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Synthesis and Crystal Structure of 1-(Cyano(4-methoxyphenyl)methyl)cyclohexyl Acetate

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Synthesis and Crystal Structure of 1-(Cyano- (4-methoxyphenyl)methyl)cyclohexyl Acetate

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The title compound, $C_{17}H_{21}NO_3$, was synthesized by the acetylation of the hydroxy group of 1-(cyano(4-methoxyphenyl)methyl)cyclohexanol, which was formed by the reaction of 4-methoxyphenyl acetonitrile with cyclohexanone. The compound was characterized spectroscopically, and the structure was investigated by X-ray crystallography. The compound crystallizes in the orthorhombic crystal class in the space group $Pbca$ with cell parameters $a = 13.412(6)$ Å, $b = 12.398(14)$ Å, $c = 19.026(19)$ Å, and $V = 3164(5)$ Å³ for $Z = 8$. The cyclohexane ring is in a chair conformation. The structure exhibits intermolecular hydrogen bonds of the type $C-H \cdots N$ and $C-H \cdots O$.

Keywords: chair conformation; hydrogen bond; venlafaxine

INTRODUCTION

Venlafaxine [1,2] is a new generation antidepressant drug, quite different from other antidepressants, with a unique structure and morphological effects. Cycloalkanols serve as important intermediates for the synthesis of potent drugs such as venlafaxine. In addition, the use of the nitrile function for C–C bond-formation reaction occupies an

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important position in organic chemistry [3,4]. Particularly, deprotonation of the α -carbon and alkylation are important reactions [5]. The nitrile group undergoes reduction with many reducing agents. Depending on the nature of the reducing agent and experimental conditions, the reaction can produce amines, aldehydes, primary alcohols, imines, or alkanes [6,7]. In pursuit of the methods for synthesis of analogs of the key intermediate, 1-(cyano-(4-methoxyphenyl)methyl)-cyclohexanol, we have synthesized the title compound under mild conditions. This protocol can be successfully employed for the synthesis of a wide variety of other natural products and commercially important pharmaceuticals [8]. The present study was undertaken to study the structural conformation of the title compound, and herein we report the synthesis and crystal structure of 1-(cyano(4-methoxyphenyl)-methyl)cyclohexyl acetate.

EXPERIMENTAL

The melting point was recorded on a Selaco-650 hot-stage apparatus and is uncorrected. The IR (KBr) spectra was recorded on a Jasco FT/IR-4100 Fourier transform infrared (FTIR) spectrometer. ^1H NMR spectra were recorded on a Shimadzu AMX 400 spectrometer using CDCl_3 as solvent and TMS as an internal standard (chemical shifts in ppm). Elemental analysis was done on a Vario-EL instrument. Thin-layer chromatography (TLC) was conducted on 0.25-mm silica-gel plates (60F₂₅₄, Merck); visualization was made with ultraviolet (uv) light. All the extracted solvents were dried over anhydrous Na_2SO_4 and evaporated with a Buchi rotary evaporator. The reagents were obtained commercially and were used as received. The reaction scheme is shown in Fig. 1.

Synthesis of 1-(Cyano-(4-methoxyphenyl)methyl)cyclohexanol

To a magnetically stirred solution of sodium hydroxide (20 g, 0.5 mol) in methanolic water at 0°C , a mixture of 4-methoxyphenyl acetonitrile (50 g, 0.340 mol) was added, and cyclohexanone (49.9 g, 0.515 mol) was dissolved in methanol slowly, followed by the addition of tetrabutyl ammonium hydrogen sulfate (5 g). The reaction mass was stirred for 6 h at room temperature ($25\text{--}30^\circ\text{C}$) and filtered. The residue was thoroughly washed with water (500 ml) and hexane (200 ml) to obtain the compound (82 g, 98%).

Mp: $122\text{--}124^\circ\text{C}$. Anal. calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.43; H, 7.80; N, 5.72. ^1H NMR (CDCl_3 , 300 MHz): δ 7.30 (d, 2H, Ar-H), 6.91 (d, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 3.75 (s, 1H, OH), 1.55 (m, 10H, cyclohexyl).

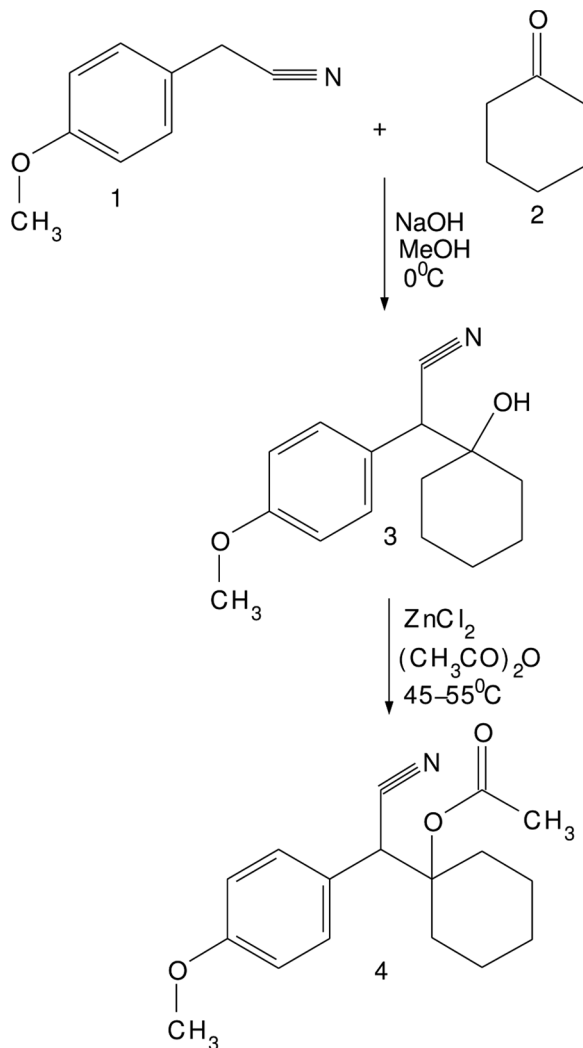


FIGURE 1 Reaction Scheme.

Synthesis of 1-(Cyano(4-methoxyphenyl)methyl)cyclohexyl Acetate

1-(Cyano(4-methoxyphenyl)methyl)cyclohexanol was dissolved in dichloromethane followed by the addition of acetic anhydride (2.3 ml, 1.5 eq) and zinc chloride (5.56 g, 2 eq). The reaction mixture was refluxed at 45–55°C for about 3 h. After completion of the reaction,

the reaction mixture was quenched with water and extracted with dichloromethane (2×50 ml). The combined organic layer was evaporated under reduced pressure. Pure colorless crystals were obtained by the slow evaporation of ethyl acetate.

Mp: 122–124°C. Anal. calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.05; H, 7.37; N, 4.88. 1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (d, 2H, Ar-H), 6.91 (d, 2H, Ar-H), 3.81 (s, 3H, $-OCH_3$), 2.12 (s, 3H, $-CH_3$), 5.01 (s, 1H, $-CH-CN$), 1.55 (m, 10H, cyclohexyl).

CRYSTAL STRUCTURE DETERMINATION

A single crystal of the title compound with dimensions $0.27 \times 0.25 \times 0.2$ mm was chosen for an X-ray diffraction study. The data were

TABLE 1 Crystal Data and Structure Refinement

Parameter	Value
CCDC deposition number	CCDC 616861
Empirical formula	$C_{17}H_{21}NO_3$
Formula weight	287.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	<i>Pbca</i>
Cell dimensions	$a = 13.412(6)$ Å $b = 12.398(14)$ Å $c = 19.026(19)$ Å
Volume	$3164(5)$ Å ³
Z	8
Density(calculated)	1.207 Mg/m ³
Absorption coefficient	0.082 mm ⁻¹
F_{000}	1232
Crystal size	$0.27 \times 0.25 \times 0.2$ mm
Theta range for data collection	2.14° to 25.03°
Index ranges	$-15 \leq h \leq 15$ $-13 \leq k \leq 13$ $-22 \leq l \leq 22$
Reflections collected	4733
Independent reflections	2583 [$R(\text{int}) = 0.0171$]
Absorption correction	None
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	2583/0/193
Goodness of fit on F^2	1.042
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0740$, $wR2 = 0.2088$
R indices (all data)	$R1 = 0.0993$, $wR2 = 0.2491$
Extinction coefficient	$0.029(5)$
Largest diff. peak and hole	0.515 and -0.389 e.Å ⁻³

collected on a DIPLabo Image Plate system equipped with a normal focus, 3-kW sealed X-ray source (graphite monochromated MoK_α). The crystal-to-detector distance is fixed at 120 mm with a detector area of 441 × 240 mm². Thirty-six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [9]. The reflections were merged with Scalepack [10]. All of the frames could be indexed using a primitive orthorhombic lattice. Absorption correction was not applied. The structure was solved by direct methods using SHELXS-97 [11]. Least-squares refinement using SHELXL-97 [12] with isotropic temperature factors for all the nonhydrogen atoms converged the residual *R*1 to 0.1677. Subsequent refinements were carried out with anisotropic thermal parameters for nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms, which were placed at chemically acceptable positions. The hydrogen

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen Atoms

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq}
C1	0.0381(2)	0.2824(2)	0.4711(2)	0.0568(7)
C2	0.0812(2)	0.1882(2)	0.5130(2)	0.0734(8)
C3	0.1076(3)	0.2184(2)	0.5885(2)	0.0832(1)
C4	0.0194(3)	0.2654(2)	0.6267(2)	0.0800(9)
C5	−0.0212(2)	0.3620(2)	0.5871(2)	0.0699(8)
C6	−0.0481(2)	0.3336(2)	0.5113(2)	0.0582(7)
O7	0.1097(2)	0.3715(2)	0.46489(9)	0.0596(6)
C8	0.2001(2)	0.3587(2)	0.4370(2)	0.0682(8)
O9	0.2306(2)	0.2757(2)	0.4109(2)	0.0953(8)
C10	0.2605(2)	0.4599(2)	0.4421(2)	0.0846(1)
C11	0.0080(2)	0.2474(2)	0.3947(2)	0.0605(7)
C12	−0.0624(2)	0.1559(2)	0.3982(2)	0.0693(8)
N13	−0.1178(2)	0.0864(2)	0.3991(2)	0.0902(9)
C14	−0.0347(2)	0.3357(2)	0.3480(2)	0.0590(7)
C15	−0.1333(2)	0.3682(2)	0.3537(2)	0.0684(8)
C16	−0.1723(2)	0.4506(2)	0.3132(2)	0.0710(8)
C17	−0.1114(2)	0.5018(2)	0.2646(2)	0.0663(8)
C18	−0.0132(2)	0.4681(2)	0.2569(2)	0.0716(8)
C19	0.0240(2)	0.3865(2)	0.2983(2)	0.0669(8)
O20	−0.1422(2)	0.5853(2)	0.2224(2)	0.0840(7)
C21	−0.2389(3)	0.6279(3)	0.2344(2)	0.0980(2)

Note. $U_{eq} = (1/3) \sum_i \sum_j U_{ij} (a_i^* a_j^*) (\mathbf{a}_i \cdot \mathbf{a}_j)$.

TABLE 3 Bond Lengths (Å)

Atoms	Length
C1–O7	1.469(3)
C1–C6	1.523(4)
C1–C2	1.528(3)
C1–C11	1.569(4)
C2–C3	1.526(4)
C3–C4	1.505(5)
C4–C5	1.516(4)
C5–C6	1.528(4)
O7–C8	1.334(3)
C8–O9	1.214(3)
C8–C10	1.496(4)
C11–C12	1.477(4)
C11–C14	1.522(4)
C12–N13	1.138(3)
C14–C19	1.383(4)
C14–C15	1.387(4)
C15–C16	1.383(4)
C16–C17	1.387(4)
C17–O20	1.373(3)
C17–C18	1.389(4)
C18–C19	1.376(4)
O20–C21	1.419(4)

atoms were allowed to ride on their parent atoms. After eight cycles of refinement, the residual converged to 0.0740. The details of crystal data and refinement are given in Table 1.[†] Table 2 gives the atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles respectively, which are in good agreement with the standard values. The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2.

The dihedral angle between the cyclohexane ring and the methoxy phenyl ring is 50.63(15)°. The methylester group is almost perpendicular to the cyclohexane ring as indicated by the dihedral angle value of 89.4(2)°. A study of torsion angles, asymmetric parameters, and least-squares plane calculations reveal that the cyclohexane ring is in a chair conformation. This is confirmed by the puckering parameters $Q = 0.5510(35)$ Å, $\theta = 2.94(36)^\circ$, and $\phi = 170(7)^\circ$. The bond C1–O7 lies

[†]CCDC 616861 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

TABLE 4 Bond Angles ($^{\circ}$)

Atoms	Angle
O7–C1–C6	102.8(2)
O7–C1–C2	111.6(2)
C6–C1–C2	110.1(2)
O7–C1–C11	107.6(2)
C6–C1–C11	112.7(2)
C2–C1–C11	111.7(2)
C3–C2–C1	113.1(2)
C4–C3–C2	111.6(3)
C3–C4–C5	110.4(3)
C4–C5–C6	111.8(2)
C1–C6–C5	113.1(2)
C8–O7–C1	122.5(2)
O9–C8–O7	124.7(3)
O9–C8–C10	123.8(3)
O7–C8–C10	111.5(2)
C12–C11–C14	109.8(2)
C12–C11–C1	109.6(2)
C14–C11–C1	116.0(2)
N13–C12–C11	178.1(3)
C19–C14–C15	117.6(3)
C19–C14–C11	120.9(3)
C15–C14–C11	121.5(2)
C16–C15–C14	122.2(3)
C15–C16–C17	119.1(3)
O20–C17–C16	123.8(3)
O20–C17–C18	116.7(2)
C16–C17–C18	119.4(3)
C19–C18–C17	120.3(3)
C18–C19–C14	121.4(3)
C17–O20–C21	117.5(2)

in the axial plane of the cyclohexane ring with an angle of $5.48(19)^{\circ}$ from the Cremer and Pople [13] plane, whereas the bond C1–C11 lies in the equatorial plane with an angle of $70.2(2)^{\circ}$. The methoxy group lies in the plane of the phenyl ring as indicated by the torsion angle value of $6.4(5)^{\circ}$ for C21–O20–C17–C16. The carbonyl group at C8 is in the *syn-periplanar* conformation as indicated by the torsion angle value of $4.1(5)^{\circ}$ for C1–O7–C8–C9. The acrylonitrile group is in an *anti-periplanar* conformation with respect to the C1–C11 bond as indicated by the torsion angle value of $151.3(1)^{\circ}$ for C1–C11–C12–N13. The molecule possesses a chiral center at C11. Because the title compound has crystallized in a centrosymmetric space group, we can surmise that the material is a racemic mixture. The structure exhibits

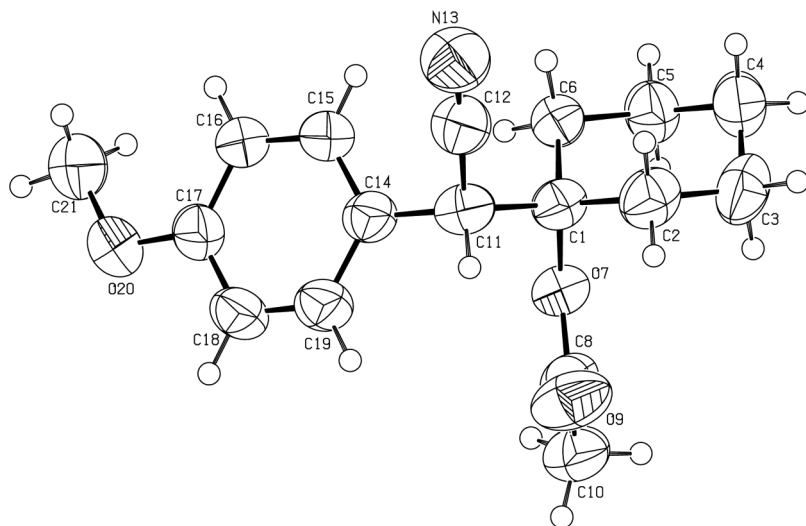


FIGURE 2 ORTEP of the molecule at 50% probability.

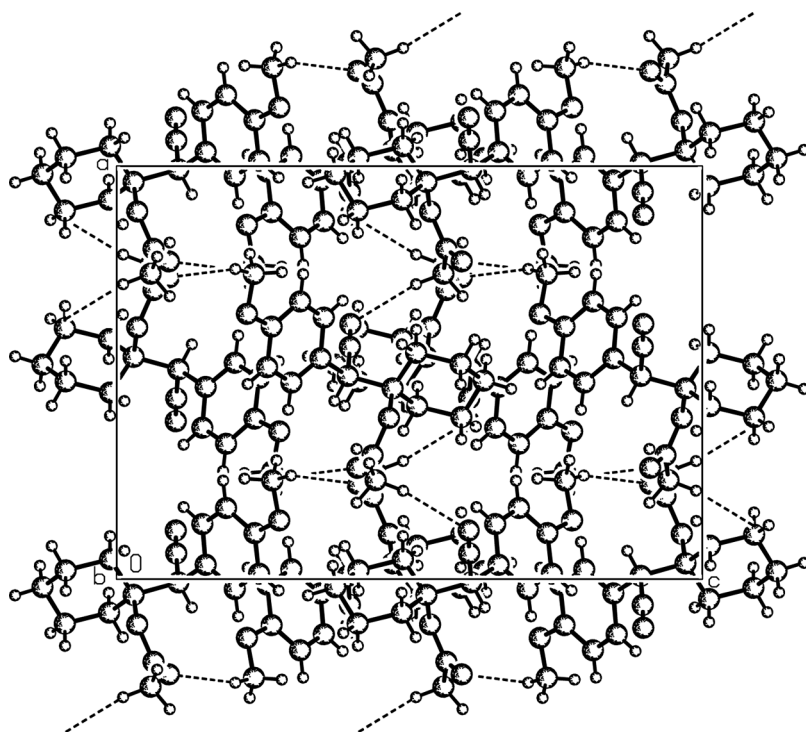


FIGURE 3 Packing of the molecules down the *b* axis. The dashed lines represent the hydrogen bonds.

intermolecular hydrogen bonds of the type C–H···N and C–H···O. The intermolecular hydrogen bonds are C10–H10A···N13, which has a length of 3.482(6) Å with an angle of 157(2)°, and C21–H21B···O9, which has a length of 3.319(6) Å and an angle of 152(1)°, with symmetry codes $1/2 + x$, $1/2 - y$, $1 - z$, and $-x$, $1/2 + y$, $1/2 - z$, respectively. The stability of the crystal structure can be accounted for by these hydrogen bonds. The packing of the molecules as shown in Fig. 3 indicates that the molecules are interlinked by the hydrogen bonds to form an infinite chain when viewed down the b axis.

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