0.15798 (10) | 0.0379 (3) |
| O4  | 0.85940 (14) | 0.78040 (12) | -0.01379 (7) | 0.0529 (3) |
| C8  | 0.89258 (14) | 0.78681 (14) | 0.13534 (9) | 0.0345 (3) |
| O2  | 1.01362 (12) | 0.99504 (11) | 0.15118 (10) | 0.0611 (4) |
| N1  | 0.75646 (15) | 0.86306 (14) | 0.02254 (9) | 0.0486 (3) |
| C12 | 0.92527 (16) | 0.70425 (14) | 0.05433 (9) | 0.0388 (3) |
| H12 | 1.0238 | 0.7064 | 0.0448 | 0.047* |
| C6  | 0.70761 (15) | 0.90170 (15) | 0.25214 (10) | 0.0430 (3) |
| C7  | 0.84395 (16) | 0.71217 (15) | 0.21507 (9) | 0.0414 (3) |
| H7A | 0.7690 | 0.6535 | 0.2002 | 0.050* |
| H7B | 0.9172 | 0.6578 | 0.2379 | 0.050* |
| C13 | 0.87935 (15) | 0.56032 (15) | 0.05508 (9) | 0.0393 (3) |
| C5  | 0.68673 (14) | 0.93267 (15) | 0.16604 (10) | 0.0400 (3) |
| C9  | 0.77408 (15) | 0.86712 (15) | 0.10356 (9) | 0.0375 (3) |
| C18 | 0.96689 (19) | 0.46419 (17) | 0.08648 (11) | 0.0493 (4) |
| H18 | 1.0513 | 0.4897 | 0.1078 | 0.059* |
| C4  | 0.58712 (16) | 1.02751 (18) | 0.14485 (13) | 0.0504 (4) |
| H4  | 0.5699 | 1.0472 | 0.0876 | 0.061* |
| C1  | 0.63491 (18) | 0.9676 (2) | 0.31638 (12) | 0.0583 (5) |
| H1  | 0.6503 | 0.9480 | 0.3739 | 0.070* |
| C11 | 1.24148 (17) | 0.8703 (2) | 0.20549 (15) | 0.0632 (5) |
| H11A| 1.2524 | 0.9471 | 0.1692 | 0.095* |
| H11B| 1.3166 | 0.8102 | 0.1971 | 0.095* |
| H11C| 1.2389 | 0.8983 | 0.2644 | 0.095* |
| C14 | 0.7525 (2) | 0.5218 (2) | 0.02478 (14) | 0.0617 (5) |
| H14 | 0.6914 | 0.5859 | 0.0050 | 0.074* |
| C2  | 0.54026 (18) | 1.0620 (2) | 0.29310 (15) | 0.0675 (6) |
| H2  | 0.4922 | 1.1071 | 0.3356 | 0.081* |
| C3  | 0.51473 (18) | 1.0916 (2) | 0.20805 (15) | 0.0632 (5) |
| H3  | 0.4489 | 1.1545 | 0.1937 | 0.076* |
| C17 | 0.9310 (3) | 0.33064 (18) | 0.08664 (12) | 0.0635 (5) |
| H17 | 0.9906 | 0.2668 | 0.1083 | 0.076* |
| C16 | 0.8070 (3) | 0.2925 (2) | 0.05466 (16) | 0.0835 (8) |
| H16 | 0.7835 | 0.2024 | 0.0536 | 0.100* |

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Table 3. Bond lengths [Å] and angles [°]

| Bond Length  | Bond Length  | Bond Angle  | Bond Angle  |
|--------------|--------------|-------------|-------------|
| C15—C16      | 1.380 (4)    | C13—C18     | 1.379 (2)   |
| C15—C14      | 1.390 (3)    | C13—C14     | 1.388 (2)   |
| C15—H15      | 0.9300       | C5—C4       | 1.402 (2)   |
| O3—C10       | 1.3219 (18)  | C5—C9       | 1.454 (2)   |
| O3—C11       | 1.445 (2)    | C18—C17     | 1.380 (3)   |
| O1—C6        | 1.3748 (19)  | C18—H18     | 0.9300      |
| O1—C7        | 1.4371 (19)  | C4—C3       | 1.374 (3)   |
| C10—O2       | 1.1847 (18)  | C4—H4       | 0.9300      |
| C10—C8       | 1.5265 (19)  | C1—C2       | 1.373 (3)   |
| O4—N1        | 1.4237 (18)  | C1—H1       | 0.9300      |
| O4—C12       | 1.4577 (19)  | C11—H11A    | 0.9600      |
| C8—C9        | 1.499 (2)    | C11—H11B    | 0.9600      |
| C8—C7        | 1.5262 (19)  | C11—H11C    | 0.9600      |
| C8—C12       | 1.542 (2)    | C14—H14     | 0.9300      |
| C6—O1—C7     | 116.44 (12)  | C5—C9—C8    | 118.61 (13) |
| N1—O4—C12    | 124.91 (14)  | C3—C4—C5    | 120.52 (18) |
| C11—O3—C11   | 109.19 (11)  | C17—C18—H18 | 119.5      |
| N1—C9—C8     | 109.19 (11)  | C17—C18—C17 | 120.94 (18) |
| C12—C13      | 111.25 (12)  | C5—C4—H4    | 119.7       |
| C13—C12      | 110.01 (12)  | C2—C1—C6    | 118.78 (19) |
| C9—C8—C12    | 100.23 (11)  | C2—C1—H1    | 120.6       |
| C7—C8—C12    | 118.09 (12)  | C6—C1—H1    | 120.6       |
| C10—C8—C12   | 110.08 (11)  | C3—C1—H11A  | 109.5       |
| C9—N1—O4     | 108.41 (13)  | C3—C1—H11B  | 109.5       |
| O4—C12—C13   | 111.75 (12)  | C11A—C11—H11B | 109.5  |
| O4—C12—C8    | 102.99 (11)  | C3—C11—H11C | 109.5       |
| C13—C12—C8   | 116.18 (12)  | C11A—C11—H11C | 109.5 |
| O4—C12—H12   | 108.5        | H11B—C11—H11C | 109.5     |
| C13—C12—H12  | 108.5        | C13—C14—C15 | 119.8 (2)   |
diagram of the molecule and molecular structure of the title compound along with the atom numbering scheme is depicted in Fig. 2 and a packing diagram is shown in Fig. 3. Table 1 shows the crystal data and crystal refinement statistics. The title compound structure has been deposited in Cambridge structural data base with
Table 5. Torsion angles [°]

| Torsion angle | Torsion angle | Torsion angle |
|---------------|---------------|---------------|
| C11—O3—C10—O2 | -0.8 (3)      | O1—C6—C5—C9  | -3.8 (2)      |
| C11—O3—C10—C8 | 177.68 (14)   | C1—C6—C5—C9  | 175.25 (14)   |
| O2—C10—C8—C9  | -0.4 (2)      | O4—N1—C9—C5  | -175.61 (13)  |
| O3—C10—C8—C9  | -178.85 (12)  | O4—N1—C9—C8  | -0.17 (18)    |
| O2—C10—C8—C7  | -118.35 (18)  | C6—C5—C9—N1  | 166.65 (16)   |
| O3—C10—C8—C7  | 63.15 (16)    | C4—C5—C9—N1  | -15.6 (2)     |
| O2—C10—C8—C12 | 109.83 (19)   | C6—C5—C9—C8  | -8.62 (19)    |
| O3—C10—C8—C12 | -68.67 (15)   | C4—C5—C9—C8  | 169.12 (14)   |
| C12—O4—N1—C9  | 14.20 (16)    | C7—C8—C9—N1  | -136.21 (14)  |
| N1—O4—C12—C13 | 104.21 (13)   | C10—C8—C9—N1 | 103.80 (15)   |
| N1—O4—C12—C8  | -21.21 (14)   | C12—C8—C9—N1 | -12.60 (17)   |
| C9—C8—C12—O4  | 19.27 (14)    | C7—C8—C9—C5  | 39.62 (16)    |
| C7—C8—C12—O4  | 134.54 (13)   | C10—C8—C9—C5 | -80.37 (16)   |
| C10—C8—C12—O4 | -98.00 (13)   | C12—C8—C9—C5 | 163.23 (12)   |
| C9—C8—C12—C13 | -103.22 (14)  | C14—C13—C18—C17 | 1.2 (3) |
| C7—C8—C12—C13 | 12.05 (19)    | C12—C13—C18—C17 | -178.40 (16) |
| C10—C8—C12—C13 | 139.51 (13)  | C6—C5—C4—C3  | 2.0 (2)       |
| C7—O1—C6—C5  | -19.5 (2)     | C9—C5—C4—C3  | 175.67 (16)   |
| C7—O1—C6—C1  | 161.37 (14)   | O1—C6—C1—C2  | -179.61 (15)  |
| C6—O1—C7—C8 | 52.42 (17)    | C5—C6—C1—C2  | 1.3 (2)       |
| C9—C8—C7—O1  | -60.00 (15)   | C18—C13—C14—C15 | -1.9 (3) |
| C10—C8—C7—O1 | 60.78 (15)    | C12—C13—C14—C15 | 177.7 (2) |
| C12—C8—C7—O1 | -171.72 (12)  | C16—C15—C14—C13 | 1.0 (4) |
| O4—C12—C13—C18 | 152.24 (14)  | C6—C1—C2—C3  | 0.7 (3)       |
| C8—C12—C13—C18 | -90.00 (17)  | C5—C4—C3—C2  | -0.1 (3)      |
| O4—C12—C13—C14 | -27.4 (2)    | C1—C2—C3—C4  | -1.3 (3)      |
| C8—C12—C13—C14 | 90.40 (19)   | C13—C18—C17—C16 | 0.5 (3) |
| O1—C6—C5—C4  | 178.30 (14)   | C18—C17—C16—C15 | -1.4 (4) |
| C1—C6—C5—C4  | -2.6 (2)      | C14—C15—C16—C17 | 0.7 (4) |

Table 6. Hydrogen-bond geometry (Å, °)

| D—H···A  | D—H(Å) | H···A(Å) | D···A(Å) | D—H···A(°) |
|----------|--------|----------|----------|-----------|
| C7—H7B···O2 | 0.97   | 2.47     | 3.318 (2) | 146       |
| C12—H12···N1 | 0.98   | 3.53     | 3.534(2) | 157       |

the CCDC reference number: 791956. Table 2 gives the atomic coordinates, Table 3 describes the bond lengths and angles; Table 4 shows anisotropic displacement parameters, Table 5 shows the torsion angles and Table 6 shows Hydrogen-bond geometry.

4. Results and Discussion

Title compound crystallizes in the orthorhombic system with P2_12_12 space group and total number molecule found in the unit cell is Z = 2. The chromene and isoxazole rings are coplanar one another. The carboxylate group is attached at the atom C8 of chromene system are almost perpendicular each other. the phenyl ring is attached to the isoxazole ring are tilted with the dihedral angle of 74.37 (2)°. The six membered ring systems offer a wide variety of conformational flexibility such as chair, distorted chair, half chair, boat and distorted.
boat conformations. However, the chair or slightly distorted chair conformation is found to be the most favored ones. But in the present study all the geometrical parameters strongly confirm that the six membered pyran ring of chromene moiety adopts sofa conformation\(^\text{[19]}\). Many of C-H...O and C-H...N type of hydrogen bonds plays a vital role for the stability of crystal packing. In this molecular structure, the C7-H7B...O2 (2-x, -1/2+y, 1/2-z) and C12-H12...N2 (1/2+x, 3/2-y, -z) hydrogen bonds has stabilized the crystal packing of the title compound.

**Symmetry codes:**
(i) 2-x, -1/2+y, 1/2-z
(ii) 1/2+x, 3/2-y, -z

5. Conclusion

Crystal structure of a novel chromene based derivatives having a wide range of applications is described. The title compound is insoluble in millipore water and it is crystallized in ethonal by slow evaporation technique. The Pyran ring adopt a sofa conformation. The title structure may be important from a medicinal point of view as well as their widespread biological significance. The structure may be useful for further investigation on the mechanism, potential activity, optimal reaction condition etc which will be further characterized as a future prospective of our project.

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